The Health Consequences of Smoking—50 Years of Progress

A Report of the Surgeon General

Supplemental Evidence Tables

2014

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Office of the Surgeon General
Rockville, MD

Suggested Citation

U.S. Department of Health and Human Services. *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General.* Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.

For more information

For more information about the Surgeon General's report, visit www.surgeongeneral.gov.

To download copies of this document, go to www.cdc.gov/tobacco.

To order copies of this document, go to www.cdc.gov/tobacco and click on Publications Catalog or call 1-800-CDC-INFO (1-800-232-4636); TTY: 1-888-232-6348.

Use of trade names is for identification only and does not constitute endorsement by the U.S. Department of Health and Human Services. Any recommendations expressed by non-governmental individuals or organizations do not necessarily represent the views or opinions of the U.S. Department of Health and Human Services.

The Health Consequences of Smoking—50 Years of Progress

Supplemental Evidence Tables

Chapter 6. Cancer *S-3*

Table 6.3*S* Case-control studies on smoking and primary liver cancer *S-3*

Table 6.4*S* Cohort studies on smoking and primary liver cancer *S-12*

Table 6.5*S* Prospective studies of cigarette smoking and colorectal cancer incidence, published 2002–2009 *S-21*

Table 6.6*S* Case-control studies of cigarette smoking and colorectal cancer incidence, published 2001–2008 *S-26*

Table 6.7*S* Prospective studies of cigarette smoking and colorectal cancer mortality, published 2002–2009 *S-28*

Table 6.8*S* Prospective cohort studies on the association between cigarette smoking and prostate cancer incidence and mortality *S-30*

Table 6.9*S* Epidemiologic cross-sectional studies on the association between cigarette smoking and stage and histologic grade at diagnosis of prostate cancer *S-45*

Table 6.10*S* Cohort studies on the association between cigarette smoking and risk of prostate cancer progression, case fatality, and all-cause mortality in men with prostate cancer *S-48*

Table 6.11*S* Reports on levels of endogenous hormones and smoking in premenopausal women (n = 22) *S-52*

Table 6.12*S* Reports on levels of endogenous hormones and smoking in postmenopausal women (n = 17) *S-57*

Table 6.14*S* Cohort study reports of the association between active cigarette smoking and risk of breast cancer, based on studies published before 2012 (n = 15) *S-60*

Table 6.15*S* Case-control study reports of the association between active cigarette smoking and risk for breast cancer, based on studies published from 2000 to 2011 (n = 34) *S-75*

Table 6.16*S* Evaluation of reports on exposure to active cigarette smoking for meta-analyses, based on cohort studies before 2012 and case-control studies published between 2000 and 2011 for meta-analyses, by location, study design, size of analytic sample, type of referent group, meta-analysis categories, and design or analysis issues (n = 65) *S-109*

Table 6.17*S* Summary of meta-analyses for measures of active cigarette smoking for all studies combined and stratified by study design, based on cohort studies published before 2012 and case-control studies published from 2000 to 2011 *S-118*

Table 6.18*S* Reports of premenopausal and postmenopausal relative risks (RRs) by study and meta-analysis RRs for the association of active smoking (ever, pack-years) with risk for breast cancer, based on cohort studies published before 2012 and case-control studies published from 2000 to 2011 (n = 20) *S-120*

Table 6.19*S* Reports of estrogen receptor status relative risks (RRs) for the association of active cigarette smoking (ever, cigarettes/day) with risk for breast cancer, based on cohort studies published before 2012 and case-control studies published from 2000 to 2011 (n = 17) *S-123*

Table 6.20*S* Reports on the association between active cigarette smoking and risk of a second primary contralateral breast cancer (n = 7) *S-125*

Table 6.21*S* Modification of risk for breast cancer associated with smoking by *NAT2* phenotype, based on two meta-analyses and one pooled analysis, stratified by menopausal status *S-126*

Table 6.22*S* Reports on cohort studies of the association between exposure to secondhand smoke and relative risk (RR) for breast cancer incidence, based on studies published before 2012 included in the 2006 Surgeon General's report (n = 7) *S-127*

Table 6.23*S* Reports on case-control studies of the association between exposure to secondhand smoke and relative risk (RR) for breast cancer incidence, based on studies published before 2012 but not included in the 2006 Surgeon General's report (n = 11) *S-132*

Table 6.24*S* Evaluation of reports on exposure to secondhand smoke among 171 nonsmokers, based on 10 cohort and 24 case-control studies of breast cancer published before 2012 for meta-analyses, by location, study design, analytic sample size, meta-analysis categories, and design or analysis issues (n = 39) *S-142*

Table 6.25*S* Summary of meta-analyses for the broadest categories of exposure to secondhand smoke (adult–any source, ever in lifetime, most comprehensive) for all studies of breast cancer combined and stratified by menopausal status, based on cohort and case-control studies published before 2012 *S-148*

Table 6.26*S* Summary of meta-analyses for specific categories of exposure to secondhand smoke (spouse, home, workplace, childhood, childhood and adulthood) for all studies of breast cancer combined and stratified by menopausal status, based on cohort and case-control studies published before 2012 *S-150*

Table 6.27*S* Comparison of relative risks (RRs) from selected summaries of meta-analyses for active smoking *versus* exposure to secondhand smoke for all studies of breast cancer combined and stratified by study design, based on cohort and case-control studies published before 2012 *S-152*

Table 6.28*S* Associations between smoking and overall mortality in cancer patients *S-153*

Table 6.29*S* Associations between smoking and overall survival in cancer patients *S-167*

Table 6.30*S* Associations between smoking and cancer-related mortality *S-173*

Table 6.31*S* Associations between smoking and developing a second primary cancer in cancer patients *S-180*

Table 6.32*S* Associations between smoking and cancer recurrence *S-184*

Table 6.33*S* Associations between smoking and cancer response *S-189*

Table 6.34*S* Associations between smoking and treatment-related toxicity in cancer patients *S-191*

Chapter 7. Respiratory Diseases *S-203*

Table 7.2*S* Population-based cohort studies of cigarette smoking and asthma induction in children and adolescents *S-203*

Table 7.3*S* Studies of cigarette smoking and asthma induction in adults *S-205*

Table 7.4*S* Studies of cigarette smoking, exacerbation of asthma, and natural history in adults *S-208*

Table 7.5*S* Studies on tobacco use and tuberculosis (TB) infection *S-211*

Table 7.6*S* Studies on tobacco use and tuberculosis (TB) disease *S-217*

Table 7.7*S* Studies on tobacco use and recurrent tuberculosis (TB) *S-241*

Table 7.8*S* Studies on tobacco use and tuberculosis (TB) mortality *S-244*

Table 7.10*S* Studies of risk of cigarette smoking and idiopathic pulmonary fibrosis (IPF), 1990–2011 *S-250*

Chapter 8. Cardiovascular Diseases *S-255*

Table 8.6*S* Detailed description of studies on smokefree laws and coronary events *S-255*

Table 8.7*S* Detailed description of studies on smokefree laws and cerebrovascular accidents *S-281*

Table 8.8*S* Detailed description of studies on the relationship between smokefree laws and other heart disease *S-287*

Chapter 9. Reproductive Outcomes *S-297*

Table 9.3*S* Summary of studies of orofacial clefts and maternal smoking, 2002–2011 *S-297*

Table 9.4*S* Summary of studies of maternal smoking and clubfoot, 1999–2011 *S-300*

Table 9.5*S* Summary of studies of maternal smoking and gastroschisis, 1999–2011 *S-302*

Table 9.6*S* Summary of studies of maternal smoking and congenital heart defects, 1999–2011 *S-304*

Table 9.7*S* Summary of studies of maternal smoking and craniosynostosis, 1999–2011 *S-307*

Table 9.8*S* Summary of studies of maternal smoking and anorectal atresia, 1999–2011 *S-308*

Table 9.10*S* Studies on associations between prenatal smoking and disruptive behavioral in children, 2000–2012 *S-309*

Table 9.11*S* Studies on associations between prenatal smoking and anxiety and depression in children, 2000–2012 *S-329*

Table 9.12*S* Studies on the associations between prenatal smoking and Tourette syndrome in children, 2000–2011 *S-333*

Table 9.13*S* Studies on associations between prenatal smoking and intellectual disability in children, 2000–2009 *S-334*

Table 9.14*S* Association between maternal smoking and ectopic pregnancy, studies included in 2001–2010 Surgeon General's reports and subsequently published through March 2013 *S-335*

Table 9.15*S* Studies on the effect of maternal active smoking on spontaneous abortion (SAB) risk *S-340*

Table 9.16*S* Experimental studies of the association between smoking and erectile dysfunction *S-342*

Table 9.17*S* Cross-sectional studies of the association between smoking and the risk of erectile dysfunction *S-343*

Chapter 10. Other Specific Outcomes *S-347*

Table 10.1*S* Summary of evidence from case-control studies on the association between smoking and age-related macular degeneration (AMD) *S-347*

Table 10.2*S* Summary of evidence from cross-sectional studies on the association between smoking and age-related macular degeneration (AMD) *S-356*

Table 10.3*S* Summary of evidence from prospective cohort studies on the association between smoking and age-related macular degeneration (AMD) *S-362*

Table 10.4*S* Summary of evidence from other types of studies on the association between smoking and age-related macular degeneration (AMD) *S-370*

Table 10.5*S* Studies on the association between active smoking and dental caries *S-374*

Table 10.6*S* Studies on exposure to tobacco smoke and dental caries *S-379*

Table 10.7*S* Studies on smoking and failure of dental implants *S-383*

Table 10.8*S* Characteristics of studies included in the meta-analysis on smoking and diabetes *S-393*

Table 10.14*S* Studies on the association between smoking and rheumatoid arthritis (RA) risk *S-400*

Table 10.15*S* Studies on the association between smoking and rheumatoid arthritis (RA) severity *S-403*

Table 10.16*S* Studies on the association between smoking and rheumatoid arthritis (RA) treatment response *S-405*

Table 10.17*S* Studies on the association between smoking and systemic lupus erythematosus (SLE) risk *S-406*

Table 10.18*S* Studies on the association between smoking and systemic lupus erythematosus (SLE) severity and manifestations *S-408*

Table 10.19*S* Studies on smoking and systemic lupus erythematosus (SLE) treatment response *S-409*

Table 10.20*S* Characteristics of the studies on the effects of current smoking on Crohn's disease or ulcerative colitis *S-410*

Table 10.21*S* Characteristics of the studies on the effects of former smoking on Crohn's disease or ulcerative colitis *S-427*

Chapter 11. General Morbidity and All-Cause Mortality *S-437*

Table 11.1*S* Studies on the association between smoking and all-cause mortality *S-437*
Table 11.2*S* Studies on the association between smoking and poor general health *S-439*
Table 11.3*S* Studies on the association between smoking and relative risk of poor functional status *S-441*
Table 11.4*S* Studies on the association between smoking and SF-36 or SF-12 scores *S-444*
Table 11.5*S* Studies on the association between smoking and other measures of health and function *S-446*
Table 11.6*S* Studies on the association between smoking and hospitalizations *S-448*
Table 11.7*S* Studies on the association between smoking and outpatient visits *S-450*
Table 11.8*S* Studies on the association between smoking and nursing home stays *S-451*
Table 11.9*S* Studies on the association between smoking and costs *S-452*
Table 11.10*S* Annual per capita spending on health care, by smoking status and age group (2008 dollars) *S-453*
Table 11.11*S* Studies on the association between smoking and workplace absenteeism (days absent) *S-454*
Table 11.12*S* Studies on the association between smoking and relative risk of workplace absenteeism *S-456*

Chapter 6
Cancer

Table 6.3*S* Case-control studies on smoking and primary liver cancer *S-3*

Table 6.4*S* Cohort studies on smoking and primary liver cancer *S-12*

Table 6.5*S* Prospective studies of cigarette smoking and colorectal cancer incidence, published 2002–2009 *S-21*

Table 6.6*S* Case-control studies of cigarette smoking and colorectal cancer incidence, published 2001–2008 *S-26*

Table 6.7*S* Prospective studies of cigarette smoking and colorectal cancer mortality, published 2002–2009 *S-28*

Table 6.8*S* Prospective cohort studies on the association between cigarette smoking and prostate cancer incidence and mortality *S-30*

Table 6.9*S* Epidemiologic cross-sectional studies on the association between cigarette smoking and stage and histologic grade at diagnosis of prostate cancer *S-45*

Table 6.10*S* Cohort studies on the association between cigarette smoking and risk of prostate cancer progression, case fatality, and all-cause mortality in men with prostate cancer *S-48*

Table 6.11*S* Reports on levels of endogenous hormones and smoking in premenopausal women (n = 22) *S-52*

Table 6.12*S* Reports on levels of endogenous hormones and smoking in postmenopausal women (n = 17) *S-57*

Table 6.14*S* Cohort study reports of the association between active cigarette smoking and risk of breast cancer, based on studies published before 2012 (n = 15) *S-60*

Table 6.15*S* Case-control study reports of the association between active cigarette smoking and risk for breast cancer, based on studies published from 2000 to 2011 (n = 34) *S-75*

Table 6.16*S* Evaluation of reports on exposure to active cigarette smoking for meta-analyses, based on cohort studies before 2012 and case-control studies published between 2000 and 2011 for meta-analyses, by location, study design, size of analytic sample, type of referent group, meta-analysis categories, and design or analysis issues (n = 65) *S-109*

Table 6.17*S* Summary of meta-analyses for measures of active cigarette smoking for all studies combined and stratified by study design, based on cohort studies published before 2012 and case-control studies published from 2000 to 2011 *S-118*

Table 6.18*S* Reports of premenopausal and postmenopausal relative risks (RRs) by study and meta-analysis RRs for the association of active smoking (ever, pack-years) with risk for breast cancer, based on cohort studies published before 2012 and case-control studies published from 2000 to 2011 (n = 20) *S-120*

Table 6.19*S* Reports of estrogen receptor status relative risks (RRs) for the association of active cigarette smoking (ever, cigarettes/day) with risk for breast cancer, based on cohort studies published before 2012 and case-control studies published from 2000 to 2011 (n = 17) *S-123*

Table 6.20*S* Reports on the association between active cigarette smoking and risk of a second primary contralateral breast cancer (n = 7) *S-125*

Table 6.21*S* Modification of risk for breast cancer associated with smoking by *NAT2* phenotype, based on two meta-analyses and one pooled analysis, stratified by menopausal status *S-126*

Table 6.22*S* Reports on cohort studies of the association between exposure to secondhand smoke and relative risk (RR) for breast cancer incidence, based on studies published before 2012 included in the 2006 Surgeon General's report (n = 7) *S-127*

Table 6.23*S* Reports on case-control studies of the association between exposure to secondhand smoke and relative risk (RR) for breast cancer incidence, based on studies published before 2012 but not included in the 2006 Surgeon General's report (n = 11) *S-132*

Table 6.24*S* Evaluation of reports on exposure to secondhand smoke among 171 nonsmokers, based on 10 cohort and 24 case-control studies of breast cancer published before 2012 for meta-analyses, by location, study design, analytic sample size, meta-analysis categories, and design or analysis issues (n = 39) *S-142*

Table 6.25*S* Summary of meta-analyses for the broadest categories of exposure to secondhand smoke (adult–any source, ever in lifetime, most comprehensive) for all studies of breast cancer combined and stratified by menopausal status, based on cohort and case-control studies published before 2012 *S-148*

Table 6.26*S* Summary of meta-analyses for specific categories of exposure to secondhand smoke (spouse, home, workplace, childhood, childhood and adulthood) for all studies of breast cancer combined and stratified by menopausal status, based on cohort and case-control studies published before 2012 *S-150*

Table 6.27*S* Comparison of relative risks (RRs) from selected summaries of meta-analyses for active smoking *versus* exposure to secondhand smoke for all studies of breast cancer combined and stratified by study design, based on cohort and case-control studies published before 2012 *S-152*

Table 6.28*S* Associations between smoking and overall mortality in cancer patients *S-153*

Table 6.29*S* Associations between smoking and overall survival in cancer patients *S-167*

Table 6.30*S* Associations between smoking and cancer-related mortality *S-173*

Table 6.31*S* Associations between smoking and developing a second primary cancer in cancer patients *S-180*

Table 6.32*S* Associations between smoking and cancer recurrence *S-184*

Table 6.33*S* Associations between smoking and cancer response *S-189*

Table 6.34*S* Associations between smoking and treatment-related toxicity in cancer patients *S-191*

Table 6.3*S* Case-control studies on smoking and primary liver cancer

Study	Design/population	Findings (95% CI)[a]	Comments
Trichopoulos et al. 1980	• 79 cases • 204 controls • 1976–1977 • Greece	• Ever smoker: 5.5 (2.0–15.6) among HBV negatives • Cigarettes/day (within 5 years of diagnosis): – 1–10: 1.3 – 11–20: 2.5[b] – 21–30: 3.7[b] – ≥31: 8.4[b]	Association confined to persons who were HBV negative; effect persisted after adjusting for alcohol consumption
Lam et al. 1982	• 106 cases • 107 controls • 1977–1980 • Hong Kong, China	• Ever smoker: 1.3 (0.7–2.4) – 1–19 cigarettes/day: 1.0 (0.5–10.7) – ≥20 cigarettes/day: 1.5 (0.8–2.8) • HBsAg positive: 0.3 (0.1–1.4) • HBsAg negative: 2.9 (0.8–10.7)	Association confined to persons who were HBV negative and had the heaviest smoking exposure
Stemhagen et al. 1983	• 265 cases • 530 controls • 1975–1980 • United States	• Ever smoker, men: 0.7 (0.5–1.1) • Ever smoker, women: 1.0 (0.6–1.7)	Adjusted for age; no difference when adjusted for alcohol consumption ; no dose-response association
Yu et al. 1983	• 78 cases • 78 controls • 1975–1979 • United States	• Current smokers compared with never and long-term former smokers: – ≤20 cigarettes/day: 1.2 (0.6–2.5) – >20 cigarettes/day: 2.6 (1.0–6.7) – Former smokers: 1.1 (0.3–4.0)	In stratified analyses, significant risk observed only among those with both heavy smoking (>20 cigarettes/day) and heaviest consumption of alcohol (>80 g/day)
Hardell et al. 1984	• 83 cases (men who died of primary liver cancer or liver cancer not designated as primary or secondary) • 200 controls • 1974–1981 • Sweden	• Current and former smokers: 1.1 (CI not reported)	Small association disappeared after controlling for alcohol consumption
Filippazzo et al. 1985	• 120 HCC cases • 360 controls (hospitalized patients with cirrhosis, other tumors, or with diagnoses other than those 2) • 1980–1984 • Italy	• Current smoker: 0.9 (CI not reported) • HCC compared with noncirrhosis, noncancer controls: 0.8 (0.4–1.5)	Compared HCC cases with 3 control groups; estimates are unadjusted
Kew et al. 1985	• 240 cases • 240 hospital controls • South Africa	• <1.0 for any smoking and also for ≥20 cigarettes/day (CI not reported) • Among HBV negatives, OR = 1.25 for ever smokers	Controls matched for age, race, gender, recruitment site, and urban/rural background
Austin et al. 1986	• 86 cases • 161 hospitalized controls • United States	• Ever smoker: 1.1 (0.5–2.4) • Current smoker: 1.6 (0.7–3.7) • Cigarettes/day among current smokers: – <20: 1.7 – ≥20: 1.2	Controls matched for age, gender, race, and residence; adjusted for consumption of alcohol; HBsAg negative only

Table 6.3*S* Continued

Study	Design/population	Findings (95% CI)[a]	Comments
Trichopoulos et al. 1987	• 194 cases • 456 hospitalized controls • 1976–1984 • Greece	• ≥30 cigarettes/day: 7.3 • HBV negative: 2.8 • HBV positive: 1.3	Association confined to persons who were HBV negative
La Vecchia et al. 1988	• 151 cases • 1,051 hospitalized controls • 1984–1987 • Italy	• Former smoker: 0.6 (0.4–1.0) • Current smoker: 0.9 (0.6–1.5)	Adjusted for age, gender, geographic area, hepatitis, cirrhosis, and consumption of alcohol; no dose-response relationship for cigarette smoking
Lu et al. 1988	• 131 cases • 207 controls • 1985 • Taiwan	• Ever smoker: – Unadjusted OR = 1.1 (0.7–1.8) – Adjusted OR = 1.33 for smokers – $\chi 2$ for trend = 0.88 (p >0.05)	Adjusted for gender and HBsAg status; in multivariate analysis, smoking behaviors (duration in years, and number of cigarettes smoked/day) were not associated with HCC
Yu et al. 1988	• 165 cases • 465 controls • 1969–1985 • United States	• 3.3; p <0.05	Association limited to current-smoking females >50 years of age
Ferraroni et al. 1989	• 151 cases • 1,944 controls • 1983–1988 • Italy	• Former smoker: 0.9 • Cigarettes/day (findings not significant): – <15: 0.9 – 15–24: 0.7 – ≥25: 0.8	Adjusted for age, gender, consumption of alcohol, education level, marital status, and coffee consumption
Hiyama et al. 1990	• 299 cases • 266 controls • 1984–1987 • Japan	• Pack-years: – <20: 1.0 (baseline) – 20–39: 1.9 (1.1–3.3) – 40–59: 2.0 (1.1–3.6) – ≥60: 1.0 (0.5–1.9)	Adjusted for HBsAg status, age, gender, consumption of alcohol, and family history of liver cancer
Kew et al. 1990	• 46 cases • 92 controls • Africa	• Ever smoker: 2.2 (0.8–6.1)	Adjusted for age and geography; included only Black females
Mayans et al. 1990	• 96 cases • 190 controls • 1986–1988 • Spain	• Cigarettes/day: – 1–20: 1.4 – >20: 1.1	No association based on unadjusted data or after adjusting for HBV or consumption of alcohol
Olubuyide and Bamgboye 1990	• 100 cases • 100 controls • 1987–1988 • Nigeria	• Ever smoker: – All: 1.7 (0.9–3.1) – Men: 1.5 (0.8–2.8) – Women: 7.1 (0.7–26.5)	Unadjusted

Table 6.3*S* Continued

Study	Design/population	Findings (95% CI)[a]	Comments
Tsukuma et al. 1990	• 229 cases • 266 controls • 1983–1987 • Japan	• Former smoker: 0.7 (0.3–1.9) • Current smoker: 2.5 (1.4–4.5) • Cigarette index (lifetime number of cigarettes): – 0–399: Reference – 400–799: 1.7 (1.0–2.8) – 800–1,199: 1.8 (1.0–3.1) – >1,200: 1.0 (0.5–1.8)	Adjusted for age and gender; index adjusted for HBsAg, history of transfusion, and family history
Chen et al. 1991	• 200 cases • 200 controls • 1985–1987 • Taiwan	• Cigarettes/day—crude OR [AOR]: – 1–10: 1.1 (0.6–2.0) [1.05] – 11–20: 1.9 (1.2–3.1) [1.48] – ≥21: 3.0 (1.5–5.8) [2.62]	Adjusted for consumption of alcohol, HBsAg/HBeAg status, family history of HCC, gender, age, ethnic group, and residence at time of cancer
Choi and Kahyo 1991	• 216 cases • 648 controls • 1986–1990 • Republic of Korea	• Former smoker: 0.6 (0.4–1.2) • Current smoker: 1.0 (0.7–1.6) • Cigarettes/day: – 1–20: 1.2 (0.8–1.8) – 21–40: 0.6 (0.3–1.2) – ≥41: 0.5 (0.1–2.6) • Duration (years): – 1–19: 0.7 (0.4–1.3) – 20–39: 1.0 (0.6–1.6) – ≥40: 1.9 (0.4–1.8)	Adjusted for age, marital status, education level, consumption of alcohol, and HBV status
Lin et al. 1991	• 200 cases (HBV-negative males without alcoholic cirrhosis in an aflatoxin-endemic region of China) • 200 controls • 1984–1986 • China	• Ever smoker: 0.6 (0.4–1.0)	Included only men because smoking among females was rare
Srivantanakul et al. 1991	• 65 cases • 65 controls • Thailand	• Current smokers compared with never and occasional smokers: 1.0 (0.4–2.4) • HBV negative: 1.8 (0.5–5.9)	Unadjusted estimates; smoking not included in multivariate models
Tzonou et al. 1991	• 185 cases • 432 controls • 1976–1984 • Greece	• HCC cases with cirrhosis: 2.3 (0.9–5.9) • HCC cases without cirrhosis: 2.1 (1.1–4.0) • HBsAg-positive cases and controls: 1.7 (0.5–5.6) • HBsAg-negative cases and controls: 2.4 (1.2–4.7)	Adjusted for age, gender, and HBsAg/HCV status
Yu et al. 1991	• 74 cases • 162 controls • 1984–1990 • United States	• Unadjusted: – Former smoker: 1.6 (0.7–3.5) – Current smoker: 2.5 (1.2–5.0) • Adjusted for consumption of alcohol: – Former smoker: 1.1 (0.4–2.6) – Current smoker: 2.1 (1.1–4.3)	

Table 6.3*S* Continued

Study	Design/population	Findings (95% CI)[a]	Comments
Yu et al. 1991	• 127 cases • 127 controls • 1986–1987 • Taiwan	• Cigarettes/day (matched OR): – 1–10: 1.1 (0.5–2.2) – 11–20: 1.8 (1.0–3.4) – >20: 1.7 (0.7–4.5) • Cigarettes/day (adjusted for HBV, HCV, consumption of alcohol, and peanut consumption): – 1–10: 0.4 (0.1–1.9) – 11–20: 1.3 (0.4–4.2) – >20: 2.1 (0.3–13.5)	Matched OR; adjusted for HBV, HCV, consumption of alcohol, and peanut consumption
Mohamed et al. 1992	• 101 cases • 101 controls • South Africa	• Cigarettes/day: – 0–19, Men: 2.2 (0.3–6.3) – 0–19, Women: 1.3 (0.5–3.4) – ≥20, Women: 0.7 (0.2–2.5)	Adjusted for consumption of alcohol, age, and HBV status
Ross et al. 1992	• 22 cases • 140 controls • 1986–1989 • China	• Ever smoker: 1.8 (0.6–5.6)	Adjusted for age, education level, residence, aflatoxin exposure, consumption of alcohol, and HBsAg; males only
Tanaka et al. 1992	• 204 cases • 410 controls • 1985–1989 • Japan	• Current smokers: 1.5 (0.8–2.7) • Former smokers: 1.5 (0.8–2.8)	Adjusted for age, gender, consumption of alcohol, HBsAg status, history of blood transfusion, and family history of liver disease; there was no significant trend in risk with years smoked
Peters et al. 1994	• 86 cases • 86 controls • 1986–1993 • Germany	• Current smoker with >40 pack-years: 1.2 (0.5–2.9)	Adjusted for consumption of alcohol and HBV/ HCV status
Pyong et al. 1994	• 90 cases • 249 controls • 1989–1992 • Japan	• Males only, cigarettes/day: – 1–20: 0.7 (0.2–2.4) – >20: 0.4 (0.1–1.6)	Adjusted for age, gender, HBV/HCV status, history of blood transfusion, and consumption of alcohol
Goritsas et al. 1995	• 51 cases • 85 controls • 1989–1992 • Greece	• Ever smoker: 1.6 (0.9–2.0)	Adjusted for age, gender, alcohol abuse, HBV/HCV status; HBsAg by smoking interaction; no HCV by smoking interaction
Siemiatycki et al. 1995	• 48 cases • 2,238 controls (had cancer at sites not previously associated with cigarette smoking) • 1979–1986 • Canada	• Ever smoker: 0.9 (0.4–2.1) • Pack-years: – <25: 1.4 (0.5–3.8) – 25–49: 0.7 (0.3–1.9) – 50–74: 0.7 (0.2–2.2) – ≥75: 0.8 (0.3–2.7)	Adjusted for age; men, 35–70 years of age only

Table 6.3*S* Continued

Study	Design/population	Findings (95% CI)[a]	Comments
Tanaka et al. 1995	• 120 cases • 257 controls • 1983–1989 • Japan	• Current smoker: 1.8 (0.9–3.4) • Former smoker: 2.8 (1.1–6.9) • Ever smoker, male: 1.9 (1.2–2.8) • Pack-years: – 0.1–12.9: 2.4 (1.1–4.9) – ≥13.0: 1.8 (0.8–3.7)	Adjusted for age, study category (except for ever smokers), HBV status, history of blood transfusion, family history of liver cancer, and consumption of alcohol; combined analysis of 3 studies; partial overlap with Tanaka et al. (1992)
Shin et al. 1996	• 203 cases • 406 controls • 1990–1993 • Republic of Korea	• Current smoker, moderate level: 2.3 (0.4–11.7) • Current smoker, high level (>20 cigarettes/day for >10 years): 1.1 (0.3–2.5)	Adjusted for HBV/HCV status, history of *Clonorchis sinensis*, history of hepatitis, other liver disease, consumption of alcohol, and SES
Mukaiya et al. 1998	• 104 cases • 104 controls • 1991–1993 • Japan	• ≥5 pack-years vs. <5 pack-years: 3.3 (1.3–8.3) • ≥10 pack-years vs. <10 pack-years: 3.3 (1.3–8.3)	
Koide et al. 2000	• 84 cases • 84 controls • 1994 • Japan	• Ever smoker: 5.4 (1.1–27)	Adjusted for age, gender, HBV/HCV infection, and *CYP2E1* genotype
Kuper et al. 2000	• 333 cases • 360 controls • 1995–1998 • Greece	• <40 cigarettes/day: – Former smoker: 1.2 (0.7–1.9) – Current smoker: 1.5 (0.7–3.0) – Ever smoker: 1.6 (0.8–2.9) • ≥40 cigarettes/day: – Former smoker: 1.2 (0.8–1.9) – Current smoker: 1.6 (0.9–2.9) – Ever smoker: 2.5 (1.1–5.5)	Adjusted for age, gender, education level, HBV, and HCV
Takeshita et al. 2000	• 85 cases • 125 controls • 1993–1996 • Japan	• Current smokers: 1.6 (0.7–3.5) • Former smokers: 0.7 (0.3–1.5)	Adjusted for age and consumption of alcohol; males only
Lam et al. 2001	• 27,507 cases • 13,054 controls • 1998 • Hong Kong, China	• Ever smoker, men: – 35–69 years of age: 1.6 (1.3–1.9) – ≥70 years of age: 1.2 (0.9–1.5) • Ever smoker, women: – 35–69 years of age: 1.4 (0.8–2.4) – ≥70 years of age: 1.4 (0.9–2.0)	Adjusted for age and education level
Hassan et al. 2002	• 115 cases • 230 hospital-based controls with cancer of skin and GI, urogenital, and respiratory tracts • 1984–1985 • United States	• Current smoker: 1.2 (0.6–2.4)	Controls were matched on age, gender, and recruitment date; adjusted for diabetes, consumption of alcohol, HBV, and HCV

Table 6.3*S* Continued

Study	Design/population	Findings (95% CI)[a]	Comments
Yu et al. 2002	• 248 cases • 248 controls • 1995–1997 • China	• Ever smokers: 0.7 (0.3–1.7)	Adjusted for age, gender, residence, and HBV infection
Chen et al. 2003	• 36,000 cases (liver cancer deaths) • 17,000 controls (deaths due to liver cirrhosis) • 1986–1988 • China	• Men: – Ever smoker: 1.4 (1.3–1.4) – 10 cigarettes/day: 1.3 – 20 cigarettes/day: 1.5 – 30 cigarettes/day: 1.6 • Women: – Ever smoker: 1.2 (1.1–1.3) – <20 cigarettes/day: 1.1 – ≥20 cigarettes/day: 1.5	Controls were indirectly controlled for HBV infection and consumption of alcohol; adjusted for age and locality; RR independent of age, urban/rural status, or age at start of smoking
Farker et al 2003	• 70 cases • 87 controls • Germany	• Former smoker: 2.5 (1.2–5.0) • Current smoker: 2.4 (0.9–6.4)	Unadjusted estimates
Matsuo 2003	• 222 cases • 222 controls • 1995–2000 • Japan	• Cumulative cigarette smoking (pack-years): – Male: 1.05 (0.82–1.36) – Female: 1.80 (0.40–8.14)	Adjusted for history of blood transfusion, consumption of alcohol, and diabetes
Munaka et al. 2003	• 78 cases • 138 controls • 1997–1998 • Japan	• Ever smoker: 1.2 (0.6–2.7)	Adjusted for age and gender
Shimada et al. 2003	• 53 cases • 80 controls • 2001 • Japan	• Smoking index (lifetime number of cigarettes): 1.2 (0.8–1.9)	Controlled for consumption of alcohol and HBV infection
Yuan et al 2004	• 295 cases • 435 controls (population-based in; included never smokers and recent ex-smokers) • 1984–2002 • Los Angeles County, California	• Current or recent exsmokers compared with never smokers or long-term exsmokers: 1.6 (1.1–2.2) • Cigarettes/day: – 1–20: 1.5 (1.0–2.5) – >20: 1.6 (1.1–2.4) • HBV negative and HCV negative: 1.7 (1.0–3.0)	Exsmokers defined as those who quit within the last 10 years; adjusted for age, gender, race, education level, consumption of alcohol, and diabetes; no clear interaction between smoking and consumption of alcohol, diabetes, or HBV/HCV
Gelatti et al. 2005	• 200 cases • 400 controls • 1999–2002 • Italy	• Pack-years: – <20: 0.9 (0.5–1.7) – ≥20: 0.7 (0.4–1.2)	Adjusted for HBV, HCV, and consumption of alcohol

Table 6.3*S* Continued

Study	Design/population	Findings (95% CI)[a]	Comments
Marrero et al. 2005	• 70 cases • 140 controls (included non-liver disease outpatients and people with cirrhosis) • 2002–2004 • United States	• Smoking status (compared with healthy controls): – Current smokers: 10.9 (3.5–34.0) – Ever smokers: 12.3 (4.4–34.2) – Former smokers: 13.3 (4.5–38.9) • Pack-years (compared with healthy controls): – <20: 1.2 (0.7–1.5) – ≥20: 63.7 (17–144) • Pack-years (compared with cirrhotic controls): – <20: 0.7 (0.4–1.2) – ≥20: 4.9 (2.2–10.6)	Not adjusted for current, ever, or former smoking effects; estimates for pack-years adjusted for race, obesity, consumption of alcohol, and HBV/HCV
Franceschi et al. 2006	• 229 cases • 431 controls • 1999–2002 • Italy	• Current smokers: 1.1 (0.6–2.2) – 1–14 cigarettes/day: 1.2 (0.6–2.4) – ≥15 cigarettes/day: 1.1 (0.5–2.5) • HBsAg positive or anti-HCV positive: 44.3 (19.7–99.3) • HBsAg negative and anti-HCV negative: 1.0 (0.5–2.0) • Former smokers: 0.8 (0.4–1.5)	Adjusted for age, gender, education level, HBV and HCV infections; when stratified by HBV/HCV infection, no association of smoking and HCC among those who were negative, strong association among positive
Zhu et al. 2007	• 168 cases • 1,910 controls • 1984–1988 • United States	• Former smokers: 1.9 (1.1–3.3) • Current smokers: 1.5 (0.8–2.7) • Packs/day (OR): – <1: 1.4 (0.7–2.7) – 1–2: 1.7 (0.9–3.0) – >2: 1.8 (0.9–3.8) – p trend = 0.068	Adjusted for demographics, SES, consumption of alcohol, and detailed medical history; risk estimates similar but less precise for HCC only; males only
Hara et al. 2008	• 209 cases • 256 hospital controls and 381 chronic liver disease controls • 2001–2004 • Japan	• Hospital controls: – Former smokers: 0.8 (0.3–2.3) – Current smokers: 1.8 (0.6–5.1) • Chronic liver disease controls: – Former smokers: 1.0 (0.6–1.7) – Current smokers: 2.5 (1.4–4.6)	Adjusted for age, gender, HBV, HCV, and consumption of alcohol; no dose-response association with intensity or pack-years of smoking; recent heavy exposure appeared to be associated most with risk among patients with chronic liver disease

Table 6.3*S* Continued

Study	Design/population	Findings (95% CI)[a]	Comments
Hassan et al 2008	• 319 cases • 1,061 controls (spouses/ family members of non-HCC cancer patients) • 2000–2006 • United States	• Ever smokers, both genders: 1.5 (1.0–2.1) • Ever smokers, men: 1.9 (1.2–3.1) – HCV positive: 136.3 (43.2–429.0) – HCV negative: 1.8 (1.1–2.9) – HBsAg1 positive or anti-HBc13 positive: 9.6 (3.9–22.4) – HBsAg1 negative and anti-HBc13 negative: 2.0 (1.2–3.3) • Ever smokers, women: 1.1 (0.5–1.8) – HCV negative: 1.2 (0.6–2.0) – HBsAg1 positive or anti-HBc13 positive: 6.7 (1.9–24.1) – HBsAg1 negative and anti-HBc13 negative: 1.1 (0.6–1.9) • Former smokers, all: 1.4 (0.9–2.1) • Former smokers, men: – Quit <10 years: 2.4 (1.2–4.9) – Quit ≥10 years: 1.7 (0.9–2.8)	Adjusted for age, race, education level, marital status, state of residency, HCV, HBV, diabetes, heavy consumption of alcohol, and family history of cancer; significant risk (without dose-response relationship) also observed for intensity, duration, and pack-years of smoking for men, nonsignificant for women; protective associations tended to be observed for noncigarette tobacco use and for passive exposure to smoke
Hassan et al 2009	• 420 cases • 1,104 controls • 2000–2008 • United States	• Ever smoker (OR): 1.8 (1.3–2.4) – ≤20 pack-years (OR): 1.4 (0.9–2.1) – >20 pack-years (OR) = 2.0 (1.4–2.9)	Extension of study by Hassan and colleagues (2008); adjusted for age, gender, race, education level, HBV, HCV, consumption of alcohol, diabetes, and family history of liver cancer
Jeng et al. 2009	• 200 cases • 200 controls • 2003–2004 • Taiwan	• Ever smoker, unadjusted: 2.3 (1.5–3.5) • Compared with nonsmokers who were negative for viral hepatitis: – Smokers without viral hepatitis had an increased risk for HCC: 44.4 (17.8–116) – Smokers with viral hepatitis had an increased risk for HCC: 90 (32.1–266)	Performed interaction analysis of smoking and viral hepatitis (HBsAg or anti-HCV); adjusted for age and gender
Soliman et al. 2010	• 150 cases • 150 controls • 2007–2009 • Egypt	• Ever smoker: 1.4 (0.7–2.8): – Moderate use: 1.8 (0.8–4.5) – Heavy use: 1.7 (0.8–3.7)	Adjusted for age, gender, and HBV/HCV status
Wan et al. 2011	• Asian immigrant patients with chronic HBV infection who were recruited from a single hospital site • 44 early-onset and 124 late-onset cases • 432 early-onset and 199 late-onset controls • 2003–2009 • United States	• Early onset of HCC among ever smokers: 3.4 (1.5–8.0) • No significant association between smoking and late onset of HCC in adjusted model	Early onset defined as males <40 years of age and females <50 years of age; adjusted for gender, cirrhosis, and family history of HCC

Table 6.3*S* Continued

Study	Design/population	Findings (95% CI)[a]	Comments
Ha et al. 2012	• Hospital-based case-control study • 259 cases • 781 controls (having chronic liver disease) • 2001–2009 • United States	• Lifetime tobacco use >11,000 packs: 1.7 (1.0–2.9)	Adjusted for race, age, gender, cirrhosis, level of alpha-fetoprotein, consumption of alcohol, diabetes, and etiology of liver disease (including HBV and HCV)
Polesel et al. 2012	• 185 cases • 412 controls • 1999–2002 • Italy	• Current smoker: 1.5 (0.8–2.7)	Adjusted for location, gender, age, birthplace, education level, HCV, HBV, heavy consumption of alcohol, diabetes, and obesity

Notes: **AOR** = adjusted odds ratio; **CI** = confidence interval; **g** = gram; **GI** = gastrointestinal; **HBc13** = hepatitis B core antibody; **HBeAG** = hepatitis B e antigen; **HBsAg** = hepatitis B surface antigen; **HBV** = hepatitis B virus; **HCC** = hepatocellular carcinoma; **HCV** = hepatitis C virus; **OR** = odds ratio; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **RR** = relative risk; **SES** = socioeconomic status.
[a]Findings are reported as RRs in comparisons with never smokers unless indicated otherwise.
[b]Results significantly higher than 1.00.

Table 6.4*S* Cohort studies on smoking and primary liver cancer

Study	Design/population	Findings (95% CI)[a]	Comments
Basa et al. 1977	• 16,492 followed • 754 cases • 1968–1973 • Philippines	• Ever smoker: – Men 1.5 (p = 0.01) – Women 2.6 (p = 0.001) • Current smoker: – Men: 1.3 – Women: 1.9 (p = 0.01)	Adjusted for age
Oshima et al. 1984	• Nested case-control study among HBsAg-positive blood donors • 9,646 followed • 20 cases • 1972–1980 • Japan	• Men, cigarettes/day: – >30: 5.8 (1.0–34.2) – ≤30: 1.7 (0.4–6.4)	
Tu et al. 1985	• HBV-positive cohort • 12,222 followed (all men) • 70 cases • 1980–1982 • China	• HBV carrier, mortality rate: – Nonsmoker: 332.8 – Current smoker: 737.9 – ≤19 cigarettes/day: 660.1 – ≥20 cigarettes/day: 1,519 (p <0.05) • HBV noncarrier, mortality rate: – Nonsmoker: 115.1 – Current smoker: 99.9 – ≤19 cigarettes/day: 96.3 – ≥20 cigarettes/day: 145.2	Adjusted for age and consumption of alcohol
Shibata et al. 1986	• Nested case-control study of male fishermen and farmers • 1,316 followed • 22 cases • Japan	• 1–19 cigarettes/day: 2.0 (0.4–9.8) • ≥20 cigarettes/day: 1.8 (0.4–8.9)	Adjusted for consumption of alcohol
Carstensen et al. 1987	• 25,129 followed (all men) • 54 cases • 1963–1979 • Sweden	• Former smoker: 1.7 • Current smoker: 3.0 • Cigarettes/day: – 1–7: 1.6 – 8–15: 3.3 – >15: 4.1	Relative death rates standardized for age and residence; χ^2 test for trend of cigarettes/day reported as significant
Kono et al. 1987	• Male physician subjects • 5,130 followed • 51 cases • 1965–1983 • Japan	• Ever smokers compared with never and occasional smokers: – 1–19 cigarettes/day: 1.1 (0.6–2.2) – ≥20 cigarettes/day: 1.0 (0.5–2.2) • Current and past smokers compared with never and occasional smokers: – 1–19 cigarettes/day: 1.1 (0.6–2.2) – ≥20 cigarettes/day: 1.0 (0.5–2.2)	Adjusted for age and consumption of alcohol
Hirayami 1989	• 265,118 followed (all men) • 123 cases • 1966–1982 • Japan	• Current smoker: 3.1 (1.8–5.4) • Cigarettes/day: – 1–29: 3.1 (1.8–5.4) – ≥30: 6.8 (3.6–13.1)	

Table 6.4*S* Continued

Study	Design/population	Findings (95% CI)[a]	Comments
Hiyama et al. 1990	• 13,171 followed (all men) • 93 cases • 1969–1985 • Japan	• Ratio of observed/expected: 1.4 (1.1–1.7)	
Hiyama et al. 1990	• Nested case-control study • 8,646 followed (all men) • 22 cases • 1972–1992 • Japan	• 10–29 cigarettes/day: – Crude OR: 1.7 (0.4–6.4) – Adjusted OR: 1.2 • ≥30 cigarettes/day: – Crude OR: 5.8 (1–34.2) – Adjusted OR: 6.3	Controls matched by age; AOR controlled for consumption of alcohol
Akiba and Hirayama 1990	• 122,261 (men) and 142,857 (women) followed • 1,050 cases (652 men and 398 women) • 1965–1981 • Japan	• Current smoker: – Men: 1.5 (1.2–1.9) – Women: 1.6 (1.2–2.0) • Cigarettes/day, men: – 1–4: 1.1 (0.5–2.0) – 5–14: 1.6 (1.3–2.0) – 15–24: 1.4 (1.2–1.8) – 25–34: 1.6 (1.1–2.4) – ≥35: 1.9 (1.1–3.2) – p trend = 0.002 • Cigarettes/day, women: – 1–4: 1.4 (0.7–2.5) – 5–14: 1.4 (1.0–2.0) – ≥15: 2.5 (1.3–4.1) – p trend = 0.001	Adjusted for prefecture, occupation, age, and observation period; no trend in risk observed in relation to calendar period
Hsing et al. 1990	• Study among military veterans • 250,000 followed • 289 cases • 1954–1980 • United States	• Current smokers: 2.4 (1.6–3.5) • Former smokers, not current cigar/pipe: 1.9 (1.2–2.9) • Cigar/pipe smokers: 3.1 (2.0–4.8) • Cigarettes/day: – <10: 2.2 (1.2–3.8) – 10–20: 2.0 (1.3–3.0) – 21–39: 2.9 (1.8–4.5) – >39: 3.8 (1.9–8.0) • Duration (years): – <35: 0.9 (0.4–2.1) – 35–39: 2.6 (1.4–4.9) – >39: 2.7 (1.5–4.9) • Age started smoking (years): – <20: 2.9 (1.6–5.3) – 20–24: 2.3 (1.2–4.3) – >24: 1.0 (0.4–2.3)	Adjusted for age and calendar period; risks increased with the number of cigarettes/day, duration of smoking >35 years, and earlier age at initiation; did not control for consumption of alcohol or HBV status
Shibata et al. 1990 (Cohort I)	• 639 followed (all men) • 22 cases • 1958–1986 • Japan	• Current smoker: 1.1 (0.2–4.7) • Cigarettes/day: – 1–9: 0.6 (0.1–3.7) – ≥10: 1.2 (0.2–5.7) – p trend = ~0.6	Adjusted for age; calculations based on small number of liver cancers; no information on HBV/HCV

Table 6.4*S* Continued

Study	Design/population	Findings (95% CI)[a]	Comments
Shibata et al. 1990 (Cohort II)	• 677 followed (all men) • 22 cases • 1960–1986 • Japan	• Former smoker: 2.9 (0.3–29.0) • Current smoker: 3.6 (0.6–22.3) • Cigarettes/day: – 1–9: 11.9 (1.5–96.8) – 10–19: 1.1 (0.1–10.6) – 20–29: 2.7 (0.4–19.2) – ≥30: 3.2 (0.4–23.7) – p trend = ~0.5 • Consumers of alcohol, number of cigarettes/day: – 1–19: 2.1 (0.4–10.0) – ≥20: 1.9 (0.4–9.4)	Adjusted for age and consumption of alcohol
Kato et al. 1992	• Participants with chronic hepatitis or cirrhosis • 1,441 followed • 122 cases • 1987–1990 • Japan	• Former smoker: 0.9 (0.4–2.0) • Current smoker: 1.0 (0.5–1.8) • Pack-years: – <30: 0.8 (0.4–1.7) – ≥30: 0.9 (0.5–1.9) – p trend = 0.824	Adjusted for age and gender
Ross et al. 1992	• Nested case-control study of males • 18,244 followed • 22 cases • 1986–1989 • China	• Ever smoker: 1.8 (0.6–5.6) • Cigarettes/day: – 1–19: 3.1 (1.0–10.3) – ≥20: 2.1 (0.6–6.9) • Duration (years): – 1–29: 2.6 (0.7–9.4) – ≥30: 2.5 (0.9–7.6)	Population-based controls matched on age, sample collection date, and residence; analysis of ever smokers adjusted for age, education level, residence, HBsAg positivity, exposure to aflatoxin, and heavy consumption of alcohol
Tsukuma et al. 1993	• Participants were patients with chronic liver disease • 917 followed • 54 cases • 1987–1991 • Japan	• Current smoker: 2.3 (0.9–5.9) • Former smoker: 1.7 (0.6–4.5)	Adjusted for age, gender, disease stage, alpha-fetoprotein level, and consumption of alcohol
Yu and Chen 1993	• Nested case-control study • 9,691 followed (all men) • 35 cases • 1987–1990 • China, Province of Taiwan	• Ever smoker: 1.2 (0.4–3.1)	Controls matched by age, date of interview, and residence; adjusted for testosterone level, consumption of alcohol, HCV/HBsAg status, consumption of vegetables, and history of liver disease
Chang et al. 1994	• Nested case-control study • 9,775 followed • 38 cases • 1984–1992 • China, Province of Taiwan	• Ever smoker: 1.2 (0.6–2.7)	Controls matched for age, residence, and date of recruitment

Table 6.4*S* Continued

Study	Design/population	Findings (95% CI)[a]	Comments
Doll et al. 1994	• 34,439 followed (all men) • 76 cases • 1951–1991 • United Kingdom	• Annual mortality rate for liver cancer (per 100,000 men): – Never smokers: 7 – Former smokers: 9 – Current smokers: 11 • Annual mortality rate for liver cancer (per 100,000 men), cigarettes/day: – 1–14: 17 – 15–24: 3 – ≥25: 15 – p trend = 0.7	No significant trend for the number of cigarettes/day
Goodman et al. 1995	• Atomic bomb survivors • 36,133 followed • 242 cases • 1978–1989 • Hiroshima and Nagasaki, Japan	• Ever smoker: 2.2 (1.5–3.2) • Current smoker: 2.2 (1.5–3.2) • Former smoker: 2.3 (1.5–3.6)	Adjusted for age, gender, and estimated radiation dose; no interaction with alcohol consumption and no dose-response relationship with smoking intensity or duration
London et al. 1995	• Nested case-control study • 60,984 followed (all men) • 183 cases • 1992–1995 • China	• Current smoker: 0.7 (0.5–1.0)	Controls matched 5:1 by age, area of residence, and HBV status; strong inverse association between recent hepatitis and current smoking
McLaughlin et al. 1995	• United States veterans, 99.5% male • 248,046 followed (all men) • 363 cases • 1954–1980 • United States	• Former smoker: 1.5 (1.2–2.0) • Current smoker: 1.8 (1.4–2.3) • Ever smoker: 1.7 (1.3–2.2) • Cigarettes/day: – 1–9: 1.8 (1.1–2.8) – 10–20: 1.4 (1.1–2.0) – 31–39: 2.3 (1.6–3.1) – ≥40: 2.6 (1.4–4.6) – p trend = <0.01	Mortality study did not control for consumption of alcohol or viral status; adjusted for age and calendar year; increased risk with increased smoking intensity
Chen et al. 1996	• 6,487 followed • 33 cases • 1991–1993 • Taiwan	• Ever smoker: 3.6 (1.3–10.6)	Age-gender-adjusted analysis was significant, but smoking was not included in the final model, which adjusted for HBV, HCV, aflatoxin exposure, and family history of HCC
Chiba et al. 1996	• 249 men and 163 women followed • 63 cases • 1977–1993 • Japan	• <20 pack-years: 1.7 (0.8–3.7) • ≥20 pack-years: 2.5 (1.1–5.5)	Adjusted for age, gender, consumption of alcohol, clinical stage of liver disease, serum alpha-fetoprotein value, HBV, history of blood transfusion, surgical procedures, and family history of liver cancer
Murata et al. 1996	• 17,200 followed (all men) • 9 cases • 1983–1994 • Japan	• Cigarettes/day: – 1–10: 1.4 – 11–20: 2.0, p <0.05 – ≥21: 0.4	

Table 6.4*S* Continued

Study	Design/population	Findings (95% CI)[a]	Comments
Yuan et al. 1996	• 18,244 followed (all men) • 79 cases • 1986–1993 • China	• Ever smoker: 1.8, p <0.05 • Cigarettes/day: – <20: 1.8 – ≥20: 1.8	Adjusted for age and consumption of alcohol
Chen et al. 1997	• 6,494 men and 2,857 women followed • 66 cases • 1972–1993 • China	• Current smoker: 2.0 (p <0.05) • Cigarettes/day: – 1–19: 2.1 – ≥20: 2.1 – p trend = 0.07	Adjusted for age, blood pressure, cholesterol, and consumption of alcohol at baseline
Lam et al. 1997	• Chinese factory workers • 1,124 men and 572 women followed • 16 cases • 1976–1996 • China	• Ever smoker, men: 1.1 (0.4–2.9)	Adjusted for age, marital status, occupation, blood pressure, triglycerides, and total cholesterol
Nordlund et al. 1997	• 28,089 followed (all women) • 41 cases • 1963–1989 • Sweden	• Current smoker: 0.7 (0.2–2.0)	Adjusted for age and place of residence
Liaw and Chen 1998	• 14,937 followed • 128 cases • 1982–1994 • Taiwan	• Current smoker, men: 2.2 (1.4–3.6) • Cigarettes/day, men: – ≤10: 2.1 (1.2–3.5) – 11–20: 1.9 (1.2–3.2) – >20: 1.8 (1.2–3.5) – p trend = 0.02 • Duration (years), men: – ≤20: 1.6 (0.8–3.2) – 21–30: 1.0 (0.5–2.1) – >30: 2.5 (1.6–4.1) • Age (years) started smoking, men: – >24: 1.4 (0.8–2.6) – 21–24: 2.3 (1.2–4.2) – ≤20: 2.2 (1.4–3.7) – p trend = <0.01 • Pack-years, men: – <20: 1.7 (1.0–2.9) – 20–40: 2.1 (1.2–3.5) – ≥41: 2.5 (1.3–4.6)	Adjusted for age, gender, alcohol intake, and HBsAg status; risk rose with increased pack-years, >30 years duration, and initiation at <25 years of age; inverse trend seen with number of cigarettes/day; study partially overlapped with Wen et al. (2004)
Liu et al. 1998	• Retrospective proportional mortality study • 21,457 followed • 87,215 cases • 1989–1991 • China	• Ever smoker: – Men: 1.4 (1.3–1.5) – Women: 1.2 (1.1–1.3)	Estimates of risk ratio (standard error) after adjustment for age and study area (county or city)

Table 6.4*S* Continued

Study	Design/population	Findings (95% CI)[a]	Comments
Gao et al. 1999	• 213,800 followed • 1983–1994 • China	• Ever smoker, men: – Urban: 1.5[b] – Suburban: 1.4 – Rural: 1.5[b] • Ever smoker, women (urban): 2.4	p trend = <0.05 for smoking intensity for men and women and for age at initiation among men only
Sun et al. 1999	• Subjects were all HBsAg positive • 145 followed (all men) • 10 cases • 1987–1998 • China	• Incidence rate/100 person-years: – Never smoker: 2.3 – Current smoker: 1.6 – p = 0.5	
Mizoue et al. 2000	• 4,050 followed (all men) • 59 cases • 1986–1996 • Japan	• Former smoker: 2.9 (1.0–8.4) • Current smoker: 3.3 (1.2–9.5) • Cigarettes/day: – 1–24: 3.5 (1.2–10.2) – ≥25: 2.8 (0.8–9.6)	Adjusted for age, area of residence, and consumption of alcohol; no dose-response effect with smoking intensity
Mori et al. 2000	• 3,052 followed • 22 cases • 1992–1997 • Japan	• Ever smoker: 2.1 (0.6–7.2) • Pack-years: – <10: 3.3 (0.4–28.2) – ≥10: 2.0 (0.6–6.9) – p trend = 0.3	Adjusted for age and gender
Evans et al. 2002	• 48,454 men and 25,430 women followed • 977 cases • 1992–2000 • China	• Current smoker (age adjusted): – Men: 0.9 (0.8–1.1) – Women: 2.0 (0.9–4.2) • Female (multivariate), cigarettes/day: – 1–5: 1.5 (0.4–6.3) – 6–10: 2.0 (0.6–6.5) – ≥10: 4.2 (1.3–13.8)	Adjusted for HBV and consumption of alcohol among women; no interaction between HBsAg status and cigarette smoking; smoking was not significantly associated with liver cancer and was excluded from multivariate model in men; dose-response association in women
Yang et al. 2002	• Nested case-control study • 1,183 followed (all men) • 111 cases • 1991–2000 • Taiwan	• Ever smoker: 1.5 (1.0–2.2)	Population-based controls matched on age, date of enrollment, and township; adjusted for age, consumption of alcohol, and HBV/HCV status
Wang et al. 2003	• 11,837 followed; 115 cases • 1991–2000 • Taiwan	• Ever smoker: 1.5 (1.1–2.3) • HBV negative: 2.5 (1.0–6.1) • HBV positive: 1.4 (0.9–2.2)	Adjusted for age, residence, and HBV and HCV infection
Jee et al. 2004	• 1,283,112 followed • 3,807 cases • 1993–2002 • Republic of Korea	• Current smoker: – Male: 1.5 (1.3–1.7) – Female 1.1 (0.8–1.7) • Former smoker: – Male: 1.1 (1.0–1.3) – Female: 1.3 (0.8–2.1) • Ever smoker, male: – HBsAg positive: 29.0 (23.7–35.4) – HBsAg negative: 1.1 (0.9–1.4)	Adjusted for age, consumption of alcohol, diabetes, and HBsAg; no interaction between smoking, consumption of alcohol, and HBsAg

Table 6.4*S* Continued

Study	Design/population	Findings (95% CI)[a]	Comments
Ogimoto et al. 2004	• 65,528 followed • 186 cases • 1988–1999 • Japan	• Current smoker, men (age): – 40–59: 2.0 (0.8–5.1) – 60–69: 2.6 (1.2–5.8) • Current smoker, women (age): – 40–59: 2.8 (0.6–13.1) – 60–69: 1.5 (0.5–4.9) • Former smoker, men (age): – 40–59: 2.4 (0.8–6.8) – 60–69: 2.7 (1.2–6.1) • Former smoker, women (age) – 60–69: 1.2 (0.2–8.7)	No adjustments; 15–19 years of age at smoking initiation increased HR from 4 to 8 for current and former smokers
Wen et al. 2004	• 86,580 followed • 245 cases • 1982–2000 • Taiwan	• Current smoker: – Men: 1.5 (1.2–1.8) – Women: 5.0 (2.4–10.7)	Adjusted for age
Yun et al. 2005	• 733,134 followed (men) • 1,434 cases • 1996–2000 • Republic of Korea	• Current smoker: 1.5 (1.3–1.7)	Adjusted for age, residence, consumption of alcohol, physical activity, BMI, and diet; no trend with increasing duration of smoking
Fujita et al. 2006	• 110,792 followed • 58 cases • 1988–1999 • Japan	• Current smokers: – HCV-positive: OR = 9.6 (1.5–61.4) – HCV-negative: OR = 1.7 (0.6–5.1) • Former smokers: – HCV-positive: OR = 7.8 (1.1–56.0) – HCV-negative: OR = 0.3 (0.0–1.7)	Adjusted for age, gender, diabetes, liver disease, and consumption of alcohol
Chen et al. 2006	• 3,653 followed (men) • 164 cases • Taiwan • 1991–1992	• Ever smoker: – Crude: 1.7 (1.2–2.3) – HBsAg positive: 1.0 (0.7–1.4) – HBsAg negative: 0.9 (0.6–1.4)	Participants were all HBsAg positive; adjusted for age, gender, consumption of alcohol, liver disease, and HBV virologic markers
Ikeda et al. 2007	• 846 followed (men) • 237 cases • 1995–2005 • Japan	• Persons with chronic hepatitis C: – <20 pack-years: IRR = 1.8 (1.1–3.3) – ≥20 pack-years: IRR = 2.1 (1.2–3.6) • Persons with HCV-related cirrhosis: – <20 pack-years: IRR = 1.1 (0.7–1.9) – ≥20 pack-years: IRR = 1.1 (0.7–1.7)	Participants had HCV-related chronic hepatitis or cirrhosis; adjusted for consumption of alcohol, age, gender, and HBV/HCV therapy
Ohishi et al. 2008	• Nested case-control study of atomic bomb survivors • 20,000 followed • 224 cases • 1970–2002 • Japan	• Current smoker: 2.0 (0.8–5.0) • Former smoker: 1.1 (0.3–5.2)	Matched on age, gender, and city; adjusted for consumption of alcohol and coffee, BMI, diabetes, HBV/HCV markers, and estimated radiation dose

Table 6.4*S* Continued

Study	Design/population	Findings (95% CI)[a]	Comments
Chen et al. 2008	• 23,567 followed • 291 cases • 1991–2004 • Taiwan	• HBV/HCV negative (comparisons with never smokers): – Current smoker: 2.4 (1.2–5.0) – Former smoker: 1.0 (0.2–4.6) • HBV positive (comparisons with never smokers): – Current smoker: 1.1 (0.8–1.5) – Former smoker: 1.0 (0.5–2.0) • HCV positive (comparisons with never smokers): – Current smoker: 1.4 (0.6–3.3) – Former smoker: 2.9 (0.9–9.1)	Adjusted for age and gender
Di Costanzo et al. 2008	• Retrospective cohort of post transfusion, HCV-infected cirrhotic patients • 138 followed • 63 cases • 1994–2004 • Italy	• Smoker: HR = 1.4 (0.80–2.3)	Adjusted for age, gender, diabetes, consumption of alcohol, and interferon therapy
Lok et al 2009	• HCV-infected patients with significant fibrosis or cirrhosis at baseline • 1,005 followed • 48 cases • 2001–2007 • United States	• Ever smoker: HR = 2.1 (p = 0.07)	Adjusted for age, race, alkaline phosphatase, des-carboxy prothrombin level, cirrhosis, esophageal varices, randomization group, and aspartate aminotransferase/platelet ratio index
Koh et al. 2011	• 61,321 followed • 394 cases • 1993–2007 • Singapore	• Smokers: – Current smoker: HR = 1.6 (1.3–2.1) – Former smoker: HR = 1.1 (0.8–1.5) • Cigarettes/day among current smokers: – 1–12: HR = 1.53 (1.10–2.12) – >12 (86 cases): HR = 1.72 (1.28–2.30) • Years of smoking: – <20: HR = 1.1 (0.7–1.8) – ≥20: HR = 1.5 (1.2–1.9) • Pack-years of smoking: – <20: HR = 1.2 (0.9–1.7) – 20–39: HR = 1.5 (1.2–2.0) – ≥40: HR = 1.5 (1.1–2.2) • Results were similar when daily drinkers were excluded from the analysis. • P values for trend were significant for number of cigarettes/day, years of smoking, and pack-years of smoking • Among HBV- and HCV- participants, ever smoking was associated with a nonsignificant increased risk for HCC in all strata of alcohol consumption	Adjusted for age, gender, year of recruitment, dialect group, education level, BMI, diabetes, daily ethanol intake and coffee intake

Table 6.4*S* Continued

Study	Design/population	Findings (95% CI)[a]	Comments
Trichopoulos et al. 2011	• Nested case-control study • Estimated 500,000 followed • 115 cases • 1992–2006 • Europe	• All subjects: – Current smoker: 4.6 (1.9–10.9) – Former smoker: 2.0 (0.90–4.4) • Men: – Current smoker: 5.4 (1.7–16.8) – Former smoker: 1.7 (0.6–4.9) • Women: – Current smoker: 1.7 (0.3–8.5) – Former smoker: 1.4 (0.3–6.0)	Matched by study site, age, gender, and calendar time of recruitment; women matched on menopausal status; adjusted for HBV/HCV status, education level, ethanol and coffee intake, and BMI
Kusakabe et al. 2011	• HBV-infected patients • 479 followed • 13 cases • 1993–2006 • Japan	• Current smoker: HR = 2.8 (0.6–13)	Adjusted for age, gender, BMI, consumption of alcohol, levels of liver enzymes, and HBV molecular characteristics
Oh et al. 2012	• 6,694 followed • 50 cases • 1993–2003 • Republic of Korea	• Current smoker: HR = 1.3 (0.6–2.6) • Former smoker: HR = 1.2 (0.4–3.3)	Models with smoking estimates did not include data pertaining to HBV and HCV; adjusted for age and gender only
Sahasrabuddhe et al. 2012	• 300,504 adults, 50–71 years of age, followed • 250 cases • 1995–2006 • United States	• Former smokers, by cigarettes/day: – ≤20: HR = 1.2 (0.9–1.7) – >20: HR = 1.3 (0.9–1.9) • Current smokers, by cigarettes/day: – ≤20: HR = 2.4 (1.5–3.8) – >20: HR = 1.8 (1.0–3.4)	Unadjusted models

Notes: **BMI** = body mass index; **CI** = confidence interval; **HBsAg** = hepatitis B surface antigen; **HBV** = hepatitis B virus; **HCV** = hepatitis C virus; **HR** = hazard ratio; **IRR** = incident rate ratio; **OR** = odds ratio; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **person-years** = the sum of the number of years that each member of a population has been smoking.
[a]Findings are reported as relative risks and compared with never smokers, unless indicated otherwise.
[b]CI does not include 1.0.

Table 6.5*S* Prospective studies of cigarette smoking and colorectal cancer incidence, published 2002–2009

Study	Design/population	Findings (95% CI)	Adjustment(s)	Comments
Terry et al. 2002b	• 89,835 women • 40–59 years of age at entry in 1980 • 363 colon cases; 164 rectal cases • Canada • 10.6 years follow-up	• Colorectal: – Current smokers: rate ratio = 1.0 (0.80–1.26) – Former smokers: rate ratio = 1.15 (0.94–1.41) • Rectal cancer: – 30–39 years since smoking initiation: rate ratio = 1.52 (95% CI, 1.01–1.26)[a] – ≥40 years since smoking initiation: rate ratio = 2.27 (95% CI, 1.06–4.87)	Age, BMI, education, physical activity, other	NA
Tiemersma et al. 2002	• DCMP • 36,000 men and women enrolled • 1987–1991 • 20–59 years of age • Case cohort: 102 cases; 537 controls • 8.5 years follow-up	• Duration of smoking (current smokers): – 1–15 years: OR = 1.0 – 16–30 years: OR = 0.4 (0.1–1.9) – >30 years: OR = 1.9 (0.5–8.2) – p = 0.28 • Duration of smoking (former smokers): – 1–15 years: OR = 1.0 – 16–30 years: OR = 2.7 (1.03–7.4) – >30 years: OR = 3.2 (1.04–9.8) – p = 0.04 • Trend significant for former smokers	Age, gender, coffee, alcohol, BMI	NA
Limburg et al. 2003	• 34,467 women • 55–69 years of age at baseline in 1986 • 869 colon, rectal, and colorectal cases • 249 fatal • United States	• Current smokers: RR = 1.10 (0.89–1.37) • Former smokers: RR = 1.21 (1.01–1.45) • Duration of smoking: – 1–19 years: RR = 1.16 (0.89–1.52) – 20–39 years: RR = 1.08 (0.88–1.32) – ≥40 years: RR = 1.30 (1.04–1.63) • Increasing duration of smoking significantly related to risk of colorectal cancer incidence (p = 0.03)	Age, BMI, physical activity, alcohol, other	NA
Otani et al. 2003	• 90,004 men and women • 40–69 years of age in 1990 • 298 colorectal cases (invasive only) • 299 colon cases (invasive and noninvasive); 148 rectal cases (invasive and noninvasive) • Japan	• Current smokers: – Colorectal: RR = 1.6 (1.1–2.1) – Colon: RR = 1.4 (0.99–1.9) – Rectal: RR = 1.4 (0.9–2.3)	Age, family history, BMI, physical activity, and study location	NA
Shimizu et al. 2003	• 29,051 participants • ≥35 years of age • 1992 baseline data • 104 colon cases in men; 57 rectal cases in men • 77 colon cases in women; 38 rectal cases in women • Japan • 8 years follow-up	• Men (colon): – ≤20 pack-years: RR = 1.36 (0.79–2.33) – >20 pack-years: RR = 1.37 (0.81–2.32) • Men (rectal): – ≤20 pack-years: RR = 1.33 (0.57–3.12) – >20 pack-years: RR = 2.44 (1.12–5.30)	Age, height, BMI, alcohol, years education	NA

Table 6.5*S* Continued

Study	Design/population	Findings (95% CI)	Adjustment(s)	Comments
van der Hel et al. 2003	• Diagnostisch Onderzoek Mammacarcinoom • 27,222 women • 249 colorectal cases (183 colon, 66 rectal) • The Netherlands • Follow-up 1987–1996	• Ever smokers: – Colon: RR = 1.36 (0.97–1.92) – Rectal: RR = 1.31 (0.76–2.25)	Age, BMI	NA
Wakai et al. 2003	• JACC • 25,260 men and 34,619 women • 40–79 years of age • Recruited 1988–1990 • 408 colon cases; 204 rectal cases • Japan • 7.6 years follow-up	• Men (colon): – Current smokers: HR = 1.23 (0.85–1.78) – Former smokers: HR = 1.07 (0.72–1.59) • Men (rectal): – Current smokers: HR = 0.83 (0.55–1.26) – Former smokers: HR = 0.88 (0.56–1.39) • Women (colon): – Current smokers: HR = 1.06 (0.55–2.02) – Former smokers: HR = 1.07 (0.39–2.92) • Women (rectal): – Current smokers: HR = 0.36 (0.05–2.65) – Former smokers: HR = 1.05 (0.14–7.69) • Number of years of smoking not related to risk (p = 0.52) • Cumulative amount smoked not related to risk (p = 0.90)	Age, education, family history, alcohol, diet, other	NA
Sanjoaquin et al. 2004	• Oxford Vegetarian Study • 11,140 participants • 16–89 years of age • 1980–1984 • Colorectal cases: 16 (current smokers), 43 (former smokers), and 36 (never smokers) • United Kingdom • 17 years follow-up	• Current smokers: RR = 1.88 (1.03–3.44) • Former smokers: RR = 1.95 (1.24–3.07)	Age, gender	NA
Lüchtenborg et al. 2005	• Netherlands Cohort Study on Diet and Cancer • 58,279 men and 62,573 women • 50–69 years of age at entry in 1986 • 661 colorectal cases (excluding the first 2.3 years of follow-up) • The Netherlands • 7.3 years follow-up	• Current smokers: IRR = 0.91 (0.71–1.18) • Former smokers: IRR = 1.30 (1.03–1.65) • No significant trend for age at smoking initiation or duration of smoking	Age, gender, family history, BMI	Weijenberg and colleagues (2008) have updated cohort analysis for *KRAS* oncogene mutation with fewer cases

Table 6.5*S* Continued

Study	Design/population	Findings (95% CI)	Adjustment(s)	Comments
Yun et al. 2005	• Korean National Health Insurance Corporation • 733,134 men • ≥30 years of age in 1996 • Current smokers: 42.4 years of age (mean) • Former smokers: 44.7 years of age (mean) • 417 colon cases; 453 rectal cases • Republic of Korea • Followed through 2000	• Colon: – Current smokers: RR = 0.81 (0.63–1.05) – Former smokers: RR = 1.37 (1.06–1.77) • Rectal: – Current smokers: RR = 0.97 (0.76–1.24) – Former smokers: RR = 1.17 (0.91–1.52)	Age, alcohol, BMI, physical activity, diet	NA
Berndt et al. 2006	• CLUE II • 22,887 residents • 250 colorectal cases • Washington County, Maryland	• Ever smokers: IRR = 1.23 (0.91–1.66)	Age, gender	NA
Kim et al. 2006	• 14,103 men and women • 100 colorectal cases • Republic of Korea	• Duration of smoking: – ≤45 years: RR = 1.51 (0.97–2.34) – >45 years: RR = 2.35 (1.16–4.74) – p ≤0.01 • Duration of smoking related to risk	Age, gender, alcohol, BMI, other	NA
Akhter et al. 2007	• 25,279 men • 40–64 years of age in 1990 • 188 colorectal cases • Japan • 7 years follow-up	• Current smokers: RR = 1.47 (0.93–2.34) • Former smokers: RR = 1.73 (1.04–2.87)	Age, family history, education, alcohol, diet, other	Age at smoking initiation significant trend (includes never smokers); duration of smoking significant trend (includes never smokers)
Driver et al. 2007	• Physicians' Health Study • 21,581 men • 381 colon cases; 104 rectal cases • United States • 20 years follow-up	• Colorectal (ever smokers): OR = 1.42 (1.17–1.72) • Colon: – Current smokers (1 pack/day): OR = 1.06 (0.57–1.98) – Current smokers (2 packs/day): OR = 1.53 (1.02–2.29) – Former smokers: OR = 1.50 (1.19–1.89) • Rectal: – Current smokers (1 pack/day): OR = 0.85 (0.26–2.77) – Current smokers (2 packs/day): OR = 1.92 (1.01–3.66) – Former smokers: OR = 1.13 (0.73–1.75)	Age, BMI, alcohol, physical activity, other	Smoking collapsed to ever smokers for combined colorectal cancer then evaluated as current smokers and former smokers by site

Table 6.5*S* Continued

Study	Design/population	Findings (95% CI)	Adjustment(s)	Comments
Paskett et al. 2007	• Women's Health Initiative • 146,877 women • 50–79 years of age in 1994 • 1,242 colorectal cases: 1,075 colon, 176 rectal • United States • 7.8 years follow-up	• Colon: – Current smokers: HR = 1.03 (0.77–1.38) – Former smokers: HR = 1.12 (0.97–1.29) • Rectal: – Current smokers: HR = 1.95 (1.10–3.47) – Former smokers: HR = 1.15 (0.80–1.67) • Duration of smoking: – Colon o <20 years: HR = 0.95 (0.79–1.15) o 20–29 years: HR = 1.27 (1.02–1.58) o 30–39 years: HR = 1.18 (0.93–1.50) o ≥40 years: HR = 1.19 (0.93–1.54) – Rectum o <20 years: HR = 0.87 (0.52–1.43) o 20–29 years: HR = 1.95 (1.20–3.17) o 30–39 years: HR = 1.24 (0.68–2.27) o ≥40 years: HR = 1.53 (0.83–2.83) • Current smokers had a significantly increased risk of rectal cancer	Age, ethnicity, study arm, alcohol, diet, physical activity, family history	NA
Tsong et al. 2007	• 61,321 men and women • 45–74 years of age • Recruited 1993–1998 • 845 colorectal cases: 516 colon, 329 rectal • Singapore • 11 years follow-up	• Colon: – Current smokers: HR = 0.83 (0.64–1.06) – Former smokers: HR = 0.96 (0.73–1.27) • Rectal: – Current smokers: HR = 1.63 (1.23–2.17) – Former smokers: HR = 1.45 (1.04–2.01)	Age, gender, education, BMI, family history, alcohol, physical activity	Age at smoking initiation related to rectal cancer but not colon cancer; duration of smoking related to rectal cancer but not colon cancer
Hooker et al. 2008	• 91,908 households in 1963 census: 20,926 men; 24,823 women • 90,225 households in 1975 census: 21,780 men; 26,372 women • Rectal cancer incidence • Washington County, Maryland	• Men (1963 cohort): – Current smokers: RR = 3.05 (1.19–7.82) – Former smokers: RR = 2.63 (0.98–7.05) • Men (1975 cohort): – Current smokers: RR = 1.80 (0.88–3.67) – Former smokers: RR = 1.92 (0.98–3.78) • Women (1963 cohort): – Current smokers: RR = 0.93 (0.48–1.80) – Former smokers: RR = 0.62 (0.19–2.08) • Women (1975 cohort): – Current smokers: RR = 1.57 (0.89–3.76) – Former smokers: RR = 1.87 (1.02–3.45)	Age, education, marital status	NA
Gram et al. 2009	• 68,160 women • 30–69 years of age at enrollment in 1996–1998 • 425 colorectal cases: 284 colon, 141 rectal • Norway • Followed through 2005	• Ever smokers: – Colorectal: rate ratio = 1.2 (1.0–1.5) – Colon: rate ratio = 1.3 (1.0–1.7) – Rectal: rate ratio = 1.1 (0.7–1.5) • Years smoked significant for colorectal cancer (p = 0.04) • No significant trends for individual sites • Pack-years smoked significant for colorectal cancer (p = 0.008)	Age, menopausal status, BMI, alcohol, hormone therapy	NA

Table 6.5*S* Continued

Study	Design/population	Findings (95% CI)	Adjustment(s)	Comments
Hannan et al. 2009	• Cancer Prevention Study II • 184,187 men and women • 50–74 years of age • 1,962 colorectal cases • 1992–2005 study period	• Current smokers: HR = 1.27 (1.06–1.52) • Former smokers: HR = 1.23 (1.11–1.36) • Among current smokers, relative risk greatest for current smokers of long duration (p = 0.052) • Risk comparable in both men and women	Age, BMI, education, family history, physical activity, race, aspirin, alcohol, other	NA

Notes: **BMI** = body mass index; **CI** = confidence interval; **CLUE II** = Campaign Against Cancer and Heart Disease; **DCMP** = Dutch Cardiovascular Monitoring Project; **HR** = hazard ratio; **IRR** = incidence rate ratio; **JACC** = Japanese Collaborative Cohort Study for Evaluation of Cancer Risk; **NA** = not applicable; **OR** = odds ratio; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **RR** = relative risk.
[a]The RR does not fall within the CI. The information presented here appears just as it does on page 481 of Terry and colleagues (2002).

Table 6.6*S* Case-control studies of cigarette smoking and colorectal cancer incidence, published 2001–2008

Study	Design/population	Findings (95% CI)	Adjustment(s)	Comments
Chiu et al. 2001	• 655 colon cases • 629 rectal cases • 2,336 controls • Iowa	• Men (colon): – Ever smokers: 1.3 (1.0–1.8) – Former smokers: 1.5 (1.1–2.0) – Current smokers: 1.0 (0.7–1.5) • Men (rectal): – Ever smokers: 1.3 (1.0–1.8) – Former smokers: 1.4 (1.0–1.8) – Current smokers: 1.3 (0.9–1.9) • Women (colon): – Ever smokers: 1.3 (0.9–1.7) – Former smokers: 1.6 (1.1–2.2) – Current smokers: 1.0 (0.7–1.4) • Women (rectal): – Ever smokers: 1.0 (0.7–1.3) – Former smokers: 1.2 (0.8–1.8) – Current smokers: 0.7 (0.5–1.1)	Age, total energy in dietary intake, other	NA
Ji et al. 2002	• 1,805 cases (colon and rectal) • 1,552 controls • China	• Men (colon): – Current smokers: 0.8 (0.6–1.0) – Former smokers: 0.9 (0.6–1.3) • Men (rectal): – Current smokers: 0.9 (0.7–1.2) – Former smokers: 1.1 (0.7–1.6) • Women (colon): – Current smokers: 0.6 (0.4–1.0) – Former smokers: 0.6 (0.3–1.5) • Women (rectal): – Current smokers: 0.9 (0.5–1.3) – Former smokers: 1.4 (0.7–3.0) • No significant trend for RRs according to duration of smoking or pack-years among men and women	Age, alcohol, other	NA
Diergaarde et al. 2003	• 176 colorectal cases • 249 controls • Europe	• Ever smokers: 1.00 (0.60–1.50)	Age, gender, alcohol	NA
Kim et al. 2003	• 125 colorectal cases • 245 controls • Republic of Korea	• Ever smokers: 1.53 (0.94–2.52)	Age, gender, BMI, diet, alcohol, other	NA
Minami and Tateno 2003	• 488 cases (colon and rectal) • 2,444 controls • Japan	• Ever smokers: – Colon: 0.97 (0.71–1.33) – Rectal: 1.65 (1.07–2.55)	Age, gender, alcohol, family history, other	NA
Ho et al. 2004	• 822 cases (colon and rectal) • 926 controls • Hong Kong, China	• Current smokers: – Colon: 0.84 (0.58–1.21) – Rectal: 1.44 (1.00–2.06) • No significant trend with duration of smoking and cigarettes smoked/day	Age, gender, diet, alcohol, family history, physical activity, other	NA
Nkondjock and Ghadirian 2004	• 402 colon cases • 688 controls • Canada	• No statistically significant differences between cases and controls	NR	No data presented

Table 6.6*S* Continued

Study	Design/population	Findings (95% CI)	Adjustment(s)	Comments
Ates et al. 2005	• 181colorectal cases • 204 controls • Europe/Turkey	• Ever smokers: 1.43 (0.94–2.18)	Age, gender	After reporting, main effect analysis focuses on *GST* genotypes and risk
Jin et al. 2005	• 140 colorectal cases • 240 controls • China	• Ever smokers: 0.67 (0.36–1.25)	Age, gender, alcohol, family history	NA
Chia et al. 2006	• 1,792 colorectal cases • 1,501 controls • United States	• Ever smokers: 1.4 (1.2–1.6) • Current smokers: 1.7 (1.4–2.1) • Former smokers: 1.2 (1.1–1.4) • Duration of smoking (>40 years): 1.6 (1.2–2.1) • Significant trend with duration of smoking (p = 0.007)	Age, gender, BMI, family history, other	NA
Verla-Tebit et al. 2006	• 540 colorectal cases • 614 controls • Germany	• Ever smokers: 1.01 (0.77–1.32)	Age, gender, BMI, diet, alcohol, family history, physical activity, other	NA
Gao et al. 2007	• 315 cases (colorectal, colon, and rectal) • 439 controls • China	• Ever smokers: – Colorectal: 1.01 (0.69–1.47) – Colon: 0.84 (0.49–1.44) – Rectal: 1.08 (0.70–1.67)	Age, gender, alcohol	NA
Hu et al. 2007	• 1,723 colon cases • 3,097 controls • Canada	• Women (ever smokers): – Proximal: 1.20 (0.90–1.50) – Distal: 1.00 (0.80–1.20) • Men (ever smokers): – Proximal: 1.20 (0.90–1.60) – Distal: 1.10 (0.90–1.40)	Age, BMI, physical activity, other	NA
Lüchtenborg et al. 2007	• 1,959 colorectal cases • 1,959 controls • Hawaii	• Men: – Current smokers: 1.32 (0.99–1.76) – Former smokers: 1.21 (0.97–1.50) • Women: – Current smokers: 1.17 (0.85–1.62) – Former smokers: 1.32 (1.02–1.71) • Trend with duration of smoking and intensity not significant	Age, BMI, diet, physical activity, alcohol, family history, other	NA
Steinmetz et al. 2007	• 674 colorectal cases • 5,456 controls • Europe	• Current smoker: RR = 1.42 (1.02–1.99) • Former smoker: RR = 1.62 (1.28–10.08)	Age, alcohol, other	NA
Goy et al. 2008	• 1,150 colon cases • 1,549 controls • Canada	• Current smokers: 0.86 (0.65–1.14) • Former smokers: – <10 years: 1.05 (0.78–1.43) – >10 years: 1.18 (0.90–1.53)	Age, gender, BMI, diet	Not related to rectal cancer

Note: Findings are presented as odds ratios unless indicated otherwise. **BMI** = body mass index; **CI** = confidence interval; **NA =** not applicable; **NR =** not reported; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **RR** = relative risk.

Table 6.7*S* Prospective studies of cigarette smoking and colorectal cancer mortality, published 2002–2009

Study	Design/population	Findings (95% CI)	Adjustment(s)	Comments
Limburg et al. 2003	• 34,467 women • 55–69 years of age at baseline in 1986 • 249 cdolorectal deaths • United States • Followed through 1999	• Current smokers: RR = 1.58 (1.09–2.29) • Former smokers: RR = 1.14 (0.80–1.62) • Duration of smoking: – 1–19 years: RR = 1.53 (0.96–2.43) – 20–39 years: RR = 1.02 (0.67–1.53) – ≥40 years: RR = 1.55 (1.04–2.31) • Increasing duration of smoking-related to increased risk of colorectal cancer mortality (p = 0.07)	Age, BMI, physical activity, alcohol, other	Cumulative pack-years (p trend = 0.05)
Colangelo et al. 2004	• Chicago Heart Association Detection Project in Industry Study • 39,299 men and women • Recruited 1967–1973 • 208 colorectal deaths (men): 141 women • 26 years follow-up	• Former smokers: RR = 0.97 (0.74–1.29)	Age, race, BMI, education, height, gender	Trend for cigarettes smoked/day significant in age-adjusted analysis, but not in multivariate analysis
Jee et al. 2004	• 1,212,906 men and women • 30–95 years of age • Up to 511 cases • Republic of Korea • 9 years follow-up	• Current smokers: RR = 1.1 (0.8–1.4) • Former smokers: RR = 1.1 (0.9–1.4)	NR	Most current smokers consumed less than 1 pack of cigarettes/day
Wen et al. 2004	• 53,091 participants (combines two cohorts: 1982–1992 and 1989–1992) • 45 colon deaths; 28 rectal deaths • Taiwan	• Current smokers: – Colon: RR = 0.84 (0.54–1.30) – Rectal: RR = 2.06 (1.01–4.18)	NR	NA
Doll et al. 2005	• 34,439 participants recruited in 1951 • 549 colon deaths; 201 rectal deaths • Europe	• Significant trend for cigarettes smoked and risk of rectal cancer • Relatively weak relationship between smoking and colorectal cancer • Implausibly strong relationship between smoking and rectal cancer • No relationship evident with smoking and colon cancer	NR	NA
Huxley 2007	• 33 cohorts • Asia • 751 colorectal deaths • 6.8 years follow-up (average)	• Ever smokers: HR = 1.43 (1.09–1.88)	Age, BMI, alcohol	NA
Ozasa 2007	• JACC Study • 607 cases • Men: 200 colon deaths; 152 rectal deaths • Women: 181 colon deaths; 74 rectal deaths • Japan	• Current smokers (men): – Colon: HR = 1.18 (0.80–1.72) – Rectal: 1 HR = 0.31 (0.85–2.01) • Current smokers (women): – Colon: HR = 0.67 (0.29–1.53) – Rectal: HR = 1.31 (0.52–3.29)	NR	NA

Table 6.7*S* Continued

Study	Design/population	Findings (95% CI)	Adjustment(s)	Comments
Batty et al. 2008	• 17,322 • 40–69 years of age at baseline • 309 colon deaths; 114 rectal deaths • Europe	• Colon: – Current smokers: HR = 1.33 (0.96–1.86) – Former smokers: HR = 1.11 (0.80–1.55) • Rectal: – Current smokers: HR = 1.51 (0.84–2.74) – Former smokers: HR = 1.94 (1.11–3.39)	NR	NA
Kenfield et al. 2008	• Nurses' Health Study • 104,519 women • 34–59 years of age at baseline in 1980, when alcohol use and physical activity were ascertained • 578 colorectal deaths • 24 years follow-up	• Current smokers: HR = 1.63 (1.29–2.05) • Former smokers: HR = 1.23 (1.02–1.49)	Age, BMI, alcohol, physical activity, other	Among current smokers, trend for cigarettes smoked/day significant in age-adjusted analysis (p = 0.02), but not significant in multivariate analysis

Note: **BMI** = body mass index; **CI** = confidence interval; **HR** = hazard ratio; **JACC** = Japanese Collaborative Cohort Study for Evaluation of Cancer Risk; **NA =** not applicable; N**R =** not reported; **RR** = relative risk.

Table 6.8*S* **Prospective cohort studies on the association between cigarette smoking and prostate cancer incidence and mortality[a]**

Study	Design/population	Findings by measure of smoking	
		Incidence: RR (95% CI)	Mortality: RR (95% CI)
Hammond and Horn 1958	• Hammond-Horn Study of the American Cancer Society • 187,783 White men, 50–69 years of age • 185 deaths • 1952–1955 • United States	NR	• Age standardized • Smoking status: – Not regular: 1.00 (referent) – Regular: 1.75 (ratio of observed to expected deaths) – p = 0.05
Hammond 1966	• CPS-I of the American Cancer Society • 440,558 men, 35–84 years of age • 319 deaths • 1959–1960 • United States	NR	• Age standardized • Smoking status, 45–64 years of age: – Never smoker: 1.00 (referent) – Ever smoker: 1.04 • Smoking status, 65–79 years of age: – Never smoker: 1.00 (referent) – Ever smoker: 1.01
Weir and Dunn 1970	• 68,153 men, 35–64 years of age, who were members of a California labor union • 37 deaths • 1954–1962	NR	• Age standardized • Smoking status: – Nonsmoker: 1.00 (referent) – Smoker: 0.78 • Packs/day: – Nonsmoker: 1.00 (referent) – ≤0.5: 0.58 – 1: 0.98 – ≥1: 0.78
Whittemore et al. 1984	• Precursors study of 47,271 men who were alumni of Harvard University and University of Pennsylvania • 243 cases • 1962–1977	• Adjusted for age, year, and school • Smoking history: 1.1 (1.0–1.3)	NR
Carstensen et al. 1987	• 25,129 Swedish men born between 1894–1945 • 193 deaths • 1963–1979	NR	• Age standardized • Smoking status (pipe): – Never smoker: 1.0 (referent) – Former smoker: 1.0 – Current smoker (1–7 g/day of tobacco): 1.1 – Current smoker: (8–15 g/day): 0.8 – Current smoker: (>15 g/day): 0.9 – p trend = 0.7

Table 6.8*S* Continued

Study	Design/population	Findings by measure of smoking	
		Incidence: RR (95% CI)	Mortality: RR (95% CI)
Mills et al. 1989a Additional information available in Mills and Beeson 1992	• Approximately 14,000 men who were Seventh-day Adventists and residents of California • 180 cases • 1976–1982	• Adjusted for age • Smoking status: – Never smoker: 1.00 (referent) – Former smoker: 1.24 (0.91–1.67) – Current smoker: 0.49 (0.16–1.57) – p trend = 0.72 • Number of cigarettes/day: – 0: 1.00 (referent) – 1–14: 1.23 (0.84–1.81) – ≥15: 1.18 (0.83–1.68) – p trend = 0.32 • Smoking duration (years): – 0: 1.00 (referent) – <10: 1.07 (0.69–1.65) – ≥10: 1.24 (0.89–1.72) – p trend = 0.23	NR
Severson et al. 1989	• 7,999 men of Japanese ancestry, who were born between 1900 and 1919 • 1965–1986 • 174 Cases • Oahu, Hawaii	• Adjusted for age • Smoking status: – Never smoker: 1.00 (referent) – Former smoker: 0.89 (0.61–1.29) – Current smoker: 0.87 (0.61–1.23)	NR
Thompson et al. 1989	• 1,776 men, 50–84 years of age, who were residents of Rancho Bernardo, California • 54 cases • 1972–1987	• Adjusted for multiple variables • Smoking status: – Not current: 1.0 (referent) – Current: 1.3 (0.8–2.3)	• NR
Akiba and Hirayama 1990[b]	• Six-Prefecture Cohort Study • 122,261 men, ≥40 years of age • 255 deaths 1966–1981 • Japan	• NR	• Adjusted for age, residence, and year • Number of cigarettes/day: – Never smoker: 1.0 (referent) – 1–4: 3.1 (1.4–6.4) – 5–14: 1.0 (0.7–1.6) – 15–24: 0.9 (0.6–1.4) – 25–34: 0.8 (0.2–2.1) – ≥35: 3.0 (1.0–7.1) – ≥1 pack: 1.1 (0.7–1.5) – p for trend >0.1

Table 6.8*S* Continued

Study	Design/population	Findings by measure of smoking	
		Incidence: RR (95% CI)	**Mortality: RR (95% CI)**
Hsing et al. 1990	• 17,633 White men who held life insurance policies with the Lutheran Brotherhood Insurance Society • 1966–1986 • 149 deaths • United States	• NR	• Adjusted for age • Smoking status: – Never smoker: 1.0 (referent) – Ever any form of tobacco: 1.8 (1.1–2.9) – Pipes and/or cigars only: 1.6 (0.7–3.5) – Cigarettes only: 2.0 (1.1–3.7) – Smokeless tobacco only: 4.5 (2.1–9.7) – Cigarettes and pipes and/or cigars: 1.7 (1.0–2.9) – Cigarettes and smokeless tobacco: 2.9 (1.3–6.5) – Smokeless tobacco and pipes and/or cigars: 1.4 (0.5–4.1) – Cigarettes and smokeless tobacco and pipes and/or cigars: 1.6 (0.8–3.1) • Number of cigarettes/day: – Never smoker: 1.0 (referent) – Occasional or former smoker: 1.9 (1.1–3.3) – 1–19: 1.6 (0.8–3.3) – 20–29:1.7 (0.8–3.5) – ≥30: 1.4 (0.4–4.4)
Ross et al. 1990	• 5,106 men who were residents of the Leisure World retirement community • 138 cases • 1964–1985 • Laguna Hills, California	• Adjusted for age • Smoking status: – Never smoker: 1.0 (referent) – Former smoker: 0.8 – Current smoker: 0.9 • Number of cigarettes/day: – 0: 1.0 (referent) – 1–10: 0.9 – 11–20: 0.7 – 21: 0.7 • Smoking duration (years): – Never: 1.0 (referent) – 1–10: 2.2 (significant) – 11–30: 0.8 – 31: 0.6 – p trend <0.02	NR

Table 6.8*S* Continued

Study	Design/population	Findings by measure of smoking	
		Incidence: RR (95% CI)	Mortality: RR (95% CI)
Hsing et al. 1991[c]	• 250,000 United States veterans who served in the armed forces between 1917–1940 • 4,607 deaths • 1954–1980	NR	• Adjusted for age • Smoking status at 26-year follow-up: – Never any tobacco: 1.00 (referent) – Cigars and pipes only: 1.10 (0.99–1.22) – Smokeless tobacco only: 1.17 (0.88–1.56) – Former cigarette smoker: 1.13 (1.03–1.24) – Current cigarette smoker: 1.18 (1.09–1.28) • Smoking status at 26-year follow-up among current cigarette smokers by number of cigarettes/day: – 1–9: 1.11 (0.97–1.27) – 10–20: 1.15 (1.05–1.27) – 21–39: 1.23 (1.09–1.38) – >39: 1.51 (1.20–1.90) – p trend <0.001 • Smoking duration (years): – <25: 1.00 (referent) – 25–29: 1.04 (0.74–1.47) – 30–34: 0.92 (0.70–1.22) – 35–39: 1.11 (0.87–1.42) – >39: 1.23 (0.97–1.56) – p trend <0.005 • Smoking status at 16-year follow-up: – Never smoker: 1.00 (referent) – Former smoker: 1.18 – Current smoker: 1.31 • Smoking status at 8.5-year follow-up: – Never smoker: 1.00 (referent) – Former smoker: 1.63 – Current smoker: 1.71 • Smoking status at 2.5-year follow-up: – Nonsmoker: 1.00 (referent) – Current smoker: 2.17

Table 6.8*S* Continued

Study	Design/population	Findings by measure of smoking	
		Incidence: RR (95% CI)	**Mortality: RR (95% CI)**
Tverdal et al. 1993 Additional information available in Thune and Lund 1994	• 44,290 Norwegian men • 1972–1988 • 32 deaths • Oslo, Tromsø, Finnmark, Sogn og Fjordane, or Oppland, Norway	NR	• Adjusted for age and place of residence • Smoking status (per 100,000 person years): – Never smoker: 3.5 – Former smoker, cigarettes: 5.3 – Current smoker, pipe only: 2.3 – Current smoker, cigarettes only: 6.4 – Current smoker, pipe and cigarettes: 10.2 • Adjusted for multiple variables per 10 cigarettes/day: 0.6 (0.3–1.4)
Hiatt et al. 1994	• 43,432 men, ≥30 years of age, who were members of the Kaiser Permanente Medical Care Program • 238 cases • 1979–1985 • Northern California	• Adjusted for multiple variables • Smoking status: – Never smoker: 1.0 (referent) – Former smoker: 1.1 (0.8–1.5) – <1 pack/day: 1.0 (0.6–1.6) – ≥1 pack/day: 1.9 (1.2–3.1)	NR
Le Marchand et al. 1994	• 20,316 men, ≥45 years of age, including Japanese, White, Filipino, Native Hawaiian, and Chinese • 198 cases • 1975–1989 • Hawaii	• Adjusted for age, ethnicity, and income • Cigarettes/day by quartile (Q): – Q1 (0): 1.0 (referent) – Q2: 0.9 (0.6–1.4) – Q3: 1.0 (0.7–1.6) – Q4 (≥20): 1.0 (0.6–1.6) – p trend = 0.92 • Pack-years of smoking by quartile (Q): – Q1 (0): 1.0 (referent) – Q2: 0.9 (0.5–1.5) – Q3: 0.7 (0.4–1.2) – Q4 (≥44): 1.2 (0.8–1.8) – p trend = 0.69	NR
Thune and Lund 1994 Additional information available in Tverdal et al. 1993	• 42,067 Norwegian men • 211 cases • 1972–1991 • Oslo, Tromsø, Finnmark, Sogn og Fjordane, or Oppland, Norway	• Adjusted for age • 10 cigarettes/day: 1.08 (0.90–1.30)	NR

Table 6.8*S* Continued

Study	Design/population	Findings by measure of smoking	
		Incidence: RR (95% CI)	**Mortality: RR (95% CI)**
Adami et al. 1996	• 135,006 Swedish male construction workers • 2,368 cases • 709 deaths • 1971–1991	• Adjusted for age • Smoking status: – Never smoker: 1.00 (referent) – Former smoker: 1.09 (0.98–1.22) – Current smoker: 1.11 (1.01–1.23) • Number of cigarettes/day: – 0: 1.00 (referent) – 1–4: 1.06 (0.93–1.20) – 5–14: 1.10 (0.99–1.31) – 15–24: 1.14 (0.99–1.31) – >25: 1.00 (0.72–1.38) – p trend = 0.04 • Smoking duration (years): – Former or never smoker: 1.00 (referent) – 1–10: 1.20 (1.00–1.44) – 11–20: 1.14 (0.97–1.34) – >21: 1.03 (0.90–1.19) – p trend = 0.33 • Smoking duration (years) among current smokers only: – Never smoker: 1.00 (referent) – 1–10: 0.68 (0.43–1.07) – 11–20: 1.27 (1.02–1.58) – 21–30: 1.09 (0.94–1.26) – 31–40: 1.13 (1.01–1.28) – >41: 1.07 (0.92–1.25) – p trend = 0.05	• Adjusted for age • Smoking status: – Never smoker: 1.00 (referent) – Former smoker: 1.03 (0.84–1.33) – Current smoker: 1.26 (1.06–1.50) • Number of cigarettes/day: – 0: 1.00 (referent) – 1–4: 0.99 (0.78–1.26) – 5–14: 1.13 (0.93–1.37) – 15–24: 1.05 (0.82–1.35) – p trend = 0.34 • Smoking duration (years): – Former or never smoker: 1.00 (referent) – 1–10: 1.12 (0.80–1.58) – 11–20: 1.06 (0.78–1.44) – >21: 0.98 (0.75–1.28) – p trend = 0.96 • Smoking duration (years) among current smokers only: – Never smoker: 1.00 (referent) – 1–10 and 11–20 (combined): 1.41 (0.99–1.99) – 21–30: 1.28 (0.98–1.67) – 31–40: 1.19 (0.96–1.48) – >41:1.28 (0.99–1.65) – p trend = 0.03
Coughlin et al. 1996	• Multiple Risk Factor Intervention Trial • 348,874 men, 35–57 years of age, who were screened for the trial • 826 deaths • 1973–1990 • United States	NR	• Adjusted for multiple variables • Number of cigarettes/day: – 0: 1.00 (referent) – 1–15: 1.54 (p <0.01) – 16–25: 1.27 (p <0.05) – 26–35: 1.23 – 36–45: 1.50 (p <0.01) – ≥46: 1.22 • Smoking status: – Nonsmoker: 1.00 (referent) – Current: 1.31 (1.13–1.52)

Table 6.8*S* Continued

Study	Design/population	Findings by measure of smoking	
		Incidence: RR (95% CI)	**Mortality: RR (95% CI)**
Engeland et al. 1996	• British-Norwegian Migrant Study • 11,863 men • 707 cases • 1966–1993	• Adjusted for age • Smoking status: – Never smoker: 1.0 (referent) – Former smoker: 0.9 (0.7–1.1) – Current smoker: 1.1 (0.9–1.3)	• NR
Grönberg et al. 1996	• Nested case-control study • Swedish male twins born between 1886–1925 • 470 cases • 1959–1989	• Adjusted for age • Smoking status: – Never smoker: 1.00 (referent) – Former smoker: 0.91 (0.68–1.21) – Current smoker: 1.00 (0.71–1.39) – p trend = 0.91 • Number of cigarettes/day: – 0: 1.00 (referent) – 1–9: 1.06 (0.77–1.45) – 10–19: 0.96 (0.66–1.39) – ≥20: 0.72 (0.43–1.15) – p trend = 0.18	• NR

Table 6.8*S* Continued

Study	Design/population	Findings by measure of smoking	
		Incidence: RR (95% CI)	**Mortality: RR (95% CI)**
Cerhan et al. 1997	• Iowa 65+ Rural Health Study (1 of the sites in the EPESE) • 1,050 men, ≥65 years of age • 71 cases • 1982–1993	• Adjusted for age • Smoking status: – Never smoker: 1.0 (referent) – Former smoker: 1.2 (0.7–2.1) – Current smoker: 2.2 (1.2–4.4) – p trend = 0.02 • Pack-years of smoking: – 0: 1.0 (referent) – <31: 1.3 (0.7–2.5) – 31–55: 1.3 (0.7–2.7) – >55: 2.0 (1.1–3.8) – p trend = 0.04 • Number of cigarettes/day by smoking status (for current only): – Never smoker: 1.0 (referent) – Former smoker: 1.2 (0.7–2.1) – Current smoker, <20: 1.8 (0.7–4.4) – Current smoker, ≥20: 2.7 (1.2–6.0) – p trend = 0.007 • Years since quitting smoking by smoking status: – Never smoker: 1.0 (referent) – Former smoker, quit ≥15 years ago: 1.3 (0.7–2.5) – Former smoker, quit <15 years ago: 1.1 (0.6–2.2) – Current smoker: 2.2 (1.2–4.4) – p trend = 0.03	NR

Table 6.8*S* Continued

Study	Design/population	Findings by measure of smoking	
		Incidence: RR (95% CI)	**Mortality: RR (95% CI)**
Rodriguez et al. 1997	• CPS-II of the American Cancer Society • 450,279 men • 1,748 deaths • 1982–1991 • United States	• NR	• Adjusted for multiple variables • Smoking status (former smoker): – Never smoker: 1.00 (referent) – Cigarettes only: 0.99 (0.87–1.12) – Pipe/cigars/cigarettes: 0.91 (0.78–1.08) • Smoking status (current smoker): – Never smoker: 1.00 (referent) – Cigarettes only: 1.34 (1.16–1.56) – Pipe/cigars/cigarettes: 0.87 (0.73–1.05) • Number of cigarettes/day (current smoker): – Never smoker: 1.00 (referent) – <10: 1.33 (0.96–1.83) – ≥10–<20: 1.58 (1.23–2.03) – 20: 1.38 (1.10–1.71) – >20: 1.25 (1.00–1.57) – p trend = 0.29 • Smoking duration (years) (current smoker): – Never smoker: 1.00 (referent) – ≤25: 1.36 (0.77–2.38) – >25–35: 1.65 (1.17–2.34) – >35–45: 1.39 (1.11–1.75) – >45: 1.26 (1.04–1.53) – p trend = 0.86
Tulinius et al. 1997	• Cardiovascular Risk Factor Study (also known as the Reykjavik Study) • 11,366 men • 524 cases • 1968–1995 • Iceland	• Adjusted for age • Smoking status: – Never smoker: 1.00 (referent) – Former smoker: NR – Current smoker: NR • Number of cigarettes/day: – 1–14: NR – 15–24: NR – ≥25: NR – p ≥ 0.10 for all categories versus never smoking	NR

Table 6.8*S* Continued

Study	Design/population	Findings by measure of smoking	
		Incidence: RR (95% CI)	**Mortality: RR (95% CI)**
Veierød et al. 1997	• 24,051 Norwegian males, 16–56 years of age, who underwent screening for cardiovascular disease • 69 cases • 1977–1992	• Adjusted for age • Number of cigarettes/day by smoking status (for current only): – Never smoker: 1.0 (referent) – Former smoker: 0.6 (0.3–1.1) – Current smoker: 0–10: 0.5 (0.3–1.1) – Current smoker: ≥11: 0.6 (0.3–1.2)	NR
Lotufo et al. 2000	• Physicians' Health Study • 22,071 men, 40–84 years of age • 1982–2000 • 996 cases • 113 deaths • United States	• Adjusted for multiple variables • Smoking status: – Never smoker: 1.00 (referent) – Former smoker: 1.11 (0.98–1.28) – Current smoker, <20 cigarettes/day: 1.04 (0.73–1.48) – Current smoker, ≥20 cigarettes/day: 1.07 (0.82–1.41) – p trend = 0.33 • Pack-years of smoking: – Never smoker: 1.00 (referent) – 0.25–19: 1.20 (1.02–1.41) – 20–39: 0.96 (0.78–1.17) – ≥40: 1.14 (0.93–1.40) – p trend = 0.38 • Smoking duration (years) among current smokers: – <29: 1.00 (referent) – 29–38: 1.69 (0.75–3.82) – ≥39: 1.05 (0.41–2.70) – p trend = 0.33	• Adjusted for multiple variables • Smoking status: – Never smoker: 1.00 (referent) – Former smoker: 1.30 (0.87–1.95) – Current smoker: – <20 cigarettes/day: 1.25 (0.45–3.49) – ≥20 cigarettes/day: 1.22 (0.54–2.74) – p trend = 0.38 • Pack-years of smoking: – Never smoker: 1.00 (referent) – 0.25–19: 1.35 (0.82–2.23) – 20–39: 1.14 (0.64–2.05) – ≥40: 0.91 (0.47–1.75) – p trend = 0.98

Table 6.8*S* Continued

Study	Design/population	Findings by measure of smoking	
		Incidence: RR (95% CI)	**Mortality: RR (95% CI)**
Lund Nilsen et al. 2000	• 22,895 men, ≥20 years of age, who participated in the National Health Screening Service from 1984–1986 • 1984–1996 • 644 cases • Nord-Trondelag, Norway	• Adjusted for age • Smoking status: – Never smoker: 1.00 (referent) – Former smoker: 0.98 (0.80–1.19) – Current smoker: 0.96 (0.78–1.19) – p trend = 0.69 • Number of cigarettes/day: – 0: 1.00 (referent) – 1–8: 0.84 (0.64–1.10) – 9–10: 1.05 (0.79–1.39) – 11–15: 1.37 (1.00–1.88) – >15: 1.27 (0.91–1.76) • Pack-years of smoking: – 0: 1.00 (referent) – 1–10: 0.95 (0.70–1.30) – 11–17: 0.84 (0.58–1.21) – 18–25: 1.24 (0.92–1.67) – >25: 1.22 (0.93–1.60)	NR
Putnam et al. 2000[d]	• 1,572 men (controls) who participated in a population-based case-control study of cancer from 1986–1989 • 101 cases • 1986–1995 • Iowa	• Adjusted for age • Smoking status: – Never smoker: 1.0 (referent) – Former smoker: 1.4 (0.9–2.3) – Current smoker, <20 cigarettes/day: 1.3 (0.6–2.8) – Current smoker, ≥20 cigarettes/day: 1.6 (0.7–3.9) – p trend = 0.2 • Pack-years of smoking: – Never smoker: 1.0 (referent) – <25: 1.7 (1.0–3.0) – 25–50: 1.2 (0.7–2.2) – >50: 1.4 (0.8–2.5) – p trend = 0.5	NR
Allen et al. 2004	• Life Span Study • 18,115 Japanese men who were residents of Nagasaki and Hiroshima at the time of the atomic bombings during World War II • 196 cases • 1963–1996	• Adjusted for age, year, city, radiation dose, and education • Smoking status: – Nonsmoker: 1.00 (referent) – Smoker: 0.80 (0.60–1.07)	NR

Table 6.8*S* Continued

Study	Design/population	Findings by measure of smoking	
		Incidence: RR (95% CI)	**Mortality: RR (95% CI)**
Doll et al. 2005[e]	• British Doctors Study • 34,439 male physicians • 878 deaths • 1951–2001	NR	• Prostate cancer mortality rate adjusted for age and year • Smoking status: – Never smoker: 89.4/100,000 men/year – Former smoker: 80.9/100,000 men/year – Current smoker: 90.0/100,000 men/year – p trend = 0.67 • Number of cigarettes/day among current smokers: – 1–14: 66.7/100,000 men/year – 15–24: 99.6/100,000 men/year – ≥25: 113.3/100,000 men/year – p trend = 0.52
Giovannucci et al. 2007[f]	• Health Professionals Follow-Up Study • 51,529 men, 40–75 years of age • 3,544 cases • 312 deaths • 1986–2002 • United States	• Adjusted for multiple variables • Smoking status: – Never smoker: 1.0 (referent) – Former smoker, quit >10 years ago: 0.98 – Current or former smoker, quit ≤10 years ago: 0.98 (0.89–1.07) – p trend = 0.53 • Organ-confined disease by smoking status: – Never smoker: 1.00 (referent) – Current or former smoker, quit ≤10 years ago: 0.88 (0.77–1.01) • Minimally extraprostatic disease by smoking status: – Never smoker: 1.00 (referent) – Current or former smoker, quit ≤10 years ago: 1.11 (0.82–1.52) • Advanced-stage disease by smoking status: – Never smoker: 1.00 (referent) – Current or former smoker, quit ≤10 years ago: 1.14 (0.90–1.45)	• Adjusted for multiple variables • Smoking status: – Never smoker: 1.00 (referent) – Former smoker, quit >10 years ago: 1.03 – Current or former smoker, quit ≤10 years ago: 1.41 (1.04–1.91) – p trend = 0.05

Table 6.8*S* Continued

Study	Design/population	Findings by measure of smoking	
		Incidence: RR (95% CI)	**Mortality: RR (95% CI)**
Rohrmann et al. 2007	• 26,810 men, ≥18 years of age, who responded to a private census • 1963–2000 • 147 cases • 240 deaths • Washington County, Maryland	• 1963 cohort adjusted for age • Smoking status: – Never smoker: 1.00 (referent) – Former smoker: 1.33 (0.85–2.10) – Current smoker: 1.00 (0.63–1.59) • Number of cigarettes/day among current smokers: – Never smoker: 1.00 (referent) – <10: 0.52 (0.20–1.33) – 10–19: 1.03 (0.60–1.79) – ≥20: 1.38 (0.75–2.54) • First 10 years of follow-up, by smoking status: – Never smoker: 1.00 (referent) – Former smoker: 1.44 (0.89–2.32) – Current smoker: 0.90 (0.54–1.51)	• 1963 cohort adjusted for age • Smoking status: – Never smoker: 1.00 (referent) – Former smoker: 1.01 (0.70–1.46) – Current smoker: 0.93 (0.67–1.29) • Number of cigarettes/day among current smokers: – Never smoker: 1.00 (referent) – <10: 1.11 (0.67–1.29) – 10–19: 0.85 (0.57–1.25) – ≥20: 0.95 (0.62–1.47) • First 10 years of follow-up, by smoking status: – Never smoker: 1.00 (referent) – Former smoker: 2.75 (1.13–6.74) – Current smoker: 2.38 (0.94–5.99)
Rohrmann et al. 2007	• 28,292 adult men • 351 cases • 184 deaths • 1975–2000	• 1975 cohort • Smoking status: – Never smoker: 1.00 (referent) – Former smoker: 1.04 (0.80–1.36) – Current smoker: 0.98 (0.73–1.33) • Number of cigarettes/day among current smokers: – Never smoker: 1.00 (referent) – <10: 1.12 (0.58–2.15) – 10–19: 0.95 (0.67–1.35) – ≥20: 1.01 (0.65–1.57) • First 10 years of follow-up by smoking status: – Never smoker: 1.00 (referent) – Former smoker: 1.03 (0.76–1.40) – Current smoker: 1.08 (0.76–1.53)	• 1975 cohort • Smoking status: – Never smoker: 1.00 (referent) – Former smoker: 1.02 (0.69–1.50) – Current smoker: 1.25 (0.84–1.87) • Number of cigarettes/day among current smokers: – Never smoker: 1.00 (referent) – <10: 1.12 (0.44–2.82) – 10–19: 1.11 (0.70–1.77) – ≥20: 1.58 (0.94–2.64) • First 10 years of follow-up by smoking status: – Never smoker:1.00 (referent) – Former smoker: 1.92 (0.67–5.49) – Current smoker: 2.21 (0.69–7.08)

Table 6.8*S* Continued

Study	Design/population	Findings by measure of smoking	
		Incidence: RR (95% CI)	**Mortality: RR (95% CI)**
Batty et al. 2008	• Whitehall Study • 17,363 men, 40–69 years of age, who were government employees • 484 deaths • 1967–2005 • London	NR	• Adjusted for multiple variables • Smoking status: – Never smoker: 1.00 (referent) – Former smoker: 1.10 (0.86–1.41) – Current: 1.30 (1.01–1.69) – p trend = 0.03 • Per 10 cigarettes/day: – Former smoker: 0.97 (0.85–1.11) – Current smoker: 1.12 (0.96–1.31) • Per 10 years of smoking: – Former smoker: 1.05 (0.93–1.20) – Current smoker: 0.93 (0.75–1.15)
Watters et al. 2009	• NIH-AARP Diet and Health Study • 283,312 men 50–71 years of age • 14,/810 cases • 394 deaths • 1995–2003 • United States	• Adjusted for multiple variables • Smoking status: – Never smoker: 1.00 (referent) – Former smoker: 0.90 (0.87–0.93) – Current smoker: 0.85 (0.80–0.90) – p trend <0.001 • Number of cigarettes/day: – Never smoker: 1.00 (referent) – 1–10: 0.93 (0.89–0.98) – 11–20: 0.90 (0.87–0.94) – 21–30: 0.88 (0.84–0.93) – 31–40: 0.86 (0.81–0.91) – 41–60: 0.87 (0.82–0.94) – >60: 0.79 (0.68–0.89) – p trend <0.001 • Dose by smoking status: – Never smoker: 1.00 (referent) – Former smoker, ≤1 pack/day: 0.92 (0.88–0.95) – Former smoker, >1 pack/day: 0.88 (0.85–0.92) – Current smoker, ≤1 pack/day: 0.91 (0.84–0.97) – Current smoker, >1 pack/day: 0.75 (0.69–0.83) – p trend <0.001	• Adjusted for multiple variables • Smoking status: – Never smoker: 1.00 (referent) – Former smoker:1.03 (0.83–1.27) – Current smoker: 1.69 (1.25–2.27) – p trend = 0.005 • Number of cigarettes/day: – Never smoker: 1.00 (referent) – 1–10: 1.07 (0.80–1.45) – 11–20: 1.11 (0.86–1.44) – 21–30: 1.10 (0.82–1.47) – 31–40: 1.31 (0.96–1.79) – 41–60: 0.96 (0.64–1.44) – >60: 1.09 (0.57–2.09) – p trend = 0.40 • Dose by smoking status: – Never smoker: 1.00 (referent) – Former smoker, ≤1 pack/day: 0.97 (0.76–1.24) – Former smoker, >1 pack/day: 1.09 (0.85–1.39) – Current smoker, ≤1 pack/day: 1.79 (1.27–2.52) – Current smoker, >1 pack/day: 1.54 (1.01–2.34) – p trend = 0.02

Table 6.8*S* Continued

Study	Design/population	Findings by measure of smoking	
		Incidence: RR (95% CI)	**Mortality: RR (95% CI)**
Weinmann et al. 2010	• Prostate Cancer Sceening and Mortality Study • Nested case-control • Men who were members of one of several health plans • 768 deaths • 1997–2001 • United States	NR	• Adjusted for age, race, health plan, and reference date • Smoking status: – Never: 1.0 (referent) – Former: 1.0 (0.81–1.3) – Current: 1.5 (1.1–2.0) • History of tobacco use (any type) by smoking status: – Never smoker: 1.0 (referent) – Former smoker: 1.1 (0.89–1.4) – Current smoker: 1.7 (1.2–2.3)

Note: **CI** = confidence interval; **CPS** = Cancer Prevention Study; **EPESE** = Established Populations for Epidemiologic Studies of the Elderly; **g** = grams; **NIH** = National Institutes of Health; **NR** = not reported; **RR** = relative risk.

[a]Excluded two prospective studies that did not report on rates, risks, or RRs (odds ratio): Heikkilä and colleagues (1999) and Eichholzer and colleagues (1999).

[b]Update of Hirayama (1979).

[c]Update of Dorn (1959), Kahn (1966), and Rogot and Murray (1980), and same data as in McLaughlin and colleagues (1995).

[d]Update of Parker and colleagues (1999).

[e]Update of Doll and Hill (1966), Doll and Peto (1976), and Doll and colleagues (1994).

[f]Update of Giovannucci and colleagues (1999).

Table 6.9*S* **Epidemiologic cross-sectional studies on the association between cigarette smoking and stage and histologic grade at diagnosis of prostate cancer**

Study	Design/population	Findings by measure of smoking: OR (95% CI)
Hussain et al. 1992	• Cases treated with external beam radiation and surgery at 1 hospital • 670 cases • Dates of diagnoses: 1980–1990	• Disease stage among nonsmokers:[a] – Stage A: 4.4% – Stage B: 35.6% – Stage C: 6.7% – Stage D: 53.3% • Disease stage among smokers:[a] – Stage A: 4.4% – Stage B: 17.4% – Stage C: 9.9% – Stage D: 68.3% • Histologic grade among nonsmokers:[b] – Well differentiated: 37.1% – Moderately differentiated : 45.2% – Poorly differentiated: 17.7% • Histologic grade among smokers:[b] – Well differentiated: 15.0% – Moderately differentiated: 27.1% – Poorly differentiated: 57.9%
Daniell 1995	• Cases seen at 1 community hospital • 359 cases • Dates of diagnoses: 1983–1990	• Disease Stage D vs. nonstage A, by smoking status: – Nonsmoker: 1.0 (referent) – Smoker: 2.1 (1.3–4.3)[c]
Kobrinsky et al. 2003	• Cases recorded in a regional cancer registry • 2,311 cases • Dates of diagnoses: 1986–2001	• Metastatic (SEER cancer stage 7) by smoking status: – Never smoker: 1.00 (referent) – Former smoker: 0.94 (0.72–1.21) – Current smoker: 1.53 (1.17–2.02) • Regional (SEER cancer stages 3, 4, 5) by smoking status: – Never smoker: 1.00 (referent) – Former smoker: 1.01 (0.63–1.63) – Current smoker: 1.83 (1.09–3.06)

Table 6.9*S* Continued

Study	Design/population	Findings by measure of smoking: OR (95% CI)
Roberts et al. 2003	• Clinically localized cases treated with surgery by 1 surgeon • Diagnosed between 1992–1999 • 352 cases	• Gleason score ≥7 vs. <7, by smoking status: – Never smoker: 1.00 (referent) – Former smoker: 0.72 (0.44–1.19) – Current smoker: 1.76 (0.66–4.72) • Extraprostatic disease vs. not, by smoking status: – Never smoker: 1.00 (referent) – Former smoker: 1.49 (0.92–2.42) – Current smoker: 3.85 (1.44–10.33) • Gleason score ≥7 or extraprostatic vs. not, by smoking status: – Never smoker: 1.00 (referent) – Former smoker: 1.47 (0.84–2.56) – Current smoker: 3.17 (1.13–8.85) • Gleason score ≥7 vs. <7, by pack-years of smoking: – Never smoker: 1.00 (referent) – ≤10: 0.57 (0.31–1.06) – >10–20: 1.03 (0.45–2.38) – >20–30: 0.68 (0.26–1.76) – >30–40: 1.76 (0.52–5.97) – >40: 2.01 (0.65–6.24) – p trend = 0.16 • Extraprostatic disease vs. not, by pack-years of smoking: – Never smoker: 1.00 (referent) – ≤10: 1.23 (0.69–2.18) – >10–20: 2.29 (1.03–5.10) – >20–30: 1.45 (0.60–3.51) – >30–40: 3.01 (0.90–10.03) – >40: 3.66 (1.18–22.29) – p trend = 0.005 • Gleason score ≥7 or extraprostatic vs. not, by pack-years of smoking: – Never smoker: 1.00 (referent) – ≤10: 1.05 (0.53–2.07) – >10–20: 2.03 (0.84–4.91) – >20–30: 1.82 (0.71–4.66) – >30–40: 3.84 (1.07–13.73) – >40: 3.37 (1.04–10.98) – p trend = 0.003

Table 6.9*S* Continued

Study	Design/population	Findings by measure of smoking: OR (95% CI)
Moreira et al. 2010	• Localized cases treated with surgery • 1,267 cases • Dates of diagnoses: 1998–2008	• Gleason score among current smokers at prostatectomy:[d] – 2–6 : 35% – 3+4: 44% – ≥4+3: 21% • Gleason score among nonsmokers at prostatectomy:[d] – 2–6: 41% – 3+4: 39% – ≥4+3: 20% • Extraprostatic extension by smoking status at prostatectomy: – Smoker: 25% – Nonsmoker: 18% – p = 0.003 • Invasion of seminal vesicles by smoking status at prostatectomy: – Smoker: 10% – Nonsmoker: 6% – p = 0.03 • Lymph-node positive by smoking status at prostatectomy: – Smoker: 2% – Nonsmoker: 2% – p = 0.52 (out of those with known lymph node status)

Note: **CI** = confidence interval; **OR** = odds ratio; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **SEER** = Surveillance, Epidemiology, and End Results Program. Gleason sum is the sum of the 2 scores given by the pathologist on examination of the prostatic tissue.
[a]Distribution of stage by smoking status; p = 0.01.
[b]Distribution of grade by smoking status; p <0.00005.
[c]Results adjusted for multiple variables, including grade.
[d]Distribution by smoking status: p = 0.15.

Table 6.10*S* Cohort studies on the association between cigarette smoking and risk of prostate cancer progression, case fatality, and all-cause mortality in men with prostate cancer

Study	Design/population	Number of progressors, prostate cancer deaths, or deaths from all causes	Findings by smoking status: RR (95% CI)[a]		
			Progression	Case fatality (prostate cancer-specific mortality)	All-cause mortality (unless otherwise noted)
Daniell 1995	• Retrospective study • 359 cases; 235 nonstage A, of which 46 were stage D2 • Dates of diagnoses: 1983–1990	57 prostate cancer deaths (30 were among men with stage D2)	NR	• 5-year cumulative incidence in nonstage A cases: – Nonsmoker: 17% – Smoker: 39% – p <0.001 • 5-year cumulative incidence in stage D2 cases: – Nonsmoker: 63% – Smoker: 88% – p <0.05	NR
Yu et al. 1997[b]	• Retrospective study • 1,820 cases: 1,079 local; 463 regional; 207 distant: 1,695 Whites; 94 Blacks • Dates of diagnoses: 1990–1995	Deaths from all causes: NR	NR	NR	• Nondrinkers: – Never smokers: 1.00 (referent) – Ever smokers: 1.98 (1.1–3.7) • White: – Never smokers: 1.00 (referent) – Ever smokers: 1.53 (1.0–2.2) • Black: – Never smokers: 1.00 (referent) – Ever smokers: 0.89 (0.1–6.7) • Local: – Never smokers: 1.00 (referent) – Ever smokers: 0.77 (0.4–1.5) • Regional: – Never smokers: 1.00 (referent) – Ever smokers: 3.07 (1.2–7.9) • Distant: – Never smokers: 1.00 (referent) – Ever smokers: 1.29 (0.7–2.3) • Pack-years of smoking: – Never smokers: 1.00 (referent) – 1–59: 1.42 – ≥60: 2.65 – p trend = 0.00

Table 6.10*S* Continued

Study	Design/population	Number of progressors, prostate cancer deaths, or deaths from all causes	Findings by smoking status: RR (95% CI)[a]		
			Progression	Case fatality (prostate cancer-specific mortality)	All-cause mortality (unless otherwise noted)
Merrick et al. 2004[c]	• Retrospective study • 582 localized cases treated with brachytherapy • Dates of diagnoses: 1995–2000 • Follow-up (median): 54.5 months	27 cases (biochemical progression or death from prostate cancer) 38 deaths (6 due to prostate cancer)	• Smoking status: – Never: 1.00 (referent) – Former: 1.31 (p = 0.586) – Current: 2.69 (p = 0.067)[d]	NR	NR
Oefelein and Resnick 2004[e]	• Retrospective study • 222 advanced-stage cases treated with hormone deprivation therapy • Dates of diagnoses: 1987–2003 • Follow-up (median): 141 months	133 Progressors (development of hormone-refractory prostate cancer) 77 Deaths (61 prostate cancer)	• Per pack-year of smoking: 3.0; p trend = 0.003 • Recent tobacco use: 2.7; p = 0.007	NR	• Per pack-year of smoking: 5.3; p trend = 0.0001 • Recent tobacco use: NR; p = 0.06
Pickles et al. 2004[c]	• Retrospective study • 601 localized cases treated with external beam radiation • Dates of diagnoses: 1994–1997 • Follow-up (median): 59 months	Progressors: NR Deaths: N	• Smoking status [OR (95% CI)]: – Never: 1.00 (referent) – Current: 1.68 (1.11–2.56) • Current vs. former: NR – p = 0.3	• 6-year cumulative incidence of death: – Never smokers: 3.7% – Current smokers: 10% – p = 0.08	• 6-year cumulative incidence of death: – Never smokers: 10.8% – Current smokers: 25.7% – p = 0.009
Jager et al. 2007	• Retrospective study • 214 cases across stages: local: ~50%; regional: ~40%; distant: ~10% • Dates of diagnoses: 1991–2001 • Follow-up (median): 50 months	47 prostate cancer deaths	NR	• 10-year survival rate: – Nonsmoker: 87% – Current smoker: 58% – p <0.02 • Smoking status: – Nonsmoker: 1.0 (referent) • Current smoker: 3	• 90-month survival rate: – Nonsmoker: 93% – Current smoker: 79%

Table 6.10*S* Continued

Study	Design/population	Number of progressors, prostate cancer deaths, or deaths from all causes	Findings by smoking status: RR (95% CI)[a]		
			Progression	Case fatality (prostate cancer-specific mortality)	All-cause mortality (unless otherwise noted)
Pantarotto et al. 2007[c]	• Retrospective study • 416 cases of clinical stage T1–T4 N0M0 (nodes 0, metastases 0) prostate cancer treated with external beam radiotherapy • Dates of diagnoses: 1990–1999 • Follow-up (median): 70.3 months	Cases (calculated from Table 6.8*S*): 97 local recurrence; 185 biochemical failure; 64 distant failure and 58 prostate cancer-specific deaths	• Biochemical failure: – Never smoker: 1.00 (referent) – Former smoker: 1.14 (p = 0.51) – Current smoker: 1.49 (0.88–2.40) – p = 0.12 • Local recurrence: – Never smoker: 1.00 (referent) – Former smoker: 1.10 (p = 0.71) – Current smoker: 0.96 – p = 0.91 • Distant failure: – Never smoker: 1.00 (referent) – Former smoker: 2.90 (1.09–7.67; p = 0.03) – Currrent smoker: 5.24 (1.75–15.7) – p = 0.003	• Never smoker: 1.00 (referent) • Former smoker: 1.78; p = 0.18 • Current smoker: 1.39; p = 0.55	• Never smoker: 1.00 (referent) • Former smoker: 1.51; p = 0.11 • Current smoker: 1.72 (0.94–3.15); p = 0.08

Table 6.10*S* Continued

Study	Design/population	Number of progressors, prostate cancer deaths, or deaths from all causes	Findings by smoking status: RR (95% CI)[a]		
			Progression	Case fatality (prostate cancer-specific mortality)	All-cause mortality (unless otherwise noted)
Gong et al. 2008[c]	• Prospective study • 752 cases across stages: local: 552; regional: 175; distant: 25 • Dates of diagnoses: 1993–1996 • Follow-up (median): 11.5 years	135 all-cause deaths (54 prostate cancer)	NR	• Smoking status: – Never smoker: 1.00 (referent) – Quit ≥10 years ago: 0.45 (0.19–1.05) – Quit <10 years ago: 1.48 (0.50–4.37) – Current smoker: 2.66 (1.10–6.43) • Pack-years of smoking within 10 years of diagnosis: – 0: 1.00 (referent) – 1–9: 2.70 (1.10–6.64 – 10–14: 2.95 (1.08–8.07) – ≥15: 5.82 (1.96–17.26) – p trend = 0.0002	• Death from all other causes by smoking status: – Never smoker: 1.00 (referent) – Quit ≥10 years ago: 1.29 (0.70–2.38) – Quit <10 years ago: 1.69 (0.81–3.56) – Current smoker: 2.42 (1.24–4.72) • Pack-years of smoking within 10 years of diagnosis: – 0: 1.00 (referent) – 1–9: 1.32 (0.66–2.63) – 10–14: 2.29 (1.26–4.16) – ≥15: 1.87 (0.81–4.33) – p trend = 0.01
Moreira et al. 2010[f]	• Retrospective study • 1,267 cases across stages: 254 extracapsular extension; 92 invasion of seminal vesicles; 17 lymph node positive (the 3 categories are not mutually exclusive) • Dates of diagnoses: 1998–2008 • Follow-up (median): 3.1 years	Biochemical recurrence: NR	• Smoking status at prostatectomy: – Nonsmoker: 1.00 (referent) – Smoker: 0.91 (0.70–1.18)	NR	NR

Note: **CI** = confidence interval; **NR** = not reported; **OR** = odds ratio; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **RR** = relative risk.
[a]Results are reported by relative risk unless noted otherwise.
[b]Results are adjusted for multiple variables, including grade.
[c]Results are adjusted for multiple variables, including stage and grade.
[d]Table 3*S* in the report by Merrick and colleagues (2004) appears to have erroneous labels for the comparisons made.
[e]Results are adjusted for multiple variables, including stage.
[f]Results are adjusted for multiple variables, including pathologic stage and grade.

Table 6.11*S* Reports on levels of endogenous hormones and smoking in premenopausal women (n = 22)

Study	Population	Sample/period	Definition of smoking (number of subjects)	Findings among smokers: Estimate of effect (95% CI or p value)	Comments
MacMahon et al. 1982	• 106 White women • 25–49 years of age	Overnight urine specimen FP (days 10–11) LP (days 21–22)	Nonsmoker (n = 44): ≤100 cigarettes smoked during lifetime Former smoker (n = 23) Current smoker (n = 39)	• Levels of E1, E2, and E3 in smokers were similar to nonsmokers during FP • Total levels of E1, E2, and E3 decreased 29% (10–43) during LP • Little difference in former smokers	Stronger effects during ovulatory cycles; adjusted for age
Michnovicz et al. 1986	• 27 nonobese women with normal-length menstrual cycle • Age (mean): approximately 30 years	Blood and urine samples over 48 hours after administration of radiolabeled E2 FP (days 1–10), in morning 5 samples during LP (days 19–25)	Smoker (n = 14): ≥15 cigarettes/day	• 2-hydroxylation increased 50% ($p < 0.001$) • Urine E3 and E3/E1 decreased 40% ($p < 0.01$)	No difference during FP vs. LP; age and BMI were similar in nonsmokers and smokers, so no adjustments were made
Ernster et al. 1987	• 562 women	Breast fluid by nipple aspiration and blood sample	Current, former, and never smoker	• E2 hydroxylation increased 50% ($p < 0.001$) • 2OHE1 increased ($p < 0.02$). E3 decreased ($p < 0.05$) • No difference in 16αOHE1, E2, E1, and total estrogens	No adjustments were made for BMI, age, etc.
Michnovicz et al. 1988	• 29 nonobese women • 21–44 years of age	Urine samples over 48 hours after administration of radiolabeled E2 Mid-FP (days 1–12)	Smoker (n = 15): 15–30 cigarettes/day Cotinine not detected in nonsmokers	• E1 increased per pack-year of smoking ($p = 0.05$)	Adjusted for previous thyroid disease
Longcope and Johnston 1988	• 88 women (47 premenopausal) • Age (mean): 50 years	Radiolabeled steroid infusion Blood and urine samples at baseline	Smoker (n = 23): 10 cigarettes/day for ≥10 years	• Metabolic clearance rates decreased for testosterone, androstenedione, and E1 were not significant in premenopausal women ($p < 0.05$) • Increased plasma androstenedione ($p < 0.02$) • No difference in E1 and E2 • No difference in SHBG, steroid production rates, and aromatization of androgens	No difference after adjusting for weight; no interaction between menopausal status and smoking for any of variables

Table 6.11*S* Continued

Study	Population	Sample/period	Definition of smoking (number of subjects)	Findings among smokers: Estimate of effect (95% CI or p value)	Comments
Zumoff et al. 1990	• 16 volunteers with normal ovulatory and luteal function • 25–35 years of age	Blood samples on 17 days over cycle, and more frequently around mid-cycle (ovulation)	Smoker (n = 8): ≥20 cig/ per day for ≥3 years	• Progesterone increased 37% during FP but not LP (p <0.0001) • E2 increased 23% during early FP (p <0.001) and 12.5% (p = approximately 0.05) through FP, but results were not significant • Slightly decreased mean LH	Smoking may stimulate adrenocortical hormone secretion
Key et al. 1991	• Women recruited from Guernsey Breast Cancer Study with menstrual cycle lengths of 21–35 days • Serum E2 and progesterone (n = 147) • Serum DHEA-S (n = 411) • Urinary steroids (n = 105) • ≥35 years of age	24-hour urine sample and 1 blood sample	Current smoker: 1–10, 11–20, and ≥21 cigarettes/ day E2 and progesterone (n = 69) DHEA-S (n = 97) Urinary steroids (n = 20)	• No difference in serum E2, progesterone, or DHEA-S • No difference in 6 urinary steroids (primarily androgens) • Overall effect was not significant	Adjusted serum values for cycle day, age, and BMI; adjusted urine values for age, BMI, and parity
Berta et al. 1992	• 684 nonobese fertile women • 25–52 years of age	24-hour urine sample and 3 blood samples on days 21–24 of LP	Smoker (n = 237): >10 cig/ per day for ≥5 years	• Plasma progesterone decreased 15% (p <0.05) • Plasma prolactin decreased 20% (p <0.002) • No difference in E1 and E2	Age did not affect results
Daniel et al. 1992	• 52 women • 20–35 years of age	Blood collected after overnight fast	Current smoker (n = 25): 16.9 (mean) cigarettes/day Former smoker (n = 11)	• No difference in cortisol, E2, and testosterone • Levels of cortisol, E2, and testosterone were not significant in adjusted model • SHBG increased (p <0.006)	Age, height, and weight were similar in both groups; data were adjusted for sum of 8 skinfold thicknesses

Table 6.11*S* Continued

Study	Population	Sample/period	Definition of smoking (number of subjects)	Findings among smokers: Estimate of effect (95% CI or p value)	Comments
Thomas et al. 1993	• 46 fertile, premenopausal women	Blood, saliva, and urine samples collected on days 8, 9–11, 12, 13–17, and 18 of menses	Smoker (n = 25): >5 cigarettes/day for ≥1 year	• No difference in plasma E2 during FP • No difference in salivary progesterone during LP • No difference in plasma testosterone, androstenedione, SHBG, and DHEA-S • No difference in urinary E1, E2, and E3 • Overall effect was not *s*ignificant	Data suggest that antiestrogenic effect does not work through changes in estrogen metabolism or pituitary/follicular endocrine function
Cramer et al. 1994	• 224 women, some with a family history of ovarian cancer • 26–50 years of age	1 blood sample during early FP (days 1–3)	Current smoker (n = 42)	• Mean FSH increased 14–21% (p = 0.03) in current and former smokers (>10 pack-years)	Effect of smoking was still significant after adjusting for age
Cooper et al. 1995	• 290 women • 38–49 years of age	1 blood sample during early FP (days 2–4)	Current smoker (n = 31): smoked in past 2 years	• Mean FSH increased 66% (28–116%) in current smokers • Mean FSH increased 57% at <10 cigarettes/day • Mean FSH increased 76% at 10–20 cigarettes/day • Mean FSH increased 39% (4–86) in those exposed to SHS • No difference in FSH in former smokers or prenatal exposure	None of the factors examined were confounders; significant interaction with age; effects investigated during menopausal transition period
Key et al. 1996	• Women recruited from Guernsey Breast Cancer Study (n = 167) • ≥34 years of age	24-hour urine sample collected 3–11 days after onset of menstruation (FP) or 3–11 days before (LP)	Current smoker (n = 53)	• E1 decreased 0–16% • E2 decreased 4–15% • E3 decreased 30% during early FP • E3 decreased 5–22% later in cycle	Findings were not significant after adjusting for time of cycle, age, and BMI
Westhoff et al. 1996	• 175 parous women with normal length menstrual cycles • 21–36 years of age	Daily first-morning urine sample on day 10 of menses Blood sample three times during LP	Current smoker (n = 48)	• No difference in mean LP progesterone in blood or urine • E2 in urine decreased 21% (p = 0.04) during LP	Four anovulatory women were excluded; adjusted for creatine (decreased differences in E2); some dose-response effects

Table 6.11*S* Continued

Study	Population	Sample/period	Definition of smoking (number of subjects)	Findings among smokers: Estimate of effect (95% CI or p value)	Comments
Backer et al. 1999	• 3,114 women from the National Health and Nutrition Examination Survey (United States national sample) • 36–60 years of age	1 convenient blood sample	Smoker: smoked during 5 days before examination	• Increased FSH ($p < 0.001$)	Cycle timing was unknown, but tried to exclude samples obtained close to time of ovulation on basis of LH-to-FSH ratio
Lucero et al. 2001	• 498 women, not in a depressive state, from Harvard Study of Moods and Cycles • 36–44 years of age	1 blood sample during early FP (days 1–5)	Current smoker (n = 52) Former smoker (n = 72)	• FSH increased 12% ($p < 0.05$) • E2 increased 8% ($p < 0.05$) • No difference in LH or SHBG	E2 was not significant in adjusted model; FSH values were not adjusted; findings for current smokers adjusted for age, BMI, calories, use of alcohol and caffeine, cholesterol, and cycle day; no difference between current smokers and former smokers, no dose-response effect
Sowers et al. 2001	• 611 women from the Michigan Bone Health & Metabolism Study • 25–50 years of age	Blood sample drawn once per year after an 8-hour fast on days 3–7 of FP	Current, former, and never smoker	• Increased testosterone levels in current and former smokers ($p < 0.0001$)	Adjusted for factors, including BMI
Verkasalo et al. 2001	• 636 women who reported having ≥10 menstrual cycles during previous 12 months • 20–44 years of age	Blood sample	Current smoker (n = 49) Former smoker (n = 171) Never smoker (n = 416)	• Increased E2 in smokers compared with former and never smokers ($p = 0.003$) • No difference in SHBG, FSH, progesterone, and LH	Adjusted for age, BMI, physical activity, use of alcohol, family history of breast cancer, age at menarche, etc.
Jernström et al. 2003	• 513 nulliparous women • 17–35 years of age	Morning blood sample on random day (timing calculated)	Current smoker (yes/no)	• 2OHE/16α-OHE increased slightly (19%) before adjustment ($p = 0.06$) but not after adjustment ($p = 0.76$) among women not using oral contraceptives • No effect on either metabolite alone	Adjusted for age, race, and cycle day

Table 6.11*S* Continued

Study	Population	Sample/period	Definition of smoking (number of subjects)	Findings among smokers: Estimate of effect (95% CI or p value)	Comments
Windham et al. 2005	• 403 women in reproductive years from the Kaiser Permanente health maintenance organization	Daily urine sample collected through 2–7 cycles Adjustment of hormone values for creatinine	Smoker: cigarettes/day, from daily diary and averaged over 100–150 cycles	• Mean FSH increased 20–35% and was significant on some days • Mean FSH increased at >10 cigarettes/day • During early FP, E1 conjugates (estrone sulfate and estrone glucuronide) increased 25% and progesterone metabolites increased 35% ($p < 0.05$) at >10 cigarettes/day • During LP, progesterone decreased 25% ($p = 0.06$) at >20 cigarettes/day	Adjusted for age, race, history of pregnancy, BMI, and use of alcohol and caffeine; some dose-response effects
Gallicchio et al. 2006	• 353 pre- and perimenopausal women • 45–54 years of age	Blood sample collected in morning	Current smoker (n = 25) Former smoker (n = 235)	• No difference in E2 and E1 • Overall effect was not significant	Findings were based on univariate analyses only
Cochran et al. 2008	• 628 pre- and perimenopausal women • 45–54 years of age	Blood sample collected in morning	Current smoker (n = 58) Former smoker (n = 242)	• Current smokers had increased levels of androstenedione ($p = 0.01$) and increased androgen/estrogen ratios ($p = 0.04$) • Former and current smokers had decreased levels of progesterone ($p = 0.04$)	Adjusted for age, race, BMI, current use of alcohol, and number of days since last menstrual period

Note: **2OHE** = 2-hydroxyestrone; **16α-OHE** = 16α-hydroxyestrone; **BMI** = body mass index; **CI** = confidence interval; **DHEAS** = dehydroepiandrosterone sulfate; **E1** = estrone; **E2** = estradiol; **E3** = estriol; **FP** = follicular phase; **FSH** = follicle-stimulating hormone; **LH** = lutenizing hormone; **LP** = luteal phase; **OHE** = hydroxyestrone; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **SHBG** = sex hormone binding globulin; **SHS** = secondhand smoke.

Table 6.12*S* Reports on levels of endogenous hormones and smoking in postmenopausal women (n = 17)

Study	Study population	Sample/period	Definition of smoking (number of subjects)	Findings in smokers: Estimate of effect (95% CI or p value)	Comments
Ernster et al. 1987	• 289 women	Breast fluid by nipple aspiration and blood sample	Current, former, and never smoker	• No difference in E1, E2, and SHBG in breast fluid or serum • Overall effect was not significant	Adjusted for menopausal estrogen use and thyroid hormone use
Friedman et al. 1987	• 25 women, after natural menopause and between 1.5–6 years before the study	Morning blood sample after 12-hour fast	Smoker (n = 9) for >20 years	• Smokers had increased levels of cortisol ($p < 0.001$), progesterone ($p < 0.05$), 17-hydroxyprogesterone ($p < 0.0005$), androstenedione ($p < 0.05$), and testosterone ($p < 0.05$) • No difference in E1, E2, dihydrotestosterone, and dehyroepiandrosterone sulfate	No difference in BMI or age at menopause
Trichopoulous et al. 1987	• 220 women, ≥1 year after menopause • 54–66 years of age	Overnight urine sample	Current smoker (n = 97)	• Smokers had increased levels of DHEAS ($p < 0.001$) and androstenedione ($p = 0.003$) • No difference in E1, E2, testosterone, and SHBG	Dose-response trend was observed; adjusted for age and BMI
Khaw et al. 1988	• 233 White women • 60–79 years of age	Plasma sample	Current smoker (n = 46)	• Decreased metabolic clearance rates for testosterone, androstenedione, and E1 were not significant in premenopausal women ($p < 0.05$) • Increased plasma androstenedione ($p < 0.02$) • No difference in E1 and E2 • No difference in SHBG, steroid production rates, and aromatization of androgens	No difference after adjusting for weight; no interaction between menopausal status and smoking for any of the variables
Longcope and Johnston 1988	• 88 women (47 premenopausal) • Age (mean): 50 years	Radiolabeled steroid infusion Blood and urine samples at baseline	Smoker (n = 23): 10 cigarettes/day for ≥10 years	• Metabolic clearance rates decreased for testosterone, androstenedione, and E1 were not significant in premenopausal women ($p < 0.05$) • Increased plasma androstenedione ($p < 0.02$) • No difference in E1 and E2 • No difference in SHBG, steroid production rates, and aromatization of androgens	No difference after adjusting for weight; no interaction between menopausal status and smoking for any of variables

Table 6.12*S* Continued

Study	Study population	Sample/period	Definition of smoking (number of subjects)	Findings in smokers: Estimate of effect (95% CI or p value)	Comments
Cauley et al. 1989	• 176 White women	Fasting blood sample	Current smoker (n = 26)	• Smokers had increased levels of androstenedione (p <0.01) • No difference in E1, E2, and testosterone	Adjusted for BMI, use of alcohol (ounces/day), age, and physical activity
Slemenda et al. 1989	• 84 peri- and postmenopausal women	Blood drawn every 4 months	<20 pack-years (n = 8) >20 pack-years (n = 13)	• No difference in serum E1, E2, testosterone, or androstenedione • Overall effect was not significant	Hormone levels based on the average of approximately 12 measurements/subject
Schlemmer et al. 1990	• 267 women, after natural menopause and between 6 months and 1 year before the study • 45–54 years of age	Blood sample after overnight fast and tobacco abstinence	Smoker (n = 146): ≥3 cigarettes/day during 6 months before the study	• Smokers had a 22% increase in androstenedione (p <0.001) and increased levels of LH (p = 0.06) • No difference in E1, E2, and FSH	No dose-response effect was observed; body weight and age at menopause differed by smoking status
Key et al. 1991	• Women recruited from the Guernsey Breast Cancer Study with menstrual cycle lengths of 21–35 days • ≥35 years of age	24-hour urine sample and 1 blood sample	Current smoker: 1–10, 11–20, and ≥21 cigarettes/day E2 and progesterone (n = 69) DHEA-S (n = 97) Urinary steroids (n = 20)	• No difference in serum E2, progesterone, or DHEA-S • No difference in 6 urinary steroids (primarily androgens) • Overall effect was not significant	Adjusted serum values for cycle day, age, and BMI; adjusted urine values for age, BMI, and parity
Cassidenti et al. 1992	• 38 postmenopausal women	Blood collected in morning before first cigarette and 3 hours later (after 5 cigarettes)	Current smoker (n = 21)	• After 5 cigarettes, smokers had a 52% increase of baseline androstenedione (p = 0.011) • No significant increase of DHEA-S and cortisol in smokers • No difference in E1, E2, or E3	Adjusted for age, age at menopause, weight, height, and use of alcohol
Baron et al. 1995	• 22 women • ≥55 years of age	Blood samples every hour for 8 hours before/after cigarette/sham and before/after corticotrophin stimulation test	Smoker (n = 11): 0.5–1.5 packs of filtered cigarettes/day	• Smokers had increased basal levels of androstenedione (p <0.05) and DHEAS (p <0.05) • Smokers had elevated average levels of cortisol (p = 0.03) and androstenedione (p <0.05) • No difference in response to corticotropin stimulation	No difference after adjusting for age, BMI, and use of alcohol

Table 6.12*S* Continued

Study	Study population	Sample/period	Definition of smoking (number of subjects)	Findings in smokers: Estimate of effect (95% CI or p value)	Comments
Newcomb et al. 1995	• 253 women from the Beaver Dam Eye Study	Serum sample	20% current smokers	• No difference in E1, DHEA-S, SHBG, and testosterone • Overall effect was not significant	Adjusted for age, BMI, and years since menopause
Key et al. 1996	• 200 women recruited from the Guernsey Breast Cancer Study	24-hour urine sample	Current smoker (n = 54)	• No difference in E1 and E2 • Smokers had a 19% decrease in levels of E3 (34–1)	Not significant after adjusting for age and BMI
Law et al. 1997	• 194 White postmenopausal women • 35–64 years of age	Serum sample	Current smoker (n = 40) Former smoker (n = 44)	• No difference in E1, E2, cortisol, FSH, LH, SHBG, androstenedione, and prolactin • Overall effect was not significant	No difference observed in former smokers; no difference after adjusting for such factors as exercise, OC, corticosteroids, age at menarche and menopause, etc.
Verkasalo et al. 2001	• 456 postmenopausal women with no menstrual cycle during previous 12 months • ≥55 years of age	Blood sample	Current smoker (n = 15) Former smoker (n = 42) Never smoker (n = 299)	• No difference in E2 and SHBG • Overall effect was not significant	Adjusted for BMI, use of alcohol, age at menarche, physical activity, etc.
Manjer et al. 2005	• 336 women from the Malmo Diet and Cancer Study and The Northern Sweden Health and Disease Study	Blood sample	Current smoker (n = 91) Former smoker (n = 82)	• Current smokers had high levels of testosterone: AOR = 1.85 (1.06–3.23) • No difference in levels of androstenedione and DHEAS	Adjusted for age, education level, age at menarche and at menopause, OC, use of hormone replacement therapy, etc.; no dose-response effect observed
Danforth et al. 2010	• 646 postmenopausal women from the Nurses' Health Study	Blood sample	Current smoker (n = 83) Former smoker (n = 260)	• Those who smoked >25 cigarettes/day had a 35% increase in androstenedione (p = 0.03), a 44% increase in testosterone (p = 0.01), and elevated levels of DHEA-S (p = 0.05) • No difference in DHEA and testosterone	No dose-response observed; adjusted for such factors as BMI, use of alcohol, family history of breast or ovarian cancer, etc.

Note: **AOR** = adjusted odds ratio; **BMI** = body mass index; **CI** = confidence interval; **DHEA-S** = dehydroepiandrosterone sulfate; **E1** = estrone; **E2** = estradiol; **E3** = estriol; **FSH** = follicle-stimulating hormone; **LH** = lutenizing hormone; **OC** = oral contraceptive; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **SHBG** = sex hormone binding globulin.

Table 6.14*S* Cohort study reports of the association between active cigarette smoking and risk of breast cancer, based on studies published before 2012 (n = 15)

Study	Design/population	Number of breast cancer events	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking: RR (95% CI)	Confounders
Manjer et al. 2000b[a]	• Malmö Department of Preventative Medicine • 10,902 women enrolled from 1974–1992 to evaluate risk factors associated with CVD • Average follow-up: 13.6 years • Age (mean): 49.7 years • Sweden	416 incident cases (in situ, invasive)	• Self-administered questionnaire at enrollment • Data collected for smoking status (never, former, current), amount of daily consumption (current), and time since cessation (former) • Subgroups stratified by menopausal status	• Significantly increased risk for breast cancer among former smokers, primarily due to association in premenopausal women	**Status:** Never: 1.00 Former: 1.31 (1.02–1.69) Current: 1.08 (0.86–1.35) **Status: Premenopausal** Never: 1.00 Former: 1.57 (1.07–2.30) Current: 1.19 (0.85–1.68) **Status: Postmenopausal** Never: 1.00 Former: 1.15 (0.82–1.62) Current: 1.00 (0.74–1.35)	Controlled for age at baseline, height, BMI, parity, OC use, HRT, alcohol use, and menstrual status
Manjer et al. 2001[a]	• Malmö Department of Preventative Medicine • 10,902 women enrolled from 1974–1992 to evaluate risk factors associated with CVD • Average follow-up: 12.4 years • Age (mean): 49.7 years Sweden	268 incident cases (invasive)	• Self-administered questionnaire at enrollment • Data collected for smoking status (never, former, current), amount of daily consumption (current), and time since cessation (former) • Subgroups evaluated and stratified by ER/PR status and histopathology type	• Trend towards increased risk with cigarettes/day • Increased risk of ER– tumors for current and former smokers • No association with histopathology type or tumor differentiation	**Status:** Never: 1.00 Former: 1.34 (0.99–1.81) Current: 1.10 (0.84–1.44) ≤19 cig/day: 1.05 (0.78–1.42) ≥20 cig/day: 1.17 (0.78–1.76)	Controlled for age at baseline, height, BMI, age at menarche, menopause status, parity, OC use, HRT, education, marital status, and alcohol use

Table 6.14*S* Continued

Study	Design/population	Number of breast cancer events	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking: RR (95% CI)	Confounders
Egan et al. 2002[a]	• Nurses' Health Study-I • 121,700 nurses enrolled in 1976 to evaluate risk factors for breast cancer and CVD • 78,206 women included in the analysis • Average follow-up: 14 years • 30–55 years of age • United States	3,140 incident cases (invasive)	• Self-administered questionnaire at enrollment; biennial questionnaires until 1994 • Data collected for smoking status (never, former, and current), cigarettes/day, duration and timing related to birth of first child • Data collected for secondhand smoke exposure (see USDHHS 2006)	• Increased risk of breast cancer in former smokers • Further increased risk when based on a no active/no passive referent group • Significant trend observed for years of smoking before first birth	**Status:** Never: 1.00 Former: 1.09 (1.00–1.18) Current: 1.04 (0.94–1.15) **Status With NA/NP:** NA/NP: 1.00 Former: 1.17 (1.01–1.34) Current: 1.15 (0.98–1.34) **Duration (Years):** Never: 1.00 <20: 1.04 (0.95–1.15) 20–29: 1.11 (1.00–1.24) 30–39: 1.08 (0.97–1.21) >40: 1.05 (0.90–1.21) p trend = 0.18 **Age at Smoking Initiation:** Never: 1.00 >22: 1.06 (0.92–1.22) 21–22: 1.04 (1.91–1.18) 19–20: 1.11 (1.00–1.13) 17–18: 1.02 (0.92–1.13) <17: 1.19 (1.03–1.37) p trend = 0.13 **Age at Smoking Initiation:** Never: 1.00 >16: 1.12 (0.96–1.31) ≤16: 1.31 (1.07–1.31) **Timing With First Pregnancy: Before (Years)** Never: 1.00 <5: 1.10 (0.96–1.26) ≥5: 1.13 (0.99–1.30) p trend = 0.03 **After (Years)** Never: 1.00 <10: 0.95 (0.81–1.12) 10–20: 0.98 (0.83–1.14) >20: 0.99 (0.86–1.13) p trend = 0.90	Controlled for age, age at menarche, age at birth of first child, history of benign disease, family history of breast cancer, menopausal status, age at menopause, weight, height, alcohol use, dietary factors, HRT

Table 6.14*S* Continued

Study	Design/population	Number of breast cancer events	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking: RR (95% CI)	Confounders
Terry et al. 2002a[a]	• Canadian National Breast Screening Study • 89,835 women enrolled from 1980–1985 into a multicenter, randomized controlled trial of mammographic screening • Average follow-up: 10.6 years • 40–59 years of age • Canada	2,552 incident cases (in situ, invasive)	• Self-administered questionnaire at enrollment • Data collected for smoking status (never, former, current), cigarettes/day, duration, and years since smoking cessation	• Risk of breast cancer was associated with current but not former smoking • Risk was significantly associated with cigarettes/day, duration, and pack-years of smoking • No association between age at smoking initiation and number of years since smoking cessation	**Status:** Never: 1.00 Former: 0.99 (0.90–1.09) Current: 1.14 (1.03–1.27) **Duration (Years):** Never: 1.00 1–9: 0.93 (0.80–1.09) 10–19: 0.97 (0.85–1.11) 20–29: 1.06 (0.94–1.19) 30–39: 1.14 (0.99–1.31) ≥40: 1.61 (1.19–2.19) p trend = 0.009 **Cigarettes/Day:** Never: 1.00 1–9: 0.97 (0.85–1.11) 10–19: 0.98 (0.86–1.11) 20–29: 1.10 (0.99–1.23) 30–39: 0.90 (0.71–1.16) ≥40: 1.34 (1.06–1.69) p trend = 0.05 **Pack-years:** Never: 1.00 1–9: 0.98 (0.87–1.10) 10–19: 0.97 (0.85–1.12) 20–29: 1.08 (0.93–1.25) 30–39: 1.21 (1.04–1.42) ≥40: 1.37 (1.15–1.62) p trend = 0.003 **Age at Smoking Initiation:** Never: 1.00 ≥20: 1.04 (0.95–1.14) 16–19: 1.05 (0.96–1.18) <16: 1.10 (0.86–1.42) p trend = 0.23	Controlled for age, treatment, study center, BMI, education, physical activity, OC use, HRT, parity, age at menarche, history of benign breast disease, breast self-exam, family history, menopausal status, alcohol use

Table 6.14*S* Continued

Study	Design/population	Number of breast cancer events	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking: RR (95% CI)	Confounders
Al-Delaimy et al. 2004	• Nurses' Health Study-II • 116,671 nurses enrolled in 1989 to evaluate risk factors for CVD and breast cancer • Average follow-up: 10 years • 25–42 years of age • United States	1,009 incident cases (invasive)	• Self-administered questionnaire at enrollment and biennial thereafter • Data collected for smoking status (never, former, current), cigarettes/day, duration, smoking before first pregnancy, and smoking before or after 20 years of age • Subgroups evaluated and stratified by ER status; vitamin A and carotenoid intake	• No overall association with smoking status or pack-years • Risk was significantly associated with duration of smoking and years of smoking before first pregnancy • Age at initiation and pack-years of smoking were associated more strongly with ER+ than ER– tumor phenotype (results not shown)	**Status:** Never: 1.00 Former: 1.18 (1.02–1.36) Current: 1.12 (0.92–1.37) **Duration (Years):** Never: 1.00 <10: 1.14 (0.85–1.52) 10–14: 1.19 (0.96–1.48) 15–19: 1.06 (0.85–1.33) ≥20: 1.21 (1.01–1.45) p trend = 0.04 **Cigarettes/Day:** Never: 1.00 1–4: 0.77 (0.44–1.33) 5–14: 1.18 (0.88–1.74) 15–24: 1.14 (0.90–1.61) ≥25: 0.98 (0.69–1.70) p trend = 0.40 **Cigarettes/Day: Former Smokers** Never: 1.00 1–4: 1.21 (0.94–1.56) 5–14: 1.32 (1.06–1.65) 15–24: 1.04 (0.82–1.33) ≥25: 1.12 (0.82–1.53) p trend = 0.60 **Pack-years:** Never: 1.00 <10: 1.16 (0.98–1.39) 10–24: 1.16 (0.97–1.38) ≥25: 1.13 (0.86–1.50) p trend = 0.20 **Age at Smoking Initiation:** Never: 1.00 ≥20: 1.18 (0.97–1.42) 15–19: 1.09 (0.93–1.29) <15: 1.29 (0.97–1.71) **Timing With First Pregnancy: Before (Years)** Never: 1.00 1–4: 1.02 (0.72–1.44) 5–9: 1.12 (0.91–1.39) 10–14: 1.19 (0.97–1.47) 15–19: 1.42 (1.10–1.83) ≥20: 1.10 (0.80–1.52) p trend = 0.01	Controlled for age, BMI, height, oral contraceptive use, parity, age at birth of first child, age at menarche, family history, benign breast disease, alcohol use, and menopausal status

Table 6.14*S* Continued

Study	Design/population	Number of breast cancer events	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking: RR (95% CI)	Confounders
Lawlor et al. 2004	• British Women's Heart and Health Study • 4,286 women (85% post-menopausal) enrolled from 1999–2001 to evaluate risk factors for breast cancer • Analysis restricted to 3,047 women with at least 1 live birth • Average follow-up: 3.5 years • 60–79 years of age • United Kingdom	139 incident and prevalent cases (invasive)	• Self-administered questionnaire, physical exam, and review of medical records at enrollment with update at 3-year follow-up • Data collected for smoking status (never, former, and current), age at initiation, and smoking in relation to first pregnancy • Subgroups evaluated by menopause (data not provided)	• No significant association was found with any smoking measure • No difference in risk when analysis restricted to postmenopausal women (results not shown)	**Timing With First Pregnancy: Incident Cases** Never: 1.00 Before: 1.08 (0.39–2.55) **Timing With First Pregnancy: Incident and Prevalent Cases** Never: 1.00 Before: 1.04 (0.68–1.57) After: 0.70 (0.36–1.36) **Within 5 Years of Menarche: Incident and Prevalent Cases** Never: 1.00 ±5 years: 1.00 (0.70–1.39)	Controlled for age, parity, age at menarche, age at menopause, hysterectomy, HRT, OC use, social class during childhood and adulthood, and BMI

Table 6.14*S* Continued

Study	Design/population	Number of breast cancer events	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking: RR (95% CI)	Confounders
Reynolds et al. 2004b	• California Teachers Study • 329,000 women enrolled from 1995–2000 to evaluate risk factors for breast cancer • 116, 544 women included in the analysis • Average follow-up: 5 years • >20 years of age • California	2,005 incident cases (in situ, invasive)	• Self-administered questionnaire at enrollment • Data collected for smoking status (never, former, and current), cigarettes/day, duration, pack-years, age at initiation, and in relation to first pregnancy • Data collected for secondhand smoke exposure (see USDHHS 2006) • Analyses based on the full sample includes a category for women with unknown menopausal status • Subgroups evaluated and stratified by menopausal status and family history of breast cancer	• Significant increased risk for current smokers (including both no active and NA/NP referent groups) • Risk mainly increased in postmenopausal current smokers • Increased risk in women who smoked ≥5 years before first pregnancy, with no difference by menopausal status • Significant trend for increased risk with duration of smoking, especially in postmenopausal women • Significant trend for increased risk with cigarettes/day and pack-years of smoking • Significant increased risk for women who started smoking before 20 years of age	**Status:** Never: 1.00 Former: 1.08 (0.98–1.19) PreM: 1.12 (0.89–1.42) PostM: 1.07 (0.95–1.20) Current: 1.32 (1.10–1.57) PreM: 1.02 (0.60–1.72) PostM: 1.29 (1.05–1.58) **Status With NA/NP:** NA/NP: 1.00 NA/Passive: 0.94 (0.82–1.07) PreM: 0.93 (0.71–1.22) PostM: 0.92 (0.78–1.08) Former: 1.03 (0.89–1.18) PreM: 1.07 (0.79–1.44) PostM: 1.01 (0.85–1.19) Current: 1.25 (1.02–1.53) PreM: 0.96 (0.55–1.68) PostM: 1.21 (0.95–1.54) **Duration (Years):** Never: 1.00 <10: 0.99 (0.85–1.17) 11–20: 1.17 (1.00–1.37) 21–30: 1.17 (0.99–1.38) ≥31: 1.15 (1.00–1.33) p trend = 0.009 **Duration (Years): Premenopausal** Never: 1.00 <10: 1.14 (0.85–1.55) 11–20: 1.10 (0.76–1.58) 21–30: 1.06 (0.67–1.66) ≥31: 0.99 (0.46–2.13) p trend = 0.616	Controlled for age, race, family history, age at menarche, pregnancy history, physical activity, BMI, menopausal status, interaction between BMI and menopausal status, alcohol use, and HRT

Table 6.14*S* Continued

Study	Design/population	Number of breast cancer events	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking: RR (95% CI)	Confounders
Reynolds et al. 2004b (continued)					**Duration (Years):** **Postmenopausal** Never: 1.00 <10: 0.95 (0.77–1.17) 11–20: 1.22 (1.02–1.47) 21–30: 1.07 (0.88–1.31) ≥31: 1.16 (0.99–1.34) p trend = 0.032 **Cigarettes/Day:** Never: 1.00 <10: 1.04 (0.92–1.18) 10–19: 1.14 (0.99–1.30) ≥20: 1.22 (1.05–1.42) p trend = 0.004 **Pack-years:** Never: 1.00 <10: 1.02 (0.91–1.16) 11–20: 1.24 (1.05–1.46) 21–30: 1.12 (0.91–1.39) ≥31: 1.25 (1.06–1.47) p trend = 0.002 **Age at Smoking Initiation:** Never: 1.00 ≥20: 1.03 (0.90–1.17) <20: 1.17 (1.05–1.30) **Timing With First Pregnancy:** Never: 1.00 Before <5 years: 0.99 (0.80–1.21) ≥5 years: 1.13 (1.00–1.28) After: 0.89 (0.65–1.21)	

Table 6.14*S* Continued

Study	Design/population	Number of breast cancer events	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking: RR (95% CI)	Confounders
Gram et al. 2005	• Norwegian-Swedish Cohort Women's Lifestyle and Health Study • 102,098 women were enrolled in 1991–1992 to evaluate risk factors for multiple health outcomes • Average follow-up: 8-9 years • 30–50 years of age • Norway and Sweden	1,240 incident breast cancer cases (invasive)	• Self-administered questionnaire at enrollment • Data collected for smoking status (never, former, current), duration, cigarettes/day, pack-years, smoking before first pregnancy and before and after menarche • Data collected for secondhand smoke exposure (see Table 6.22*S*) • Subgroups evaluated by alcohol use	• Estimates based on both no active and NA/NP referent groups • Significant trends for smoking duration, pack-years and cigarettes/day among current smokers compared to a NA/NP referent group (n = 28,624) • Similar and slightly higher risks for ever smokers with 20+ years of smoking (n = 26,724) • Analyses restricted to nondrinkers generally showed higher risk estimates for both long-term and current smokers	**Status:** Never: 1.00 Ever: 1.00 (0.98–1.50) **Status With NA/NP:** NA/NP: 1.00 Passive: 1.21 (0.98–1.50) Former: 1.15 (0.94–1.41) Current: 1.17 (0.95–1.40) **Duration (Years) With NA/NP:** NA/NP: 1.00 1–19: 0.93 (0.68–1.28) 20–24: 1.09 (0.81–1.45) ≥25: 1.26 (0.98–1.63) p trend = 0.05 **Cigarettes/Day With NA/NP:** NA/NP: 1.00 1–9: 0.96 (0.74–1.25) ≥10: 1.28 (1.01–1.63) p trend = 0.03 **Pack-years With NA/NP:** NA/NP: 1.00 0–14: 0.95 (0.74–1.20) 15–19: 1.28 (0.96–1.72) ≥20: 1.48 (1.14–1.96) p trend = 0.001 **Age at Smoking Initiation With NA/NP:** NA/NP: 1.00 ≥20: 1.02 (0.78–1.35) 15–19: 1.15 (0.91–1.47) 10–14: 1.51 (1.00–2.28) p trend = 0.07 **Timing With First Pregnancy With NA/NP: Before** NA/NP: 1.00 No: 0.99 (0.72–1.37) Yes: 1.18 (0.92–1.52) p trend = 0.14	Controlled for age, menopausal status, number of children, age at birth of first child, HRT, BMI, and alcohol use

Table 6.14*S* Continued

Study	Design/population	Number of breast cancer events	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking: RR (95% CI)	Confounders
Hanaoka et al. 2005	• Japan Public Health Center • 27,398 women enrolled in 1990 to evaluate risk factors for cancer and CVD • 21,805 women included in the analysis • Average follow-up: 10 years • 40–59 years of age • Japan	180 incident cases (invasive)	• Self-administered questionnaire at enrollment • Data collected for smoking status (never, former, and current), age at initiation and cessation, and smoking intensity and duration • Data for cancer incidence and mortality collected through 1999 by a cancer registry established for the Japan Public Health Center and a registry of deaths in Japan • Data collected for exposure to secondhand smoke (see USDHHS 2006) • Subgroups evaluated and stratified by menopausal status	• Significantly increased risk for breast cancer among current smokers • When excluding women with exposure to secondhand smoke from the referent group, the RR increased 10-20% compared with results based on a no-active only referent group • Risk primarily observed among premenopausal women	**Ever With NA/NP: Premenopausal** NA/NP: 1.00 Passive: 2.60 (1.30–5.20) Ever, active: 3.90 (1.50–9.90) **Ever With NA/NP: Postmenopausal** NA/NP: 1.00 Passive: 0.60 (0.40–1.00) Ever, active: 1.10 (0.50–2.50) **Status:** Never: 1.00 Former: 1.10 (0.40–3.50) Current: 1.70 (1.00–3.10) **Status With NA/NP:** NA/NP: 1.00 Passive: 1.10 (0.80–1.60) Former: 1.20 (0.40–4.00) Current: 1.90 (1.00–3.60)	Controlled for age, geographic area, education, employment status, BMI, family history of breast cancer, benign breast disease, age at menarche, parity, menopausal status, HRT, and alcohol use
Olson et al. 2005	• Iowa Women's Health Study • 41,386 enrolled in 1986 • 37,105 women included in the analysis • Average follow-up: 14 years • 55–69 years of age • United States	2,017 incident cases (stage not specified)	• Self-administered questionnaire at enrollment and at follow-up (1987, 1989, 1992, and 1997) • Data for active cigarette smoking collected for smoking status (never, former, current) and timing in relation to first pregnancy • Subgroups evaluated and stratified by childbearing history and parity	• Significantly increased risk in current smokers • Risk significantly increased with long duration of smoking (>40 years) • Risk significantly increased among women who initiated smoking after 18 years of age • Risk significantly increased with smoking before first pregnancy	**Status:** Never: 1.00 Former: 1.08 (0.95–1.22) Current: 1.19 (1.03–1.37) **Duration (Years):** Never: 1.00 1–19: 1.01 (0.83–1.21) 20–39: 1.13 (0.99–1.29) ≥40: 1.18 (1.00–1.38) **Pack-years:** Never: 1.00 1–19: 1.05 (0.91–1.21) 20–39: 1.18 (1.02–1.37) ≥40: 1.15 (0.96–1.37) **Age at Smoking Initiation:** Never: 1.00 ≤18: 1.12 (0.92–1.36) >18: 1.11 (1.00–1.24) **Timing With First Pregnancy:** Never: 1.00 Before: 1.21 (1.07–1.37) After: 1.03 (0.88–1.21)	Controlled for age, education, family history, age at menarche, age at menopause, OC use, HRT, BMI, waist-to-hip ratio, height, BMI at 18 years of age, physical activity, and alcohol; overall risk additionally adjusted for parity and age at birth of first child

Table 6.14*S* Continued

Study	Design/population	Number of breast cancer events	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking: RR (95% CI)	Confounders
Cui et al. 2006[a]	• Canadian National Breast Screening Study • 89,835 women enrolled from 1980–1985 into a multicenter, randomized controlled trial of mammographic screening • Average follow-up: 16 years • 40–59 years of age • Canada	4,445 incident cases (in situ, invasive)	• Self-administered questionnaire at enrollment. • Data collected for smoking status (never, former, and current), cigarettes/day, duration, pack-years of smoking • Subgroups evaluated and stratified by levels of physical activity	• Significantly increased risk in current but not former smokers. • Risk significantly associated with duration, cigarettes/day, pack-years of smoking, age at smoking initiation and smoking before first pregnancy • Risk associated with age at smoking initiation but not with number of years since cessation • Significant trends for duration, cigarettes/day, pack-years, age at smoking initiation, and smoking before first pregnancy	**Status:** Never: 1.00 Former: 1.00 (0.93–1.08) Current: 1.18 (1.09–1.27) **Duration (Years):** Never: 1.00 1–9: 1.00 (0.90–1.12) 10–19: 1.02 (0.93–1.13) 20–29: 1.09 (1.00–1.19) 30–39: 1.14 (1.03–1.27) ≥40: 1.50 (1.19–1.89) p trend = 0.0003 **Cigarettes/Day:** Never: 1.00 1–9: 1.02 (0.92–1.13) 10–19: 1.06 (0.96–1.16) 20–29: 1.12 (1.03–1.21) 30–39: 1.08 (0.92–1.28) ≥40: 1.20 (1.00–1.44) p trend = 0.0018 **Pack-years:** Never: 1.00 1–9: 1.02 (0.93–1.11) 10–19: 1.02 (0.92–1.13) 20–29: 1.13 (1.02–1.27) 30–39: 1.21 (1.07–1.36) ≥40: 1.17 (1.02–1.34) p trend = 0.0002 **Age at Smoking Initiation:** Never: 1.00 ≥20: 1.07 (0.99–1.14) 16–19: 1.10 (1.01–1.21) <16: 1.11 (0.97–1.28) p trend = 0.01 **Timing With First Pregnancy: Before (Years)** Never: 1.00 >0–5: 1.01 (0.91–1.13) >5: 1.13 (1.01–1.25) p trend = 0.041	Controlled for age, randomization group (intervention, control), study center, BMI, education, physical activity, OC use, HRT, parity, age at menarche, history of benign breast disease, breast self-exam, family history, menopausal status, and alcohol use

Table 6.14*S* Continued

Study	Design/population	Number of breast cancer events	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking: RR (95% CI)	Confounders
Ha et al. 2007	• United States Radiologic Technologists Study • 146,022 women, enrolled in 1983 if registered for at least 2 years between 1926–1982 through the American Registry of Radiologic Technologists to assess lifestyle and health information • Average follow-up: 15 years • Age (mean): 37.5 (22–92) years • United States	906 incident breast cancer cases (stage not specified) 781 cases based on self-report only and 125 cases from death certificates Ascertained from subcohort of 54,222 women with updated data during 1994–1998 and 1,520 women deceased from 1983–1998	• Self-administered questionnaire at enrollment and at follow-up (1994–1998) • Data collected for smoking status (never, former, and current), number of cigarettes and duration of smoking • Data collected for smoking at 3 reproductive time periods: menopause, age at birth of first birth, and age at menarche • Subgroups evaluated and stratified by menopausal status	• No association with current or former smoking • Trend showing increased risk with earlier age at initiation and with smoking before first pregnancy, but statistically significant in only postmenopausal women	**Status:** Never: 1.00 Former: 1.17 (0.99–1.38) Current: 1.13 (0.96–1.32) **Age at Smoking Initiation:** Never: 1.00 >20: 0.97 (0.60–1.57) 18–20: 1.09 (0.64–1.86) 15–17: 1.19 (0.68–2.06) <15: 1.48 (0.77–2.84) p trend = 0.06 **Age at Smoking Initiation: Premenopausal** Never: 1.00 >20: 1.15 (0.47–2.81) 18–20: 1.06 (0.39–2.87) 15–17: 1.35 (0.49–3.69) <15: 0.87 (0.25–3.07) p trend = 0.93 **Age at Smoking Initiation: Postmenopausal** Never: 1.00 >20: 1.00 (0.55–1.78) 18–20: 1.17 (0.61–1.78) 15–17: 1.17 (0.60–2.30) <15: 2.01 (0.92–4.37) p trend = 0.05 **Timing With First Pregnancy: Before (Years)** Never: 1.00 <10: 0.97 (0.61–1.54) ≥10: 1.39 (0.82–2.35) p trend = 0.002 **Timing With First Pregnancy: Premenopausal, Before (Years)** Never: 1.00 <10: 0.81 (0.33–2.00) ≥10: 1.38 (0.51–3.73) p trend = 0.12 **Timing With First Pregnancy: Postmenopausal, Before (Years)** Never: 1.00 <10: 1.04 (0.61–1.78) ≥10: 1.37 (0.74–2.56) p trend = 0.01	Controlled for age, birth cohort, alcohol use, age at menarche, age at birth of first live child, parity, family history, HRT, time period working as a radiologic technologist, BMI, and menopausal status

Table 6.14*S* Continued

Study	Design/population	Number of breast cancer events	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking: RR (95% CI)	Confounders
Lin et al. 2008	• Collaborative Cohort Study for Evaluation of Cancer Risk • 34,401 women enrolled between 1988–1990 from 24 areas for which incidence data were available to evaluate risk factors for cancer • Average follow-up: 11–13 years • 40–79 years of age • Japan	208 incident cases (stage not specified)	• Self-administered questionnaire at enrollment • Data collected for smoking status (never, former, and current), age at smoking initiation, cigarettes/day, duration of smoking, and years since cessation • Data collected for secondhand smoke exposure (see Table 6.22*S*) • Subgroups evaluated and stratified by menopausal status but data for postmenopausal women only reported because of insufficient data for premenopausal women	• No association between risk for breast cancer and status or dose of smoking • No association with risk for breast cancer and current smoking in postmenopausal women HR = 1.20, (95%CI; 0.52–2.80) • Use of NA/NP referent group did not alter results (data not shown)	**Status:** Never: 1.00 Former: 1.27 (0.46–3.48) Current: 0.67 (0.32–1.38) **Cigarettes/Day:** Never: 1.00 0–10: 0.84 (0.34–2.06) >11: 0.55 (0.17–1.75)	Controlled for age, geographic area, BMI, family history, alcohol use, daily walking, age at menarche, age at birth of first child, menopausal status at baseline, parity, and HRT

Table 6.14*S* Continued

Study	Design/population	Number of breast cancer events	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking: RR (95% CI)	Confounders
Luo et al. 2011b	• Women's Health Initiative Observational Cohort • 93,676 women enrolled in 40 clinical centers (1993–1998) to evaluate major causes of morbidity and mortality • 79,990 women included in the analysis • Average follow-up: 10.3 years • 50–79 years of age • United States	3,520 incident cases (invasive)	• Self-administered questionnaire at enrollment • Data collected for smoking status (never, former, current), age at initiation, duration, cigarettes/day, pack-years, years since cessation, age at initiation, and before first pregnancy • Data collected for secondhand smoke exposure (See Table 6.22*S*) • Subgroups evaluated and stratified by tumor subgroups, hormone receptor status and histology	• Risk significantly increased in former and current smokers compared to never smokers with slightly higher risk when referent group was based on active/no passive exposure • Significant trends for increased risk with duration, cigarettes/day, pack-years and younger age at initiation • Risk significantly increased with smoking before first pregnancy • Risk of breast cancer was significantly elevated among former and current smokers with ER+/PR+ receptor status (results not shown)	**Status:** Never: 1.00 Former: 1.09 (1.02–1.17) Current: 1.16 (1.00–1.34) **Status With NA/NP:** NA/NP: 1.00 Former: 1.16 (0.98–1.38) Current: 1.24 (1.00–1.54) **Duration (Years):** Never: 1.00 <5: 0.97 (0.84–1.11) 5–9: 1.05 (0.90–1.22) 10–19: 1.09 (0.98–1.22) 20–29: 1.09 (0.97–1.22) 30–39: 1.21 (1.07–1.36) 40–49: 1.14 (0.98–1.34) ≥50: 1.35 (1.03–1.77) p-trend: 0.0002 **Cigarettes/Day:** Never: 1.00 <5: 1.05 (0.94–1.17) 5–14: 1.11 (1.01–1.23) 15–24: 1.14 (1.03–1.27) ≥25: 1.08 (0.95–1.22) p trend = 0.01 **Pack-years:** Never: 1.00 <10: 1.04 (0.95–1.14) 10–<20: 1.21 (1.08–1.36) 20–<30: 1.13 (0.98–1.30) 30–<40: 1.01 (0.86–1.19) 40–<50: 1.16 (0.91–1.47) ≥50: 1.18 (1.02–1.37) p trend = 0.005 **Age at Smoking Initiation:** Never: 1.00 <15: 1.12 (0.92–1.36) 15–19: 1.13 (1.04–1.23) 20–24: 1.09 (0.99–1.20) 25–29: 1.02 (0.84–1.24) ≥30: 0.94 (0.75–1.18) p trend = 0.002 **Timing With First Pregnancy: Before** Never: 1.00 Yes: 1.21 (1.11–1.33) No: 1.12 (0.92–1.36) Uncertain: 1.07 (0.97–1.18)	Controlled for age at enrollment, ethnicity, education, BMI, physical activity, alcohol use, parity, family history, history of HRT, age at menarche, and age of first live birth.

Table 6.14*S* Continued

Study	Design/population	Number of breast cancer events	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking: RR (95% CI)	Confounders
Xue et al. 2011[a]	• Nurses' Health Study-I • 121,700 nurses enrolled to evaluate risk factors for breast cancer and CVD • Analysis restricted to 111,140 women for active cigarette smoking analysis • Average follow-up: 14 years • 30–55 years of age • United States	8,772 incident cases (invasive)	• Self-administered questionnaire at enrollment • Data collected for smoking status (never, former, current), cigarettes/day, duration, pack-years, timing in relation to menarche, first birth, and menopause, and time since cessation (former) • Data collected for secondhand smoke exposure (See Table 6.22*S*) • Subgroups evaluated and stratified by menopausal status, passive smoking status, timing of smoking status, and changes in BMI	• Risk significantly increased in ever, former and current smokers • Risk significantly positively associated with cigarettes/day, duration, and pack-years of smoking • Positive association with pack-years of smoking before menopause; inverse association after menopause (results not shown)	**Status:** Never: 1.00 Ever: 1.07 (1.02–1.12) Former: 1.06 (1.01–1.11) Current: 1.09 (1.02–1.17) **Duration (Years):** Never: 1.00 <20: 1.04 (0.98–1.11) 20-39: 1.07 (1.00–1.14) ≥40: 1.15 (1.04–1.27) p-trend = 0.01 **Cigarettes/Day: Current** Never 1.00 1–14: 1.04 (0.94–1.15) 15–24: 1.06 (0.96–1.17) ≥25: 1.14 (1.02–1.29) p trend = 0.02 **Cigarettes/Day: Former** Never: 1.00 1–14: 1.02 (0.97–1.09) 15–24: 1.11 (1.04–1.18) ≥25: 1.08 (0.99–1.18) p trend = 0.003 **Pack-years:** Never: 1.00 1–10: 1.00 (0.94–1.07) 11–20: 1.08 (1.01–1.16) 21–30: 1.07 (1.00–1.15) 31–40 1.16 (1.07–1.26) 41–50 1.05 (0.94–1.18) ≥50 1.19 (1.07–1.33) p trend = 0.001 **Age at Smoking Initiation:** Never: ≥20: 1.07 (0.99–1.15) 18-19: 1.08 (1.01–1.14) ≤17: 1.04 (0.99–1.11) p trend = 0.01	Controlled for age, family history, age at menarche, height, BMI at 18 years of age, oral contraceptive use, history of benign breast disease, physical activity, alcohol use, passive smoking at home and at work, age at first birth, parity, and current BMI, age at menopause, menopausal status, and HRT use

Table 6.14*S* Continued

Note: Study-specific results are not intended to be a complete reporting of all findings. When available, results for ever, status, duration, cigarettes/day, pack-years, age at initiation, and timing with first pregnancy (smoking before or during first pregnancy) are reported. Unless otherwise specified, the definition of the reference group is based on a no active-only exposure, which includes individuals with exposure to secondhand smoke. When available, results for ever smoking using a NA/NP reference group are reported; however, similar results for the other measures are not reported in the table. Data from cohort studies for exposure to secondhand smoke are summarized in Table 6.22*S*. All results reported by the study may not appear in the summary table. **BMI** = body mass index; **cig/day** = cigarettes smoked per day; **CI** = confidence interval; **CVD** = cardiovascular disease; **ER** = estrogen receptor; **HR** = hazard ratio; **HRT** = hormone replacement therapy; **NA/NP** = no active/no passive; **OC** = oral contraceptive; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **PostM** = postmenopausal; **PR** = progesterone receptor; **RR** = relative risk; **USDHHS** = United States Department of Health and Human Services.

[a]Report that overlaps with another from the same study population shown in this table and reported in Table 6.16*S*A.

Table 6.15*S* **Case-control study reports of the association between active cigarette smoking and risk for breast cancer, based on studies published from 2000 to 2011 (n = 34)**

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
Delfino et al. 2000	• Clinic-based study designed to evaluate the interaction of polymorphisms in the *NAT2* gene with smoking on risk for breast cancer • Time period unknown • >40 years of age • 113 incident cancer cases (in situ, invasive) ascertained through 1 of 3 breast care centers for women evaluated for a suspicious breast mass • 278 controls selected from those with benign breast disease being treated at same clinic as cases • Orange County, California	• Self-administered mailed questionnaire at enrollment; 59 cases excluded from analysis because the questionnaire was received after receipt of diagnosis or refusal of blood draw • Data collected for status (never, former, and current), duration (years), and cigarettes/day • Data collected for exposure to secondhand smoke (see USDHHS 2006) • Assays for *NAT2* genotype • Subgroups evaluated and stratified by type of benign breast disease	• No statistically significant association between risk for breast cancer and any measure of active smoking • No difference when results were stratified by menopausal status (data not reported) • No significant interaction (p >0.30) between active smoking and NAT2 genotype for all women and pre- and postmenopausal women	**Status with NA/NP:** NA/NP: 1.00 Passive Only: 1.32 (0.69–2.52) Former: 0.94 (0.53–1.68) Current: 0.55 (0.18–1.67) **Duration (years) with NA/NP:** NA/NP: 1.00 <13: 0.94 (0.43–2.03) 13–26: 0.70 (0.30–1.62) >26: 0.74 (0.34–1.61) **Cigarettes/day with NA/NP:** NA/NP: 1.00 <8: 1.04 (0.50–2.13) 8–25: 0.75 (0.35–1.58) >25: 0.51 (0.19–1.35)	Controlled for age, menopausal status, and family history in first- and second-degree relatives

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
Johnson et al. 2000	• National Enhanced Cancer Surveillance System • Population-based study of cancer risk profiles collected on 19,453 cases diagnosed with 18 different incident cancers and 4,523 controls • Analysis based on data from 8 of 10 provinces • 1994–1997 • 25–74 years of age • 2,317 incident cases (invasive) ascertained through tumor registries • 2,438 controls selected randomly from provincial health insurance plans in 5 provinces, databases of the Ministry of Finance Property Assessment in one province, and random-digit dialing in two provinces • Canada	• Self-administered questionnaire at time of enrollment • Data collected for status (never, former, current), pack-years, duration, age at smoking initiation, and years since smoking cessation • Data collected for exposure to secondhand smoke (see USDHHS 2006) • Subgroups evaluated and stratified by menopausal status	• Statistically significant increased risk for breast cancer among former or current (ever) smokers when referent groups is no active/no passive exposure in both pre- and postmenopausal women • Significant trend involving increased risk with greater duration and greater pack-years among postmenopausal but not premenopausal women • Increased risks across all levels of age at smoking initiation with no significant trends	**Status: premenopausal** Never: 1.00 Former: 1.20 (0.90–1.50) Current: 0.90 (0.70–1.20) Former or Current: 1.00 (0.80–1.30) **Status: postmenopausal** Never: 1.00 Former: 1.10 (0.90–1.30) Current: 1.30 (1.10–1.60) Former or Current: 1.20 (1.00–1.40) **Status with NA/NP: premenopausal** NA/NP: 1.00 Passive: 2.30 (1.20–4.60) Former: 2.60 (1.30–5.30) Current: 1.90 (0.90–3.80) Former or Current: 2.30 (1.20–4.50) **Status with NA/NP: postmenopausal** NA/NP: 1.00 Passive: 1.20 (0.80–1.80) Former: 1.40 (0.90–2.10) Current: 1.60 (1.00–2.50) Former or Current: 1.50 (1.00–2.30) **Duration (years) with NA/NP: premenopausal** NA/NP: 1.00 1–11: 2.70 (1.20–6.10) 12–20: 1.90 (0.80–4.50) ≥21: 2.10 (0.90–4.70) p trend = 0.91 **Duration (years) with NA/NP: postmenopausal** NA/NP: 1.00 1–20: 1.20 (0.80–1.90) 21–35: 1.30 (0.80–2.10) ≥35: 1.70 (1.10–2.70) p trend = 0.003	Active smoking controlled for 10-year age groups, province, education, BMI, use of alcohol, physical activity, age at menarche, age at end of first pregnancy, number of live births, months breastfeeding, and height; exposure to passive smoke controlled for in analyses that evaluated status of cigarette smoking

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
Johnson et al. 2000 (continued)				**Cigarettes/day with NA/NP: premenopausal** NA/NP: 1.00 <10: 2.50 (1.20–5.20) 10–19: 2.30 (1.10–4.60) ≥20: 2.00 (1.00–4.00) p trend = 0.99 **Cigarettes/day with NA/NP: postmenopausal** NA/NP: 1.00 <10: 1.40 (0.80–2.20) 10–19: 1.50 (0.90–2.30) ≥20: 1.40 (0.90–2.10) p trend = 0.08 **Pack-years with NA/NP: premenopausal** NA/NP: 1.00 1–10: 2.40 (1.20–4.70) 11–20: 2.30 (1.10–4.70) 21–30: 1.70 (0.80–3.90) >30: 1.50 (0.40–5.90) p trend = 0.92 **Pack-years with NA/NP: Ppstmenopausal** NA/NP: 1.00 1–10: 1.40 (0.90–2.10) 11–20: 1.20 (0.70–1.90) 21–30: 1.90 (1.10–3.10) >30: 1.60 (1.00–2.60) p trend = 0.01 **Age at smoking initiation with NA/NP: premenopausal**: NA/NP: 1.00 ≥20: 2.10 (0.90–4.80) 16–19: 2.40 (1.20–4.90) ≤15: 2.10 (1.00–4.30) p trend = 0.63 **Age at smoking initiation with NA/NP: postmenopausal** NA/NP: 1.00 ≥20: 1.40 (0.90–2.30 16–19: 1.50 (1.00–2.40) ≤15: 1.20 (0.70–1.90) p trend = 0.19	

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
Marcus et al. 2000[a]	• Carolina Breast Cancer Study (Phase I) • Population-based study designed to evaluate the association between risk of breast cancer and adolescent exposure to cigarette smoking, alcohol use, passive smoke, and ionizing radiation treatment in White and African American women • 1993–1996 • 20–74 years of age • 864 incident breast cancer cases (invasive) ascertained by North Carolina Central Cancer Registry • 790 controls frequency-matched by age and residence and selected from North Carolina Division of Motor Vehicles list (<65 years of age) and from Medicare list (>65 years of age) • North Carolina	• Telephone interview or in-person if subject could not be reached by telephone • Data collected for status (never, former, current), age at smoking initiation, and duration. • Data collected for exposure to secondhand smoke (see USDHHS 2006)	• No statistically significant association between active smoking and risk of breast cancer among former and current smokers • Statistically significant increased risk among women who smoked for 20 or more years)	**Status:** Never: 1.00 Former: 1.10 (0.80–1.30) Current: 1.20 (0.90–1.50) **Duration (years):** Never: 1.00 <20: 0.90 (0.70–1.20) ≥20: 1.30 (1.10–1.80) **Age at smoking initiation:** Never: 1.00 10–14: 1.50 (0.90–2.50) 15–19: 1.00 (0.80–1.30) ≥20: 1.20 (0.80–1.50)	Controlled for race, age at diagnosis or selection, and sampling design

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
Morabia et al. 2000	• Population-based study designed to evaluate the interaction of smoking and the *NAT2* genotype with risk for breast cancer 1992–1993 • 30–74 years of age • 177 incident cases (stage not specified) identified via computerized database of residents in Geneva • 170 controls selected from a computerized database of residents; frequency-matched to cases and proportionate for each 10-year age group • Geneva, Switzerland	• In-person interview data from parent study • Data collected for ever smoking • Data collected for exposure to secondhand smoke (see note for Table 6.24*S*) • Data collection included DNA buccal samples for NAT2 genotyping • Subgroups evaluated and stratified by menopausal status and *NAT2* acetylator status	• Risk for breast cancer was statistically significant and 3-fold higher for ever active smokers.	**Ever with NA/NP:** Never: 1.00 Ever: 3.30 (1.70–6.50)	Controlled for age, education, and family history
Innes and Byers, 2001	• Population-based study designed to evaluate whether smoking during pregnancy was associated with an increased risk of breast cancer • 1989–1995 • 319 incident cases (invasive) ascertained through the New York State Department of Health Cancer Registry and Vital Statistics Registry if a state resident and gave birth to at least 1 child after 1987 • 768 primiparous controls selected from the same registry and vital statistics registry as cases and matched to cases on county of residence and delivery date • 26–45 years of age • New York	• Data abstracted for maternal history of smoking, including smoking during first pregnancy, and for potential confounders available on birth certificate	• Smoking during pregnancy increased risk of breast cancer three-fold • Additional adjustment for use of alcohol during pregnancy, pre-eclampsia, multifetal gestation, and prepregnancy weight further increased RR to 4.8 (1.6–14.6) • Women who were at or above median body weight and smoked were more likely to develop breast cancer (data not provided).	**Status: during first pregnancy** Nonsmoker: 1.00 Smoker: 3.00 (1.30–7.20)	Controlled for attained age, age at birth of first child, maternal education, maternal race

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
Band et al. 2002	• Population-based study designed to assess the association between cigarette smoking and breast cancer (based on a previous case-control study that evaluated occupational exposures to cigarette smoke) • 1988–1989 • <75 years of age • 1,431 cases (stage not provided) ascertained cases through the British Columbia Cancer Registry; 1,018 cases (68%) included in analyses • From 1,502 eligible controls, selected randomly from a list of provincial voters and matched by age (±5 years); 1,025 controls (67%) included in analyses • British Columbia, Canada	• Self-administered questionnaire at enrollment • Data collected for status (never and ever), duration, pack-years of smoking, and cigarettes/day, timing with respect to menarche, first pregnancy, and first full-term pregnancy • Subgroups evaluated and stratified by menopausal status, BMI, and parity	• Statistically significant increased risk for breast cancer with ever smoking and for duration, pack-years of smoking, and cigarettes/day for premenopausal women only	**Ever: premenopausal** Never: 1.00 Ever: 1.50 (1.09–2.07) **Ever: postmenopausal** Never: 1.00 Ever: 0.96 (0.77–1.19) **Duration (Years): Premenopausal** Never: 1.00 <20: 1.34 (0.91–1.99) ≥20: 1.60 (1.08–2.37) **Duration (years): postmenopausal** Never: 1.00 <20: 0.77 (0.54–1.08) ≥20: 1.01 (0.80–1.28) **Cigarettes/day: premenopausal** Never: 1.00 <20: 1.37 (0.94–2.01) ≥20: 1.58 (1.06–2.37) **Cigarettes/day: postmenopausal** Never: 1.00 <20: 0.93 (0.72–1.18) ≥20: 1.02 (0.76–1.36) **Pack-years: premenopausal** Never: 1.00 <20: 1.30 (0.90–1.87) ≥20: 1.69 (1.10–2.61) **Pack-years: postmenopausal** Never: 1.00 <20: 0.84 (0.64–1.09) ≥20: 1.03 (0.79–1.34) **Timing with first pregnancy: premenopausal** Never: 1.00 Before: 1.51 (1.07–2.13) After: 0.83 (0.38–1.86) **Timing with first pregnancy: postmenopausal** Never: 1.00 Before: 0.97 (0.77–1.23) After: 0.63 (0.41–0.96)	Controlled for age only in final model; multiple covariates were available and tested for confounding including: ethnicity, marital status, education, use of alcohol, ages at menarche and menopause, family history, history of benign breast disease, body size, use of oral contraceptives, HRT, number of pregnancies and live births, age at first pregnancy, age at first full-term birth and breastfeeding

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
Kropp and Chang-Claude 2002	• Population-based study designed to assess risk factors for breast cancer • 1992–1995 • <51 years of age • 468 incident cases (in situ, invasive) ascertained through hospital admission records • 1,093 controls selected randomly from population registries and matched (2:1) to cases by age and study region • 2 regions in southern Germany	• Self-administered questionnaire at enrollment • Data collected for status (never, former, and current), age at initiation, duration, cigarettes/day, type of tobacco product, intensity of inhalation, cessation, and changes in smoking • Data collected for exposure to secondhand smoke and categorized into low and high passive exposure categories (see USDHHS 2006) • Subgroups evaluated for joint effects of active and passive smoking	• Increased risk for breast cancer for ever smokers and current smokers • Significant trend of increased risk for long duration of smoking and for age at smoking initiation • No association between risk and smoking before first pregnancy	**Status with NA/NP:** NA/NP: 1.00 Passive only: 1.61 (1.08–2.39) Ever: 1.31 (0.90–1.92) Former: 1.15 (0.76–1.74) Current: 1.47 (0.99–2.20) **Status with NA/NP: current smoker** NA/NP: 1.00 Active: 1.11 (0.63–1.96) Low Passive: 1.06 (0.69–1.64) High Passive: 1.46 (0.97–2.18) **Duration (years) with NA/NP:** NA/NP: 1.00 1–9: 0.99 (0.61–1.60) 10–19: 1.40 (0.90–2.16) ≥20: 1.45 (0.96–2.19) p trend = 0.047 **Pack-years with NA/NP:** NA/NP: 1.00 ≤10: 1.19 (0.80–1.76) 11–20: 1.84 (1.17–2.88) ≥20: 1.13 (0.68–1.88) p trend = 0.211 **Age at smoking initiation with NA/NP:** NA/NP: 1.00 9–15: 1.02 (0.62–1.68) 16–18: 1.29 (0.86–1.94) ≥19: 1.54 (0.99–2.37) p trend = 0.015 **Timing with first pregnancy with NA/NP:** NA/NP: 1.00 Before: 0.92 (0.52–1.65) After: 1.64 (0.90–2.97) Before and After: 1.32 (0.86–2.03)	Controlled for average daily alcohol use, months breastfeeding, education, family history, menopausal status, and BMI; category of exposure to only passive smoke included in all models

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
Lash and Aschengrau 2002	• Population-based study designed to evaluate the effect of active smoking and exposure to passive smoke on risk for breast cancer • 1987–1993 • Age criteria unknown • 666 incident cases (invasive) identified through Massachusetts Cancer Registry for eight towns on Cape Cod • 615 controls, matched to cases by age and vital status, selected by random-digit dialing (<65 years of age) and from Medicare beneficiaries (≥65 years of age) • Massachusetts	• Mixture of in-person and telephone interviews for study participants or their proxies • Information was not provided on the number of proxy interviews or the source of the information • Data collected for status (never and ever), duration, packs/day, age at smoking initiation, and in relation to first pregnancy • Data collected for exposure to secondhand smoke (see USDHHS 2006)	• No statistically significant association between the risk for breast cancer and any measure of active smoking • Statistically significant inverse association for ever smoking and a nonsignificant inverse association for all other measures	**Status with NA/NP:** NA/NP: 1.00 Ever: 0.72 (0.55–0.95) **Duration (Years) with NA/NP:** NA/NP: 1.00 <20: 0.69 (0.48–1.00) 20–40: 0.87 (0.74–1.00) ≥40: 0.90 (1.80–1.00) p trend = 0.87 **Packs/day with NA/NP:** NA/NP: 1.00 <1: 0.77 (0.57–1.00) 1–2: 0.69 (0.50–0.94) ≥2: 0.57 (0.33–0.98) p trend = 0.40 **Age at smoking initiation with NA/NP:** NA/NP: 1.00 <13: 0.61 (0.30–1.20) 14–15: 0.81 (0.54–1.20) 16–17: 0.67 (0.47–1.00) 18–21: 0.78 (0.57–1.10) 21–29: 0.71 (0.47–1.10) ≥30: 0.59 (0.32–1.10) p trend = 0.81 **Timing with first pregnancy with NA/NP:** NA/NP: 1.00 Before: 0.73 (0.42–1.30) After: 0.66 (0.42–1.00) Before and After: 0.69 (0.49–0.96) Nulliparous: 0.82 (0.48–1.40)	Controlled for history of medical radiation therapy, BMI, family history, history of benign breast disease, alcohol use, age at first birth, and parity

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
Zheng et al. 2002a	• Hospital-based study designed to evaluate the association of GSTs with risk of breast cancer and to determine if they modify the relationship between selected environmental factors and risk for breast cancer • 1994–1998 • 30–80 years of age • 338 incident cases (invasive) ascertained through Yale–New Haven Hospital • 345 controls frequency-matched to cases by age (5-year intervals) and selected through Yale–New Haven Hospital in clinic for breast-related surgery but with no histological confirmation of breast cancer • Connecticut	• In-person interview • Data collected for status (never, ever, former, and current), age at smoking initiation, duration, pack-years of smoking, and cigarettes/day • Subgroups evaluated and stratified by menopausal status *GSTM1A/B* and *GSTT1*	• No statistically significant association between risk for breast cancer and ever smoking, duration, pack-years, and cigarettes/day, or age at initiation • No difference when stratified by menopausal status • Possible modification of the risk of smoking by GSTT1 genotype in postmenopausal women	**Status:** Never: 1.00 Ever: 1.10 (0.80–1.50) Former: 1.10 (0.80–1.60) Current: 1.00 (0.60–1.60) **Duration (years):** Never: 1.00 <15: 0.90 (0.60–1.40) 15–30: 1.10 (0.70–1.60) >30: 1.30 (0.80–2.00) **Pack-years:** Never: 1.00 <5: 1.00 (0.70–1.60) 5–20: 1.20 (0.80–1.80) >20: 1.00 (0.60–1.50) **Cigarettes/day:** Never 1.00 <10: 1.20 (0.80–1.80) 10–20: 1.10 (0.80–1.60) >20: 0.80 (0.40–1.50) **Age at smoking initiation:** Never: 1.00 <18: 1.10 (0.80–1.60) 18–24: 1.00 (0.70–1.50) >24: 1.60 (0.70–3.70)	Controlled for age, BMI, age at first full-term pregnancy, breastfeeding, and family history of breast cancer

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
Egan et al. 2003[a]	• Collaborative Breast Cancer Study • Population-based study designed to investigate factors related to breast cancer • 1997–1998 • 20–69 years of age • 791 incident cases (invasive) ascertained through state cancer registries • 797 controls selected randomly within age strata from driver's license lists (<65 years of age) and Medicare beneficiaries lists (>65 years of age) • Massachusetts and Wisconsin	• Telephone interview • Data collected for status (never, former, and current), age at smoking initiation, duration, and timing with first full-term pregnancy • DNA buccal specimens collected by mail for *NAT2* genotyping • Subgroups evaluated and stratified by menopausal status and *NAT2* acetylation type (fast/slow)	• Statistically significant increased risk for breast cancer among ever smokers • Nonsignificant increased risk for women who initiated smoking at or before 16 years of age • No difference in risk by menopausal status for the highest dose category of pack-years of smoking and statistically significant for only postmenopausal women	**Ever:** Never: 1.00 Ever: 1.37 (1.12–1.69) **Pack-years: premenopausal** ≤25: 0.90 (0.87–1.33) >25: 1.54 (0.87–2.71) p trend = 0.11 **Pack-years: postmenopausal:** ≤25: 1.57 (1.12–2.19) >25: 1.53 (1.10–2.13) p trend = 0.02 **Age at smoking initiation:** ≤16: 1.23 (0.83–1.83) >16: 1.19 (0.86–1.66)	Controlled for state, age, education, age at menarche, parity, age at first birth, benign breast disease, recent BMI, family history, age at menopause, and alcohol use

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
Fink and Lash 2003	• Population-based study designed to evaluate whether smoking during pregnancy is associated with an increased risk for breast cancer • 1987–1999 • 25–55 years of age • 1,665 cases (invasive) ascertained through linkage of Massachusetts Cancer Registry and Registry of Vital Records for women who were state residents and gave birth to at least 1 child • 4,972 controls selected from the Registry of Vital ecords and matched to cases (3:1) on age (±6 months), year of giving birth, and birth facility • Massachusetts	• Data abstracted for maternal history of smoking, including smoking during first pregnancy, duration, and intensity of smoking and for potential confounders available on birth certificates • Subgroups evaluated and stratified by age at birth of first child for smokers and nonsmokers	• No association between risk for breast cancer and smoking during pregnancy	**Status: during first pregnancy** Nonsmoker: 1.00 During: 0.97 (0.80–1.20) **Cigarettes/day: during first pregnancy** Nonsmoker: 1.00 Any: 1.00 (0.81–1.20) 1–10: 0.94 (0.73–1.20) ≥11: 1.00 (0.79–1.40) **Age at first pregnancy:** Nonsmoker: 1.00 All Women: 0.90 (0.66–1.20) <30: 1.10 (0.65–1.80) 30–34: 0.72 (0.43–1.20) ≥35: 0.90 (0.49–1.70)	Controlled for age, year of birth, parity, birth terminations (miscarriage, abortions, stillbirths), race, mother and father's education

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
van der Hel et al. 2003b	• Monitoring Project on Cardiovascular Disease Risk Factors • Nested case-control study of a population-based sample of >36,000 women and men enrolled from municipal registries to investigate risk factors associated with CVD • 1987–1991 • 20–59 years of ages • 229 first incident cases (invasive) identified at follow-up via Netherlands Cancer Registry • 264 controls frequency-matched on age (5-year groups), menopausal status and residence • The Netherlands	• Self-administered questionnaire at enrollment • Data collected for status (never, former, and current) and duration (years) and intensity of smoking • Assays for *NAT1, NAT2, GSTM1,* and *GSTT1* genotypes • Subgroups evaluated and stratified by menopausal status for cigarettes/day and by genotype	• Nonsignificant increase in risk for breast cancer among ever smokers for cigarettes/day and duration • Statistically significant increased risk (OR = 2.17, 95% CI, 1.04–4.51 for postmenopausal women at the highest category of exposure for cigarettes/day (≥20)	**Duration (years):** Never: 1.00 <15: 1.22 (0.68–2.18) 15–30: 1.37 (0.86–2.16) ≥30: 1.55 (0.92–2.61) p trend = 0.07 **Cigarettes/day:** Never: 1.00 <10: 1.22 (0.72–2.06) 10–20: 1.37 (0.86–2.18) ≥20: 1.55 (0.94–2.54) p trend = 0.06	Controlled for age, menopausal status, and residence

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
Alberg et al. 2004	• Nested case-control study to evaluate *NAT2* genotype and cigarette smoking on breast cancer risk within the Campaign against Cancer and Heart Disease II cohort designed to evaluate cancer and heart disease in 14,625 women • 1989 baseline • Mean age: 60 years • 115 incident cases (stage not specified) ascertained from Washington County Cancer Registry and Washington County Hospital (for those who were deceased) • 115 controls matched on age (±1 year), race, menopausal status, and date of blood collection • Washington County, Maryland	• In-person interview and blood collection • Self-administered questionnaire at follow-up in 1995 • Data collected for smoking status (never, former, and current), duration, and intensity of smoking • Data collected for exposure to secondhand smoke (see Table 6.23*S*) • Subgroups evaluated and stratified by menopausal status and NAT2 acetylator status	• No significant association between former and current smoking and risk of breast cancer • Nonsignificant increased risk with increasing pack-years	**Status:** Never: 1.00 Former: 1.10 (0.56–2.10) Current: 0.66 (0.30–1.40) **Status with NA/NP:** NA/NP: 1.00 Passive: 1.20 (0.59–2.40) Active: 1.40 (0.70–2.90) p trend = 0.45 **Pack-years:** Never: 1.00 0.1–15: 1.40 (0.58–3.40) 16–82.5: 1.70 (0.70–4.20) p trend = 0.26	Controlled for age and menopausal status

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
Gammon et al. 2004a[a]	• Long Island Breast Cancer Study Project • Population-based study to evaluate environmental risk factors for breast cancer • 1996–1997 • 24–98 years of age • 1,356 incident cases (in situ, invasive) identified through 31 pathology departments • 1,383 controls frequency-matched to cases by age (±5 years) and selected through random-digit dialing (<65 years of age) and from rosters of the Health Care Financing Administration (≥65 years) • Nassau and Suffolk counties, New York	• In-person interview • Data collected for status (never, former, and current), duration, cigarettes/day, pack-years of smoking, and timing with first pregnancy • Data collected for exposure to secondhand smoke (see USDHHS 2006) • Subgroups evaluated and stratified by menopausal status, BMI, use of alcohol, hormone replacement therapy, use of oral contraceptives, and family history, and ER/PR status	• No statistically significant association between risk for breast cancer and any measure of active smoking • Increased risk for women exposed to active smoking and to passive smoke who had ER+/PR+ tumors OR = 1.42 (1.00–2.00)	**Ever with NA/NP:** NA/NP: 1.00 Passive: 1.04 (0.81–1.35) Active: 1.06 (0.76–1.48) Active and Passive: 1.15 (0.90–1.48) **Ever with NA/NP: premenopausal** NA/NP: 1.00 Passive: 1.21 (0.78–1.90) Active: 0.98 (0.54–1.78) Active and Passive: 1.43 (0.93–2.21) **Ever with NA/NP: postmenopausal** NA/NP: 1.00 Passive: 0.93 (0.68–1.29) Active: 1.08 (0.72–1.62) Active and Passive: 1.02 (0.74–1.38) **Cigarettes/day with NA/NP: current smokers** NA/NP: 1.00 1–9: 1.38 (0.86–2.23) 10–19: 1.30 (0.84–2.00) >20: 1.31 (0.94–1.82) **Pack-years with NA/NP: current smokers:** NA/NP: 1.00 <20: 1.41 (0.95–2.08) >20: 1.33 (0.97–1.83) **Age at smoking initiation with NA/NP:** NA/NP: 1.00 Before 18: 0.66 (0.49–0.90) **Timing with first pregnancy with NA/NP:** NA/NP: 1.00 Before: 0.72 (0.49–1.05) After: 1.20 (0.76–1.89) Before and After: 1.08 (0.82–1.43)	Controlled for age, history of benign breast disease, BMI at age 20, family history of breast cancer, history of fertility problems, number of pregnancies, menopausal status, and weight in year before reference date

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
Li et al. 2005	• Population-based study designed to examine the association between hormone replacement therapy and risk for breast cancer among older women • 1997–1999 • 65–79 years of age • 975 incident cases (invasive) ascertained through the Cancer Surveillance System • 1,007 controls selected from records from the Health Care Financing Administration and matched on age (±5 years) • Washington state	• In-person interview • Data collected for status (never, ever, former, and current), duration, pack-years of smoking, and timing with first full-term pregnancy • Subgroups evaluated and stratified by alcohol use, HRT, and ER/PR status	• Statistically significant increased risk for breast cancer among ever smokers former and current smokers • Risk statistically significant for increased pack-years • Risk statistically significant for women who initiated smoking before the age of 20 ($p < 0.05$); trend across levels also statistically significant ($p<0.05$) • Alcohol use reported to be a significant confounder, but not an effect modifier • Possible interaction between smoking and hormone replacement therapy	**Status:** Never: 1.00 Ever: 1.30 (1.00–1.50) Former: 1.20 (1.00–1.50) Current: 1.40 (1.00–1.90) **Duration (years):** Never: 1.00 <20: 1.00 (0.80–1.40) 20–39: 1.30 (1.00–1.70) ≥40: 1.40 (1.10–1.70) p trend = 0.006 **Cigarettes/day:** Never: 1.00 <10: 1.30 (1.00–1.70) 10–19: 1.30 (1.00–1.70) ≥20: 1.20 (0.90–1.50) p trend = 0.057 **Pack-years:** Never: 1.00 <11: 1.00 (0.70–1.30) 11–27: 1.40 (1.10–1.90) 28–52: 1.30 (1.00–1.80) ≥53: 1.30 (1.00–1.70) p trend = 0.009 **Age at smoking initiation:** Never: 1.00 ≥20: 1.20 (1.00–1.60) <20: 1.30 (1.00–1.60) p trend = 0.028 **Timing with first pregnancy:** Never: 1.00 Before: 1.30 (1.00–1.60) After: 1.10 (0.80–1.50)	Controlled for age, reference year, BMI, alcohol use, and HRT

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
Metsola et al. 2005[a]	• Hospital-based study designed to evaluate the main effects for genotypes and to examine the effects of these genotypes on modification of other risk factors for breast cancer (e.g., smoking) • 1990–1995 • 37–92 years of age • 483 cases (invasive) referred to Kuopio University Hospital • 488 controls randomly selected from same area as cases using Finnish Population Register Centre • Finland	• In-person interviews • Data collected for cigarettes/day (with/without filter), duration, and time since smoking cessation (among women who smoked daily for more than 3 months) • Data collected for exposure to secondhand smoke (see Table 6.23*S*) • Genotype assays for DNA repair genes (*XRCC1* and *XPD*) • Subgroups evaluated and stratified by DNA repair genes	• No significant association between ever smoking and risk for breast cancer • Results evaluated for main effects of genotypes by smoking status but not for modification of effects of smoking by genotypes	**Pack-years with NA/NP:** NA/NP: 1.00 Ever: 0.91 (0.65–1.28) <5: 0.75 (0.48–1.16) ≥5: 1.08 (0.72–1.62)	Controlled for age
Sillanpaa et al. 2005a[a]	• Hospital-based study designed to evaluate the main effects for genotypes and to examine the effects of these genotypes on modification of other risk factors for breast cancer (e.g., smoking) • 1990–1995 • 37–92 years of age • 483 cases (invasive) referred to Kuopio University Hospital • 488 controls randomly selected from same area as cases using Finnish Population Register Centre with no evidence for previous or current breast problems • Finland	• In-person interviews • Data collected on status (never, former, current), cigarettes/day, duration (years), and time since cessation • Data collected for exposure to secondhand smoke (see Table 6.23*S*) • Genotype assays for *NAT2* • Subgroups evaluated and stratified by *NAT2*	• No significant associations found between smoking status, pack-years, and risk of breast cancer • Results evaluated for main effects of genotypes by smoking status but not for modification of effects of smoking by genotypes	**Status with NA/NP:** NA/NP: 1.00 Former: 0.87 (0.56–1.37) Current: 1.34 (0.86–2.09) **Pack-years with NA/NP:** NA/NP: 1.00 <5: 0.88 (0.55–1.41) ≥5: 1.23 (0.80–1.90)	Controlled for age, age at menarche, age at first full-term pregnancy, number of pregnancies, family history, history of benign breast disease, and alcohol use

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
Lissowska et al. 2006	• Population-based study designed to evaluate risk factors for breast cancer • 2000–2003 • 20–74 years of age • 2,386 incident cases (in situ, invasive) ascertained from 5 participating hospitals that covered 90% of both cities, supplemented by cancer registry • 2,502 controls randomly selected from Polish electronic database for residents of Poland and matched on city and by 5-year age groups • Warsaw and Lodz, Poland	• In-person interview • Data collected for status (never, ever, former, and current), age at initiation, duration, cigarettes/day, and smoking before and after first full-term pregnancy • Hormone receptor data abstracted from medical records • Genotype assays for NAT2 • Data collected for exposure to secondhand smoke (see Table 6.23*S*) • Subgroups evaluated and stratified by age group, ER status and NAT2 acetylation status	• For all women and for women ≥45 years of age there were few statistically significant associations and no significant trends for ever smoking, age at smoking initiation, duration, and cigarettes/day or in relation to birth of first child • Significant associations among women <45 years of age for ever and current smoking, a combination of active and passive exposure; age at initiation <24 years but no significant trend, and for smoking before or after first full-term pregnancy • Statistically significant increased trend for women <45 years of age for duration and for cigarettes/day • Exclusion of women with exposure to passive smoke slightly increased results • Statistically significant increased risks for both smoking before and after first full-term pregnancy and ER+ tumor status for all women (OR = 1.25, 1.04–1.50) • Increased risk in premenopausal women <45 years of age with NAT2 slow phenotype	**Ever with NA/NP:** NA/NP: 1.00 Active: 1.23 (0.83–1.83) Active and Passive: 1.21 (0.93–1.59) **Ever with NA/NP: women <45 years** NA/NP: 1.00 Active: 1.28 (0.52–3.11) Active and Passive: 2.40 (1.00–5.72) **Status:** Never: 1.00 Ever: 1.10 (0.97–1.24) Former: 1.09 (0.93–1.29) Current: 1.12 (0.97–1.29) **Status: women <45 years** Never: 1.00 Ever: 1.95 (1.38–2.76) Former: 1.63 (0.97–2.72) Current: 2.03 (1.40–2.95) **Duration (years):** Never: 1.00 <10: 1.04 (0.85–1.29) 10–20: 1.06 (0.85–1.32) >20: 0.99 (0.83–1.20) p trend = 0.86 **Duration (years): women <45 years** Never: 1.00 <10: 1.57 (1.01–2.44) 10–20: 1.83 (1.15–2.91) >20: 2.33 (1.32–4.13) p trend = 0.04 **Cigarettes/day:** Never: 1.00 <10: 1.06 (0.86–1.31) 10–14: 1.17 (0.97–1.43) >14: 0.99 (0.83–1.20) p trend = 0.42	Controlled for age, site, education, age at menarche, number of full-term births, age at first full-term birth, age at menopause, BMI, family history, prior benign breast biopsy, previous screening mammography, OC, and HRT

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
Lissowska et al. 2006 (continued)				**Cigarettes/day: women <45 years** Never: 1.00 <10: 2.02 (1.26–3.27) 10–14: 2.49 (1.53–4.04) >14: 1.35 (0.83–2.19) p trend = 0.05 **Age at smoking initiation:** Never: 1.00 <17: 1.07 (0.80–1.42) 17–19: 1.23 (1.04–1.46) 20–24: 1.03 (0.87–1.21) >24: 1.10 (0.90–1.34) **Age at smoking initiation: women <45 years** Never: 1.00 <17: 1.96 (1.08–3.56) 17–19: 2.19 (1.42–3.39) 20–24: 1.77 (1.13–2.78) >24: 1.86 (0.79–4.26) p trend = 0.60 **Timing with first pregnancy:** Never: 1.00 After: 1.06 (0.87–1.29) Before: 1.14 (0.98–1.32) **Timing with first pregnancy: women <45 years** Never: 1.00 After: 2.40 (1.27–4.53) Before: 2.03 (1.40–2.94)	

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
Mechanic et al. 2006[a]	• Carolina Breast Cancer Study • Population-based study designed to evaluate causes of breast cancer among African American and White women (Phase I invasive; Phase II in-situ) • 1993–2001 • 20–74 years of age • 2,308 incident cases (in situ, invasive) ascertained through North Carolina Cancer Registry for counties in central and eastern North Carolina • 2,022 controls selected from lists provided by the North Carolina Division of Motor Vehicles for women younger than 65 years of age and from records of the United States Health Care Financing Administration (65–74 years of age) • North Carolina	• In-person interview • Data collected for status (never, former, and current), age at smoking initiation, duration, packs/day, and time since smoking cessation • Clinical data collected from medical records • Genotype assays for polymorphisms in nucleotide excision repair genes • Data collected for exposure to secondhand smoke (see Table 6.23*S*) • Subgroups evaluated and stratified by menopausal status, ethnicity, nucleotide excision repair polymorphisms and alcohol use (data not provided)	• Risk for breast cancer significantly associated with age at smoking initiation, duration, and packs/day for only African American women • Risk significantly associated with status, duration, and packs/day for African American women with ≥4 at risk genotypes	**Status: african american** NA/NP: 1.00 Former: 1.80 (1.30–2.50) Current: 1.20 (0.90–1.70) **Status: white** NA/NP: 1.00 Former: 1.20 (0.90–1.50) Current: 0.80 (0.60–1.00) **Duration (Years): african american** NA/NP: 1.00 ≤10: 1.30 (0.90–1.90) 11–20: 1.40 (1.00–2.10) >20: 1.80 (1.20–2.60) p trend = 0.003 **Duration (years): white** NA/NP: 1.00 ≤10: 0.90 (0.70–1.20) 11–20: 0.90 (0.70–1.30) >20: 1.10 (0.90–1.50) p trend = 0.43 **Packs/day: african american** NA/NP: 1.00 <0.5: 1.50 (1.00–2.00) 0.5–1: 1.70 (1.20–2.40) >1: 1.50 (0.90–2.30) p trend = 0.02 **Packs/day: white** NA/NP: 1.00 <0.5: 0.90 (0.70–1.20) 0.5–1: 1.00 (0.80–1.30) >1: 1.10 (0.80–1.40) **Age at smoking initiation: african american** NA/NP: 1.00 <18: 1.50 (1.10–2.20) ≥18: 1.50 (1.10–2.10) **Age at smoking initiation: white** NA/NP: 1.00 <18: 0.90 (0.70–1.20) ≥18: 1.10 (0.80–1.40)	Controlled for age, age at menarche, age at first full-term birth, parity, family history, and alcohol use

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
Kruk 2007	• Hospital-based study designed to evaluate the association between the risk for breast cancer risk and lifestyle factors by menopausal status • 2003–2007 • 28–78 years of age • 858 incident cases (invasive) ascertained from Szczecin Regional Cancer Registry • 1,085 controls frequency-matched on 5-year age groups and place of residence (urban/rural); majority of controls (79%) from the same patient clinic and remainder from hospital patients • Western Pomerania region, Poland	• Self-administered questionnaire • Data collected for smoking status (never and ever) and cigarettes/day • Data collected for exposure to secondhand smoke (see Table 6.23*S*) • Subgroups evaluated and stratified by menopausal status for cigarettes/day	• Risk for breast cancer significantly associated with smoking, regardless of menopausal status	**Cigarettes/day: premenopausal** Never: 1.00 <10: 2.09 (1.42–3.09) >10: 2.55 (1.81–3.60) p trend <0.0001 **Cigarettes/day: postmenopausal** Never: 1.00 <10: 1.73 (1.23–2.44) >10: 1.78 (1.33–2.37) p trend <0.0001	Controlled for age; final models included confounders that influenced goodness of fit and that were statistically significant for risk of breast cancer

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
Magnusson et al. 2007	• Population-based study designed to evaluate the association between smoking and breast cancer • 1993–1995 • 50–74 years of age • 3,345 cases (invasive) ascertained through the Regional Cancer Registries • 3,454 controls, randomly selected using registry of the total population, and frequency-matched on 5-year age groups • Sweden	• Self-administered questionnaire completed by cases; telephone interviews conducted for 14% of controls who declined mailed questionnaire • Data collected for smoking status (never and ever), duration, pack-years, age at initiation of smoking cigarettes/day, and timing with first pregnancy • Subgroups evaluated and stratified by menopausal status	• No association between risk for breast cancer and active smoking based on ever smoked, duration (years) of smoking, cigarettes/day, pack-years, age at smoking initiation, or smoking relative to first birth • Data missing for nearly 17% of cases and 25% of controls	**Ever:** Never: 1.00 Ever: 1.00 (0.90–1.20) **Ever: menopausal status** Never: 1.00 PreM: 1.40 (0.70–2.50) PostM: 1.00 (0.90–1.20) **Duration (years):** Never: 1.00 1–10: 0.70 (0.40–1.30) 11–30: 1.00 (0.80–1.30) >30: 1.10 (0.90–1.20) p trend = 0.58 **Cigarettes/day:** Never: 1.00 1–10: 1.00 (0.90–1.30) 11–20: 1.10 (0.90–1.30) >20: 0.80 (0.40–1.40) p trend = 0.71 **Pack-years:** Never: 1.00 1–10: 0.90 (0.70–1.20) 11–20: 1.00 (0.80–1.20) 21–30: 1.40 (1.10–1.70) >30: 0.90 (0.70–1.20) p trend = 0.77 **Age at smoking initiation:** Never: 1.00 <20: 1.20 (1.00–1.40) 20–29: 0.90 (0.70–1.10) >30: 1.00 (0.70–1.30) **Timing with first pregnancy:** Never: 1.00 Before: 1.20 (0.90–1.40) After: 1.00 (0.70–1.40)	Controlled for age, age at birth of first child, BMI, and alcohol use

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
Prescott et al. 2007	• Population-based study designed to examine the effects of cigarette smoking on risk for breast cancer at an early age among United States-born non-Hispanic White, Hispanic White, and African American women • 1998–2003 • 20–49 years of age • 1,728 incident cases (invasive) recruited through the Los Angeles County Cancer Surveillance Program • 441 controls recruited through neighborhood controls and matched on age (±5 years) and ethnicity • Los Angeles, California	• In-person interviews • Data collected for status (never, former, and current), duration, age at smoking initiation, lifetime average cigarettes/week, average cigarettes in past 5 years, 5-year period after menarche, smoking before 18 years of age, and before first full-term pregnancy	• No significant association between risk for breast cancer and any measure of smoking • First-degree family history of breast or ovarian cancer did not modify the risk association between smoking and risk for breast cancer • Results reported to be comparable when analysis was restricted to long-term smokers (≥20 years) and never smokers and when restricted to Stage I, II, III/IV of cancer (data not shown)	**Status:** Never: 1.00 Ever: 0.99 (0.78–1.25) Former: 1.04 (0.80–1.36) Current: 0.89 (0.64–1.24) **Duration (years):** Never: 1.00 ≤11: 0.94 (0.68–1.30) >11–≤20: 0.93 (0.66–1.31) >20: 1.12 (0.79–1.59) p trend = 0.74 **Cigarettes/week:** Never: 1.00 ≤8: 0.87 (0.62–1.23) >8–≤52: 1.06 (0.76–1.47) >52: 1.03 (0.73–1.45) p trend = 0.79 **Age at smoking initiation:** Never: 1.00 >18: 0.94 (0.66–1.33) >15–≤18: 1.20 (0.86–1.67) ≤15: 0.83 (0.59–1.16) p trend = 0.68 **Timing with first pregnancy:** Never: 1.00 Years Before First Birth: ≤10: 0.95 (0.71–1.27) >10: 1.03 (0.75–1.43) Years After First Birth: 0.97 (0.48–1.95)	Controlled for age, race, education, age at menarche, number of full-term pregnancies, age at first full-term pregnancy, alcohol use, and family history

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
Roddam et al. 2007	• Designed to study the association between OC use and breast cancer risk in premenopausal women • 1987–1990 • 36–45 years of age • 639 cases (invasive) ascertained through regional and hospital registries • 640 age-matched controls and randomly selected by general practitioners of the respective cases • Thames, Oxford, and Yorkshire regions, United Kingdom	• In-person interviews • Data collected for status, age at smoking initiation, duration, and cigarettes/day • Analyses for duration, intensity (cigarettes/day), and age at smoking initiation based on continuous measures (results not shown) • Data collected for exposure to secondhand smoke (see Table 6.23*S*)	• No association for active smoking and risk for breast cancer for current or former smoking, duration, or age at smoking initiation	**Status:** Never: 1.00 Former: 1.15 (0.87–1.53) Current: 1.04 (0.79–1.36) **Status with NA/NP:** NA/NP: 1.00 Passive: 0.89 (0.64–1.25) Former, NP: 1.12 (0.72–1.73) Former, P: 1.09 (0.75–1.56) Current, NP: 1.19 (0.72–1.95) Current, P: 0.93 (0.67–1.30) **Duration (years):** Per 5 years: 1.00 (0.91–1.11) **Cigarettes/day:** Never: 1.00 5/day: 1.00 (0.89–1.12) **Age at smoking initiation:** Per 5 years: 0.97 (0.79–1.19)	Controlled for age, geographic region, socioeconomic status, alcohol use, BMI, parity, age at first live birth, OC use, family history, age at menarche, menopausal status, and active/passive exposure

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
Rollison et al. 2008	• Population-based study designed to evaluate smoking and breast cancer risk • 2000–2002 • 40–79 years of age • 287 primary incident cases (invasive) ascertained through the Delaware Cancer Registry • 311 controls selected from motor vehicle driver's license records (<65 years) and from Health Care Financing Administration records for Delaware (≥65 years) • Delaware	• Telephone interviews • Data collected for ever, age at smoking initiation, duration, number of years smoked before 18 years of age and before first live birth, pack-years, cigarettes/day, types of tobacco products used, and inhalation pattern • Data collected for exposure to secondhand smoke (see Table 6.23*S*) • Subgroups evaluated and stratified by menopausal status	• No significant association between risk for breast cancer and any smoking measure • No significant association between risk and any smoking measure when a no active/no passive referent group was used, regardless of definition of passive exposure no residential smoking before the age of 18; ≤10 years of residential and occupational smoking; and no residential and occupational smoking	**Ever:** Never: 1.00 Ever: 1.43 (1.03–1.99) PreM: 1.53 (0.60–3.95) PostM: 1.36 (0.95–1.94) **Ever with NA/NP:** NA/NP: 1.00 Ever, no residential: 1.23 (0.76–1.98) **Duration (years):** Never: 1.00 <10: 1.36 (0.72–2.55) 10–19: 1.13 (0.64–2.01) 20–29: 1.80 (1.02–3.20) 30–39: 1.31 (0.76–2.25) 40–49: 1.50 (0.79–2.82) 50–62: 1.21 (0.52–2.84) **Cigarettes/day:** Never: 1.00 <10: 1.60 (1.01–2.53) 10–19: 1.53 (0.99–2.35) 20–29: 1.12 (0.61–2.04) 30–68: 0.84 (0.34–2.08) **Pack-years:** Never: 1.00 <5: 1.45 (0.85–2.45) 5–9: 1.65 (0.81–3.35) 10–19: 1.83 (1.04–3.23) 20–29: 1.24 (0.69–2.24) 30–39: 1.06 (0.44–2.56) 40–49: 1.92 (0.81–4.55) 50–102: 0.75 (0.34–1.65) **Timing with first pregnancy: before (years)** Never: 1.00 <5: 1.25 (0.73–2.13) 5–9: 1.37 (0.87–2.16) 10–14: 0.69 (0.33–1.45) 15–39: 1.99 (0.76–5.18)	Controlled for age, education, and menopausal status in final models; further adjustment for reproductive factors, alcohol use, BMI, and FH did not change estimates by more than 10%

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
Slattery et al. 2008	• 4-Corners Breast Cancer Study • Population-based study designed to evaluate risk factors for breast cancer among Hispanic, American Indian, and non-Hispanic White women in southwestern United States • 1999–2004 • 25–79 years of age • 2,325 incident cases (in situ, invasive): ascertained through cancer registries • 2,525 controls frequency-matched on ethnicity and 5-year age groups; women <65 years of age selected from commercial mailing lists (in Arizona and Colorado) or from driver license lists; women ≥65 years of age selected from Centers for Medicare & Medicaid Services list • Statewide for Utah, New Mexico, and Colorado and 7 counties in Arizona	• In-person interview • Data collected for smoking status (never, former, and current), age at initiation, duration, usual amount smoked, and smoking before or after first pregnancy • Genotype assays for 5 *IL6* markers and 1 *ESR1* marker • Data collected for exposure to secondhand smoke (see Table 6.23*S*) • Subgroups evaluated and stratified by menopausal status ethnicity, and genotype	• Risk for breast cancer significantly associated with ever smoked, pack-years, and smoking before first full-term birth in premenopausal non-Hispanic White women only.	**Status: premenopausal, non-Hispanic White** Never: 1.00 Ever: 1.30 (1.00–1.70) Former: 1.40 (1.00–1.80) Current: 1.30 (0.90–1.90) p trend = 0.09 **Hispanic** Never: 1.00 Ever: 1.10 (0.70–1.50) Former: 1.10 (0.80–1.70) Current: 0.90 (0.50–1.60) p trend = 0.98 **Status: postmenopausal, non-Hispanic White** Never: 1.00 Ever: 1.00 (0.90–1.20) Former: 1.10 (0.90–1.30) Current: 1.00 (0.70–1.30) p trend = 0.96 **Hispanic** Never: 1.00 Ever: 1.00 (0.70–1.30) Former: 0.90 (0.70–1.30) Current: 1.00 (0.70–1.50) p trend = 0.84 **Pack-years: premenopausal, non-Hispanic White** Never: 1.00 1–15: 1.10 (0.80–1.60) >15: 1.60 (1.10–2.40) p trend = 0.03 **Hispanic** Never: 1.00 1–15: 1.00 (0.70–1.60) >15: 0.90 (0.50–1.70) p trend = 0.88	Controlled for age, center, BMI, aspirin use, NSAIDs, parity, alcohol use, physical activity, and recent (±2 years) estrogen exposure for postmenopausal women

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
Slattery et al. 2008 (continued)				**Pack-Years: postmenopausal, non-Hispanic White** Never: 1.00 1–15: 1.20 (0.90–1.50) >15: 1.00 (0.80–1.20) p trend = 0.90 **Hispanic** Never: 1.00 1–15: 0.70 (0.50–1.00) >15: 1.20 (0.80–1.70) p trend = 0.96 **Age at smoking initiation: premenopausal, non-Hispanic White** Never: 1.00 ≥20: 1.40 (0.90–2.30) 17–19: 1.20 (0.80–1.80) ≤16: 1.30 (0.90–1.90) p trend = 0.08 **Hispanic** Never: 1.00 ≥20: 1.10 (0.60–1.90) 17–19: 1.10 (0.60–1.90) ≤16: 1.00 (0.60–1.70) p trend = 0.84 **Age at smoking initiation: postmenopausal, non-Hispanic White** Never: 1.00 ≥20: 1.20 (0.90–1.60) 17–19: 1.00 (0.80–1.20) ≤16: 0.90 (0.70–1.20) p trend = 0.51 **Age at smoking initiation: postmenopausal, hispanic** Never: 1.00 ≥20: 1.00 (0.70–1.40) 17–19: 1.00 (0.70–1.60) ≤16: 0.90 (0.60–1.30) p trend = 0.65	

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
Slattery et al. 2008 (continued)				**Timing with first pregnancy: premenopausal, non-Hispanic White** **Before** Never: 1.00 No: 1.20 (0.60–2.40) Yes: 1.40 (1.00–1.90) p trend = 0.03 **Timing with first pregnancy: premenopausal, hispanic** **Before** Never: 1.00 No: 1.00 (0.50–2.10) Yes: 1.10 (0.80–1.70) p trend = 0.56 **Timing with first pregnancy: postmenopausal, non-Hispanic White** **Before** Never: 1.00 No: 1.00 (0.70–1.40) Yes: 1.00 (0.80–1.30) p trend = 0.83 **Timing with first pregnancy: postmenopausal, hispanic** **Before** Never: 1.00 No: 1.20 (0.80–1.80) Yes: 0.90 (0.70–1.20) p trend = 0.66	

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
Ahern et al. 2009[a]	• Population-based study designed to evaluate the association between breast cancer risk and lifestyle factors • 1989–1991 • 28–75 years of age • 557 incident cases (invasive) ascertained through the Massachusetts Cancer Registry • 432 controls selected randomly from the driver's license bureau (<65 years) and from Massachusetts Medicare rosters (≥65 years) • Massachusetts	• Telephone interview • Data collected for smoking status (never, former, and current), age at smoking initiation, age at smoking cessation, and pack-years • Age at smoking initiation and cessation reported only as continuous measures • Data collected for exposure to secondhand smoke (see Table 6.23*S*) • Subgroups evaluated and stratified by menopausal status for pack-years	• No association between risk for breast cancer and pack-years, regardless of whether a no active or a no active/no passive referent group was used • No association in analyses stratified by menopausal status (data not reported)	**Pack-years:** Never: 1.00 1–23: 1.20 (0.90–1.70) ≥24: 0.90 (0.70–1.30) NA/NP: 1.00 1–23: 0.70 (0.40–1.50) ≥24: 0.60 (0.30–1.20) **Pack-years: premenopausal** Never: 1.00 1–23: 1.50 (0.90–2.40) ≥24: 0.80 (0.40–1.60) **Pack-years: postmenopausal** Never: 1.00 1–23: 1.10 (0.70–1.60) ≥24: 1.00 (0.60–1.40)	Controlled for age, BMI, menopausal status, parity, alcohol use, and family history Active smoking additionally adjusted for exposure to secondhand smoke

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
Young et al. 2009	• Secondary analysis to evaluate the association between smoking and breast cancer risk using data from 2 population-based studies with similar target populations and data collection methods. • OWHS • 1996–1998 • OWDHS • 2002–2003 • 25–75 years of age • 6,235 incident cases (invasive) ascertained through Ontario Cancer Registry (50% random sample of cases from OWHS, and all cases in 11-month window from OWDHS) • 6,533 controls frequency-matched by 5-year age groups and selected randomly (age-stratified) from the Ontario Ministry of Finance rolls (for OWHS) and from a random-digit dialing list (for OWDHS) • Canada	• Self-administered, mailed questionnaire • Data collected for a history of smoking 100 or more cigarettes, age at smoking initiation and in relation to timing of first birth • Data collected for exposure to secondhand smoke (see Table 6.23*S*) • Subgroups evaluated and stratified by age at menarche and age at first live birth	• No association between risk for breast cancer and only active smoking • Increased risk detected for active smoking combined with exposure to secondhand smoke • Trend for increased risk associated with older age at smoking initiation • Increased risk associated with smoking >5 years before and after first birth • Risk patterns similar when analyses stratified by age at menarche and by age at first live birth	**Ever with NA/NP:** NA/NP: 1.00 Active: 1.10 (0.98–1.23) Active and Passive: 1.13 (1.01–1.25) **Age at smoking initiation with NA/NP:** NA/NP: 1.00 <12: 0.88 (0.59–1.31) 12–15: 1.02 (0.90–1.16) 16–20: 1.12 (1.01–1.24) 21–25: 1.13 (0.96–1.33) ≥26: 1.26 (1.03–1.55) **Timing with first pregnancy with NA/NP: before (years)** NA/NP: 1.00 >5: 1.16 (1.04–1.31) ≤5: 0.96 (0.84–1.09) **Timing with first pregnancy with NA/NP: after** NA/NP: 1.00 After 1.24 (1.02–1.52)	Controlled for age at menarche, age at first live birth, parity, menopausal status, family history of benign breast disease, BMI, OC use, HRT, alcohol use, and household income

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
Andonova et al. 2010[a]	• GENICA (Gene Environment Interaction and Breast Cancer in Germany) study • Population-based study designed to evaluate the risk of breast cancer among lifestyle, tumor, and genetic factors (polymorphisms in *GST*) • 2000–2004 • <80 years of age • 1,143 incident cancer cases (in situ, invasive) ascertained through linkage with 14 surrounding hospitals in the study region; analyses based on 1,021 (89%) • 1,155 controls selected randomly through population registries in 31 communities and frequency-matched to cases by year of birth (5-year groups); analyses based on 1,015 (88%) • Greater Bonn region, Germany	• In-person interviews • Data collected for status (never, former, current) • Genotype assays for 9 *GST* polymorphisms	• No significant association with smoking status and risk of breast cancer • No significant association with smoking status and *GST* polymorphisms (data not shown) • Results evaluated for main effects of genotypes by smoking status but not for modification of effects of smoking by genotypes	**Status:** Never: 1.00 Former: 0.95 (0.75–1.19) Current: 0.84 (0.66–1.06)	Controlled for menopausal status, family history of breast cancer, OC use, HRT, and BMI

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
Brown et al. 2010	• Population-based study designed to evaluate the effect of alcohol consumption and cigarette smoking on risk for breast cancer among Asian-Americans (Chinese, Japanese, Filipino) • 1983–1987 • 20–55 years of age • 597 incident cases (in situ, invasive) ascertained through linkage with SEER • 966 controls • selected by random-digit dialing in San Francisco-Oakland and Los Angeles; and the Health Surveillance Program of the Hawaii State Department of Health and frequency-matched to cases (2:1) by study area, age (5-year groups), and ethnicity • San Francisco-Oakland, Los Angeles, California; Oahu, Hawaii	• In-person interview • Data collected for status (never, former, and current), duration, cigarettes/day, age at initiation and cessation, and years since cessation • Current smokers were those who reported smoking regularly for ≥6 months; former smokers were those who had not smoked for ≥2 years	• No association between risk for breast cancer and ever or current status, duration, or cigarettes/day • Risk for breast cancer significantly increased for former smoking and age at initiation <16 years • No difference when assessing migration history and risk of breast cancer when including cigarettes/day as a confounder	**Status:** Never: 1.0 Ever: 1.2 (0.9-1.6) Former: 1.6 (1.1–2.2) Current: 0.9 (0.6–1.3) **Duration (years):** Never: 1.0 <10: 1.3 (0.8–2.1) 10–19: 1.1 (0.7–1.7) 20–29: 1.4 (0.9–2.0) >29: 0.9 (0.5–1.6) **Cigarettes/day:** Never: 1.0 <10: 1.2 (0.8–1.7) 10–19: 1.3 (0.9–2.1) 20: 1.2 (0.8–1.9) ≥21: 0.9 (0.5–1.9) **Age at smoking initiation:** Never: 1.00 <16: 2.92 (1.1–7.9) 16–18: 1.18 (0.7–1.9) 19–21: 1.03 (0.7–1.5) ≥22: 1.20 (0.8–1.8)	Controlled for age, study area, ethnicity, age at menarche, age at first live birth, number of live births, menopausal status, age at menopause, family history, and history of benign breast disease

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
Gibson et al. 2010	• Nested case-control study within a clinical cohort trial to evaluate use of clinical breast exams as an alternative to mammography. • 1995–2001 • 35–64 years of age • 123 incident cancer cases (invasive) ascertained through cancer society and cancer registries • 978 controls selected and matched to cases by age, residence, date of clinical breast exam in an 8:1 ratio • Manila, Philippines	• In person interview • Data on status (never, ever)	• No association among ever smokers and risk of breast cancer	**Status:** Never: 1.00 Ever: 1.3 (0.6–2.9)	Controlled for age, municipality, parity, age at first full-term pregnancy, and education
Kaushal et al. 2010	• Population-based study to evaluate association of genetic polymorphisms with breast cancer risk • 2005–2008 • Mean age: 45–46 years • 117 incident cancer cases (invasive) ascertained through hospital referral and cancer registry • 174 controls selected from individuals accompanying the hospital patient; matched to cases by gender and age (±5 years) • Northeast India	• In-person interviews • Data collected for current smoking status • Genotype assays for *GSTT1*, *GSTM1*, *GSTP1*, *TP53* and *CYP17*	• No association of cigarette smoking with risk of breast cancer	**Ever:** No: 1.00 Yes: 1.15 (0.62–2.13)	None listed

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
Rabstein et al. 2010[a]	• GENICA (Gene Environment Interaction and Breast Cancer in Germany) study • Population-based study designed to evaluate the risk of breast cancer among lifestyle, tumor, and *NAT2* polymorphisms • 2000-2004 • <80 years of age • 1,143 incident cancer cases (in situ, invasive) ascertained through linkage with 14 surrounding hospitals in the study region • 1,155 controls selected randomly through population registries in 31 communities and frequency-matched to cases by year of birth (5-year groups) • Greater Bonn region, Germany	• In person interviews • Data collected on status (never, former, current) • Genotype assays for *NAT2* • Subgroups evaluated and stratified by *NAT2* and hormone-receptor status	• No association with smoking status • No association with ER status or NAT2 genotype; interaction term was not significant	**Status:** Never: 1.00 Former: 0.82 (0.65–1.03) Current: 0.99 (0.71–1.11)	Controlled for family history, HRT, mammogram frequency, physical activity, and lifetime breastfeeding
Cerne et al. 2011	• Institute of Oncology • Population-based study designed to evaluate risk factors for breast cancer • 2006–2008 • 50–69 of age • 825 incident cancer cases (in situ, invasive) ascertained through the Institute of Oncology • 732 controls selected from the Department of Obstetrics and Gynecology, University Medical Centre • Ljubljana, Slovenia	• Self-administered questionnaire • Data collected on current smoking status and cigarettes/day	• Significant increase in risk for breast cancer among current smokers who smoke ≥10 cigarettes/day	**Cigarettes/day: current** Nonsmoker: 1.00 <10: 1.56 (0.88–2.77) ≥10: 1.70 (1.20–2.43)	Controlled for age and education

Table 6.15*S* Continued

Study	Study population and design	Data collection/subgroup analyses	Findings for active cigarette smoking	Measures of active cigarette smoking RR (95% CI)	Confounders
DeRoo et al. 2011a	• Case-control study designed to evaluate the association between smoking during first pregnancy and breast cancer risk. • 1985–2000 • ≤65 years of age • 1,099 incident cases (in-situ, invasive) ascertained through the population-based cancer registries • 10,922 controls selected by linkage with Department of Licensing data; up to 10 controls were matched to cases by year, age at first birth, race/ethnicity and birth outcome • Washington state	• Data was collected by linkage to state birth and fetal death records and vital records for maternal characteristics • Any smoking reported during first pregnancy was defined as exposure	• No association for smoking during first pregnancy and risk of breast cancer	**Status: during first pregnancy** No: 1.00 Yes: 0.8 (0.7–0.9) **Status during first pregnancy: residents for at least 5 years** No: 1.00 Yes: 1.0 (0.8–1.1)	Controlled for age at first birth, year of delivery, race/ethnicity, birth outcome, and imputed and known maternal prenatal alcohol use

Note: Study-specific results are not intended to be a complete reporting of all findings. When available, results for ever, status, duration, cigarettes/day, pack-years, age at initiation, and timing with first pregnancy (smoking before or during first pregnancy) are reported. Unless otherwise specified, the definition of the reference group is based on a no active-only exposure, which includes individuals with secondhand smoke exposure. When available, results for ever smoking using a no active/no passive reference group are reported; however, similar results for the other measures are not reported in the table. Data from case-control studies for exposure to secondhand smoke are summarized in Table 6.25*S*. All results reported by the study may not appear in the summary table. **BMI** = body mass index; **cig/day =** cigarettes smoked per day; **CI** = confidence interval; **CVD** = cardiovascular disease; **ER** = estrogen receptor; **HRT** = hormone replacement therapy; **NAT2** = Nacetyltransferase 2; **NA/NP** = no active/no passive; **NSAIDs** = nonsteroidal anti-inflammatory drugs; **OC** = Oral contraceptive; **OR** = odds ratio; **OWDHS** = Ontario Women's Diet and Health Study; **OWHS** = Ontario Women's Health Study; **P** = passive; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **PostM** = postmenopausal; **PreM** = premenopausal; **PR** = progesterone receptor; **RR** = relative risk; **SEER** = Surveillance, Epidemiology, and End Results; **USDHHS** = United States Department of Health and Human Services.

[a]Report that overlaps with another from the same study population shown in this table and reported in Table 6.16*S*A.

Table 6.16*S* **Evaluation of reports on exposure to active cigarette smoking for meta-analyses, based on cohort studies before 2012 and case-control studies published between 2000 and 2011 for meta-analyses, by location, study design, size of analytic sample, type of referent group, meta-analysis categories, and design or analysis issues (n = 65)**

			Type of referent group		Meta-analysis categories							Design and analysis issues			
Study	**Design/population**	**Analytic sample size**	**No active-only**	**No active/no passive**	**Ever**	**Current**	**Former**	**Duration**	**Cigarettes/day**	**Pack-years**	**Age at initiation**	**Before/during first pregnancy**	**Small sample**	**Mixed referent or inadequate adjustment or proxy**	**Cut-point/outlier**
A. Overlapping reports, included in meta-analyses only if most recent or most complete (n = 26)															
Hiatt and Bawol et al. 1984[a]	• KPMCP • 1964–1972 • Cohort • United States	1,169 of 88,477	1	—	1	—	—	—	—	—	—	—	—	—	—
Hiatt and Fireman 1986[b]	—	1,363 of 84,172	1	—	1	1	1	—	1	—	—	—	—	—	—
Willett et al. 1987[a]	• NHS-I • Cohort • United States	1,224 of 5,599	1	—	1	—	—	—	—	—	—	—	—	—	—
London et al. 1989	—	1,788 of 117,557	1	—	1	1	1	—	1	—	—	—	—	—	—
Hunter et al. 1997	• Nested case-control	466/466	1	—	1	1	1	—	1	1	—	1	—	—	—
Egan et al. 2002[b]	—	3,140 of 78,206	1	1	1	1	1	1	—	—	1	1	—	—	—
Xue et al. 2011[b,c]	—	8,772 of 111,140	1	—	1	1	1	1	1	1	1	1	—	—	—

Table 6.16*S* Continued

Study	Design/population	Analytic sample size	Type of referent group		Meta-analysis categories							Design and analysis issues			
			No active-only	No active/no passive	Ever	Current	Former	Duration	Cigarettes/day	Pack-years	Age at initiation	Before/during first pregnancy	Small sample	Mixed referent or inadequate adjustment or proxy	Cut-point/outlier
Gapstur et al. 1992[a]	• IWHS • Cohort • United States	679 of 2,725	1	—	1	—	—	—	—	—	—	—	—	—	—
Olson et al. 2005[b]	—	2,017 of 37,105	1	—	1	1	1	1	—	1	1	1	—	—	—
Friedenreich et al. 1993[a]	• NBSS • Cohort • Canada	181 of 662	1	—	1	—	—	—	—	—	—	—	—	—	—
Terry et al. 2002	—	2,552 of 56,837	1	—	1	1	1	1	1	1	1	—	—	—	—
Cui et al. 2006[b]	—	4,434 of 49,613	1	—	1	1	1	1	1	1	1	1	—	—	—
Kabat et al. 2011	• WHI • Cohort • United States	300 (TNBC) & 2,479 (ER+) of 148,030	1	—	1	1	1	1	1	1	1	—	—	—	—
Luo et al. 2011b[b]	—	3,520 of 79,990	EV ST D CD PY AI FB	EV ST D CD PY AI FB	1	1	1	1	1	1	1	1	—	—	—
Manjer et al. 2000b[b]	• Cohort • Malmo, Sweden	414 of 10,849	1	—	1	1	1	—	1	—	—	—	—	—	—
Manjer et al. 2001	—	297 of 10,849	1	—	1	1	1	—	1	—	—	—	—	—	—

Table 6.16*S* Continued

Study	Design/population	Analytic sample size	Type of referent group		Meta-analysis categories							Design and analysis issues			
			No active-only	No active/no passive	Ever	Current	Former	Duration	Cigarettes/day	Pack-years	Age at initiation	Before/during first pregnancy	Small sample	Mixed referent or inadequate adjustment or proxy	Cut-point/outlier
Marcus et al. 2000	• Carolina BCS • Case-control • United States	864/790	1	—	1	1	1	1	1	—	1	—	—	—	—
Mechanic et al. 2006[b]	—	2,308/2,022	—	1	1	1	1	1	1	—	1	—	—	—	—
Egan et al. 2003[b]	• Case-control	791/797	1	—	1	—	—	—	—	1	1	—	—	—	—
Ahern et al. 2009[b]	—	557/432	EV PY	EV PY	1	—	—	—	—	1	—	—	—	—	—
Gammon et al. 2004a[b]	• Case-control	1,356/1,383	—	1	1	1	1	—	1	1	1	1	—	—	—
Mordukhovich et al. 2010	—	128 p53+, 731 p53$^-$	—	1	1	1	1	—	—	—	—	—	—	—	—
Metsola et al. 2005	• KBCS • Case-control • Finland	475/481	—	1	1	—	—	—	—	1	—	—	—	1	1
Sillanpaa et al. 2005a[b]	—	479/482	—	1	1	1	1	—	—	1	—	—	—	—	1
Andonova et al. 2010[b]	• GENICA • Case-control • Germany	1,020/1,015	1	1	1	1	1	—	—	—	—	—	—	—	—
Rabstein et al. 2010	—	1,019/1,047	1	1	1	1	1	—	—	—	—	—	—	1	—

Table 6.16*S* Continued

Study	Design/population	Analytic sample size	Type of referent group		Meta-analysis categories							Design and analysis issues			
			No active-only	No active/no passive	Ever	Current	Former	Duration	Cigarettes/day	Pack-years	Age at initiation	Before/during first pregnancy	Small sample	Mixed referent or inadequate adjustment or proxy	Cut-point/outlier
B. Nonoverlapping reports (n = 39)															
Hiatt et al. 1988	• KPMCP • 1978–1984 • Cohort • United States	303 of 68,674	1	—	1	1	1	—	1	—	—	—	—	—	—
Schatzkin et al. 1989	• Framingham Heart Study • Cohort • Massachusetts	143 of 2,636	1	—	1	1	—	—	—	—	—	—	1	1	—
Vatten and Kvinnsland 1990	• Cohort • Norway (3 counties)	242 of 24,329	1	—	1	1	—	—	—	—	—	—	—	1	—
van den Brandt et al. 1995[a]	• Netherlands Cohort Study • Cohort • Netherlands	119 of 504	1	—	1	—	—	—	—	—	—	—	—	—	—
Engeland et al. 1996	• The Migrant Study • Cohort • Norway site	603 of 14,269	1	—	1	1	1	—	—	—	—	—	—	1	—
Nordlund et al. 1997	• Cohort • Linkopings, Sweden	996 of 26,032	1	—	1	1	1	—	1	—	1	—	—	1	—
Million Women Study Collaborative Group 1999[a]	• MWS • Cohort • United Kingdom	324 of 1,291	1	—	1	—	—	—	—	—	—	—	—	—	—
Innes and Byers 2001	• Case-control • New York	310/732	1	—	—	—	—	—	—	—	—	1	—	—	—

Table 6.16*S* Continued

Study	Design/population	Analytic sample size	Type of referent group		Meta-analysis categories							Design and analysis issues			
			No active-only	No active/no passive	Ever	Current	Former	Duration	Cigarettes/day	Pack-years	Age at initiation	Before/during first pregnancy	Small sample	Mixed referent or inadequate adjustment or proxy	Cut-point/outlier
Delfino et al. 2000	• Case-control • California	109/270	—	1	1	1	1	1	1	—	—	—	1	—	—
Johnson et al. 2000	• NECSS • Case-control • Canada	2,304/2,429	EV ST	EV ST D CD PY AI	1	1	1	1	1	1	1	—	—	—	—
Morabia et al. 2000	• Case-control • Geneva, Switzerland	160/162	—	1	1	—	—	—	—	—	—	—	1	1	—
Band et al. 2002	• Case-control • British Columbia, Canada	1,018/1,025	1	—	1	—	—	1	1	1	—	1	—	—	—
Kropp and Chang-Claude 2002	• Case-control • Mannheim, Germany	468/1,087	—	1	1	1	1	1	—	1	1	1	—	—	
Lash and Aschengrau 2002	• Case-control • Massachusetts	441/419	—	1	1	—	—	1	1	—	1	1	—	1	—
Zheng et al. 2002b	• Case-control • Connecticut	338/345	1	—	1	1	1	1	1	1	1	—	—	—	
Fink and Lash 2003	• Case-control • Massachusetts	1,878/5,632	1	—	—	—	—	—	—	—	—	1	—	—	—
van der Hel et al. 2003	• MPCDRF • Case-control • Netherlands	229/263	1	—	1	—	—	1	1	—	—	—	—	—	

Table 6.16*S* Continued

Study	Design/population	Analytic sample size	Type of referent group		Meta-analysis categories							Design and analysis issues			
			No active-only	No active/no passive	Ever	Current	Former	Duration	Cigarettes/day	Pack-years	Age at initiation	Before/during first pregnancy	Small sample	Mixed referent or inadequate adjustment or proxy	Cut-point/outlier
Alberg et al. 2004[d]	• CLUE-II/U.S. • Case-control • United States	115/115	EV ST	EV ST	1	1	1	—	—	1	—	—	1	1	—
Al-Delaimy et al. 2004	• NHS-II • Cohort • United States	1,007 of 112,844	1	—	1	1	1	1	1	—	1	1	—	—	
Reynolds et al. 2004b	• CTS/U.S. • Cohort • United States	2,005 of 116,544	EV ST CD AI FB	EV ST	1	1	1	1	1	1	1	1	—	—	
Lawlor et al. 2004	• Cohort • Bristol, United Kingdom	139 of 3,407	1	—	—	—	—	—	—	—	—	1	—	—	—
Gram et al. 2005	• N-SWLHCS • Cohort • Norway, Sweden	1,130 of 102,098	EV	EV ST D CD PY AI FB	1	1	1	1	1	1	1	1	—	—	—
Hanoaka et al. 2005	• JPHC • Cohort • Japan	180 of 21,805	EV ST	EV ST	1	1	1	—	—	—	—	—	1	—	—

Table 6.16*S* Continued

Study	Design/population	Analytic sample size	Type of referent group		Meta-analysis categories							Design and analysis issues			
			No active-only	No active/no passive	Ever	Current	Former	Duration	Cigarettes/day	Pack-years	Age at initiation	Before/during first pregnancy	Small sample	Mixed referent or inadequate adjustment or proxy	Cut-point/outlier
Li et al. 2005	• Case-control • Washington	939/963	1	—	1	1	1	1	1	1	1	1	—	—	1
Lissowska et al. 2006	• Case-control • Warsaw and Lodz, Poland	2,374/2,498	EV ST D CD AI FB	EV	1	1	1	1	1	—	1	1	—	—	1
Ha et al. 2007	• RTS • Cohort • United States	906 of 56,042	1	—	1	1	1	—	—	—	1	1	—	—	1
Kruk 2007	• Case-control • West Pomerania, Poland	857/1,084	1	—	1	1	—	—	1	—	—	—	—	—	1
Magnusson et al. 2007	• Case control • Sweden	2,784/2,583	1	—	1	1	1	1	1	1	1	1	—	—	1
Prescott et al. 2007	• Case-control • California	1,728/441	1	—	1	1	1	1	—	—	1	1	—	—	—
Roddam et al. 2007[c]	• Case-control • Thames, Oxford, and Yorkshire, United Kingdom	639/640	EV ST D CD AI	EV ST	1	1	1	1	1	—	1	—	—	—	1
Lin et al. 2008	• JCCS • Cohort • Japan	208 of 34,401	1	—	1	1	1	—	—	—	—	—	1	—	—

Table 6.16*S* Continued

Study	Design/population	Analytic sample size	Type of referent group		Meta-analysis categories							Design and analysis issues			
			No active-only	No active/no passive	Ever	Current	Former	Duration	Cigarettes/day	Pack-years	Age at initiation	Before/during first pregnancy	Small sample	Mixed referent or inadequate adjustment or proxy	Cut-point/outlier
Rollison et al. 2008	• Case-control • Delaware	287/311	EV D PY AI FB	EV D PY AI FB	1	—	—	1	1	1	1	1	—	—	—
Slattery et al. 2008	• 4-CBCS • Case-control • Arizona, Colorado, New Mexico, and Utah	2,400/2,473	1	—	1	1	1	—	—	1	1	1	—	—	—
Young et al. 2009	• OWHS and OWDHS • Case-control • Canada	5,246/5,564	—	1	1	—	—	—	—	—	1	1	—	—	—
Brown et al. 2010	• Case-control • California and Hawaii	591/960	1	—	1	1	1	1	1	—	1	—	—	—	—
Gibson et al. 2010	• Case-control • Manila, Philippines	123/965	1	—	1	—	—	—	—	—	—	—	1	—	—
Kaushal et al. 2010	• Case-control • Northeast India	117/174	1	—	1	—	—	—	—	—	—	—	1	1	—

Table 6.16*S* Continued

Study	Design/population	Analytic sample size	Type of referent group		Meta-analysis categories							Design and analysis issues			
			No active-only	No active/no passive	Ever	Current	Former	Duration	Cigarettes/day	Pack-years	Age at initiation	Before/during first pregnancy	Small sample	Mixed referent or inadequate adjustment or proxy	Cut-point/outlier
Cerne et al. 2011	• Case-control • Ljubljana, Slovenia	784/709	1	—	1	1	—	—	1	—	—	—	—	1	—
DeRoo et al. 2011a	• Case-control • Washington	1,027/777	1	—	—	—	—	—	—	—	—	1	—	—	—

Note: Analytic sample size is based on sample size reported for the ever smoking or smoking status category; for case-control studies, n of cases/n of controls, and for cohort studies, n of cases of total cohort. Measures of smoking are reported by meta-analysis category for studies with only 1 type of referent group. Measures of smoking are reported by each referent group for studies reporting both types of referent groups. **4-CBCS** = 4–Corners Breast Cancer Study; **AI** = age at initiation; **Carolina BCS** = Carolina Breast Cancer Study; **CD** = cigarettes/day; **D** = duration; **ColBCS** = Collaborative Breast Cancer Study; **CTS** = California Teachers Study; **ER+** = estrogen receptor positive; **FB** = timing in relation to first pregnancy/first birth; **CLUE-II** = Campaign Against Cancer and Heart Disease; **EV** = ever; **GENICA** = Gene Environment Interaction and Breast Cancer in Germany; **IWHS** = Iowa Women's Health Study; **JCCS** = Japan Collaborative Cohort Study for Evaluation of Cancer Risk; **JPHC** = Japan Public Health Center based prospective study; **KBCS** = Kuopio Breast Cancer Study; **KPMCP** = Kaiser Permanente Medical Care Program; **LIBCSP** = Long Island Breast Cancer Study Project; **LSS-RERF** = Life-Span Study of the Radiation Effects Research Foundation; **MPCDRF** = Monitoring Project on Cardiovascular Disease Risk Factors; **MS** = Migrant Study (Norwegian Component); **MWS** = Million Women Study; **N-SWLHCS** = Norwegian-Swedish Women's Lifestyle and Health Cohort Study; **NBSS** = Canadian National Breast Screening Study; **NECSS** = National Enhanced Cancer Surveillance System; **NHS** = Nurses' Health Study; **OWHS** = Ontario Women's Health Study; **OWDHS** = Ontario Women's Diet and Health Study; **PY** = pack-years: the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **ST** = status (never, current, former); **TNBC** = triple negative breast cancer; **U.S.-RTS** = U.S. Radiologic Technologists Study; **WHI** = Women's Health Initiative Observational Study. Estimates were abstracted either directly or pooled using other measures of smoking to calculate an estimate for the appropriate category.

[a]Studies included in the pooled analysis restricted to nondrinkers conducted by the Collaborative Group on Hormonal Factors in Breast Cancer (Collaborative Group on Hormonal Factors in Breast Cancer et al. 2002). Smoking data was not provided in the publications cited and sample sizes are those provided in the collaborative report from the pooled analysis with the exception of 1 cohort study (Hiatt and Bawol 1984). This study was combined in the collaborative report with 3 other studies, and it is not possible to determine the individual sample sizes used in the pooled analysis based on 1,923 cases out of a combined cohort of 9,578 nondrinkers. The analytic sample size reported in the above table is based on each study and is the total number of cases out of the total cohort, regardless of drinking status.

[b]Indicates those reports that overlap with another report and which contribute to at least 1 meta-analysis. In the case of 1 cohort study (NHS-I) and 1 case-control study (ColBCS), 2 reports contributed to separate meta-analyses because they offered different measures (NHS-I: Egan et al., 2002 and Xue et al., 2011; ColBCS: Egan et al. 2003 and Ahern et al. 2009).

[c]Some data not included in meta-analyses when reported only as a continuous measure: Roddam et al. 2007 for duration, age at initiation and cigarettes/day.

[d]This study was excluded from the comparison of the no active/no passive referent group with the no-active only referent group, as it was deleted after the meta-analysis of ever smoking due to small sample size and insufficient covariate adjustment.

Table 6.17*S* Summary of meta-analyses for measures of active cigarette smoking for all studies combined and stratified by study design, based on cohort studies published before 2012 and case-control studies published from 2000 to 2011

Measure of smoking	n	All studies: RR (95% CI)	Q test (p_h)	n	Cohort studies: RR (95% CI)	Q test (p_h)	n	Case-control studies: RR (95% CI)	Q test (p_h)
Ever[a]	46	1.12 (1.07–1.17)	<.001	19	1.10 (1.07–1.13)	.793	27	1.15 (1.06–1.25)	<.001
Ever[b]	33	1.11 (1.06–1.16)	<.001	12	1.10 (1.07–1.13)	.717	21	1.13 (1.04–1.23)	<.001
Ever[c]	30	1.09 (1.06–1.12)	.500	11	1.10 (1.07–1.13)	.659	19	1.08 (1.03–1.13)	.340
No-active only[d]	25	1.09 (1.06–1.13)	.308	11	1.10 (1.07–1.14)	.720	14	1.08 (1.02–1.15)	.149
No active/no passive[e]	14	1.15 (1.09–1.21)	.572	4	1.16 (1.09–1.24)	.964	10	1.14 (1.02–1.28)	.282
Former[f]	25	1.09 (1.05–1.13)	.062	11	1.09 (1.03–1.14)	.021	14	1.09 (1.03–1.16)	.354
Current[f]	25	1.12 (1.08-1.16)	.347	11	1.14 (1.10–1.18)	.746	14	1.07 (1.00–1.16)	.209
Duration, ≥20y[g]	19	1.16 (1.12–1.21)	.318	7	1.15 (1.10–1.19)	.819	12	1.23 (1.12–1.36)	.146
Duration, <20y[g]	19	1.04 (1.01–1.07)	.922	7	1.04 (1.00–1.08)	.843	12	1.04 (0.97–1.12)	.751
Cigarettes/day, ≥20[h]	18	1.13 (1.09–1.17)	.903	8	1.12 (1.08–1.17)	.851	10	1.19 (1.06–1.33)	.756
Cigarettes/day, <20[h]	18	1.10 (1.06–1.16)	.031	8	1.07 (1.04–1.10)	.547	10	1.23 (1.11–1.37)	.033
Pack-years, ≥20[i]	16	1.16 (1.11–1.21)	.304	6	1.15 (1.10–1.19)	.346	10	1.21 (1.09–1.34)	.314
Pack-years, <20[i]	16	1.09 (1.03–1.15)	.099	6	1.04 (1.00–1.09)	.872	10	1.20 (1.05–1.37)	.023
Age at smoking initiation, <20y[j]	22	1.11 (1.07–1.16)	.088	8	1.09 (1.06–1.13)	.541	14	1.12 (1.02–1.22)	.029
Age at smoking initiation, ≤16y[k]	19	1.08 (1.00–1.15)	.065	7	1.09 (1.02–1.17)	.327	12	1.04 (0.92–1.17)	.053
Age at smoking initiation, ≥20y[l]	19	1.08 (1.05–1.12)	.673	8	1.07 (1.03–1.11)	.952	11	1.12 (1.04–1.19)	.291
Smoking before/during first pregnancy[m]	22	1.10 (1.04–1.17)	<.001	9	1.16 (1.12–1.20)	.746	13	1.05 (0.94–1.18)	.001

Note: **CI** = confidence interval; **n** = sample size (number of studies); **RR** = relative risk; **y** = years. Estimates were either abstracted directly or pooled using other measures of smoking to calculate an estimate for the appropriate category (Table 6.16*S* provides more details about which studies contributed to exposure categories and reasons for exclusions). Cochran's $\chi 2$ test, reported as the Q-test statistic, was used to assess between-study heterogeneity (p_h); p_h values reported in SAS as 0.000 due to rounding shown in table as <0.001. Summary estimates for all meta-analyses are based on random effects models.

[a]Excludes 15 overlapping reports from 11 studies that were not the most recent or most complete report (Table 6.16*SA*) and 4 studies designed to evaluate smoking only before or during first pregnancy (Table 6.16*SB*), except for 2 meta-analyses. The estimates for the age at initiation meta-analysis were extracted from Egan and colleagues (2003) because estimates for age at initiation were not reported by Ahern and colleagues (2009). The estimates for the no active/no passive meta-analysis were extracted from Egan and colleagues (2002) rather than Xue and colleagues (2011), because the latter report used a no active-only referent group. See Figure 6.28 and 6.29.

[b]Excludes 19 reports (*note a*), 2 cohort studies reported in the pooled analysis restricted to nondrinkers (Collaborative Group on Hormonal Factors in Breast Cancer et al. 2002), 8 studies with <210 cases, and 3 studies with a mixed referent group or insufficient adjustment (Table 6.16*SB*).

[c]Excludes 32 reports (*note b*) and the remaining 3 studies with a design or analysis issue in Table 6.16B (Nordlund et al. 1997; Lash and Aschengrau 2002; Kruk 2007) (see Figure 6.30).

[d]Excludes 35 reports (*note c*) and 5 studies that did not have a no active-only referent group (Table 6.16*S*). See Figure 6.31.

[e]Excludes 35 reports (*note c*) and 16 studies that did not have a no active/no passive referent group (Table 6.16*S*). See Figure 6.32.

[f]Excludes 35 reports (*note c*) and 5 studies that did not have an estimate for former or current smoking (Table 6.16*S*). See Figures 6.33 and 6.34.

[g]Excludes 35 reports (*note c*), 1 study with a continuous measure only (Roddam et al. 2007), 10 studies with no available estimate for smoking duration (Hiatt and Fireman 1986; Hiatt et al. 1988; Manjer et al. 2000b; Gammon et al. 2004a; Sillanpaa et al. 2005a; Ha et al. 2007; Slattery et al. 2008; Ahern et al. 2009; Young et al. 2009; Andonova et al. 2010) (Table 6.16*S*). See Figure 6.35 for 20 or more years of smoking duration.

Table 6.17*S* Continued

[h]Excludes 35 reports (*note c*), 1 study with a continuous measure only (Roddam et al. 2007), 2 studies where the highest category was for less than 20 cigarettes/day (Gram et al. 2005; Lissowska et al. 2005), and 9 studies with no available estimate for cigarettes/day (Olson et al. 2005; Ahern et al. 2009; Sillanpaa et al. 2005a; Andonova et al. 2010; Kropp and Chang-Claude 2002; Ha et al. 2007; Prescott et al. 2007; Slattery et al. 2008; Young et al. 2009) (Table 6.16*S*). See Figure 6.36 for 20 or more cigarettes/day.
[i]Excludes 35 reports (*note c*), 1 study where the highest category was for five or more pack-years (Sillanpaa et al. 2005a), and 13 studies with no available estimate for pack-years (Hiatt and Fireman 1986; Hiatt et al. 1988; Manjer et al. 2000b; van der Hel et al. 2003b; Al-Delaimy et al. 2004; Lissowska et al. 2006; Mechanic et al. 2006; Ha et al. 2007; Prescott et al. 2007; Roddam et al. 2007; Young et al. 2009; Andonova et al. 2010; Brown et al. 2010) (Table 6.16*S*). See Figure 6.37 for 20 or more pack-years.
[j]Excludes 35 reports (*note c*), 1 study with a continuous measure only (Roddam et al. 2007), and 7 studies with no available estimate for age at initiation of smoking (Hiatt and Fireman 1986; Hiatt et al. 1988; Manjer et al. 2000b; Band et al. 2002; van der Hel et al. 2003b; Sillanpaa et al. 2005a; Andonova et al. 2010) (Table 6.16*S*). See Figure 6.38 for less than 20 years of age at smoking initiation.
[k]Excludes 43 reports (*note j*) and 3 studies that did not report a cutpoint of ≤16 years for age at initiation (Reynolds et al. 2004a, Li et al. 2005; Magnusson et al. 2007) (Table 6.16*S*B).
[l]Excludes 43 reports (*note j*) and 3 studies that did not report a cutpoint of ≥20 years for age at initiation (Gammon et al. 2004a; Rollison et al. 2008; Egan et al. 2003) (Table 6.16*S*B).
[m]Excludes the 15 overlapping reports (*note a*), 16 studies with a design or analysis issue and included in meta-analyses for only overall ever smoking (see Table 6.16*S*B), and 12 studies with no available estimate for smoking before first pregnancy (Hiatt and Fireman 1986; Hiatt et al. 1988; Manjer et al. 2000b; Johnson et al. 2000; Zheng et al. 2002a; van der Hel et al. 2003b; Sillanpaa et al. 2005a; Mechanic et al. 2006; Roddam et al. 2007; Ahern et al. 2009; Andonova et al. 2010; Brown et al. 2010) (Table 6.16*S*). See Figure 6.39.

Table 6.18*S* Reports of premenopausal and postmenopausal relative risks (RRs) by study and meta-analysis RRs for the association of active smoking (ever, pack-years) with risk for breast cancer, based on cohort studies published before 2012 and case-control studies published from 2000 to 2011 (n = 20)

A. Cohort Studies (n = 6)

		Ever smoking: RR (95% CI)		Pack-years of smoking: RR (95% CI)	
Study	**Number of cases/total cohort**	**Premenopausal (n = 4)**	**Postmenopausal (n = 6)**	**Premenopausal (n = 2)**	**Postmenopausal (n = 4)**
Hiatt and Fireman, 1986[a]	1,363/74,564	1.19 (1.03–1.38)	1.17 (0.97–1.41)	—	—
Manjer et al. 2000b[b]	416/10,902	1.35 (1.03–1.76)	1.06 (0.85–1.33)	—	—
Reynolds et al. 2004b[a]	2,005/116,544	1.10 (0.89–1.36)	1.15 (0.96–1.38)	≤10: 1.03 (0.78–1.35) 11–20: 1.31 (0.87–1.98) 21–30: 0.46 (0.17–1.24) >30: 2.05 (1.20–3.49) Pooled:[c] 1.03 (0.24–4.44)	≤10: 1.02 (0.88–1.88) 11–20: 1.23 (1.02–1.50) 21–30: 1.13 (0.89–1.44) >30: 1.19 (0.99–1.42) Pooled:[c] 1.17 (1.01–1.35)
Olson et al. 2005[a]	2,017/37,105	—	1.13 (1.03–1.24)	—	1–19: 1.05 (0.91–1.21) 20–39: 1.18 (1.02–1.37) >39: 1.15 (0.96–1.37) Pooled:[c] 1.17 (1.04–1.31)
Luo et al. 2011b[a]	3,520/79,990	—	1.10 (1.04–1.17)	—	<10: 1.04 (0.95–1.14) 10–19: 1.21 (1.08–1.36) 20–29: 1.13 (0.98–1.30) 30–39: 1.01 (0.86–1.19) 40–49: 1.16 (0.91–1.47) >50: 1.18 (1.02–1.37) Pooled:[c] 1.12 (1.03–1.21)
Xue et al. 2011[d]	8,772/111,140	1.14 (1.04–1.24)	0.91 (0.86–0.96)	1–10: 1.01 (0.95–1.08) 11–20: 1.14 (1.06–1.22) 21–30: 1.15 (1.07–1.24) >30: 1.27 (1.16–1.38) Pooled:[c] 1.21 (1.09–1.33)	1–5: 0.94 (0.86–1.02) 6–10: 0.89 (0.80–0.99) 11–15 0.90 (0.79–1.02) >15 0.88 (0.79–0.99)

Table 6.18*S* Continued

B. Case-control studies (n = 14)

Study	Number of cases/controls	Ever smoking: RR (95% CI)		Pack-years of smoking: RR (95% CI)			
		Premenopausal (n = 13)	Postmenopausal (n = 11)	Premenopausal (n = 5)		Postmenopausal (n = 6)	
Johnson et al. 2000[e]	2,317/2,438	1.00 (0.80–1.30)	1.20 (1.00–1.40)	1–10: 11–20: 21–30: >30: **Pooled:[c]**	2.40 (1.20–4.70) 2.30 (1.10–4.70) 1.70 (0.80–3.90) 1.50 (0.40–5.90) **1.65 (0.83–3.26)**	1–10: 11–20: 21–30: >30: **Pooled:[c]**	1.40 (0.90–2.10) 1.20 (0.70–1.90) 1.90 (1.10–3.10) 1.60 (1.00–2.60) **1.73 (1.22–2.46)**
Band et al. 2002	1,018/1,025	1.50 (1.09–2.07)	0.96 (0.77–1.19)	<20: ≥20:	1.30 (0.90–1.87) 1.69 (1.10–2.61)	<20: ≥20:	0.84 (0.64–1.09) 1.03 (0.79–1.34)
Zheng et al. 2002a	338/345	0.80 (0.50–1.40)	1.20 (0.80–1.80)	<5: 5–20: >20:	0.80 (0.40–1.70) 1.00 (0.50–2.10) 0.40 (0.10–1.40)	<5: 5–20: >20:	1.10 (0.60–2.10) 1.30 (0.80–2.10) 1.20 (0.70–1.90)
Li et al. 2005	975/1,007	—	1.30 (1.00–1.50)	—		<11: 11–27: 28–52: >52: **Pooled:[c]**	1.00 (0.70–1.30) 1.40 (1.10–1.90) 1.30 (1.00–1.80) 1.30 (1.00–1.70) **1.30 (1.07–1.58)**
Slattery et al. 2008[g]	1,527/1,601	1.23 (0.99–1.53)	1.00 (0.88–1.14)	See insert C			
Ahern et al. 2009[d]	557/432	1.15 (0.63–2.12)	1.05 (0.78–1.41)	0–23: >23:	1.50 (0.90–2.40) 0.80 (0.40–1.60)	0–23: >23:	1.10 (0.70–1.60) 1.00 (0.60–1.40)
Kropp and Chang-Claude 2002[f]	468/1,093	1.31 (0.90–1.92)	—	—		—	
Gammon et al. 2004a	1,356/1,383	0.98 (0.54–1.78)	1.08 (0.72–1.62)	—		—	
Lissowska et al. 2006[h]	2,386/2,502	1.95 (1.38–2.76)	0.91 (0.77–1.09)	—		—	
Kruk 2007[b]	858/1,085	2.34 (1.81–3.02)	1.76 (1.41–2.19)	—		—	
Magnusson et al. 2007[i]	3,345/3,454	1.40 (0.70–2.50)	1.00 (0.90–1.20)	—		—	
Prescott et al. 2007	1,728/441	0.99 (0.78–1.25)	—	—		—	
Roddam et al. 2007[a]	639/640	1.09 (0.90–1.33)	—	—		—	
Rollison et al. 2008	287/311	1.53 (0.60–3.95)	1.36 (0.95–1.94)	—		—	

Table 6.18*S* Continued

Study	Number of cases/controls	Ever smoking: RR (95% CI)		Pack-years of smoking: RR (95% CI)	
		Premenopausal (n = 13)	Postmenopausal (n = 11)	Premenopausal (n = 5)	Postmenopausal (n = 6)
Cohort studies RR	—	1.16 (1.08–1.24)	1.07 (0.97–1.19)	1.21 (1.10–1.34)	1.08 (0.95–1.23)
Case-control studies RR	—	1.30 (1.04–1.62)	1.13 (1.01–1.27)	1.23 (0.84–1.80)	1.18 (1.01–1.38)
Exclusion of outlier[j]		1.20 (1.02–1.42)	1.07 (0.98–1.16)	—	—
All studies RR	—	1.26 (1.11–1.43)	1.10 (1.02–1.19)	1.24 (1.03–1.49)	1.12 (1.02–1.23)
Exclusion of outlier[j]		1.18 (1.08–1.29)	1.07 (1.00–1.14)	—	—

Note: One study reported data for pack-years, but estimates were restricted to parous women only and are not included in this table (Ha et al. 2007). Direct nonpooled estimates for ever smoking for the following studies: (Johnson et al. 2000; Band et al. 2002; Kropp and Chang-Claude 2002; Zheng et al. 2002a; Gammon et al. 2004a; Li et al. 2005; Lissowska et al. 2006; Magnusson et al. 2007; Prescott et al. 2007; Rollison et al. 2008). None of the summary estimates shown was associated with a statistically significant result for publication bias using the Begg or Egger statistic (p ≥0.05). Results for the Q-test for heterogeneity are not shown in the table.
CI = confidence interval; **H** = Hispanic; **NHW** = non-Hispanic White.
[a]Summary estimate for ever smoking pooled from estimates for former and current smokers reported within menopausal status (Hiatt and Fireman 1986; Reynolds et al. 2004a; Olson et al. 2005; Roddam et al. 2007; Luo et al. 2011b).
[b]Summary estimate for ever smoking pooled from estimates for levels of cigarettes/day within menopausal status (Kruk 2007; Manjer et al. 2000b).
[c]Estimates for categories of pack-years ≥20 pooled for meta-analysis.
[d]Summary estimate for ever smoking pooled from estimates for levels of pack-years reported within menopausal status (Ahern et al. 2009; Xue et al. 2011). The estimates for pack-years reported in Xue and colleagues (2011) are defined as pack-years from menarche to before menopause (premenopausal); and pack-years after menopause (postmenopausal).
[e]The estimates for ever smoking are based on the full study sample using no-active only as the referent group. However, the estimates for pack-years are based on the subsample using the no active/no passive exposure referent group for those reporting a lifetime residential smoking history of >90%, which reduces the total sample size by 38%. Estimates for pack-years were not available for the no-active only referent group (Johnson et al. 2000).
[f]Approximately 80% of the study population was premenopausal; approximately 13-16% classified as menopause unknown (Kropp and Chang-Claude 2002).
[g]Summary estimates for ever smoking pooled across estimates for non-Hispanic White and Hispanic women within menopausal status; estimates for pack-years pooled across ethnicity for both 1–15 and >15 pack-years (Slattery et al. 2008).
[h]Estimate for premenopausal, based on women <45 years of age; estimate for postmenopausal, based on women >55 years of age; estimate for women 45–55 years of age excluded (Lissowska et al. 2006).
[i]The estimates by menopausal status are based on current smokers compared to never smokers; former smokers appear to be excluded. The majority of women were postmenopausal (age range: 50–74 years). The exact percent for premenopausal women could not be determined (Magnusson et al. 2007).
[j]The exclusion of the outlier estimate reported for the study by Kruk (2007).

Table 6.19*S* **Reports of estrogen receptor status relative risks (RRs) for the association of active cigarette smoking (ever, cigarettes/day) with risk for breast cancer, based on cohort studies published before 2012 and case-control studies published from 2000 to 2011 (n = 17)**

A. Cohort studies (n = 2)

Study	Age group and location	Sample size of cases (% with ER)	Ever smoking: RR (95% CI)		Cigarettes/day: RR (95% CI)	
			ER+	ER–	ER+	ER–
London et al. 1989[a]	30–55 years of age United States	1,788 (50)	1.18 (1.04–1.35)	1.01 (0.82–1.24)	1–14: 1.13 (0.82–1.54) 15–24: 1.08 (0.82–1.43) ≥25: 1.38 (1.04–1.84)	1–14: 0.68 (0.41–1.12) 15–24: 1.15 (0.81–1.63) ≥25: 1.05 (0.69–1.59)
Al-Delaimy et al. 2004[b]	25–42 years of age United States	785 (78)	1.30 (1.13–1.51)	1.07 (0.86–1.34)	1–4: 1.45 (1.09–1.93) 5–14: 1.46 (1.14–1.87) 15–24: 1.06 (0.81–1.38) ≥25: 1.16 (0.64–2.09)	1–4: 0.62 (0.14–2.71) 5–14: 1.14 (0.78–1.68) 15–24: 1.23 (0.86–1.75) ≥25: 0.99 (0.50–1.93)

B. Case-control studies (n = 15)

Study	Age group and location	Sample size of cases (% with ER)	Ever smoking: RR (95% CI)		Cigarettes/day: RR (95% CI)	
			ER+	ER–	ER+	ER–
Luo et al. 2011b[c]	50–79 years of age United States	3,520 (89)	1.15 (1.07–1.23)	1.00 (0.83–1.19)	—	—
McTiernan et al. 1986[d]	25–54 years of age United States	329 (73)	1.03 (0.73–1.47)	0.79 (0.52–1.20)	—	—
Stanford et al. 1987	20–54 years of age United States	561 (82)	1.03 (0.70–1.40)	1.00 (0.70–1.40)	—	—
Cooper et al. 1989	20–74 years of age Australia	451 (84)	0.95 (0.66–1.37)	1.63 (1.00–2.66)	—	—
Yoo et al. 1997	≥25 years of age Japan	1,154 (40)	1.42 (1.04–1.94)	1.33 (0.87–2.02)	—	—
Morabia et al. 1998[e]	30–74 years of age Switzerland	264 (92)	2.28 (1.56–3.35)	4.01 (1.90–8.46)	<20: 2.20 (1.30–3.60) ≥20: 2.40 (1.40–4.50)	<20: 3.80 (1.40–10.3) ≥20: 4.30 (1.40–13.2)
Huang et al. 2000a[d]	20–74 years of age United States	862 (91)	1.10 (0.84–1.45)	0.86 (0.48–1.54)	—	—
Manjer et al. 2001[d]	50 years of age Sweden	268 (100)	0.94 (0.74–1.21)	2.41 (1.57–3.71)	≤19: 0.87 (0.60–1.25) ≥20: 0.82 (0.49–1.39)	≤19: 2.04 (1.07–3.88) ≥20: 2.62 (1.17–5.87)

Table 6.19*S* Continued

Study	Age group and location	Sample size of cases (% with ER)	Ever smoking: RR (95% CI)		Cigarettes/day: RR (95% CI)	
			ER+	ER–	ER+	ER–
Britton et al. 2002[f]	20–44 years of age United States	1,556 (78)	0.87 (0.65–1.17)	0.94 (0.78–1.33)	—	—
Cotterchio et al. 2003[g]	25–74 years of age Canada	3,748 (87)	1.08 (0.94–1.25)	1.21 (0.94–1.56)	—	—
Gammon et al. 2004a[h]	24–98 years of age United States	894 (66)	1.17 (0.92–1.48)	1.06 (0.75–1.51)	—	—
Li et al. 2005[i]	65–79 years of age United States	900 (92)	1.22 (1.02–1.46)	1.30 (0.80–2.00)	<10: 1.27 (0.97–1.68) 10–19: 1.22 (0.95–1.57) ≥20: 1.20 (0.96–1.51)	<10: 1.00 (0.50–2.00) 10–19: 2.00 (1.10–3.50) ≥20: 1.10 (0.60–2.00)
Lissowska et al. 2006[j]	Poland 20–74 years of age	1,716 (72)	1.16 (0.99–1.36)	1.04 (0.86–1.27)	<10: 1.06 (0.82–1.37) 10–14: 1.26 (0.99–1.60) >14: 1.02 (0.81–1.29)	<10: 1.07 (0.77–1.48) 10–14: 1.13 (0.84–1.53) >14: 0.73 (0.73–1.32)
Trivers et al. 2009[k]	20–54 years of age United States	831 (57)	0.98 (0.51–1.91)	1.22 (0.67–2.22)	—	—
Rabstein et al. 2010[d]	<80 years of age Germany	1,020 (75)	0.79 (0.65–0.95)	1.12 (0.84–1.49)	—	—

Note: **CI** = confidence interval; **ER** = estrogen receptor; **HER2** = human epidermal growth factor receptor 2; **PR** = progesterone receptor.
[a]Estimates for ex-smokers and for categories of cigarettes/day among current smokers pooled for an estimate of ever smoking (London et al. 1989).
[b]Estimates for the four categories of duration pooled for an estimate of ever smoking (Al-Delaimy et al. 2004).
[c]Estimates for current and former smoking pooled across ER/PR status for an estimate of ever smoking (Luo et al. 2011b). Overlaps with an analysis restricted to an evaluation of triple negative (n = 300) and ER+ (n = 2,479) (Kabat et al. 2011) (See Table 6.16*S* in this report).
[d]Estimates for current and former smoking pooled for an estimate of ever smoking (McTiernan et al. 1986; Huang et al. 2000a; Manjer et al. 2001; Rabstein et al. 2010).
[e]Estimates for levels of numbers of cigarettes/day among ever smokers pooled for an estimate of ever smoking (Morabia et al. 1998).
[f]Estimates for current and former smoking pooled across PR categories for an estimate of ever smoking (Britton et al. 2002).
[g]Estimates for pack-years pooled across menopausal status pooled for an estimate of ever smoking (Cotterchio et al. 2003). Discordant ER/PR results were not included in the manuscript.
[h]Estimates for active smoking only and passive and active smoke exposure pooled across PR categories for an estimate of ever smoking. Referent group based on no active/no passive exposure (Gammon et al. 2004a).
[i]Estimates for ever smokers pooled across PR categories (ER+/PR+, ER+/PR-) to calculate an estimate for ever smoking by ER+ status; (ER–/PR+) did not have a calculated estimate as there were only 6 cases (Li et al. 2005).
[j]CI for >14 cigarettes/day for ER– status appears to have a typographical error (Lissowska et al. 2006).
[k]Estimates for current and former smoking pooled across ER/PR/HER2 status for an estimate of ever smoking (Trivers et al. 2009).

Table 6.20*S* Reports on the association between active cigarette smoking and risk of a second primary contralateral breast cancer (n = 7)

Study	Design/population	Cases/noncases	Measure of smoking: RR (95% CI)
Kato et al. 1986[a]	• Case control • 1964–1984 • 49 years of age • Japan	115/230	≥10 cigarettes/day: 0.41 (p = 0.05)
Horn and Thompson 1988[b]	• Case control • 1975–1983 • 20–93 years of age • 8 hospitals • Connecticut	292/264	Ever: 0.8 (0.5–1.3) ≥40 years duration: 1.5 (0.7–3.2) ≥1 pack/day: 1.7 (0.9–3.1) ≥40 pack-years: 1.5 (0.7–3.2)
Bernstein et al. 1992[b]	• Cohort • Cancer and Steroid Hormone Study (8 SEER sites) • 1980–1982 • 20–54 years of age	136/4,550	Ever: 1.24 (0.87–1.77) <19 years of age at smoking initiation: 1.24 (0.80–1.92)
Fowble et al. 2001[c]	• Cohort • 1978–1994 • 22–88 years of age • Pennsylvania	87/1,253	Ever: ~0.5 (p = 0.04)
Trentham-Dietz et al. 2007a[b]	• Cohort • 1987–2000 • 18–79 years of age • Wisconsin	488/10,953	Current: 1.00 (0.78–1.28) Former: 1.09 (0.89–1.35)
Knight et al. 2009[d]	• Case control • WECARE • 1985–2001 • <55 years of age • Iowa, Los Angeles and Orange County in California, Seattle, Denmark	708/1,399	Ever: 1.1 (0.9–1.6) Ever, risk period: 1.2 (0.9–1.5) ≥20 years duration: 1.1 (0.9–1.5) >0.5 packs/day (mean): 1.1 (0.8–1.4) 19 pack-years: 1.1 (0.8–1.4) <20 years of age at smoking initiation: 1.1 (0.9–1.4)
Li et al. 2009[e]	• Nested case control • 1990–2005 • 40–79 years of age • Seattle-Puget Sound • 4 counties in Western Washington	365/726	Current, baseline: 1.8 (1.1–3.2) Current, reference: 2.2 (1.2–4.0)

Note: **CI** = confidence interval; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **RR** = relative risk; **SEER** = Surveillance, Epidemiology, and End Results Program; **WECARE** = Women's Environmental Cancer and Radiation Epidemiology Study.

[a]Ascertained from women identified through a cancer clinic; no information on stage is provided. The referent group for measure of smoking is based on women who smoked <10 cigarettes/day.

[b]Ascertained from women identified through either the state cancer registry (Horn and Thompson 1988; Trentham-Dietz et al. 2007a) or through the SEER Program (Bernstein et al. 1992) and diagnosed with a first primary breast cancer (controls) or a second primary breast cancer diagnosed in the contralateral breast (cases).

[c]Ascertained from women identified through clinics with Stage I–II breast cancer over a median follow-up time of 8.9 years. Rate ratio calculated for this table based on cumulative incidence for smokers = 5% and 10% for nonsmokers at 10-year follow-up. Missing data for smoking history for 38% of subjects.

[d]Ascertained from women identified through population-based cancer registries with either a first primary invasive breast cancer with no regional lymph node involvement (controls) or a second primary in situ or invasive breast cancer diagnosed in the contralateral breast no more than 1 year after the first breast cancer diagnosis (cases). The referent group was never smokers for all categories with the exception of 'Ever, risk period', which was defined as starting prior to or during the period between the first diagnosis and the reference date and stopping during or after this period.

[e]Ascertained from women identified through a population-based cancer registry with Stage I–IIIB and ER+ breast cancer; baseline = first breast cancer diagnosis; reference = date of contralateral breast cancer diagnosis for cases and for controls the date of the matched patient's contralateral diagnosis.

Table 6.21*S* Modification of risk for breast cancer associated with smoking by *NAT2* phenotype, based on two meta-analyses and one pooled analysis, stratified by menopausal status

		Slow acetylation status			Fast acetylation status		
Study	**Measure of smoking**	**All women: RR (95% CI)**	**Premenopausal: RR (95% CI)**	**Postmenopausal: RR (95% CI)**	**All women: RR (95% CI)**	**Premenopausal: RR (95% CI)**	**Postmenopausal: RR (95% CI)**
Terry and Goodman 2006[a]		1.50 (1.20–1.80)	1.40 (0.90–2.20)	2.40 (1.70–3.30)	1.20 (1.00–1.50)	1.50 (0.90–2.40)	1.30 (0.80–2.00)
Ambrosone et al. 2008[b]	Ever smoking	1.27 (1.16–1.40) $p_h = 0.30$[c]	1.28 (1.09–1.50) $p_h = 0.89$	1.34 (1.17–1.53) $p_h = 0.39$	1.05 (0.95–1.17) $p_h = 0.61$	1.08 (0.89–1.30) $p_h = 0.26$	1.07 (0.92–1.24) $p_h = 0.51$
	<20 pack-years	1.21 (1.08–1.35)	1.21 (1.00–1.45)	1.28 (1.08–1.50)	1.06 (0.93–1.21)	1.00 (0.80–1.24)	1.12 (0.93–1.36)
	≥20 pack-years	1.44 (1.23–1.68)	1.47 (1.08–2.01)	1.41 (1.15–1.72)	1.04 (0.87–1.25)	1.34 (0.94–1.89)	0.98 (0.77–1.26)
Cox et al. 2011[d]	Duration (years), continuous	1.01 (1.00–1.01)	1.00 (0.99–1.01)	1.01 (1.00–1.01)	1.01 (1.00–1.01)	1.00 (0.99–1.01)	1.00 (1.00–1.01)
	Pack-years, continuous	1.01 (1.00–1.01)	1.00 (0.99–1.01)	1.01 (1.00–1.01)	1.01 (1.00–1.01)	1.00 (0.99–1.01)	1.01 (1.00–1.01)
	≤15 years duration	1.07 (0.95–1.21)	—	—	1.14 (0.98–1.32)	—	—
	>15 years duration	1.18 (1.07–1.29)	—	—	1.17 (1.04–1.30)	—	—
	≤20 pack-years	1.08 (0.92–1.19)	—	—	1.13 (1.01–1.27)	—	—
	>20 pack-years	1.25 (1.11–1.39)	—	—	1.24 (1.08–1.42)	—	—

Note: **CI** = confidence interval; **RR** = relative risk.

[a]Ever smokers compared with never smokers for 13 studies (4,837 cases, 6,017 controls). (Ambrosone et al. 1996; Hunter et al. 1997; Millikan et al. 1998; Delfino et al. 2000; Morabia et al. 2000; Krajinovic et al. 2001; Chang-Claude et al. 2002; Egan et al. 2003; van der Hel et al. 2003b; Alberg et al. 2004; Lilla et al. 2005; van der Hel et al. 2005; Sillanpaa et al. 2005a).

[b]Referent group based on never smokers. Acetylator status based on common use across studies: rapid equals presence of one rapid acetylator allele, and slow equals presence of three common variant alleles (*NAT2*5, NAT2*6,* and *NAT2*7*). Summary estimates for ever smokers based on 13 studies (6,757 cases, 7,454 controls) (Ambrosone et al. 1996; Hunter et al. 1997; Millikan et al. 1998; Morabia et al. 2000; Krajinovic et al. 2001; Chang-Claude et al. 2002; Egan et al. 2003; van der Hel et al. 2003b; Alberg et al. 2004; Kocabas et al. 2004; van der Hel et al. 2005; Sillanpaa et al. 2005a; Lissowska et al. 2006). Estimates for pack-years based on 8 studies (Ambrosone et al. 1996; Morabia et al. 2000; Chang-Claude, et al. 2002; Egan et al. 2003; van der Hel et al. 2003b; Alberg et al. 2004; Sillanpaa et al. 2005a; Lissowska et al. 2006). There was no significant heterogeneity across studies for pack-years. Summary estimates, independent of acetylator status: <20 pack-years (RR = 1.14; 95% CI, 1.03–1.25); ≥20 pack-years (RR = 1.26; 95% CI, 1.12–1.43).

[c]p_h for heterogeneity.

[d]Based on a pooled analysis of nested case-control studies from 7 cohorts (6,900 cases, 9,903 controls). Fast acetylation status is based on the combination of rapid plus intermediate phenotypes.

Table 6.22*S* Reports on cohort studies of the association between exposure to secondhand smoke and relative risk (RR) for breast cancer incidence, based on studies published before 2012 included in the 2006 Surgeon General's Report (n = 7)

Study	Design/population	Number of breast cancer events	Data collection/subgroup analyses	Findings for exposure to secondhand smoke	Measures of exposure to secondhand smoke: RR (95% CI)	Confounders
Gram et al. 2005	• Women's Lifestyle and Health Study Norwegian-Swedish Cohort • 102,098 women were enrolled in 1991–1992 to evaluate lifestyle risk factors for multiple health outcomes • Average follow-up: 8–9 years • Ages 30–50 years • Norway and Sweden	Approximately 377 incident cases (invasive) among 36,773 never active smokers (estimate for case number derived from the incidence for never smokers, 114/100,000 person-years, and total number of never smokers 36,773, assuming 9 years of followup)	• Self-administered questionnaire at enrollment • Data collected from never smokers who reported having lived with a smoker or lived with a smoker during childhood • Data collected for active cigarette smoking (see Table 6.14*S*)	• Nonsignificant increased risk for breast cancer among subjects ever exposed to passive smoke • Nonsignificant results reported for different combinations of exposure during childhood and adulthood (data not provided)	**Ever in Lifetime:** NA/NP: 1.00 Passive, ever: 1.21 (0.98–1.50)	Controlled for age at enrollment, menopausal status, number of children, age at birth of first child, HRT, use of oral contraceptives, BMI, alcohol use
Lin et al. 2008	• Collaborative Cohort Study for Evaluation of Cancer Risk • 34,401 women enrolled from 1988 to 1990 from 24 areas • Average follow-up: 11–13 years • Ages 40–79 years • Japan	140–178 incident cases (stage not specified), depending on the location of exposure to secondhand smoke, among 32,023 never smokers	• Self-administered questionnaire at enrollment. • Data collected from nonsmokers exposed at home and in public, (1–2, 3–4 days/week, almost every day), and exposure during childhood. • Data collected for active cigarette smoking (see Table 6.14*S*)	• No association between risk for breast cancer and exposure at home or outside the home • Small but nonsignificant increase in risk for exposure during childhood • No association when analyses were based on referent group composed of nonsmokers that had no exposure to secondhand smoke at home or in public places	**Adulthood, household:** NA/NP: 1.00 Sometimes: 0.59 (0.33–1.05) Almost daily: 0.71 (0.48–1.05) **Adulthood, public places:** NA/NP: 1.00 Sometimes: 0.77 (0.51–1.15) Almost daily: 0.84 (0.51–1.40) **Childhood:** NA/NP: 1.00 Yes: 1.24 (0.84–1.85)	Controlled for age, geographic area, BMI, family history, alcohol use, daily walking, age at menarche, age at birth of first child, menopausal status, parity, and HRT

Table 6.22*S* Continued

Study	Design/population	Number of breast cancer events	Data collection/subgroup analyses	Findings for exposure to secondhand smoke	Measures of exposure to secondhand smoke: RR (95% CI)	Confounders
Pirie et al. 2008	• Million Women Study • 224,917 women who reported being never smokers and enrolled in 66 breast cancer screening clinics from 1996 to 2001 to evaluate the association between exposure to passive smoke and breast cancer • Average follow-up: 3.5 years • Ages 50–64 years • United Kingdom	2,344 incident cases (invasive) among 210,647 never active smokers with complete data	• Self-administered questionnaire at enrollment • Data collected for exposure to maternal or paternal smoking at birth, at age 10, and from partner	• No association between risk for breast cancer and exposure to secondhand smoke during childhood or adulthood or combined	**Childhood:** NA/NP: 1.00 Birth: 0.98 (0.89–1.07) Age 10: 0.96 (0.88–1.06) **Childhood, maternal:** NA/NP: 1.00 Birth or age 10: 0.96 (0.88–1.05) **Childhood, paternal:** NA/NP: 1.00 Birth or age 10: 1.03 (0.93–1.14) **Childhood, both parents:** NA/NP: 1.00 Birth or age 10: 1.00 (0.91–1.10) **Adulthood:** NA/NP: 1.00 Yes: 1.02 (0.89–1.16) **Child and adulthood:** NA/NP: 1.00 Yes: 1.03 (0.90–1.19) **Child or adulthood:** NA/NP: 1.00 Yes: 0.98 (0.88–1.09)	Controlled for age, region of residence, socioeconomic group, age at menarche, parity, age at birth of first child, menopausal status, BMI, physical activity, alcohol use, and HRT

Table 6.22*S* Continued

Study	Design/population	Number of breast cancer events	Data collection/subgroup analyses	Findings for exposure to secondhand smoke	Measures of exposure to secondhand smoke: RR (95% CI)	Confounders
Reynolds et al. 2009[a]	• California Teachers Study • 329,000 women enrolled from 1995 to 2000 to evaluate risk factors for breast cancer • Average follow-up: 12 years • Age >20 years • United States	1,754 incident cases (invasive) among 57,523 never active smokers	• Self-administered questionnaire at time of enrollment and during Wave II in 1997. • Data collected for exposure at home, work, and social settings during childhood (age <20 years) and/or adulthood (age ≥20 years), including variables for duration (sum of years across all settings) and intensity. • Subgroups evaluated and stratified by menopausal status, family history of breast cancer, and estrogen receptor status (data not shown)	• No significant associations among lifetime passive exposure and risk of breast cancer • Results not significant when evaluated by menopausal status and duration • Risk was statistically significant only in postmenopausal women exposed in adulthood (age >20 years) with the highest intensity-years of exposure (RR = 1.25; 95% CI, 1.01–1.56)	**Ever:** NA/NP: 1.00 Ever Passive: 1.10 (0.94–1.30) **Ever, premenopausal:** NA/NP: 1.00 Ever Passive: 1.04 (0.79–1.38) **Ever, postmenopausal:** NA/NP: 1.00 Ever Passive: 1.22 (0.97–1.52) **Childhood:** NA/NP: 1.00 Any: 1.06 (0.94–1.19) **Adulthood:** NA/NP: 1.00 Any: 1.04 (0.91–1.19) Any Work: 1.02 (0.93–1.13) **Duration (years):** NA/NP: 1.00 Low (≤15): 1.10 (0.92–1.32) Medium (15–30): 1.10 (0.92–1.32) High (>30): 1.12 (0.93–1.33)	Controlled for age, race, family history, age at menarche, pregnancy history, lifetime duration of breastfeeding, physical activity, alcohol use, BMI, menopausal status, and HRT
Chuang et al. 2011	• EPIC • Women and men recruited from 23 centers in 10 countries in Europe to investigate risk factors for cancer from 1992 to 1998 • Average follow-up: 10 years • Ages 25–70 years • Europe	3,187 incident cases (invasive) among 92,956 never active smoking women	• In-person or self-administered interviews were conducted depending on each center. • Data collected for exposure during childhood and for frequency of exposure from French and Italian centers only.	• No significant association between breast cancer and passive smoke exposure in childhood.	**Status:** NA/NP: 1.00 Yes: 0.98 (0.91–1.06) **Frequency:** NA/NP: 1.00 Few times/week: 0.98 (0.88–1.10) Daily: 1.06 (0.95–1.19) p-trend: 0.40	Controlled for education, baseline alcohol use, BMI, physical activity, vegetable intake, fruit intake, nonalcoholic energy intake, adult passive smoking, age at menarche, use of oral contraceptives, parity, and menopausal status

Table 6.22*S* Continued

Study	Design/population	Number of breast cancer events	Data collection/subgroup analyses	Findings for exposure to secondhand smoke	Measures of exposure to secondhand smoke: RR (95% CI)	Confounders
Luo et al. 2011b[a]	• Women's Health Initiative Observational Study • 93,676 women enrolled in 40 United States clinical centers from 1993 to 1998 to evaluate major causes of morbidity and mortality among postmenopausal women • Average follow-up; 10.3 years • Ages 50–79 years • United States	1,692 incident cases (invasive) among 41,022 never active smokers	• Self-administered questionnaire at enrollment. • Data collected for exposure during childhood (<18 years), adulthood at home and at work, and duration of exposure • Data for exposure to active smoking collected (see Table 6.14*S*) • Subgroups evaluated and stratified by hormone receptor status and histology (ductal and lobular)	• No significant association between breast cancer and passive smoke exposure, except in the highest combined category of exposure (RR = 1.32; 95% CI, 1.04–1.67) based on exposure in childhood ≥10 years plus adult at home ≥20 years plus adult at work ≥10 years • No significant dose response observed for any combination of time period and place. • No significant association between risk and hormone receptor status or histologic type of breast cancer was observed	**Ever:** NA/NP: 1.00 Any: 1.09 (0.92–1.29) **Childhood:** NA/NP: 1.00 Yes: 1.19 (0.93–1.53) **Adulthood:** NA/NP: 1.00 Home only: 0.91 (0.70–1.19) Work only: 1.01 (0.82–1.26) Home and work: 1.15 (0.93–1.41) **Childhood and adulthood:** NA/NP: 1.00 Home only: 1.04 (0.83–1.30) Work only: 1.17 (0.94–1.45) Home and work: 1.11 (0.92–1.34)	Controlled for age at enrollment, ethnicity, education, BMI, physical activity, alcohol use, parity, family history, history of HRT, age at menarche, and age of first live birth

Table 6.22*S* Continued

Study	Design/population	Number of breast cancer events	Data collection/subgroup analyses	Findings for exposure to secondhand smoke	Measures of exposure to secondhand smoke: RR (95% CI)	Confounders
Xue et al. 2011[a]	• Nurses' Health Study • 121,700 registered nurses completed a mailed questionnaire in 1976 for information about factors related to breast cancer incidence and cardiovascular disease • 78,206 women were followed prospectively for 14 years (1976–2006) • Ages 30–55 years • United States	2,890 incident cancer cases (invasive) among 36,017 nonsmokers who completed the 1982 questionnaire	• Self-administered questionnaire at enrollment • Data collected for parental smoking, duration, and frequency of exposure in adulthood at home and work • Data collected for exposure to active smoking (see Table 6.14*S*) • Subgroups evaluated and stratified by menopausal status	• No association between breast cancer and any measure of exposure to passive smoke • No significant trend for duration of exposure or combination of duration and frequency	**Childhood:** NA/NP: 1.00 Mother only: 0.83 (0.66–1.05) Father only: 1.01 (0.93–1.10) Both parents: 0.90 (0.79–1.03) **Adulthood, work:** NA/NP: 1.00 Occasionally: 0.99 (0.89–1.09) Regularly: 0.87 (0.78–0.98) **Adulthood, home:** NA/NP: 1.00 Occasionally: 1.06 (0.97–1.17) Regularly: 1.02 (0.90–1.14) **Years living with smoker:** NA/NP (<1): 1.00 1–4: 1.09 (0.96–1.24) 5–9: 0.98 (0.84–1.13) 10–19: 0.96 (0.86–1.08) 20–29: 0.96 (0.85–1.08) 30–39: 0.97 (0.84–1.13) ≥40: 0.99 (0.74–1.32) p-trend: 0.24	Controlled for age, family history, history of benign breast disease, current BMI and at age 18 years, height, alcohol use, age at menarche, parity, age at first birth, physical activity, use of oral contraceptives, menopausal status, postmenopausal HRT, and age at menopause; mutual adjustment for passive smoking at home and at work

Note: Data from cohort studies for active cigarette smoking are summarized in Table 6.14*S*. Numbers for cases and controls are based on nonsmokers, which is a smaller percentage of subjects than the total included for analyses of active cigarette smoking. All results reported by the study may not appear in the summary table. **BMI** = body mass index; **CI** = confidence interval; **EPIC** = European Prospective Investigation into Cancer and Nutrition; **HRT** = hormone replacement therapy; **NA/NP** = no active/no passive.

[a]Overlapping reports based on the same study population.

Table 6.23*S* Reports on case-control studies of the association between exposure to secondhand smoke and relative risk for breast cancer incidence, based on studies published before 2012 but not included in the 2006 Surgeon General's Report (n = 11)

Study	Design/population	Data collection/ subgroup analyses	Findings for exposure to secondhand smoke	Measures of exposure to secondhand smoke: RR (95% CI)	Confounders
Alberg et al. 2004	• Nested case-control study to evaluate *NAT2* genotype and cigarette smoking on breast cancer risk within the Campaign against Cancer and Stroke (CLUE II) cohort designed to evaluate cancer and heart disease in 14,625 women • 1989 baseline • Mean age: 60 years • 62 incident nonsmoker cases (stage not specified) from a total of 115 ascertained by Washington County Cancer Registry and Washington County Hospital • 66 nonsmokers from a total of 115 controls matched on age (±1 year), race, menopausal status, and date of blood collection (115 total controls) • Washington County, Maryland	• In-person interview • Self-administered questionnaire for smoking in 1995 • Data collected on spouse's smoking status • Data collected on exposure to active smoking (see Table 6.15*S*) • Genotype assays for *NAT2* • Subgroups evaluated and stratified by NAT2 acetylator status	• No association with exposure to secondhand smoke from spouse's smoking • No interaction of the *NAT2* genotype with secondhand smoke and risk for breast cancer	**Adulthood:** NA/NP: 1.00 Passive only: 1.20 (0.59–2.40)	Controlled for age and menopausal status

Table 6.23*S* Continued

Study	Design/population	Data collection/ subgroup analyses	Findings for exposure to secondhand smoke	Measures of exposure to secondhand smoke: RR (95% CI)	Confounders
Sillanpaa et al. 2005a[a]	• Hospital-based study designed to evaluate the main effects for genotypes and modification of other risk factors for breast cancer • 153 nonsmoker cases (invasive) from a total of 483 referred to Kuopio University Hospital • 169 nonsmokers from a total of 482 controls randomly selected from same area as cases using Finnish National Population register • 1990–1995 • 37–92 years of age • Finland	• In-person interviews • Data collected for duration of exposure at home and at the workplace • Data collected on exposure to active smoking (see Table 6.15*S*) • Genotype assays for *NAT2* • Subgroups evaluated and stratified by exposure to passive smoke for *NAT2*	• No association between exposure to secondhand smoke and risk for breast cancer • No significant effect modification by *NAT2* genotype • Risk increased in slow *NAT2* phenotype RR = 1.22 (0.75–1.98)	**Adulthood:** NA/NP: 1.00 Passive Only: 0.85 (0.62–1.16	Controlled for age, age at menarche, age at first full-term pregnancy, parity, history of benign breast disease, family history, and alcohol use

Table 6.23*S* Continued

Study	Design/population	Data collection/ subgroup analyses	Findings for exposure to secondhand smoke	Measures of exposure to secondhand smoke: RR (95% CI)	Confounders
Lissowska et al. 2006 (Results by menopausal status from Lissowska et al. 2007)	• Population-based study designed to evaluate risk factors for breast cancer • 1,034 incident nonsmoker cases (in situ, invasive) from a total of 2,386 ascertained from five hospitals covering 90% of both cities, supplemented by cancer registry 2000–2003 • 1,162 nonsmokers from a total of 2,502 controls randomly selected from the Polish resident database and matched on city and 5-year age groups • 20–74 years of age • Warsaw and Lodz, Poland	• In-person interview • Data collected on exposure at home and/ or at the workplace for at least 1 hour/day for at least 1 year during adulthood • Data collected on exposure to active smoking (see Table 6.15*S*) • Subgroups evaluated by menopausal status and age group (<45, 45–55, and >55 years)	• Nonsignificant association between risk for breast cancer and exposure to passive smoke at home or the workplace • Trend toward increased risk for premenopausal but not postmenopausal women for hours/day-years • No association between risk and exposure by age group	**Adulthood:** NA/NP: 1.00 Work or home: 1.10 (0.84–1.45) Home only: 1.08 (0.80–1.46) Work only: 1.36 (0.94–2.00) Home and work: 1.05 (0.77–1.41) **Premenopausal, Hours/Day-Years:** NA/NP: 1.00 <100: 1.36 (0.67–2.73) 101–200: 1.52 (0.73–3.13) >200: 2.02 (0.94–4.36) p trend: 0.08 **Postmenopausal, Hours/Day-Years:** NA/NP: 1.00 <100: 0.96 (0.67–1.39) 101–200: 0.90 (0.63–1.30) >200: 1.04 (0.73–1.47) p trend: 0.74	Controlled for age, site, education, age at menarche, number of full-term births, age at first full-term birth, age at menopause, BMI, family history, prior benign breast biopsy, previous screening mammography, use of oral contraceptives, and HRT

Table 6.23*S* Continued

Study	Design/population	Data collection/ subgroup analyses	Findings for exposure to secondhand smoke	Measures of exposure to secondhand smoke: RR (95% CI)	Confounders
Mechanic et al. 2006[a]	• Carolina Breast Cancer Study • Population-based study designed to evaluate causes of breast cancer among African American and White women (Phase I invasive, Phase II in-situ) • 1,211 incident nonsmoker cases (in situ, invasive) from a total of 2,308 ascertained from the North Carolina Cancer Registry for 24 counties in central and eastern North Carolina 1993–2001 • 1,087 nonsmokers from a total of 2,022 controls selected from motor vehicle lists (<65 years) and from the Health Care Financing Administration list (≥65 years) • 20–74 years of age • North Carolina	• In-person interviews • Data for exposure to secondhand smoke collected on living with a smoker after 18 years of age • Data collected on exposure to active smoking (see Table 6.15*S*) • Genotypes in *NER* genes • Subgroups evaluated and stratified by ethnicity and *NER* genotype	• Significant association between exposure to passive smoke and risk for breast cancer in African American women only • Nonsignificant trend in risk associated with increasing number of at-risk genotypes in African Americans	**Adulthood, African American:** NA/NP: 1.00 Passive only: 1.40 (1.00–1.90) **Adulthood, White:** NA/NP: 1.00 Passive only: 1.00 (0.80–1.20)	Controlled for age, age at menarche, age at first full-term pregnancy, parity, family history, and alcohol use

Table 6.23*S* Continued

Study	Design/population	Data collection/ subgroup analyses	Findings for exposure to secondhand smoke	Measures of exposure to secondhand smoke: RR (95% CI)	Confounders
Kruk 2007	• Hospital-based study designed to evaluate association between risk for breast cancer and lifestyle factors by menopausal status • 445 incident nonsmoker cases (invasive) from a total of 858 ascertained from Szczecin Regional Cancer Registry • 730 nonsmokers from a total of 1,085 controls frequency-matched to cases on 5-year age groups and place of residence (urban/rural) • 2003–2007 • 28–78 years of age • Western Pomerania region, Poland	• Self-administered questionnaire • Data collected for number of cigarettes/ day by life partner • Data collected on exposure to active smoking (see Table 6.15*S*) • Subgroups evaluated and stratified by menopausal status	• Risk for breast cancer associated with exposure to secondhand smoke regardless of menopausal status • Risk estimate higher for premenopausal women than postmenopausal women • Interaction not significant for menopausal status and exposure to passive smoke (p = 0.77)	**Premenopausal:** Nonsmoker husband: 1.00 Smoking husband: <20 cig/day: 2.16 (1.49–3.14) ≥20 cig/day: 3.79 (2.63–5.47) p trend: <0.0001 **Postmenopausal:** Nonsmoker husband: 1.00 Smoking husband: <20 cig/day: 2.11 (1.56–2.85) ≥20 cig/day: 3.15 (2.28–4.35) p trend: <0.0001	Controlled for age among premenopausal women and age and breast feeding among postmenopausal women

Table 6.23*S* Continued

Study	Design/population	Data collection/ subgroup analyses	Findings for exposure to secondhand smoke	Measures of exposure to secondhand smoke: RR (95% CI)	Confounders
Roddam et al. 2007	• Population-based approach designed to study the association between use of oral contraceptives and risk for breast cancer in premenopausal women • 297 incident nonsmoker cases (invasive) from a total of 639 ascertained through regional and hospital registries • 310 nonsmokers from a total of 640 controls randomly selected from the general practitioners of cases and age-matched • July 1987–February 1990 • 36–45 years of age • Thames, Oxford, and Yorkshire regions of the United Kingdom	• In-person interviews • Data collected on living with a smoker for ≥1 year and number of years of exposure • Data collected on exposure to active smoking (see Table 6.15*S*) • Subgroups evaluated and stratified by menopausal status, BMI, family history, and lifestyle factors	• No association between exposure to passive smoke and risk for breast cancer regardless of duration of exposure • No association when results were stratified by menopausal status (only 23 postmenopausal women), use of alcohol, family history, parity, age at birth of first child, SES, BMI, and age at menarche	**Adulthood (Years):** NA/NP: 1.00 1–10: 0.99 (0.64–1.53) ≥11: 0.84 (0.56–1.25) **Menopausal Status:** NA/NP: 1.00 Pre: 0.83 (0.59–1.17) Post: 1.51 (0.19–12.2)	Controlled for SES, alcohol use, BMI, parity, age at birth of first child, use of oral contraceptives, family history, age at menarche, menopausal status, and mutual adjustment for active/passive exposure

Table 6.23*S* Continued

Study	Design/population	Data collection/ subgroup analyses	Findings for exposure to secondhand smoke	Measures of exposure to secondhand smoke: RR (95% CI)	Confounders
Rollison et al. 2008	• Population-based study designed to evaluate detailed exposure data on active smoking and exposure to secondhand smoke at home and the workplace during critical reproductive time periods • 287 total cases; 124 incident nonsmoker cases (invasive) from a total of 287 ascertained through the cancer registry 2000–2002 • 116 nonsmokers from a total of 311 controls, frequency-matched by 10-year age groups and selected from motor vehicle driver's license records (<65 years) and from Health Care Financing Administration records for Delaware (≥65 years) • 40–79 years of age • Delaware	• Telephone interviews • Data collected for exposure at home during childhood (<18 years of age) and adulthood by number of smokers in household, packs/day, hours/day, and during adulthood at the workplace for number of jobs, duration of employment (hours/day), and intensity of exposure (light, moderate, heavy) • Data collected on exposure to active smoking (see Table 6.15*S*)	• No association between risk for breast cancer and exposure to passive smoke during childhood or adulthood	**Lifetime (Both) (Years):** NA/NP: 1.00 1–17: 1.30 (0.57–2.98) 18–20: 1.04 (0.49–2.25) 21–35: 0.79 (0.33–1.87) >36: 1.11 (0.50–2.46) **Adulthood (Home):** NA/NP: 1.00 Yes: 1.06 (0.56–2.02) Work: NA/NP: 1.00 Any Exposure: 0.80 (0.49–1.32) **Childhood (Years):** NA/NP: 1.00 1–8: 0.89 (0.30–2.67) 9–17: 0.90 (0.41–1.97) >18: 0.78 (0.43–1.39)	Controlled for age, menopausal status, BMI, age at menarche, age at birth of first child, use of oral contraceptives, family history, and alcohol use

Table 6.23*S* Continued

Study	Design/population	Data collection/ subgroup analyses	Findings for exposure to secondhand smoke	Measures of exposure to secondhand smoke: RR (95% CI)	Confounders
Slattery et al. 2008	• 4-Corners Breast Cancer Study • Population-based study designed to evaluate risk factors for breast cancer among Hispanic, American Indian, and non-Hispanic White women in the southwestern region of the United States • 1,527 total cases; 1,347 incident cases among nonsmokers ascertained through cancer registries (in situ, invasive), premenopausal women (329 Hispanics and American Indians, 535 non-Hispanic Whites), and postmenopausal women (450 Hispanics and American Indians, and 967 non-Hispanic Whites) • 1,601 total controls; 1,442 nonsmokers, frequency matched on ethnicity and 5-year age groups • Women <65 years selected from commercial mailing lists (in Arizona and Colorado) or from driver license lists. • Women ages >65 years selected from Center for Medicare Services list • 1999–2004 • 25–79 years of age • Statewide for Utah, New Mexico, and Colorado and 7 counties in Arizona	• In-person interviews. • Data collected for hours/ week in and out of the house during the referent year and at ages 15, 30, and 50 years • Data collected on exposure to active smoking (see Table 6.15*S*) • Genotype assays for 5 IL6 markers and 1 ESR1 marker • Subgroups evaluated and stratified by menopausal status ethnicity, and genotype	• Risk for breast cancer associated with exposure to secondhand smoke for smokers and nonsmokers among pre- and perimenopausal women only • Significant associations limited to Hispanic pre- and perimenopausal women • No association between risk for breast cancer and exposure to secondhand smoke for postmenopausal Hispanic and non-Hispanic White women	**Hours/Week, Premenopausal, Non-Hispanic White:** NA/NP: 1.00 1–10: 1.20 (0.70–1.90) >10: 1.20 (0.60–2.70) p trend: 0.44 **Hours/Week, Postmenopausal, Non-Hispanic White:** NA/NP: 1.00 1–10: 1.00 (0.70–1.50) >10: 1.00 (0.60–1.70) p trend: 0.95 **Hours/Week, Premenopausal, Hispanic Women:** NA/NP: 1.00 1–10: 0.80 (0.50–1.20) >10: 2.30 (1.20–4.50) p trend: 0.13 **Hours/Week, Postmenopausal, Hispanic Women:** NA/NP: 1.00 1–10: 1.00 (0.60–1.50) >10: 1.00 (0.60–1.80) p trend = 0.96	Controlled for age, center, BMI, aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), parity, alcohol use, physical activity, recent (+2 years) estrogen exposure for postmenopausal women, and active smoking (pack-years)

Table 6.23*S* Continued

Study	Design/population	Data collection/ subgroup analyses	Findings for exposure to secondhand smoke	Measures of exposure to secondhand smoke: RR (95% CI)	Confounders
Ahern et al. 2009[a]	• Population-based study designed to evaluate the association between risk for breast cancer and lifestyle factors • 557 total cases; 242 incident cases (invasive) among nonsmokers ascertained through the Massachusetts Cancer Registry • 432 total controls; 195 nonsmokers selected randomly from the driver's license bureau (ages <65 years) and from Medicare rosters (ages ≥65 years) in Massachusetts 1989–1991 • 28–75 years of age • Massachusetts	• Self-administered, mailed questionnaire • Data collected for ≥2 hours/day of exposure during childhood or adulthood or both • Data collected on exposure to active smoking (see Table 6.15*S*)	• No association between risk for breast cancer and exposure to passive smoke	**Lifetime:** NA/NP: 1.00 Passive: 0.97 (0.88–1.08)	Controlled for age at menarche, age at birth of first child, parity, BMI, use of oral contraceptives, hormone replacement therapy, alcohol use, menopausal status, family history, history of benign breast disease, and household income

Table 6.23*S* Continued

Study	Design/population	Data collection/ subgroup analyses	Findings for exposure to secondhand smoke	Measures of exposure to secondhand smoke: RR (95% CI)	Confounders
Young et al. 2009	• Population-based study of secondary analysis to evaluate the association between breast cancer and smoking using combined data from 2 studies with similar target populations, data collection methods, and measures of smoking: • 6,065 total cases; 2,751 incident cases (invasive) among nonsmokers ascertained through the Ontario Cancer Registry • 6,371 total controls; 3,097 nonsmokers frequency matched by 5-year age groups and selected randomly (age-stratified) from the Ontario Ministry of Finance rolls (for OWHS) and from a random-digit dialing list (for OWDHS) OWHS (June 1996–May 1998) • OWDHS (June 2002–April 2003) • Ages 25–75 years • Canada	• Self-administered, mailed questionnaire • Data collected for ≥2 hours/day of exposure during childhood or adulthood or both • Data collected on exposure to active smoking (see Table 6.15S)	• No association between risk for breast cancer and exposure to passive smoke	**Lifetime:** NA/NP: 1.00 Passive: 0.97 (0.88–1.08)	Controlled for age at menarche, age at birth of first child, parity, BMI, use of oral contraceptives, hormone replacement therapy, alcohol use, menopausal status, family history, history of benign breast disease, and household income

Note: Data from case-control studies for active cigarette smoking are summarized in Table 6.15*S*. Numbers for cases and controls are based on nonsmokers, a smaller percentage of subjects than the total included for analyses of active cigarette smoking. All results reported by the study may not appear in the summary table.
BMI = body mass index; **CI** = confidence interval; **HRT** = hormone replacement therapy; **NA/NP** = no active/no passive; **NSAIDs** = nonsteroidal anti-inflammatory drugs; **OWDHS** = Ontario Women's Diet and Health Study; **OWHS** = Ontario Women's Health Study; **SES** = socioeconomic status.
[a]Overlapping reports based on the same study population.

Table 6.24S Evaluation of reports on exposure to secondhand smoke among 171 nonsmokers, based on 10 cohort and 24 case-control studies of breast cancer published before 2012 for meta-analyses, by location, study design, analytic sample size, meta-analysis categories, and design or analysis issues (n = 39)

			Meta-analysis categories									
Study	**Design/population**	**Analytic sample size**	**Premenopausal**	**Postmenopausal**	**Spouse/partner**	**Adult–home**	**Adult–workplace**	**Childhood**	**Adulthood and childhood**	**Adult–any source**	**Ever in lifetime**	**Most comprehensive: Adult–any source vs. ever in lifetime**
Millikan et al. 1998[a,b]	• Carolina Breast Cancer Study • Case-control • United States	274/253	1[c]	1[c]	—	2	—	—	—	1	—	—
Marcus et al. 2000[a,b]	—	445/423	—	—	—	—	—	1[c]	—	—	—	—
Mechanic et al. 2006[b]	—	1,211/1,087	—	—	2[c]	1[c]	—	—	—	2[c]	—	Adult–any source
Reynolds et al. 2004a[a,d]	• California Teachers Study • Cohort • United States	1,174 of 77,708	1[c]	1[c]	2[c]	2[c]	—	1	1[c]	1	1	—
Reynolds et al. 2009[d]	—	1,754 of 57,523	1[c]	1[c]	—	—	1[c]	1[c]	—	1[c]	1[c]	Ever in lifetime
Metsola et al. 2005[e,f]	• Kuopio Breast Cancer Study • Case control • Finland	363/351	—	—	—	—	—	—	—	1	—	—
Sillanpaa et al. 2005a[f]	—	363/351	—	—	—	—	—	—	—	1[c]	—	Adult–any source
Egan et al. 2002[a]	• Nurses Health Study I • Cohort • United States	1,359 of 35,193	—	—	—	1	—	1	—	1	—	—
Xue et al. 2011[g]	—	2,890 of 36,017	—	—	2[c]	1[c]	1[c]	1[c]	—	2[c]	1[c]	Ever in lifetime
Sandler et al. 1985a[a,e,h]	• Case-control • North Carolina (hospital)	32/178	1	1	1	2	—	—	—	2	—	Adult–any source
Smith et al. 1994[a,e,i]	• National case-control study group • Case-control • United Kingdom	94/99	1	—	1	1	1	1	1	2	1	Ever in lifetime

Table 6.24*S* Continued

Study	Design/population	Analytic sample size	Meta-analysis categories									
			Premenopausal	Postmenopausal	Spouse/partner	Adult–home	Adult–workplace	Childhood	Adulthood and childhood	Adult–any source	Ever in lifetime	Most comprehensive: Adult–any source vs. ever in lifetime
Hirose et al. 1995	• Aichi Cancer Center hospital • Case-control • Nagoya, Japan	560/1,1276	1	1	1	1	—	—	—	2	—	Adult–any source
Morabia et al. 1996[a,e,j]	• Case-control • Geneva, Switzerland (hospital)	126/620	1	—	1	2	—	—	—	2	1	Ever in lifetime
Jee et al. 1999[a,e,k]	• Korea Medical Insurance Corporation • Cohort • Republic of Korea	138 of 157,436	—	—	1	1	—	—	—	2	—	Adult–any source
Lash and Ashengrau 1999[a,e]	• Case-control • Cape Cod, Massachusetts	120/406	—	1	—	—	—	—	—	—	1	Ever in lifetime
Zhao et al. 1999[a,e]	• Case-control • Chengdu, China (hospital)	259/252	—	—	—	—	—	—	—	—	1	Ever in lifetime
Delfino et al. 2000[a,e]	• Case-control • Orange County, California	64/147	1	1	—	2	—	—	—	1	—	Adult–any source
Johnson et al. 2000[a]	• National Enhanced Cancer Surveillance System • Case-control • Canada	708/727	1	1	—	—	—	1	1	1	1	Ever in lifetime
Liu et al. 2000[a]	• Case-control • Chongqing, China	186/186	—	—	—	1	1	1	—	2	—	Adult–any source
Nishino et al. 2001[a,e,l]	• Cohort • Miyagi Prefecture, Japan	67 of 9,675	—	—	1	2	—	—	—	2	—	Adult–any source
Kropp and Chang-Claude 2002[a,m]	• Case-control • Mannheim, Germany	197/459	—	—	—	—	—	1	1	1	1	Ever in lifetime
Lash and Ashengrau 2002[a,e]	• Case-control • Cape Cod, Massachusetts	305/249	—	—	—	—	—	—	—	—	1	Ever in lifetime

Table 6.24*S* Continued

Study	Design/population	Analytic sample size	Meta-analysis categories									
			Premenopausal	Postmenopausal	Spouse/partner	Adult–home	Adult–workplace	Childhood	Adulthood and childhood	Adult–any source	Ever in lifetime	Most comprehensive: Adult–any source vs. ever in lifetime
Alberg et al. 2004[e]	• Campaign Against Cancer and Heart Disease II • Case-control • Washington County, Maryland	62/66	—	—	1	1	—	—	—	2	—	Adult–any source
Gammon et al. 2004a[a,n]	• Long Island Breast Cancer Study Project • Case-control • United States	598/627	1	1	1	2	—	1	—	2	1	Ever in lifetime
Shrubsole et al. 2004[a,o]	• Shanghai Breast Cancer Study • Case-control • China	1,013/1,117	1	1	1	2	1	—	—	1	—	Adult–any source
Bonner et al. 2005[a]	• Western New York Exposures and Breast Cancer Study • Case-control • United States	525/1,010	1	1	—	—	1	1	—	2	1	Ever in lifetime
Gram et al. 2005	• Norwegian-Swedish Women's Lifestyle and Health Cohort Study • Cohort • Norway and Sweden	1,130 of 36,773	—	—	—	—	—	—	—	—	1	Ever in lifetime
Hanaoka et al. 2005[a,p]	• Japan Public Health Center-based Prospective Study • Cohort • Japan	162 of 20,169	1	1	—	—	1	—	—	2	1	Ever in lifetime
Lissowska et al. 2006[q]	• Case control • Warsaw and Lodz, Poland	1,034/1,162	1	1	—	1	1	—	—	1	—	Adult–any source
Kruk 2007[e]	• Case control • Western Pomerania region, Poland	445/730	1	1	1	2	—	—	—	2	—	Adult–any source

Table 6.24S Continued

Study	Design/population	Analytic sample size	Meta-analysis categories									
			Premenopausal	Postmenopausal	Spouse/partner	Adult–home	Adult–workplace	Childhood	Adulthood and childhood	Adult–any source	Ever in lifetime	Most comprehensive: Adult–any source vs. ever in lifetime
Roddam et al. 2007[r]	• Case-control • Thames, Oxford, and Yorkshire, United Kingdom	297/310	1	1	1	2	—	—	—	2	—	Adult–any source
Lin et al. 2008[s]	• Japan Collaborative Cohort Study for Evaluation of Cancer Risk • Cohort • Japan	140 of 32,023	—	—	—	1	—	1	—	2	—	Adult–any source
Pirie et al. 2008[t]	• Million Women Study • Cohort • United Kingdom	2,344 of 210,647	1	1	1	2	—	1	1	2	1	Ever in lifetime
Rollison et al. 2008[u]	• Case-control • Delaware	124/116	—	—	—	—	1	1	—	—	1	Ever in lifetime
Slattery et al. 2008	• 4-Corners Breast Cancer Study • Case-control • Arizona, Colorado, New Mexico, and Utah	1,347/1,442	1	1	—	—	—	—	—	—	1	Ever in lifetime
Ahern et al. 2009[v]	• CBCS • Case-control • Massachusetts	242/195	—	—	—	—	—	1	1	1	2	Ever in lifetime
Young et al. 2009	• Ontario Women's Health Study • Ontario Women's Diet and Health Study • Case-control • Canada	2,751/3,097	—	—	—	—	—	—	—	—	1	Ever in lifetime
Chuang et al. 2011	• European Prospective Investigation Into Cancer and Nutrition • Cohort • Europe	3,187 of 92,956	—	—	—	—	—	1	—	—	2	Ever in lifetime

Table 6.24*S* Continued

Study	Design/population	Analytic sample size	Meta-analysis categories									
			Premenopausal	Postmenopausal	Spouse/partner	Adult–home	Adult–workplace	Childhood	Adulthood and childhood	Adult–any source	Ever in lifetime	Most comprehensive: Adult–any source vs. ever in lifetime
Luo et al. 2011b[w]	• Women's Health Initiative Observational Study • Cohort • United States	1,692 of 41,022	—	1	—	1	1	1	1	1	1	Ever in lifetime
Total nonoverlapping reports			**17**	**17**	**15**	**20**	**10**	**15**	**7**	**26**	**20**	**34**

Note: Two studies based entirely on deceased subjects were excluded from all meta-analyses based on exposure to secondhand smoke (Hirayama 1984; Wartenberg et al. 2000). These studies are considered in the section, "Exposure to Tobacco Smoke and Breast Cancer Mortality." Estimates for Adult-any Source and Ever in Lifetime are based on different measures of smoking for those reports providing both measures. Analytic sample size is based on reported number of nonsmokers; for case-control studies, n of cases/n of controls and for cohort studies, n of cases of total count. **1** = estimate directly reported; **2** = estimate inferred (i.e., any adult from spouse). Estimates were abstracted either directly or pooled using other measures of smoking to calculate an estimate for the appropriate category. **USDHHS** = United States Department of Health and Human Services.

[a]Study included in the 2006 Surgeon General's Report (USDHHS 2006).

[b]A series of three reports provide data on the Carolina Breast Cancer Study. Changes were made to the three estimates (Adult–Any Source, Adult–Home, Most Comprehensive) for "All Women" used in the meta-analysis for the 2006 Surgeon General's report. Marcus and colleagues (2000) reported on only exposure to passive smoke during childhood. The study by Mechanic and colleagues (2006), published after the 2006 Surgeon General's Report, was based on a larger number of nonsmokers and provided data on estimates for Adult–Any Source, Adult–Home, Spouse, and Most Comprehensive, which replaced the estimates from Millikan and colleagues (1998), as used in the 2006 Surgeon General's report. However, because Mechanic and colleagues (2006) did not report results by menopausal status, these estimates are based on the initial report (Millikan et al. 1998), which included considerably fewer nonsmokers.

[c]Indicates which report contributes estimates to the meta-analyses when there are overlapping studies.

[d]Two reports provide data on the California Teachers Study. Estimates for Childhood, Adult–Work, Adult–Any Source, Ever in Lifetime, and Most Comprehensive were based on the most recent report (Reynolds et al. 2009). The estimate for Adult–Work exposure was based on any exposure at an age younger than 20 years for 17% of subjects. The estimates for Adult–Spouse, Adult–Home, and both Adulthood and Childhood were based on the earlier report (Reynolds et al. 2004a). The measure for Adult–Home was based on the earlier report because it was specific to exposure at home as an adult, whereas the estimate in the later report included childhood or adulthood exposure at home. Estimates for pre- and postmenopausal status for each exposure measure come from the respective reports. There was no reported estimate for Adult–Work exposure by menopausal status.

[e]Eleven studies excluded after the initial meta-analysis because of design or analysis issues due to inclusion of smokers in passive analyses, inclusion of deceased subjects for whom information was collected from proxies, inclusion of prevalent cases, or small sample size (<100 cases) or insufficient adjustment for relevant covariates (Sandler et al. 1985a; Smith et al. 1994; Morabia et al. 1996; Jee et al. 1999; Lash and Aschengrau 1999, 2002; Zhao et al. 1999; Delfino et al. 2000; Nishino et al. 2001; Alberg et al. 2004; Kruk 2007).

[f]The study reported by Metsola and colleagues (2005) was excluded from all meta-analyses because it was based on the same study population as that reported by Sillanpaa and colleagues (2005a), which adjusted for reproductive factors, use of alcohol, and family history. The latter study was based primarily on postmenopausal women (60%) but did not adjust for menopausal status.

Table 6.24*S* Continued

[g]The estimates from Xue and colleagues (2011) for Adult–Work and Adult–Home were pooled across two categories (occasionally and regularly). The estimate for Childhood was pooled across three categories (mother only, father only, and both parents). The estimate for Ever in Lifetime was pooled across four categories based on frequency (occasional/regular), location (home/work), and age (<20 or ≥20 years).
[h]Estimates by menopausal status based on Wells' (1991) reanalysis of data provided by Sandler and colleagues (1985a).
[i]Estimates reported by Smith and colleagues (1994) for all women are also used in the analyses for premenopausal women because all subjects were diagnosed before 36 years of age (Smith et al. 1994). Changes were made to two of the eight estimates extracted from the report by Smith and colleagues (1994) as used in the meta-analysis for the 2006 Surgeon General's report. The estimate for Adult–Any Source was replaced to be the same as that used for Adult–Home, based on the pooled estimates across years of "Adult Exposure from Living with Other Smokers" (RR = 1.33; 95% CI, 0.74–2.40; n = 94 cases, 100 controls), rather than the original "Adult Only, Period of Exposure" (RR = 3.13; 95% CI, 0.73–13.31; n = 21 cases, 27 controls), which increased the sample size and the precision of the RRs and CIs. The estimate for Childhood was replaced with a pooled estimate across two levels of cigarette years under "Total Childhood Exposure" (RR = 1.18; 95% CI, 0.64–2.17; n = 94 cases, 100 controls), rather than the original "Child Only, Period of Exposure" (RR = 1.33; 95% CI, 0.16–10.83; n = 8 cases, 17 controls). These changes were also applied to the premenopausal estimates.
[j]Estimates reported by Morabia and colleagues (1996) appear to be based primarily on postmenopausal women (approximately 70% for cases, 60% for controls), and not adjusted for menopausal status. A single estimate is reported for premenopausal women (RR = 3.6; 95% CI, 1.6–8.2), but the estimate may not have been adjusted for potential confounders; no data are provided. Comments do not address postmenopausal women specifically. The report from Morabia and colleagues (2000) was not included because it presented results from a subsample of the study population previously reported in the earlier study (Morabia et al. 1996).
[k]Changes were made to the estimates for all women extracted from the report by Jee and colleagues (1999) as used in the meta-analysis for the 2006 Surgeon General's report. The category Home was added and based on the pooled estimates used for Spouse (Jee et al. 1999).
[l]Changes were made to three of the four estimates extracted from the report by Nishino and colleagues (2001) as used in the meta-analysis for the 2006 Surgeon General's report. The estimate for Adult–Home was replaced with the pooled estimate for "Husband, and Other Members for Smoking Status in the Household" (RR = 0.69; 95% CI, 0.44–1.06), rather than the original pooled estimate (RR = 0.49; 95% CI, 0.33–0.74), which was based on three estimates that adjusted for only age. Estimates for Adult–Any Source and Most Comprehensive were based on this new estimate. There was no adjustment for menopausal status.
[m]Estimates from Kropp and Chang-Claude (2002) based primarily on premenopausal women (approximately 80%).
[n]Changes were made to the estimates for Spouse, Adult–Home, and Adult–Any Source extracted from Gammon and colleagues (2004a), as used in the meta-analysis for the 2006 Surgeon General's Report. The estimate for Spouse was replaced with the pooled estimate levels for months across "Ever Passively Exposed to Spouse" (n = 260), which was based on Adult-Only Exposure, rather than the set of nonpooled estimates for "Exposed to Passive Smoke Only" (n = 433), based on lifetime exposure as either an adult or as a child in the residence. This resulted in the deletion of menopausal estimates for these three categories because estimates were not associated with pre- and postmenopausal status. An estimate for Ever in Lifetime exposure was added and based on the general category "Exposed to Passive Smoke Only," as noted previously.
[o]Estimates from Shrubsole and colleagues (2004) based on only women who reported being married
[p]Estimates from Hanaoka and colleagues (2005) by menopausal status measured at baseline rather than at diagnosis. Approximately 1% of cases were ascertained through death records.
[q]Estimates originally reported in Lissowska and colleagues (2006) are primarily for postmenopausal women (80%). Estimates for adult exposure by menopausal status were reported in a subsequent publication by Lissowska and colleagues (2007), in response to an editorial by Johnson (2007).
[r]Estimate from Roddam and colleagues (2007) based primarily on premenopausal women (93%).
[s]Estimates from Lin and colleagues (2008) based primarily on postmenopausal women (76%).
[t]Estimates from Pirie and colleagues (2008) based primarily on postmenopausal women (93%). Estimate for passive exposure to tobacco smoke as a child or as an adult were reported by menopausal status and were used for only the Ever in Lifetime and Most Comprehensive categories.
[u]Estimates from Rollison and colleagues (2008) based primarily on postmenopausal women (84%).
[v]Estimates from Ahern and colleagues (2009) for some categories—including estimates for all women by Spouse, Home, and the Workplace and the estimates for menopausal status by Adult–Any Source, Child, and Both—were excluded from the meta-analyses because active smokers were included.
[w]Estimate from Luo and colleagues (2011b) for Childhood and Adulthood was based on pooled estimates across several categories (Childhood and Adult at Home, Childhood and Adult at Work, Childhood and Adult at Home and at Work). All women were postmenopausal.

Table 6.25*S* Summary of meta-analyses for the broadest categories of exposure to secondhand smoke (adult–any source, ever in lifetime, most comprehensive) for all studies of breast cancer combined and stratified by menopausal status, based on cohort and case-control studies published before 2012

	All studies[a]			Premenopausal			Postmenopausal		
Category of exposure to secondhand smoke	**N**	**RR (95% CI)**	**Q test (p_h)**	**N**	**RR (95% CI)**	**Q test (p_h)**	**N**	**RR (95% CI)**	**Q test (p_h)**
Adult–Any source	**26**	**1.15 (1.03–1.28)**	**<0.001**	**13**	**1.36 (1.07–1.72)**	**<0.001**	**13**	**1.11 (0.94–1.31)**	**0.001**
Cohort studies	8	1.02 (0.92–1.12)	0.028	2	1.44 (0.60–3.41)	0.001	3	1.01 (0.75–1.36)	0.044
Case-control studies	18	1.28 (1.07–1.54)	<0.001	11	1.37 (1.04–1.79)	<0.001	10	1.16 (0.93–1.45)	0.001
Exclusion, analysis[b]	25	1.08 (0.99–1.18)	<0.001	12	1.26 (1.00–1.57)	<0.001	12	1.04 (0.93–1.16)	0.208
Exclusion, design[c]	24	1.07 (0.98–1.17)	<0.001	—	—[d]	—	—	—[d]	—
Exclusion, small study bias[e]	19	1.07 (0.98–1.17)	<0.001	9	1.16 (0.93–1.45)	<0.001	10	1.04 (0.92–1.18)	0.111
Exclusion, outlier[f]	18	1.04 (0.96–1.13)	0.004	—	—[d]	—	—	—[d]	—
2006 Surgeon General's Report	*18*	*1.15 (1.02–1.29)*	*<0.001*	*10*	*1.45 (1.04–2.01)*	*<0.001*	*9*	*0.90 (0.81–1.01)*	*0.691*
Ever in lifetime	**20**	**1.11 (1.03–1.20)**	**<0.001**	**9**	**1.49 (1.14–1.96)**	**0.008**	**9**	**1.05 (0.94–1.17)**	**0.072**
Cohort studies	7	1.02 (0.98–1.07)	0.457	3	1.23 (0.69–2.19)	0.027	4	1.01 (0.85–1.20)	0.035
Case-control studies	13	1.28 (1.08–1.51)	<0.001	6	1.64 (1.21–2.23)	0.077	5	1.09 (0.92–1.28)	0.242
Exclusion, analysis[b]	19	1.08 (1.01–1.16)	0.003	—	—[d]	—	—	—[d]	—
Exclusion, design[c]	17	1.08 (1.01–1.15)	0.009	—	—[d]	—	8	1.03 (0.94–1.13)	0.198
Exclusion, small study bias[e]	16	1.07 (1.00–1.13)	0.028	8	1.42 (1.08–1.87)	0.013	—	—[d]	—
Exclusion, outlier[f]	15	1.03 (0.99–1.07)	0.389	7	1.30 (1.02–1.65)	0.073	—	—[d]	—
2006 Surgeon General's Report	*10*	*1.40 (1.12–1.76)*	*<0.001*	*6*	*1.85 (1.19–2.87)*	*0.001*	*5*	*1.04 (0.84–1.30)*	*0.048*
Most comprehensive	**34**	**1.14 (1.06–1.23)**	**<0.001**	**17**	**1.45 (1.20–1.75)**	**<0.001**	**17**	**1.11 (0.99–1.25)**	**0.001**
Cohort studies	10	1.02 (0.95–1.10)	0.038	3	1.23 (0.69–2.19)	0.027	4	1.01 (0.85–1.20)	0.035
Case-control studies	24	1.27 (1.11–1.44)	<0.001	14	1.52 (1.23–1.87)	<0.001	13	1.18 (1.00–1.39)	0.004
Exclusion, analysis[b]	32	1.08 (1.01–1.14)	0.001	16	1.37 (1.15–1.64)	0.001	16	1.05 (0.97–1.14)	0.182
Exclusion, design[c]	29	1.07 (1.01–1.13)	0.002	—	—[d]	—	15	1.04 (0.97–1.11)	0.361
Exclusion, small study bias[e]	24	1.06 (1.00–1.12)	0.010	13	1.27 (1.07–1.49)	0.010	13	1.04 (0.96–1.13)	0.233
Exclusion, outlier[f]	23	1.04 (0.99–1.09)	0.131	12	1.21 (1.04–1.40)	0.063	—	—[d]	—
2006 Surgeon General's Report	*21*	*1.20 (1.08–1.35)*	*<.001*	*11*	*1.64 (1.25–2.14)*	*0.001*	*10*	*1.00 (0.88–1.12)*	*0.321*

Note: Estimates were abstracted either directly or pooled using other measures of smoking to calculate an estimate for the appropriate category. Cochran's $\chi 2$ test, reported as the Q-test statistic, was used to assess between-study heterogeneity (p_h); p_h values reported in SAS as 0.000 due to rounding shown in table as <0.001. Table 6.24*S* provides more details about which studies contributed to exposure categories and reasons for exclusions. Summary estimates for all meta-analyses are based on random-effects models. **CI** = confidence interval; **N** = sample size (number of studies); **RR** = relative risk.

Table 6.25*S* Continued

[a]All studies regardless of whether the majority of subjects were primarily premenopausal or postmenopausal. This includes those studies that had a small percentage (<20%) of either pre- or postmenopausal women (Kropp and Chang-Claude 2002; Sillanpaa et al. 2005a; Roddam et al. 2007; Pirie et al. 2008; Rollison et al. 2008; Lin et al. 2008), no premenopausal women (Luo et al. 2011b) or no postmenopausal women (Smith et al. 1994). Because some studies did not stratify results by menopause, the numbers of pre- and postmenopausal studies do not always sum to equal All Studies.
[b]Excludes two studies (Zhao et al. 1999; Kruk 2007) from the appropriate categories (Table 6.24*S*).
[c]Excludes two studies (*note b*) and three studies (Jee et al. 1999; Lash and Aschengrau 1999; Lash and Aschengrau 2002) from the appropriate categories (Table 6.24*S*).
[d]Indicates that the estimate did not change because studies were excluded based on previous sensitivity analyses or did not include an estimate for the specific measure of smoking by menopausal status.
[e]Excludes five studies (*notes b and c*) and five studies (Sandler et al. 1985a; Smith et al. 1994; Delfino et al. 2000; Nishino et al. 2001; Alberg et al. 2004) from the appropriate categories (Table 6.24*S*).
[f]Excludes 10 studies (*notes b, c, and e*) and 1 study (Morabia et al. 1996) (Table 6.24*S*, *note e*), an extreme outlier from All Studies for all three measures of smoking and from premenopausal estimates for Ever in Lifetime and Most Comprehensive. See Figure 6.43.

Table 6.26*S* Summary of meta-analyses for specific categories of exposure to secondhand smoke (spouse, home, workplace, childhood, childhood and adulthood) for all studies of breast cancer combined and stratified by menopausal status, based on cohort and case-control studies published before 2012

	All studies[a]			Premenopausal			Postmenopausal		
Category of exposure to secondhand smoke	**N**	**RR (95% CI)**	**Q test (p_h)**	**N**	**RR (95% CI)**	**Q test (p_h)**	**N**	**RR (95% CI)**	**Q test (p_h)**
Adulthood									
Spouse	15	1.22 (1.05–1.42)	<0.001	7	1.32 (0.97–1.80)	0.002	6	1.19 (0.78–1.82)	<0.001
Cohort studies	5	1.02 (0.93–1.13)	0.151	1	1.01 (0.66–1.54)	—	1	0.88 (0.71–1.09)	—
Case-control studies	10	1.43 (1.09–1.87)	<0.001	6	1.41 (0.98–2.04)	0.001	5	1.30 (0.77–2.17)	0.002
Exclusions[b]	8	1.05 (0.97–1.13)	0.185	4	1.05 (0.89–1.22)	0.479	4	1.00 (0.70–1.40)	0.037
2006 Surgeon General's Report	*9*	*1.17 (0.96–1.44)*	*0.002*	*4*	*1.40 (0.92–2.12)*	*0.100*	*3*	*0.86 (0.67–1.12)*	*0.645*
Home	20	1.16 (1.02–1.31)	<0.001	9	1.35 (1.03–1.78)	0.003	9	1.13 (0.85–1.50)	<0.001
Cohort studies	7	0.97 (0.87–1.08)	0.031	1	1.01 (0.66–1.54)	—	2	0.89 (0.76–1.05)	0.846
Case-control studies	13	1.38 (1.11–1.71)	<0.001	8	1.44 (1.05–1.97)	0.002	7	1.25 (0.86–1.83)	0.006
Exclusions[c]	12	1.02 (0.94–1.11)	0.061	5	1.07 (0.92–1.24)	0.450	6	1.00 (0.81–1.23)	0.097
2006 Surgeon General's Report	*8*	*1.01 (0.85–1.19)*	*0.006*	*4*	*1.28 (0.94–1.74)*	*0.355*	*3*	*0.92 (0.76–1.11)*	*0.591*
Workplace	10	1.03 (0.92–1.15)	0.034	4	1.21 (0.70–2.09)	<0.001	4	0.92 (0.72–1.16)	0.120
Cohort studies	4	1.00 (0.92–1.08)	0.349	1	2.30 (1.40–3.79)	—	2	0.69 (0.28–1.69)	0.029
Case-control studies	6	1.10 (0.85–1.43)	0.011	3	0.98 (0.60–1.58)	0.014	2	0.92 (0.75–1.13)	0.311
Exclusions[d]	9	1.02 (0.91–1.13)	0.039	3	1.15 (0.59–2.24)	<0.001	—	—[e]	—
2006 Surgeon General's Report	*6*	*1.06 (0.84–1.35)*	*0.008*	*4*	*1.21 (0.70–2.19)*	*<0.001*	*3*	*0.83 (0.53–1.29)*	*0.086*
Childhood	**15**	**1.01 (0.95–1.07)**	**0.199**	**4**	**1.12 (0.90–1.40)**	**0.262**	**4**	**1.15 (1.03–1.28)**	**0.888**
Cohort studies	6	1.00 (0.95–1.05)	0.349	1	0.95 (0.77–1.18)	—	2	1.14 (1.00–1.30)	0.683
Case-control studies	9	1.01 (0.88–1.17)	0.138	3	1.34 (1.02–1.75)	0.862	2	1.17 (0.95–1.43)	0.513
Exclusions[d]	14	1.01 (0.95–1.07)	0.160	3	1.14 (0.84–1.54)	0.141	—	—[e]	—
2006 Surgeon General's Report	*9*	*1.01 (0.90–1.12)*	*0.101*	*4*	*1.14 (0.90–1.45)*	*0.342*	*3*	*1.04 (0.86–1.26)*	*0.242*
Childhood and Adulthood	**7**	**1.09 (0.95–1.24)**	**0.102**	**3**	**1.63 (0.68–3.91)**	**0.016**	**3**	**1.05 (0.89–1.24)**	**0.162**
Cohort studies	3	1.03 (0.94–1.14)	0.234	1	0.87 (0.60–1.26)	—	2	1.02 (0.84–1.23)	0.092
Case-control studies	4	1.49 (1.10–2.04)	0.439	2	2.61 (1.36–5.02)	0.988	1	1.30 (0.82–2.06)	—
Exclusions[d]	6	1.07 (0.95–1.21)	0.124	2	1.43 (0.49–4.15)	0.011	—	—[e]	—
2006 Surgeon General's Report	*4*	*1.39 (0.88–2.18)*	*0.021*	*3*	*1.63 (0.68–3.91)*	*0.016*	*2*	*1.02 (0.74–1.42)*	*0.160*

Note: Estimates were abstracted either directly or pooled using other measures of smoking to calculate an estimate for the appropriate category. Cochran's $\chi 2$ test, reported as the Q-test statistic, was used to assess between-study heterogeneity (p_h). Table 6.24*S* provides more details about which studies contributed to exposure categories and reasons for exclusions. Summary estimates for all meta-analyses are based on random-effects models. **CI** = confidence interval; **N** = sample size (number of studies);

Table 6.26*S* Continued

RR = relative risk.

[a]All studies regardless of whether the majority of subjects were primarily premenopausal or postmenopausal. This includes those studies that had a small percentage (<20%) of either pre- or postmenopausal women (Kropp and Chang-Claude 2002; Sillanpaa et al. 2005a; Roddam et al. 2007; Pirie et al. 2008; Rollison et al. 2008; Lin et al. 2008), no premenopausal women (Luo et al. 2011b) or no postmenopausal women (Smith et al. 1994). Because some studies did not stratify results by menopause, the numbers of pre- and postmenopausal studies do not always sum to equal All Studies.

[b]Excludes seven studies from All Studies: (Sandler et al. 1985a; Smith et al. 1994; Morabia et al. 1996; Jee et al. 1999; Nishino et al. 2001; Alberg et al. 2004; Kruk 2007); three studies from Premenopausal: (Sandler et al. 1985a; Smith et al. 1994; Kruk 2007); and two studies from Postmenopausal (Sandler et al. 1985a; Kruk 2007).

[c]Excludes seven studies (*note b)* in addition to one more (Delfino et al. 2000) from All Studies and from Premenopausal due to small sample size and insufficient adjustment for relevant covariates.

[d]Excludes one study (Smith et al. 1994) from All Studies and from Premenopausal due to small sample size and insufficient adjustment for relevant covariates.

[e]Indicates that the estimate did not change because studies were excluded based on previous sensitivity analyses or did not include an estimate for the specific measure of smoking by menopausal status.

Table 6.27*S* Comparison of relative risks (RRs) from selected summaries of meta-analyses for active smoking *versus* exposure to secondhand smoke for all studies of breast cancer combined and stratified by study design

Measures of smoking	N	All studies: RR (95% CI)	N	Cohort studies: RR (95% CI)	N	Case-control studies: RR (95% CI)
Active smoking						
Ever smoker[a]	46	1.12 (1.07–1.17) 1.10 (1.07–1.12)	19	1.10 (1.07–1.13) 1.10 (1.07–1.13)	27	1.15 (1.06–1.25) 1.11 (1.07–1.15)
Ever smoker, most restricted[b]	30	1.09 (1.06–1.12) 1.09 (1.06–1.12)	11	1.10 (1.07–1.13) 1.10 (1.07–1.13)	19	1.08 (1.03–1.13) 1.07 (1.03–1.12) 1.10 (1.07–1.12)
No active-only[b]	25	1.09 (1.06–1.13) 1.09 (1.06–1.12)	11	1.10 (1.07–1.14) 1.10 (1.06–1.14)	14	1.08 (1.02–1.15) 1.06 (1.02–1.11)
Current smoker[b]	25	1.12 (1.08-1.16) 1.12 (1.08-1.16)	11	1.14 (1.10–1.18) 1.14 (1.10-1.18)	14	1.07 (1.00–1.16) 1.07 (1.00–1.14)
Former smoker[b]	25	1.09 (1.05–1.13) 1.08 (1.05–1.10)	11	1.09 (1.03–1.14) 1.07 (1.04–1.10)	14	1.09 (1.03–1.16) 1.09 (1.03–1.15)
Duration of smoking, ≥20 years[b]	19	1.16 (1.12–1.21) 1.16 (1.12–1.20)	7	1.15 (1.10–1.19) 1.15 (1.10–1.19)	12	1.23 (1.12–1.36) 1.21 (1.12–1.30)
Cigarettes/day, ≥20[b]	18	1.13 (1.09–1.17) 1.13 (1.09–1.17)	8	1.12 (1.08–1.17) 1.12 (1.08–1.17)	10	1.19 (1.06–1.33) 1.19 (1.06–1.33)
Pack-years, ≥20[b]	16	1.16 (1.11–1.21) 1.15 (1.11–1.19)	6	1.15 (1.10–1.19) 1.14 (1.10–1.19)	10	1.21 (1.09–1.34) 1.21 (1.10–1.33)
Exposure to secondhand smoke						
Most comprehensive[a]	34	1.14 (1.06–1.23) 1.06 (1.02–1.09)	10	1.02 (0.95–1.10) 1.02 (.97–1.06)	24	1.27 (1.12–1.44) 1.13 (1.07–1.19)
Most comprehensive, most restricted[b]	23	1.04 (0.99–1.09) 1.03 (.99–1.06)	8	1.02 (0.96–1.09) 1.01 (.97–1.06)	15	1.07 (1.00–1.14) 1.05 (.99–1.12)
Adult–Any source, most restricted[b]	18	1.04 (0.96–1.13) 1.01 (.97–1.06)	6	1.01 (0.93–1.11) 1.00 (.96–1.05)	12	1.08 (0.94–1.24) 1.05 (.96–1.13)
Ever in Lifetime, most restricted[b]	15	1.03 (0.99–1.07) 1.03 (.99–1.07)	7	1.02 (0.98–1.07) 1.02 (.98–1.07)	8	1.07 (0.97–1.18) 1.04 (.97–1.12)
Lifelong, Childhood & Adulthood, most restricted[b]	6	1.07 (0.95–1.21) 1.06 (.98–1.14)	3	1.03 (0.94–1.14) 1.04 (.96–1.12)	3	1.44 (1.05–1.99) 1.44 (1.05–1.99)

Note: **CI** = confidence interval; **N** = sample size (number of studies). Sumary estimates for meta-analyses based on random effects models with exception of fixed-effects estimates shown in italics.

[a]Based on total studies.

[b]Restricted set of studies based on criteria notes to Tables 6.16*S*–6.17*S* and 6.24*S*–6.26*S*.

Table 6.28*S* Associations between smoking and overall mortality in cancer patients

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Goodman et al. 1990	• 675 lung cancer patients	C/F/N	• Males: – Never: 1.0 – Former: 1.0 (0.6–1.5) – Current: 0.8 (0.5–1.3) • Females: – Never: 1.0 – Former: 1.6 (1.0–2.4) – Current: 1.5 (0.9–2.4)	1979-1985; detailed interview
Sobue et al. 1991	• 267 lung adenocarcinoma patients	C/F/N	• Former: 1.89 (0.88–4.04) • Current: – <50 Pack-years: 1.28 (0.68–2.40) – 50+ Pack-years: 2.38 (1.21–4.67)	1978–1987
Browman et al. 1993	• 115 Stage III–IV head/neck cancer patients	Current/noncurrent	• 2.3 (1.2–4.2)	Smoking during RT; patients treated with RT +/- chemotherapy
Kirschner et al. 1995	• 136 vulvar cancer patients	Smoker/ Nonsmoker	• 6.34 (p <0.01)	Smoking not clearly defined; chart review
Deleyiannis et al. 1996	• 649 head/neck cancer patients	C/F/N	• Current ≥ 20 cpd 1.0 (referent) • Current <20 cpd 0.68 (0.38–1.24) • Quit <15 yrs ago 0.99 (0.54–1.80) • Never/quit ≥15yrs: 0.42 (0.24–0.74)	1983–1987; structured interview; referent category = current smokers with ≥20 cpd
Boffetta et al. 1997	• 222 male laryngeal cancer patients	Cigarettes per day	• 0–15 cpd 1.0 (referent) • 16–25: 1.4 (0.9–2.2) • ≥26: 1.8 (1.1–2.9)	1979–1982; chart review
Yu et al. 1997	• 25,436 cancer patients from institutional tumor registry.	Ever/never	• 1.47 (1.4–1.6)	
Fujusawa et al. 1999	• 369 Stage I NSCLC patients	Pack-years	• <30: 1.0 (referent) • 30+: 2.41 (1.24–4.96)	1981–1993; patients treated with surgery
de Perrot et al. 2000	• 1046 Stage I–IV NSCLC patients	Pack-years	• 0: 1.0 (referent) • 1-40: 1.82 (1.22–2.72) • >40: 1.48 (0.99–2.21)	1977–1996; chart review, patients treated with surgery
Hommura et al. 2000	• 215 Stage I–IV NSCLC patients	Ever/Never	• 1.73 (0.80–3.73)	1976–1994; chart review; smoking not clearly defined
Huang et al. 2000	• 877 gastric cancer patients	C/F/N	• Ever: 2.10 (1.06–4.18) • Current: 2.54 (1.22–5.29)	1988–1994; only male results, no analyses performed for women.

Table 6.28*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Palli et al. 2000	• 382 gastric cancer patients	C/F/N	• Former: 1.07 (0.78–1.47) • Current: 1.04 (0.75–1.45)	1985–1987; structured questionnaire in year prior to surgery
Sweeney et al. 2000	• 555 renal cell cancer patients	C/F/N	• Former: 1.2 (0.8–1.7) • Current: 1.7 (1.2–2.5)	1995–1997; chart review
Lippman and Farrow 2001	• 1166 T1–3 NSCLC patients	C/F/N	• Former: 2.28 (0.58–8.92) • Current: 4.39 (1.11–17.29)	Randomized trial; patients treated with isoretinoin
Browman et al. 2002	• 148 Stage III–IV head/neck cancer patients	Current/noncurrent	• 1.17 (p = 0.07)	Comparison group is recent quitters who stopped smoking within 12 weeks prior to RT; patients treated with RT
Chiyo et al. 2003	• 931 lung cancer patients	Ever/Never	• 1.51 (1.14–2.08)	1980–1990; chart review; smoking not clearly defined (smoking history)
de Cassia Braga Ribeiro et al. 2003	• 530 head/neck cancer patients	Smoker/nonsmoker	• 1.5 (p = 0.03)	1990–1997; smoking not clearly defined; chart review; patients treated with curative surgery
Myrdal et al. 2003	• 395 Stage I–III NSCLC patients	Current, non-current	• 1.3 (1.1–1.6)	1987–1999; chart review; patients treated with surgery
Tan et al. 2003	• 326 women with Stage I NSCLC	Ever, never	• 1.3 (1.0–1.8)	1996–1998
Videtic et al. 2003	• 186 limited stage SCLC patients	Current, non-current	• 1.86 (1.34–2.57)	1989–1999; chart review, patients treated with chemoradiotherapy
Chang et al. 2004b	• 114 CML patients	Ever/Never	• 1.72 (0.86–3.46)	1997–2001; patients treated with hematopoietic stem cell transplant. 1-year mortality
Nordquist et al. 2004	• 654 Stage I–IV NSCLC patients	Current, Never	• 1.33 (1.04–1.69)	(1985–2000, Moffitt)
Pickles et al. 2004	• 601 prostate cancer patients	Current/ Noncurrent	• 2.38 (p = 0.009)	1994–1997; 6 year mortality; patients treated with external beam RT; reference category includes never and former smokers
Sawabata et al. 2004	• 242 Stage IA NSCLC patients	Smoker	• Preoperative smoking yes: 5.706, p=0.1	1991–2003; patients treated with surgery; chart review; smoking not clearly defined

Table 6.28*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Tammemagi et al. 2004	• 1,155 lung cancer patients	Current, non-current	• 1.26 (1.08–1.47)	1995–1998; chart review
Toh et al. 2004	• 317 Stage I–IV NSCLC patients	Ever/Never	• 0.98 (0.704–1.375)	1999–2002; chart review
Dikshit et al. 2005a	• 931 laryngeal or hypopharyngeal cancer patients	Current cpd	• 1–15 cpd: 1.8 (1.1–3.1) • 16–25 cpd: 1.7 (1.0–2.9) • >25 cpd: 1.8 (1.1–3.1)	1979–1982
Ebbert et al. 2005	• 5229 lung cancer patients	C/F/N	• NSCLC – Former: 0.99 (0.86–1.13) – Current: 1.15 (1.00–1.32) • SCLC – Former: 1.05 (0.57–1.94) – Current: 1.08 (0.58–1.99)	1997–2002
Kawai et al. 2005	• 3082 Stage IA NSCLC patients	Pack-years	• <40 Pack-years: 1.0 • 40+ Pack-years: 1.129 (0.948–1.344)	1982–1997; chart review; patients treated with surgery
Sardari et al. 2005	• 321 Stage I–IIIB NSCLC patients	C/F/N	• Current: 1.0 • Recent quitters: 0.34 (0.16–0.71) • Former: 0.54 (0.35–0.84) • Never: 0.45 (0.21–0.97)	1991–2001; patients treated with surgery; detailed smoking information; recent quit within 3 months
Trivers et al. 2005	• 1,142 esophageal and gastric cancer patients	Ever/Never	• Esophageal adenocarcinoma – 0.86 (0.64–1.16) • Gastric cardia adenocarcinoma – 0.99 (0.71–1.38) • Esophageal squamous cell carcinoma – 0.99 (0.62–1.59) • Other gastric adenocarcinomas – 1.02 (0.79–1.32)	1993–1995
Wright et al. 2005	• 255 IB-IIB cervical cancer patients	Current/Noncurrent	• 3.69 (1.08–12.62)	Reference category includes former and never smokers
Wu et al. 2005	• 301 Stage I–III NSCLC patients	Smoker	• Stage I–III: 1.40 (0.997–1.97) • Stage II-III: 1.76 (1.17–2.66)	1990–2001; smoking not clearly defined in analysis; patients treated with surgery
Ando et al. 2006	• 1,976 NSCLC patients	Ever/Never	• 1.41 (1.19–1.67)	2002; chart review; patients from 84 institutions treated with gefitinib

Table 6.28*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Battaglioli et al. 2006	• 1,138 NHL patients	C/F/N	• Former: 0.91 (0.73–1.14) • Current: 1.04 (0.84–1.29)	1991–1993; structured questionnaire after diagnosis
Heist et al. 2006	• 382 Stage I NSCLC patients	C/F/N, Pack-years	• Former: 1.39 (0.74–2.59) • Current: 1.61 (0.86–3.03) • Pack-years: 1.007 (1.003–1.01)	1992–2001; patients treated with surgery
Iyoda et al. 2006	• 335 Stage IA NSCLC patients	Index	• 0: 1.0 (referent) • 1+: 1.24 (0.53–2.92)	1988–2003; chart review; smoking not clearly defined in analysis
Khuri et al. 2006	• 1,190 Stage I–II head/neck cancer patients	C/F/N	• Current vs. former: 1.60 (1.23–2.07) • Current vs. never: 2.51 (1.54–4.10)	Patients treated with surgery +/- RT and on randomized phase III trial of isotretinoin vs. placebo
Merrick et al. 2006	• 938 consecutive T1b-T3a prostate cancer patients	C/F/N	• Former: 2.15 (p = 0.007) • Current: 4.27 (p <0.001)	1995–2002; patients treated with brachytherapy +/- androgen deprivation therapy
Modesitt et al. 2006	• 3,562 endometrial cancer patients	Current/Notcurrent	• 1.41 (1.20–1.66)	1995–2002; reference category includes never and former smokers
Mulligan et al. 2006	• 907 NSCLC patients	Pack-years	• <40: 1.0 (referent) • 40-60: 1.11 (0.79–1.56) • >60: 1.00 (0.72–1.39) • Duration of smoking cessation – 0 years: 1.00 (referent) – 0–7 years: 1.17 (0.82–1.67) – 7–15 years: 0.70 (0.49–0.99) – >15 years: 1.03 (0.71–1.50)	1980–2000. Walter Reed Army Medical Center Tumor Registry; referent group includes smokers with <40 Pack-years
Saito-Nakaya et al. 2006	• 238 Stage I–IIIA NSCLC patients	C/F/N	• Smoking at 1 month after surgery – Never: 1.0 (referent) – Former: 3.4 (1.5–7.6) • Quit in past year: 2.9 (1.4–6.3) • Current: 6.4 (1.7–23.9)	1996–1999
Sun et al. 2006	• 5,730 Stage I–IV NSCLC patients	C/F/N	• Former: 1.13 (1.00–1.28) • Current: 1.09 (0.97–1.23)	1997–2003; chart review
Tsao et al. 2006	• 1370 Stage III–IV patients	C/F/N	• Never: 1.0 (referent) • Former: 1.47 (p=0.003) • Current: 1.55 (p=0.0004)	1993–2002; patients received chemotherapy; chart review

Table 6.28*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Waggoner et al. 2006	• 315 advanced cervical cancer patients	Current/ Noncurrent	• 1.51 (1.01–2.27)	Data from GOG 165 trial; reference category includes former and never smokers
Yoshino et al. 2006	• 999 Stage I–IV NSCLC patients	Smoker	• Stage I: 1.73 (1.01–3.04) • Stage II: NS (p=0.90) • Stage III–IV: NS (p=0.61)	Chart review; smoking defined as smoking within 10 years of diagnosis
Zhou et al. 2006	• 543 Stage I–IIB NSCLC patients	C/F/N	• Current: 1.0 (referent) • Former: – Quit 1-8 yr: 0.82 (0.59–1.13) – Quit 9-17 yr: 0.69 (0.49–0.97) – Quit 18+ yr: 0.66 (0.45–0.95) • Never: 0.54 (0.29–1.00)	1992–2002; current smoking is referent group
Ademuyiwa et al. 2007	• 208 Stage III NSCLC patients	Current/Non-current	• 0.90 (0.55–1.44)	2002–2006; patients treated with chemoradiotherapy +/- adjuvant chemotherapy on Hoosier Oncology Group Study
Bryant et al. 2007	• 730 Stage I–IV NSCLC patients	Ever/Never	• 1.21 (0.98–1.39)	1999–2005
Chia et al. 2007	• 745 endometrial cancer patients	C/F/N	• Former: 1.2 (0.8–1.8) • Current: 1.2 (0.7–2.1)	1991–1994; structured health behavior assessment
Holmes et al. 2007	• 5,056 breast cancer patients	C/F/N	• Former: 1.04 (0.90–1.19) • Current: 1.43 (1.24–1.65)	Nurses' Health Study; repeated structured questionnaires
Hung JJ et al. 2007	• 445 Stage I NSCLC patients with tumors 3 cm or less	Pack-years	• 1.01 (1.01–1.02)	1980–2000; chart review; pack-years analyzed as continuous variable
Kato et al. 2007	• 267 Stage I–IIIA NSCLC patients	Ever/Never	• 1.88 (1.09–3.24)	Smoking not clearly defined in analysis
Kikuchi et al. 2007	• 161 Stage I–IV NSCLC patients	Ever/Never	• 2.04 (0.99–4.64)	1982–1994; chart review; patients treated with surgery
Pantarotto et al. 2007	• 416 prostate cancer patients	C/F/N	• Former: 1.51 (p = 0.11) • Current: 1.72 (p = 0.08)	1990–1999; patients treated with external beam RT; chart review

Table 6.28*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Sagiv et al. 2007	• 1,273 breast cancer patients	C/F/N	• Obese – Former: 1.70 (0.94–3.07) – Current: 2.10 (1.03–4.27) • Overweight – Former: 0.92 (0.51–1.67) – Current: 1.10 (0.52–2.35) • Normal weight – Former: 1.08 (0.62–1.87) – Current: 1.00 (0.54–1.86)	1996–1997; Long Island Breast Cancer Study Project; questionnaire following breast cancer diagnosis
Samadi et al. 2007	• 420 esophageal or gastric cancer patients	Smoker/Nonsmoker	• 1.81 (1.02–3.23)	1994–2005; smoking not clearly defined in analysis
Wang et al. 2007	• 426 Stage I NSCLC patients	Ever/Never	• 1.11 (0.77–1.58)	1995–2000; chart review; smoking not clearly defined; patients treated with surgery
Arduino et al. 2008	• 334 oral cavity cancer patients,	Smoker/nonsmoker	• 1.3 (p = 0.15)	10-year mortality; chart review
Dal Maso et al. 2008	• 1,453 breast cancer patients	C/F/N	• Former: .41 (1.11–1.78) – Current <15 cpd: 1.48 (1.12–1.94) – Current ≥15 cpd: 1.35 (0.94–1.93)	1991–1994; structured questionnaire 1 year prior to diagnosis
Hanagiri et al. 2008	• 770 stage I–IV NSCLC patients	Ever/Never	• 1.03 (0.76–1.45)	1994–1995; chart review; patients treated with surgery
Karvonen-Gutierrez et al. 2008	• 495 head/neck cancer patients	Smoke/No smoke past month	• 1.72 (1.29–2.29)	2000–2002; structured health habits assessment
Matsuguma et al. 2008	• 455 state I NSCLC patients	Ever/Never	• 1.27 (0.72–2.24)	1986–2003; chart review; patients treated with surgery
Meyer et al. 2008	• 540 head/neck cancer patients	Current/noncurrent	• 2.26 (1.29–3.97) (β-carotene treated pts.)	1994–2000; patients treated with RT, randomized to β-carotene; reference category includes never and former smokers
Molina et al. 2008	• 20,915 head/neck cancer patients	Ever/Never	• 1.34 (1.19–1.50)	1998–2002; Florida Cancer Data System
Nakamura et al. 2008	• 571 lung cancer patients	C/F/N	• Former: 1.70 (1.25–1.31) • Current: 1.99 (1.51–2.62)	1980–2003

Table 6.28*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Ramamoorthy et al. 2008	• 64 anal cancer patients	Smoker/Nonsmoker	• 2.25 (p=0.05)	1999–2005; smoking within 5 years of treatment; 5-year mortality; chart review
Saito-Nakaya et al. 2008	• 1,230 Stage I–IV NSCLC patients	C/F/N	• Males – Former: 1.6 (0.9–2.6) – Current: 1.7 (1.1–2.8) • Females – Former: 1.1 (0.7–1.9) – Current: 2.0 (1.4–2.9)	1999–2004
Sundelof et al. 2008	• 580 esophageal or gastric cardia cancer patients	C/F/N	• Oesophageal adenocarcinoma – Former: 0.9 (0.6–1.4) – Current: 1.0 (0.6–1.7) • Squamous cell carcinoma – Former: 2.1 (1.0–4.4) – Current: 1.4 (0.7–2.8) • Gastric cardia adenocarcinoma – Former: (0.9 (0.6–1.4) – Current: 1.4 (0.8–2.2)	1994–2007; Swedish Oesophageal and Cardia Cancer Study; current includes smoking within 2 years of diagnosis
Talamini et al. 2008	• 268 NHL patients	Ever/Never	• 1-19 cpd: 1.22 (0.80–1.86) • ≥20 cpd: 1.70 (1.06–2.73) • Duration of smoking (years) – <30: 1.41 (0.89–2.23) – ≥30: 1.32 (0.85–2.05)	1983–2002
Tian et al. 2008	• 233 Stave I–IV NSCLC patients	Ever/Never	• 1.74 (0.90–3.39)	
Toyooka et al. 2008	• 408 advanced or recurrent NSCLC patients	Ever/Never	• ≥20 Pack-years: 1.0 (referent) • <20 Pack-years: 0.95 (0.62–1.46) • Never: 0.83 (0.58–1.20)	Chart review; analyses based upon pack year
Chansky et al. 2009	• 2,467 stage I–IIIA NSCLC patients	C/F/N	• Current vs. former: 1.21, p <0.0001 • Current vs. never: 1.41, p = 0.0017 • Former vs. never: 1.16, p = 0.16	1990–2000; patients treated with surgery and part of IASLC Lung Cancer Staging Project
Coker et al. 2009	• 2,661 women with cervical cancer	Current/ Notcurrent	• 1.35 (1.17–1.56)	1995–2005; reference category includes never and former smokers
Duffy et al. 2009	• 504 head neck cancer patients	C/F/N	• Former: 2.02 (1.16–3.51) • Current: 2.36 (1.28–4.37)	2003–2008; structured health habits assessment

Table 6.28*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Guo et al. 2009	• 327 stage I–III NSCLC patients	Heavy/ Non-heavy	• 61 or less: 1.0 (referent) • >61 Pack-years: 1.41 (1.03–1.94)	Referent group includes ever and never smokers; patients pooled from 4 lung cancer cohorts
Hayashibara et al. 2009	• 626 NSCLC patients	Ever/Never	• 1.20 (0.94–1.52)	2002–2007; chart review; patients treated with gefitinib
Hotta et al. 2009	• 365 NSCLC patients	Ever/Never	• Males: 1.012 (1.00–1.02) • Females: 1.007 (0.98–1.03)	2000–2003; risks stated per pack year; patients treated with gefitinib
Hsu et al. 2009a	• 695 stage I–IV NSCLC patients	Ever/Never	• 1.27 (0.97–1.65)	2002–2006; more than 50% of patients were stage IV
Huang et al. 2009	• 671 postmenopausal females with primary lung cancer	Ever/Never	• 1.41 (p = 0.03)	1995–2005; chart review
Koch et al. 2009	• 289 Stage IIIB–IV NSCLC patients	Current/ Noncurrent	• 1.50 (1.11–2.02)	2002–2007; chart review; patients treated with chemotherapy
Li et al. 2009b	• 325 stage I NSCLC patients	Ever/Never	• 1.56 (0.882–2.759)	1998–2003; chart review; patients treated with surgery
Lin et al. 2009	• 109 thoracic esophageal SCC patients	Ever/Never	• 2.47 (1.36–4.51)	2000–2004; smoking not clearly defined in analysis; chart review; patients treated with surgery
Marks et al. 2009	• 2,818 HLA identical sibling or matched unrelated donor allogeneic transplants for CML	Ever (High dose, low dose)/Never	• HLA-identical sibling donor group – Low dose: 1.01 (0.84–1.22) – High dose: 1.44 (1.07–1.93) • Unrelated donor group – Ever: 0.96 (0.75–1.21)	1990–2004
Myrdal et al. 2009	• 4,791 NSCLC patients	C/F/N	• Former: 1.15 (1.01–1.29) • Current: 1.30 (1.15–1.46)	1995–2003; current includes patients who quit <12 months prior
Mayne et al. 2009	• 264 Stage I–II head/neck cancer patients	C/F/N	• Current at diagnosis: 4.91 (0.67–35.98) • Current after diagnosis: 1.83 (0.85–3.94)	1991–1998; randomized beta-carotene chemoprevention trial
Ou et al. 2009a	• 20,140 NSCLC patients	Ever/Never	• 1.07 (1.01–1.13)	1991–1995; chart review; patients from California Cancer Surveillance Program
Ou et al. 2009b	• 3,428 extensive stage SCLC patients	Ever, never	• 1.31 (1.06–1.62)	1991–2005; chart review; patients from California Cancer Surveillance Program

Table 6.28*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Chang et al. 2010	• 110 NSCLC patients	Ever/Never	• 1.86 (1.09–3.17)	2006–2008; chart review
Chen et al. 2010c	• 284 limited stage SCLC	Current/ Noncurrent	• Current: 1.0 (referent) • Former/Never: 0.72 (0.52–1.00) • Quit at or after diagnosis: 0.55 (0.38–0.79)	1997–2007; chart review; continued smoking is referent group
Chen et al. 2010d	• 203 stage IIIB–IV NSCLC patients age 80+ at diagnosis	Ever/Never	• Univariate: 1.44 (1.06–1.95) • Multivariate: NS	2000–2006; chart review
Fontaine et al. 2010	• 412 stage I–III NSCLC patients	Ever/Never	• 1.82 (p = 0.007)	2001–2009; patients taking aspirin and treated with surgery
Geyer et al. 2010	• 471 NHL patients	C/F/N	• Former: 1.59 (1.12–2.26) • Current: 1.50 (0.97–2.29)	1998–2000; follow-up structured health behavior interview
Hellmann et al. 2010	• 528 breast cancer patients	C/F/N	• Former: 1.04 (0.88–1.23) • Current: 1.16 (1.05–1.29)	1976–2003, Copenhagen City Heart Study; repeated structured questionnaires
Hung et al. 2010	• 525 stage IB NSCLC patients	Smoking	• 1.003 (0.999–1.007)	1980–2000; analysis of risk according to pack year; patients treated with surgery
Ioffe et al. 2010	• 130 Stage III-IV epithelial ovarian cancer patients	Current/ Notcurrent	• 2.25 (1.30–3.87)	1996–2003; patients treated with cytoreductive surgery; chart review current defined as smoking at time of surgery
Janjigian et al. 2010	• 2,010 stage IIIB–IV NSCLC patients	Ever/Never	• 15 or less vs. never: 1.15 (0.92–1.43) • >15 vs. 15 or less: 1.23 (1.03–1.48) • >15 vs. never: 1.42 (1.20–1.67)	2003–2006; ever according to pack-years
Kawaguchi et al. 2010b	• 26,957 NSCLC patients	Ever/Never	• 1.07 (1.01–1.31)	1990–2005; patients from National Hospital Organization Study Group for Lung Cancer
Kim et al. 2010	• 342 NSCLC patients	Ever/Never	• 1.41 (0.99–2.00)	2006–2008; chart review; patients treated with erlotinib or gefitinib
Lee et al. 2010b	• 237 stage I–II NSCLC patients	Smoker	• 1.31 (0.73–2.35)	2003–2007; smoking not clearly defined in analysis; patients treated with surgery
McCleary et al. 2010	• 1,045 participants with stage III colon cancer	C/F/N	• Former: 1.17 (0.87–1.57) • Current: 1.38 (0.87–2.18)	Data from CALGB 89803 randomized trial treated with 5-FU/leucovorin +/- irinotecan
Meguid et al. 2010	• 4,536 NSCLC patients	C/F/N	• Never: 1.0 (referent) • Current: 1.08 (0.95–1.22)	1975–2004

Table 6.28*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Naito et al. 2010	• 826 stage T1a–T2a NSCLC patients	Ever/Never	• <30 Pack-years: 1.0 (referent) • ≥30 Pack-years: 1.58 (0.92–2.71)	1993–2003; chart review; analysis according to pack year history
Olson et al. 2010	• 475 pancreatic cancer patients	C/F/N	• Resected patients – Former: 0.83 (0.34–2.03) – Current: 0.99 (0.58–1.69) • Unresected patients – Former: 1.00 (0.73–1.36) – Current: 0.79 (0.52–1.20)	2001–2006; Familial Pancreatic Cancer Registry; current smoking included patients who smoked in the year prior to diagnosis
Sardari et al. 2010	• 239 NSCLC patients	Current/ Noncurrent	• 1.46 (1.04–2.04)	1991–2001; patients treated with surgery
Shitara et al. 2010	• 363 patients with SCC of the esophagus	Heavy (≥20 Pack-years)/Not Heavy	• 1.73 (1.12–2.68)	2001–2005; referent category combined never smokers + smokers with <20 Pack-years history; patients treated with RT+chemotherapy or surgery
Syrigos et al. 2010	• 1,725 stage IIIB–IV NSCLC patients	Ever/Never	• Nonsquamous histology: 1.75 (1.42–2.15) • Squamous histology: 1.50 (0.94–2.42)	Patients enrolled on randomized trial of chemotherapy
Ali et al. 2011	• 170 inflammatory bowel disease patients from 22,325 CRC cases	C/F/N	• Current vs. former: 1.15 (1.07–1.23) • Current vs. never: 1.20 (1.13–1.28)	1994–2005; Irish National Cancer Registry
Dandona et al. 2011	• 355 pancreatic cancer patients	C/F/N	• Former: 1.07 (0.80–1.44) • Current: 1.07 (0.78–1.48)	1995–2000; patients treated with surgery; chart review.
Dragun et al. 2011	• 11,914 stage 0–II breast cancer patients	Ever/Never	• 1.43 (1.28–1.60)	1998–2007; Kentucky Tumor Registry; chart review; patients treated with breast conservation surgery
Ehlers et al. 2011	• 148 leukemia patients	C/F/N	• Former: 1.17 (0.721.91) • Current: 1.75 (1.00–3.06)	1999–2005; patients treated with hematopoietic stem cell transplant; current includes smoking within the prior year; chart review
Farshadpour et al. 2011	• 2,012 head/neck cancer patients	Current/ Noncurrent	• 1.50 (1.16–1.93)	1980–2004; smoking combined with drinking in analysis
Kato et al. 2011	• 358 stage IA–IIIB NSCLC patients	Ever/Never	• Univariate: 1.63 (1.03–2.57) • Multivariate: 0.86 (0.49–1.48)	1992–2004; chart review

Table 6.28*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Kenfield et al. 2011	• 5,366 prostate cancer patients	C/F/N	• Former: 1.23 (1.10–1.37) • Current: 2.28 (1.87–2.80)	Health Professionals Follow-Up Study; structured questionnaire every 2 years
Kountourakis et al. 2011	• 49 patients with T2 esophageal cancer	Smoker/ Nonsmoker	• 5.93 (1.32–26.57)	1997–2009; patients treated with surgery, RT, and chemotherapy
Kroeger et al. 2011	• 802 renal cell carcinoma patients	Ever/Never	• 1.36 (1.13–1.64)	1989–2007; chart review
Kvale et al. 2011	• Cardiovascular Health Study • 789 elderly cancer patients matched with 3,119 elderly noncancer patients	Current/ Noncurrent	• 1.72 (1.23–2.42)	
Li et al. 2011	• 1,139 lung cancer patients	Ever/Never	• 1.28 (1.04–1.58)	1998–2004; chart review
Maeda et al. 2011a	• 2,295 stage I–III NSCLC patients	Ever/Never	• Stage I: 1.83 (1.27–2.64) • Stage II: p = 0.74 • Stage III: p = 0.90	1992–2006; ever smoking defined as >43 Pack-years
Maeda et al. 2011a	• 1,870 stage I–II NSCLC patients	Ever/Never	• 1.77 (p <0.001)	1992–1997; 5-year mortality; chart review; patients treated with curative surgery
Ngô et al. 2011	• 257 patients with cervical cancer <4 cm in diameter	Current smokers >10 cpd vs. ≤10 cpd	• 3.07 (1.58–5.97)	1985–2008; referent category includes light current smokers + former + never smokers; patients treated with preoperative brachytherapy and surgery; 5-year mortality
Phipps et al. 2011	• 2,264 colorectal cancer patients	C/F/N	• Former: 1.26 (1.07–1.49) • Current: 1.51 (1.24–1.83)	1998–2007; structured questionnaire post-diagnosis
Richards et al. 2011	• 423 Stage I-III colorectal cancer patients	C/F/N	• 1.30 (1.07–1.57)	1997–2007; smoking not clearly defined but appears to be current; patients treated with curative surgery
Richey et al. 2011	• 188 metastatic renal cell cancer patients	Current/ Noncurrent	• 1.71 (1.06–2.78)	2003–2009; patients treated with targeted therapy and no surgery; chart review; reference category includes never and former smokers
Schlumbrecht et al. 2011	• 194 low grade serous adenocarcinoma of the ovary	Current/ Noncurrent	• 1.57 (0.99–2.48)	1977–2009; reference category includes former and never smokers

Table 6.28*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Sfakianos et al. 2011	• 623 consecutive patients with high grade superficial, carcinoma in situ, or T1 invasive bladder cancer	C/F/N	• Former: 1.20 (0.82–1.74) • Current: 1.03 (0.63–1.68)	1994–2008; chart review; patients treated with BCG and surgery
Taira et al. 2011	• 1,656 prostate cancer patients	C/F/N	• Former: 1.43 (p = 0.017) • Current: 2.86 (p <0.001)	1995–2006; treated with brachy-therapy +/- androgen deprivation therapy +/- external beam RT
Yafi et al. 2011	• 2,287 bladder cancer cases	Smoker/ Nonsmoker	• 1.31 (1.05–1.63)	1998–2008; chart review; treated with radical cystectomy
Bostrom et al. 2012	• 564 bladder cancer patients	Ever/Never	• 1.4 (1.1–1.8)	1991–2008; treated with radical cystectomy; chart review
Gajdos et al. 2012	• 20,413 gastrointestinals, thoracic, and urologic cancer patients	C/F/N	• Gastrointestinal – Former: 1.22 (1.08–1.38) – Current: 1.62 (1.43–1.85) • Thoracic – Former: 1.19 (0.92–1.54) – Current: 1.50 (1.17–1.92) • Urologic – Former: 1.04 (0.77–1.41) – Current: 1.19 (0.90–1.58)	VA Surgery Quality Improvement Program; 1-year mortality; patients treated with major surgery
Gillison et al. 2012	• 502 stage III–IV head/neck cancer patients	Current/ Noncurrent	• 2.34 (1.56–3.50)	Data from RTOG 9003 and RTOG 0129 randomized phase III trials treating with RT +/- chemotherapy; reference category includes never and former smokers
Gridelli et al. 2012	• 780 stage IIIB-IV NSCLC patients	Ever/Never	• 1.27 (1.06–1.54)	Patients treated on randomized TORCH trial
Hoff et al. 2012	• 232 head/neck cancer patients treated with RT	Current/ Noncurrent	• 2.01 (1.28–3.15)	1983–1991; reference category includes never and former smokers
Holgersson et al. 2012	• 1,146 NSCLC patients	C/F/N	• Former: 1.10 (0.82–1.45) • Current: 1.06 (0.80–1.41)	1990–2000; chart review; patients treated with curative RT
Hung et al. 2012	• 756 stage I NSCLC patients	C/F/N	• Never: 1.0 (referent) • 1–20 Pack-years: 1.48 (1.11–1.98) • >20 Pack-years: 1.99 (1.60–2.47)	1980–2010; analysis according to Pack-years history; patients treated with lobar resection

Table 6.28*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Kawaguchi et al. 2012	• 2,966 stage IIIB-IV NSCLC patients ≥70 years old	C/F/N	• Current: 1.0 (referent) • Former: – 70–74: 0.91 (0.80–1.04) – 75–79: 1.06 (0.92–1.22) – 80+: 1.08 (0.90–1.29) • Never: – 70–74: 0.78 (0.66–0.93) – 75–79: 0.80 (0.66–0.97) – 80+: 0.99 (0.80–1.21)	1990–2005; current smoking is referent group; analysis according to age; patients treated with chemotherapy
Kawakita et al. 2012	• 222 patients with oral cavity cancer	Current/ Noncurrent	• Light smokers: 1.0 (referent) • Moderate: 2.44 (1.07–5.57) • Heavy: 2.66 (0.97–7.33)	2001–2005; referent category is light smokers
Lee et al. 2012a	• 924 stage IIIB–IV NSCLC patients	Ever/Never	• Not significant (Forest plot)	2006–2008; patients enrolled on phase III ZEPHYR trial in patients who failed EGFR therapy
Lee et al. 2012b	• 670 stage IIIB-IV NSCLC patients	C/F/N	• Former: 1.09 (0.85–1.41) • Current: 1.56 (0.88–2.78)	Patients treated with erlotinib on TOPICAL trial
Liu et al. 2012	• 282 women <40 years old with lung cancer	Current/ Noncurrent	• 3.32 (1.73–8.79)	1985–2007
Maeda et al. 2012	• 1,070 stage IA lung cancer patients	Ever/Never	• 20 or less: 1.0 (referent) • >20: 1.83 (1.29–2.57)	1992–1997; analysis according to Pack-years history; Patients treated with curative surgery
Nawa et al. 2012	• 210 lung cancer patients	Ever/Never	• 4.7 (1.3–16.5)	1998–2006; 5-year mortality; smoking not clearly defined in analysis; patients in chemotherapy screening program
Paik et al. 2012	• 675 NSCLC patients	Ever/Never	• 1.9 (1.4–2.5)	2009–2010
Pirker et al. 2012	• 1,125 stage IIIB-IV NSCLC patients	C/F/N	• Current: 1.0 (referent) • Former: 0.86 (0.73–1.02) • Never: 0.72 (0.58–0.88)	Patients enrolled on phase III trial adding cetuximab to chemotherapy
Ryu et al. 2012	• 569 stage I NSCLC patients	Ever/Never	• 1.18 (0.76–1.83)	1997–2005; patients treated with curative surgery
Toffalorio et al. 2012	• 467 stage T2N0 NSCLC patients	C/F/N	• Former: 1.45 (0.70–3.00) • Current: 1.61 (0.75–3.46)	1998–2009; chart review; patients treated with surgery

Table 6.28*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Varadarajan et al. 2012	• 280 acute myeloid leukemia patients	Ever/Never	• 1.64 (1.21–2.21)	1990–2008; chart review; patients treated with high dose cytarabine and idarubicin
Wang et al. 2012	• 301 stage II–IIIA NSCLC patients	Ever/Never	• 0.89 (0.67–1.19)	2000–2006; chart review; patients treated with surgery
Dahlstrom et al. 2013	• 2,299 oropharyngeal cancer patients.	Ever/never	• 1955–1994 cohort: 1.4 (1.2–1.7) • 1995–2004 cohort: 2.3 (1.7–3.2)	1955–2004; chart review
Ferketich et al. 2013	• 4,200 NSCLC patients	Current, recent quit, former, never	• Current: 1.0 (referent for each Stage) • Stage I-II: – Never: 0.47 (0.26–0.85) – Former <12 months: 0.80 (0.51–1.24) – Former >12 months: 0.84 (0.65–1.08) • Stage III: – Never: 0.51 (0.38–0.68) – Former <12 months: 0.79 (0.59–1.07) – Former >12 months: 0.85 (0.70–1.03) • Stage IV: (stratified by age) – Never: significant for all under age 85 – Former: significant for all under age 65	Patients from NCCN Database Project
Johnson et al. 2013	• 1,036 stage IV lung cancer patients	Ever/Never	• Univariate: 1.18 (1.01–1.37) • Multivariate: 1.00 (0.85–1.18)	2002–2009; chart review; patient analysis corrected for *EGFR* and *KRAS* mutations
Poullis et al. 2013	• 2,485 stage I-III NSCLC patients	Current/ Noncurrent	• 1.33 (1.14–1.54)	2001–2011; patients treated with curative surgery
Tanaka et al. 2013	• 244 stage III–IV NSCLC patients	Ever/Never	• 1.67 (1.13–2.47)	2004-2009; smoking not well defined in analysis; patients treated with chemotherapy
Warren et al. 2013	• 5,185 cancer patients with 13 types of malignancy.	Current/recent quit/ former/never	• Current vs. never: 1.38 (1.23–1.54) • Current vs. former: 1.29 (1.17–1.42) • Current vs. recent quit: 1.17 (1.03–1.32)	1982–1998; structured tobacco assessment within 30 days of diagnosis; referent category = current smokers

Note: **C/F/N** = current/former/never; **CALCB** = cancer and leukemia group B; **CML** = chronic myelogenous leukemia; **cpd** = cigarettes per day; **5-FU** = 5-fluorouracil; **GOG** = Gynecologic Oncology Grpup; **HLA** = human leukocyte antigen; **IASLC** = International Association for the Study of Lung Cancer; **NSCLS** = non-small-cell lung cancer; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **RT** = radiotherapy; **RTOG** = Radiation Therapy Oncology Group.

Table 6.29*S* Associations between smoking and overall survival in cancer patients

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Herr et al. 1990	• 122 CML patients, Retrospective	Smoker/ nonsmoker	• 0.74 (p = 0.02)	1968–1987; median survival; chart review; smoking defined as current tobacco use of ≥5 Ppck years within the 10 years prior to diagnosis
Hopkins et al. 1991	• 345 stage IB cervical cancer patients	Smoking history	• Reported as not statistically significant in the text. (p. 1521)	1970–1985; chart review; smoking not clearly defined
Harpole et al. 1995	• 271 consecutive Stage I NSCLC patients	Pack-years	• 0: 59% (p = 0.63) • 1–20: 63% • 21–50: 60% • >50: 55%	1980–1988; 10-year survival; chart review
Fountzilas et al. 1997	• 154 Stage III–IV head/neck cancer patients	Ever/never	• 0.66 (p = 0.03)	1984–1991; median survival; patients treated with induction chemotherapy followed by surgery or RT
Holli et al. 1999	• 792 Stage I–IV NSCLC patients	Pack-years	• <25: 1.00 • 25–40: 0.84 (0.61–1.15) • >40: 0.94 (0.68–1.29)	1983–1987; overall survival; chart review
Suzuki et al. 1999	• 430 Stage I NSCLC patients	Pack-years	• 0–5 pack-years: 89.8% (p = 0.002) • 5+ pack-years: 79.1%	1987–1997; 5-year survival; chart review; patients treated with surgery
Oh et al. 2000	• 148 renal cell cancer patients	Ever/never	• "When stratified by metastatic status, however, a significant difference in overall survival was noted between smokers and nonsmokers among patients with Stage M0 (P = 0.039)." (p. 32)	1980–1994; chart review; patients treated with surgery
de Graeff et al. 2001	• 208 head/neck cancer patients	Current smoking amount	• Reported as not statistically significant in the text. (p. 336)	1994–2006; patients treated with surgery and/or RT
Chelghoum et al. 2002	• 642 acute myeloid leukemia patients	Ever/never	• 0-20 pack-years: 1.0 (referent) • ≥20 pack-years: 0.77 (p = 0.02) • Duration smoked (years): – 0–30: 1.0 (referent) – ≥30: 0.65 (p = 0.004)	1984–1998; pack-years and median survival; structured tobacco assessments by patients or relatives
Ganti et al. 2002	• 308 pancreatic cancer patients, Retrospective	Ever/Never	• 1.14 (p = 0.97)	1985–2001; median survival; chart review; smoking not clearly defined in analysis

Table 6.29*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Yang et al. 2002	• 250 Stage I–IV NSCLC patients	C/F/N with pack-years	• Never: 83% (p=0.078) • Current 40+ pack-years: 71% • Current <40 pack-years: 74% • Past 40+ pack-years: 82% • Past <40 pack-years: 65%	1997–1999; 1-year survival
Lo et al. 2003	• 378 oral cavity cancer patients	Ever/Never	• 0.92 (p <0.01)	1975–96; 5-year survival; chart review; smoking not clearly defined; patients treated with surgery +/- RT +/- chemotherapy
Wu et al. 2003	• 321 Stage I NSCLC patients	Pack-years	• 20 or less: 40.7% • >20: 26.4% (p<0.0007)	1980–1990; 10-year survival; chart review
Fox et al. 2004	• 237 Stage I–III NSCLC patients	Current, non-current	• Stage I–II – Current: 13.7 mo – Non-current: 27.9 mo (p = 0.01) • Stage III – Current: 19.5 mo – Non-current: 17.7 mo (p = 0.46)	1991–2001; median survival; chart review; current smoking include patients who quit within 12 months of RT; patients treated with RT
Gorsky et al. 2004	• 322 patients with tongue cancer	Smoker/ nonsmoker	• Reported as not statistically significant in the text. (p. 549)	1979–1994; chart review; smoking not clearly defined in analysis
Iizasa et al. 2004	• 402 Stage I lung cancer patients	Pack-years	• 30+: 47.9% • <30: 75% (p = 0.0012)	1985–1997; 10-year survival; patients treated with surgery
Oefelein et al. 2004	• 222 advanced prostate cancer including 133 hormone refractory patients	C/F/N	• Never: 1.0 (referent) • Former: 0.78 • Current: 0.63 (p = 0.00001)	1987–2003; median survival; chart review
Yamamoto et al. 2004	• 207 Stage I–IIIA NSCLC	Smoking habit	• Yes: 75.1% • No: 71.8% (not significant)	1990–1995; smoking not clearly defined; chart review.
Brumund et al. 2005	• 270 patients with T1–T3 true vocal cord cancer	Pack year	• Reported as not statistically significant in the text. (p. 319)	1975–2000; chart review

Table 6.29*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Herbst et al. 2005	• 1079 Stage IIIB–IV NSCLC patients	C/F/N	• Chemotherapy + Erlotinib: – Current: 8.4 mo, – Former: 10.0 mo – Never: 22.5 mo (p=0.01) • Chemotherapy alone: – Current: 9.1 mo – Former: 10.9 mo – Never: 10.1 mo	2001–2002; median survival; TRIBUTE trial; randomized trial of chemotherapy +/- Erlotinib
Videtic et al. 2005	• 215 limited stage SCLC	Current	• Survival (p=0.0046): – Male smoker: 9.1% – Male nonsmoker: 22.1% – Female smoker: 21.6% – Female nonsmoker: 38.7%	1989–1999; overall survival; chart review; patients treated with CRT; smoking defined as smoking during CRT
Donat et al. 2006	• 1,159 renal cell carcinoma patients	Ever/never	• 0.91 (p = 0.10)	1995–2003; 5-year survival; patients treated with surgery
Ganti et al. 2006	• 498 women with lung cancer	Ever/never	• Ever, HRT+: 39 mo • Ever, HRT-: 73 mo • Never, HRT+: 92 mo • Never, HRT-: 98 mo	1994–1997; median survival; chart review; ever defined as 5+ pack-years
Gautschi et al. 2006	• 244 Stage I–IV NSCLC patients	Pack-years	• "The extent of smoking (<40 pack-years versus >40 pack-years) correlated neither with response to chemotherapy, nor with survival (data not shown)." p. 306	2001–2003
Guntinas-Lichius et al. 2006	• 69 patients with unknown primary of the head/neck	Smoker/ nonsmoker	• 0.36 (p = 0.02)	1987–2002; 5-year survival; chart review; smoking not clearly defined
Lee et al. 2006	• 575 stage IIIB–IV patients	Ever/never	• Never: 15.1 mo • Ever: 6.1 mo (p<0.001) • Multivariate: p=0492 (pg. 343)	2002–2005; median survival; chart review; patients treated with gefitinib
Tsuchiya et al. 2006	• 322 Stage IA NSCLC patients	Pack-years	• <40 pack-years: 87.9% • 40+ pack-years: 80.1% (p=0.442)	1979–2004; 5-year survival; chart review; patients treated with surgery; referent group includes smokers and nonsmokers

Table 6.29*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Gillespie et al. 2007	• 325 head/neck cancer patients	Smoker/ nonsmoker	• 1.24 (0.60–2.57)	Chart review; case control study for COX2 inhibitors; smoking not clearly defined in analysis
Hidaka et al. 2007	• 185 esophageal cancer patients	Brinkman index ≥800 vs. <800	• 0.95 (p = 0.53)	1978–2005; 5-year survival; referent category includes never and former smokers with up to 20 pack year history; patients treated with surgery
Satouchi et al. 2007	• 221 NSCLC patients	Ever/never	• 0.41 (0.29–0.58)	2002–2005; chart review; patients treated with gefitinib
Yildizeli et al. 2007	• 218 NSCLC patients	Current/ noncurrent	• p=0.45 (pg. 99)	1981–2005; chart review; patients treated with sleeve resection
Bryant and Cerfolio 2008	• 186 African American men with NSCLC matched with 744 White men	Ever/never	• "Smoking rate and time until presentation for treatment were the only independent predictors on Cox Hazards analysis (p=0.007) for African American men." (p. 713)	1997–2007
Florescu et al. 2008	• 731 stage IIIB–IV patients	C/F/N	• Former: 0.82 (p <0.001) • Current: 0.53 (p <0.001)	Patients enrolled on BR21 trial of patients who failed prior therapy treated with erlotinib
Rajappa et al. 2008	• 294 stage IIIB–IV NSCLC patients	Ever/never	• 0.78 (p = 0.0074)	2002–2006; median survival
Sakao et al. 2008	• 121 NSCLC patients with tumors <2 cm	Ever/never	• 0.84 (p = 0.05)	1996–2006; 5-year survival; chart review; patients treated with surgery
Spigel et al. 2008	• 229 stage IIIB-IV NSCLC patients	Ever/never	• 0.71 (no statistics)	2004; analysis according to pack-years; patients treated on phase III trial of erlotinib
Bostrom et al. 2009	• 248 bladder cancer patients	Ever/never	• 0.71 (p = 0.03)	1986–2005; chart review; 10-year survival; patients treated with radical cystectomy
Fortin et al. 2009	• 1,871 head/neck cancer patients	C/F/N	• Former: 0.81 • Current: 0.74 (p = 0.0005)	1989–2006; 5-year survival; chart review; patients treated with RT +/- chemotherapy +/- surgery

Table 6.29*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Gupta et al. 2009	• 203 stage III–IV NSCLC patients	Ever/Nnver	• 0.22 (0.19–0.61)	2006–2008; 2-year survival; structured tobacco interview
Hsu et al. 2009b	• 217 stage I NSCLC patients	Smoker/ Nonsmoker	• 0.89 (p = 0.460)	2000–2006; 5-year survival; chart review; smoking not clearly defined
Ahn et al. 2010	• 13,469 NSCLC patients	Ever/never	• Korean: 0.87 (p = 0.0141) • White: 0.93 (p = 0.0397)	1995–2008; 2-year survival; analyzed according to race; chart review; California Cancer Surveillance Program
Ang et al. 2010	• 721 Stage III–IV head neck cancer patients	Pack-years	• Smoking decreased survival by 1% per pack year (p = 0.002)	Data from 2 randomized cancer treatment trials
Chen et al. 2010b	• 122 stage III–IV NSCLC patients	Ever/never	• 0.57 (p = 0.010)	2002–2007; chart review; patients treated with gefitinib monotherapy
Jamal et al. 2010	• 94 unresectable pancreatic cancer patients	Smoker/ nonsmoker	• 0.39 (p = 0.09)	2001–2006; chart review; smoking within 5 years of diagnosis
Kawaguchi et al. 2010a	• 28,517 NSCLC patients	Ever/never	• Japanese: 0.74 (p <0.0001) • United States: 0.92 (p = 0.1282)	1991–2007; 2-year survival; chart review
Liao et al. 2010	• 409 unresectable NSCLC patients	Current/ noncurrent	• 0.93 (0.69–1.25)	1999–2006; chart review; patients treated with RT
Liu et al. 2010b	• 698 patients with oral cavity cancer	Ever/never	• 1.13 (p = 0.24)	1995–2005; 5-year survival; chart review; patients treated with surgery +/- adjuvant therapy
Na et al. 2010	• 162 female stage IIIB–IV NSCLC	Ever/never	• 1.01 (p = 0.291)	2002–2008; median survival; chart review; patients treated with gefitinib monotherapy
Nugent et al. 2010	• 111 stage IB2–IV cervical cancer patients	Ever/never	• Reported as not statistically significant in the text. (p. 440)	2003–2007; chart review; patients treated with RT + chemotherapy
Sakao et al. 2010	• 106 NSCLC patients with multilevel nodal metastases	Ever/never	• 0.57 (p = 0.12)	1988–2007; 5-year survival; chart review; patients treated with surgery
Wang et al. 2010b	• 257 stage I lung cancer patients	Smoking	• 0.91 (p = 0.154)	1995–2000; 5-year survival; patients treated with surgery
Yang et al. 2010	• 1,725 stage IIIB–IV NSCLC patients	Ever/never	• 0.93 (0.81–1.05)	Patients enrolled on randomized trial of chemotherapy

Table 6.29*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Chen et al. 2011a	• 202 head/neck cancer patients	Current/ Nnncurrent	• 0.45 (p <0.001)	1998–2008; chart review; patients treated with RT +/- surgery
Li et al. 2011	• 1,214 stage IIIB–IV NSCLC patients	C/F/N	• Former: 0.905 (0.65–1.26) • Current: 0.955 (0.57–1.60)	Patients treated with gemcitabine-based chemotherapy
Michigan et al. 2011	• 257 localized renal cell carcinoma patients	Smoker/ nonsmoker	• 0.54 (0.06–4.93)	2006–2010; smoking not clearly defined; patients treated with surgery
Roxburgh et al. 2011	• 302 CRC patients	Ever/never	• 0.81 (p = 0.07)	1997–2005; 5-year survival; patients treated with surgery
Santini et al. 2011	• 248 metastatic breast cancer patients	C/F/N	• Reported as not statistically significant in the text. (p. 1547–8)	2004–2007; chart review; current included patients who quit within 6 months; patients treated with trsztuzumab +/- chemotherapy
Simsir et al. 2011	• 140 patients with urothelial or TCC of the upper urinary tract	Ever/never	• 0.68 (p = 0.02)	2000–2007; 5-year survival; chart review; patients treated with surgery
Thompson et al. 2011	• 276 head/neck cancer patients who survived at least 2 years	Current/ noncurrent	• 0.91 (p = 0.04 univariate, 0.17 multivariate)	2001–2008; 5-year survival; current defined as smoking 2 years after treatment
Arrieta et al. 2012	• 914 stage I–IV lung cancer patients	Ever/never	• Unadjusted 0.56 (p = 0.002) • Adjusted: 1.04 (0.74–1.5)	2007–2010; median survival
Jerjes et al. 2012	• 67 oral cavity cancer patients treated with surgery	Smoking after treatment	• Smoking cessation: 1.0 (referent) • Reduced smoking: 0.98 • Smoker 20+ CPD: 0.14(p <0.001)	1998–2003; 5-year survival

Note: **C/F/N** = current/former/never; **CML** = chronic myelogenous leukemia; **cpd** = cigarettes per day; **HRT** = hormone replacement therapy; **NSCLS** = non-small-cell lung cancer; **RT** = radiotherapy; **TCC** = transitional cell carcinoma.

Table 6.30*S* Associations between smoking and cancer-related mortality

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
A) Cancer-related mortality				
Thrasher et al. 1994	• 531 transitional cell cancer patients	Ever/never	• p = 0.85	1969–1990; chart review; smoking not clearly defined; patients treated with radical cystectomy
Fujusawa et al., 1999	• 369 Stage I NSCLC patients	Pack-years	• ≥30 Pack-years: 1.39 (0.66–2.91)	1981–93. Patients treated with surgery
Manjer et al. 2000a	• 792 breast cancer patient	C/F/N	• Former: 1.62 (0.51–5.07) • Current: 3.31 (1.57–6.95)	1977–1986; chart review; Malmo Mammographic Screening Trial
Browman et al. 2002	• 148 Stage III–IV head/neck cancer patients	Current/noncurrent recent quitters	• 1.23 (p = 0.056)	Referent is quitters who stopped smoking within 12 weeks prior to RT; patients treated with RT
Frank et al. 2002	• 1,801 clear cell renal cell carcinoma patients	Ever/never	• 1.07 (0.91–1.26)	1970–1998; patients treated with surgery
Gorsky et al. 2004	• 322 patients with tongue cancer	Smoker/nonsmoker	• Reported as not statistically significant in the text. (p. 549)	1979–1994;chart review; smoking not clearly defined
Pickles et al. 2004	• 601 prostate cancer patients	Current/noncurrent	• 2.89 (p = 0.08)	1994–1997; patients treated with external beam RT
Kawai et al. 2005	• 3082 Stage IA NSCLC patients	Pack-years	• <40 Pack-years: 1.0 • 40+ Pack-years: 1.22 (0.98–1.51)	1982–97. Disease specific survival. Chart review. Patients treated with surgery
Wright et al. 2005	• 255 IB–IIB cervical cancer patients	Current/noncurrent	• 4.06 (1.15–14.38)	
Kjaerbye-Thygesen et al. 2006	• 295 Stage III ovarian cancer patients	C/F/N	• Former: 0.93 (0.67–1.30) • Current: 1.65 (1.22–2.24)	1994–1999; Danish Malignant Ovarian Cancer Study
Merrick et al. 2006	• 938 consecutive T1b–T3a prostate cancer patients	C/F/N	• Former: p = 0.19 • Current: p = 0.48	1995–2002; patients treated with brachytherapy +/- androgen deprivation therapy
Modesitt et al. 2006	• 3,562 endometrial cancer patients	Current/notcurrent	• 1.38 (1.09–1.75)	1995–2002

Table 6.30*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Munro et al. 2006	• 284 CRC patients	Current/Noncurrent	• 2.55 (1.40–4.64)	1997–1999; current defined as active smoking at first postoperative visit; patients treated with curative surgery
Nagle et al. 2006	• 676 primary epithelial ovarian cancer cases	C/F/N	• Former: 1.09 (0.86–1.39) • Current: 1.36 (1.01–1.84)	1990–1993
Williams et al. 2006	• 1073 Stage I–IIIB NSCLC patients treated with curative surgery	Pack-years	• <30 : 1.0 (referent) • 30-50: 1.12 (0.81–1.54) • 50-75: 1.38 (1.01–1.90) • >75: 1.19 (0.86–1.65) • Smoking at diagnosis: 0.95 (0.73–1.24)	1997–2001. Post-recurrence mortality. Patients treated with curative surgery. Referent group includes patients with <30 Pack-years history
Chia et al. 2007	• 745 endometrial cancer patients	C/F/N	• Former: 1.4 (0.7–2.9) • Current: 0.5 (0.1–2.1)	1991–1994; structured health behavior assessment
Giovannucci et al. 2007	• 3,544 prostate cancer patients	Ever/Never	• 1.41 (1.04–1.91)	Health Professional Follow-Up Study; questionnaire every 2 years
Holmes et al. 2007	• 5,056 breast cancer patients	C/F/N	• Former: 0.93 (0.79–1.10) • Current: 1.00 (0.83–1.19)	Breast cancer mortality; Nurse's Health Study; repeated structured questionnaires
Hung JJ et al. 2007	• 445 Stage I NSCLC patients with tumors 3 cm or less	Pack-years	• 1.011 (1.004–1.018)	1980–2000; chart review; pack-years analyzed as continuous variable
Odongua et al. 2007	• Cervical cancer patients from 475,398 women in screening program	C/F/N	• Former: 1.31 (0.68–2.52) • Current: 2.00 (1.23–2.91)	1992
Sagiv et al. 2007	• 1,273 breast cancer patients	C/F/N	• Obese – Former: 0.91 (0.40–2.07) – Current: 1.97 (0.89–4.36) • Overweight – Former: 0.66 (0.29–1.54) – Current: 0.84 (0.31–2.29) • Normal weight – Former: 1.07 (0.53–2.16) – Current: 0.80 (0.35–1.79)	1996–1997 Long Island Breast Cancer Study; Questionnaire following breast cancer diagnosis
Bittner et al. 2008	• 1,354 prostate cancer patients	C/F/N	• Reported as not statistically significant in the text. (p. 437)	1993–2004; patients treated with brachytherapy +/- androgen deprivation +/- external beam RT

Table 6.30*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Dal Maso et al. 2008	• 1,453 breast cancer patients	C/F/N	• Former: 1.27 (0.97–1.67) • Current <15 cpd: 1.39 (1.02–1.90) • Current ≥15 cpd: 1.23 (0.82–1.83)	1991–1994; structured questionnaire 1 year prior to diagnosis
Gong et al. 2008	• 752 prostate cancer patients	C/F/N	• Former ≥10 years: 0.45 (0.19–1.05) • Former <10 years: 1.48 (0.50–4.37) • Current: 2.66 (1.10–6.43)	1993–1996; cases from case-control study; structured interview
Parker et al. 2008	• 2,242 renal cell carcinoma patients	C/F/N	• Current: 0.93 (0.77–1.12)	1970–2002; patients treated with surgery.
Perng et al. 2008	• 299 stage IIIB–IV NSCLC	Ever/Never	• 1.52 (1.18–1.94)	2005–2006; patients who failed chemotherapy and treated with erlotinib
Toyooka et al. 2008	• 408 advanced or recurrent NSCLC patients	Ever/Never	• ≥20 pack-years: 1.0 (referent) • <20 pack-years: 1.0 (0.74–1.61) • Never: 0.76 (0.54–1.07)	Chart review; analyses based upon pack year
Yang et al. 2008	• 635 ovarian cancer patients responding to follow-up questionnaire	C/F/N	• Former: 0.91 (0.69–1.25) • Current: 0.94 (0.70–1.26)	1994–1995; follow-up questionnaire only answered by surviving patients
Coker et al. 2009	• 2,661 women with cervical cancer	Current/Not current	• 1.21 (1.01–1.46)	1995–2005
Hotta et al. 2009	• 365 NSCLC patients	Per pack year	• Males: 0.97 (0.95–1.00) • Females: 1.00 (0.96–1.04)	2000–2003; cancer related mortality; risks stated per pack year; patients treated with gefitinib
Marks et al. 2009	• 2,818 HLA identical sibling or matched unrelated donor allogeneic transplants for CML	Ever (High dose, low dose)/Never	• HLA-identical sibling donor group – Low dose: 1.14 (0.95–1.37) – High dose: 1.52 (1.14–2.04) • Unrelated donor group – Ever: 0.97 (0.76–1.25)	1990–2004
Nose et al. 2009	• 477 NSCLC patients tested for EGFR mutation	Ever/Never	• 2.0 (0.86–4.76)	1993–2007
Tiseo et al. 2009	• 651 stage IIIB–IV NSCLC	Ever/Never	• 1.71 ($p<0.001$)	Patients treated with gefitinib
Watters et al. 2009	• 16,640 prostate cancer patients	C/F/N	• Former: 1.03 (0.83–1.27) • Current: 1.69 (1.25–2.27)	1995–1996; NIH-AARP Diet and Health Study

Table 6.30*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Kim et al. 2010	• 342 NSCLC patients	Ever/Never	• 1.15 (0.82–1.62)	2006–8; chart review; patients treated with erlotinib or gefitinib
Nugent et al. 2010	• 111 stage IB2-IV cervical cancer patients	Ever/Never	• Reported as not statistically significant in the text. (p. 440)	2003–2007; chart review; patients treated with RT + chemotherapy
Sardari et al. 2010	• 239 NSCLC patients	Current/Noncurrent	• 1.62 (1.08–2.41)	1991–2001; patients treated with surgery
Weinmann et al. 2010	• 768 prostate cancer patients matched to 929 non-cancer controls	C/F/N	• Former: 1.0 (0.81–1.3) • Current: 1.5 (1.1–2.0)	1997–2001
Farshadpour et al. 2011	• 2,012 head/neck cancer patients	Current/Noncurrent	• 1.26 (0.86–1.85)	1980–2004; smoking combined with drinking in analysis
Kenfield et al. 2011	• 5,366 prostate cancer patients	C/F/N	• Former: 1.05 (0.86–1.27) • Current: 1.61 (1.11–2.32)	Health Professionals Follow-Up Study; questionnaire every 2 years
Kountourakis et al. 2011	• 49 patients with T2 esophageal cancer	Smoker/Nonsmoker	• 4.82 (1.38–16.81)	1997–2009; patients treated with surgery, RT, and chemotherapy
Maeda et al. 2011a	• 1,870 stage I–II NSCLC patients	Ever/Never	• ($p<0.001$)	1992–2007; chart review; patients treated with curative surgery
Ngô et al. 2011	• 257 patients with cervical cancer < 4 cm in diameter	Current smokers >10 cpd vs. ≤10 cpd	• 2.63 (1.30–5.34)	1985–2008; referent category includes light current + former + never smokers; patients treated with preoperative brachytherapy and surgery. 5-year mortality
Phipps et al. 2011	• 2,264 colorectal cancer patients	C/F/N	• Former: 1.14 (0.93–1.38) • Current: 1.30 (1.09–1.74)	1998–2007; structured questionnaire post-diagnosis
Richards et al. 2011	• 423 Stage I–III CRC patients	C/F/N	• 1.25 (1.02–1.53) univariate, $p = 0.09$ multivariate	1997–2007; smoking not clearly defined, likely current; patients treated with curative surgery
Shiono et al. 2011	• 201 stage I NSCLC patients	Ever/Never	• 1.3 (0.04–43.3)	2004–2008; chart review; smoking not clearly defined; patients treated with surgery
Yafi et al. 2011	• 2,287 bladder cancer cases	Smoker/Nonsmoker	• 1.30 (1.005–1.69)	1998–2008; chart review; treated with radical cystectomy
Bostrom et al. 2012	• 564 bladder cancer patients	Ever/Never	• Men: 1.7 (1.1–2.5) • Women: 1.2 (0.7–2.1)	1991–2008; chart review; treated with radical cystectomy

Table 6.30*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Gillison et al. 2012	• 502 stage III–IV head/neck cancer patients	Current/Noncurrent	• RT: 2.19 (1.48–3.25) • RT+CT: 2.73 (1.37–5.45)	Data from RTOG 9003 + RTOG 0129, phase III trials treating with RT +/- chemotherapy
Gridelli et al. 2012	• 780 stage IIIB–IV NSCLC patients	Ever/Never	• 1.24 (1.04–1.48)	Patients treated on randomized TORCH trial
Haughey et al. 2012	• 211 p16+ oropharyngeal cancer patients	C/F/N	• Disease free mortality – Current: 5.25 (1.39–19.85) • Disease specific mortality – Current: 5.36 (0.55–51.53)	1996–2010; patients treated with laser microdissection
Kawakita et al. 2012	• 222 patients with oral cavity cancer	Current/Noncurrent	• 2.08 (1.04–4.15)	2001–2005; disease free mortality; referent category is light smokers
Kroeger et al. 2012	• 802 renal cell carcinoma patients	Ever/Never	• 1.35 (1.09–1.67)	1989–2007; chart review
Lee et al. 2012b	• 670 stage IIIB–IV NSCLC patients	C/F/N	• Former: 1.02 (0.79–1.32) • Current: 1.61 (0.91–2.86)	Patients treated with erlotinib on TOPICAL trial
Lee et al. 2012a	• 924 stage IIIB–IV NSCLC patients	Ever/Never	• Not significant (Forest plot)	2006–2008; patients enrolled on phase III ZEPHYR trial in patients who failed EGFR therapy
Wang et al. 2012	• 301 stage II–IIIA NSCLC patients	Ever/Never	• 0.97 (0.72–1.29)	2000–2006; chart review; patients treated with surgery
Chang et al. 2013	• 245 stage IIIB–IV NSCLC patients	Ever/Never	• 1.20 (0.80–1.82)	2002–2011; patients treated with chemotherapy
Warren et al. 2013	• 5,185 cancer patients with 13 types of malignancy.	Current/Recent quit/ Former/Never	• Current vs. former: 1.23 (1.09–1.39) • Current vs. recent quit: 1.08 (0.94–1.25) • Current vs. never: 1.18 (1.03–1.36)	1982–1998; structured tobacco assessment; current smoking vs. variable referent categories
B) Cancer-related survival				
Chelghoum et al. 2002	• 642 AML patients	Ever/Never	• Pack-years – 0-20: 12.6 months – ≥20: 9.1 month (NS) • Duration smoked (years) – 0–30: 12.6 months – ≥30: 8.2 months (p = 0.03)	1984–1998; median survival; structured tobacco assessments by patients or relatives

Table 6.30*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Videtic et al. 2003	• 186 limited stage SCLC	Current, non-current	• Current: 15.8 mo • Non-current: 14.8 mo (not significant)	1989–99. Disease free survival. Chart review. Patients treated with chemoradiotherapy
Wu et al. 2003	• 321 Stage I NSCLC patients	Pack-years	• 20 or less: 63.6% • >20: 49.5% (p<0.002)	1980–90. 10 year cancer related survival. Chart review. Patients treated with surgery
Fox et al. 2004	• 237 Stage I–III NSCLC patients	Current, non-current	• Stage I–II – Current: 25.3 mo – Non-current: 28.1 mo (p=0.32) • Stage III – Current: 20.3 mo – Non-current: 18.9 mo (p=0.65)	1991–2001. Median cancer specific survival. Chart review. Current smoking include patients who quit within 12 months of RT. Patients treated with RT
Iizasa et al. 2004	• 402 Stage I lung cancer patients	Pack-years	• Cancer specific survival – 30+: 70.7% – <30: 79.3% (p=0.46) • Non-cancer specific survival – 30+: 67.7% – <30: 94.3% (p<0.0001)	1985–97. 10 year survival. Patients treated with surgery
Yamamoto et al. 2004	• 207 Stage I–IIIA NSCLC	Smoking habit	• Yes: 69.9% • No: 63.4% (not significant)	1990–5. Disease free survival. Smoking not clearly defined. Chart review
Guntinas-Lichius et al. 2006	• 69 patients with unknown primary of the head/neck	Smoker/Nonsmoker	• Reported as not statistically significant in the text	1987–2002; 5-year survival; chart review; smoking not clearly defined
Lee et al. 2006	• 575 stage IIIB–IV NSCLC patients	Ever/Never	• Progression free survival – Never: 3.7 mo – Ever: 1.7 mo (p<0.001)	2002–5. Median progression free survival. Chart review. Patients treated with gefitinib
Pine et al. 2007	• 731 Stage I-IV NSCLC patients	Pack-years	• White: 1.00 (0.99–1.00) • African American: 1.00 (0.99–1.01)	1998–2004. Pack-years analyzed as continuous variable
Hanagiri et al. 2008	• 770 stage I–IV NSCLC	Ever/Never	• Never: 70.2% • 20 Pack-years or less: 69.6% • >20 Pack-years: 67.3% (not significant)	1994–1995; chart review; patients treated with surgery
Sakao et al. 2008	• 121 NSCLC patients with tumors <2 cm	Ever/Never	• Ever: 80.4% • Never: 98.0% (p = 0.03)	1996–2006; chart review; patients treated with surgery
Bostrom et al. 2009	• 248 bladder cancer patients	Ever/Never	• 0.88 (p=0.055)	1986–2005; chart review; patients treated with radical cystectomy

Table 6.30*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Chang et al. 2010	• 110 NSCLC patients	Ever/Never	• Ever: 2.07 months • Never: 3.22 (p = 0.116)	2006–2008; median survival chart review
Chen et al. 2011a	• 202 head/neck cancer patients	Current/Noncurrent	• 0.65 (p = 0.01)	1998–2008; chart review; patients treated with RT +/- surgery
Junor et al. 2012	• 254 head/neck cancer patients	C/F/N	• Current: 55.8% • Former: 67.2% • Never: 82.0% (p = 0.045)	5-year cancer related survival

Note: **Cancer related mortality** = disease specific, disease free, cancer specific mortality or survival; **chart review** = tobacco information collected by chart review or where tobacco collection information is not clearly defined; **NMIBC =** nonmuscle invasive bladder cancer.

Table 6.31*S* Associations between smoking and developing a second primary cancer in cancer patients

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Hiyama et al. 1992	• 472 male laryngeal cancer patients	Current cpd	• 1–19: 2.0 (p <0.01) • 20–39: 2.2 (p <0.01) • ≥40: 2.5 (p <0.01)	1965Ð1975; observed/expected; chart review
Kaldor et al. 1992	• 98 HD patients with subsequent lung cancer matched to 259 HD controls	Ever/never	• 13.0 (3.0–59)	Lung cancer; chart review
Richardson et al, 1993	• 540 SCLC patients	Current smokers compared to general population	• General population: 1.0 (referent) • Continue after diagnosis: 32 (12–69) • Quit after diagnosis: 11 (4.4–23)	1973–1989; patients enrolled on clinical trials through National Cancer Institute
van Leeuwen et al. 1995	• 30 HD patients with subsequent lung cancer matched to 82 HD controls	Current/noncurrent	• <1: 1.0 (referent) • 1–10: 2.9 (1.1–8.0) • >10: 6.2 (1.2–3.1)	1966–1986; lung cancer; chart review; current defined as smoking after diagnosis (pack-years)
Barbone et al. 1996	• 380 head/neck cancer patients	Smoking history	• All: – Never or very light: 1.0 (referent) – Light: 1.5 (0.5–4.9) – Intermediate: 2.7 (0.5–13.4) – Heavy: 4.3 (0.7–26.9) • Head and neck – Never or very light: 1.0 (referent) – Light: 2.3 (0.4–12.2) – Intermediate: 2.7 (0.5–13.4) – Heavy: 4.3 (0.7–26.9)	1984–1991; referent category included very light or never
Tucker et al. 1997	• 611 2-year survivors of SCLC	Current smokers compared to general population	• General population: 1.0 (referent) • Continued after diagnosis: 17 (11–16) • Quit at diagnosis: 9.9 (5.3–17) • Quit prior to diagnosis: 9.4 (4.7–17)	Chart review; Lung Cancer Working Cadre
Kawahara et al. 1998	• 980 SCLC patients	Current smokers compared to general population	• General population: 1.0 (referent) • Continue after diagnosis: 5.4 (2.7–9.6) • Quit after diagnosis: 1.6 (0.3–4.6)	1978–1992. Chart review; analysis in 70 patients with at least 2 years of survival
Kinoshita et al. 2000	• 1,614 stage I-III gastric cancer patients	C/F/N	• Former: 0.95 (0.42–2.13) • Current: 1.82 (1.02–3.26)	1978–1992; second primary; chart review
Obedian et al. 2000	• 1,029 early stage breast cancer patients	C/F/N	• Never: 1.0 (referent) • Former: 7.01 • Current: 8.96 (p = 0.06)	1970–1990; lung cancer incidence at 14.6 years; chart review; patients treated with surgery + RT

Table 6.31*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Kokawa et al. 2001	• 368 resected superficial esophageal cancers	Brinkman Index	• 1000+: 1.70 (p = 0.006)	1966–1998; second primary; referent group includes smokers and nonsmokers
Lippman et al. 2001	• 1166 T1-3 NSCLC patients	C/F/N	• Former: 3.10 (0.75–12.84) • Current: 2.72 (0.64–11.51)	Randomized trial
Travis et al. 2002	• 222 HD patients with lung cancer and 444 matched controls	Heavy/nonheavy	• Nonheavy: – RT-, chemotherapy-: 1.0 (referent) – RT+, chemotherapy-: 7.2 (2.9–21.2) – RT-, chemotherapy+: 4.3 (1.8–11.7) – RT+, chemotherapy+: 7.2 (2.8–21.6) • Heavy: – RT-, chemotherapy-: 6.0 (1.9–20.4) – RT+, chemotherapy-: 20.2 (6.8–68) – RT-, chemotherapy+: 16.8 (6.2–53) – RT+, chemotherapy+: 49.1 (15.1–187)	Lung cancer; chart review; nonheavy includes <1 PPD, former, and never
Ford et al. 2003	• 280 breast cancer patients with subsequent primary lung cancer matched to 300 breast cancer patients without lung cancer	C/F/N	• All: – Former: 3.68 (2.09–6.48) – Current: 12.90 (8.17–20.37) • Smoking and RT treatment – Noncurrent, No RT: 1.0 (referent) – Noncurrent, Yes RT: 0.54 (0.26–1.13) – Current, No RT: 6.00 (3.55–10.13) – Current, Yes RT: 9.00 (5.08–15.9)	1960–1997; lung cancer following breast cancer; chart review
Franchin et al. 2003	• 410 T1-T2 laryngeal cancer patients	Current/noncurrent	• 2.07 (calculated from data in text p. 769)	Chart review; no statistical testing
Gilbert et al. 2003	• HD patients: 199 with subsequent lung cancer matched with 393 without lung cancer	C/F/N	• Former: 6.8 (2.8–19.5) • Current: 24.0 (10.3–68)	1965–1994; lung cancer; chart review; all patients treated with RT
Matsubara et al. 2003	• 679 squamous cell esophageal cancer patients	Smoking habit	• 2.92 (p=0.02)	1989–2001; chart review; smoking not clearly defined
Kim et al. 2004	• 342 Stage I-IV NSCLC patients treated with surgery	Current, noncurrent	• 2.32 (1.28–8.97)	1994–1999; chart review

Table 6.31*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Dikshit et al. 2005b	• 876 male laryngeal or hypopharyngeal cancer patients	Pack-years	• All: – 0–20: 1.0 (referent) – 21–40: 1.3 (0.8–2.3) – 41–60: 0.9 (0.5–1.7) – >60: 1.6 (0.8–3.0) • Lung: – 0–20: 1.0 (referent) – 21–40: 3.3 (0.9–11.0) – 41–60: 2.4 (0.7–8.6) – >60: 3.9 (1.0–14.6)	Structured interviews; referent category included never smokers plus smokers of up to 20 pack-years
Lin et al. 2005	• 1,257 head/neck cancer patients	Ever/never	• 5.2 (1.3–22)	1984–1998; smoking not clearly defined (implied as ever)
Prochazka et al. 2005	• 182 breast cancer patients with subsequent lung cancer	Ever/never	• 2.09 (p <0.001)	1958–2000; relative risk of lung cancer in smokers vs. nonsmokers who received RT; chart review
Khuri et al. 2006	• 1,190 Stage I-II head/neck cancer patients	C/F/N	• Former: 1.63 (0.94–2.83) • Current: 2.20 (1.28–3.78)	Smoking-related second primary; patients treated with surgery +/- RT; Phase III trial of isotretinoin
Moser et al. 2006	• 748 aggressive NHL patients	Ever/never	• 2.11 (1.33–4.11)	1980–1999; second primary; patients enrolled in 1 of 4 European Organisation for Research and Treatment of Cancer trials
Boorjian et al. 2007	• 9,780 prostate cancer patients	Current/noncurrent	• No RT (all): 1.0 (referent) • Yes RT (all): 1.59 (0.97–2.6) • Current (all): 2.08 (1.09–3.97) • Current + RT: 3.65 (1.45–9.16)	Bladder cancer; CaPSURE study
Park et al. 2007	• 14,181 male cancer patients including 204 patients with second primary cancer	C/F/N	• All: – Former: 0.87 (0.56–1.35) – Current: 1.13 (0.77–1.67) • Smoking related: – Former: 1.03 (0.46–2.31) – Current: 2.02 (1.02–4.03)	1996–2002; patients part of National Health Insurance Corporation Study
van den Belt-Dusebout et al. 2007	• 2,707 testicular cancer patients with at least 5 years of survival	Current/noncurrent	• 1.8 (1.3–2.4)	1965–1995; second primary; chart review; current = smoking at or following diagnosis; Netherlands Testicular Cancer Survivors Study

Table 6.31*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Kaufman et al. 2008	• 114 breast cancer patients with primary lung cancer 10+ years after diagnosis matched to 380 breast cancer controls without lung cancer	Ever/never	• No RT: – Never: 1.0 (referent) – Ever: 12.7 (2.8–57.3) • Patients treated with RT: – Never: 1.9 (0.3–14.0) – Ever: 32.5 (6.6–160.3)	1965–1989; lung cancer following breast cancer
Rossini et al. 2008	• 326 head/neck cancer patients	Smoking	• None: 0% • Ethanol only: 20% • Tobacco only: 0% • Both: 14.3% ($p < 0.05$)	1995–2000; esophageal cancer risk; chart review; smoking combined with ethanol in analysis
Sanchez et al. 2008	• Breast cancer patients: 267 with second nonbreast primary cancer vs. 465 without second primary	Smoker/nonsmoker	• 3.16 (1.23–9.15)	1975–2003; second primary; chart review
Knight et al. 2009	• 708 asynchronous contralateral breast cancer vs. 1,399 unilateral breast cancer patients	C/F/N	• Ever: 1.1 (0.9–1.6) • Ever after diagnosis: 1.2 (0.9–1.5)	1985–2001; contralateral breast cancer; structured interview; includes patients treated +/- RT
Leon et al. 2009	• 514 case control study in head/neck cancer patients	Current cpd	• 0: 1.0 (referent) • 1–10: 0.7 (0.2–1.1) • 11–20: 2.8 (1.2–7.1) • >20: 10.9 (2.1–55.4)	Chart review; current defined as tobacco use after diagnosis; referent group includes former tobacco use
Li et al. 2009a	• 365 patients with ER+ breast cancer and contralateral second breast cancer compared with 726 patients with ER+ breast cancer and no contralateral cancer	C/F/N	• At diagnosis: – Former: 1.2 (0.8–1.7) – Current: 1.8 (1.1–3.2) • At most recent follow-up: – Former: 1.2 (0.8–1.7) – Current: 2.2 (1.2–4.0)	1990–2007; contralateral breast cancer; structured interview
Farshadpour et al. 2011	• 2,012 head/neck cancer patients	Current/noncurrent	• 1.34 (0.96–1.88)	1980–2004; second primary tumor mortality; smoking combined with drinking in analysis
Peck et al. 2012	• 356 oropharyngeal cancer patients	Ever/never	• HPV-, never: 17.6% • HPV-, ever: 13.2% • HPV+, never: 0%HPV+, ever: 10.5%	1995–2004; 5-year second primary rate in HPV seropositive patients

Note: **C/F/N** = current/former/never; **CaPSURE** = Cancer of the Prostate Strategic Urologic Research Endeavor; **cpd** = cigarettes per day; **CT** = chemotherapy; **ER** = estrogen receptor; **HD** = Hodgkin's disease; **NSCLS** = non-small-cell lung cancer; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **RT** = radiotherapy.

Table 6.32*S* Associations between smoking and cancer recurrence

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Scanlon et al. 1995	• 835 breast cancer patients	Packs smoked	• 0: 1.0 (referent) • <10,000: 1.06 (0.51–2.20) • 10,001–20,000: 3.10 (1.54–6.25) • >20,000: 3.73 (1.58–8.92)	1982–1991; lung metastases after diagnosis; current included smoking within 2 years of diagnosis
Fleshner et al. 1999	• 286 superficial transitional cell (NMIBC) cancer patients	Current/noncurrent	• 1.40 (1.03–1.91)	1985–1995; chart review
Lippman et al. 2001	• 1166 T1-3 NSCLC patients	C/F/N	• Former: 0.87 (0.46–1.67) • Current: 0.73 (0.37–1.44)	Recurrence; randomized trial
Leibovich et al. 2003	• 1,671 clear cell renal cell carcinoma patients	Ever/never	• 1.02 (0.85–1.22)	1970–2000; progression to metastases; patients treated with surgery
Muscat et al. 2003	• 244 breast cancer patients	Current/noncurrent	• 2.1 (0.9–5.1)	1994–1996
Yokoyama et al. 2003	• 185 women with CIN I-II	C/F/N	• Former: 2.75 (0.79–9.58) • Current: 1.42 (0.46–4.42)	1995–1996; progression
Chang et al. 2004a	• 114 CML patients	Pack-years	• 1.7% per pack-year (p = 0.01)	1997–2001; patients treated with hematopoietic stem cell transplant; 1-year mortality
Oefelein et al. 2004	• 222 advanced prostate cancer including 133 hormone refractory patients	C/F/N	• Never: 35 months • Former: 23 months • Current: 12 months (p = 0.00001)	1987–2003; median progression to hormone refractory disease; chart review
Pickles et al. 2004	• 601 prostate cancer patients	Current/noncurrent	• 1.68 (1.11–2.56)	1994–1997; patients treated with external beam RT
Brumund et al. 2005	• 270 patients with T1-T3 true vocal cord cancer	Pack-years	• Reported as not significant in text (p. 319)	1975–2000; chart review
Leibovici et al. 2005	• 465 Caucasian bladder cancer patients (MIBC + NMIBC) matched to 450 controls	C/F/N	• Recurrence in NMIBC – Former: 1.11 (0.73–1.70) – Current: 0.81 (0.47–1.37) • Progression in NMIBC – Former: 1.30 (0.53–3.16) – Current: 0.59 (0.17–2.03)	1995–2003; current include patients who quit in 12 months prior to diagnosis

Table 6.32*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Sardari et al. 2005	• 321 Stage I-IIIB NSCLC patients	C/F/N	• Current: 1.0 (referent) • Recent quitters: 0.54 (0.30–1.00) • Former: 0.53 (0.34–0.84) • Never: 0.66 (0.34–1.27)	1991–2001; recurrence and metastasis; patients treated with surgery. detailed smoking information.;recent quit within 3 months
Donat et al. 2006	• 1,159 renal cell carcinoma patients	Ever/never	• 1.10 (0.73–1.67)	1995–2003; progression; patients treated with surgery
Heist et al. 2006	• 382 Stage I NSCLC patients	C/F/N, pack-years	• Former: 1.25 (0.72-2.18) • Current: 1.49 (0.84-2.61) • Pack-years: 1.005 (1.002-1.008)	1992–2001; recurrence; pack-years analyzed as continuous variable; patients treated with surgery
Khuri et al. 2006	• 1,190 Stage I-II head/neck cancer patients	C/F/N	• Current vs. former: 1.12 (0.76–1.65) • Current vs. never: 1.37 (0.76–2.46)	Patients treated with surgery +/- RT; randomized phase III trial of isotretinoin vs. placebo
Merrick et al. 2006	• 938 consecutive T1b-T3a prostate cancer patients	C/F/N	• Former: 0.952 (0.434) • Current: 2.101 (0.038)	1995–2002; patients treated with brachytherapy +/- androgen deprivation therapy
Waggoner et al. 2006	• 315 advanced cervical cancer patients	Current/noncurrent	• Unadjusted: 1.45 (1.05–1.99) • Adjusted: 1.35 (0.93–1.94)	Progression; GOG 165 trial
Zhou et al. 2006	• 543 Stage I-IIB NSCLC patients	C/F/N	• Current: 1.0 (referent) • Former: – Quit 1–8 years: 0.76 (0.56–1.03) – Quit 9–17 years: 0.69 (0.50–0.95) – Quit 18+ years: 0.68 (0.49–0.96) • Never: 0.55 (0.31–0.97)	1992–2002; recurrence free survival; current smoking is referent group
Chen et al. 2007a	• 265 men with NMIBC	Current, quitter, former, never	• Quitting: 1.0 (referent) • Never: 2.2 (1.1–4.5) • Former: 1.4 (0.7–2.7) • Current: 2.2 (1.2–4.0)	1997–2005; referent category is quitting smoking between 1 year prior and 3 months after diagnosis
Gillespie et al. 2007	• 325 head/neck cancer patients	Smoker/nonsmoker	• 1.22 (0.58–2.55)	Chart review; case control study for COX2 inhibitors; smoking not clearly defined
Kim et al. 2007	• 106 recurrent head/neck cancer patients	C/F/N	• Current: 95% • Former: 71% • Never: 67% (p = 0.02)	1996–2006; recurrence after salvage surgery; chart review; patients treated with salvage surgery and reconstruction
Mai et al. 2007	• 68 anal cancer patients	Current/noncurrent	• 2.75 (0.55–13.64)	1990–2006; chart review; patients treated with RT + chemotherapy

Table 6.32*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Pantarotto et al. 2007	• 416 prostate cancer patients	C/F/N	• Former: 2.90 (p = 0.03) • Current: 5.24 (p = 0.003)	1990–1999; distant failure; patients treated with external beam RT; chart review
Ritoe et al. 2007	• 402 laryngeal cancer patients	Current/noncurrent	• 1.46 (0.93–2.29)	1990–1995; chart review; current = continued smoking after treatment
Duffy et al. 2008	• 444 head/neck cancer patients	C/F/N	• Former: 1.15 (0.66–2.02) • Current: 1.39 (0.76–2.53)	2003–2007; structured health assessment
Meyer et al. 2008	• 540 head/neck cancer patients	Current/noncurrent	• 2.41 (1.25–4.64) (β-carotene treated pts.)	1994–2000; patients treated with RT, randomized to β-carotene
Rades et al. 2008	• 181 nonmetastatic lung cancer patients	Current/noncurrent	• 1.74 (1.06–2.89)	2000–2005; chart review; patients treated with RT
Ramamoorthy et al. 2008	• 64 anal cancer patients	Smoker/nonsmoker	• 1.43 (p = 0.17)	1999–2005; smoking within 5 years of treatment; chart review
Guo et al. 2009	• 327 stage I-III NSCLC patients	Current/noncurrent	• 0: 1.0 (referent) • 10 cigarettes/day: 1.12 (1.1204–1.1217) • 20 cigarettes/day: 1.2567 (1.2559–1.2575) • 40 cigarettes/day: 1.5793 (1.5783–1.5802)	Patients pooled from 4 lung cancer cohorts
Marks et al. 2009	• 2,818 HLA identical sibling or matched unrelated donor allogeneic transplants for CML	Ever (high dose, low dose)/never	• HLA-identical sibling donor group – Low dose: 1.75 (1.23–2.49) – High dose: 1.02 (0.44–2.36) • Unrelated donor group – Ever: 0.67 (0.0.28–1.56)	1990–2004
Sandoval et al. 2009	• 146 oral cavity cancer patients	C/F/N	• Current: 1.0 (referent) • Former: 0.75 (0.34–1.66) • Never: 0.42 (0.05–3.46)	1996–1999; referent category = current smokers; structured health behavior assessment
Chade et al. 2010	• 155 patients with carcinoma in situ of the bladder	C/F/N	• Former: 1.02 (0.63–1.66) • Current: 0.86 (0.35–2.11)	1990–2008; progression; chart review; patients treated with BCG
Hefler et al. 2010	• 136 women with CIN I	Current/noncurrent	• 2.0 (1.1–3.7)	Progression; patients in phase II trial of progresterone
Ioffe et al. 2010	• 130 Stage III-IV epithelial ovarian cancer patients	Current/notcurrent at surgery	• Current: 8 months • Noncurrent: 19 months (p = 0.001)	1996–2003; median time to progression; patients treated with cytoreductive surgery; chart review

Table 6.32*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Liao et al. 2010	• 409 unresectable NSCLC patients	Current/noncurrent	• Recurrence: 0.80 (0.49–1.13) • Distant metastasis: 0.89 (0.61–1.3)	1999–2006; chart review; patients treated with RT
McCleary et al. 2010	• 1045 participants with stage III colon cancer	C/F/N	• Former: 1.15 (0.89–1.48) • Current: 0.90 (0.58–1.41)	CALGB 89803 trial treated with 5-FU/ leucovorin +/- irinotecan
Moreira et al. 2010	• 1,276 prostate cancer patients	Current/noncurrent	• All patients: 1.19 (0.95–1.49) • Obese patients: 1.37 (1.09–2.08)	1998–2008; chart review; SEARCH study, treated with surgery
Murthy et al. 2010	• 285 stage I NSCLC patients	Ever/never	• p = 0.007	Recurrence
Sun et al. 2010	• 250 stage IIIB-IV NSCLC patients	Ever/never	• Ever: 1.87 months • Never: 3.27 months (p = 0.011 unadjusted, p = 0.92 adjusted)	2007–2008; median time to progression; chart review; patients who failed chemotherapy and treated with pemetrexed
Hwang et al. 2011	• 251 patients with NMIBC	Smoking history	• 1.63 (1.1–2.5)	2000–2010; chart review; smoking not clearly defined; patients treated with surgery
Joshu et al. 2011	• 1416 prostate cancer patients	C/F/N	• Never: 1.0 (referent) • 5 years before surgery: 1.19 (0.55–2.57) • 1 year after surgery: 2.31 (1.05–5.10)	1993–2006; current reported as 5 years pre and 1 year post surgery; patients treated with surgery
Kenfield et al. 2011	• 5,366 prostate cancer patients	C/F/N	• Former: 1.11 (0.96–1.29) • Current: 1.61 (1.16–2.22)	Health Professionals Follow-Up Study; structured questionnaire every 2 years
Lammers et al. 2011	• 718 NMIBC patients	Ever/never	• EORTC model: 1.47 (1.00–2.15) • CUETO model: 1.57 (1.06–2.31)	1998–2004; patients treated with surgery and enrolled on phase III trial of intravesicle chemotherapy
Maeda et al. 2011b	• 2,295 stage I-III NSCLC patients	Ever/never	• Stage I: – 1.511 (1.033–2.210) – Stage II: – Ever: 40.2% – Never: 55.8% (p = 0.049) • Stage III: – Ever: 68.6% – Never: 83.5% (p = 0.004)	1992–2006; ever smoking defined as >43 pack-years
Ngo et al. 2011	• 630 prostate cancer patients	Pack-years	• Biochemical recurrence increase by 1% per pack year (p = 0.03)	1989–2005; chart review
Schlumbrecht et al. 2011	• 194 low grade serous adenocarcinoma of the ovary	Current/noncurrent	• 1.72 (1.00–2.96)	1977–2009; progression

Table 6.32*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Sfakianos et al. 2011	• 623 patients with high grade superficial, carcinoma in situ, or T1 invasive bladder cancer	C/F/N	• Former: 1.05 (0.84–1.32) • Current: 1.04 (0.77–1.40)	1994–2008; chart review; patients treated with BCG and surgery
Simsir et al. 2011	• 140 patients with urothelial or TCC of the upper urinary tract	Ever/never	• Local Recurrence: – Ever: 11.8 mon,ths – Never: 19.5 months (p = 0.01) • Metastasis: – Ever: 19.6 months – Never: 21.3 months (p = 0.24)	2000–2007; recurrence (median time); chart review; patients treated with surgery
Hoff et al. 2012	• 232 head/neck cancer patients treated with RT	Current/noncurrent	• 1.96 (1.09–3.52)	1983–1991
Hung et al. 2012	• 756 stage I NSCLC patients	C/F/N	• Never: 1.0 (referent) • 1–20 Pack-years: 1.039 (0.672–1.604) • >20 Pack-years: 1.457 (1.069–1.986)	1980–2010; patients treated with lobar resection
Segal et al. 2012	• 278 high grade T1 bladder cancer patients	Ever/never	• 1.15 (0.75–1.76)	1995–2000; progression; chart review
Varadarajan et al. 2012	• 280 AML patients	Ever/never	• Ever: 43.01 months • Never: 65.36 months (p = 0.02)	1990–2008; median time to progression; chart review; patients treated with high dose cytarabine and idarubicin

Note: **BCG** = Bacillus Colmette-Guerin; **CALGB** = cancer and leukemia group B; **C/F/N** = current/former/never; **CIN** = cervical intraepithelial neoplasia; **CIN I** = cervical dysplasia; **CML** = chronic myelogenous leukemia; **CUETO** = Spanish Urological Club for Oncological Treatment; **EORTC** = European Organisation for Research and Treatment of Cancer; **5-FU** = 5-fluorouracil; **GOG** = Gynecologic Oncology Grpup; **HLA** = human leukocyte antigen; **MIBC** = muscle-invasive bladder cancer; **NMIBC =** nonmuscle invasive bladder cancer; **NSCLS** = non-small-cell lung cancer; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **Recurrence** = local recurrence, distant recurrence, metastasis after diagnosis, progression, progression free survival, biochemical recurrence or progression, recurrence free survival; **RT** = radiotherapy.

Table 6.33*S* Associations between smoking and cancer response

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Fountzilas et al. 1992	• 115 Stage III-IV head/neck cancer patients	Ever/never	• 0.24 (p = 0.008)	1984–1999; complete response to chemotherapy; patients treated with induction chemotherapy followed by surgery or RT
Browman et al. 1993	• 115 Stage III-IV head/neck cancer patients	Current/noncurrent	• 0.61(p = 0.008)	Complete response; smoking during RT; patients treated with RT +/- chemotherapy
Scanlon et al. 1995	• 835 breast cancer patients	Packs smoked	• 0: 1.0 (referent) • <10,000: 1.06 (0.51–2.20) • 10,001–20,000: 3.10 (1.54–6.25) • >20,000: 3.73 (1.58–8.92)	1982–1991; lung metastases after diagnosis.
Fountzilas et al. 1997	• 154 Stage III-IV head/neck cancer patients	Ever/never	• 0.35 (p = 0.01)	1984–1991; complete response; patients treated with induction chemotherapy followed by surgery or RT
Marshak et al. 1999	• 207 T1-T2 laryngeal cancer patients	>30 Pack-years vs. ≤30 pack-years	• .90 (p = 0.043)	1974–1994; local control; patients treated with RT
Ando et al. 2006	• 1976 NSCLC patients	Ever/never	• 0.47 (0.34–0.65)	2002; response. chart review; patients from 84 institutions treated with gefitinib
Lee et al. 2006	• 575 stage IIIB-IV NSCLC patients	Ever/never	• Never: 2.48 (1.48-3.94) • Ever: 1.0 (referent)	2002-2005; response; chart review. patients treated with gefitinib
Duarte et al. 2008	• 285 NSCLC patients	Ever/never	• <40 Pack-years: 1.0 (referent) • ≥40: 0.096 (0.047–0.195)	2000–2005; chart review; patients treated with chemotherapy +/- RT
Spigel et al. 2008	• 229 stage IIIB-IV NSCLC patients	Ever/never	• 20 or less: 17.1% • >20: 3.6% (no statistics)	2004. response; analysis according to pack-years; patients treated on phase iii trial of erlotinib
Fortin et al. 2009	• 1,871 head/neck cancer patients	C/F/N	• Never: 1.0 (referent) • Former: 1.07 • Current: 0.89 (p <0.0000001)	1989–2006; 5-year local control; chart review
Hayashibara et al. 2009	• 626 NSCLC patients	Ever/never	• 0.71 (p = 0.006)	2002–2007; response. chart review; patients treated with gefitinib
Khan et al. 2009	• 80 women with vulvar intraepithelial neoplasia grade	Current/noncurrent	• 30.17 (2.07–439.56)	1985–2005; persistent disease; smoking not clearly defined

Table 6.33*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Ang et al. 2010	• 721 Stage III-IV head neck cancer patients	Pack-years	• Smoking decreased progression-free survival by 1% per pack year (p = 0.002)	Data from randomized cancer treatment trials of accelerated-fractionation RT with standard-fractionation RT, each combined with cisplatin therapy; smoking history used in recursive partition analysis
Liu et al. 2010b	• 698 patients with oral cavity cancer	Ever/never	• 1.18 (p = 0.36)	1995–2005; 5-year local control; chart review; patients treated with surgery +/- adjuvant therapy
Matsumoto et al. 2010	• 516 cervical low-grade squamous interceptihelial lesion patients	C/F/N	• Former: 0.73 (0.56–0.95) • Current: 0.64 (0.44–0.93)	1998–2004; Response; current include patients who quit in 12 months prior to diagnosis; Japan HPV and Cervical Cancer Study
Na et al. 2010	• 162 female stage IIIB-IV NSCLC	Ever/never	• 1.10 (0.38–3.17)	2002–2008; response; chart review; patients treated with gefitinib monotherapy
Algotar et al. 2011	• 140 prostate cancer patients	Pack-years	• Never: 1.0 (referent) • ≥49 Pack-years: 2.38 (p = 0.04)	Progression (PSA velocity) as fold-change; patients treated with watchful waiting
Sfakianos et al. 2011	• 623 patients with high grade superficial, carcinoma in situ, or T1 invasive bladder cancer	C/F/N	• Former: 0.78 (0.49–1.24) • Current: 0.90 (0.48–1.68)	1994–2008; response; chart review; patients treated with BCG and surgery

Note: **C/F/N** = current/former/never; **NSCLS** = non-small-cell lung cancer; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **PSA** = prostate-specific antigen; **Recurrence** = local recurrence, distant recurrence, metastasis after diagnosis, progression, progression free survival, biochemical recurrence or progression, recurrence free survival; **RT** = radiotherapy.

Table 6.34*S* Associations between smoking and treatment-related toxicity in cancer patients

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Kearney et al. 1994	• 331 pulmonary surgery patients	Ever/never	• Never: 9% (p<0.05) • Ever: 20%	1989–1991; postoperative complications. chart review
McCulloch et al. 1997	• 114 head/neck cancer patients treated with surgery	Ever/never	• <50 Pack-years: 8.50 • >50 Pack-years: 24.3 (p <0.01)	1985–1991; pulmonary complications; chart review
Bluman et al. 1998	• 410 pulmonary surgery patients	C/F/N	• Never: 1.0 • Former: 1.9 (0.50–6.50) • Current: 4.2 (1.20–14.80) • Reduced: 6.7 (2.60–17.10)	1990–1992; pulmonary complications. reduced smoking were patients who decreased tobacco use prior to surgery
van der Voet et al. 1998	• 383 T1 laryngeal cancer patients treated with RT	Current/noncurrent	• Current: 1.0 (referent) • Former: 0.50 • Quit after diagnosis: 0.39 • Never: 0.93 (p = 0.031)	1965–1995; laryngeal complications; chart review; never smokers only with 12 patients
Fleshner et al. 1999	• 286 superficial transitional cell cancer patients	Current/former	• 1.46 (0.98–2.14)	1985–1995; adverse events; chart review
Harpole et al. 1999	• 3516 patients treated with lobectomy or pneumonectomy	Current	• 1.27 (p=0.0049)	VA Surgical Quality Improvement Program database
Redaelli de Zinis et al. 1999	• 246 head/neck cancer patients treated with laryngectomy	Ever/never	• 0.89 (p = 0.81)	1988–1995; fistula formation; smoking not clearly defined
Bernard et al. 2001	• 639 cancer patients treated with pneumonectomy	Not clearly defined	• "Factors not affecting morbidity or mortality included corticosteroid use, chronic renal failure, cirrhosis, nonpulmonary malignancy, smoking within 8 weeks of pneumonectomy, …" p. 1079	1985–1998; surgical complications. chart review
Myrdal et al. 2001	• 616 lung or pleural cancer patients treated with surgery	Ever/never	• Ever: Univariate: 5.5 (1.3–22.8)	1987–1999.;surgical complications. national registry data
Eifel et al. 2002	• 3,489 stage I-II cervical cancer patients treated with RT	C/F/N	• Former: 1.40 (0.81–2.41) • Current: – <1 pack/day: 1.25 (0.88–1.79) – ≥1 pack/day: 2.43 (1.95–3.04)	1960–1994; pelvic complications; chart review
Griffin et al. 2002	• 228 cancer patients with esophagectomy	Current/noncurrent	• 1.49 (p = 0.03)	1990–2000; pulmonary complications

Table 6.34*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Sørensen et al. 2002	• 425 patients with breast surgery	Current/noncurrent	• Infection: – Nonsmoker: 1.0 (referent) – 1–14 g/day: 2.95 (1.07–8.16) – ≥15 g/day: 3.46 (1.52–7.85) • Necrosis: – Nonsmoker: 1.0 (referent) – 1–14 g/day: 6.85 (1.96-23.90) – ≥15 g/day: 9.22 (2.91–29.25) • Epidermolysis: – Nonsmoker: 1.0 (referent) – 1–14 g/day: 3.98 (1.52–10.43) – ≥15 g/day: 4.28 (1.81–10.13)	1994–2006; surgical complications
Vaporciyan et al. 2002	• 261 Stage I-III NSCLC patients	Quit duration	• 1+ month prior to surgery: 1.0 (referent) • <1 month prior to surgery: 2.70 (1.18–6.17)	1990–1999; pulmonary complications. chart review; comparisons based upon timing of cessation prior to pneumonectomy
Eckardt et al. 2003	• 258 head/neck cancer patients with free flap reconstruction	Ever/never	• 1.94 (p = 0.043)	1982–2000; overall complications; chart review; smoking not clearly defined
Garces et al. 2004	• 1019 lung cancer patients	C/F/N	• Current: 28.7 (p<0.001) • Former: 19.8 • Never: 20.0	1997–2002; lung cancer symptom score
Barrera et al. 2005	• 300 primary or secondary lung cancer patients treated with thoracotomy	Pack-years	• Overall complications: – 60 or less: 1.0 – >60: 2.54 (1.28–5.04) • Pneumonia: – 60 or less: 1.0 – >60: 3.10 (1.35–6.94)	1999–2001; smoking cessation did not increase complication rate
Bullard et al. 2005	• 160 rectal cancer patients treated with surgery	Ever/never	• 1.5 (0.76–2.98)	1998–2002; wound complication; chart review; smoking not clearly defined
Goodwin et al. 2005	• 515 breast cancer patients with breast reconstruction	Current/noncurrent	• 2.51 (p <0.001)	2002–2003; total complications; current include quit <4 weeks

Table 6.34*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Kuri et al. 2005	• 188 head/neck or esophageal cancer patients with free flap reconstruction	Current/ Noncurrent	• Current smokers: 1.0 (referent) • Quit 8–21 days prior to operation: 0.31 (0.08–1.24) • Quit 22–42 days prior to operation: 0.17 (0.04–0.75) • Quit ≥43 days prior to operation: 0.17 (0.05–0.60) • Nonsmokers: 0.11 (0.03–0.51)	1996–2001; wound healing; chart review
Nickelsen et al. 2005	• 5,181 colorectal cancer patients treated with surgery	C/F/N	• Former: 1.23 (1.03–1.47) • Current: 1.35 (1.01–1.80)	2001–2002; overall complications
Ando et al. 2006	• 1976 NSCLC patients	Ever/Never	• 4.79 (1.69-13.54)	2002; interstitial lung disease; chart review; patients from 84 institutions treated with gefitinib
Baser et al. 2006	• 206 consecutive NSCLC patients	C/F/N	• Smoking cessation after diagnosis: 1.0 (referent) • Continued smoking after diagnosis: • 0-12 months: 6.99 (1.76–27.71)	2001; decrease in performance status at 6 or 12 months. chart review
Gold et al. 2006	• 2,198 stage I-IIIA breast cancer patients taking tamoxifen	C/F/N	• Former: 1.40 (1.10–1.78) • Current: 2.12 (1.19–3.78)	1995–2000; Vasomotor symptoms; Women's Healthy Eating and Living Study
Mason et al. 2006	• 336 Stage I-IV NSCLC patients treated with pneumonectomy	Pack-years	• "Higher pack-years of smoking was identified as a preoperative risk factor for venous thromboemcolism" p. 713; "Risk factors for death included male sex, preoperative radiotherapy, lower forced expiratory volume in 1 second (percentage of normal value), higher pT, and increased pack-years of smoking (Table 2)" p. 7–13 p=0.02	1990-2001; chart review
Mehrara et al. 2006	• 952 breast cancer patients with free flap reconstruction	Ever/Never	• No significant difference stated in text (p. 1103)	1991–2002; overall complications; chart review
Pinsolle et al. 2006	• 266 breast cancer patients with reconstruction	Current/ Noncurrent	• Skin necrosis: 2.86 (p = 0.02) • Reconstruction failure: 4.82 (p = 0.015) • Infection: 0.69 (not significant)	1990–2002; reconstruction failure; chart review; current include patients quit <1 month
Song et al. 2006	• 635 Stage I-IV NSCLC patients treated with surgery	C/FN	• Former: 2.76 (p <0.001) • Current: 2.70	2001–2004; pulmonary complications; chart review
Clark et al. 2007	• 185 head/neck cancer patients with free flap reconstruction	Current/ Noncurrent	• 2.34 (1.03–5.31)	1999–2001; major complications; chart review

Table 6.34*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Kruschewski et al. 2007	• 267 rectal cancer patients treated with surgery	Ever/never	• 6.42 (2.68–15.36)	1995–2004; anastamotic leak
Lilla et al. 2007	• 416 breast cancer patients treated with surgery + RT	C/F/N	• Former: 1.74 (0.99–3.04) • Current: 1.45 (0.66–3.18)	1998–2001; telangiectasia
Yildizeli et al. 2007	• 218 NSCLC patients	Current/non-current	• Increased risk p=0.01 (p. 98)	1981–2005; postoperative complications. chart review; patients treated with sleeve resection
Weinstein et al. 2007	• 191 patients with lung surgery for primary or metastatic cancer	Not clearly defined	• "In univariate analysis, length of stay was increased by a history of heavy smoking (p=0.005), …" p. 199	1999–2002; chart review
Woerdeman et al. 2007	• 309 breast cancer patients with mastectomy and immediate reconstruction	Ever/never	• 3.00 (1.61–5.57)	2000–2004; implant failure
Zhan et al. 2007	• 138 breast cancer patients taking tamoxifen	C/F/N	• Depression: – Former: 3.1 (0.8–12.3) – Current: 5.9 (1.4–24.3) • Nausea: – Former: 1.1 (0.2–5.9) – Current: 5.9 (1.2–30.5) • Migraines: – Former: 1.1 (0.07–19.9) – Current: 14.8 (1.5–148.1)	Tamoxifen side effect
Kirschbaum et al. 2008	• 156 Stage I-II NSCLC patients treated with pneumonectomy	Current/noncurrent	• 30 day mortality: 1.6 (0.4–7.5) • Complications: 2.4 (1.1–5.2)	1995–2004; chart review
Marin et al. 2008	• 89 stage III-IV head/neck cancer patients with reconstructive surgery	Current/noncurrent	• Self-reported: – Never: 1.0 (referent) – Former: 0.7 (0.2–1.9) – Current: 1.3 (0.5–3.4) • Cotinine validated (serum): – 10 or less ng/ml: 1.0 referent) – >10 ng/ml: 1.9 (1.1–3.3)	1995–2008; wound complications

Table 6.34*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Martel et al. 2008	• 220 rectal cancer patients treated with surgery	Current/noncurrent	• 6.37 (1.8–22.2)	2000–2005; anastamotic leak; smoking not clearly defined, implied as current
McCarthy et al. 2008	• 884 breast cancer patients with reconstruction	Current/noncurrent	• 2.2 (1.4–3.5)	2003–2004; total complications; current include quit <4 weeks
Shimizu et al. 2008	• 194 lung cancer patients treated with surgery	Ever/never	• 2.2 (p = 0.04)	2003–2006. postoperative complications
Soensen et al. 2008	• 208 gastrointestinal cancer patients treated with chemotherapy	Smoker/nonsmoker	• No significant difference stated in text (p. 1603)	2001–2005; mucositis; smoking not clearly defined
Wright et al. 2008	• 4,979 lung cancer patients with lobectomies	Ever/never	• 1.08 (p = 0.0007)	2002–2006; length of hospital stay; Society of Thoracic Surgeons General Thoracic Surgery Database
Bagan et al. 2009	• 159 NSCLC patients treated with surgery +/- chemotherapy	Ever/never	• "Overall operative morbidity was higher in the group of patients with a history of current smoking or recent smoking cessation" (p. 1734)	1984–2005; chart review
Bianchi et al. 2009	• 352 patients with free flap reconstructions	Smoking history	• 1.41 (p = 0.67)	2000–2007; surgical complications; chart review
Cheung et al. 2009	• 13,469 lung cancer patients treated with surgery	C/F/N	• Current: 1.0 (referent) • Former: 0.84 (0.79–0.89) • Never: 0.77 (0.69–0.86)	1998–2002; postoperative death; chart review
Cooke et al. 2009	• 1,133 cancer patients with esophagectomy	Current/noncurrent	• 1.46 (1.01–2.13)	1996–2006; anastamotic leak; chart review
Hocevar-Boltezar et al. 2009	• 75 T1 larynx cancer patients treated with RT	Current/noncurrent	• 1.59 (p = 0.02)	Poor voice quality; chart review
Joo et al. 2009	• 111 laryngeal cancer patients treated with surgery	C/F/N	• Never: 0% • Former: 30% • Current: 37% (p = 0.02)	1993–2008; pulmonary complications; chart review
Little et al. 2009	• 205 patients with forehead flap reconstruction	Current/noncurrent	• 4.34 (1.26–14.93)	1995–2008; flap necrosis; chart review

Table 6.34*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Marks et al. 2009	• 2,818 HLA identical sibling or matched unrelated donor allogeneic transplants for CML	Ever (high dose, low dose)/never	• HLA-identical sibling donor group – Low dose: 0.95 (0.77–1.88) – High dose: 1.57 (1.14–2.14) • Unrelated donor group – Ever: 1.02 (0.79–1.33)	1990–2004; treatment-related mortality
Mason et al. 2009	• 7,990 lung cancer patients	C/F/N	• Hospital mortality, former: – 14 days–1 month: 4.6 (1.2–18) – 1 month–12 months: 2.6 (0.65–11) – >12 months: 2.5 (0.82–7.6) – Current: 3.5 (1.1–11) • Pulmonary complications, former: – 14 days–1 month: 1.6 (0.85–3.1) – 1 month–12 months: 1.5 (0.81–2.8) – >12 months: 1.3 (0.77–2.2) – Current: 1.8 (1.05–3.1)	1999–2007; Society of Thoracic Surgeons General Thoracic Surgery Database
Merkow et al. 2009	• 23,098 patients with colorectal surgery	Current/noncurrent	• 1.32 (1.15–1.52)	2006–2007; reoperation; current include smoking within past year; National Surgical Quality Improvement Program
Ogihara et al. 2009	• 209 head/neck cancer patients treated with surgery	Ever/never	• 1.42 (p = 0.39)	2002–2003; surgical site infection; chart review; smoking not clearly defined, implied as ever
Rabaglio et al. 2009	• 4,895 breast cancer patients treated with surgery + estrogen receptor therapy	Ever/never	• 1.24 (1.00–1.52)	1998–2003; fracture; breast international group 1–98 trial
Ulrich et al. 2009	• 485 rectal cancer patients treated with surgery	Current/noncurrent	• Medical complication: 3.1 (1.4–6.4) • Surgical complication: not significant	2001–2006; complications
Wright et al. 2009	• 2,315 patients treated with esophagectomy	Ever/never	• 1.27 (1.03–1.56)	2002–2007; postoperative morbidity; smoking not clearly defined
Zevallos et al. 2009	• 87 head neck cancer patients treated with RT	Current/noncurrent	• 1.3 (1.02–1.68)	Hospitalization during treatment; patients enrolled in structured tobacco cessation program
Baumann et al. 2010	• 228 breast cancer patients with reconstructive surgery	Current/noncurrent	• 3.9 (1.3–2.4)	2001–2006; fat necrosis; smoking not clearly defined

Table 6.34*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Begum et al. 2010	• 374 ovarian cancer patients treated with surgery	C/F/N	• Former: 1.29 (0.69–2.40) • Current (vs. former): 0.93 (0.49–1.77)	1994–1999. postoperative complications
Berry et al. 2010	• 705 breast cancer patients with mastectomy and reconstruction	Ever/never	• 2.17 (p = 0.10)	2000–2006. surgical complications; chart review; never includes patients who quit >10 years prior to surgery
Bertelsen et al. 2010	• 1,495 colorectal cancer patients treated with surgery	C/F/N	• Former: 1.46 (0.82–2.59) • Current: 1.88 (1.02–3.46)	2000–2004. anastamotic leak
Cowen et al. 2010	• 141 breast cancer patients with mastectomy and immediate reconstruction followed by RT	Current/noncurrent	• 5.9 (2–17)	1998–2006. reconstruction failure; smoking not clearly defined
Isobe et al. 2010	• 865 lung cancer patients	Smoking index	• 0.2% cigarettes/day/year (p = 0.025)	1999–2007. respiratory deterioration; chart review
Patel et al. 2010	• 796 head/neck cancer patients with free flap reconstruction	Current/noncurrent	• 1.54 (1.02–2.32)	1999–2007. surgical complications; chart review; smoking not clearly defined, implied as current
Wedlake et al. 2010	• 193 patients treated with pelvic RT	C/F/N	• "Current smokers had the lowest presenting mean IBDQ-B score (63.7), suffered a fall during treatment (–12.0) and failed to recover at 1 year to within 3 points of presenting score (4.3-point difference between baseline and 1 year)." (p. 1167)	2004–2006. bowel toxicity
Alsadius et al. 2011	• 836 prostate cancer patients treated with external beam RT	Current/never	• Abdominal cramps: 9.0 (p = 0.004) • Urgency: 2.65 (p <0.001) • Diarrhea: 2.67 (p = 0.017) • Incomplete emptying: 2.57 (p = 0.003) • Sudden emptying: 4.6 (p = 0.003)	1993–2006. rectal toxicity
Angarita et al. 2011	• 199 breast cancer patients with mastectomy	Current/noncurrent	• 2.0 (p <0.0001)	2005–2007. surgical site infections; chart review; current include patients who quit <6 months
Chen et al. 2011a	• 202 head/neck cancer patients treated with RT +/- surgery	Current/noncurrent	• Acute: 0.92 (p = 0.74) • Late: 1.58 (p = 0.01)	1998–2008. grade 3+ toxicity; chart review
Ehlers et al. 2011	• 148 leukemia patients treated with stem cell transplant	C/F/N	• Former: 1.16 • Current: 1.80 (p = 0.009)	1999–2005. hospitalization days; chart review; current include smoking within past year

Table 6.34*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Kasuya et al. 2011	• 228 uterine or cervical cancer patients treated with surgery + RT	Smoker/nonsmoker	• 3.62 (1.32–10.0)	1984–2004; radiation enterocolitis; chart review
Kelly et al. 2011	• 2,322 patients with distal pancreatectomy	Current/noncurrent	• 1.29 (p = 0.013)	2005–2008; morbidity and mortality combined; current include smoking within past year; national surgical quality improvement program
Kim et al. 2011	• 215 colorectal cancer patients with surgery	C/F/N	• Former: 3.95 (0.52–30.1) • Current: 2.28 (0.13–41.7) • >40 Pack-years: 10.5 (1.11–99.6)	2004–2009; anastamotic complications; chart review
Lee et al. 2011	• 697 head/neck or thyroid cancer patients treated with surgery	Smoking history	• 2.34 (p <0.001 unadjusted, NS adjusted)	2006–2009; surgical site infection; chart review; smoking not clearly defined
Millan et al. 2011	• 773 colorectal cancer patients treated with surgery	Smoker/nonsmoker	• 1.55 (0.96–2.49)	2006–2009; postoperative ileus; chart review; smoking not clearly defined
Richards et al. 2011	• 423 stage I-III colorectal cancer patients treated with surgery	C/F/N	• Current: 1.32 (1.01–1.74)	1997–2007; surgical complications.
Roxburgh et al. 2011	• 302 colorectal cancer patients treated with surgery	Ever/never	• "Postoperative infective complications were associated with a smoking history, higher levels of deprivation, and increased burden of comorbidity measured by the NIA/NCI index only" (p. 1001)	1997–2005
Takamochi et al. 2011	• 1,073 lung cancer patients treated with surgery	Pack year	• <70 years old: – 40 or less Pack-years: 1.0 (referent) – >40 Pack-years: 1.89 (1.35–2.65) • ≥70 years old: – 40 or less Pack-years: 1.0 (referent) – >40 Pack-years: 2.18 (1.38–3.33)	2006–2009; postoperative morbidity; chart review
Zingg et al. 2011	• 858 patients treated with esophagectomy	Current/noncurrent	• 1.47 (1.08–2.01)	1998–2008; overall pulmonary morbidity; smoking not clearly defined

Table 6.34*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Gajdos et al. 2012	• 20,413 gastrointestinal, thoracic, and urologic cancer patients treated with major surgery	C/F/N	• Surgical site infection – Gastrointestinal o Former: 1.25 (1.09–1.44) o Current: 1.20 (1.05–1.38) – Thoracic – Former: 0.69 (0.38–1.26) – Current: 0.93 (0.54–1.60) – Urologic o Former: 1.18 (0.70–1.99) o Current: 1.23 (0.78–1.93) • Pulmonary complications – Gastrointestinal o Former: 1.60 (1.38–1.87) o Current: 1.96 (1.68–2.29) – Thoracic o Former: 1.08 (0.81–1.42) o Current: 1.62 (1.25–2.11) – Urologic o Former: 1.09 (0.63–1.86) o Current: 1.57 (1.09–2.27) • 30-day mortality – Gastrointestinal – Former: 1.50 (1.19–1.89) – Current: 1.41 (1.13–1.82) – Thoracic o Former: 1.43 (0.88–2.34) o Current: 1.30 (0.79–2.13) – Urologic o Former: 1.26 (0.68–2.34) o Current: 1.19 1.16 (0.62–2.17)	VA Surgery Quality Improvement Program
Endoh et al. 2012	• 296 NSCLC patients 75+ years old with pulmonary resection	Ever/never	• 3.11 (1.55–6.80)	1998–2008; postoperative complications; chart review
le Nobel et al. 2012	• 304 head/neck cancer patients with surgical reconstruction	Pack-years	• No significant difference stated in text (p. 1014)	2003–2010; complications; chart review

Table 6.34*S* Continued

Study	Design/population	Smoking definition	Findings (all comparisons are vs. never unless otherwise specified)	Comments
Nakagawa et al. 2012	• 3,488 unresectable, advanced, or recurrent NSCLC treated with erlotinib	Ever/never	• 2.99 (1.99–4.50)	2007–2009; interstitial lung disease; smoking not clearly defined
Wuketich et al. 2012	• 298 solid tumor cancer patients treated with chemotherapy	Current/noncurrent	• 2.82 ($p < 0.05$)	Mucositis

Note: **C/F/N** = current/former/never; **HLA** = human leukocyte antigen; **g** = grams; **IBDQ-B** = Inflammatory Bowel Disease Questionnaire-Bowel subset; **NCI** = National Cancer Institute; **NIA** = National Institute on Aging; **NS** = not significant; **NSCLS** = non-small-cell lung cancer; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **RT** = radiotherapy.

Chapter 7
Respiratory Diseases

Table 7.2*S* Population-based cohort studies of cigarette smoking and asthma induction in children and adolescents *S-203*

Table 7.3*S* Studies of cigarette smoking and asthma induction in adults *S-205*

Table 7.4*S* Studies of cigarette smoking, exacerbation of asthma, and natural history in adults *S-208*

Table 7.5*S* Studies on tobacco use and tuberculosis (TB) infection *S-211*

Table 7.6*S* Studies on tobacco use and tuberculosis (TB) disease *S-217*

Table 7.7*S* Studies on tobacco use and recurrent tuberculosis (TB) *S-241*

Table 7.8*S* Studies on tobacco use and tuberculosis (TB) mortality *S-244*

Table 7.10*S* Studies of risk of cigarette smoking and idiopathic pulmonary fibrosis (IPF), 1990–2011 *S-250*

Table 7.2*S* **Population-based cohort studies of cigarette smoking and asthma induction in children and adolescents**

Study	Design/population	Definition of asthma	Findings	Estimates of effects (95% CI)	Comments
Genuneit et al. 2006	• Population-based cohort study • 9–11 years of age at baseline • Germany • 2,936 of 6,399 subjects followed up 7 years later (mean age at follow-up, 17.1 years)	Self-reported history of wheeze and self-reported physician-diagnosed asthma	• Smoking during adolescence associated with increased risk of incident asthma • Exposure-response relationship for duration of smoking (years) and intensity of smoking (cigarettes/day)	• Ever smoker: adjusted IRR = 2.56 (1.55–4.21) • Exposure-response (duration in years): – Never: 1.0 – <2: adjusted IRR = 1.43 (0.65–3.17) – 2–4: adjusted IRR = 3.11 (1.71–5.65) – >4: adjusted IRR = 3.97 (1.84–8.57) • Exposure-response (daily smoking): – Never: 1.0 – Occasional: adjusted IRR = 0.63 (0.58–4.58) – ≤10 cigarettes: adjusted IRR = 2.46 (1.31–4.63) – >10 cigarettes: adjusted IRR = 3.34 (1.80–6.19)	Limitations: no evaluation of changes in smoking from baseline to follow-up; no statistical control for SES
Gilliland et al. 2006	• Population-based cohort study (Children's Health Study) • 8–15 years of age at enrollment • 2,609 children • Southern California • Median follow-up time, 5–8 years	Self-reported physician-diagnosed asthma (new cases)	• Smoking associated with increased risk of incident asthma • Evidence of exposure-response relationship for weekly and yearly smoking • Synergy of frequent regular smoking and maternal smoking during pregnancy	• Ever smoker: RR = 1.3 (0.9–2.0) • Cigarettes smoked weekly: – None: 1.0 – 1–6 cigarettes: RR = 1.8 (0.9–3.6) – ≥7 cigarettes: RR = 3.1 (1.5–6.2) • Cigarettes smoked yearly: – None: 1.0 – 1–99: RR = 1.1 (0.7–1.7) – 100–299: RR = 1.8 (0.6–5.0) – ≥300: RR = 3.9 (1.7–8.5)	Strengths: private interviews to ascertain smoking, yearly assessment of smoking and asthma; evaluation of smoking as time-dependent covariate, examined smoking as 1-year lag to asthma/no lag/concurrent with asthma; control for extensive confounders; Limitations: self-reported history of asthma; did not follow cohort from birth
Van de Ven et al. 2007	• Population-based cohort study • 12.9 years of age (mean) at baseline • The Netherlands • 7,426 of 10,087 subjects followed up (74%); 14.8 years of age at follow-up	Asthma defined using two methods: respiratory symptoms score and self-reported physician-diagnosed asthma	• Association of baseline smoking with incident asthma (greater magnitude of association for symptom-based asthma definition) • Suggestion of exposure-response relationship	• Symptom-based asthma definition: – Never smokers: 1.0 – Occasional smokers: OR = 1.43 (1.19–1.73) – Regular smokers: OR = 3.19 (2.28–4.46) • Self-reported physician-diagnosed asthma: – Never smokers: 1.0 – Occasional smokers: OR = 0.96 (0.55–1.66) – Regular smokers: OR = 2.08 (0.88–4.90)	Strengths: extensive control for confounders; Limitations: no evaluation of change in smoking status; modest losses to follow-up; symptom-based asthma definition did not distinguish asthma from other respiratory conditions

Table 7.2*S* **Continued**

Study	Design/population	Definition of asthma	Findings	Estimates of effects (95% CI)	Comments
Vogelberg et al. 2007	• Population-based cohort study • 6,399 children, 9–11 years of age • 2,910 children without prior wheezing analyzed • Germany • 3,785 of 4,893 subjects followed up (76%) at 7 years	Self-reported wheezing during past 12 months	• Association of active smoking with incident wheeze	• Active smoker: OR = 2.5 (1.9–3.2)	Strengths: controlled for extensive confounders, including SES; Limitations: asthma not a study outcome

Note: **CI** = confidence interval; **IRR** = incidence risk ratio; **OR** = odds ratio; **RR** = relative risk; **SES** = socioeconomic status.

Table 7.3*S* **Studies of cigarette smoking and asthma induction in adults**

Study	Design/population	Definition of asthma	Findings	Estimates of effects (95% CI)	Comments
Eagan et al. 2002	• Population-based cohort study • 15–70 years of age • Norway • 2,819 subjects followed up at 11 years	Self-reported asthma	• No clear relationship between change in smoking status and cumulative incidence of asthma at 11- year follow-up • Size of increase in pack-years of smoking associated with greater incidence of asthma	• Change in smoking status and incidence of asthma: – None to none: 1.0 (referent) – None to current: OR = 1.1 (0.4–3.2) – Current to current: OR = 1.0 (0.5–2.0) – Current to former: OR = 1.2 (0.6–2.6) – Former to former: OR = 0.9 (0.5–1.8) • Pack-years (increase): OR = 1.2 (1.0–1.4) per 10 pack-years	Limitations: loss to follow-up; definition of asthma; no statistical control for SES; analysis not time-dependent; Conclusion: inconsistent evidence linking smoking and asthma incidence
Toren et al. 2002	• Population-based, nested case-control study • 21–51 years of age • 235 cases of adult-onset asthma • 2,044 controls • Sweden	Self-reported physician-diagnosed adult-onset asthma (no reported wheeze before 16 years of age)	• Current smoking associated with a greater risk of adult-onset asthma • Greater effects for atopics, females • PAF: 15% (95% CI, 4–24%)	• Current smoker: OR = 1.5 (1.1–2.1)	Limitations: definition of adult-onset asthma relied on retrospective report of no wheeze before 16 years of age; no evaluation of past smoking history; no statistical control for SES; Conclusion: supports association between current smoking and adult-onset asthma
Sears et al. 2003	• Population-based birth cohort study • 1,139 children born in 1972 and 1973 • New Zealand • Follow-up at 26 years of age (92%); 54% completed all exams	Self-reported wheezing at multiple follow-up waves	• Smoking at 21 years of age associated with higher risk of persistent wheezing at 21 years of age	• Smoking at 21 years of age and risk of persistent wheezing: OR = 1.84 (1.13–3.00)	Limitations: asthma not assessed; no statistical control for SES; multiple comparisons performed without adjustment

Table 7.3*S* Continued

Study	Design/population	Definition of asthma	Findings	Estimates of effects (95% CI)	Comments
Piipari et al. 2004	• Population-based case-control study • 21–63 years of age • 521 newly diagnosed adult asthma cases • 932 controls • Finland	Clinical asthma diagnosis requiring at least 1 asthma symptom and reversible airway obstruction	• Current and past smoking associated with increased risk of incident asthma • No clear exposure-response relationship with either current cigarettes/day or cumulative lifetime exposure (cigarette-years)	• Never smoker: 1.0 (referent) • Former smoker: OR = 1.49 (1.12–1.97) • Current smoker: OR = 1.33 (1.00–1.77)	Strengths: incident asthma; clinically diagnosed asthma; control for extensive confounders, including SES and occupational exposures; Limitations: exposure misclassification if newly diagnosed asthmatics misestimated their smoking
Hedlund et al. 2006	• Population-based cohort study • 4,754 cases • Sweden • 83% follow-up at 10 years	Self-reported physician-diagnosed asthma	• Smoking related to increased incidence of asthma	• Persistent nonsmoker: 1.0 (referent) • Persistent former smoker: OR = 2.0 (1.5–2.8) • Persistent smoker: OR = 1.4 (0.95–2.0) • Starter: OR = 1.3 (0.17–10) • Restarter: OR = 0.99 (0.30–3.3) • Quitter: OR = 2.0 (1.4–3.0)	Strengths: incident asthma; controlled for extensive confounders, including SES and occupational exposures; Limitations: asthma defined by self-report, losses to follow-up
Butland and Strachan 2007	• Population-based birth cohort study • 18,558 children born during 1 week in 1958 • United Kingdom • 9,377 followed up at 17, 33 and 42 years of age	Self-reported physician-diagnosed asthma or self-reported wheezing	• Smoking associated with higher incidence of asthma or wheezing between ages 17–33 years of age and between 34–42 years of age	• Smoking and risk of asthma or wheezing at 17–33 years of age: – Never smoker: 1.00 – Former smoker: OR = 1.73 (1.36–2.21) – Current smoker: OR = 3.44 (2.79–4.25)	Strengths: incident asthma/wheeze; Limitations: failure to separate asthma and wheeze; losses to follow-up; lack of statistical control for SES and some other confounders
Polosa et al. 2008	• Clinic-based (allergy clinic) cohort study • Patients with allergic rhinitis but no asthma at baseline • 806 patients • Catania, Italy • 325 completed follow-up; follow-up at 10-year visit	Incident clinical diagnosis of asthma, including methacholine challenge	• Smoking related to greater risk of incident asthma at 10-year follow-up • Evidence of exposure-response relationship • Risk for current smoking higher in females, former smoking in males	• Smoker vs. nonsmoker: OR = 2.98 (1.81–4.92) • Exposure-response relationship (pack-years): – 0: 1.00 – 1–10: OR = 2.05 (0.99–4.27) – 11–20: OR = 3.71 (1.77–7.78) – ≥21: OR = 5.05 (1.93–13.20)	Strengths: rigorous asthma definition; Limitations: high losses to follow-up; smoking history from review of medical record; lack of statistical control for SES

Table 7.3*S* **Continued**

Study	Design/population	Definition of asthma	Findings	Estimates of effects (95% CI)	Comments
Nakamura et al. 2009	• Population-based cohort study • 14,975 subjects • Japan • 67% follow-up at 10 years	Self-reported physician-diagnosed asthma	• Smoking associated with increased risk of asthma among men but not women • Low prevalence of ever smoking among women (12.6%) • Exposure-response relationship with cigarettes/day among men	• Men: – Never smoker: 1.0 (referent) – Former smoker: HR = 1.86 (0.75–4.63) – Current smoker: HR = 2.79 (1.18–6.55) • Women: – Never smoker: 1.0 (referent) – Ever smoker: HR = 1.18 (0.58–2.38)	Strengths: extensive control for confounding; Limitations: losses to follow-up; few female smokers (low statistical power); wide confidence intervals

Note: **CI** = confidence interval; **HR** = hazard ratio; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **OR** = odds ratio; **PAF** = population-attributable fraction; **SES** = socioeconomic status.

Table 7.4*S* **Studies of cigarette smoking, exacerbation of asthma, and natural history in adults**

Study	Design/population	Outcome measure	Findings	Estimate of effects (95% CI)	Comments
Apostol et al. 2002	• Population-based cohort study (CARDIA) • 18–30 years of age at baseline • 5,115 cases • United States • 3,950 subjects followed for 10 years	Estimated mean annual divergence of FEV_1/ht^2 between groups over 10 years	• Active smoking associated with greater decline in FEV_1	• Mean predicted decline in FEV_1 between 18–40 years of age of 18% among baseline current smokers with asthma vs. 10% among never smokers with asthma	Strengths: multiple lung function tests over time; control for confounding variables (age, gender, race, height); Limitations: losses to follow-up; no mesures of changes in smoking status; lung function, as a long-term measure of asthma status, not necessarily reflective of acute exacerbations
Diette et al. 2002	• Cohort study • 6,590 adult managed-care enrollees with asthma • United States	Hospitalization for asthma (self-reported)	• Smoking associated with increased risk of hospitalization, but CI includes 1.0	• Ever smoker vs. never smoker, OR = 1.20 (0.96–1.52)	Limitations: possible diagnostic misclassification because definition of asthma based on utilization in administrative dataset and self-reports of hospitalization; wide CIs; controlled for multiple confounders but possible overadjustment of statistical models (e.g., functional status treated as potential confounder, but was possibly on causal pathway between smoking and hospitalization)

Table 7.4S Continued

Study	Design/population	Outcome measure	Findings	Estimate of effects (95% CI)	Comments
James et al. 2005	• Population-based cohort study • 9,317 adults in 1994–1995 who had participated in any previous Busselton Health Study between 1966–1983 • Australia	Yearly decline of FEV_1	• Additive effects of smoking and asthma in reducing FEV1	• Yearly decline of FEV_1 among women with asthma:[a] – Never smoker: -28.35 mL/year – Former smoker: -31.62 mL/year – Current light smoker: -31.35 mL/year – Current heavy smoker: -35.69 mL/year • Yearly decline of FEV_1 among men with asthma:[a] – Never smoker: -39.71 mL/year – Former smoker: -43.52 mL/year – Current light smoker: -48.13 mL/year – Current heavy smoker: -53.68 mL/year	Limitations: no statistical control for SES; losses to follow-up; no examination of changes in smoking status; lung function not necessarily reflective of acute exacerbations
Chaudhuri et al. 2006	• Cohort study convenience sample • 18–60 years of age • 32 cases • Scotland	FEV_1 at 6 weeks	• Voluntary smoking cessation (compared with continued smoking) associated with improved lung function	• Mean increase in FEV_1 of 407 mL (21–493 mL) for cessation compared with continued smoking	Limitations: possible responsibility of voluntary smoking cessation for introducing selection bias; small sample; imprecise estimates; lack of statistical control for confounding variables
de Marco et al. 2006	• Population-based cohort study (ECRHS) • 20–44 years of age at baseline • 856 subjects with asthma at baseline (1991–1993) • Australia, Europe, North America • Follow-up in 2002 with 54% completion rate (mean follow-up at 8.7 years)	GINA severity classification	• Change in smoking habits not related to asthma severity at follow-up	• Change in smoking habits by severity classification at follow-up:[b] • Unchanged smoking status: 84.7% in persistent severe asthma vs. 85.9% in mild intermittent asthma • Quitters: 10.0% in persistent severe asthma vs. 7.6% in mild intermittent asthma • Starters: 5.3% in persistent severe asthma vs. 6.5% in mild intermittent asthma	Limitations: losses to follow-up; lack of statistical control for key confounding variables; low statistical power of multinomial logistic model (5 categories of asthma severity)

Table 7.4*S* Continued

Study	Design/population	Outcome measure	Findings	Estimate of effects (95% CI)	Comments
Eisner et al. 2006	• Cohort study • 865 cases with severe asthma; analyzed subset of 465 cases who were younger than 65 years of age and had a history of participation in labor force • United States	Complete work disability (cessation) Partial work disability (absenteeism, decreased work effectiveness)	• Smoking related to higher risk of complete work disability, but not partial work disability	• Complete work disability: – Never smoker: 1.0 – Current smoker: OR = 1.80 (0.69–4.70) – Former smoker: OR = 3.17 (1.54–6.54) • Partial work disability: – Never smoker: 1.0 – Current smoker: OR = 1.30 (0.50–3.34) – Former smoker: OR = 1.47 (0.74–2.93)	Strengths: extensive control for confounders; Limitations: work disability as a long-term outcome may not reflect acute exacerbation; work disability measure was self-reported
Eisner and Iribarren 2007	• Cohort study • 865 cases with severe asthma who were recruited from managed-care organization • United States	Acute asthma exacerbation resulting in hospitalization for asthma	• At baseline, current smoking associated with increased asthma severity, asthma-specific quality of life, and generic health status • Longitudinally, current smoking associated with increased risk of hospitalization and hospital-based care	• Emergency department visit: – Never smoker: 1.0 (referent) – Current smoker: OR = 1.60 (0.92–2.77) – Former smoker: OR = 1.29 (0.91–1.84) • Hospitalization: – Never smoker: 1.0 (referent) – Current smoker: OR = 1.86 (1.03–3.36) – Former smoker: OR = 0.97 (0.65–1.45) • Any hospital-based care: – Never smoker: 1.0 (referent) – Current smoker: OR = 1.76 (1.05–2.95) – Former smoker: OR = 1.12 (0.81–1.55)	Strengths: statistical control for confounders; ascertainment of study outcomes; Limitations: cohort with severe asthma would possibly have less generalizability
Ronmark et al. 2007	• Cohort study • 20–60 years of age at baseline • 309 cases with adult-onset asthma • Sweden • Follow-up at average of 5 years	Asthma remission vs. continued symptoms (4.8% had remission) at follow-up; GINA severity classification	• Suggestion of association between smoking and decreased likelihood of asthma remission • Lack of relationship between smoking status and severity at follow-up	• 0 out of 12 subjects with remission of asthma smoked during study period vs. 23% with persistent asthma (p = 0.074) • No statistical association between smoking status and 4 category asthma severity classification (p = 0.465)	Limitations: underpowered; lack of baseline smoking, follow-up of severity; and smoking status change; lack of statistical control for SES

Note: **CARDIA** = Coronary Artery Risk Development in Young Adults; **CI** = confidence interval; **ECRHS** = European Community Respiratory Health Survey; **FEV_1/ht^2**= forced expiratory volume in 1 second/height squared; **GINA** = Global Initiative for Asthma; **mL** = milliliter; **OR** = odds ratio; **SES** = socioeconomic status.
[a]Smoking defined at baseline (e.g., heavy = ≥15 cigarettes/day).
[b]p >0.05 (exact p values not provided).

Table 7.5*S* **Studies on tobacco use and tuberculosis (TB) infection**

Study	Design/ population	Definition of smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Kuemmerer and Comstock 1967	• Census linked with TST • 7,787 junior and senior high school students • Washington County, Maryland	NR	Latent TB infection: TST >10 mm	Age, gender, history of household TB exposure, parents' smoking history, and other social factors; No multivariate analyses conducted	• Children classified as infected with latent TB were twice as likely to live in a household with two parents who smoked compared to children with at least 1 parent who did not smoke	No multivariate analyses
CDC 1992	• Cross-sectional/ surveillance study • U.S. residents of Cuban descent	**Smoker:** ≥100 cigarettes in lifetime	Latent TB infection: TST ≥10 mm		• Prevalence of latent TB infection by smoking status and gender: – Smokers: 12.0% – Nonsmokers: 7.1% – Men smokers: 14.4% – Men nonsmokers: 8.9% – Women current smokers: 13.6% – Women nonsmokers: 6.1%	
Nisar et al. 1993	• Cross-sectional study Liverpool, United Kingdom • 2,665 (75% women) residents of nursing or residential homes for the elderly	NR	Heaf test ≥3[a]	Age, gender, and length of stay in home	• Compared with never smokers, risk of a positive Heaf test was increased among current smokers (OR = 1.59) and former smokers (OR = 1.20) • Increasing number of pack-years[b] was associated with increased risk of a positive Heaf test, and after adjusting for age, the association was less evident but still significant • After adjusting for age and smoking, men had increased risk of a positive Heaf test: OR = 1.62 (1.32–1.99)	Some of the difference between men and women in tuberculin positivity may have been due to higher rates of smoking among men

Table 7.5*S* Continued

Study	Design/ population	Definition of smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Anderson et al. 1997	• Nested case-control study • 293 inmates from 11 correctional facilities • Cases: TST converters (n = 116) • Controls: Non-converters (n = 177) • South Carolina	NR	TST ≥10 mm; ≥5 mm for those HIV infected	Age, race, gender, BMI, education level, employment, alcohol use, intravenous drug use, marijuana use, silicosis, diabetes, partial gastrectomy, HIV, cancer, immunosuppressive therapy, exposure to known infectious TB case, and lodging and duration of stay in a high-risk environment	• 75% of the inmate population smoked, which is consistent with previously published estimates for such populations • After adjusting for age and living conditions, current smokers, OR = 1.78 (0.98–3.21), were more likely to convert their TST than never or former smokers • After adjusting for age, race, gender, and living conditions, current smokers were more likely to convert than nonsmokers, and the number of cigarettes smoked/day since incarceration did not change the risk estimates: – 1–10 cigarettes smoked/day, OR = 1.88 (0.96–3.69) – >10 cigarettes smoked/day, OR = 1.87 (0.92–3.78) • After adjusting for age, gender, and living conditions, inmates who smoked >15 years, OR = 2.12 (1.03–4.36), were more likely to convert than nonsmokers	Compared with non-converters (controls), converters (cases) were older and more likely to have been exposed to an active TB case, to have lived in high-risk conditions, and to have been incarcerated longer
McCurdy et al. 1997	• Cross-sectional study • Migrant farm workers who lived in Northern California	Ever smokers Former smokers	TST ≥10 mm; report of a positive TST on questionnaire	Age, gender, and place of birth	• After adjusting for age, gender, and place of birth and compared with never smokers, former smokers were 3 times as likely to be latently infected with TB, OR = 3.11 (1.20–8.09), and current smokers were almost 2 times more likely to be latently infected, OR = 1.87 (0.73–4.80)	Low prevalence of a positive TST (17%) may have resulted from selection bias

Table 7.5*S* Continued

Study	Design/ population	Definition of smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Adib et al. 1999	• Cross-sectional survey • 3,391 inmates in 21 jails • Lebanon	NR	TST >7 mm; TST 5–7 mm borderline	Age, gender, area of residence, education level, occupation, and duration of incarceration	• 45% of inmates were latently infected with TB • 75% of inmates were current smokers • After adjusting for age, gender, area of residence, occupation, and duration of incarceration, current smokers were 1.2 times as likely to be latently infected with TB: OR = 1.2 (1.1–1.3) • A dose-response relationship was not observed	
Solsona et al. 2001	• Cross-sectional study • 447 homeless people admitted to homeless shelters • Barcelona, Spain	NR	TST ≥5 mm	Age, gender, alcohol use (>40 g/day), BCG vaccination, and injection drug use	• After adjusting for age, current smokers who smoked at least 10 cigarettes/day were 1.72 times as likely to be latently infected with TB, OR = 1.72 (1.02–2.86)	75% of all participants were latently infected with TB; final model included only age; alcohol use was not associated with TB
Jentoft et al. 2002	• Cross-sectional study • Random sample of adults, 20–44 years of age • 588 adults with a TST result • Norway	**Current smoker:** 1 cigarette or cigar/week for past year **Ex-smoker:** No smoking 1 month before questionnaire **Never smoker:** Denied smoking	TST >3 mm	Age, gender, and education	• 95% had been vaccinated with BCG; 64% had a positive TST • After adjusting for age, gender, and education level, current smokers were about twice as likely to be latently infected with TB • A dose-response relationship was not observed	

Table 7.5*S* Continued

Study	Design/ population	Definition of smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Plant et al. 2002	• Cross-sectional study • 1,395 Vietnamese people, 16–81 years of age, who had applied to migrate to Australia • Majority were young adults and female (76%) • Vietnam	NR	Latent TB infection: TST >5, 10, and 15 mm	Age, gender, education level, living situation, English proficiency, BMI	• 8.9% of sample were current smokers; 5.2% were former smokers; and 85.9% were lifetime nonsmokers • 90.9% of males and 9.1% of females were ever smokers • Smoking duration was similar (~10%) across genders • The following TSTs were significantly associated with ever smokers: – 5 mm: AOR = 2.31 (1.58–3.38) – 10 mm: AOR = 1.53 (1.13–2.09) – 15 mm: AOR = 1.37 (0.95–1.97) • The following TSTs were significantly associated with duration of smoking: – 5 mm: OR = 1.09 (1.04–1.14) – 10 mm: OR = 1.04 (1.02–1.07) – 15 mm: OR = 1.03 (1.04–1.06) • Number of cigarettes smoked/day and time since quitting smoking were not associated with result of TST	Potential misclassification of smokers as nonsmokers may have been due to a fear of reporting smoking to migration authorities; smoking may explain gender differences in tuberculin reactivity
Hussain et al. 2003	• Cross-sectional study • 425 male inmates (225 smokers and 200 nonsmokers), 18–60 years of age, from 5 prisons • North West Frontier Province, Pakistan	**Smoker** (by number of cigarettes/day): 1–5: 122 6–10: 77 >10: 26	Latent TB infection: TST >9 mm in those not vaccinated with BCG; TST ≥15 mm in those vaccinated with BCG	Age, education level, duration of incarceration, and mean area of prisoner barrack	• 48% were latently infected with TB • Current smokers were more likely than nonsmokers to be latently infected with TB, with a dose effect expressed through number of cigarettes smoked/day: – 1–5: OR = 2.6 (1.6–4.4) – 6–10: OR = 2.8 (1.6–5.2) – >10: OR = 3.2 (1.3–8.2)	Exposure to smoke was not the primary exposure of interest

Table 7.5*S* Continued

Study	Design/ population	Definition of smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
den Boon et al. 2005	• Cross-sectional population survey • 2,401 adults, ≥15 years of age, with interview and TST results • All participants received TST and risk factor questionnaire • Cape Town, South Africa	**Ever smoker:** Smoked for at least 1 year	Latent TB infection: TST ≥10 mm	Age, gender, education level, BMI, and monthly income	• 82% of ever smokers and 70% of never smokers had positive TST: OR = 1.99 (1.62–2.45) and AOR = 1.77 (1.41–2.21) • Despite a similar positive relationship with pack-years, a dose-response relationship was not observed: – <5: AOR = 1.77 (1.33–2.35) – 5–15: AOR = 1.77 (1.25–2.30) – >15: AOR = 1.90 (1.28–2.81)	Association was not confounded by age or gender
Singh et al. 2005	• Cross-sectional study in India • Children, >5 years household contacts of 100 smear-positive and 100 sputum smear-negative adults with pulmonary TB diagnoses	NR	TST >10 mm	Age, gender, malnutrition, BCG vaccination, contact with sputum-positive adult	• Sputum-positive and sputum-negative cases had similar prevalence of smoking (38% and 32%, respectively) and duration of smoking (13.8 years and 14.3 years, respectively) • After adjusting for age, malnutrition, BCG vaccination, and contact with a sputum-positive TB case, exposure to secondhand smoke independently increased risk of TB infection, OR = 2.68 (1.52–4.71)	Multivariate results were not presented, although the discussion stated that contacts of sputum-positive smokers had a higher TB infection rate than sputum-positive nonsmokers in multivariate models; study did not adjust for SES

Table 7.5*S* **Continued**

Study	Design/ population	Definition of smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
den Boon et al. 2007	• Cross-sectional community survey • Children, <15 years of age, in 2 adjacent urban low- to middle-income communities • Cape Town, South Africa	**Exposure to secondhand smoke:** Living in household with at least 1 adult who smoked for at least 1 year	TST ≥10 mm	Age, TB patient in household, average household income level, clustering at household level	• 32% of children were infected with latent TB • 34% of passive smokers and 21% of nonpassive smokers had a positive TST, crude OR = 1.89 (1.24–2.86) • After adjusting for age, income level, and presence of a patient with TB in the household, the OR decreased to 1.35 (0.86–2.12) and was not significant • When limited to households with a patient with TB, passive smoking was strongly associated with risk of a positive TST, AOR = 4.60 (1.29–16.45)	Smoking increased the risk of latent TB infection in children who were exposed to secondhand smoke and exposed to a TB case in the household

Note: **AOR** = adjusted odds ratio; **BCG** = Bacillus Calmette-Guérin (vaccination); **BMI** = body mass index; **CDC** = Centers for Disease Control and Prevention; **CI** = confidence interval; **g** = grams; **mm** = millimeter; **NR** = not reported; **OR** = odds ratio; **SES** = socioeconomic status; **TST** = tuberculin skin test.

[a]The Heaf test is a diagnostic skin test performed to determine exposure to tuberculosis. It is administered by a spring-loaded instrument with six needles arranged in a circular formation. Results are read 2–7 days later. The Heaf test was replaced by newer test in 2005.

[b]Pack-years is the number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Table 7.6*S* **Studies on tobacco use and tuberculosis (TB) disease**

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Lowe 1956	• Case-control study • Cases: n = 1,200 TB patients (Birmingham Chest Clinic [766]; 3 principal Birmingham sanitoria [434]) • Controls: 979 patients (588 at Birmingham Accident Hospital with minor injuries; 391 surgical ward patients in Dudley Road Hospital) • United Kingdom	**Non-smoker:** Never smoked as much as 1 cigarette/day **Light smoker:** <10 cigarettes/day **Moderate smoker:** 10–19 cigarettes/ day **Heavy smoker:** ≥20 cigarettes/day	No clear definition; notification of TB at sanatoria or chest clinic	No adjustments but results stratified by age and gender	• 11.7% of cases and 21.0% of controls were nonsmokers or light smokers • 50.1% of cases and 43.4% of controls smoked ≥20 cigarettes/day	Study suggests that smoking is a more important factor in reactivation of TB disease than in primary TB disease because males smoke longer and in greater amounts than females and TB rates in older ages are greater in men than women
Shah et al. 1959	• Cross-sectional study • 439 employees of the Haffkine Institute • Bombay, India	Smoker Nonsmoker	Pulmonary TB diagnosed by mass radiography and confirmed by physician	No adjustments	• Among TB patients, 78.3% were smokers • Among non-TB individuals, 54.7% were smokers.	The population in the study had a high rate of TB (57%)

Table 7.6*S* Continued

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Brown and Campbell 1961	• Case-control study • 102 TB patients at MacLeod Repatriation Sanatorium and 104 ex-servicemen randomly selected admissions to the surgical wards of Repatriation Hospital • Case group 1: 102 consecutive new TB diagnoses • Control group 1: 104 ex-servicemen randomly selected from surgical wards • Case group 2: Ex-servicemen with TB in Queensland • Control group 2: Age-matched patients in casualty wards Brisbane hospitals • Australia	Not defined, but stratified by number of cigarettes smoked/ day: 0, 1–9, 10–19, 20–29, 30–39, and ≥40	No clear definition of TB; notification of TB at sanatoria and hospital	Matched by alcohol status to compare independent effect of smoking on TB	• Tobacco consumption was significantly greater in TB patients ($p < 0.05$) • When cases and controls were matched according to alcohol consumption, the distribution of smokers did not differ between cases and controls • When cases and controls were matched according to tobacco consumption, the cases included an excess number of heavy alcohol consumers	In TB patients in Queensland, smoking habits declined following detection of TB; smoking was more prevalent among TB patients only because smokers were more likely than nonsmokers to be heavy users of alcohol, which had a stronger independent relationship with TB than did smoking

Table 7.6*S* Continued

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Lewis and Chamberlain 1963	• Case-control study • Pulmonary TB patients at Brompton Hospital (London, United Kingdom) and medical and surgical patients at Charing Cross Hospital (London) • Cases: First 100 consecutive cases in which TB diagnosis was proven bacteriologically • Control group 1: Male patients in medical and surgical beds of same hospital, matched for social class and age • Control group 2: Male patients in acute medical and surgical wards of a general hospital (Charing Cross), matched for social class and age • London, United Kingdom	**Regular smoker:** Smoked ≥10 cigarettes/day	No clear definition of TB; bacteriologically proven	No adjustments, but alcohol use and marital status was investigated	• Proportion of smokers among cases and both control groups was very similar (62–68%) • In lower social classes, TB patients in the case group were more likely to drink alcohol than those in the 2 control groups	This study is one of only a few to report no association between smoking and TB, although an association between alcohol and smoking was observed

Table 7.6*S* Continued

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Adelstein and Rimington 1967	• Mass chest x-ray survey • 76,589 volunteers • Mid-Cheshire and East Cheshire, United Kingdom	**Not defined:** Nonsmoker, exsmoker, and present smoker	Cases in the study that received treatment for TB	Controlled for age and gender; collected information about marital status, occupation, address, and relevant medical history	• Among males, the TB rate (per 1,000) varied by smoking status: – Present smokers: 2.09 – Ex-smokers: 1.04 – Nonsmokers: 0.42 • Among females, the TB rate (per 1,000) varied by smoking status: – Present smokers: 1.55 – Ex-smokers: 1.24 – Nonsmokers: 0.42	Study included a very small number of TB cases; study suggested that those who reported themselves to be ex-smokers likely developed their symptoms while still smoking, and thus they may have been misclassified as ex-smokers
Yu et al. 1988	• Routine mass chest x-ray survey of pulmonary TB (prevalence survey) • Employees of the Shanghai Bureau of Sanitation, China	**Nonsmoker:** 0 cigarettes/ year **Light smoker:** 1–199 cigarettes/year **Moderate smoker:** 200–399 cigarettes/ year **Heavy smoker:** ≥400 cigarettes/year	TB not clearly defined; determined through chest radiograph, sputum smear, and/or usual clinical examination	Age, gender, history of contact, area of housing, and type of work	• After adjusting for age, gender, history of contact, area of housing, and type of work, heavy smokers were twice as likely as nonsmokers to develop pulmonary TB: RR = 2.17 (1.29–3.63) • Light and moderate smokers did not have an excess risk of developing pulmonary TB	15% of TB cases were attributed to smoking; differences between age and gender were due largely to smoking

Table 7.6*S* Continued

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Buskin et al. 1994	• Population-based analysis and case-control study • 14,321 TB patients attending the Seattle/ King County TB Clinic in Seattle, Washington • Cases: Residents of King County, >17 years of age, who were seeking care at clinic for newly diagnosed TB disease • Controls: Residents of King County, >17 years of age, who were seeking care at the clinic without active TB • King County, Washington	**Heavy smoker:** Current smoker ≥1.5 packs/day and/or those with ≥20 years of smoking	Criteria from the CDC and confirmed through culture	Gender, age, race, place of birth, alcohol use, and SES	• Current and former cigarette smokers had a risk of TB about 30–50% higher than that of never smokers • After adjusting for age and alcohol use ("heavy" vs. "other"), the estimated RR associated with current smoking was 1.3 (0.8–2.2) • There was a slight trend toward increasing TB risk with increasing number of cigarettes smoked/day, but the excess risk associated with current smoking was greatest for persons who had smoked for ≥20 years; their risk was 2 to 3 times as high as that of never smokers	Alcohol was a stronger independent risk factor than smoking; study did not define current and former cigarette smoking

Table 7.6*S* Continued

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Alcaide et al. 1996	• Case-control study • Young adults (15–24 years of age) who were close contacts of new pulmonary TB patients who were sputum smear- positive for AFB • Cases: Contacts with active TB diagnosis • Controls: Contacts who were TST positive but did not have evidence of active pulmonary TB • Barcelona, Spain	**Daily smoker:** Smoked a tobacco product every day at time of survey **Occasional smoker:** Smoked a tobacco product less than 1/ day **Active smoker:** Smoked daily or occasionally **Nonsmoker:** Did not smoke during the 6 months before index case was diagnosed **Passive smoker:** Nonsmoker exposed to combustion products of tobacco smoked by others	Infected: TST >4 mm Disease: Culture positive from bronchopulmonary specimen or clinical and radiological evidence of active TB disease with a positive TST	Age, gender, and SES	• 72% of cases and 41% of controls were active smokers • 76% of cases and 54% of controls were passive smokers • After adjusting for age, gender, and SES, active smokers were more than 3 times as likely as nonsmokers to develop pulmonary TB: OR = 3.6 (1.5–9.8) • After adjustments, passive smokers had an elevated risk of pulmonary TB: OR = 2.5 (1.0–6.2) • After adjustments, young adults with both active and passive exposure had a 5-fold increased risk for TB: OR = 5.1 (2.0–13.2) • A strong dose-response relationship was observed between daily cigarette consumption and risk for TB: – Smoked 1–20 cigarettes/day: OR = 3.0 (1.34–7.9), $p < 0.05$ – Smoked >20 cigarettes/day: OR = 13.0 (2.3–73.8), $p < 0.001$	Study served as a unique assessment of combinative effects of active and secondhand smoke exposure to tobacco
Altet et al. 1996	• Case-control study • Children who were close contacts of new smear positive pulmonary TB patients • Controls: Contacts who were TST positive but had no evidence of active disease • Barcelona, Spain	**Passive smoker:** Person exposed to tobacco smoked by others at the time of the survey and during the previous 6 months	Infected: TST >4 mm Disease: Culture positive from bronchopul-monary specimen or clinical and radiological evidence of active disease with a positive TST	SES relationship between index case-contact pairs, frequency of contact, index case's radiological pattern (cavitary vs. noncavitary), urinary cotinine concurrent diagnoses, BCG vaccination, and prior TB diagnosis or treatment	• After adjusting for age and number of cigarettes smoked/day by index case, children exposed to passive smoke had a 5-fold increased risk of developing active TB disease: OR = 5.39 (2.44–11.91) • Strong dose effect for number of cigarettes smoked/day in the household and risk of TB ($p < 0.001$)	Concentration of cotinine in the urine was used to measure exposure to tobacco smoke and was correlated with findings

Table 7.6*S* Continued

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Gupta et al. 1997	• Case-control study • Rural farmers and urban controls • Lucknow District, India	Smoker	Pulmonary TB determined by chest x-ray, history, clinical examination, and/ or sputum	Age, gender, animal contact, and rural vs. urban location	• After adjusting for age, gender, animal contact, and rural living, smokers had an increased risk of developing TB disease, OR = 1.38 (0.80–2.39), but the association was not significant	NR
Hnizdo and Murray 1998	• Prospective cohort study • 2,255 White, gold miners, starting at 45–55 years of age • South Africa • Followed for more than 20 years	Tobacco consumption was calculated in pack-years[a] of smoking at baseline	Pulmonary TB: Reported in medical record (based on sputum examination and x-ray films) or at necropsy through the presence of epithelioid granulomas associated with caseous necrosis	Age, cumulative exposure to dust, and presence of radiologically diagnosed silicosis	• In all models, RR for pack-years of cigarette smoking was significant, with a 2% increase for each additional pack-year of smoking: RR = 1.02 (1.01–1.03)	Smoking was a very minor consideration in this study

Table 7.6*S* Continued

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Chang et al. 2001	• Retrospective cohort analysis of a silicotic cohort • 707 subject records were abstracted from the pneumoconiosis clinic and supplementary information was obtained from the TB Notifications Register, Pneumoconiosis Compensation Fund Board, and the Death Registry • Hong Kong	No clear definition other than "smoking status" at time of silicosis diagnosis	TB before silicosis diagnosis: Episode of TB diagnosed by an attending physician and having been prescribed ≥2 anti-TB drugs; TB after silicosis diagnosis: ≥2 positive cultures for *M. tuberculosis;* 1 positive culture and compatible clinical history and radiological picture; ≥1 positive smear for AFB and compatible clinical history and radiological picture; Compatible clinical history and radiological picture or histological evidence and improvement after anti-TB treatment	Age, gender, other predisposing conditions, duration of exposure to occupational dust, radiographic features of silicosis, and occupational history	• 90% of subjects were ever smokers, and 55% had a history of TB • After adjusting for history of TB before silicotic diagnosis, progressive massive fibrosis, small opacity exceeding 1.5 mm, and caisson work, risk for TB increased with each additional pack-year of smoking: RR = 1.012 (1.005–1.019)	Association was weak in this population at high risk for TB; risk was not present when limited to bacteriologically positive patients

Table 7.6*S* Continued

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Perez-Padilla et al. 2001	• Case-control study • NIRD • Cases: Patients with pulmonary TB • Controls: Patients with an initial diagnosis of ear, nose, or throat ailment • Mexico City, Mexico	Past or present smoker Never smoker Passive smoker	Pulmonary TB determined through positive sputum smear or culture	Age, gender, state of birth, residence, education, income, crowding, and SES	• Among new active TB cases, smoking status did not increase the risk for TB: – Past or present smoking: crude OR = 1.2 (0.8–1.6) – Current smoking: crude OR = 0.8 (0.5–1.2) – Passive smoking did not increase risk for TB: crude OR = 1.3 (0.8–2.2)	The study found that smoking had no effect on risk for TB
Tocque et al. 2001	• Case-control study • TB cases and matched non-TB cases • Cases: 112 cases of TB reported to the Consultants for Communicable Disease Control (Liverpool and South Sefton authorities) • Controls: Patients recruited from the general practitioner databases in Liverpool and Sefton and matched to cases by age, gender, postal code, and ethnicity • Liverpool, United Kingdom	Not specifically defined	TB determined by culture or with an abnormal radiograph (or positive for AFB and granuloma and caseation) and positive TST and response to treatment	Age, gender, postal code, and ethnicity (matched); exposure factors; SES; and blood pressure	• After adjusting for exposure to TB, SES, and blood pressure, patients who had smoked ≥30 years were slightly more than twice as likely to develop TB: OR = 2.3 (1.2–4.2) • More cases than controls had quit smoking (and reduced alcohol exposure) during the course of follow-up • In univariate analysis, 2 years before TB diagnosis, cases were twice as likely as controls to smoke, OR = 2.33 (1.4–3.88), and to smoke ≥20 cigarettes/day, OR = 2.39 (1.48–3.86) • At time of interview, ORs were reduced and not significant in univariate analysis	Alcohol was not a significant factor
Gupta et al. 2002	• Cross-sectional study • Seven villages in the R.S. Pura Tehsil of Jammu District, India	Smoker Nonsmoker	Definition was not provided, but sputum specimens were collected and chest radiographs were conducted	No adjustments were made, but other factors were analyzed (e.g., age, gender, occupation, level of literacy, size of family, SES, and crowding)	• Among 287 smokers, 13 TB (4.5%) cases were detected • Among 4,688 nonsmokers, 12 TB (0.3%, $p < 0.001$) cases were detected	NR

Table 7.6*S* Continued

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Kolappan and Gopi 2002	• Case-control study • Participants in a TB disease survey in two Panchayat unions • Cases: 85 men, 20–50 years of age, with smear- and/or culture-positive TB • Controls: 459 men randomly selected from the village and matched but without TB • Questionnaire obtained information about smoking status, type of tobacco smoked, quantity of tobacco smoked, and duration of tobacco smoking • Tiruvallur District of Tamil Nadu, India	**Mild smoker:** 1–10 cigarettes/day **Moderate smoker:** 11–20 cigarettes/day **Heavy smoker:** >20 cigarettes/ day	Pulmonary TB determined through sputum smear and/or positive culture		• 75% of cases and 55% of controls were smokers; 91% of all smokers were bidi smokers • After adjusting for age, prevalence of current smoking was 2-fold higher in TB patients: OR = 2.24 (1.27–3.94) • Compared with nonsmokers, a significant dose-response relationship for higher rates of TB was observed among the following types of smokers: – Mild: OR = 1.75 – Moderate: OR = 3.17 – Heavy: OR = 3.68 • A similar trend was observed with increasing duration of smoking: – <10 years of smoking: OR = 1.72 – 11–20 years of smoking: OR = 2.45 – >20 years of smoking: OR = 3.23	Study adjusted for age only

Table 7.6*S* Continued

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Tekkel et al. 2002	• Case-control study • 248 adult cases of pulmonary TB who were routinely admitted to the TB department of the Kivimae Hospital in Tallinn, Estonia, and who resided in 1 of 4 counties • 5 controls/case randomly selected from the Estonian Population Registry and individually matched by gender, year of birth, and county of residence; only 1 control/ case was used in analyses • Estonia	**Current smoking status:** Regular smoker, past regular smoker, or nonsmoker **Exposure to secondhand smoke status:** At home, workplace, home and workplace, none	Pulmonary TB verified according to European definition	Education level, occupation, income level, marital status, place of birth, alcohol consumption, and BMI	• After adjusting for education level, marital status, and place of birth and compared with nonsmokers, past smokers, OR = 2.27 (1.00–5.14), and current smokers, OR = 4.62 (2.44–8.73), had increased risk for TB • After adjusting for education level, marital status, and place of birth, location of passive exposure to smoke affected the risk of pulmonary TB: – Those with passive exposure to smoke at home were more than twice as likely to have developed pulmonary TB, OR = 2.31 (1.25–4.24) – Passive exposure to smoke at the workplace was not associated with increased risk for pulmonary TB	The study offered little discussion about the association between smoking and TB

Table 7.6*S* Continued

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Leung et al. 2003	• Case-control study • Cases: 851 TB patients from TB notification registry (1996) • Controls: obtained from 1996 General Household Survey • Hong Kong	**Current smoker:** Smoked at the time of TB diagnosis **Ex-smoker:** Previously smoked daily for a continuous period of at least 6 months but not at the time of TB diagnosis **Ever smoker:** Either current or ex-smoker	Age and gender	Active case of TB disease determined by isolation of *M. tuberculosis,* or diagnosed on clinical, radiological, and/ or histological grounds, together with an appropriate response to treatment	• Among younger male TB patients (16–64 years of age), 52% were current smokers, 12% ex-smokers, and 36% nonsmokers; and ever smokers were 2.44 times as likely to be TB patients: weighted OR = 2.40 (1.71–3.39) • Among older males (>64 years of age), 32% were current smokers, 43% ex-smokers, and 25% nonsmokers; and ever smokers were 2.09 times as likely to be TB patients: weighted OR = 2.19 (1.60–2.98) • Among younger females, ever smokers were 2.08 times as likely to be TB patients: weighted OR = 2.40 (1.71–3.39) • Among older females, ever smokers were 2.83 times as likely to be TB patients: weighted OR = 2.19 (1.60–2.98)	Analyses focused on differences in clinical presentation of TB among ever and nonsmokers; more serious presentations were associated with ever smokers
Miguez-Burbano et al. 2003	• Case-control study • 259 HIV-infected subjects participating in a nutritional chemo-prevention trial • Cases: 27 cases with lower respiratory infections (15 pneumocystis carinii pneumonia, 12 TB) • Controls: 27 age-, gender-, SES-, and HIV status-matched controls without a history of respiratory diseases • Miami, Florida	Never Once in past 30 days Once per week 3–4 times/week Daily More than daily Past use	Definition not presented	NR	• Persons who smoked ≥20 years (i.e., long-term smokers) had a dramatically increased risk (2-fold to 3-fold, p trend = 0.04) of developing TB disease compared with those who smoked <20 years	Smokers were at risk for TB even in the presence of antiretroviral therapy

Table 7.6*S* Continued

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Ariyothai et al. 2004	• Case-control study • Cases: 100 new pulmonary TB cases (HIV negative and diabetes mellitus negative) diagnosed at Taksin Hospital • Controls: 100 age- and gender-matched, non-TB cases from patients admitted to Taksin Hospital and healthy subjects from annual physical check-ups • Bangkok, Thailand	**Nonsmoker:** Never smoked and was never exposed to passive smoke ≥3 times per week; or never smoked but exposed to secondhand smoke <3 times per week **Current active smoker:** Smoked a tobacco product at time of study, or used to smoke but had stopped during the past 6 months **Ex-active smoker:** Used to smoke but had stopped ≥6 months before the study **Current passive smoker**: Nonsmoker exposed to tobacco smoke >3 times/week **Ex-passive smoker**: Nonsmoker exposed to tobacco smoke but not for ≥6 months	Pulmonary TB determined by ≥2 sputum specimens positive for AFB, or ≥1 sputum specimen positive for AFB and radiographic abnormalities relevant to pulmonary TB and a physician's decision to treat for TB	Age, gender, alcohol consumption, BMI, household environments, TB history, and BCG vaccination	• Among cases, 44% were current active smokers, and 36% were passive smokers • After adjusting for BMI and compared with non-active/ nonpassive smokers increased risk for TB was similar by smoking status: – Current active smokers: OR = 2.70 (association was significant) – Ex-active smokers: OR = 2.88 – Current passive smokers: OR = 2.37 • Increased duration and greater intensity of smoking, measured several ways, were tied to increased risk for TB: – Among active smokers, those who started smoking at 15–20 years of age had a 3-fold increased risk for TB: OR = 3.18 (1.15–8.77), compared with nonsmokers – Among active smokers, those who started smoking when older than 20 years of age had no increased risk for TB: OR = 1.35 (0.42–4.39), compared with nonsmokers • Similar increased risks were seen with duration or amount of smoking: – Smoked >10 years: OR = 2.96 (1.06–8.22) – Smoked >10 cigarettes/day: OR = 3.98 (1.26–12.60) – Smoked >3 days/week: OR = 2.68 (1.01–7.09)	This is one of a few studies to address effects of exposure to both active and passive smoke

Table 7.6*S* Continued

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Ariyothai et al. 2004 (continued)					• Among passive smokers, those exposed to outdoor smoke: OR = 3.13 (1.07–9.17), and office/ neighborhood smoke: OR = 4.62 (1.47–14.51), had increased risk of TB; household tobacco exposure increased risk, but sample was too small to approach statistical significance	
Crampin et al. 2004	• Case-control study • Cases: 598 TB cases, ≥15 years of age, who were not previously diagnosed with TB • Controls: 992 age, gender-, and area-matched participants with no history of TB • Karonga District, Malawi	Definitions not provided	Pulmonary TB: confirmed or probable if at least 1 smear or culture was positive, excluding those with only a single smear with <10 AFB/100 fields Extra-pulmonary TB: confirmed or probable if a smear, culture, or biopsy was positive	Age, gender, SES, exposure to biomass fuel, alcohol use	• After adjusting for age, gender, area, and HIV, ex-smokers, OR = 1.9 (1.1–3.5), and those smoking ≥5 cigarettes/day, OR = 1.5 (0.9–2.4), were more likely to develop TB than never smokers; this magnitude decreased after adjusting for HIV • Compared with smoking, alcohol use was a stronger factor for TB disease	This study did not include smoking in the larger multivariate model because it was not significant in that model after adjusting for age, gender, and area; even when limited to older men, smoking was not statistically significant

Table 7.6*S* Continued

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Leung et al. 2004	• Prospective cohort study • 42,655 clients, ≥65 years of age, who were first registered with the Elderly Health Service and followed for TB outcomes through 18 elderly health centers • Hong Kong	**Never smoker:** Never smoked ≥1 cigarette/ day for ≥1 year **Ever smoker:** Smoked ≥1 cigarette/ day for ≥1 year **Ex-smoker:** Ever smoker who stopped smoking for ≥1 year **Current smoker:** Ever smoker who smoked during previous year	Active TB disease confirmed by isolation of *M. tuberculosis* on culture, or, in the absence of bacteriological confirmation, disease diagnosed on clinical, radiological, and/ or histological grounds and response to anti-TB therapy	Gender, age, alcohol use, language, marital status, education level, type of housing, work status, public financial assistance status, monthly expenditures, participation in social activities, self-rated health status, hospital admission status in previous 12 months, diabetes, chronic obstructive pulmonary disease, hypertension, heart disease, and cerebrovascular disease	• After adjusting for gender, age, alcohol use, language, marital status, education level, housing, and other comorbidities, current smokers had a 3-fold increased risk of active TB compared with never smokers: HR = 2.87 (2.00–4.11) • No excess risk was observed for extra-pulmonary TB: HR = 1.04 (0.33–3.30) • Among current smokers, those who developed TB smoked more cigarettes/day than those who did not develop TB: 13.43 vs. 10.96 (mean number of cigarettes), p = 0.01 • Smoking accounted for 33% of the TB risk among men, 9% among women, and 19% among the entire cohort	Approximately 45% of the gender difference in TB risk was attributable to smoking

Table 7.6*S* Continued

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Lienhardt et al. 2005	• Multicenter case-control study • Cases: Newly detected, smear- positive TB patients • Controls: 2 for each case, 1 from the household of the case and one from the community • Guinea, Guinea-Bissau, and The Gambia	Never smoker Past smoker Current smoker	Pulmonary TB determined by 2 consecutive AFB-positive smears and/or a positive culture	Gender, family history of TB, BCG vaccination, alcohol use, anemia, HIV infection, and history of or treatment for worm infection	• Among host-related factors and after adjusting for gender, family history of TB, and HIV infection, past smokers and current smokers had a greater risk of developing active TB disease than never smokers: – Past smoker: OR = 1.82 (1.05–3.15) – Current smoker: OR = 2.54 (1.77–3.66) • After adjusting for additional factors, current smokers were twice as likely, OR = 2.03 (1.22–3.39), as never smokers to develop TB, and the OR for past smokers decreased from 1.82 to 1.53 (1.11–2.10)	A significant dose-response relationship was observed with duration of smoking and with alcohol and drug use
Tipayamong-kholgul et al. 2005	• Case-control study • Children, <15 years of age, attending Siriraj Hospital and Queen Sirikit National Institute of Child Health in Thailand • Cases: 130 TB patients diagnosed and treated from 2001 to 2003 at Siriraj Hospital • Controls: 130 age- and gender-matched children who attended the Orthopedic Department at Queen Sirikit National Institute of Child Health • Thailand	No passive exposure Not close passive exposure Close (and very close) passive exposure	TB diagnosed and treated, including pulmonary TB and TB of the lymph nodes	Age, gender, education level of parents, household income level, level of contact with known TB case	• After adjusting for age, persons per room, and frequency of illness, the study revealed the following: – Children unexposed to persons with TB but closely exposed to passive smoke were more than nine times as likely as those with no exposure to passive smoke to develop TB: OR = 9.31 (3.14–27.58) – "Not close" passively exposed children had a protective but statistically insignificant effect: OR = 0.54 (0.25–1.16)	Effect of passive smoking was strong even after removing the effect of close contact with a TB patient, which was the strongest risk factor for TB

Table 7.6*S* Continued

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Jick et al. 2006	• Case-control study • General Practice Research Database • Investigated the relationship between glucocorticoid use and TB risk between 1990–2001 • Cases: 497 TB cases diagnosed for the first time • Controls: 1,996 age-, gender-, and date-matched participants from database • United Kingdom	Current smoker Past smoker Unknown	TB defined as first-time diagnosis, followed by treatment by ≥3 different anti-TB drugs for ≥6 months	Age, gender, BMI, use of antirheumatic or immunosuppressive agents, history of diabetes, and history of pulmonary disease (e.g., emphysema, bronchitis, and asthma)	• After adjusting for BMI, history of diabetes, glucocorticoid use, pulmonary diseases, and use of antirheumatic or immunosuppressive agents, current smokers were at greater risk for TB than nonsmokers: OR = 1.6 (1.4–2.4) • No association was observed for past smokers	Smoking was not the primary exposure of interest in this study and specific definitions of smoking were not provided
Shetty et al. 2006	• Case-control study • Cases: Newly diagnosed pulmonary TB cases among outpatients at the St. John's Medical College Hospital • Controls: Age- and gender-matched participants among relatives accompanying non-TB patients in the hospital • Bangalore, India	**Never smoker** **Past smoker:** >6 months ago **Current smoker:** Within past 6 months	Pulmonary TB: Diagnosed using the case definition of the RNTCP; all cases confirmed by either sputum smear or chest x-ray	Age, gender, marital status, religion, education level, employment status, occupation, SES, crowding, separate kitchen, other chronic diseases, exposure to cooking fuel, income level, alcohol use, BMI, and contact with a TB patient	• In crude analyses, former smoking increased risk for TB: OR = 2.31 (1.12–4.79), but current smoking did not: OR = 1.17 (0.59–2.33) • After adjusting for education level, income level, crowding, separate kitchen, exposure to cooking fuel, alcohol use, and other chronic diseases, risk for TB differed by smoking status: – Former smoking remained significantly associated with risk for TB: OR = 2.37 (1.0–5.62) – Current smoking remained insignificant: OR = 0.80 (0.34–1.89)	This is one of a few studies to find no effect of current smoking on TB incidence, although past smoking history was associated

Table 7.6*S* Continued

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Leung et al. 2007	• Prospective cohort study • 435 silicotic males with TST results • Hong Kong • Followed for TB disease outcomes for 3–10 years	**Never smoker:** Never smoked as many as 1 cigarette/day or equivalent for ≥1 year **Ever smoker:** Smoked ≥1 cigarette/ day for ≥1 year **Ex-smoker:** Ever smoker who had stopped smoking for ≥1 year before the study began	TB confirmed by isolation of *M. tuberculosis,* or in the absence of bacteriological confirmation, on clinical, radiological, and/ or histological grounds together with an appropriate response to treatment	Age, gender, alcohol use, BMI, BCG vaccination, and coexisting medical conditions	• After adjusting for alcohol use, BMI, and profusion of nodules per grade, current smokers were almost three times as likely as never smokers to be TST positive at baseline: OR = 2.72 (1.37–5.40) • Smoking at time of TST accounted for 32% of the risk of active TB • Crude rates and rates excluding regular users of alcohol were similar in that risk for TB was 2-fold higher in current smokers than in noncurrent smokers (includes both ex-smokers and never smokers) • A dose-response relationship was observed with increasing number of cigarettes smoked/day and with increasing pack-years of smoking	For ex-smokers, there was no significant difference in risk for TB between those who had given up smoking for ≥10 years and those who had given up smoking more recently
Pednekar and Gupta 2007	• Cross-sectional study • Recruitment of a cohort of >90,000 registered voters who were interviewed in their households to obtain information on cause-specific tobacco-attributable mortality • Mumbai, India	Ever smoker Never smoker Mostly bidi smoker	Self-reported prevalence of TB (current or previous history of TB)	Age, gender, and education level	• Among 70,364 individuals, after adjusting for age, education level, and smokeless tobacco use, risk for TB was increased among cigarette smokers, OR = 3.77 (2.93–4.85), and bidi smokers, OR = 5.34 (4.08–6.98) • A significant trend was observed for greater daily frequency of bidi smoking	Bidi smokers were at a greater risk for TB than cigarette smokers; study reported prevalence data; mortality increased in the cohort

Table 7.6*S* Continued

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Harling et al. 2008	• Retrospective, multilevel analysis • Self-reported TB disease in a nationally representative sample • Data from the 1998 South African Demographic and Health Survey and 1996 South African national census • South Africa	**Ever smoker:** Ever smoked ≥100 cigarettes	Self-reported "recent TB": Diagnosed by health care professional during the previous year Self-reported "lifetime TB": Ever diagnosed by a health care professional	Age, gender, race, alcohol use, BMI, crowding, SES, and urban vs. rural living	• After adjusting for age, race, alcohol use, BMI, and crowding, and SES, ever smokers were more than two times as likely to have been diagnosed with recent TB, OR = 2.20 (1.20–4.02), and 1.6 times as likely to have had TB during their lifetimes, : OR = 1.62 (1.02–2.58) • Two other factors were significantly associated with recent TB: – CAGE score >1: OR = 1.97 (1.21–3.22) – BMI <18.5: OR = 3.94 (1.68–9.23)	The wealthiest patients were protected against recent TB but not lifetime TB; TB data was self-reported and thus may have been underreported; the analysis did not consider HIV
Ramin et al. 2008	• Case-control study • Cases: 72 male patients, 18–65 years of age, who were treated for pulmonary TB for at least 2 weeks • Controls: 81 relatives of cases, matched for age within 5 years, with no history of TB • Addis Ababa, Ethiopia	Smoker Nonsmoker	Being treated for pulmonary TB for at least 2 weeks	Age, education level, and self-reported HIV status	• The overall risk for TB was more than twice as high for ever smokers as for never smokers: AOR = 2.3 (1.1–4.8) • Compared with never smokers, risk for TB increased by smoking duration: – Smoked for <10 years: AOR = 1.2 (0.5–3.1) – Smoked for ≥10 years: AOR = 5.0 (1.7–14.7) • Compared with never smokers, risk for TB increased by smoking intensity: – Smoked <10 cigarettes/day: AOR = 1.8 (0.7–4.0) – Smoked ≥10 cigarettes/day: AOR = 4.4 1.3–15.5)	Hospital-based study used a small sample from an urban population

Table 7.6*S* Continued

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Gajalakshmi and Peto 2009	• Case-control study • Men and women diagnosed by state TB clinics and interviewed at home in rural south India; analyses focused on men because women in the study did not smoke or drink alcohol • Cases: TB patients identified from the registers of local, state-run TB clinics • Controls: Randomly chosen adults, ages ≥35 years of age, from streets in a case village • India	**Ever smokers:** Smoked at least once a month for ≥6 months **Never smokers:** Never smoked at least once a month for ≥6 months	TB reported at registry, including new pulmonary, new extra-pulmonary, and re-treated TB	Alcohol use, age, and education level	• Smoking and alcohol use were closely correlated: among controls 35–64 years of age, 83% of alcohol users had smoked, but only 28% of nonalcohol users had smoked • Among those 35–64 years of age, 81.5% of new pulmonary TB cases were smokers, compared with 55.2% of controls • Among men 35–64 years of age—after adjusting for alcohol use, age, education level, smokers were 2 times as likely as never smokers to develop pulmonary TB, RR = 2.2 (1.7–2.7), more specifically RR = 2.4 (1.7–2.7) for bidi smokers and RR = 1.2 (0.9–1.5) for cigarette smokers • Alcohol use was a significant risk factor for TB, but much less than smoking after adjusting for age, education level, and smoking status: RR = 1.5 (1.2–1.9) • Men who used tobacco or alcohol or both were at least twice as likely as men with neither habit to develop pulmonary TB: – Men reporting both tobacco and alcohol use: RR = 3.5 (2.8–4.4) – Men reporting tobacco use but not alcohol use:: RR = 2.6 (2.0–3.5) – Men reporting alcohol use but not tobacco use: RR = 2.1 (1.4–3.0)	Adding alcohol use to the multivariate model for smoking significantly reduced the RR for smoking; adding smoking to the multivariate model for alcohol use significantly reduced the RR for alcohol; risk of TB was greater for bidi smokers than for cigarette smokers

Table 7.6*S* Continued

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Jee et al. 2009	• Prospective cohort study • 1,294,504 South Koreans (827,333 men and 467,171 women), 30–95 years of age, who participated in a biennial National Health Insurance Corporation medical evaluation between 1992–1995 • Participants were largely employed, middle-class, and middle-aged (median age = 45 years) • South Korea • Also reported in Table 7.7*S*, and Table 7.8*S*	**Current smoker:** For prevalence and mortality analyses, smoked at time of baseline survey; for incidence and recurrence analyses, smoked at follow-up survey **Ex-smoker:** For prevalence and mortality analyses, smoked before baseline survey but not currently; for incidence and recurrence analyses, smoked before follow-up survey but not currently **Nonsmoker:** No reported history of smoking	Prevalent TB: Self-reported history of past or prevalent TB at baseline and received ≥3 months of treatment Incident TB: ≥1 hospitalization for TB, or ≥2 outpatient visits for TB, or received ≥3 anti-TB medications Recurrent TB: Incident or prevalent TB as reported above, and incident TB between 2001–2005 TB mortality: TB as the underlying cause of death, as reported to national statistical office	Age, gender, alcohol use, and BMI	• After adjusting for age and alcohol use, male current smokers had increased risk for TB and risk increased with the number of cigarettes smoked/day: HR = 1.4 (1.3–1.5)	After adjusting for BMI, the effect of smoking was generally reduced; this is 1 of a few studies to address the risk of recurrent TB among smokers; alcohol use increased the risk for TB incidence among men but not mortality or recurrence

Table 7.6*S* Continued

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Kolappan and Subramani 2009	• Nested case-control study • TB prevalence survey conducted in 50 rural villages and 3 urban units • Cases: 255 bacteriologically positive TB cases diagnosed by either sputum smear or culture • Controls: 1,275 age- and gender-matched participants selected from noncases residing in same village or unit • Tiruvallur District of Tamil Nadu, India	**Smoker:** Ever smoked any type of tobacco product at any time **Nonsmoker:** Never smoked any type of tobacco product at any time	Pulmonary TB confirmed through sputum positive for AFB or a positive culture	Alcohol use, SES, and exposure to biomass cooking fuel	• After adjusting for alcohol use, SES, and exposure to cooking fuel, current smokers were at increased risk for TB: OR = 1.4 (1.0–2.0) • Risk for TB from alcohol use was similar but not significant: OR = 1.3 (0.9–1.8) • Risk for TB from exposure to biomass cooking fuel was slightly higher compared with cooking with non-biomass fuel: OR = 1.7 (1.0–2.9)	Primary aim of study was to determine risk of TB from exposure to biomass cooking fuel, which accounted for 36% of all cases, compared with 14% for smoking

Table 7.6*S* Continued

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Lin et al. 2009a	• Prospective cohort study • 17,699 adults, ≥12 years of age, who participated in the Taiwan National Health Interview Survey • After initial interview, incident TB cases were identified from the National Health Insurance database • Taiwan	**Ever smoker:** Ever smoked >100 cigarettes **Current smoker:** Ever smoker who smoked during the month before the interview **Former smoker:** Ever smoker who did not smoke during the month before the interview	Incident TB cases, as reported in the National Health Insurance database	Age, gender, alcohol use, SES, employment status, marital status, education level, and residence	• 40% of men and 4.2% of women smoked at baseline • After adjusting for age, gender, alcohol use, low-income household (SES), employment status, marital status, education level, and residing in a crowded home in an indigenous community, current and ever smokers had a greater risk for TB than never smokers: – Current smokers: OR = 1.94 (1.01–3.73) – Ever smokers: OR = 1.71 (0.90–3.26) • Compared with smoking, alcohol use was a much stronger risk factor for TB • A strong dose-response relationship was observed with number of cigarettes smoked/day, number of years of smoking, and pack-years of smoking	When analysis was restricted to pulmonary TB only, no significant change was observed

Table 7.6*S* Continued

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Prasad et al. 2009	• Case-control study • Cases: 111 sputum smear-positive pulmonary TB patients • Controls: 3 age-, gender-, and place-matched controls (n = 333) from among the healthy bystanders of the case, excluding those with comorbid conditions (diabetes mellitus, HIV, malignancy, use of immunosuppressive drugs) • Uttar Pradesh, India	**Smoker:** >100 cigarettes or bidis during lifetime **Nonsmoker:** <100 cigarettes or bidis during lifetime	TB confirmed through sputum smear-positive for pulmonary TB	Alcohol use, type of house, SES, BMI	• 33% of TB cases and 14% of controls were smokers • After adjusting for type of house, SES, and BMI, the risk for TB increased almost 4-fold for smokers compared with nonsmokers: OR = 3.8 (2.0–7.0) • Risk for TB increased with pack-years of smoking: – Smoked ≥5 pack-years: AOR = 4.6 (2.1–10.1) – Smoked <5 pack-years: AOR = 2.9 (1.2–6.8)	Duration of smoking was more significant than number of cigarettes or bidis smoked/ day; chewing tobacco and alcohol use were not associated with TB

Note: **AFB =** acid-fast bacilli; **AOR** = adjusted odds ratio; **BCG =** Bacillus Calmette-Guérin (vaccination); **BMI** = body mass index; **CAGE** = **C**ut down on drinking, **A**nnoyances with criticisms about drinking, **G**uilt about drinking, and using alcohol as an **E**ye opener (score); **CDC** = Centers for Disease Control and Prevention; **CI** = confidence interval; **HR** = hazard ratio; **mm** = millimeters; **NIRD** = National Institute of Respiratory Disease; **NR =** not reported; **OR** = odds ratio; **RR** = relative risk; **RNTCP** = Revised National Tuberculosis Control Programme; **SES** = socioeconomic status; **TST =** tuberculin skin test.
[a]Pack-years is the number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Table 7.7*S* Studies on tobacco use and recurrent tuberculosis (TB)

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Chang et al. 2004	• Nested case-control study • 12,183 pulmonary TB patients identified from a computerized registry in Hong Kong between 1998 and 2000 who had completed TB treatment and were followed for relapse for 30 months • 113 detected relapse cases were compared with 226 matched controls • Hong Kong	Specific definition was not provided for ever smokers	Active pulmonary TB confirmed by isolation of *M. tuberculosis* in sputum or bronchial aspirate; or compatible clinical, radiographical, and/or histological findings together with appropriate response to anti-TB treatment Relapse TB: Patient became or remained culture negative while receiving anti-TB drugs but after completing therapy became either culture positive again or met the definition of active pulmonary TB	Treatment-related factors, employment status, alcohol use, drug use, and residence	• In univariate analysis, being an ever smoker had no association with risk of TB relapse: OR = 1.3 (0.7–2.3)	Exposure to smoke and history of smoking was not the primary factor of interest in this study
Leung et al. 2004	• Prospective cohort study • 42,655 clients, ≥65 years of age, who were registered with the Elderly Health Service • Followed for TB outcomes through 18 elderly health centers • Hong Kong	**Never smoker:** Never smoked ≥1 cigarette/ day for ≥1 year **Ever smoker:** Smoked ≥1 cigarette/ day for ≥1 year **Ex-smoker:** Ever smoker who stopped smoking for ≥1 year **Current smoker:** Ever smoker who smoked during previous year	Re-treatment TB was not defined	Gender, age, alcohol use, language, marital status, education level, type of housing, work status, public financial assistance status, monthly expenditures, participation in social activities, self-rated health status, hospital admission status in previous 12 months, diabetes, chronic obstructive pulmonary disease, hypertension, heart disease, and cerebrovascular disease	• After adjusting for many factors, current smokers had a greater risk of recurrent TB, than never smokers: OR = 2.48 (1.04–5.89)	Study did not differentiate between TB relapse and TB reinfection

Table 7.7*S* Continued

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Thomas et al. 2005	• Prospective cohort study • 503 cured TB patients • South India • Followed for 18 months after completing treatment	**Smoker:** TB patients who smoked habitually and were currently smoking	Relapse TB: TB patient cured under DOTS (Directly Observed Treatment, Short course) program who had 2 acid-fast bacillus-positive sputum samples by direct smear, or 1 smear and 1 culture positive from separate samples, or 2 positive cultures	Age, gender, education level, occupation, alcohol use, drug use, and weight TB factors: Drug sensitivity profile, adherence to TB drug, smear conversion at 2 months, and initial smear grading	• After adjusting for adherence to TB drug and drug sensitivity profiles, current smokers were 3 times as likely as nonsmokers to have TB relapse: OR = 3.1 (1.6–6.0)	Smoking was the only non-treatment-related factor to increase risk of TB relapse
d'Arc Lyra Batista et al. 2008	• Prospective cohort study • Newly diagnosed TB cases between 2001–2003 • Recife, Brazil • Followed for TB relapse through 2006	**Current smoker:** Smoker at the time of the interview **Never smoker:** Never smoked **Ex-smoker:** Not current smoker but smoked in past **Ever smoker:** Current smoker and ex-smoker who had given up smoking less than 1 year before time of interview	TB diagnosis reported in Surveillance System for Infectious Diseases	Age, gender, alcohol use, literacy, employment status, crowding, income level, education level, commodity ownership, availability of health services, treatment delay, HIV status, and known contact with TB	• After adjusting for age, gender, and alcohol use, ever smokers were 2 times as likely as never smokers and ex-smokers (those who had given up smoking 1 year or more prior to time of interview) to have recurrent TB: OR = 2.34 (1.17–4.68) • Other than smoking, living in an area with no family health program was the only factor to increase risk of TB recurrence	NR

Table 7.7*S* Continued

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Jee et al. 2009	• Prospective cohort study • 1,294,504 South Koreans (827,333 men and 467,171 women), 30–95 years of age, who participated in a biennial National Health Insurance Corporation medical evaluation between 1992–1995 • Participants were largely employed, middle-class, and middle-aged (median age = 45 years) • South Korea • Also reported in Table 7.7*S* and Table 7.8*S*	**Current smoker:** Smoked at time of baseline survey **Ex-smoker:** Smoked before baseline survey but not currently **Nonsmoker:** No reported history of smoking	Recurrent TB: Participants with prior or prevalent TB that was reported during the initial site visit or follow-up visit were considered to have recurrent TB if incident TB was detected after the initial TB diagnosis	Age, gender, alcohol use, and body mass index	• After adjusting for age and alcohol use and compared with nonsmokers, risk of recurrent TB increased for both genders: – Men: Increased 30%: HR = 1.3 (1.2–1.4) – Women: Increased 20%, HR = 1.2 (0.8–1.6) but association was not significant – A dose-response relationship was not observed • Risk of recurrent TB increased 20% in men with heavy alcohol use (≥50 g/ day)	
Millet et al. 2009	• Population-based, retrospective, longitudinal study • 681 patients with culture-confirmed TB and drug susceptibility testing between 1995–1997 • Barcelona, Spain • Followed for TB recurrence through December 2005	Smoker was not defined	TB case: Culture confirmed with drug-susceptibility test TB recurrence: New clinical and/ or microbiological diagnosis of TB in any patient who had correctly completed treatment for her/his first episode and had been free of TB for ≥1 year	Gender, age, country of birth, drug use, HIV status, alcohol use, homelessness, incarceration in prison, and resistant TB	• In univariate analysis, smoking increased risk for TB recurrence, HR = 2.6 (1.1–6.2), but this association was lost when adjusting for other factors	Study used a poor definition of smoker

Note: **CI** = confidence interval; **g** = grams; **HR** = hazard ratio; **NR** = not reported; **OR** = odds ratio.

Table 7.8*S* Studies on tobacco use and tuberculosis (TB) mortality

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Doll and Hill 1956; Doll et al. 1994; Doll 1999	• Prospective cohort study • 34,494 men and 6,207 women physicians responded to a questionnaire about smoking habits in 1951 • United Kingdom • Followed for 50 years with cause of death ascertained from death registry	**Current smoker:** Smoked at the time the questionnaire was administered **Former smoker:** Smoked in the past but had quit **Never smoker:** Never smoked as much as 1 cigarette/day or its equivalent in pipe tobacco for as long as 1 year	TB listed as cause of death	Age and gender	• Per the 1956 report: – Among men ≥35 years of age, no TB deaths were reported among nonsmokers, compared with 0.20/1,000 among smokers – The rate of death from TB rose with increasing daily average number of cigarettes smoked: o 1–14 cigarettes smoked/day: 0.16/1,000 o 15–24 cigarettes smoked/day: 0.18/1,000 o >24 cigarettes smoked/day: 0.29/1,000 • Per the 1994 report: – Rates of TB mortality were 4/100,000 among nonsmokers, 8/100,000 among former smokers, and 11/100,000 among current smokers – The rate of death from TB rose with increasing daily average number of cigarettes smoked: o 1–14 cigarettes smoked/day: 7/100,000 o 15–24 cigarettes smoked/day: 9/100,000 o >24 cigarettes smoked/ day: 20/100,000	This is the longest follow-up study of smokers; this study did not adjust for other factors

Table 7.8*S* Continued

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Liu et al. 1998	• Retrospective cohort study • Surviving family members of 1 million people who died in 98 areas of China were interviewed to determine smoking status of the deceased • China	Ever smokers and never smokers were not defined well	TB listed as a cause of death on death certificate, supplemented by a review of medical records or discussions with local health workers, community leaders, and family members	NR	• Compared with men nonsmokers, men smokers had an increased risk of TB mortality (RR): – Urban: 1.42 (SE = 0.05) – Rural: 1.17 (SE = 0.04) – Overall: 1.20 (SE = 0.04) • Compared with women nonsmokers, women smokers had an increased risk of TB mortality (RR): – Urban: 1.56 (SE = 0.09) – Rural: 1.25 (SE = 0.09) – Overall: 1.29 (SE = 0.08) • In both urban and rural settings, increasing numbers of cigarettes smoked/day increased the risk of TB mortality: – Urban patients (RR): o 1–19 cigarettes smoked/day: 1.24 (SE = 0.06) o 20 cigarettes smoked/day: 1.48 (SE = 0.07) o >20 cigarettes smoked/day: 2.03 (SE = 0.14) – Rural patients (RR): o 1–19 cigarettes smoked/day: 1.01 (SE = 0.06) o 20 cigarettes smoked/day: 1.23 (SE = 0.07) o >20 cigarettes smoked/day: 1.57 (SE = 0.15) • Younger age at start of tobacco smoking increased risk of TB in urban patients (RR): – <20 years of age: 1.86 (SE = 0.08) – 20–24 years of age: 1.42 (SE = 0.06) – ≥25 years of age: 1.22 (SE = 0.06)	11.3% of deaths among men and 2.8% of deaths among women were attributable to TB

Table 7.8*S* Continued

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Lam et al. 2001	• Case-control study • Death registries in Hong Kong; households of persons who died were visited and a living household member was interviewed • Cases: Ethnic Chinese people, ≥35 years of age, whose deaths were registered in Hong Kong in 1998 or thereabouts • Controls: Living person in household who was not the informant • Informants: reported habits of cases and controls; only one-half as many controls as cases • Hong Kong	Ever smoker Never smoker	TB listed as cause of death in death registry	Age, gender, alcohol use, employment status, type of housing, place of birth, and education level	• After adjusting for age and education level and compared with nonsmokers, increased risk of TB mortality among middle-aged smokers (35–69 years of age) was observed for both genders: – Men: RR = 2.54 (1.24–5.22) – Women: RR = 1.49 (0.18–12.57) • Compared with older nonsmokers (≥70 years of age), increased risk of TB mortality among older smokers was observed for both genders: – Men: RR = 1.63 (1.01–2.64) – Women: RR = 1.03 (0.49–2.15) • Among middle-aged and older men, a strong dose-response relationship was observed with number of cigarettes smoked/day	This study adjusted for only age and education level

Table 7.8*S* **Continued**

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Gajalakshmi et al. 2003	• Case-control study • Urban and rural men who died from medical causes • Cases: 27,000 urban and 16,000 rural men, ≥25 years of age, who died and whose household could be visited by interviewers • Controls: 20,000 urban and 15,000 rural men, ≥25 years of age, living in a household in which a female member had died during the same year as cases • Tamil Nadu, India	**Ever smoker:** Smokers and former smokers were combined into a single category **Cigarette smoker:** <10 smokes/day and ≥10 smoked/day **Bidi smoker:** <15 smoked/day and ≥15 smoked/day **Never smoker**	Urban setting: Death records from the Chennai Vital Statistics Department were reviewed and, when nonspecific, field interviewers surveyed family members and locally experienced doctors who coded the cause of death Rural setting: Verbal autopsy was conducted after reviewing all formal and informal records of deaths in the village	Age, education level, and chewing tobacco status	• Urban settings: – 79% of TB deaths involved a history of smoking – After adjusting for age, education level, and chewing tobacco status in urban settings, risk of TB mortality was nearly 4 times as high for ever smokers as for never smokers, and 56% of TB deaths were attributed to smoking, RR = 3.8 (3.5–4.2) • Rural settings: – 73% of TB deaths involved a history of smoking – After adjusting for age, education level, and chewing tobacco status in rural settings, risk of TB mortality was more than 4 times as high for ever smokers as for never smokers, and 56% of TB deaths were attributed to smoking, RR = 4.2 (3.7–4.8) • Compared with never smokers, ever smokers had a greater prevalence of TB history	
Sitas et al. 2004	• Case-control study • 16,230 new death notifications from 1998 used to estimate tobacco-attributable mortality • Cases: Deaths from diseases known to be associated with tobacco use, including TB • Controls: Deaths from other defined medical conditions expected to be largely unrelated to smoking • South Africa	Current smoker at time of death Nonsmoker at time of death	Reported on death notification	Age, gender, education level, ethnicity, and disease status	• After adjusting for age, gender, education level, and ethnicity and compared with nonsmokers, smokers had an increased risk of death from TB, OR = 1.61 (1.23–2.11) • 20% of deaths from TB were attributed to smoking: 28% among men and 7% among women	NR

Table 7.8*S* Continued

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Gupta et al. 2005; Pednekar and Gupta 2007	• Prospective cohort study • 99,570 registered voters were interviewed • Mumbai, India • Follow-up 5.5 years later, death records were abstracted to determine the cause of death for those who died	**Nonsmoker:** Person who did not report using tobacco in any smokeless or smoking form **Smokeless user only:** Person who reported using only smokeless tobacco **Smoker:** Person who reported smoking; some could be smokeless tobacco users; past smokers were combined with current smokers for analysis	TB reported on death registry	Age, gender, and education level	• After adjusting for age and education level and compared with nonsmokers, risk of TB mortality was greater among tobacco users in both genders: – Male smokeless tobacco users: RR = 1.46 (1.07–2.00) – Male smokers: RR = 2.30 (1.68-3.15) – Female smokeless tobacco users: RR = 1.40 (0.99–2.00) – Female smokers: RR = 5.92 (2.31–15.17) • Among female smokers, the RR for TB was 3 times as high as for any other disease studied; several outcomes had similar or greater magnitudes of association among males • Among males, an estimated 37.2% of deaths from TB were attributed to smoking; bidi smokers had a greater risk for TB than did cigarette smokers • Among males only in the 2007 report and compared with nonsmokers, risk of TB mortality was greater among smokers: – Cigarette smokers: RR = 2.12 (1.70–2.66) – Bidi smokers: RR = 2.60 (2.02–3.33)	Compared with nonsmokers, the overall RR of 1.37 for smokers was lower than expected, perhaps because of a low number of cigarettes smoked/day; the study did not adjust for alcohol use; strong follow-up of patient status by the conclusion of the study

Table 7.8*S* Continued

Study	Design/ population	Smoking variables	Definition of TB infection or disease	Factors adjusted for or considered in the analyses	Study results (95% CI)	Comments
Jha et al. 2008	• Case-control study • Men and women from urban and rural India. • Cases: 41,000 men and 33,000 women, ≥20 years of age, who died between 2001–2003 and whose deaths had been recorded controls: 43,000 men and 35,000 women	No details provided; smokers and nonsmokers were compared at time of death or at time of interview for controls	TB reported at verbal autopsy	Age, gender, education level, and alcohol use	• Among men, 30–69 years of age, 66% of deaths from TB involved a history of smoking • After adjusting for age, education level, and alcohol use and compared with nonsmokers, risk of TB mortality among men was greater among smokers, RR = 2.3 (2.1–2.6), and 38% of deaths from TB were attributed to smoking • Among women, 30–69 years of age, 13% of deaths from TB involved a history of smoking • After adjusting for age, education level, and alcohol use and compared with nonsmokers, risk of TB mortality among women was greater among smokers, RR = 3.0 (2.4–3.9), and 9% of deaths from TB were attributed to smoking	NR
Jee et al. 2009	• Prospective cohort study • 1,294,504 South Koreans (827,333 men and 467,171 women) 30–95 years of age, who participated in a biennial national medical evaluation between 1992 and 1995 • Participants were largely employed, middle class	**Current smoker:** Smoked at time of baseline survey **Ex-smoker:** Smoked before baseline survey but not currently **Nonsmoker:** No reported history of smoking	TB mortality: TB was the underlying cause of death, as reported to the national statistical office	Age, gender, alcohol use, and BMI	• After adjusting for age and alcohol use and when compared with nonsmokers, risk of TB mortality was greater among current smokers of both genders: – Men: HR = 1.58 (1.27–1.97) – Women: HR = 1.55 (1.00–2.41) • Risk of TB mortality was elevated among former smokers of both genders: – Men: HR = 1.45 (1.14–1.85) – Women: HR = 2.16 (1.35–3.46) • After adjusting for BMI, the effect of smoking was generally reduced • Among men, alcohol use increased the risk of TB incidence but not TB mortality or recurrence	NR

Note: **BMI** = body mass index; **CI** = confidence interval; **HR =** hazard ratio; **NR =** not reported; **OR** = odds ratio; **RR** = relative risk; **SE** = standard error.

Table 7.10*S* Studies of risk of cigarette smoking and idiopathic pulmonary fibrosis (IPF) 1990–2011

Study	Design/ population	Adjustment(s) for potential confounders	Findings (95% CI or p value)	Comments
Scott et al. 1990	• Patients seen by respiratory physician or tested in PFT laboratory • 40 cases • 106 community controls • Nottingham, United Kingdom	NR	• Ever smoker – OR = 0.93 (0.37–2.35)	
Iwai et al. 1994	• Patients identified by members of two research committees • 86 cases • 172 healthy controls • 86 hospital controls • Japan	NR	• Smoker – RR = 2.9 (p <0.01)	RR estimate limited to comparison with healthy controls
Hubbard et al. 1996	• Patients identified from 4 teaching and 5 general hospitals • 225 cases • 569 community controls • Studied during 1992–1994 • United Kingdom	None	• Ever smoker – OR = 1.57 (1.01–2.43) – 10 pack-years of smoking – OR = 11.05 (0.99–1.12)	Community controls from same general practitioner as cases
Baumgartner et al. 1997	• Patients identified from 16 institutions Untied States • 248 cases and 491 age-, gender-, and region-matched controls • Studied during 1989–1993		• Ever smoker – OR = 1.59 (1.1–2.4) • Pack-years – ≤20, OR = 1.00 – 21–40, OR = 2.26 (1.3–3.8) – >40, OR = 1.12 (0.7–3.9)	
Baumgartner et al. 2000	• Patients identified from 16 institutions • 248 cases • 491 age-, gender-, and region-matched controls (identified by random-digit dialing) • Studied during 1989–1993 • United States	Age, hairdressing, raising birds, stone cutting/ polishing, metal dust, talc, livestock	• Ever smoker – OR = 1.59 (1.1–2.4) • Ever smoker (adjusted) – OR = 1.8 (1.2–2.7)	
Enomoto et al. 2003	• Patients admitted to Nippon Medical School Hospital • 52 cases • 184 controls (randomly selected from clinic patients undergoing medical examination with no evidence of lung disease on chest radiograph, 1999–2000) • Studied during 1995–2000 • Japan	Obesity, hypertension, diabetes mellitus, hyperlipidemia, hyperuricemia	• Ever smoker – OR = 5.4 (2.30–12.66)	Diagnosis based on clinical history and examination, high-resolution CT scan along with lung biopsy, transbronchial lung biopsy, and/ or bronchoalveolar lavage, when available

Table 7.10*S* Continued

Study	Design/ population	Adjustment(s) for potential confounders	Findings (95% CI or p value)	Comments
Miyake et al. 2005	• Patients identified from 50 hospitals • 102 cases • 59 controls (>40 years of age, without prior respiratory disease, treated at the same hospital for respiratory illness as cases during same time period) • Studied during 2001 • Japan	Age, gender, region	• Former smoker – OR = 2.21 (0.82–6.04) • Current smoker – OR = 0.5 (0.10–2.24) • Pack-years – 0.6–19.9, OR = 0.87 (0.25–3.10) – 20.0–39.9, OR = 3.23 (1.01–10.84) – 40.0–59.9, OR = 2.22 (0.70–7.23) – ≥60.0, OR = 1.59 (0.46–5.64)	Diagnosis based on clinical history, examination, high-resolution CT scan, and, when available, lung biopsy, transbronchial lung biopsy, and bronchoalveolar lavage
Steele et al. 2005	• Patients identified from Web-based advertising and direct mailing to physician members of ATS • 111 families having ≥2 members with idiopathic interstitial pneumonia • 309 cases • 360 controls (unaffected family members) • United States	Age, gender	• Ever smoker – OR = 3.6 (1.3–9.8)	IPF comprised 80% of affected cases
Gustafson et al. 2007	• Swedish Oxygen Register • 140 cases • 757 controls (general population) • Studied during 1997–2000 • Sweden	None	• Ever smoker – Males, OR = 3.36[a] – Females, OR = 0.90[a]	
Hubbard et al. 2008	• Longitudinal, electronic primary care database • 920 cases • 3,593 (age-, gender-, and community-matched controls) • United Kingdom	None	• Ever smoker – OR = 1.11 (0.94–1.31)	Primary aim of study was to determine association between IPF and cardiovascular disease
Schenker et al. 2009	• Autopsy series of 112 Hispanic males • 21 cases • 58 ever smoked • Studied during 1994–1995 • Fresno County, California	Age, mineral dust	• Ever smoker – OR=5.03 (1.12–22.68)	Cases of interstitial fibrosis diagnosed at autopsy, smoking status determined by pathologic criteria

Table 7.10*S* Continued

Study	Design/ population	Adjustment(s) for potential confounders	Findings (95% CI or p value)	Comments
Garcia-Sancho et al. 2011	• Newly diagnosed patients at National Institute of Respiratory Diseases • 100 cases • 263 neighborhood controls • Studied during 2007–2009 • Mexico	Parent or sibling with IPF; past or current occupational exposure to dusts, smokes, gases, or chemicals; past or current gastroesophageal reflux; type 2 diabetes	• Former smoker – OR=2.5 (1.4-4.6)	

Note: **ATS** = American Thoracic Society; **CI** = confidence interval; **CT** = computed tomography; **NR** = not reported; **OR** = odds ratio; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **PFT** = pulmonary function testing; **RR** = relative risk.
[a]Crude ORs calculated from data in study.

Chapter 8
Cardiovascular Diseases

Table 8.6*S* Detailed description of studies on smokefree laws and coronary events *S-255*

Table 8.7*S* Detailed description of studies on smokefree laws and cerebrovascular accidents *S-281*

Table 8.8*S* Detailed description of studies on the relationship between smokefree laws and other heart disease *S-287*

Table 8.6*S* Detailed description of studies on smokefree laws and coronary events

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
Acute myocardial infarction (AMI)–workplace-only laws					
Dautzenberg 2008	• AMI • <65 years of age • Effective February 1, 2007; restaurants, bars, and casinos added January 1, 2008 • January 2006–February 15, 2008 • France	Partial law: Pre: 13 Post: 12.5	• Rate per 100,000 admissions	• Partial law: 0.99 (0.94–1.04)*[a]	Smoking ended in public places in February 2007, but restaurants, bars, and casinos were given exceptions until January 2008; law permits ventilated smoking rooms under strict conditions; between January 2007 (before law) and January 2008 (after law), secondhand smoke exposure dropped from 57% to 14%; $PM_{2.5}$ levels also dropped; also reported substantial drops in respiratory symptoms among hospitality workers
Villalbí et al. 2009	• AMI (*ICD-9* 410.x1) • >24 years of age • N = 13,317 • January 2004–December 2005 vs. January 2006–December 2006 • Barcelona, Spain	Pre: 24 Post: 12	• Comparison of age- and gender-specific annual hospitalization rates	• Female: .88 (0.84–0.92)*[b] • Male: .87 (0.84–0.90)*[b] • Adjusted rates (per 100,000 population) for men were 185.6 (179.2–192.1) in 2004, 175.0 (168.9–181.2) in 2005, and 156.4 (150.6–162.1) in 2006 (postlaw) • Adjusted rates for women were 81.2 (77.1–85.3) in 2004, 75.6 (71.7–79.6) in 2005, and 69.0 (65.3–72.7) in 2006 (postlaw)	Law in workplaces, but not cafés, bars, restaurants, night clubs, or discotheques; antismoking legislation also included law on advertising and reduction in sales outlets; in men, the decline in 2006 (-10.68%) was much greater than in 2005 (-5.69%); in women, it was only slightly greater in 2006 (-8.76% vs. -6.85%); this decline was apparent in all age groups except men <45 years of age

Table 8.6*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
Naiman et al. 2010	• AMI (*ICD-9* 410, *ICD-10* I21) • ≥45 years of age • Effective May 2006 • January 1996–May 2006 • Toronto, Canada	Pre: 36 Postphase 1: 24	• ARIMA on crude rates of hospital admission • Subgroup analyses by age, gender • Comparison with Durham Region and Thunder Bay, 2 Ontario municipalities with no smokefree laws; no significant reductions were observed in control cities • Smokefree legislation occurred in 3 phases: smokefree public places and workplaces in October 1999; smokefree restaurants, dinner theaters, and bowling centers except designated smoking rooms in June 2001; smokefree bars, billiard halls, bingo halls, casinos, racetracks except designated smoking rooms in June 2004	• Postphase 1 vs. prelaw: 1.03 (0.94–1.12)*	Legislation required all public places and workplaces to be smokefree and was implemented in 3 phases; the largest declines were seen after the phase of the law affecting restaurants came into effect, including a 17% (14%, 19%) decrease in AMI; crude rates of hospital admissions decreased 39% (38%, 40%) for cardiovascular conditions; no significant reductions were observed in number of hospital admissions attributable to control conditions (cholecystitis, appendicitis, bowel obstruction) in Toronto
Shetty et al. 2010	• AMI (*ICD-9* and *ICD-10*) • Nationwide inpatient sample: 673,631 • Multiple cause of death dataset: 2,018,548 • Medicare patients: 2,382,387 • United States		• Region-level fixed effects multivariate linear regression model • Stratified by age • Regression model included hospital beds/person, county population, physicians/person, percent population in labor force, cigarette taxes • Compared trends in regions where smoking laws were implemented with control regions having no laws	• Deaths in 18–64: 0.964 (0.904–1.025)*	Does not differentiate between weak and strong laws; assumes that county-level laws apply in cities and unincorporated places (varies by county), causing significant misclassification; no statistically significant reduction of hip fracture admissions (control condition); effective date varies; study uses American Nonsmokers' Rights Foundation smoking law database and national health outcomes datasets to analyze effect of smokefree laws in various places

Table 8.6*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
Villalbí et al. 2011	• AMI deaths (*ICD-10* CM 055) • 34+ years of age • N = 90,382 • Effective January 1, 2006 • January 2006–December 2007 vs. January 2004–December 2005 • Spain	Pre: 24 Post: 24	• Comparison of age- and sex-specific mortality rates • Poisson regression to calculate annual RR	• First postlaw year: 0.90 (0.88–0.92) – Female: 0.90 (0.87–0.92) – Male: 0.90 (0.88–0.93) • Second postlaw year: 0.86 (0.84–0.88)* – Female: 0.86 (0.84–0.89) – Male: 0.86 (0.83–0.88) • Significant reduction in the RRs of AMI death in both men and women; magnitude of reduction appeared greater among the elderly	Law in workplaces, but not cafes, bars, restaurants, night clubs, or discotheques; antismoking legislation also included law on advertising and reduction in sales outlets; a population-based surveillance system showed that the percentage of employed workers reporting smokefree jobs rose from 54% to 91% after implementation

Table 8.6*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
AMI–workplace and restaurant laws					
Seo and Torabi 2007	• AMI (*ICD-9* 410), confirmed with troponin or CPK excluding past cardiac procedures, no cardiac risk factors (e.g., hypertension or hypercholesterolemia) • N = 37 • August 2001–May 2003 vs. August 2003–May 2005 (same months selected to control for seasonality) • Effective August 1, 2003, bars added January 1, 2005 • Monroe County, Indiana	Pre: 22 Post: 22	• Poisson test • Comparison with Delaware County, Indiana (no law); no significant decrease in admissions observed in Delaware County	• 0.48 (0.24–0.96)* • Decrease of 12 (from 17 to 5 [-21.29, -2.81]) in admissions in the number of nonsmoking patients from prelaw to postlaw period	Public smoking law in effect for all restaurants, retail stores, and workplaces since August 2003; bar provisions only in effect since January 2005 (last 5 months of study period); there was a 69% reduction in AMIs (16 vs. 5) among documented nonsmokers before and after the law; no significant change in number of smokers admitted; the study is limited by unrealistically stringent exclusionary criteria and small sample
Naiman et al. 2010	• AMI (*ICD-9* 410, *ICD-10* I21) • ≥45 years of age • January 1996–May 2006 • Effective May 2006 • Smokefree legislation occurred in 3 phases: smokefree public places and workplaces in October 1999, smokefree restaurants, dinner theaters, and bowling centers except designated smoking rooms in June 2001, smokefree bars, billiard halls, bingo halls, casinos, racetracks except designated smoking rooms in June 2004 • Toronto, Canada	• Pre: 36 • Postphase 2: 36, not included in length of follow-up analysis because the prelaw period did not immediately precede the postlaw phase	• ARIMA on crude rates of hospital admission • Subgroup analyses by age, gender • Comparison with Durham Region and Thunder Bay, 2 Ontario municipalities with no smokefree laws; no significant reductions were observed in control cities	• Phase 2 vs. prelaw: 0.99 (0.92–1.07)*	Legislation required all public places and workplaces to be smokefree and was implemented in 3 phases; the largest declines were seen after the phase of the law affecting restaurants came into effect, including a 17% (14%, 19%) decrease in AMI; crude rates of hospital admissions decreased 39% (38%, 40%) for cardiovascular conditions; no significant reductions were observed in number of hospital admissions attributable to control conditions (cholecystitis, appendicitis, bowel obstruction) in Toronto

Table 8.6*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
Hahn et al. 2011	• AMI (primary discharge diagnosis *ICD-9* 410) • ≥35 years of age • N = 2,692 • May 2004–December 2006 vs. January 2001–April 2004 • Effective April 27, 2004 • Lexington-Fayette County, Kentucky	Pre: 40 Post: 32	• Age-adjusted rates for AMI hospitalizations; Poisson regression and first-order autoregressive time-series model • Age, gender, county-level smoking rate, secular trend, seasonal variation	• Female: 0.77 (0.62–0.96)* • Male: 1.11 (0.91–1.36)*	Smokefree enclosed public places law prohibited smoking in restaurants, bars, bowling alleys, bingo halls, convenience stores, laundry facilities, and other businesses open to the public; buildings not open to the public, including government office buildings or workplaces, were excluded; manufacturing facilities were also excluded; rates for men and women were relatively stable during the 32-month postlaw period; there was a dramatic improvement in air quality in hospitality venues and immediate reduction in hair nicotine among bar and restaurant workers following implementation of the law; within 3 months of implementation, there was a 56% decline in hair nicotine; among AMI hospitalizations, there was an overrepresentation of women in the hospitality industry and a disproportionate number of men working in manufacturing facilities and government worksites not mandated by law; AMI prevalence and hospitalization rate for CVD showed a steady upward trend from 2001–2006 in Kentucky

Table 8.6*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
Hurt et al. 2011	• AMI validated using biomarkers, cardiac pain, and Minnesota coding of the EKG • October 2007–March 2009 vs. July 2000–December 2001 • Effective January 1, 2002 (Ordinance 1: smokefree restaurants) • Effective October 1, 2007 (Ordinance 2: smokefree workplaces) • Olmsted County, Minnesota	Preordinance 1: 18 Postordinance 1: 18	• Age and gender-adjusted rate per 100,000; adjusted HR	• Ordinance 1 vs. no law: 0.90 (0.73–1.10)*	Law was initiated in 2 steps, smokefree restaurants in January 2002, and smokefree workplaces in 2007; AMI rate per 100,000 dropped from 212.3 to 168.7 following the restaurant law (HR = 0.90; 0.73, 1.10; p = 0.30) and from 130.0 to 102.9 following the workplace law (HR = 0.79; 0.63, 0.98; p = 0.04); during this period, the prevalence of hypertension, diabetes, hypercholesterolemia, and obesity either remained constant or increased while the prevalence of smoking among the adults declined by 23%
Sargent et al. 2012	• Acute myocardial infarction (*ICD-10* I21.0-I21.9) excluding recurrent AMI within 28 days of the initial event • ≥30 years of age • N = 39,224 • January 2004–December 2008 • Nationwide: September 1, 2007 • Statewide: varies • Germany	Pre: varies Post: 1	• Rate of hospitalization for AMI; logistic regression and interrupted time series linear regression model • Confounders: age, gender, occupation	• 0.914 (0.878–0.950)* • In the first year after implementation, 449 AMI hospitalizations were prevented	Legislation addressed smoking in federal buildings and the transportation system; private employers were allowed to introduce a total or partial smoking law in workplaces; states were permitted to decide how to limit smoking in the hospitality sector (hotels, restaurants, bars); nonsignificant trend toward decreasing rate of admissions after law; hospitality smoking laws were passed in all states and implemented between August 1, 2007 and July 1, 2008; most states continued to allow smoking in small bars without any food delivery and in separate rooms in large restaurants; a population-based survey revealed a significant decrease of cigarettes smoked in Germany after the law; hospital admissions for control condition fractures increased slightly from 65,100 in 2007 to 66,954 in 2009; bronchitis cases, which might be affected by smokefree laws, declined from 16,900 in 2007 to 15,391 in 2009; hospitalization costs for AMI decreased significantly by 20.1% (16.0–24.2%), or about €5.2 million

Table 8.6*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
AMI–workplace, restaurant, and bar laws					
Sargent et al. 2004	• AMI (primary and secondary diagnoses of *ICD-9* 410, some validated with troponin or CPK) • N = 304 • December 1997–November 2003 • Effective June 5, 2002–December 3, 2002 • Helena, Montana	Pre: same 6 months for 4 pre-years and 1 year after law suspended Post: 6	• Number of admissions during 6-month period the law was in effect compared with the average for the same 6 months in other years by Poisson test • Comparison with number of admissions from surrounding area (not covered by law). No significant change in control area outside Helena	• 0.60 (0.36–0.99)*[c] • Drop in number of admissions of -16 (-31.7, -0.03) from 40 cases to 24	Law prohibited smoking in public and in workplaces but was suspended by a court order after 6 months; analysis did not consider fact that admissions were increasing with time, which biases comparison toward null
Barone-Adesi et al. 2006	• AMI (primary discharge diagnosis *ICD-9* 410) and hospital deaths due to AMI • N = 17,153 • Compared October–December 2004 (before law) and February–June 2005 (after law) with same periods 1 year earlier • Effective January 10, 2005 • Piedmont, Italy	Pre: 3 Post: 6	• Age-standardized rates (using European standardized population)	• (0.97–1.06) • <60 years: 0.89 (0.81–0.98)* – Female: 0.75 (0.58–0.96) – Male: 0.91 (0.82–1.01) • ≥60 years: 1.05 (1.00–1.11) – Female: 1.05 (0.97–1.14) – Male: 1.03 (0.96–1.11)	See entry for Italy (4 regions); no changes from 1 year before for prelaw period; change compared with 1 year earlier for postlaw period; estimated that 1% out of the 11% reduction in AMI is attributable to reduced smoking among smokers rather than passive smoking
Heinz et al. 2007	• AMI (primary diagnosis using *ICD-9* classification) • N = 1,197 • July 1, 2004–June 30, 2005 vs. July 1, 2002–June 30, 2004 • Effective July 1, 2004 • Boise, Idaho	Pre: 24 Post: 12	• Poisson test • Weather, outdoor air quality, time	• All patients: 0.82 (0.66–1.01)*[d] • Nonsmokers: 0.68 (0.53–0.87)[d] • Significant 32% decrease in MI rate among nonsmokers (p = 0.002) and nonsignificant 18% decrease in MI rate among all patients (p = 0.068)	Law on smoking in public buildings, including restaurants; control condition (urinary tract infection) demonstrated nonsignificant increase during study period

Table 8.6*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
Juster et al. 2007	• AMI (primary diagnosis code *ICD-9* 410) • N = 462,396 • ≥35 years of age • January 1995–December 2004 • Effective July 24, 2003 • New York state	Pre: 99 Post: 21	• Multiple regression time series • Age-adjusted (New York population in 2000) • Existence of strong local ordinance, time (linear secular trend), seasonality, county • Analyzed comprehensive laws (smoking prohibited in restaurants, bars, and other hospitality venues) vs. moderate laws (smoking permitting in hospitality venues)	• In absence of preexisting local laws: 0.8004 (0.7985–0.8023)*[f] • In 2004, there were 3,813 fewer hospital admissions for AMI than expected in the absence of the comprehensive smoking law	July 2003 law prohibited smoking in all workplaces, including restaurants and bars; limited statewide restrictions since 1989 limited smoking in many public places, including schools, hospitals, public buildings, and retail stores; local laws varied by county; by 2002, 75% of New Yorkers were subject to strong local laws as well as limited restrictions at the state level implemented in 1989; authors performed analysis to compare effects assuming hypothetical case of no preexisting local laws; no sudden change with law; rate of decline in AMI admissions increased significantly over moderate or no local laws; enactment of a moderate smoking restriction in a county would reduce monthly trend rate in AMI hospital admissions by 0.15 per 100,000/month in that county, and a statewide comprehensive smoking law would reduce AMI hospitalizations by 0.32 per 100,000/ month in all counties; after implementation of the state law, exposure to secondhand smoke declined by nearly 50%; saliva cotinine dropped from 0.078 to 0.041 ng/mL; direct health care cost savings of $56 million in 2004
Dautzenberg 2008	• AMI • <65 years of age • January 2006–February 15, 2008 • Effective February 1, 2007; restaurants, bars, and casinos added January 1, 2008 • France	Complete law: Pre: 24 Post: 1.5; not included in length of follow-up analysis because the prelaw period did not immediately precede the postlaw phase	• Rate per 100,000 admissions	• Complete law: 0.84 (0.77–0.92)*[a]	Smoking ended in public places in February 2007, but restaurants, bars, and casinos were given exceptions until January 2008; law permits ventilated smoking rooms under strict conditions; between January 2007 (before law) and January 2008 (after law), secondhand smoke exposure dropped from 57% to 14%; $PM_{2.5}$ levels also dropped; also report substantial drops in respiratory symptoms among hospitality workers

Table 8.6*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
Lemstra et al. 2008	• AMI (*ICD-10*) • N = 1,689 • July 2004–June 2005 vs. July 2000–June 2004 • Effective July 1, 2004 • Saskatoon, Canada	Pre: 48 Post: 12	• Incidence ratio and CI postlaw compared with prelaw • Age-standardized AMI incidence rate • Stratification was used to test for confounding by age, gender, and previous MI in the unadjusted rates, which were then directly age-standardized to the 2001 Canadian population	• Age-adjusted: 0.87 (0.84–0.90)* • Age-standardized incidence rate fell from 176.1 (165.3–186.8) cases per 100,000 to 152.4 (135.3–169.3) cases per 100,000	Citywide smoking law prohibited smoking or holding lighted tobacco products in any enclosed public area that is open to the public or to which the public is customarily admitted or invited; also applied to outdoor seating areas for restaurants and licensed premises; a previous bylaw prohibited smoking in enclosed government buildings only; 914 of 924 eligible business establishments were inspected by a public health inspector within the first 6 months of the law; only 13 required an initial warning for noncompliance; reinspection required the issuing of only 1 citation during the first year of the law; smoking prevalence in Saskatoon fell from 24.1% in 2003 (95% CI, 20.4–27.7%) to 18.2% in 2005 (15.7–20.9%); smoking in the rest of Saskatchewan Province (which includes Saskatoon) remained stable from 2003 to 2005 at 23.8% (22.6–25.3); 1 year after implementation (July 2005), 79% responded that the "smoking law was a good idea"

Table 8.6*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
Vasselli et al. 2008	• AMI (primary discharge diagnosis *ICD-9* 410) • N = 7,305 • 40–64 years of age • January 10–March 10, 2005 (after law) vs. January–March 2001–2004 (before law) • Effective January 10, 2005 • Italy (4 regions)	Pre: 12 (over 4 years) Post: 2	• Age-standardized rates (using European standard population) • Comparison of observed rate after law with expected value based on linear secular trend for same months during the 4 years before the law went into effect • Age, gender, region	• 0.86 (0.83–0.92)* – Female: 0.98 (0.87–1.11) – Male: 0.85 (0.81–0.91) • 40–44: 0.98 (0.82–1.19) • 45–49: 0.77 (0.68–0.89) • 50–54: 0.74 (0.67–0.85) • 55–59: 0.92 (0.84–1.02) • 60–64: 0.99 (0.88–1.06)	National law prohibited smoking in all indoor public places, including cafes, bars, restaurants, and discotheques; effect largest among young men and people 45–54 years of age; some regional variation; small decreases in smoking prevalence (30.0 to 29.3% in men and 22.5% to 22.1% in women) and consumption (16.7 to 16.3 cigarettes/day for men and 13.7 to 12.4 cigarettes/day for women) led to 7.6% decline in cigarette consumption; fewer than 100 violations in 6,000 checks by police; 90–95% reduction in air nicotine in pubs and discos; 8.9% decline in cigarette sales in 2005
CDC 2009b	• AMI (primary diagnosis code *ICD-9* 410) • N = 4,954 • January 2005–June 2006 ("Phase II") vs. July 2003–December 2004 ("Phase I") vs. January 2002–June 2003 (prelaw) • Effective July 1, 2003 • Pueblo, Colorado	Pre: 18 Post: 36	• Comparison of rate ratios with χ^2 test • Comparison with people living in surrounding Pueblo County (not covered by ordinance) and with nearby El Paso County (which did not have an ordinance); no significant change in surrounding area (1.03; 0.68–1.39) or El Paso County (0.95; 0.87– 1.03)	• Phase II vs. prelaw: 0.59 (0.49–0.70)* – Female: 0.48 (0.36–0.60) – Male: 0.67 (0.52–0.82) • Phase II vs. Phase I: 0.81 (0.67–0.96)	Municipal ordinance ended smoking in enclosed workplaces, including restaurants and bars; assuming all fatal AMIs reached hospital reduced the risk estimate to 0.66 (0.55–0.77) from prelaw to Phase II; rate of AMI hospitalizations decreased from 257 per 100,000 person-years before law to 187 in Phase I and 152 in Phase II

Table 8.6*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
Barnett et al. 2009	• AMI (principal diagnosis code CD-10 I21.0-I22.9), excluding repeat admissions • N = 3,079 • ≥30 years of age • February 2005–December 2006 vs. February 2003–December 2004 (bimonthly intervals) • Effective December 2004 • Christchurch, New Zealand	Pre: 24 Post: 24	• Poisson regression • Gender, age, smoking status, neighborhood social deprivation	• 0.92 (0.86–0.99) – Female: 0.94 (0.84–1.05) – Male: 0.90 (0.82–0.99) • 30–55: 1.15 (0.94–1.40)* • 55–74: 0.86 (0.77–0.97)* • ≥75: 0.89 (0.81–0.98)	2004 law covered all workplaces, including bars and restaurants; earlier restrictions in 1990 prohibited smoking in most workplaces, public interiors (i.e. shops), and one-half of seating in restaurants; higher rates of AMI reduction observed in affluent neighborhoods
Gasparrini et al. 2009	• AMI as principal discharge diagnosis (*ICD-9* 410) or principal death diagnosis (*ICD-9* 410-414) • N = 13,456 • 30–64 years of age • January 2000–December 2004 vs. January 2005–December 2005 • Effective January 10, 2005 • Tuscany, Italy	Pre: 48 Post:12	• Age-standardized rates of annual AMI episodes using European population as reference; Poisson regression analysis of the time series • Age, gender, seasonality, and long-term trend	• Linear trend model: 0.95 (0.89–1.00)* – Female: 0.94 (0.82–1.09) – Male: 0.95 (0.89– 1.01) • Nonlinear trend model: 1.01 (0.93–1.10) – Female: 1.05 (0.87–1.27) – Male: 1.01 (0.92–1.10)	See entry for Italy (4 regions)

Table 8.6*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
Dove et al. 2010	• Death due to AMI (*ICD-10* I21) • N = 26,982 • ≥35 years of age • July 2004–December 2006 vs. January 1999–June 2004 • Effective July 5, 2004 • Massachusetts	Pre: 66 Post: 30	• Daily number of deaths from AMI by city or town; Poisson regression • Long-term trend, season, air particulate matter, influenza, city/town-specific demographic data, prior local smoking law, gender, age • Separate analyses for cities and towns with prior comprehensive local laws vs. those without such prior laws	• No prior local law: 0.90 (0.86–0.95)* • With prior local law: 1.01 (0.92–1.11) • Effect of local law: 0.95 (0.86–1.05) • Overall: 0.93 (0.89–0.97) – Female: 0.90 (0.85–0.96) – Male: 0.95 (0.89–1.01) – 35–64: 0.92 (0.82–1.04) – 65–74: 0.99 (0.89–1.11) – ≥75: 0.91 (0.86–0.96)	State law prohibited smoking in all workplaces, including restaurants and bars; prior to the statewide smoking law, about 25% of the Massachusetts population was covered by a local law; in cities and towns without prior local laws, there was a significant 9.2% decrease in AMI mortality; estimated 270 fewer AMI deaths per year associated with the state law; for cities and towns with no prior local laws, AMI mortality rates decreased by 1.6% (-4.0%, 7.0%) in the first 12 months and 18.6% (13.6%, 23.3%) thereafter
McMillen et al. 2010	• AMI (primary diagnosis *ICD-9* 410) • N = 1,754 • January 1, 2007-June 30, 2009 vs. April 21, 2005-December 31, 2006 • Effective January 1, 2007 • Hattiesburg, Mississippi	Pre: 20 Post: 30	• AMI admissions/day compared with standardized rate prior to implementation • Compared the number of heart attack admissions among people living outside of city limits and not protected by smokefree ordinance; a 3.8% reduction was observed in the Hattiesburg-adjacent control region compared to a 13.4% reduction in Hattiesburg	• 0.87 (0.74–1.01)*[c] • There were 299 heart attack admissions compared to a standardized rate of 345 admissions before law	Smoking law in enclosed workplaces, including restaurants and bars; reductions in AMI admissions resulted in cost savings of $2,367,909 in 2010 dollars

Table 8.6*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
McMillen et al. 2010	• AMI (primary diagnosis *ICD-9* 410) • N = 100 • May 20, 2006–April 7, 2009 vs. July 29, 2004–May 19, 2006 • Effective May 20, 2006 • Starkville, Mississippi	Pre: 22 Post: 35	• AMI admissions/day compared to standardized rate prior to implementation • Compared the number of heart attack admissions among people living outside of city limits and not protected by smokefree ordinance; a 14.8% reduction was observed in the Starkville-adjacent control region compared to a 27.7% reduction in Starkville	• 0.72 (0.48–1.10)*[c] • There were 38 heart attack admissions compared to a standardized rate of 52.57 admissions before law	Smoking law in indoor public places, including restaurants and bars; reductions in AMI admissions resulted in cost savings of $288,270 in 2010 dollars
Moraros et al. 2010	• AMI (primary discharge diagnosis *ICD-9* 410) • ≥18 years of age • N = 10,210 • January 2003–December 2004 vs. January 1999–September 2002 • Effective November 1, 2002 • Delaware	Pre: 45 Post: 24	• Quarterly rates of events; Poisson regression • Seasonal effects • Compared with non-Delaware residents admitted in Delaware for AMI; AMI RR in non-Delaware residents was similar preordinance and postordinance period (0.98; 0.90, 1.08)	• 0.91 (0.87, 0.95)* • Estimated 169 AMI cases prevented in 2 year post-ordinance period	*Delaware Clean Indoor Air Act* of 1994 became comprehensive in 2002 with an amendment to include all enclosed indoor areas accessible to the general public, including restaurants, bars, and casinos; a model including ordinance, season, and linear trend using preordinance and postordinance data showed that the linear trend is not significant (p = 0.557); Delaware Department of Public Health reported 99.6% compliance in bars and restaurants, and the Delaware Department of Labor reported 100% compliance in other workplaces in first year

Table 8.6*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
Naiman et al. 2010	• AMI (*ICD-9* 410, *ICD-10* I21) • ≥45 years of age • January 1996–May 2006 • Effective May 2006 • Toronto, Canada	Pre: 36 Post phase 3: 36; not included in length of follow-up analysis because the prelaw period did not immediately precede the postlaw phase	• ARIMA on crude rates of hospital admission • Subgroup analyses by age, gender • Comparison with Durham Region and Thunder Bay, 2 Ontario municipalities with no smokefree laws; no significant reductions were observed in control cities	• Phase 3 vs. pre: 0.81 (0.75–0.88)*[c]	Legislation required all public places and workplaces to be smokefree and was implemented in 3 phases; the largest declines were seen after the phase of the law affecting restaurants came into effect, including a 17% (14%, 19%) decrease in AMI; crude rates of hospital admissions decreased 39% (38%, 40%) for cardiovascular conditions; no significant reductions were observed in number of hospital admissions attributable to control conditions (cholecystitis, appendicitis, bowel obstruction) in Toronto; smokefree legislation occurred in 3 phases: smokefree public places and workplaces in October 1999; smokefree restaurants, dinner theaters, and bowling centers except designated smoking rooms in June 2001; smokefree bars, billiard halls, bingo halls, casinos, racetracks except designated smoking rooms in June 2004
Sims et al. 2010	• AMI (primary diagnosis code *ICD-10* I21) excluding repeat admissions within 28 days • ≥18 years of age • N = 342,361 • July 2007–September 2008 vs. July 2002–May 2007 • Effective July 1, 2007 • England	Pre: 60 Post: 15	• Interrupted time series design with hospital episode statistics data; segmented Poisson regression • Long-term trend, temporal fluctuations (temperature, week of year, holidays), population size • Stratified by age and gender	• 0.98 (0.96–0.99)* • <60 years: – Female: 0.98 (0.92–1.03) – Male: 0.97 (0.94–0.99) • ≥60 years: – Female: 0.96 (0.94–0.99) – Male: 0.96 (0.95–0.99) • About 1,600 emergency admissions for AMI prevented in 12 months	Law affected bars and restaurants most; some of these venues went smokefree before July 1 in preparation for the law, which may create a less marked decrease; no evidence of a change in the slope of the AMI trend line after the legislation; prior to the law, many public places and workplaces were already smokefree; in the year before implementation, 55% of employed adults already worked in smokefree environments; subgroup analysis shows significant 3.07% drop in admissions in 60+ group ($p = 0.001$) and 3.46% drop in men <60 ($p < 0.01$)

Table 8.6*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
Barone-Adesi et al. 2011	• AMI (*ICD-9* 410) • Primary analysis was for ACEs (AMI and other acute and subacute IHD) • N = 936,519 (all ACEs) • January 2005-November 2006 vs. January 2002–December 2004 • Effective January 10, 2005 • Italy (20 regions)	Pre: 36 Post: 24	• Admission rates; Poisson test with mixed effect regression models with fixed coefficients describing the national trend and random coefficients describing region-specific deviations • Seasonality, long term trends • Separate analyses conducted based on age, gender	• <70 years: 0.97 (0.95–0.99)* – Female: 0.98 (0.94–1.02) – Male: 0.97 (0.95–0.99) • ≥70 years: 1.01 (0.99–1.04) – Female: 1.02 (0.99–1.04) – Male: 1.00 (0.98– 1.03)	See entry for Italy (4 regions); the observed reduction was stable over the study period, similar in different geographic areas, and stronger among young people; no evidence of a gradual effect over time, as there was no change in the underlying trend in admissions for ACEs after law
Bonetti et al. 2011b	• AMI (defined as detectable troponin in a clinical setting consistent w/ myocardial ischemia, identified by *ICD-10* codes) undergoing coronary angiography (may be viewed as representative of overall incidence in the region) • N = 842 • March 2006–February 2008 vs. March 1, 2008 • Effective March 2008–February 2010 • Graubünden, Switzerland	Pre: 24 Post: 24	• AMI incidence • Air quality (PM_{10} and NO_2), sales of lipid lowering drugs • Separate analyses based on resident status, gender, smoking status, medical history • Compared with Lucerne, a nearby region without smokefree law; AMI incidence increased in Lucerne during the postlaw period in Graubünden	• 0.79 (0.69–0.90)*[a] • The number of AMI patients decreased 21% in the 2 years before vs. 2 years after law • For each of the 4 years of the study, incidence rate of AMI was 89.4 (pre), 93.8 (pre), 69.8 (1 year post), and 68.8 (2 years post) per 100,000 residents	Smoking law in public places, including cafes, bars, and restaurants; based on the large number of visitors, the population of the Canton of Graubünden may almost double during the holiday season, hence the resident vs. nonresident analysis; the most pronounced reduction in AMI was in patients with documented coronary artery disease; female AMI patients showed a more pronounced drop in the second year of the law compared to the first, while male patients experienced a diminished magnitude of decrease; changes in outdoor air pollution or use of lipid-lowering drugs (potential confounders) did not substantially contribute to the decrease in the incidence of AMI

Table 8.6*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
Bruckman and Bénnett 2011	• AMI (principal discharge diagnosis *ICD-9* 410) • January 2005–April 2007 vs. May 2007–December 2009 • Effective May 2007 • Ohio	Pre: 28 Post: 32	• Age- and gender-adjusted discharge rate per 1,000 (converted to per 100,000); mixed linear models with a varying covariance structure to determine if rates decreased yearly; spline polynomial functions to determine inflection point in monthly rate data • Age, gender, linear trend, seasonality	• 0.96 (0.95–0.98)*[a] • AMI discharge rates dropped from 198 per 100,000 in 2005 to 168 per 100,000 in 2009	Law prohibits smoking in a public place or a place of employment; inflection point identified as June 2007, 1 month after implementation; average decrease in MI discharge of 7 per 100,000 each year from 2005 to 2009; conservative estimate of $737,782 in hospital stay costs in first year after law (estimate does not account for physician fees); direct system savings of $1.1 million from 69 cases prevented by smoking law
Bruintjes et al. 2011	• AMI (primary diagnosis *ICD-9* 410) and biomarker confirmation (troponin I or CKMB) • N = 706 • January 2004–June 2006 vs. July 2002–November 2003 • Effective December 2003 • Greeley, Colorado	Pre: 17 Post: 30	• Population-adjusted monthly hospitalization rates; Poisson regression • Seasonality (nonsignificant), linear trends (nonsignificant), smoking status, type of MI • Compared with adjacent area immediately surrounding Greeley; a smaller, nonsignificant decrease was noted in the area immediately surrounding Greeley (0.83; 0.61, 1.14); comparison of RR reductions between Greeley and the control area was not significant (p = 0.48)	• 0.73 (0.59–0.90)*	Law prohibits smoking in all places of public assembly, including restaurants, bars, bowling alleys, bingo halls, and outdoor public gathering places where seating is provided; smoking law underwent various legal challenges through November 2004, during which compliance was variable; significant reductions in AMI among smokers (0.44; 0.29, 0.65); nonsignificant reduction among nonsmokers (0.86; 0.67, 1.09); smokers from control area also experienced a significant decrease (0.58; 0.35, 0.97) that was not significantly different from Greeley smokers (p = 0.38); reduction in events was similar in patients with STEMI (0.79; 0.34, 1.83) and NSTEMI (0.66; 0.37, 1.17); linear trends were tested and not significant
Di Valentino et al. 2011	• ST-elevation myocardial infarction (*ICD-10*) • N = 1,272 • 2007–2008 vs. 2004–2006 • Effective April 2007 • Canton Ticino, Switzerland	Pre: 36 Post: 24	• Comparison of annual frequency of hospitalizations due to STEMI	• 0.79 (0.70–0.88)*[b] • 22.4% (p <.0001) and 20.6% (P <.0002) reduction in hospitalizations during first and second postlaw years, respectively	Smokefree public places, including restaurants, bars, and discos; smoking rooms permitted; this study population overlaps with that of another study also conducted in Ticino examining rates of STEMI (a subset of Acute coronary syndrome) following the law

Table 8.6*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
Herman et al. 2011	• AMI (primary diagnosis *ICD-9* 410.x0) • N = 5,025 (counties without previous laws) • May 2007–May 2008 vs. January 2004–April 2007 • Effective May 1, 2007 • Arizona	Pre: 40 Post: 13	• Rate of admissions per 100,000 annually • Poisson regression • Seasonality, population, annual linear trend • Separate analyses for counties with preexisting smokefree laws vs. those without such laws	• 0.84 (0.60–0.93)*[e] • Estimated 159 fewer cases of hospital admissions (-13%) for AMI than expected for counties with no preexisting law	Law ended smoking in all enclosed workplaces, including bars and restaurants; cost-savings analysis estimates $16.8 million for AMI, unstable angina, acute stroke, and acute asthma in 13 months after law in non-law counties ($7.2 million savings for AMI alone); no change in rates of control diseases (acute appendicitis, kidney stones, acute cholecystitis, and ulcers) pre- and postlaw
Hurt et al. 2011	• AMI validated using biomarkers, cardiac pain, and Minnesota coding of the ECG • October 2007–March 2009 vs. July 2000–December 2001 • Effective January 1, 2002 (Ordinance 1: smokefree restaurants) • Effective October 1, 2007 (Ordinance 2: smokefree workplaces) • Olmsted County, Minnesota	Preordinance 2: 18 Postordinance 2: 18; not included in length of follow-up analysis because the prelaw period did not immediately precede the postlaw phase	• Age and gender-adjusted rate per 100,000; adjusted HR	• Ordinance 2 vs. no law: 0.55 (0.44–0.68)*	Alhough the law was initiated in 2 steps (smokefree restaurants in January 2002 and smokefree workplaces in 2007), this study was included in the meta-analysis because authors compared the period before any law to the period after full implementation, thus capturing the true effect of the law; AMI rate per 100,000 dropped from 212.3 to 168.7 following the restaurant law (HR 0.90; 0.73, 1.10; p = 0.30) and from 130.0 to 102.9 following the workplace law (0.79; 0.63, 0.98; p = 0.04); during this period, the prevalence of hypertension, diabetes, hypercholesterolemia, and obesity either remained constant or increased while the prevalence of smoking among the adults declined by 23%
North Carolina Tobacco Prevention and Control Branch 2011	• AMI (diagnosis code *ICD-9* 410.x1 to 410.x0) • N = 24,848 • ≥18 years of age • January 2010–December 2010 vs. January 2008–December 2009 • Effective January 1, 2010 • North Carolina	Pre: 24 Post: 12	• Rate of emergency visits for AMI; Poisson regression • Age, gender, Christmas holidays, time, average weekly temperature, log-transformed weekly flu rates, week of year	• 0.79 (0.75–0.83)*	Law prohibits smoking in bars, restaurants, government buildings, and vehicles; projected cost savings $3.3–4.8 million from AMIs prevented

Table 8.6*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
Cronin et al. 2012	• AMI, diagnosed in hospital by physician using troponin T or I, allowing repeat admissions • Primary data set: N = 3,041 • Secondary data set: N = 3,195 • ≥18 years of age • Primary data set: April 2004–March 2007 vs. March 2003–March 2004 • Secondary data set: July 2003–March 2004 vs. April 2004–June 2007 • Effective March 29, 2004 • Cork and Kerry Counties, Ireland	Primary: Pre: 13 Post: 36 Secondary: Pre: 9 Post: 39	• AMI admissions and rate per 100,000; Poisson regression • Linear time trend • Sensitivity analyses were undertaken by gender, smoking status, and type of Acute coronary syndrome • According to mortality data, there was no change in all cause mortality and overall 6.5% decrease in deaths from circulatory causes in Cork and Kerry counties, and so results were not attributable to changes in coronary death patterns outside of hospital	• All AMI: 0.84 (0.76–0.91)*[b] • NSTEMI: 0.80 (0.71–0.90)[b] • STEMI: 0.92 (0.78–1.07)[a] • Estimates derived from secondary data set	Primary analysis was for overall Acute coronary syndrome; see description of law in entry for Ireland; the first year's reduction in admissions for Acute coronary syndrome was due to fewer cases among men and current smokers; the third year's reduction in admissions for Acute coronary syndrome was due to fewer cases among men, current smokers, and never smokers; increased effect on Acute coronary syndrome over time evidenced by 12% decrease in year 1 and 13% decrease in year 3; this paper supersedes an abstract of the same study used in the 2009 meta-analysis
Kent et al. 2012	• AMI • 20–70 years of age • April 2004–March 2006 vs. April 2002–March 2004 • Effective March 29, 2004 • Ireland	Pre: 24 Post: 24	• Change in emergency hospital admissions for AMI • Population, weather, pollution, and influenza • Stratified by age and gender	• 0.89 (0.70–1.13)*	March 2004 law applied to workplaces (including bars and restaurants); prior to this law, smoking had been outlawed in public buildings, hospitals, public pharmacies, schools, banking halls, cinemas, restaurant kitchens, part of all restaurants, public transport aircraft and buses, and some trains; significant reduction in emergency cardiopulmonary admissions in the 2 years following the smoking law (RR: 0.87; 0.78–0.98)

Table 8.6*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
Sebrié et al. 2013	• AMI (primary diagnosis code *ICD-10* I21.0-I21.9); noncountry residents and patients with AMI after a coronary angioplasty or bypass, or as a complication of another disease (secondary diagnosis) were excluded • N = 7,949 • March 2006–February 2008 vs. March 2004–February 2006 • Effective March 2006 • Uruguay	Pre: 24 Post: 24	• Number of AMI hospitalizations per month; multiple linear regression and negative binomial regression • Seasonal variation, population changes, time trend • Stratified by public vs. private hospital, gender, age	• 0.81 (0.72–0.89)* • 2 years after the smokefree policy adoption in enclosed public places and workplaces, hospital admissions for AMI were reduced by 22% • Reductions in monthly AMI admissions between 15% and 22% were observed for private hospitals, men, women, and people 40–65 years of age and over 65; there was a nonsignificant trend toward fewer monthly AMIs in people under 40	Law prohibited smoking in all indoor public places and workplaces including restaurants and bars; no evidence that overall effect grew or fell over time following the law; in public hospitals only, AMI trend increased before the law and decreased after the law; study covered 37 hospitals, capturing 79% of the Uruguay population; air particulate matter ($PM_{2.5}$) decreased dramatically (210 to 18 $\mu m/m^3$) and adults reported decreased exposure to secondhand smoke 1 year after implementation, suggesting a high level of compliance

Table 8.6*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
Acute coronary syndrome–workplace only laws					
Ferrante et al. 2012	• Acute coronary syndrome (*ICD-10* I20–I25) • N = 3,307 • ≥18 years of age • October 2006–December 2008 vs. January 2004–September 2006 • Effective October 2006 • Buenos Aires, Argentina	Pre: 33 Post: 15	• Monthly age-adjusted admission rates; multiple linear regression analysis using standard methods for interrupted time series analysis • Age, secular trends, seasonality	• 0.92 (0.87–0.97)*[a] • 5.3% reduction in admissions in year before vs. year after law • Implementation not significantly associated with immediate change: increase of 1.74 admissions per 100,000 (-1.42, 4.92)	Law ended smoking in workplaces but allowed for designated smoking areas up to 30% in bars and restaurants if >100 m^2; no significant change in trend after law: increase of 0.01 admissions per 100,000 per month (-0.12, 0.14); Buenos Aires served as a control for Santa Fe, to compare partial smoking laws with comprehensive smoking laws; data from Buenos Aires suggest the ineffectiveness of the implementation of partial smokefree legislation; nonsignificant decrease in smoking prevalence from 27.4% 1 year before law to 26.1% 3 years after law; self-reported secondhand smoke exposure decreased from 52.9% to 31.7%

Table 8.6*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
Acute coronary syndrome–workplace and restaurant laws					
Gupta et al. 2011	• Acute coronary syndrome (primary diagnostic code *ICD-9* 410, 411.1, 411.81, 411.89, 413.0, 413.1, 413.9; an analysis performed for AMI yielded similar results that were not shown • N = 14,245 • ≥18 years of age • January 2004–September 2008 vs. January 2000–December 2003 • Effective January 1, 2004 • Kanawha County, West Virginia	Pre: 48 Post: 57	• Age-adjusted Acute coronary syndrome hospital admission rates; Poisson regression • Age, gender, year, season, tobacco use, diabetes	• 1.02 (0.92–1.12)* • Age-adjusted Acute coronary syndrome hospitalization rates decreased 37% during entire study period; no additional significant change due to removal of smoking areas in restaurants after accounting for the sustainable decline of Acute coronary syndrome hospitalizations since the 2002 revision • Stratification showed that the observed decline was significant only among nonsmokers	Effective May 22, 1995, a modest smoking regulation was enacted prohibiting smoking in all enclosed public places; restaurants were allowed to designate up to 50% of their seating capacity as smoking areas; on July 20, 2000 the law was modified to increase penalties for violations; on April 3, 2003, a revised regulation prohibited smoking in all restaurants and at most worksites; however, to come into compliance, the regulation allowed several businesses an exemption until January 1, 2004; the likelihood of hospital admissions for Acute coronary syndrome was significantly lower among nonsmokers, people without diabetes, and women; incidence of hospital admissions for Acute coronary syndrome decreased significantly by 6% per year (CI 4–8%) throughout the study; among male smokers, there was a significant decline in time trend (7%; 0.4%, 12%) in admission rates after 2004; smoking rate decreased from 32% to 24% from 2002 to 2008, a nonsignificant change; in conjunction with steady tobacco sales, authors dismiss the notion that changes in Acute coronary syndrome can be attributed to a decline in smoking

Table 8.6*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
ACE (acute coronary events)–workplace, restaurant, and bar laws					
Pell et al. 2008	• Acute coronary syndrome (detectable troponin after emergency admission for chest pain, *ICD-10* I21) • N = 5,919 • April 2006–March 2007 vs. June 2005–March 2006 • April 2006 • Scotland	Pre: 10 Post: 10	• χ^2 and test for trend • Stratified on gender and age (men ≤55; women ≦65) • Used data from England as historical control; admissions for Acute coronary syndrome in England dropped 4% during a similar period compared to 17% in Scotland	• 0.83 (0.82–0.84)*	Legislation prohibited smoking in all enclosed public places; 17% drop overall, 14% among smokers, 19% among former smokers, 21% among nonsmokers; 67% of the decrease in Acute coronary syndrome involved nonsmokers; larger risk reductions in older people; decrease in monthly admissions became more pronounced over time after implementation of legislation (p = 0.02); percentage of people who had never smoked who reported no exposure to secondhand smoke increased from 57% to 78% (p <0.001); there was a reduction in geometric mean serum cotinine from 0.68 to 0.56 ng/mL (p <0.001)
Gudnason et al. 2009	• Patients undergoing coronary angiography for Acute coronary syndrome, defined as clinical symptoms of unstable coronary artery disease (chest pain at rest) as well as at least one of the following: (1) elevated cardiac enzymes, (2) ischemic changes on the EKG at rest, or (3) an abnormal exercise stress test during the same unstable episode • N = 535 • June 2007–October 2007 vs. January 2007–May 2007 • Effective June 1, 2007 • Iceland	Pre: 5 Post: 5	• Comparison of Acute coronary syndrome incidence before vs. after smoking law	• 0.83 (0.68–1.02)*[c] • Number of events before vs. after law, given in PowerPoint presentation based on abstract (http://spo.escardio.org/eslides/view.aspx?eevtid=33&id=978) • Nonsmokers demonstrated 21% reduction in Acute coronary syndrome incidence among men (p <0.05) but no significant effect observed among women; in the total population, there was a nonsignificant trend of a 20% reduction in Acute coronary syndrome (p = 0.08)	Legislation prohibited smoking in public places; initial analysis considered only nonsmoking patients; numbers for overall population obtained by personal communication with Dr. Gudnason

Table 8.6*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
Di Valentino et al. 2010	• Acute coronary syndrome (*ICD-10*) • N = 2,426 • 2007–2008 vs. 2005–2006 • April 2007 • Canton Ticino, Switzerland	Pre: 24 Post: 24	• Comparison of annual frequency of hospitalizations due to Acute coronary syndrome	• 0.82 (0.76–0.89)*[b] • 15.5% (p <0.001) and 14.7% (p <0.001) reduction in hospitalizations during first and second postlaw years, respectively	Smokefree public places, including restaurants, bars, and discos; smoking rooms permitted; this study population overlaps with that of another study also conducted in Ticino examining rates of STEMI (a subset of Acute coronary syndrome) following the law
Ferrante et al. 2012	• Acute coronary syndrome (*ICD-10* I20-I25) • N = 2,889 • ≥18 years of age • August 2006–December 2008 vs. January 2004–July 2006 • August 2006 • Santa Fe, Argentina	Pre: 31 Post: 17	• Monthly age-adjusted admission rates; multiple linear regression analysis using standard methods for interrupted time series analysis • Age, secular trends, seasonality	• 0.65 (0.59–0.70)*[a] • 20.8% reduction in admissions in year before vs. year after law • Implementation resulted in immediate change of -2.5 admissions per 100,000 (-4.74, -0.26)	100% smokefree law in all enclosed public places; law also ended tobacco ads, promotion, and sponsorship; persistent change after law of 0.26 fewer admissions per 100,000 per month (-0.39, -0.13); Buenos Aires served as a control for Santa Fe, to compare partial smoking laws with comprehensive smoking laws; data from Buenos Aires suggest the ineffectiveness of the implementation of partial smokefree legislation; high levels of compliance, per National Tobacco Control Program; nonsignificant decrease in smoking prevalence from 27.3% 1 year before law to 26.6% 3 years after law; self-reported secondhand smoke exposure decreased from 51.6% to 31.7%

Table 8.6*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
ACE (acute coronary events)–workplace, restaurant, and bar laws					
Cesaroni et al. 2008	• ACEs, including AMI (ICD-9 410) and "other acute and subacute forms of IHD" (ICD-9 411). Cases were included with principal diagnosis of AMI or secondary diagnosis of AMI when principal diagnosis indicated AMI complications (ICD-9 427.1, 427.41, 427.42, 427.5, 428.1, 429.5, 429.6, 429.71, 429.79, 429.81, 518.4, 780.2, 785.5, 414.10, 423.0) • Out-of-hospital deaths from IHDs (ICD-9 410-414) if no evidence of hospitalization for coronary causes in the previous 28 days or any cause in the last 2 days • N = 2,136 • 35–84 years of age • January 2005–December 2005 vs. January 2000–December 2004 • Effective January 10, 2005 • Rome, Italy	Pre: 48 Post: 12	• Age standardized rates (based on European standard population) • Poisson regression on number of daily events after January 10, 2005, compared with before that date • Separate analyses done for out-of-hospital deaths and hospitalizations and an analysis of incident cases only • Age, gender, PM_{10} air pollution, flu epidemics, holidays, temperature, secular trend, all-cause hospitalizations, SES	• 35–64: 0.89 (0.85–0.93)* • 65–74: 0.92 (0.88–0.97) • 75–84: 1.02 (0.98–1.07) • Adjusted for time trends and all-cause hospitalization rates: – 35–64: 0.94 (0.88–1.01) – 65–74: 0.90 (0.84–0.96)	See entry for Italy (4 regions); no effect in 75–84 year olds; protective effect of law seemed stronger in low SES areas; prevalence of smoking decreased from 34.9% to 30.5% in men and from 20.6% to 20.4% in women; cigarette sales decreased in Rome by 5.5% in 2005 compared to 2004; estimated reduction in coronary events attributable to changes in active smoking habits was <2%; concentrations of urinary cotinine among nonsmoking workers decreased from 17.8 to 5.5 mg/mL at 3 months postlaw and 3.7 mg/mL 12 months postlaw

Table 8.6*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
Barone-Adesi et al. 2009	• ACE (ICD-9 410, 411) • January 2005–June 2007 vs. January 2001–December 2004 • Effective January 2005 • Piedmont, Italy	Pre: 48 Post: 30	• Poisson regression; standard methods for interrupted time-series adopted to assess the role of immediate and gradual effects of the smokefree law • Long-term trends, seasonality, age, day of the week	• <70: 0.94 (0.90–0.97)* • ≥70: 1.00 (0.97–1.03) • Weekends: 0.87 (0.80–0.93) • Weekdays: 0.96 (0.92–1.00)	See entry for Italy (4 regions); the observed reduction in the number of admissions for ACEs started in the same month in which the law came into effect and remained evident for the entire study period; no change (p = 0.51) in the underlying trend was found; this study population overlaps with that of another study also conducted in Piedmont examining rates of AMI (a subset of ACE) following the Italian national law

Table 8.6*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
CHD–workplace, restaurant, and bar laws					
Barone-Adesi et al. 2011	• Non-AMI acute and subacute forms of CHD (ICD-9 411) • Primary analysis was for ACEs (AMI and other acute and subacute CHD) • N = 936,519 (all ACEs) • January 2005–November 2006 vs. January 2002–December 2004 • January 10, 2005 • Italy (20 regions)	Pre: 36 Post: 24	• Admission rates; Poisson test with mixed effect regression models with fixed coefficients describing the national trend and random coefficients describing region-specific deviations • Seasonality, long-term trends • Separate analyses conducted based on age, gender	• <70: 0.95 (0.93–0.98)* – Female: 0.92 (0.88–0.98) – Male: 0.96 (0.93–0.99) • ≥70: 0.98 (0.96–1.00) – Female: 0.98 (0.95–1.01) – Male: 0.97 (0.94–1.01)	See entry for Italy (4 regions); the observed reduction was stable over the study period, similar in different geographic areas, and stronger among young people; no evidence of a gradual effect of the law, as there was no change in the underlying trend in admissions for ACEs after law

Source: Adapted from Tan and Glantz 2012 with permission from Wolters Kluwer Health, © 2012.
Note: Observed risk is presented as a risk ratio unless otherwise specified. If number of events is N/A, then events were recorded as rates and absolute counts are not available. **ACE** = acute coronary event; **AMI** = acute myocardial infarction; **ARIMA** = autoregressive integrated moving average; **CDC** = Centers for Disease Control and Prevention; **CHD** = coronary heart disease; **CI** = confidence interval; **CKMB** = creatine kinase muscle-brain isoenzyme; **CPK** = creatine phosphokinase; **CVD** = cardiovascular disease; **EKG** = electrocardiogram; **HR** = hazard ratio; **ICD-10-CM** = International Classification of Diseases-10-Clinical Modification; **mg/mL** = milligram per milliliter; **ng/mL** = nanogram per milliliter; **NO_2** = nitrogen dioxide; **person-years** = the sum of the number of years that each member of a population has been smoking; **$PM_{2.5}$** =particulate matter <2.5 micrometers in diameter; **PM_{10}** = particulate matter <10 micrometers in diameter; **RR** = relative risk; **SES** = socioeconomic status; **STEMI** = ST segment elevation myocardial infarction; **$\mu m/m^3$** = microgram per cubic meter.
[a]RR and CI calculated using negative binomial regression with model including effect of law and seasonality (if applicable).
[b]RR and CI calculated by Monte Carlo simulation run 100,000 times; rate ratio calculated by dividing postlaw rates with mean prelaw rates.
[c]RR and CI calculating using number of events before vs. after law.
[d]CI calculated from p-value presented in paper.
[e]RR and CI computed using Poisson regression with model described in paper for counties with no prior law.
[f]CI obtained from communication with author of paper.
*Estimate used in meta-analysis.

Table 8.7*S* Detailed description of studies on smokefree laws and cerebrovascular accidents

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
Stroke–workplace only laws					
Dautzenberg 2008	• Stroke • <66 years of age • January 2006–February 15, 2008 • February 1, 2007; restaurants, bars, and casinos added effective January 1, 2008 • France	Partial law: Pre: 13 Post: 12.5	• Rate per 100,000 admissions	• Partial law: 0.96 (0.8–1.03)*[a]	Smoking ended in public places in February 2007, but restaurants, bars, and casinos were given exceptions until January 2008; law permits ventilated smoking rooms under strict conditions; between January 2007 (before law) and January 2008 (after law), secondhand smoke exposure dropped from 57% to 14%; $PM_{2.5}$ levels also dropped; also report substantial drops in respiratory symptoms among hospitality workers
Naiman et al. 2010	• Stroke (*ICD-9* 433, 434, 435, 436; *ICD-10* I63, I64, I65, I66, G45, G46) • 45+ years of age • January 1996–May 2006 • Effective May 2006 • Toronto, Canada	Pre: 36 Post phase 1: 24	• ARIMA on crude rates of hospital admission • Subgroup analyses by age, gender • Comparison with Durham Region and Thunder Bay, 2 Ontario municipalities with no smokefree laws; no significant reductions were observed in control cities	• Phase 1 vs. prelaw: 0.91 (0.80–1.0)*	Legislation required all public places and workplaces to be smokefree and was implemented in 3 phases; crude rates of hospital admissions decreased 39% (38%, 40%) for cardiovascular conditions; no significant reductions were observed in number of hospital admissions attributable to control conditions (cholecystitis, appendicitis, bowel obstruction) in Toronto; smokefree legislation occurred in 3 phases: smokefree public places and workplaces in October 1999; smokefree restaurants, dinner theaters, and bowling centers except designated smoking rooms in June 2001; smokefree bars, billiard halls, bingo halls, casinos, racetracks except designated smoking rooms in June 2004

Table 8.7*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
Stroke–workplace and restaurant laws					
Naiman et al. 2010	• Stroke (*ICD-9* 433, 434, 435, 436; *ICD-10* I63, I64, I65, I66, G45, G46) • ≥45 years of age • January 1996–May 2006 • Effective May 2006 • Toronto, Canada	Pre: 36 Post phase 2: 36; not included in length of follow-up analysis because the prelaw period did not immediately precede the postlaw phase	• ARIMA on crude rates of hospital admission • Subgroup analyses by age, gender • Comparison with Durham Region and Thunder Bay, 2 Ontario municipalities with no smokefree laws; no significant reductions were observed in control cities	• Phase 2 vs. pre: 0.76 (0.68–0.85)*	Legislation required all public places and workplaces to be smokefree and was implemented in 3 phases; crude rates of hospital admissions decreased 39% (38%, 40%) for cardiovascular conditions; no significant reductions were observed in number of hospital admissions attributable to control conditions (cholecystitis, appendicitis, bowel obstruction) in Toronto; smokefree legislation occurred in 3 phases: smokefree public places and workplaces in October 1999; smokefree restaurants, dinner theaters, and bowling centers except designated smoking rooms in June 2001; smokefree bars, billiard halls, bingo halls, casinos, racetracks except designated smoking rooms in June 2004

Table 8.7*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
Stroke–workplace, restaurant, and bar laws					
Juster et al. 2007	• Stroke (primary diagnosis code *ICD-9* 410.00-410.99) • N = 584,833 • ≥35 years of age • January 1995–December 2004 • Effective July 24, 2003 • New York state	Post: 21 Pre: 99	• Multiple regression time series • Age-adjusted (New York population in 2000) • Existence of strong local ordinance, time (linear secular trend), seasonality, county • Analyzed comprehensive laws (smoking prohibited in restaurants, bars, and other hospitality venues) vs. moderate laws (smoking permitting in hospitality venues)	• No significant negative association between the stroke admission rate and moderate or comprehensive restrictions on smoking • No estimate was available for stroke rates in places without local smokefree laws prior to the state law, and so this study was excluded from the analysis for stroke	July 2003 law prohibited smoking in all workplaces including restaurants and bars; limited statewide restrictions since 1989 limited smoking in many public places, including schools, hospitals, public buildings, and retail stores; local laws varied by county; by 2002, 75% of New Yorkers were subject to strong local laws, as well as limited restrictions at the state level implemented in 1989; authors performed analysis to compare effects assuming hypothetical case of no pre-existing local laws; change in monthly admission trend rate not significantly different from null; after implementation of the state law, exposure to secondhand smoke declined by nearly 50%; saliva cotinine dropped from 0.078 to 0.041 ng/mL
Dautzenberg 2008	• Stroke • <66 years of age • January 2006–February 15, 2008 • Effective February 1 2007; restaurants, bars, and casinos added January 1, 2008 • France	Complete law: Pre: 24 Post: 1.5; not included in length of follow-up analysis because the prelaw period did not immediately precede the postlaw phase	• Rate per 100,000 admissions	• Complete law: 0.83 (0.77–0.91)*[a]	Smoking ended in public places in February 2007, but restaurants, bars, and casinos were given exceptions until January 2008; law permits ventilated smoking rooms under strict conditions; between January 2007 (before law) and January 2008 (after law), secondhand smoke exposure dropped from 57% to 14%; $PM_{2.5}$ levels also dropped; also report substantial drops in respiratory symptoms among hospitality workers

Table 8.7*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
Naiman et al. 2010	• Stroke (*ICD-9* 433, 434, 435, 436; *ICD-10* I63, I64, I65, I66, G45, G46) • ≥45 years of age • January 1996–May 2006 • Effective May 2006 • Toronto, Canada	Pre: 36 Post phase 3: 36; not included in length of follow-up analysis because the prelaw period did not immediately precede the postlaw phase	• ARIMA on crude rates of hospital admission • Subgroup analyses by age, gender • Comparison with Durham Region and Thunder Bay, 2 Ontario municipalities with no smokefree laws; no significant reductions were observed in control cities	• Phase 3 vs. pre: 0.63 (0.56–0.71)*[b]	Legislation required all public places and workplaces to be smokefree and was implemented in 3 phases; crude rates of hospital admissions decreased 39% (38%, 40%) for cardiovascular conditions; no significant reductions were observed in number of hospital admissions attributable to control conditions (cholecystitis, appendicitis, bowel obstruction) in Toronto; smokefree legislation occurred in 3 phases: smokefree public places and workplaces in October 1999; smokefree restaurants, dinner theaters, and bowling centers except designated smoking rooms in June 2001; smokefree bars, billiard halls, bingo halls, casinos, racetracks except designated smoking rooms in June 2004
Herman et al. 2011	• Acute stroke (*ICD-9* 430-434.xx, 436.xx, 437.1x) • N = 6,018 (counties without previous laws) • May 2007–May 2008 vs. January 2004–April 2007 • Effective May 1, 2007 • Arizona	Pre: 40 Post: 13	• Rate of admissions per 100,000 annually • Poisson regression • Seasonality, population, annual linear trend • Separate analyses for counties with preexisting smokefree laws vs. those without such laws	• 0.86 (0.79–0.96)*[c]	Law ended smoking in all enclosed workplaces, including bars and restaurants; cost-savings analysis estimates $16.8 million in savings for AMI, unstable angina, acute stroke, and acute asthma in 13 months after law in non-law counties ($4.9 million for acute stroke alone); no change in rates of control diseases (acute appendicitis, kidney stones, acute cholecystitis, and ulcers) pre- and postlaw

Table 8.7*S* **Continued**

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
Kent et al. 2012	• Stroke • 20–70 years of age • April 2004–March 2006 vs. April 2002–March 2004 • Effective March 29, 2004 • Ireland	Pre: 24 Post: 24	• Change in emergency hospital admissions for stroke • Population, weather, pollution, and influenza • Stratified by age and gender	• 0.93 (0.73–1.20)*	March 2004 law applied to workplaces (including bars and restaurants); prior to this law, smoking had been outlawed in public buildings, hospitals, public pharmacies, schools, banking halls, cinemas, restaurant kitchens, part of all restaurants, public transport aircraft and buses, and some trains; significant reduction in emergency cardiopulmonary admissions in the 2 years following the smoking law (RR 0.87, 0.78–0.98)

Table 8.7*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
TIA–workplace, restaurant, and bar laws					
Kent et al. 2012	• TIA • 20–70 years of age • April 2004–March 2006 vs. April 2002–March 2004 • Effective March 29, 2004 • Ireland	Pre: 24 Post: 24	• Change in emergency hospital admissions for transient ischemic attack • Population, weather, pollution, and influenza • Stratified by age and gender	• 1.00 (0.70–1.42)*	March 2004 law applied to workplaces (including bars and restaurants); prior to this law, smoking had been outlawed in public buildings, hospitals, public pharmacies, schools, lawking halls, cinemas, restaurant kitchens, part of all restaurants, public transport aircraft and buses, and some trains; significant reduction in emergency cardiopulmonary admissions in the 2 years following the smoking law (RR 0.87, 0.78–0.98)

Source: Tan and Glantz 2012.
Note: Observed risk is presented as a risk ratio unless otherwise specified. If number of events is N/A, then events were recorded as rates and absolute counts are not available. **AMI** = acute myocardial infarction; **ARIMA** = autoregressive integrated moving-average; **CI** = confidence interval; **ICD** = International Classification of Diseases; $\mathbf{PM_{2.5}}$ = particulate matter <2.5 micrometers in diameter; **RR** = relative risk; **TIA** = transient ischemic attack.
[a]RR and CI calculated using negative binomial regression with model including effect of law and seasonality (if applicable)
[b]RR and CI calculated using number of events before vs. after law
[c]RR and CI computed using Poisson regression with model described in paper for counties with no prior law
*Estimate used in meta-analysis.

Table 8.8*S* Detailed description of studies on the relationship between smokefree laws and other heart disease

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
Angina–workplace only laws					
Naiman et al. 2010	• Angina (*ICD-9* 411, 413; *ICD-10* I20) • ≥45 years of age • January 1996-May 2006 • Effective May 2006 • Toronto, Canada	Pre: 36 Post phase 1: 24	• ARIMA on crude rates of hospital admission • Subgroup analyses by age, gender • Comparison with Durham Region and Thunder Bay, 2 Ontario municipalities with no smokefree laws; no significant reductions were observed in control cities	• Phase 1 vs. prelaw: 0.88 (0.69–1.14)*[a]	Legislation required all public places and workplaces to be smokefree and was implemented in 3 phases; crude rates of hospital admissions decreased 39% (38%, 40%) for cardiovascular conditions; no significant reductions were observed in number of hospital admissions attributable to control conditions (cholecystitis, appendicitis, bowel obstruction) in Toronto; smokefree legislation occurred in 3 phases: smokefree public places and workplaces in October 1999; smokefree restaurants, dinner theaters, and bowling centers except designated smoking rooms in June 2001; smokefree bars, billiard halls, bingo halls, casinos, racetracks except designated smoking rooms in June 2004

Table 8.8*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
Angina–workplace and restaurant laws					
Naiman et al. 2010	• Angina (*ICD-9* 411, 413; *ICD-10* I20) • ≥45 years of age • January 1996–May 2006 • Effective May 2006 • Toronto, Canada	Pre: 36 Post phase 2: 36; not included in length of follow-up analysis because the prelaw period did not immediately precede the postlaw phase	• ARIMA on crude rates of hospital admission • Subgroup analyses by age, gender • Comparison with Durham Region and Thunder Bay, 2 Ontario municipalities with no smokefree laws; no significant reductions were observed in control cities	• Phase 2 vs. prelaw: 0.65 (0.52–0.82)*[a]	Legislation required all public places and workplaces to be smokefree and was implemented in 3 phases; crude rates of hospital admissions decreased 39% (38%, 40%) for cardiovascular conditions; no significant reductions were observed in number of hospital admissions attributable to control conditions (cholecystitis, appendicitis, bowel obstruction) in Toronto; smokefree legislation occurred in 3 phases: smokefree public places and workplaces in October 1999; smokefree restaurants, dinner theaters, and bowling centers except designated smoking rooms in June 2001; smokefree bars, billiard halls, bingo halls, casinos, racetracks except designated smoking rooms in June 2004
Sargent et al. 2012	• Stable or unstable angina pectoris (*ICD-10* I20.0-I20.9) • N = 39,224 • ≥30 years of age • January 2004–December 2008 • Nationwide: effective September 1, 2007 • Statewide: effective date varies • Germany	Pre: varies Post: 12	• Rate of hospitalization for AMI; logistic regression and interrupted time series linear regression model • Age, gender, occupation	• 0.87 (0.82–0.92)* • In the first year after implementation, 1431 angina hospitalizations were prevented	Legislation addressed smoking in federal buildings and the transportation system; private employers were allowed to introduce a total or partial smoking law in workplaces; states were permitted to decide how to limit smoking in the hospitality sector (hotels, restaurants, bars); hospitality smoking laws were passed in all states in implemented between August 1, 2007 and July 1, 2008; most states continued to allow smoking in small bars without any food delivery and in separate rooms in large restaurants; a population-based survey revealed a significant decrease in cigarettes smoked in Germany after the law; after the law, there was a significant downward trend, with slope resulting in a decline of 5.33 (7.18, 3.48) hospitalizations per month; hospital admissions for control condition fractures increased slightly from 65,100 in 2007 to 66,954 in 2009; bronchitis cases, which might be affected by smokefree laws, declined from 16,900 in 2007 to 15,391 in 2009; hospitalization costs for angina decreased significantly by 9.6 (2.5, 16.6%), or about €2.5 million

Table 8.8*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
Angina–workplace, restaurant, and bar laws					
Naiman et al. 2010	• Unstable angina (ICD9-411.1x) • N = 670 (counties without previous laws) • May 2007–May 2008 vs. January 2004–April 2007 • Effective May 1, 2007 • Arizona	Pre: 40 Post: 13	• Rate of admissions per 100,000 annually • Poisson regression • Seasonality, population, annual linear trend • Separate analyses for counties with preexisting smokefree laws vs. those without such laws	• 0.64 (0.46–0.88)*[b]	Law ended smoking in all enclosed workplaces including bars and restaurants; cost-savings analysis estimates $16.8 million in savings for AMI, unstable angina, acute stroke, and acute asthma in 13 months after law in non-law counties ($0.9 million for angina alone); no change in rates of control diseases (acute appendicitis, kidney stones, acute cholecystitis, and ulcers) pre- and postlaw
Naiman et al. 2010	• Angina (*ICD-9* 411, 413; *ICD-10* I20) • ≥45 years of age • January 1996–May 2006 • Effective May 2006 • Toronto, Canada	Pre: 36 Post phase 3: 36; not included in length of follow-up analysis because the prelaw period did not immediately precede the postlaw phase	• ARIMA on crude rates of hospital admission • Subgroup analyses by age, gender • Comparison with Durham Region and Thunder Bay, 2 Ontario municipalities with no smokefree laws; no significant reductions were observed in control cities	• Phase 3 vs. prelaw: 0.38 (0.30–0.48)*[a]	Legislation required all public places and workplaces to be smokefree and was implemented in 3 phases; crude rates of hospital admissions decreased 39% (38%, 40%) for cardiovascular conditions; no significant reductions were observed in number of hospital admissions attributable to control conditions (cholecystitis, appendicitis, bowel obstruction) in Toronto; smokefree legislation occurred in 3 phases: smokefree public places and workplaces in October 1999; smokefree restaurants, dinner theaters, and bowling centers except designated smoking rooms in June 2001; smokefree bars, billiard halls, bingo halls, casinos, racetracks except designated smoking rooms in June 2004

Table 8.8*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
Cronin et al. 2012	• Unstable angina, diagnosed in hospital by physician using troponin T or I, allowing repeat admissions (primary analysis was for overall acute coronary syndrome) • N = Primary data set: 1,236 • N = Secondary data set: 1,314 • ≥18 years of age • Primary data set: April 2004–March 2007 vs. March 2003–March 2004 • Secondary data set: July 2003–March 2004 vs. April 2004–June 2007 • Effective March 29, 2004 • Cork and Kerry counties, Ireland	Pre: 13 Post: 36 Pre: 9 Post: 39	• Unstable angina admissions and rate per 100,000; Poisson regression • Linear time trend • Sensitivity analyses were undertaken by gender, smoking status, and type of Acute coronary syndrome	• 0.89 (0.75–1.06)*[c] • Estimates derived from secondary data set	See description of law in entry for Ireland; the first year's reduction in admissions for Acute coronary syndrome was due to fewer cases among men and current smokers; the third year's reduction in admissions for Acute coronary syndrome was due to fewer cases among men, current smokers, and never smokers; increased effect on Acute coronary syndrome over time evidenced by 12% decrease in year 1 and 13% decrease in year 3; this paper supersedes an abstract of the same study used in the 2009 meta-analysis; according to mortality data, there was no change in all-cause mortality and an overall 6.5% decrease in deaths from circulatory causes in Cork and Kerry counties, and so results were not attributable to changes in coronary death patterns outside of hospital
Kent et al. 2012	• Unstable angina • 20–70 years of age • April 2004–March 2006 vs. April 2002–March 2004 • Effective March 29, 2004 • Ireland	Pre: 24 Post: 24	• Change in emergency hospital admissions for unstable angina • Population, weather, pollution, and influenza • Stratified by age and gender	• 0.77 (0.61–0.96)*	March 2004 law applied to workplaces (including bars and restaurants); prior to this law, smoking had been outlawed in public buildings, hospitals, public pharmacies, schools, banking halls, cinemas, restaurant kitchens, part of all restaurants, public transport aircraft and buses, and some trains; significant reduction in emergency cardiopulmonary admissions in the 2 years following the smoking law (RR 0.87, 0.78–0.98)

Table 8.8*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
CHD–workplace and restaurant laws					
Khuder et al. 2007	• CHD (ICD-9 410-414, 428) • ≥18 years of age • January 1999–February 2002 vs. March 2002–June 2005 • Effective March 2002 • Bowling Green, Ohio	Pre: 38 Post: 40	• Age-standardized rates • ARIMA • Ordinance effect assumed to start in October 2002 • Comparison with control community of Kent, Ohio (not covered by law); no significant change in Kent	• 12 months postlaw: 0.61 (0.55–0.67) • 40 months postlaw: 0.53 (0.45–0.59)*	Smoking was prohibited in all public places within the city, except for bars and restaurants with bars, provided that the bar area was isolated within a separate smoking room; smoking was allowed in bars and bowling alleys at the discretion of the owners; 39% reduction in CHD in 12 months and 47% reduction in 40 months; projected that 17% of reduction may be due to decreased secondhand smoke exposure, while the remaining 21% is due to decreased smoking prevalence and cigarette consumption; no differences in admissions for unspecified nonsmoking related conditions

Table 8.8*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
SCD–workplace and restaurant laws					
Hurt et al. 2011	• SCD defined as out-of-hospital deaths assigned to CHD (ICD-9 410-414) • October 2007–March 2009 vs. July 2000–December 2001 • Effective January 1, 2002 (Ordinance 1: smokefree restaurants) • Effective October 1, 2007 (Ordinance 2: smokefree workplaces) • Olmsted County, Minnesota	Pre ordinance 1: 18 Post ordinance 1: 18	• Age and gender-adjusted rate per 100,000; adjusted HR	• Ordinance 1 vs. no law, HR: 0.72 (0.58–0.89)*	Although the law was initiated in 2 steps (smokefree restaurants in January 2002 and smokefree workplaces in 2007), this study was included in the meta-analysis because authors compared the period before any law to the period after full implementation, thus capturing the true effect of the law; SCD rate per 100,000 dropped from 152.5 to 112.2 following the restaurant law (HR 0.72, 0.58–0.89; $p < 0.01$) and from 78.0 to 76.6 following the workplace law (HR 0.99, 0.76–1.28; $p = 0.91$); during this period, the prevalence of hypertension, diabetes, hypercholesterolemia, and obesity either remained constant or increased while the prevalence of smoking among the adults declined by 23%

Table 8.8*S* Continued

Study	Design/population	Pre/postduration (months)	Measure/statistical method	Findings (95% CI)	Comments
SCD–workplace, restaurant, and bar laws					
Hurt et al. 2011[53]	• SCD defined as out-of-hospital deaths assigned to CHD (ICD-9 410-414) • October 2007–March 2009 vs. July 2000–December 2001 • Effective January 1, 2002 (Ordinance 1: smokefree restaurants) • Effective October 1, 2007 (Ordinance 2: smokefree workplaces) • Olmsted County, Minnesota	Pre-ordinance 2: 18 Post-ordinance 2: 18; not included in length of follow-up analysis because the prelaw period did not immediately precede the postlaw phase	• Age and sex-adjusted rate per 100,000; adjusted HR	• Ordinance 2 vs. no law, hazard ratio: 0.72 (0.58–0.89)*	Although the law was initiated in 2 steps (smokefree restaurants in January 2002 and smokefree workplaces in 2007), this study was included in the meta-analysis because authors compared the period before any law to the period after full implementation, thus capturing the true effect of the law; SCD rate per 100,000 dropped from 152.5 to 112.2 following the restaurant law (HR 0.72, 0.58–0.89; p <0.01) and from 78.0 to 76.6 following the workplace law (HR 0.99; 0.76–1.28; p = 0.91); during this period, the prevalence of hypertension, diabetes, hypercholesterolemia, and obesity either remained constant or increased while the prevalence of smoking among the adults declined by 23%

Source: Tan and Glantz 2012.
Note: Observed risk is presented as a risk ratio unless otherwise specified. If number of events is N/A, then events were recorded as rates and absolute counts are not available. **AMI** = acute myocardial infarction; **ARIMA** = autoregressive integrated moving-average; **CHD** = coronary heart disease; **CI** = confidence interval; **HR** = hazard ratio; **ICD** = International Classification of Diseases; **RR** = relative risk; **SCD** = sudden cardiac death.
[a]RR and CI calculated using number of events before vs. after law.
[b]RR and CI computed using Poisson regression with model described in paper for counties with no prior law.
[c]RR and CI calculated using negative binomial regression with model including effect of law and seasonality (if applicable).
*Estimate used in meta-analysis.

Chapter 9
Reproductive Outcomes

Table 9.3*S* Summary of studies of orofacial clefts and maternal smoking, 2002–2011 *S-297*

Table 9.4*S* Summary of studies of maternal smoking and clubfoot, 1999–2011 *S-300*

Table 9.5*S* Summary of studies of maternal smoking and gastroschisis, 1999–2011 *S-302*

Table 9.6*S* Summary of studies of maternal smoking and congenital heart defects, 1999–2011 *S-304*

Table 9.7*S* Summary of studies of maternal smoking and craniosynostosis, 1999–2011 *S-307*

Table 9.8*S* Summary of studies of maternal smoking and anorectal atresia, 1999–2011 *S-308*

Table 9.10*S* Studies on associations between prenatal smoking and disruptive behavioral in children, 2000–2012 *S-309*

Table 9.11*S* Studies on associations between prenatal smoking and anxiety and depression in children, 2000–2012 *S-329*

Table 9.12*S* Studies on the associations between prenatal smoking and Tourette syndrome in children, 2000–2011 *S-333*

Table 9.13*S* Studies on associations between prenatal smoking and intellectual disability in children, 2000–2009 *S-334*

Table 9.14*S* Association between maternal smoking and ectopic pregnancy, studies included in 2001–2010 Surgeon General's reports and subsequently published through March 2013 *S-335*

Table 9.15*S* Studies on the effect of maternal active smoking on spontaneous abortion (SAB) risk *S-340*

Table 9.16*S* Experimental studies of the association between smoking and erectile dysfunction *S-342*

Table 9.17*S* Cross-sectional studies of the association between smoking and the risk of erectile dysfunction *S-343*

Table 9.3*S* Summary of studies of orofacial clefts and maternal smoking, 2002–2011

Study	Design/population	Definition of smoking	Findings (95% CI)
Little et al. 2004a	• Infants with nonsyndromic orofacial clefts • 112 CL/P and 78 CP cases • 248 unaffected controls • Study period: September 1997–January 2000 • England (some regions) and Scotland	Self-reported smoking in the first trimester, with frequency and duration of smoking also obtained, collected by interview after the end of the pregnancy; questions also on exposure to secondhand smoke at home, work, and other locations	• First-trimester maternal smoking was associated with all orofacial clefts combined, OR = 2.0 (1.3–3.1), with CL/P, OR = 1.9 (1.1–3.1), and with CP, OR = 2.3 (1.3–4.1) • There was evidence of a dose-response effect for both CL/P and CP
Tamura et al. 2005	• Recruited mothers of children with and without orofacial clefts in 2003 • 57 with CL/P, 17 with CP, and 283 controls • Philippines	Self-reported smoking during pregnancy	• No association between maternal smoking and orofacial clefts (OR = 0.84) • Relatively low prevalence of maternal smoking (11% in control mothers)
Krapels et al. 2006	• Case-control triad study of nonsyndromic orofacial clefts • 284 CL/P and 66 CP cases • 222 control families (friends and convenience sample) • Births 1998–2003 • The Netherlands	Self-reported smoking in the periconceptional period, defined as 3 months before pregnancy through the end of the first trimester; data collected approximately 24 months after periconceptional period	• Reported maternal smoking (any amount) during the periconceptional period was not significantly associated with CL/P, OR = 1.2 (0.8–1.8), or with CP, OR = 0.9 (0.5–1.8) • Reported paternal smoking had borderline associations with CL/P, OR = 1.5 (1.0–2.1), and CP, OR = 1.5 (0.9–2.6)
Bille et al. 2007	• Singleton infants • 134 CL/P and 58 CP cases • Random sample of all births (n = 828) • Births 1997–2003 • Denmark	Self-reported smoking, with data collected during pregnancy, mean gestational age at data collection (week 17); any smoking during pregnancy; number of cigarettes/day in first trimester	• Combined effect estimate for all orofacial clefts excluding syndromes, OR = 1.52 (1.05–2.14) • Any smoking during pregnancy was moderately associated with CL/P, OR = 1.48 (0.97–2.24) and with CP, OR = 1.53 (0.83–2.82) • Strongest effect estimates were observed for those reporting the heaviest smoking (>20 cigarettes/day), but CIs were very wide
Romitti et al. 2007	• NBDPS • 10 sites • Excluded infants with syndromes and single-gene disorders • 1,128 CL/P and 621 CP cases • 4,094 control infants without birth defects • Infants born after October 1, 1997, with an estimated date of delivery on or before December 31, 2002 • United States	Self-reported periconceptional smoking, data collected after pregnancy completion; any reported smoking from the month before pregnancy through the end of the first trimester	• Periconceptional smoking was associated with all orofacial clefts combined, OR = 1.37 (1.20–1.57) • Prior analyses in this dataset (Honein et al. 2007) showed a stronger association for heavy smoking (>25 cigarettes/day) and CL/P, OR = 1.8 (1.0–3.2), in particular for heavy smoking and bilateral CL/P, OR = 4.2 (1.7–10.3)
van den Boogaard et al. 2008	• 181 infants with orofacial clefts • Clinic-based case-control study in nine large cleft teams • Births from 1997–2000 • The Netherlands	Self-reported maternal periconceptional smoking (3 months before to 3 months after conception)	• Periconceptional smoking was associated with orofacial clefts, but the finding was nonsignificant, with OR = 1.6 (0.9–2.7)

Table 9.3*S* Continued

Study	Design/population	Definition of smoking	Findings (95% CI)
Chevrier et al. 2008	• Nonsyndromic orofacial clefts: 164 infants with CL/P and 76 infants with CP • All orofacial clefts were combined in analyses • Hospital-based controls • 1998-2001 • France	Self-reported regular smoking of at least one cigarette per day in the first trimester of pregnancy	• First trimester smoking was not associated with orofacial clefts, OR = 1.0 (0.7–1.6) • Among nonsmokers, exposure to tobacco smoke was associated with orofacial clefts, OR = 1.8 (1.2–2.8)
Grewal et al. 2008	• 502 infants with CL/P and 199 infants with CP • Births from selected counties (Los Angeles, San Francisco, and Santa Clara) • Births July 1999–June 2003 • California	Self-reported smoking during the first month of pregnancy, data collected after pregnancy completion; smoking categorized as >5 or ≤5 cigarettes/day for the first month of pregnancy	• Infants with an isolated cleft were analyzed separately from those with multiple major unrelated defects • There were no significant associations observed for smoking in the first month of pregnancy for any of the phenotypes assessed
Leite and Koifman 2009	• Hospital-based study • 208 CL/P and 66 CP cases 0–24 months of age • 548 controls • Study period: 2005 • Rio de Janeiro, Brazil	Maternal smoking in the year before pregnancy and maternal smoking in the first trimester	• Maternal smoking in the year before pregnancy was associated with CL/P, OR = 1.59 (1.04–2.44), but not with CP • No significant associations for first-trimester smoking with CL/P or CP
Shaw et al. 2009	• 89 infants with CL/P and 409 unaffected infants • Mid-pregnancy serum specimens from the 15th to 18th week of pregnancy collected from 2003–2005 • Women in selected regions of California	Mid-pregnancy serum cotinine levels of ≥2 ng/mL defined as exposed to maternal smoking; <2 ng/mL defined as unexposed	• Maternal smoking was associated with CL/P, AOR = 2.4 (1.1–5.3)
Wang et al. 2009	• Orofacial clefts identified from a population based birth defects surveillance program • Births 2000–2007 • Controls matched by gender, address, and date of birth • 606 infants with orofacial clefts and no other major birth defects • Shenyang, China	Self-reported smoking from one month before to two months after last menstrual period	• Prevalence of maternal smoking was very low (2.0% of case-mothers and 1.4% of control-mothers) • Maternal smoking was higher among case-mothers, but association was not significant, OR = 1.50 (0.52–4.36) • Paternal smoking was associated with orofacial clefts, OR = 2.05 (1.47–2.87)
Lebby et al. 2010	• Births (birth certificate records) • Study period: 2005 • United States	Smoking during pregnancy, reported on the birth certificate	• Maternal smoking was associated with orofacial clefts, OR = 1.66 (1.32–2.09)
Li et al. 2010	• 4 counties • Study period: 2003–2006 • Shanxi province, China	Exposure to passive smoking at least once a week from 1 month before to 2 months after conception	• Exposure to passive smoking was associated with CL/P, AOR = 2.0 (1.2–3.4) • Stronger effect estimate for those exposed >6 times per week, OR = 2.8, than for those exposed 1–6 times per week, OR = 1.6

Table 9.3*S* Continued

Study	Design/population	Definition of smoking	Findings (95% CI)
Johansen et al. 2009	• All children surgically treated for an orofacial cleft • Births from 1996-2001 • Norway	Self-reported smoking in the first trimester from a questionnaire completed by mothers	• First trimester smoking was associated with orofacial clefts combined, OR = 1.52 (1.21–1.90)
Zandi and Heidari 2011	• Hospital births • Study period: 1993–2008 • Hamedan, Iran	Smoking during pregnancy	• Smoking during pregnancy was more common among mothers of infants with clefts than controls, but it was very rare overall
Jia et al. 2011	• Sichuan University, Department of Cleft Lip and Palate Surgery • Cases with nonsyndromic CL/P and CP • Unaffected controls • Study period: 2008–2010 • West China	Self-reported maternal, paternal, and passive smoking	• Maternal passive exposure to tobacco during early pregnancy was associated with nonsyndromic orofacial clefts combined, AOR = 1.42 (6.87–19.00) • In unadjusted analyses, the association with passive smoking was reported for both CL/P and CP
Mirilas et al. 2011	• Aristotle University, Pediatric Surgery Department • 35 cases operated on for nonsyndromic CL/P • 35 residence-matched controls • Study period: 2004–2009 • Greece	Self-reported maternal smoking and passive smoking before and during pregnancy (first 3 months)	• Maternal passive exposure to tobacco was associated with increased risk of CL/P, OR = 1.81 (0.69-4.74), but the association was not significant
Zhang et al. 2011	• 304 infants with nonsyndromic orofacial clefts (140 with CLP, 77 with CP, and 86 with CLO) • 454 controls • Study period: 2006–2009 • Harbin, China	Self-reported maternal smoking (6 months before pregnancy and in the first trimester), paternal smoking (1 month before pregnancy through first trimester), and passive smoking	• AOR for maternal smoking before pregnancy was 4.97 (1.39–17.76) for CLO and 3.37 (1.04–10.88) for CLP for those reporting smoking 1–9 cigarettes/day before pregnancy; estimates were similar for maternal smoking in the first trimester • No association with maternal smoking and CP • Paternal smoking in the periconceptional period was strongly associated with CLP, CLO, and CP • The medium level of exposure to environmental tobacco smoke at home or work was associated with orofacial clefts

Notes: **AOR** = adjusted odds ratio; **CI** = confidence interval; **CL/P** = cleft lip with or without cleft palate; **CLO** = cleft lip only; **CLP** = cleft lip with cleft palate; **CP** = cleft palate; **mL =** milliliters; **n =** sample size; **NBDPS =** National Birth Defects Prevention Study; **ng** = nanogram; **OR** = odds ratio.

Table 9.4*S* Summary of studies of maternal smoking and clubfoot, 1999–2011

Study by defect	Design/population	Definition of smoking	Findings (95% CI)
Honein et al. 2000	• 346 infants with isolated talipes equinovarus, or isolated clubfoot, NOS • 3,029 infants with no major birth defects • Births 1968–1980 • 5 counties in metropolitan Atlanta, GA	Self-reported maternal smoking, from telephone interviews conducted in 1981–1982	• Clubfoot was associated with maternal smoking among those with no family history of clubfoot, OR = 1.34 (1.04–1.72) • Much stronger association was found between clubfoot and maternal smoking among those with a first-degree family history of clubfoot, OR = 20.30 (7.9–52.17)
Honein et al. 2001	• U.S. natality data • Study period: 1997–1998 • 45 states, New York City, and District of Columbia	Birth certificate report of number of cigarettes/day during pregnancy by four categories: 1–5, 6–10, 11–20, and ≥21	• Maternal smoking during pregnancy was associated with clubfoot, PR = 1.62 (1.49–1.75) • Strongest effect at highest reported smoking level (≥21 cigarettes/day)
Skelly et al. 2002	• 239 infants with idiopathic talipes equinovarus • 356 unmatched controls selected by random-digit dialing • Births on or after January 1, 1986, of children who were treated through May 1994 • Western Washington state	Self-reported smoking during pregnancy, collected after pregnancy	• Smoking during pregnancy was associated with clubfoot • There was some evidence of a dose-response effect, with the strongest effect for those smoking ≥20 cigarettes/day, OR = 3.9 (1.6–9.2); a somewhat similar effect for those smoking 10–19 cigarettes/day, OR = 3.1 (1.7–5.8); and a weaker effect for those smoking <10 cigarettes/day, OR = 1.5 (0.9–2.5) • No information was available on the timing of smoking during pregnancy
Cardy et al. 2007	• 194 infants with talipes equinovarus and 60 controls • Children/parents recruited July 1993 – July 1997 • United Kingdom		• Maternal smoking was more common among case- than control-mothers, but the association was not significant, OR = 1.37 (0.72–2.62)
Dickinson et al. 2008	• 443 singleton infants diagnosed with isolated talipes equinovarus, or isolated clubfoot, NOS • Random sample of 4,492 live births without major birth defects • Births 1999–2003 • North Carolina	Maternal smoking as reported on birth certificates; reliability of exposure assessed by matching to the North Carolina PRAMS, giving a Kappa = 0.77	• Clubfoot was associated with any maternal smoking during pregnancy, OR = 1.40 (1.07–1.83) • There was no evidence of a dose-response effect • No information was available on the timing of maternal smoking
Parker et al. 2009	• 10 population-based birth defects surveillance programs • 6,139 infants with talipes equinovarus, or clubfoot, NOS, among 4,744,711 live births • Births 2001–2005	Birth certificate data on smoking during pregnancy	• Maternal smoking was associated with clubfoot, OR = 1.57 (1.45–1.70) • Case definition excluded infants with neural tube defects, lower limb defects, bilateral renal agenesis, and chromosomal abnormalities because the clubfoot was presumed to be secondary to these defects • Dose-response effect was observed

Table 9.4*S* Continued

Study by defect	Design/population	Definition of smoking	Findings (95% CI)
Kancherla et al. 2010	• Study period: 1997–2005 • Iowa	Smoking during pregnancy as reported on the birth certificate	• Smoking was associated with clubfoot, POR = 1.5 (1.2–1.9)

Note: **CI** = confidence interval; **NOS =** not otherwise specified; **OR** = odds ratio; **POR** = prevalence odds ratio; **PRAMS** = Pregnancy Risk Assessment Monitoring System.

Table 9.5*S* Summary of studies of maternal smoking and gastroschisis, 1999–2011

Study by defect	Design/population	Definition of smoking	Findings (95% CI)
Källén 2000	• Isolated and multiple defects among all births • Births 1983–1996 • Sweden	Prenatal assessment of smoking during antenatal visit typically at 10–12 weeks gestation	• Maternal smoking was associated with isolated gastroschisis, OR 1.59 (1.00–2.54)
Stoll et al. 2001	• Birth defects registry • 1979–1998 • France (Strasbourg)		• No association between maternal smoking and gastroschisis, OR = 1.02 (0.44–2.37)
Werler et al. 2003b	• 205 infants with gastroschisis • 381 malformed controls • 416 nonmalformed controls • Study period: June 1995–March 1999 • 15 U.S. and Canadian cities	Self-reported exposures in the first 2.5 months of pregnancy of mothers interviewed within 6 months of delivery	• First-trimester smoking was associated with gastroschisis, OR = 1.5 (1.1–2.2) • Stronger effect was observed for the combination of vasoconstrictive medications and maternal smoking
Hougland et al. 2005	• Gastroschisis surgeries • 1998–2002 • Utah	Maternal tobacco use	• Maternal smoking was associated with gastroschisis, OR = 2.60 (1.48–4.55)
Lam et al. 2006a	• 55 singleton infants with gastroschisis • 94 age-matched controls • Study period: March 1988–August 1990 • California	Mothers interviewed 3–6 months after delivery to ascertain periconceptional exposures	• Smoking more than 1 pack of cigarettes/day had a borderline association with gastroschisis, OR = 2.0 (0.9–4.9) • Any smoking of marijuana was associated with gastroschisis, OR = 2.1 (1.0–4.4) • Study found some suggestion of an interaction between high exposure to carbon monoxide (from tobacco or marijuana) and low BMI
Chambers et al. 2007	• Case-control study recruiting in prenatal diagnosis centers • 1986–2003 • Southern California	Tobacco use in the first trimester	• Effect estimate was elevated, but there was no significant association between maternal smoking and gastroschisis, OR = 1.37 (0.63–2.96)
Zamakhshary and Yanchar 2007	• 54 gastroschisis cases • Study period: January 1990–December 2001 • 3 Canadian provinces	Maternal smoking in the first trimester abstracted from prenatal care medical records	• Study compared complicated gastroschisis cases (n = 17) with simple gastroschisis cases (n = 37) • Maternal smoking was more common in complicated gastroschisis but not significantly so, OR = 2.1 (0.6–7.2)
Draper et al. 2008	• Matched case-control study • 144 infants with gastroschisis and 432 control-mothers • January 2001–August 2003 • United Kingdom (3 regions)		• After adjustment for other risk factors, maternal smoking was associated with gastroschisis, OR = 1.70 (1.1–2.6)
Feldkamp et al. 2008	• 189 gastroschisis cases • 423,499 live-born infants without major defects • Births January 1997–December 2005 • Utah	Birth certificate information on smoking during pregnancy	• Maternal smoking was associated with gastroschisis after adjusting for maternal age, OR = 1.6 (1.1–2.3) • Study excluded infants with ventral body wall defects, amniotic band sequence, and chromosomal abnormalities

Table 9.5*S* Continued

Study by defect	Design/population	Definition of smoking	Findings (95% CI)
Bird et al. 2009	• NBDPS • Excluded infants with syndromes and single-gene disorders • 485 infants with gastroschisis, 168 with omphalocele • 4,967 controls • Infants born after October 1, 1997, and with an estimated date of delivery on or before December 31, 2003 • 10 U.S. sites	Self-reported maternal smoking from 1 month before conception to 3 months after conception, categorized as light (<1 pack/day), medium (1 pack/day), or heavy (>1 pack/day)	• Heavy smokers were twice as likely to have an infant with gastroschisis, but finding not significant, OR = 2.08 (0.90–4.78) • Heavy smoking was associated with omphalocele, OR = 4.26 (1.58–11.52)
Salemi et al. 2009	• Cohort with the birth defects registry identified cases • Births 1998–2003 • Florida	Smoking during pregnancy as reported on the birth certificate	• In the crude analyses, maternal smoking was associated with gastroschisis • After adjustment for maternal age, marital status, education, race/ethnicity, parity, and place of residence, there was no association, OR = 0.97 (0.73–1.28)
Werler et al. 2009b	• NBDPS • Excluded infants with syndromes and single-gene disorders • 514 mothers of infants with gastroschisis • 3,277 maternal age-matched controls • Infants born after October 1, 1997, and with an estimated date of delivery on or before December 31, 2003 • 10 U.S. sites	Self-reported smoking in the time period from 2 weeks before the last menstrual period to 14 weeks after the last menstrual period	• Maternal smoking was associated with gastroschisis, OR = 1.5 (1.2–1.9) • There was no association between maternal smoking and gastroschisis among mothers <19 years of age • The strongest association between maternal smoking and gastroschisis was observed for mothers ≥25 years of age, OR = 3.0 (1.8–5.0)
Chabra et al. 2011	• Birth certificate data • Study period: 1987–2006 • Washington state	Any smoking during pregnancy	• Smoking during pregnancy was associated with gastroschisis, adjusted RR = 1.58 (1.19–2.09)

Note: **BMI** = body mass index; **CI** = confidence interval; **NBDPS =** National Birth Defects Prevention Study; **OR** = odds ratio; **RR** = relative risk.

Table 9.6*S* Summary of studies of maternal smoking and congenital heart defects, 1999–2011

Study by defect	Design/population	Definition of smoking	Findings (95% CI)
Källén 1999a	• 3,384 infants with congenital heart defects (excluding those with chromosomal abnormalities) among 1,413,811 infants • Study period: 1983–1996 • Sweden	Maternal smoking during pregnancy (none, <10 cigarettes/day, ≥10 cigarettes/day), reported at first antenatal visit	• Significant associations with maternal smoking were observed for transposition of the great arteries, OR = 1.32 (1.02–1.71); atrial septal defects, OR = 1.63 (1.04–2.57); and full-term infants with PDA, OR = 1.30 (1.05–1.62).
Woods and Raju 2001	• TriHealth Hospital system births • 18,016 live births; examined 22 categories of birth defects • Study period: January 1998–December 1999 • Cincinnati, Ohio	Self-reported maternal smoking during pregnancy, collected at the time of admission for delivery (prior to actual delivery)	• Congenital heart defects were more common among smoking mothers than nonsmoking mothers, RR = 1.56 (1.12–2.19) (p <0.01) • No other defect categories were significantly associated (p ≤0.01) with maternal smoking
Botto et al. 2001	• Case-control study • 905 infants with nonsyndromic congenital heart defects and 3029 controls • Births 1968-1980 • Metropolitan Atlanta	Self-reported maternal smoking	• Maternal smoking was not associated with all congenital heart defects combined, OR = 1.11 (0.95–1.30)
Steinberger et al. 2002	• Baltimore-Washington Infant Study • 55 infants with single ventricle • 3,572 control infants • Study period: 1981–1989 • District of Columbia, Maryland, and some counties in Northern Virginia	Maternal and paternal smoking (none, 1–20, 20–39, and ≥40 cigarettes/day), collected by interview after the pregnancy	• Paternal smoking was associated with single ventricle, and there was some evidence of a dose-response effect (ORs were 1.0, 1.9, and 3.7 for increasing smoking dose, p for trend = 0.02) based on 6 exposed cases • No significant association was found between maternal smoking and single ventricle
Morales-Suarez-Varela et al. 2006	• 76,768 pregnancies resulting in 3,767 infants with birth defects, 746 congenital heart defects • Limited to singletons • Study period: 1997–2003 • Denmark	Self-reported maternal smoking and use of nicotine substitutes (gum, patches, inhalers), collected by interview during pregnancy	• A modest but significant association was found between maternal smoking and congenital heart defects, OR = 1.20 (1.03–1.40)
Malik et al. 2008	• NBDPS • Excluded infants with syndromes and single-gene disorders • 3,067 congenital heart defects • 3,947 controls • Study period: October 1997–December 2002 • 8 U.S. sites	Self-reported smoking in the month before pregnancy through the first trimester, categorized as light (<1/2 pack/day), medium (1/2–1 pack/day), and heavy (≥25 cigarettes/day), reported by interview after pregnancy	• Light, medium, and heavy smoking were all associated with septal heart defects and especially atrial septal defects

Table 9.6*S* Continued

Study by defect	Design/population	Definition of smoking	Findings (95% CI)
Grewal et al. 2008	• Case-control study • 320 infants with conotruncal heart defects and 639 controls • Births from selected counties (Los Angeles, San Francisco, and Santa Clara) • Births July 1999–June 2004 • California	Self-reported smoking during the first month of pregnancy, data collected after pregnancy completion; smoking categorized as >5 or ≤5 cigarettes/day for the first month of pregnancy	• Smoking in the first month of pregnancy was not associated with conotruncal heart defects, OR = 0.78 (0.45–1.34)
Kučienė and Dulskienė 2009	• 187 newborns with congenital heart defects • 643 randomly selected newborns without defects • Study period: 1999–2005 • Kaunas, Lithuania	Maternal smoking during pregnancy and duration of smoking prior to pregnancy	• Smoking during pregnancy was associated with congenital heart defects, OR = 2.45 (1.43–4.20), and after adjusting for occupation and education, the OR was reduced, 1.48 (0.82–2.67) • Study found a stronger association for mothers who had smoked longer (≥3 years) prior to pregnancy
Kučienė and Dulskienė 2010	• 261 cases with congenital heart defect from newborns' register database • 1,122 controls with no defects • Study period: 1995–2005 • Kaunas, Lithuania	Self-reported maternal smoking before and during the first trimester and self-reported paternal smoking	• Increased risk of congenital heart septal defects was associated with maternal smoking, AOR = 2.20 (1.01–4.79); paternal smoking, AOR = 1.45 (1.03–2.03),; and both parents smoking, AOR = 2.27 (1.49–3.46)
Van Beynum et al. 2010	• Study period: 1996–2005 • Northern Netherlands	Maternal smoking, on the basis of questionnaire after pregnancy	• Smoking during pregnancy was not associated with congenital heart defects (p = 0.47)
Alverson et al. 2011	• Baltimore-Washington Infant Study • 2,525 infants with congenital heart defects but no other birth defects • 3,435 controls • Study period: 1981–1989	Self-reported maternal cigarette smoking during first trimester	• Smoking during first trimester was associated with increased risk of secundum-type atrial septal defects, OR = 1.36 (1.04–1.78); pulmonary valve stenosis, OR = 1.35 (1.05–1.74); truncus arteriosus, OR = 1.90 (1.04–3.45); and l-transposition of the great arteries, OR = 1.79 (1.04–3.10) • Associations were not observed for maternal smoking and most other congenital heart defects
Cresci et al. 2011	• 360 infants with congenital heart defects • 360 infants without defects from a pediatric cardiac center and maternity and pediatric units • Study period: 2008–2010 • Italy	Self-reported maternal and paternal smoking at conception	• Paternal smoking was associated with an increased risk of congenital heart defects, OR = 1.7 (1.1–2.6), but there was no significant association for maternal smoking, OR = 1.2 (0.7–1.8)

Table 9.6*S* Continued

Study by defect	Design/population	Definition of smoking	Findings (95% CI)
Karatza et al. 2011	• 157 neonates with congenital heart defects • 208 unaffected neonates • Study period: June 2006–June 2009 • Greece	Self-reported maternal smoking (1 month before conception through first trimester) obtained by interview prior to echocardiographic exam of the infant	• Congenital heart defects were identified in 61% of the neonates whose mother smoked and 36% of neonates whose mother did not smoke (p <0.001) • In the adjusted analyses, maternal smoking was associated with congenital heart defects, OR = 2.74 (1.66–4.53)
Baardman et al. 2012	• 797 cases, born with isolated nonsyndromic congenital heart defect and identified from a population-based birth defects registry • 322 infants/fetuses with chromosomal anomalies but without cardiac anomalies served as controls • Study period: 1997–2008 • The Netherlands	Self-reported maternal smoking before and through first trimester of pregnancy	• Periconceptional smoking was associated with congenital heart defects among women with a high BMI, AOR = 2.65 (1.20–5.87) • Significant and elevated AORs were observed for septal heart defects and outflow tract defects based on the interaction between smoking and high BMI
Mateja et al. 2012	• Data from PRAMS, linked to state birth certificates • 237 infants with a congenital heart defect, as indicated on birth certificate, with no indication of Down syndrome • 948 controls with no indication of any congenital defect • Cases and controls limited to singletons • Study period: 1996–2005 • 9 U.S. states	Self-reported smoking 3 months before pregnancy	• Smoking during pregnancy was not associated with congenital heart defects • There was a significant interaction between exposure to alcohol and smoking before pregnancy (p <0.01)

Note: **AOR** = adjusted odds ratio; **BMI** = body mass index; **CI** = confidence interval; **NBDPS =** National Birth Defects Prevention Study; **OR** = odds ratio; **PDA** = Patent ductus arteriosus; **PRAMS** = Pregnancy Risk Assessment Monitoring System; **RR** = relative risk.

Table 9.7*S* Summary of studies of maternal smoking and craniosynostosis, 1999–2011

Study by defect	Design/population	Definition of smoking	Findings (95% CI)
Källén 1999b	• 304 infants with craniosynostosis and no chromosomal abnormality among 1,413,811 live births • Study period: 1983–1996 • Sweden	Self-reported smoking, ascertained during pregnancy at prenatal consultations with midwife	• Smoking was associated with craniosynostosis, OR = 1.45 (1.13–1.87), but the effect was limited to those with an isolated defect (i.e., they had no other major birth defect unrelated to craniosynostosis) • Strongest effect was found for sagittal craniosynostosis • Study found some evidence for a dose-response effect between maternal smoking and craniosynostosis
Honein and Rasmussen 2000	• Study period: 1968–1980 • 5 central counties of metropolitan Atlanta, Georgia	Reported smoking at any time in the first 3 months of pregnancy	• Smoking in the first trimester was associated with isolated craniosynostosis, OR = 1.92 (1.01–3.66)
Carmichael et al. 2008	• NBDPS • 531 infants with craniosynostosis • 5,008 controls • Study period: 1997–2003 • 10 U.S. sites	Self-reported number of cigarettes/day in the month before pregnancy, each month of the first 3 months of pregnancy, and the second and third trimesters of pregnancy	• There was a borderline association with heavy maternal smoking (≥15 cigarettes/day) for mothers still smoking in the third month of pregnancy, OR = 1.6 (0.9–2.6) • Study found some evidence for a stronger effect of maternal smoking among those without exposure to folic acid until very late in pregnancy
Butzelaar et al. 2009	• Surgical sagittal synostosis patients in 1 hospital • Study period: 2006 • The Netherlands	Smoking during pregnancy	• Smoking among case mothers did not differ from that reported by the general population

Note: **CI** = confidence interval; **NBDPS** = National Birth Defects Prevention Study; **OR** = odds ratio.

Table 9.8*S* Summary of studies of maternal smoking and anorectal atresia, 1999–2011

Study by defect	Design/population	Definition of smoking	Findings (95% CI)
Källén, 2000	• Isolated and multiple defects among all births • Births 1983–1996 • Sweden	Prenatal assessment of smoking during antenatal visit typically at 10–12 weeks gestation	• Maternal smoking was associated with isolated anal atresia, OR = 1.45 (1.11–1.90)
Honein et al. 2001	• U.S. natality data • Study period: 1997–1998 • 45 states, New York City, and District of Columbia • 564 infants with rectal atresia/stenosis indicated on birth certificate	Birth certificate report of number of cigarettes/day during pregnancy by four categories: 1–5, 6–10, 11–20, and ≥21	• Maternal smoking during pregnancy was modestly associated with anal atresia but not significant, PR = 1.19 (0.94–1.50) • No evidence of dose-response effect
Miller et al. 2009	• NBDPS • 464 infants with anorectal atresia (216 of the defects were isolated) • 4,940 controls • Study period: October 1997–December 2003 • 10 U.S. sites	Self-reported periconceptional smoking, defined as smoking in the month before conception or first 3 months of pregnancy, interviewed after pregnancy; exposure to environmental tobacco smoke defined as reported exposure at home or work in the same time period	• Any maternal smoking had borderline association with anorectal atresia, OR = 1.2 (1.0–1.5) • Exposure to secondhand smoke at home and work was associated with anorectal atresia, OR = 2.3 (1.2–4.1)
Van Rooij et al. 2010	• Radbound University, Pediatric Surgery Department • Children born between January 1996 and April 2008 who were treated for anorectal malformation (85 cases) • 650 controls who were boys with persistent middle ear infections and were participating in another study • Study period: 1996–2008 • The Netherlands	Maternal smoking from 3 months before conception and during pregnancy; paternal smoking from 3 months before pregnancy to conception	• Paternal smoking was significantly associated with increased risk of anorectal malformations: crude, OR = 1.8 (1.1–2.9) • Maternal smoking was not associated with anorectal malformations

Note: **CI** = confidence interval; **NBDPS** = National Birth Defects Prevention Study; **OR** = odds ratio; **PR** = prevalence ratio.

Table 9.10*S* Studies on associations between prenatal smoking and disruptive behavioral disorders in children, 2000–2012

Study	Design/population	Estimate of effects (95% CI)	Findings
Breslau and Chilcoat 2000	• Random sample of hospital cohort of 823 low birth weight births from socioeconomically disparate communities followed to 11 years of age • Parent and teacher report on behavior symptoms • Prenatal daily smoking assessed retrospectively at 6 years of age	Attention: $\beta = 0.90$ (0.60) NS Externalizing: $\beta = 2.55$ (0.78) $p < 0.05$ Internalizing: $\beta = 0.68$ (0.71) NS	• Prenatal smoking significantly predicted externalizing behavior, but not internalizing or attention symptoms
Hill et al. 2000	• 150 children 8–18 years of age at high or low familial risk for alcoholism • Diagnostic interview for condition • Prenatal smoking rate reported retrospectively at assessment	Depression NS Conduct NS Oppositional NS Anxiety NS Phobia NS ADHD NS Adjusted OR not reported	• Prenatal smoking was associated with depression, conduct disorder, and oppositional disorder, but not ADHD, anxiety or phobia • These findings were no longer significant after controlling for other risk factors
Maughan et al. 2001	• Prospective birth cohort study of all children born in the first week of April 1970 • Parental report on hyperactivity, conduct problems, adolescent self-report on conduct problems and depressive symptoms • Prenatal smoking rate assessed retrospectively at birth • Followed up at ages 5, 10, and 16 years • England, Scotland, and Wales	Conduct problems adjusted OR (value not reported); $p = 0.238$	• Prenatal smoking was not associated with hyperactivity, conduct problems, or depressive symptoms after controlling for postnatal smoking
Wakschlag and Keenan 2001	• Sample of 129 predominantly minority 2–5-year-old children referred to behavior problem clinic plus control • Diagnosis of disruptive behavior disorder via clinical interview • Prenatal smoking rate assessed retrospectively at assessment	Disruptive behavior: $\beta = 2.48$, $t = 3.45$, $p = 0.0008$	• Prenatal smoking was significantly associated with disruptive behavior disorder after controlling for other risks
Burke et al. 2002	• 177 clinic referred boys 7–12 years of age; follow up to 13–17 years of age • Conduct disorder based on parent and teacher interview • Prenatal smoking rate assessed retrospectively at initial assessment	Persistent CD: $\beta = 0.45$, OR = 1.58, $p = 0.047$	• Prenatal smoking significantly predicts CD persisting into adolescence

Table 9.10*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Mick et al. 2002	• Retrospective, hospital-based, case-control study with 280 ADHD cases and 242 non-ADHD controls 6–17 years of age • Psychopathology assessed via interview of children and parents • Retrospective assessment of heavy prenatal smoking	ADHD cases: OR = 2.1 (1.1–4.1)	• Heavy prenatal smoking was associated with ADHD diagnosis
Wakschlag and Hans 2002	• 77 participants of longitudinal follow-up study of African American youth from pregnancy until 10 years of age • Conduct symptoms assessed via clinical interview of mother and child • Prenatal smoking assessed during pregnancy	CD: Overall correlation: $r = 0.22$, $p < 0.05$ Boys: $\beta = 0.36$, $t = 2.14$, $p < 0.05$ Girls: $r = -0.07$, NS	• Prenatal smoking related to CD risk, specifically for boys but not girls
Batstra et al. 2003	• Birth cohort of 1,186 children followed up at 5.5–11 years of age • Parent and teacher report of attention and externalizing symptoms • Prenatal smoking assessed during pregnancy	Attention symptoms: $\beta = 0.46$ (0.15–0.76), $p = 0.01$, explained variance = 5.1% Externalizing: $\beta = 0.19$ (0.07–0.32), $p = 0.01$, explained variance = 2.0%	• Prenatal smoking associated with attention deficit symptoms and externalizing symptoms, controlling for other risks
Kahn et al. 2003	• Cohort of 161 children followed prospectively from 6–60 months of age • Parent rating on behavioral symptoms • Prenatal smoking assessed retrospectively at 6 months	Hyperactive-impulsive scores: 65.4 vs. 59.7, $p < .05$ Oppositional: 66.5 vs. 56.7, $p < 0.01$ Inattentive: 58.3 vs. 55.7, NS	• Prenatal smoking was associated with hyperactive and oppositional symptoms, but not inattentive symptoms
Kotimaa et al. 2003	• 9,357 children from 1985–1986 birth cohort followed to 8 years of age • Parent and teacher report on behavioral symptoms • Prenatal smoking assessed in pregnancy	Overall: Hyperactivity: OR = 1.30 (1.08–1.58) Smoking status: Quit before pregnancy: OR = 1.52 (1.16–2.01) Reduced OR = 1.84 (1.47–2.31) Unchanged or increased: OR = 2.12 (1.62–2.77)	• Prenatal smoking was associated with hyperactivity after controlling for other risks • Positive dose-response relationship between prenatal smoking and hyperactivity
Silberg et al. 2003	• 538 boys 8–16 years of age from the initial wave of a statewide cohort study of all twin boys • Child self-report of conduct symptoms • Prenatal smoking reported retrospectively at initial assessment	Conduct symptoms: NS	• Prenatal smoking was not associated to conduct symptoms after controlling for other risks

Table 9.10*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Thapar et al. 2003	• Population-based sample of twins • 1,452 twin pairs 5–16 years of age • Parent and teacher report of ADHD symptoms • Prenatal smoking rates reported retrospectively at assessment	Teacher ratings of ADHD: F = 9.42, df = 3,1432, p <0.0001 Rates of cigarettes/day and mean scores: None: 3.18 (2.87–3.52) 1– 10: 4.81 (3.69–6.20) 11–20: 5.36 (4.44–6.48) >20: 5.17 (2.87–8.76) Parent ratings of ADHD: F = 9.45, df = 3,2041 , p <0.0001 Rates of cigarettes/day and mean scores: None : 7.33 (6.93–7.80) 1–10: 9.18 (7.92–10.56) 11–20: 10.02 (9.00–11 .33) >20: 10.59 (7.36–14.97)	• Prenatal smoking is associated with offspring ADHD symptoms when controlling for other risks
Gray et al. 2004	• Prospective intervention RCT of 869 low birth weight infants • Parent report on behavior problems • Prenatal smoking assessed retrospectively at birth • Followed up at 3, 5, and 8 years of age	Behavior problems: OR = 1.57 (1.20–2.04)	• Prenatal smoking was a significant predictor of the development of behavior problems from 3–8 years of age, controlling for other risks
Maughan et al. 2004	• Representative sample of 1,116 twin pairs assessed at 5 and 7 years of age • Parent and teacher report of conduct problems • Prenatal smoking assessed retrospectively at 1 year of age	Conduct problems: 5 years of age (F3, 1,054 = 13.75; p <0.001) 7 years of age (F3, 1,030 = 13.92; p <0.001) Multivariate: heavy smoking: 5 years of age: β = 0.09 (-0.03–0.21) NS 7 years of age: β = 0.17 (0.02–0.32), p <0.05	• Heavy prenatal smoking significantly predicts conduct problems at 7 years of age, controlling for other factors • No significant relation to 5 years of age
Button et al. 2005	• 1,896 cases from a population-based twin study, followed to 5–18 years age • Parent-reported ADHD symptoms • Prenatal smoking rate assessed retrospectively at initial assessment	Antisocial behavior: r = 0.17, p <0.001 ADHD: r = 0.14, p <0.001	• Prenatal smoking was associated with antisocial behavior and ADHD, controlling for other risks

Table 9.10*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Knopik et al. 2005	• 1,936 female twin pairs from a longitudinal sample, identified through birth records and enrolled in adolescence, 11–19 years of age • ADHD diagnosis based on maternal report on symptoms and impairment • Prenatal smoking assessed retrospectively at assessment	OR of prenatal smoking NS at any dose for either first trimester or beyond first trimester Maternal smoking during pregnancy: • First trimester: OR = 0.97 (0.50–1.86) 10 cigarettes/day: OR = 1.05 (0.48–2.37) 11–19 cigarettes/day: OR = 0.42 (0.11–1.63) ≥20 cigarettes/day: OR = 1.40 (0.48–4.07) • Beyond first trimester: OR = 1.50 (0.86–2.63) 1–10 cigarettes/day: OR = 1.24 (0.61–2.52) 11–19 cigarettes/day: OR = 1.83 (0.89–3.76) ≥20 cigarettes/day: OR = 1.79 (0.79–4.07)	• Prenatal smoking did not increase risk for ADHD diagnosis, controlling for other risk factors
Linnet et al. 2005	• Nested case-control study • 170 children with hyperkinetic disorder • 3,765 population-based control subjects, matched by age, gender, and date of birth • Diagnosis from psychiatric medical records • Prenatal smoking assessed during pregnancy	Hyperkinetic disorder: RR = 1.9 (1.3–2.8) Excluding children of parents with psychiatric hospitalization: RR =2.2 (1.5–3.2)	• Controlling for other risk factors, prenatal smoking increased risk for hyperkinetic disorder
Rodriguez and Bohlin 2005	• 393 participants from sample recruited during pregnancy and followed up to 7 years of age • ADHD diagnosis based on mother and teacher report on symptoms and impairment • Prenatal smoking assessed during pregnancy	Number of symptoms Total: $r = 0.18$, $p < 0.001$ boys: $r = 0.21$, $p < 0.01$ girls: $r = 0.10$, NS Smoking during the first half of pregnancy: $\beta = 0.16$, $p < 0.01$ Smoking during the latter half: NS for unique contribution ADHD diagnosis: $\beta = 0.14$, NS	• Prenatal smoking was correlated with ADHD symptoms, but was not significantly associated with ADHD diagnosis after controlling for other risk
Knopik et al. 2006	• Case-control with or without alcohol abuse, children-of-twin design, adult female twin mothers with a child 13–24 years of age • Offspring ADHD diagnosis based on maternal report on symptoms and impairment • Prenatal smoking rate assessed retrospectively at assessment	ADHD for heaviest smoking: >15 cigarettes beyond first trimester, OR = 3.83 (1.09–13.45) Regular smoker not during pregnancy: OR = 0.72 (0.23–2.22) First trimester only: OR = 1.88 (0.45–7.81) Smoking beyond first trimester: 1–15 cigarettes, OR = 0.54 (0.16–1.83)	• Controlling for other risks, heavy smoking was independently associated with ADHD

Table 9.10*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Mathews et al. 2006	• 3 cohorts of individuals with tic disorders (DSM-IV) • 180 individuals 3–59 years of age (72% under 18 years of age). • Rating scales of severity, self-report • Prenatal smoking reported retrospectively at assessment	Increase total tic severity: F = 9.27, p <0.00001 Increase phonic tic severity: F = 25.84, p <0.00001 Motor tic severity: NS	• In this sample with tic disorders, prenatal smoking was associated with tic severity • There was no significant association between exposure to prenatal tobacco and presence of comorbid ADHD, controlling for other risks
Monuteaux et al. 2006	• Community sample of 682 pregnant women followed longitudinally from prenatal life to 22 years of age • Mothers reported overt and covert symptoms of CD • Prenatal smoking rate assessed during pregnancy	Overt CD symptoms for low SES: No smoking vs. moderate smoking, RR = 2.1 (1.2–3.9) No smoking vs. heavy smoking, RR = 2.1 (1.1–4.0) Moderate smoking vs. heavy smoking, RR = 1.0 (0.6–1.6) Overt CD symptoms for high SES: No smoking vs. moderate smoking, RR = 0.7 (0.4–1.2) No smoking vs. heavy smoking, RR = 0.8 (0.5–1.3) Moderate smoking vs. heavy smoking, RR = 1.2 (0.6–2.3) Covert CD symptoms: No smoking vs. moderate smoking, RR = 1.1 (0.8–1.6) No smoking vs. heavy smoking, RR = 1.0 (0.8–1.2) Moderate smoking vs. heavy smoking, RR = 0.9 (0.7–1.0)	• Prenatal smoking was significantly associated with increased overt CD symptoms for participants of low SES, but not for participants of high SES, whereas covert CD symptoms were not associated with prenatal smoking, adjusted for other risks
Romano et al. 2006	• Nationally representative longitudinal survey • 2,946 children assessed at 0–2 years of age and followed to 7 years of age • Parent report on hyperactivity symptoms • Prenatal smoking reported retrospectively at first assessment	High and persistent hyperactive symptoms: OR = 2.75 (1.63–4.64)	• Prenatal smoking was significant predictor for high and persistent hyperactivity when controlling for other risks

Table 9.10*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Schmitz et al. 2006	• Case-control study • Nonreferred public school sample • 100 children with ADHD-I • 100 non-ADHD controls • 6–18 years of age, matched by gender and age • Clinical diagnosed of ADHD • Retrospective report of smoking at assessment time	ADHD-I diagnosis: ≥10 cigarettes vs. none, OR=3.44 (1.17–10.06) 1–9 cigarettes vs. none: OR = 1.09 (0.32–3.66)	• Prenatal smoking is associated with ADHD diagnosis, controlling for other risk factors
Wakschlag et al. 2006b	• Representative school based sample oversampled for delinquency risk • 448 boys • Parental report on ADHD and ODD symptoms • Prenatal smoking reported retrospectively at assessment	ODD: OR = 2.61 (1.14–5.97) ADHD + ODD: OR = 2.66 (0.99–7.16) ADHD alone: OR = 1.16 (0.69–1.94)	• Boys exposed to prenatal smoking were significantly more likely to develop ODD and comorbid ODD/ADHD but not ADHD alone
Wakschlag et al. 2006a	• 93 cases from a prenatal clinic sample oversampled for smoking followed to 24 months of age • Behavior problems assessed via maternal report and observation and combined into pervasiveness aggregate • Prenatal smoking assessed during pregnancy	Pervasiveness ($\chi 2 = 21.7$, $p < 0.000$) No problems for maternal report or observation: 25% of exposed vs. 70% of nonexposed Pervasive problems in both contexts: 30% of exposed vs. 2% of nonexposed toddlers	• Prenatal smoking is associated with increased problem behavior based on both maternal report and observational measures from 18–24 months
Whitaker et al. 2006	• Cohort study • Maternal report of behaviors (CBCL) at 3 years of age (n = 2,886) • Report at birth of smoking none, <1 pack, or at least 1 pack/day during pregnancy	Adjusted odds of behavior problems by smoking rate (nonsmoker as referent group) Aggressive: <1 pack/day, OR = 0.91 (0.64–1.30) ≥1 pack/day, OR = 1.40 (0.70–2.82 Anxious/depressed: <1 pack/day, OR = 0.75 (0.53–1.06) ≥1 pack/day, OR = 1.28 (0.65–2.54) Inattention/hyperactivity: <1 pack/day, OR = 0.92 (0.64–1.32) ≥1 pack/day, OR = 1.78 (0.90–3.49)	• After controlling for other risks, prenatal smoking was not associated with aggressive, anxious/depressed, or inattention/hyperactivity

Table 9.10*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Cornelius et al. 2007	• Prospective longitudinal study • 357 teen mothers • Maternal report on child behavioral symptoms • Prenatal smoking assessed each trimester during pregnancy • 6-year follow up	CBCL total: t = 2.5, p <0.01 Externalizing: t = 2.5, p <0.01 Internalizing: t = 2.39, p <0.01 Attention: t = 2.01, p <0.025 Aggression: t = 2.58, p <0.01 Delinquency: t = 2.5, p <0.05 Routh activity: t = 2.63, p <0.01 SNAP impulsivity: t = 2.3, p <0.025 Peer problem: t = 1.68, p <0.05	• Prenatal smoking was significantly associated with activity, impulsivity, aggression, externalizing, and behavior problems, controlling for other risks
Whitaker et al. 2006	• Cohort study • Maternal report of behaviors (CBCL) at 3 years of age (n = 2,886) • Report at birth of smoking none, <1 pack, or at least 1 pack/day during pregnancy	Adjusted odds of behavior problems by smoking rate (nonsmoker as referent group) Aggressive: <1 pack/day, OR = 0.91 (0.64–1.30) ≥1 pack/day, OR = 1.40 (0.70–2.82 Anxious/depressed: <1 pack/day, OR = 0.75 (0.53–1.06) ≥1 pack/day, OR = 1.28 (0.65–2.54) Inattention/hyperactivity: <1 pack/day, OR = 0.92 (0.64–1.32) ≥1 pack/day, OR = 1.78 (0.90–3.49)	• After controlling for other risks, prenatal smoking was not associated with aggressive, anxious/depressed, or inattention/hyperactivity
Cornelius et al. 2007	• Prospective longitudinal study • 357 teen mothers • Maternal report on child behavioral symptoms • Prenatal smoking assessed each trimester during pregnancy • 6-year follow-up	CBCL total: t = 2.5, p <0.01 Externalizing: t = 2.5, p <0.01 Internalizing: t = 2.39, p <0.01 Attention: t = 2.01, p <0.025 Aggression: t = 2.58, p <0.01 Delinquency: t = 2.5, p <0.05 Routh activity: t = 2.63, p <0.01 SNAP impulsivity: t = 2.3, p <0.025 Peer problem: t = 1.68, p <0.05	• Prenatal smoking was significantly associated with activity, impulsivity, aggression, externalizing, and behavior problems, controlling for other risks

Table 9.10*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Gatzke-Kopp and Beauchaine 2007	• 171 (136 male) children between 7–15 years of age referred for psychiatric concerns • Parental report on behavioral and psychiatric symptoms • Prenatal smoking for each trimester reported retrospectively at assessment	Nonsmoking vs. smoking m(SD): CSI conduct disorder: 4.98 (4.66), 9.05 (5.41), p = 0.006, d = 0.81 CSI ADHD: 29.51 (11.67), 38.24 (9.75) p = 0.005, d = 0.82 CBCL aggression: 71.34 (12.29), 77.14 (10.44), p = 0.024, d = 0.14 CSI depression: 6.77 (4.61), 9.29 (6.08), NS CSI dysthymia: 6.65 (3.86), 8.71 (5.18), NS CBCL anxious/depressed: 73.51 (11.64), 71.57 (14.66), NS CD symptoms: β = 0.24, p = 0.013 ADHD symptoms: β = 0.25, p = 0.007	• Prenatal smoking predicted conduct disorder and ADHD symptoms, after controlling for other risks
Huijbregts et al. 2007	• Population sample • 1,745 children born in Quebec • Parent report on behavioral symptoms • Prenatal smoking rate assessed retrospectively at 5 months	Physical aggression: $\chi2$ (2) = 8.4, p = 0.015; high vs. no aggression, OR = 1.33 (1.10–1.61) Hyperactivity: $\chi2$ (2) = 5.8, p = 0.121 Contrast between co-occurring PA+ADHD and PA only: OR = 1.39 (1.01–1.92)	• Prenatal smoking independently predicted co-occurring high PA and high hyperactivity-impulsivity compared to low levels of both behaviors, to high PA alone, and to high hyperactivity-impulsivity alone
Indredavik et al. 2007	• Prospective study of mothers enrolled before 20 weeks gestation • Behavior symptoms measured by youth and parent report • Prenatal smoking rates assessed during pregnancy • Follow-up assessment of offspring at 14 years of age (n = 84, 32 had mothers who had reported smoking during pregnancy)	ADHD symptoms (p = 0.04) Externalizing behaviors (p = 0.003) Internalizing behaviors (p = 0.04)	• Controlling for confounding factors, smoking during pregnancy was associated with higher levels of ADHD symptoms and both internalizing and externalizing behaviors in adolescent offspring
Langley et al. 2007	• Clinical sample of 356 children diagnosed with ADHD 6 and 16 years of age • Psychiatric symptoms assessed by parent interview and teacher report • Prenatal smoking reported retrospectively at assessment	Diagnosis of CD: OR = 3.14 (1.54–6.41) CD symptoms (r2 = 0.04, β = 0.18, t = 3.34, p = 0.001) ODD symptoms (r2 = 0.01 β = 0.12, t = 2.20, p = 0.03) Hyperactive-impulsive symptoms (r2 = 0.02, β = 0.11, t = 1.96, p = 0.05) Inattentive symptoms (r2 = <0.001, β = 0.02, t = 0.36, p = 0.72)	• Prenatal smoking was associated with CD symptoms and diagnosis, ODD symptoms, and with hyperactive-impulsive symptoms, but not inattentive symptoms
Lehn et al. 2007	• 95 twin pairs from longitudinal twin register study followed to 12 years of age • Maternal report on behavior symptoms • Prenatal smoking reported retrospectively	Prenatal smoking in twins with concordantly high attention problems (6/17, 35%) vs. concordant-low twins (6/59, 10%): $\chi2(1)$ = 6.27, p = 0.012	• Prenatal smoking was associated with the likelihood that both twins had high attention problems

Table 9.10*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Neuman et al. 2007	• Birth-record sample • 564 male and female twin pairs and 183 randomly chosen controls, 7–19 years of age • Maternal report on behavioral symptoms • Prenatal smoking assessed retrospectively at assessment	ADHD diagnosis: Any ADHD: OR = 1.58 (1.03–2.43) Combined: OR = 1.91 (0.97–3.76) Inattentive: OR = 1.52 (0.89–2.58) ADHD symptom count: Combined: OR = 1.92 (1.04–3.57) Inattentive: OR = 1.40 (0.79–2.46) Few symptoms: OR = 0.65 (0.49–0.92)	• Prenatal smoking is associated with ADHD diagnosis, and with overall symptoms, but not with inattentive symptoms
Nigg and Breslau 2007	• Population-based longitudinal study of 823 children 6–17 years of age • Parent and teacher report for ADHD, parent and child self-report interview for ODD, and child self-report interview for CD • Prenatal smoking assessed retrospectively at assessment	ODD: OR = 2.07 (1.13–3.81) CD: OR = 2.25 (1.03–4.91) ADHD: OR = 1.27 (0.85–1.90)	• Prenatal smoking predicted CD and ODD, but not ADHD when controlling for other risks
Smidts and Oosterlaan 2007	• Community based sample • 652 preschoolers 3–6 years of age • Randomly selected schools and centers • Parent report on behavior problems • Retrospective report on smoking	Hyperactive symptoms: $\beta = 0.088$, $p = 0.028$ Impulsive symptoms: $\beta = 0.122$, $p = 0.001$ Inattention: NS	• Prenatal smoking predicted ADHD behaviors, specifically hyperactivity and impulsivity
Todd and Neuman 2007	• Birth record drawn sample of 1,441 complete • Male and female twin pairs and 6 individual twins 7–19 years of age • Parent report on ADHD symptoms • Prenatal smoking reported retrospectively at assessment	ADHD symptoms or diagnosis: NS Interaction with all the 3 gene polymorphisms: severe ADHD, OR = 14.9 (1.6–136.1) Combined type ADHD: NS	• Prenatal smoking interacted with genotype to increase risk for severe combined type ADHD, but was not independently associated with ADHD

Table 9.10*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Altink et al. 2008	• 539 clinic-referred children with the combined subtype of ADHD and their 407 unaffected siblings, 6–17 years of age • Parent and teacher report of symptoms and clinical interview • Prenatal smoking rate reported retrospectively at assessment	ADHD diagnosis: $\chi2 = 6.91$, $p = 0.009$ 7-repeat allele by ADHD diagnosis: carriers ($\chi2 = 5.8$, $p = 0.015$); non-carriers ($\chi2 = 2.2$, $p = 0.142$) Behavioral symptoms: Teacher: Total: $F = 9.58$, $p = 0.002$ Hyperactive: $F = 10.87$, $p = 0.001$ Inattentive: $F = 6.87$, $p = 0.009$ Oppositional: $F = 1.66$, $p = 0.20$ Parent: Total: $F = 0.09$, $p = 0.76$ Hyperactive: $F = 0.20$, $p = 0.66$ Inattentive: $F = 0.00$, $p = 0.95$ Oppositional: $F = 2.22$, $p = 0.14$	• Affected children were more often exposed to prenatal smoking than unaffected children • There were limited main effects of prenatal smoking on severity of symptoms
Becker et al. 2008	• Prospective longitudinal study of 305 children from birth into early adulthood • Parent or teen report on ADHD, CD/ODD symptoms • Prenatal smoking assessed retrospectively at 3 months of age	Regression model of ADHD hyperactive-inattentive symptoms: Prenatal smoking: $\beta = -0.647$, $p = 0.024$ Prenatal smoking by *DAT1*+/+ genotype: $\beta = 0.907$, $p=0.012$ Inattentive: Prenatal smoking: $\beta = -0.103$, $p = 0.724$ Prenatal smoking by *DAT1*+/+ genotype: $\beta = 0.11$, $p = 0.784$ ODD/CD: Prenatal smoking: $\beta = -0.426$, $p = 0.141$ Prenatal smoking by *DAT1*+/+ genotype: $\beta = 0.6$, $p = 0.1$ Note: Data in text and table do not appear to match	• Prenatal smoking was associated with ADHD hyperactive-inattentive symptoms but not inattentive symptoms or ODD/CD
D'Onofrio et al. 2008	• Longitudinal follow-up study of nationally representative sample • 4,886 participants followed from youth through adulthood and their 8,889 children, 4–10 years of age • Maternal report on behavioral symptoms of ADHD and ODD • Prenatal smoking assessed during pregnancy	Offspring ADHD symptoms not significant when controlling for household. Note: text says there is residual effect but table does not show significance.	• When offspring were compared to their own siblings who differed in their exposure to prenatal nicotine, there was no effect of SDP on offspring ADHD CP and ODP

Table 9.10*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Kukla et al. 2008	• Longitudinal follow-up of 1,460 cases from a birth cohort followed at 8, 11, and 13 years of age • Data collected from parents, physicians, teachers • Prenatal smoking reported retrospectively at assessment	Selected outcomes: Behavior problems in class: Age 11: 30.3% vs. non 14.8%, p <0.001 Age 13: 31.7% vs. 16.0%, p <0.001 Attention: Age 11: 43.8% vs. 31.2%, p <0.01 Age 13: 50.0% vs. 29.8%, p <0.001 Memory: Age 11: 37.8% vs. 21.9%, p <0.001 Age 13: 21.0% vs. 16.8%, NS	• Prenatal smoking was associated with a range of externalizing behavior items as well as learning and school difficulties
Robinson et al. 2008	• Prospective cohort study of 2,868 live-born children to 2,979 mothers recruited at 18-weeks gestation • Parent report on behavioral checklist (CBCL) at 2 and 5 years of age • Prenatal smoking measured as number of cigarettes smoked/day at 18 weeks gestation	2-year, total behavior: OR = 1.30 (1.06–1.59) 2-year, internalizing: OR = 1.26 (1.02–1.55) 2-year, externalizing: OR = 1.23 (1.02–1.49) 5-year, total behavior: OR = 1.19 (1.03–1.17) 5-year, internalizing: OR = 0.97 (0.83–1.14) 5-year, externalizing: OR = 1.34 (1.17–1.54)	• Increasing rates of cigarettes smoked/day during pregnancy was predictive of internalizing and externalizing behaviors in young offspring, after controlling for other risks
Altink et al. 2009	• 50 clinic-referred children with the combined subtype of ADHD • 23 siblings • 105 controls • Parent and teacher report of symptoms and clinical interview • Prenatal smoking rate reported retrospectively at assessment	ADHD status: OR = 3.29 (1.48–7.30) ADHD status mediated by attentional control: OR = 2.42 (1.04–5.61)	• Prenatal smoking was associated with ADHD while controlling for other risks
Biederman et al. 2009	• Longitudinal case-control family studies • 536 siblings of children with and without ADHD from 2 identically designed • Clinical diagnosis with parental report • Retrospective report on prenatal smoking frequency	ADHD: OR = 2.5 (1.39–4.51) CD significant in control families only: OR = 3.3 (1.23–8.88) Bipolar disorder: HR = 3.28 (1.60–6.71) (exploratory) Depression: HR = 0.90 (0.49–1.64) Anxiety: HR = 1.20 (0.73–1.97) Alcohol dependence: HR = 1.12 (0.63–2.01) Smoking dependence: HR = 1.49 (0.94–2.36) Illicit drug dependence: HR = 1.03 (0.47–2.27)	• Prenatal smoking is a risk for ADHD and CD, independently of each other • The risk for CD appears to be conditional on family risk status • There was also an increased risk for bipolar disorder after controlling for other risk factors; prenatal smoking not associated with depression, anxiety disorders, or drug dependence

Table 9.10*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Buschgens et al. 2009	• Prospective population-based cohort study • 2,230 cases • Enrolled at 10–12 years of age • Maternal and teacher report on child behavior • Prenatal smoking rate assessed retrospectively at initial assessment	Inattention: (parent) β = 0.12; (teacher) β = 0.14 Hyperactive/impulsive: (teacher) β = 0.10 Aggression: (parent) β = 0.08; (teacher) β = 0.10 Delinquency: (parent) β = 0.11; (teacher) β = 0.07 Severe vs. no/some prenatal smoking: Hyperactive/impulsive: (teacher) β = 0.06 Aggression: (teacher) β = 0.07 Delinquency: (teacher) β = 0.10	• Prenatal smoking was associated with inattention, hyperactivity/impulsivity, aggression, and delinquency reported by parents and teachers
Froehlich et al. 2009	• Cross-sectional, nationally representative sample • 2,588 participants 8–15 years of age • ADHD diagnosis based on parental report of symptoms • Prenatal smoking reported retrospectively at assessment	ADHD diagnosis: OR = 2.4 (1.5–3.7) Prenatal smoking with third-tertile lead levels: OR = 8.1 (3.5–18.7)	• Prenatal smoking is associated with ADHD controlling for other factors • Children exposed to prenatal smoking and lead are at particular risk
Knopik et al. 2009	• Longitudinal female twin study • 2,892 adolescent twin pairs • Maternal report on inattentive, hyperactive/impulsive and conduct symptoms • Prenatal smoking reported retrospectively at assessment	Hyperactive/impulsive symptoms: First trimester: 1–10 cigarettes/day: β = 0.288, p <0.01 ≥11 cigarettes/day, β = 0.070, NS Beyond 1st trimester: 1–10 cigarettes/day, β = 0.199, p <0.01 ≥11 cigarettes/day, β = 0.134, p <0.05 Inattentive symptoms: First trimester: 1–10 cigarettes/day: β = 0.165, p <0.05 ≥11 cigarettes/day: β = 0.106, NS Beyond first trimester: 1–10 cigarettes/day: β = 0.214, p <0.01 ≥11 cigarettes/day: β = 0.082, NS Conduct problems: First trimester: 1–10 cigarettes/day: β = 0.140, p <0.01 ≥11 cigarettes/day: β = 0.097, NS Beyond first trimester: 1–10 cigarettes/day: β = 0.110, p <0.01 ≥11cigarettes/day: β = 0.059, NS	• Prenatal smoking of light to moderate frequency predicted risk for externalizing behavior • Heavy smoking only significant for hyperactivity/impulsivity beyond the first trimester

Table 9.10*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Kollins et al. 2009	• 151 children between 5–12 years of age with ADHD and 97 siblings • ADHD diagnosis based on parent report and clinical diagnosis • Prenatal smoking reported retrospectively at assessment	Adjusted for maternal postnatal smoking: Parent: Oppositional problems(log): 4.16 vs. 4.23, NS Inattentive: 74.60 vs. 76.78, NS Hyperactive: 76.70 vs. 80.38, NS Teacher Oppositional problems: OR = 1.46 (0.25–8.43) Inattentive: 72.92 vs. 61.69, p <0.001 (negatively associated) Hyperactive (log): 4.19 vs. 4.18, NS Adjusted for paternal postnatal smoking: Parent: Oppositional problems(log): 4.10 vs. 4.31, p <0.01 Inattentive: 73.29 vs. 79.11, NS Hyperactive:75.10 vs. 84.06, NS Teacher: Oppositional problems: OR = 2.75 (0.60–12.65) Inattentive: 68.25 vs. 67.11, NS Hyperactive(log): 4.16 vs. 4.24, NS	• After accounting for other factors, including postnatal smoking by mothers and fathers, few relations between prenatal smoking and behavioral symptoms emerged and in opposite direction
Obel et al. 2009	• Population-based pregnancy cohorts followed up to 7–8 years of age • 20,936 women with singleton pregnancies • Parent and teacher report on behavioral symptoms • Prenatal smoking assessed during pregnancy	Parent ratings of hyperactive symptoms: Low to moderate (1–9 cigarettes): Site 1: OR = 1.3 (1.0–1.6) Site 2: OR = 1.0 (0.8–1.3) Heavy (≥10): Site 1: OR = 1.6 (1.3–1.9) Site 2: OR = 1.4 (1.1–1.8) Teacher ratings: Low to moderate: Site 2: OR = 1.3 (0.9–1.7) Site 3: OR = 1.5 (1.1–2.1) Heavy: Site 2: OR = 1.5 (1.2–2.0) Site 3: OR = 1.3 (0.8–2.2)	• Prenatal smoking was associated with hyperactivity-inattention, controlling for other risks

Table 9.10*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Pringsheim et al. 2009	• Nested case-control study of children 5–17 years of age • Tourette syndrome + ADHD cases (n=181) • Tourette syndrome, no ADHD controls (n = 172) • Diagnoses established via clinical diagnostic interview • Prenatal smoking reported retrospectively at assessment	Tourette syndrome + ADHD vs. Tourette syndrome/no ADHD: OR = 2.43 (1.23–4.82)	• Children with Tourette syndrome + ADHD were more likely to have been exposed to prenatal smoking compared to children with Tourette syndrome but no ADHD, controlling for other risks
Rodriguez et al. 2009	• Population-based pregnancy cohorts followed up to 7–8 years of age • 21,678 women with singleton pregnancies • Parent and teacher report on behavioral symptoms • Prenatal smoking reported during pregnancy	Behavior problems: Boys: Site 1: (parent) OR = 1.15 (0.90–1.47) Site 1: (teacher) OR = 1.40 (1.09–1.80) Site 2: (parent) OR = 1.48 (1.22–1.79) Site 3: (teacher) OR = 1.64 (1.33–2.02) Girls: Site 1: (parent) OR = 1.46 (1.05–2.02) Site 1: (teacher) OR = 1.52 (0.92–2.51) Site 2: (parent) OR = 1.84 (1.37–2.47) Site 3: (teacher) OR = 1.57 (1.04–2.38)	• Prenatal smoking was consistently associated with an increase in risk of child symptoms (inattention/hyperactivity) when controlling for other risks
Stene-Larsen et al. 2009	• Population-based prospective cohort study • Followed 22,545 mothers from pregnancy to 18 months • Maternal report on behavior symptoms; prenatal smoking rate assessed during pregnancy	Externalizing behavior: ≥10 cigarettes: OR = 1.32 (1.03–1.70) 1–9 cigarettes: OR = 1.12 (0.94–1.35)	• Higher levels of prenatal smoking were associated with subsequent externalizing behaviors among 18-month-old children, controlling for other risk • Lower levels of prenatal smoking were not predictive
Thapar et al. 2009	• 815 families of children 4–11 years of age conceived with assisted reproductive technologies recruited from 20 fertility clinics • Parental report on behavior symptoms • Prenatal smoking rates reported retrospectively at assessment	ADHD symptoms: Related pairs: $\beta = 0.102$, $p < 0.02$ Unrelated pairs: $\beta = -0.052$, $p > 0.10$	• Association between prenatal smoking and outcome is higher in related siblings, suggesting an inherited effect
Agrawal et al. 2010	• Telephone interview data on 1,342 unique pregnancies, offspring of male twins aged 12–32, from 2 studies • Assessment of ADHD and CD not defined • Prenatal smoking rate assessed retrospectively at initial assessment	No significant association with ADHD or CD	• Prenatal smoking and ADHD or CD not significantly associated once controlling for other risks

Table 9.10*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Anselmi et al. 2010	• Birth cohort, hospital based sample • 4,423 children followed to 11 years of age • Parental report on behavior problems • Prenatal smoking assessed retrospectively at birth	Attention and hyperactivity problems at 11 years of age: PR = 1.28 (1.13–1.45)	• Prenatal smoking is associated with increased prevalence of attention and hyperactivity problems at 11 years of age
Ball et al. 2010	• 2,024 participants of pregnancy cohort study followed to adulthood • Child self-report on ADHD symptoms and diagnosis • Prenatal smoking assessed during pregnancy	ADHD diagnosis (comparison group = no smoking group): < half pack/day: OR = 1.2 (0.81–1.7) > half pack vs. < full pack/day: OR = 1.1 (0.75–1.6) > Full pack/day OR= 1.1 (0.57 – 1.8) Clinical characteristics (none vs. < half pack vs. > half pack) Severe ADHD impairment: $\chi2(2) = 1.5$, $p = 0.47$ Any treatment: $\chi2(2) = 0.76$, $p = 0.68$ Age of ADHD onset: $F(2,105) = 1.4$, $p = 0.26$ Duration: $F(2,104) = 0.90$, $p = 0.41$ Remission for ≥1 years: $\chi2(1) = 0.07$, $p = 0.80$	• No association was found between prenatal smoking and offspring ADHD diagnosis or clinical features
Boden et al. 2010	• 926 members of a longitudinal birth cohort, followed up to 14–16 years of age • Parent report and child self-report on CD and ODD symptoms for diagnostic clinical interview • Prenatal smoking assessed retrospectively at birth	CD: $\beta = 0.14$ (SE = 0.04), $p = 0.001$ ODD: $\beta = 0.09$ (SE = 0.04), $p = 0.008$	• Prenatal smoking is significantly associated with conduct disorder and ODD at 14–16 years of age controlling for other risks
Bos-Veneman et al. 2010	• Clinic sample of 75 children 6–18 years of age with Tourette syndrome (62) or chronic motor (12) or vocal tic (1) disorder • 11 participants exposed to prenatal smoking • Parent report of symptom severity; prenatal smoking reported retrospectively (any vs. none)	Children with a tic disorder and a first-degree relative with a mental disorder: Prenatal smoking was associated with a higher hyperactive-impulsive score (17.2 vs. 10.3) , $t = -4.07$, $p < 0.01$. Tic severity: NS	• In this sample of children with tic disorders, prenatal smoking exposure was associated with severity of ADHD symptoms, but not tic symptoms
Hay et al. 2010	• Longitudinal sample of 178 pregnant women from a representative urban population followed to 16 years of age • Parent report on antisocial (CD diagnosis and arrest) and violent (aggressive CD symptoms, arrests for violence) • Prenatal smoking rate assessed in pregnancy	Antisocial behavior or violent behavior: NS Cigarettes/day, m(SD): Antisocial = 6.0 (9.0) Not antisocial = 3.6 (6.0) Violent = 6.9 (7.7) Not violent =4.0 (7.1)	• Prenatal smoking did not predict antisocial or violent behavior outcomes for the children

Table 9.10*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Hutchinson et al. 2010	• Prospective study of 13,000 children from a child benefit registry followed to 3 years of age (13,788 for conduct problems and 13,654 for hyperactivity) • Parental report on behavioral symptoms • Prenatal smoking rates assessed retrospectively at 9 months	Boys: Conduct problems: Quit smoking: OR = 1.21 (0.83–1.78) Light smoking: OR = 1.44 (1.01–2.06) Heavy smoking: OR = 1.80 (1.28–2.54) Hyperactivity: Quit smoking: OR = 0.94 (0.67–1.32) Light smoking: OR = 1.56 (1.12–2.15) Heavy smoking: OR = 1.62 (1.13–2.33) Girls: Conduct problems: Quit smoking: OR = 0.61 (0.39–0.97) Light smoking: OR = 1.06 (0.70–1.63) Heavy smoking: OR = 1.34 (0.88–2.03) Hyperactivity: Quit smoking: OR = 0.96 (0.66–1.41) Light smoking: OR = 1.28 (0.90–1.81) Heavy smoking: OR = 1.17 (0.79–1.72)	• Prenatal smoking was associated with increased conduct problems and attention problem for boys, quitting smoking was associated with decreased conduct problems for girls, controlling for other risks
Lindblad and Hjern 2010	• Register study of 927,007 cases from a nationwide medical registry • ADHD medication use retrieved from medical records • Prenatal smoking rate assessed during pregnancy	ADHD medication: OR = 2.86 (2.66–3.07) 2 pregnancies of the same mother analyzed in a within-subjects design: OR = 1.26 (0.95–1.58)	• Prenatal smoking has a strong association with ADHD medication use, but this risk is primarily explained by genetic and socioeconomic confounding
Motlagh et al. 2010	• Case control study • Cases recruited from clinics and controls from community • Diagnostic interview of 222 children (7–18 years of age): 45 Tourette syndrome, 52 ADHD, 60 Tourette syndrome + ADHD • 65 controls: N = 1 exposed; control, 3 exposed Tourette syndrome only; 7 Tourette syndrome + ADHD; 9 with ADHD/no Tourette syndrome; low participation rate • Retrospective report of heavy smoking (>10 cigarettes/day) during pregnancy	ADHD: OR = 13.5 (1.6–113.2) TS: OR = 4.6 (0.45–46.6) TS+ADHD: OR = 8.5 (0.97–75.2)	• After controlling for sex, there was an association between heavy prenatal smoking and ADHD, but no association between heavy prenatal smoking and Tourette syndrome in offspring

Table 9.10*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Murray et al. 2010	• Prospective population survey • More than 16,000 children born in 1970, followed up to 34 years of age • Parent report on behavioral symptoms at 10 years of age, child self-report on criminal conviction at 30–34 years of age • Prenatal smoking assessed retrospectively shortly after birth	CP at age 10: Girls: OR = 1.8 (1.3–2.5) Boys: OR= 1.7 (1.4–2.2) Convictions at age 16–34: Girls: OR = 1.8 (1.2–2.7) Boys: OR = 1.4 (1.1–1.7)	• Prenatal smoking was predictive of conduct problems and criminal conviction, controlling for other risk
Nomuraet al. 2010	• Longitudinal study • 214 preschool children at risk for ADHD • Parent and teacher report on behavioral symptoms • Clinical interview for diagnoses • Prenatal smoking rate assessed retrospectively at 3–4 years of age	Behavioral symptoms: Inattention ($\chi2(3) = 8.03$, $p = 0.045$) Hyperactivity ($\chi2(3) =10.49$, $p = 0.015$) Total ADHD ($\chi2(3 = 9.28$, $p = 0.015$ Diagnoses: ADHD: OR = 4.00 (1.36–11.12) ODD: OR = 3.37 (0.22–38.46) ADHD+ODD: OR = 5.05 (1.47–12.50)	• Prenatal smoking was significantly associated with elevated inattention, hyperactivity/impulsivity, and total ADHD symptoms, comorbid ADHD and ODD and ADHD, but not ODD, controlling for other risks
Wakschlag et al. 2010	• Follow-up of 176 children into adolescence, from a prospective pregnancy cohort study over-sampled for exposure to prenatal smoking • Parent and youth report on behavioral symptoms • Prenatal smoking assessed in pregnancy via maternal report and cotinine	Parent reported CD symptoms: Girls: $\beta = 0.066$ (0.034), $p = 0.048$ Boys: $\beta = 0.213$ (0.069), $p = 0.004$	• Boys exposed to prenatal smoking with the low-activity *MAOA5´uVNTR* genotype were at increased risk for CD symptoms • In contrast, exposed girls with the high-activity *MAOA5´uVNTR* genotype were at increased risk for CD symptoms
Xu et al. 2010	• Nationally representative sample of 5,305 of children 4–15 years of age • Parent report of ADHD diagnosis • Prenatal smoking reported retrospectively at assessment	ADHD: OR = 2.06 (1.40–3.03)	• Prenatal smoking was significantly associated with parent reported ADHD diagnosis
Brennan et al. 2011	• 430 adolescents, hospital birth cohort sampled to include mothers with and without depression, followed up to 15, 20–21 years of age • Parent and youth report on externalizing behavior • Prenatal smoking assessed during pregnancy	Aggressive behavior Age 15: $\beta = 0.16$, $p < 0.01$ Age 20: $\beta = 0.11$, $p < 0.05$. Not associated with attention problems	• Prenatal smoking was associated with aggressive behavior in adolescence and young adulthood, including genetic risk • Not significant for youth attention problems

Table 9.10*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Gustafsson and Kallen 2011	• Case control sample • 237 children with ADHD and 31,775 without ADHD from a city wide birth register • Diagnoses from medical records; prenatal smoking assessed from medical records	ADHD diagnosis: OR = 1.35 (1.14–1.60)	• Prenatal smoking is predictive of a diagnosis of ADHD, controlling for other risks
Koshy et al. 2011	• Cross-sectional community study • 1,074 school children 5–11 years of age • Parent report of ADHD diagnosis • Prenatal smoking reported retrospectively at assessment	ADHD: Presence of smoking: OR = 3.19 (1.08–9.49) Heavy maternal smoker: OR = 10.03 (1.62–61.99)	• Prenatal smoking was associated with ADHD diagnosis, and there was a positive dose–response association of ADHD with the number of cigarettes smoked, while controlling for other risks
Lavigne et al. 2011	• Community sample • 678 preschool children (4 years of age) and their families • Diagnostic interviews, in-home visit using observation, interviews, and questionnaires conducted to assess symptoms of targeted conditions • Prenatal smoking reported retrospectively at assessment.	ADHD, ODD, anxiety, and depression measures: NS	• Prenatal smoking was not associated with symptoms of ADHD, ODD, anxiety, or depression among 4-year olds, controlling for other risks
Motlagh et al. 2011	• 81 clinic or CHADD referred children with ADHD, 8–18 years of age • Diagnoses established via clinical evaluation, parent and child interview, and rating scales • Retrospective report of heavy prenatal smoking at time of assessment	Exposed to heavy smoking: 12 out of 81 overall (15%) 9 out of 58 ADHD combined (16%, ns) 0 out of 3 ADHD hyperactive (0%, ns) 3 out of 20 ADHD inattentive (15%, ns) 4 out of 38 Tourette syndrome (11%, ns).	• Prenatal smoking was not associated with type of ADHD or Tourette syndrome comorbidity
Obel et al. 2011	• Population-based longitudinal birth cohort • Linked record set of 868,449 cases followed up to 5–19 years of age • Diagnoses from medical record set • Prenatal smoking recorded during pregnancy	Hyperkinetic disorder: Entire cohort: HR = 2.01 (1.90–2.12) Matched siblings: HR = 1.20 (0.97–1.49)	• Prenatal smoking and hyperkinetic disorder were not related when controlling for other risks using sibling-matched comparison
Palili et al. 2011	• Nationally representative longitudinal study • Following 2,695 children from birth to 7 and 18 years of age • Parent and teacher report on single item behavioral symptoms • Prenatal smoking assessed at birth	Prenatal smoking and outcome at age 7: Hyperactivity: OR = 3.24 (1.95–5.36) Inattention: OR = 1.68 (1.04–2.72) Impulsivity: OR = 1.89 (1.14–3.13) Age 18: Hyperactivity: OR = 8.78 (1.73–44.62) Inattention: OR = 4.19 (1.38–12.71) (impulsivity not analyzed due to now n)	• Prenatal smoking was predictive of ADHD-like symptoms at 7 and 18 years of age, controlling for psychosocial factors

Table 9.10*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Bandiera et al. 2011	• Nationally representative cross-sectional survey • 2,901 children and adolescents 8–15 years of age • Parental report on ADHD diagnosis • Prenatal smoking reported retrospectively at assessment	ADHD: OR = 2.62 (1.58–4.33)	• Prenatal smoking during pregnancy was positively associated with a diagnosis of ADHD, controlling for other risks
Sciberras et al. 2011	• Longitudinal study • 3,474 participants assessed at 4–5 years of age and followed to 6–7 years of age • Parent report of ADHD and SDQ hyperactivity symptoms • Prenatal smoking rate assessed retrospectively at 4–5 years of age	ADHD: Prenatal smoking on most days: OR = 3.31 (1.49–7.39) Occasional prenatal smoking: OR = 0.62 (0.17–.26) Hyperactive/inattentive symptoms: Prenatal smoking most days: OR = 1.86 (1.31–2.66) Occasionally prenatal smoking: OR = 1.26 (0.87–1.83)	• Prenatal smoking on most days was significantly predictive of parent reported ADHD diagnosis and symptoms, controlling for other risks; occasional smoking was not significant
St Pourcain et al. 2011	• Longitudinal birth cohort study • 5,383 singletons followed up from pregnancy to 18 years of age • Maternal report on behavior symptoms. Prenatal smoking assessed at 18 weeks of pregnancy.	Persistently impaired symptoms: OR = 1.95 (1.34–2.85) Intermediate symptoms: OR = 1.31 (0.94–1.83) Childhood limited symptoms: OR = 1.33 (0.91–1.96)	• Prenatal smoking during the first trimester was significantly associated with hyperactive-inattentive traits, specifically trajectories of persistent impairment, controlling for other risks
Wakschlag et al. 2011	• Follow-up of 211 children into adolescence, from a prospective pregnancy cohort study over-sampled for exposure to prenatal smoking • Parent report on composite symptoms for aggression, non-compliance, temper loss, low concern • Prenatal smoking assessed in pregnancy	Noncompliance ($\beta = 0.003$, $p < 0.01$) Aggression ($\beta = 0.002$, $p < 0.05$) Temper loss ($\beta = -0.001$, NS) Low concern ($\beta = 0.000$, NS) Paternal responsive engagement × exposure with disruptive behavior ($\beta = -0.004$, $p < 0.01$)	• Prenatal smoking uniquely predicted aggression and noncompliance, controlling for other risks • Paternal responsive engagement moderated exposure effects • Low concern and loss of temper were not significant
Biederman et al. 2012	• Case-control • 262 ADHD cases only 6–17 years of age • Parental report on psychiatric symptoms, also child report for children over 12 years of age • Heavy prenatal smoking assessed retrospectively	Lifetime prevalence of ADHD symptoms, ADHD subtype, age of ADHD onset, and persistent ADHD: NS ADHD subtype: Inattentive: OR = 1.3, p = 0.50 Hyperactive-impulsive: OR = 1.0, p = 0.98 Age of ADHD onset: $\beta = 0.1$, $p = 0.29$ ADHD impairment: OR = 1, p = 0.89 ADHD persistence: OR = 1, p = 0.98 Lifetime history of medication for ADHD: χ 2 (1) = 0.0009, p = 0.98	• No significant differences were found between persistent prenatal smoking and offspring ADHD diagnosis or clinical features, controlling for other risks

Table 9.10*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Ellis et al. 2012	• Birth cohort sample • 995 children 4 years of age 4 (citywide community stratified by SDQ scores) • Diagnoses established via parent interview • Prenatal smoking reported retrospectively at assessment	ADHD: OR = 2.59 (1.5–4.34) ODD: OR = 2.69 (1.84–3.91) Comorbid ADHD/ODD: OR = 2.68 (1.84–3.91)	• Prenatal smoking was found to increase the odds for ADHD, ODD, and comorbid ADHD/ODD, controlling for other risk factors
Freitag et al. 2012	• 275 clinic-referred children with ADHD, aged 5–13 years • Diagnoses via structured child interview and parent and teacher report • Prenatal smoking reported retrospectively at assessment	CD: β = 0.84 (0.10–1.58), p = 0.027 Hyperactive/impulsive: β = 1.82 (0.05–3.59), p = 0.044 Inattentive symptoms: β = 0.83 (-0.40–2.81), p = 0.176 Comorbid anxiety: β = 0.25 (-0.33–0.84) p = 0.396 ODD: β = 0.46 (-0.16–1.07), p = 0.149	• Among youth with ADHD, prenatal smoking was only associated with co-occurring conduct disorder, but not with hyperactive-impulsive symptoms, inattentive symptoms, ODD or anxiety
Langley et al. 2012	• 8,324 children from a prospective cohort study followed to 7 years of age • Parent and teacher report on ADHD symptoms • Prenatal smoking assessed during pregnancy	ADHD symptoms: β = 0.19 (0.12–0.27) p <0.001	• Prenatal smoking is associated with ADHD, controlling for other risk factors
Sagiv et al. 2013	• Population-based sample • 604 children followed from birth to 8 years of age • Parent and teacher report on behavior problems. • Pediatric medical record of ADHD diagnosis and medication use • Prenatal smoking rate assessed retrospectively at 2 weeks	CRS t-score difference: 1–10 cigarettes: 1.5 >10 cigarettes: 2.3; p for trend = 0.02 ADHD diagnosis in pediatric record: 1–10 cigarettes: RR = 0.9 (0.4–1.8) >10 cigarettes: RR = 1.6 (0.8–3.2) ADHD diagnosis based on parent record: 1–10 cigarettes: RR = 0.6 (0.2–1.6) >10 cigarettes: RR = 2.0 (0.7–5.5)	• Prenatal smoking was associated with behavior ratings but not significantly associated with ADHD diagnosis or medication use when controlling for other risks
Wilson et al. 2013	• Nationally representative sample • 2,070 children from a nested case-control study, follow up at 3, 4, and 5 years of age • Parent report of behavioral symptoms • Prenatal smoking reported retrospectively at assessment	Inconsistent CP vs. never: OR = 1.52 (1.08–2.15) Persistent CP vs. never: OR = 5.02 (2.6–9.71)	• Prenatal smoking is associated with conduct problems, controlling for other risks

Note: **ADHD** = Attention deficit hyperactivity disorder; **CBCL** = child behavior checklist; **CD** = conduct disorder; **CHADD** = children and adults had attention deficit disorder; **CI** = confidence interval; **CSI** child symptom inventory; **DSM** = *Diagnostic and Statistical Manual of Mental Disorders;* **HR** = hazard ratio; **m(SD)** = mean (standard deviation); **NS** = not shown; **ODD** = oppositional defiant disorder; **ODP** = offspring of diabetic parents; **OR** = odds ratio; **PA** = physical aggression; **RCT** = randomized clinical trials; **RR** = relative risk; **SDP** = smoking during pregnancy; **SES** = socioeconomic status; **SNAP** = Swanson, Nolan and Pelham rating scale.

Table 9.11*S* Studies on associations between prenatal smoking and anxiety and depression in children, 2000–2012

Study	Design/population	Estimate of effects (95% CI)	Findings
Hill et al. 2000	• 150 children 8–18 years of age at high or low familial risk for alcoholism • Diagnostic interview for conditions • Prenatal smoking rate reported retrospectively at assessment	• Depression: NS • Conduct: NS • Oppositional: NS • Anxiety: NS • Phobia: NS • ADHD: NS • Adjusted OR: not reported	• Prenatal smoking associated with depression, conduct disorder, and oppositional disorder, but not ADHD, anxiety or phobia • These findings were no longer significant after controlling for other risk factors
Maughan et al. 2001	• Prospective birth cohort study of all children born in the first week of April 1970 • Parental report on hyperactivity, conduct problems, adolescent self-report on conduct problems and depressive symptoms • Prenatal smoking rate assessed retrospectively at birth • England, Scotland, Wales • Followed up at 5, 10, and 16 years of age	• Conduct problems AOR (value not reported), p = 0.238	• Prenatal smoking not associated with hyperactivity, conduct problems, or depressive symptoms after controlling for postnatal smoking
Kardia et al. 2003	• 257 daily smokers from community • 207 with data on maternal smoking during pregnancy (not stated how defined/collected)	• Depression: CES-D (mean±SD): – Never smoker: 11.0 ± 9.1 – Ever smoker, not during pregnancy: 11.7 ± 7.5 – Ever smoker, during pregnancy: 13.8 ± 9.3, NS • Anxiety: STAI-Trait (mean±SD): – Never smoker: 37.3 ± 9.4 – Ever smoker, not during pregnancy: 39.7 ± 10.7 – Ever smoker, during pregnancy: 40.2 ± 8.8, NS	• Maternal smoking during pregnancy not associated with symptoms of depression or anxiety among current smokers
Teramoto et al. 2005	• Cohort study • 670 Japanese children 3 years of age • Maternal report of behaviors (CBCL) • Retrospective report of smoking during pregnancy, by dose	• Internalizing problems: OR = 1.28 (1.05–1.55) Total and externalizing problems: NS	• After controlling for other risks, smoking during pregnancy increased internalizing problems in 3-year-old children, but was not associated with total or externalizing behavioral problems
Mathews et al. 2006	• 3 cohorts of individuals with tic disorders (*DSM-IV*) • 180 individuals 3–59 years of age (72% under 18 years of age) • Rating scales of severity, self-report • Prenatal smoking reported retrospectively at assessment	• Increase total tic severity: F = 9.27, p <0.00001 Increase phonic tic severity: F = 25.84, p <0.00001 Motor tic severity: NS	• In this sample with tic disorders, prenatal smoking was associated with tic severity; there was no significant association between exposure to prenatal tobacco and presence of comorbid ADHD, controlling for other risks

Table 9.11*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Whitaker et al. 2006	• Cohort study • Maternal report of behaviors (CBCL) at 3 years of age (n = 2,886) • Report at birth of smoking none, <1 pack, or at least 1 pack/day during pregnancy	• Adjusted odds of behavior problems by smoking rate (nonsmoker as referent group) • Aggressive: – <1 pack/day: OR = 0.91 (0.64–1.30) – ≥1 pack/day: OR = 1.40 (0.70–2.82 • Anxious/depressed: – <1 pack/day: OR = 0.75 (0.53–1.06) – ≥1 pack/day: OR = 1.28 (0.65–2.54) • Inattention/hyperactivity: – <1 pack/day: OR = 0.92 (0.64–1.32) – ≥1 pack/day: OR = 1.78 (0.90–3.49)	• After controlling for other risks, prenatal smoking was not associated with aggressive, anxious/depressed, or inattention/hyperactivity
Indredavik et al. 2007	• Prospective study • Mothers enrolled before 20 weeks gestation • Behavior symptoms measured by youth and parent report • Prenatal smoking rates assessed during pregnancy • Follow-up assessment of offspring at 14 years of age (n = 84, 32 had mothers who had reported smoking during pregnancy)	• ADHD symptoms (p = 0.04) – Externalizing behaviors (p = 0.003) – Internalizing behaviors (p = 0.04)	• Controlling for confounding factors, smoking during pregnancy was associated with higher levels of ADHD symptoms and both internalizing and externalizing behaviors in adolescent offspring
Gatzke-Kopp and Beauchaine 2007	• 171 (136 male) children between 7–15 years of age referred for psychiatric concerns • Parental report on behavioral and psychiatric symptoms • Prenatal smoking for each trimester reported retrospectively at assessment	• Nonsmoking vs. smoking m(SD) • CSI – conduct disorder: 4.98 (4.66), 9.05 (5.41), p = 0.006, d = 0.81 – ADHD: 29.51 (11.67), 38.24 (9.75), p = 0.005, d = 0.82 – depression: 6.77 (4.61), 9.29 (6.08), NS – dysthymia: 6.65 (3.86), 8.71 (5.18), NS • CBCL – aggression: 71.34 (12.29), 77.14 (10.44), p = 0.024, d = 0.14. – anxious/depressed: 73.51 (11.64), 71.57 (14.66), NS • CD symptoms: $\beta = 0.24$, p = 0.013 • ADHD symptoms: $\beta = 0.25$, p = 0.007	• Prenatal smoking predicted conduct disorder and ADHD symptoms, after controlling for other risks
Robinson et al. 2008	• Prospective cohort study • 2,868 live-born children to 2,979 mothers recruited at 18-weeks gestation • Parent report on behavioral checklist (CBCL) at 2 and 5 years of age • Prenatal smoking measured as number of cigarettes smoked/day at 18 weeks gestation	• 2-year, total behavior: OR = 1.30 (1.06–1.59) • 2-year, internalizing: OR = 1.26 (1.02–1.55) • 2-year, externalizing: OR = 1.23 (1.02–1.49) • 5-year, total behavior: OR = 1.19 (1.03–1.17) • 5-year, internalizing: OR = 0.97 (0.83–1.14) • 5-year, externalizing: OR = 1.34 (1.17–1.54)	• Increasing rates of cigarettes smoked/day during pregnancy was predictive of internalizing and externalizing behaviors in young offspring, after controlling for other risks

Table 9.11*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Biederman et al. 2009	• 2 identically designed, longitudinal case-control family studies • 536 siblings of children with and without ADHD from • Clinical diagnosis with parental report • Retrospective report on prenatal smoking frequency	• ADHD: OR = 2.5 (1.39–4.51) • CD significant in control families only: OR = 3.3 (1.23 –8.88) • Bipolar disorder: HR = 3.28 (1.60 – 6.71) (exploratory) • Depression: HR = 0.90 (0.49–1.64) • Anxiety: HR = 1.20 (0.73–1.97) • Alcohol dependence: HR = 1.12 (0.63–2.01) • Smoking dependence: HR = 1.49 (0.94–2.36) • Illicit drug dependence: HR = 1.03 (0.47–2.27)	• Prenatal smoking is a risk for ADHD and CD, independently of each other • The risk for CD appears to be conditional on family risk status • Increased risk for bipolar disorder after controlling for other risk factors. • Prenatal smoking not associated with depression, anxiety disorders, or drug dependence
Liu et al. 2011	• Collaborative Perinatal Project • 611 adult offspring (38–48 years of age) of mothers enrolled in the cohort study • Self report on symptom scales • Prospective report of smoking.	• Anger temperament: T score 7.4 higher, β = 7.4 (0.5–14.4) • Depression: β = -0.2 (-1.3–0.9), NS • Anxiety: β = -0.5 (-2.7–1.8), NS	• Maternal smoking during pregnancy was not associated with symptoms of depression or anxiety in adulthood, but was associated with anger temperament, after controlling for other risks
Lavigne et al. 2011	• Community sample • 678 preschool children (4 years of age) and their families • Diagnostic interviews, in-home visit using observation, interviews, and questionnaires conducted to assess symptoms of targeted conditions • Prenatal smoking reported retrospectively at assessment	• ADHD, ODD, anxiety, and depression measures: NS	• Prenatal smoking was not associated with symptoms of ADHD, ODD, anxiety, or depression among 4-year olds, controlling for other risks
Freitag et al. 2012	• 275 clinic-referred children with ADHD, 5–13 years of age • Diagnoses via structured child interview and parent and teacher report • Prenatal smoking reported retrospectively at assessment	• CD: β = 0.84 (0.10–1.58), p = 0.027 • Hyperactive/impulsive: β = 1.82 (0.05–3.59) p = 0.044 • Inattentive symptoms: β = 0.83 (-0.40–2.81), p = 0.176 • Comorbid anxiety: β = 0.25 (-0.33–0.84), p = 0.396 • ODD: β = 0.46 (-0.16–1.07), p = 0.149	• Among youth with ADHD, prenatal smoking was only associated with co-occurring conduct disorder, but not with hyperactive-impulsive symptoms, inattentive symptoms, ODD or anxiety

Note: **ADHD** = attention deficit hyperactivity disorder; **AOR** = adjusted odds ratio; **CBCL** = child behavior checklist; **CD** = conduct disorder; **CES** = Center for Epidemiologic Studies for Depression; **CI** = confidence interval; **CSI** = Children's Somatization Inventory; ***DSM-IV*** = *Diagnostic and Statistical Manual of Mental Disorder-IV*; **HR** = hazard ratio; **NS** = not shown; **ODD** = oppositional defiant disorder; **OR** = odds ratio; **SD** = standard deviation; **STAI-Trait** = State Trait Anxiety Inventory-Triat.

Table 9.12*S* Studies on associations between prenatal smoking and Tourette syndrome in children, 2000–2011

Study	Design/population	Estimate of effects (95% CI)	Findings
Motlagh et al. 2010	• Case control study • Cases recruited from clinics and controls from community; diagnostic interview • 222 children (7–18 years of age): 45 Tourette syndrome, 52 ADHD, 60 Tourette syndrome + ADHD, 65 control • N = 1 exposed; control, 3 exposed Tourette syndrome only, 7 Tourette syndrome+ADHD, 9 with ADHD/no Tourete syndrome • Low participation rate • Retrospective report of heavy smoking (>10 cigarettes/day) during pregnancy • United States	• ADHD: OR = 13.5 (1.6–113.2) • ADHD: OR = 13.5 (1.6–113.2) • Tourette syndrome: OR = 4.6 (0.45–46.6) • Tourette syndrome + ADHD: OR = 8.5 (0.97–75.2)	• After controlling for sex, there was an association between heavy prenatal smoking and ADHD, but no association between heavy prenatal smoking and Tourette syndrome in offspring
Motlagh et al. 2011	• 81 clinic or CHADD referred children with ADHD, 8–8 years of age • Diagnoses established via clinical evaluation, parent and child interview, and rating scalesRetrospective report of heavy prenatal smoking at time of assessment	• Exposed to heavy smoking: – 12 out of 81 overall (15%) – 9 out of 58 ADHD combined (16%, ns) – 0 out of 3 ADHD hyperactive (0%, ns) – 3 out of 20 ADHD inattentive (15%, ns) – 4 out of 38 Tourette syndrome (11%, ns)	• Prenatal smoking not associated with type of ADHD or Tourette syndrome comorbidity

Note: **ADHD** = attention deficit hyperactivity disorder; **CHADD** = children and adults with attention deficit/hyperactivity disorder; **CI** = confidence interval; ***DSM-IV*** = *Diagnostic and Statistical Manual of Mental Disorder*; **NS** = not shown; **OR** = odds ratio.

Table 9.13*S* Studies on associations between prenatal smoking and intellectual disability in children, 2000–2009

Study	Design/population	Estimate of effects (95% CI)	Findings
Fried et al. 2000	• Ottawa Prenatal Prospective Study • 146 children 9–12 years of age • 44% female • 58% exposed to tobacco smoke • Canada	• Exposure associated with poorer scores on intelligence ($\beta = -0.10$, $p < .05$)	• Maternal cigarette smoking during pregnancy appears to have an impact on the fundamental aspects of visuoperceptual and cognitive functioning
Cornelius et al. 2001	• Maternal Health and Child Development Project • 593 children and adolescents 9–14 years of age • 50% female • 52% exposed to tobacco smoke • United States	• Reduced performance on verbal learning ($\beta = -0.04$, $p < .01$) • Assessment of cognitive efficiency errors ($\beta = 0.03$, $p < .025$)	• Observed significantly lower scores on standardized IQ tests among children and adolescents of mothers who smoked during pregnancy compared to offspring of mothers who did not smoke was accounted for entirely by maternal IQ • Smoking during pregnancy is unlikely to be a causal factor in children's IQ
Fried et al. 2003	• Ottawa Prenatal Prospective Study • 145 adolescents 13–16 years of age • 46% female • 56% exposed to tobacco smoke • Canada	• Heavy exposure associated with reduced overall intelligence ($\beta = -11.8$, $p \leq .001$)	• Association between maternal cigarette exposure during pregnancy and intelligence scores remained after adjusting for maternal education at birth
Breslau et al. 2005	• Randomly selected from lists of newborns from 2 hospitals • 713 children, adolescents, and young adults 6, 11, 17 years of age • 51.4% female • 31% exposed to tobacco smoke • United States	• ($\beta = -3.52$, $p \leq .005$) but attenuated after adjustment for mother's cognitive performance ($\beta = 0.04$, $p > .05$)	• Controlling for maternal education and IQ, eliminated association between maternal smoking during pregnancy and offspring IQ • Maternal smoking has no direct causal effect on child's IQ
Motensen et al. 2005	• Copenhagen Perinatal Cohort • 1,829 adolescent and young adults 16–26 years of age • 0% female • 50% exposed to tobacco smoke • Denmark	• Heavy exposure associated with an increased risk: OR = 3.4 (1.60–7.00) after controlling for parental social status, education, maternal age, maternal height, gestational age, birth weight.	• Maternal cigarette smoking during the third trimester, showed significant negative associations with young adult intelligence
Batty et al. 2006	• National Longitudinal Survey of Youth • 5,578 young people between 5–14 years of age on January 1, 1979 • % female not given • United States	• Light exposure associated with a 1.73-point decrement and heavy exposure associated with a 2.87-point decrement compared to no exposure (trend $p \leq .0001$); ≤0.3-point decrement when adjusted for mother's education (trend $p > .05$)	• Controlling for maternal education and maternal IQ eliminated the association between maternal smoking and reduced offspring IQ and cognitive ability

Table 9.13*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Huijbregts et al. 2006	• Québec Longitudinal Study of Children's Development • 1,544 children 3.5 years of age • 27% exposed to tobacco smoke • Canada	• Exposure associated with reduced intelligence ($\beta = -.126$, $p < .001$); after adjustment for additional covariates ($\beta = -.006$, $p = .805$)	• Prenatal smoking was related to performance on the WPPSI-R, the PPVT, and the VCR, although it did not independently predict any cognitive ability after maternal education was taken into account
Lambe et al. 2006	• Population-based registers • 375,942 adolescents 15 years of age • 49% female • 30% exposed to tobacco smoke in utero • Sweden	• Heavy exposure associated with increased risk of poor school performance: OR = 1.92 (1.86–1.98)	• Observed associations between maternal smoking during pregnancy and poor cognitive performance in the offspring might not be causal
Alati et al. 2008	• Avon Longitudinal Study of Parents and Children • 14, 541 singleton babies still alive at 1 year of age • Data collected from mothers and partners at approximately 8- and 18-week gestation (for the assessment of maternal and paternal alcohol and smoking) and from the assessment conducted as part of (clinic assessments) the children at 8 years of age	• Exposure not associated with increased risk: OR = 0.93 (0.75–1.16) after adjustment for sex, social class, parity, ethnicity, house ownership, crowding, maternal education, maternal smoking	• No strong statistical evidence that maternal alcohol and tobacco consumption during pregnancy were associated with childhood IQ with any greater magnitude than paternal alcohol and tobacco consumption
Braun et al. 2009	• Autism and Developmental Disabilities Monitoring Network Surveillance Project • 105,572 children 8 years of age • 49% female • 11% exposed to tobacco smoke • United States	• Exposure not associated with increased risk: RR = 1.34 (0.96–1.87) after adjustment for maternal age, maternal race, maternal education, marital status, child sex	• The risk of ID was mildly elevated among children whose mothers smoked ≥20 cigarettes/day during pregnancy but the risk was attenuated after adjustment for maternal factors
Kafouri et al. 2009	• Saguenay Youth Study • 503 adolescent and young adults 12–18 years of age • 52% female • 47% exposed to tobacco smoke • Canada-French speakers	• Exposure not associated with any cognitive measures with or without adjustment (full scale IQ: mean difference = 0.0, $p = .99$)	• No effect of maternal cigarette smoking during pregnancy on cognitive abilities of the adolescent offspring, after adjusting for maternal education (the most common confounder of maternal cigarette smoking during pregnancy)
Lundberg et al. 2009	• Population-based registers • 161,048 adolescents 15 years of age • 49% female • 30% exposed to tobacco smoke in utero • Sweden	• Heavy exposure of ≥10 cigarettes/day associated with increased risk of OR = 1.22 (1.14–1.31) after adjustment for parental factors	• Exposure associated with increased risk of intellectual impairment compared to no exposure

Note: **CI** = confidence interval; **ID** = intellectual disability; **IQ** = intelligence quotient; **OR** = odds ratio; **PPVT** = Peabody Picture Vocabulary Test; **RR** = relative risk; **VCR** = visually cued recall; **WPPSI-R** = Wechsler Preschool and Primary Scale of Intelligence-Revised.

Table 9.14*S* Association between maternal smoking and ectopic pregnancy, studies included in 2001–2010 Surgeon General's reports and subsequently published through March 2013

Study	Design/population	Source and definition of smoking status	Estimate of effects (95% CI)	Findings
WHO 1985	• Case-control study • 1,108 cases ectopic pregnancy (histologically confirmed, presenting to OB-GYN wards) • First subjects who met matching criteria and were admitted within 6 months of case presentation (matched to cases on age, parity, marital status) • 1,108 pregnant and 1,108 nonpregnant women • Nonpregnant women first eligible subjects admitted within 6 months of each case who presented for nongynecological related surgery (trauma, acute medical condition, elective surgery) • Study period: 1978–1980 • 12 centers (8 in developing countries and 4 developed countries)	Source: interview Current smoking = smoking at the time of conception [cases and pregnant controls] or at the time of interview [non-pregnant controls]	RR Pregnant controls: 3.1 (2.3-4.2) Non-pregnant controls: 1.8 (1.3-2.4)	• RRs calculated using referent group of women not using contraception, and with no history of PID, STI, or prior ectopic pregnancy • Adjustment for past PID or STI, ectopic pregnancy, and IUD use did not change RR estimates • Developing countries, pregnant controls (RR = 3.9, 95% CI, 2.7–5.9) and non-pregnant controls (RR = 2.4, 95% CI, 1.7–3.5) • Developed countries, pregnant controls (RR = 2.0, 95% CI, 1.2 -2.4) and nonpregnant controls (RR = 1.0, 95% CI, 0.6-1.8) • Did not collect data on sexual practices (too sensitive)
Handler et al. 1989	• Case-control study using medical record abstraction • 634 cases, women with ectopic pregnancy • 4,287 controls, women who delivered a singleton, live-born infant. • Excluded from cases and controls women with prior ectopic pregnancy • Excluded from controls women with history of spontaneous abortion or fetal deaths • Study period: 1983–1987 • University of Illinois Perinatal Network, 12 hospitals	Source: medical records Current smoking: smoking during pregnancy as recorded in medical record (ascertainment similar for cases and controls)	AOR* Overall: 2.5 (1.9-3.2) By cigarettes/day <10: 1.4 (.8-2.5) 10–19: 2.3 (1.5-3.4) 20–29: 3.2 (2.3-4.7) ≥ 30: 5.0 (2.9-8.7) Smoking as a continuous variable showed evidence of a dose-response relationship (regression coefficient = 0.049, S.E.=0.006)	• Results adjusted for maternal age and race • Adjustment for gravidity, parity, and prior abortion did not change findings (range of estimates 2.2–2.4) • Among women with a prior spontaneous abortion OR= 1.6, 95% CI, 1.1–2.3 • Among women with no prior spontaneous abortion OR=2.5, 95% CI, 2.1–3.1, AOR=2.5, 95% CI, 1.9–3.2 • Did not collect data on past or present PID, contraceptive use, or history of delayed fertility • Had no information on smoking at conception or duration of smoking

Table 9.14*S* Continued

Study	Design/population	Source and definition of smoking status	Estimate of effects (95% CI)	Findings
Coste et al. 1991	• Case-control study • 7 Paris maternity hospitals • 279 cases women with ectopic pregnancy confirmed by celioscopy or laparotomy • 279 control women who delivered in the same center, immediately following the operation of index case • Study period: 1988 • France	Source: Interview Current smoking: smoking at the time of conception	COR Overall: 1.6 (1.1-2.3) Cigs/day 1-10: 1.2 (0.8-2.0) 11-20: 1.4 (1.2-3.1) >20: 1.6 (0.9-6.6) AOR* Cigs/day 1-10: 1.3 11-20: 2.0 >20: 2.5 (CIs not shown)	• Adjusted for hospital, age, prior appendectomy, prior ectopic pregnancy, prior tubal surgery, prior spontaneous abortion, previous use of IUD, history of PID, induced conception, type of contraception at conception • Restriction of analysis to married women not using contraception at conception did not change findings
Kalandidi et al. 1991	• Case-control study • Maternity hospital and outpatient clinics • 63 cases, women with ectopic pregnancy admitted to hospital • 133 controls, women visiting outpatient clinic of the same hospital, matched for age, education, residence, hospital, date of interview, socioeconomic status and parity, and stage of pregnancy • Study period: 1986–1987 • Athens, Greece	Source: interview Current smoking: not clearly defined	ARR* 2.35 (1.19-4.67)	• Adjusted for being married, ever users of IUDs, and any induced abortions
Stergachis et al. 1991	• Group Health Cooperative HMO case-control study • 274 cases (women diagnosed with tubal ectopic pregnancy, hospitalized in participating hospitals • 727 control (women of childbearing age selected randomly from HMO's membership files, then matched by age and county of residence) • Reference date assigned to each control, excluded women >4 months pregnant at the reference date • Study period: 1981–1986 • Washington	Source: interview Current smoking: at the time of conception (if pregnant) or the corresponding reference frame (non-pregnant controls)	AOR* Overall: (1.0-2.0) Cigarettes/day <10: 1.8 (1.0-3.2) 10-19: 1.6 (0.8-2.4) ≥ 20: 1.2 (0.8-1.8) Test for linear trend not significant	• Adjusted for age, reference date, county of residence, gravidity, and lifetime number of sex partners • Assessed confounding of additional variables: race, education, income, history of gonorrhea, history of IUD use, age at first intercourse, douching history, use of contraception at the reference date, type of contraception used at the reference date) • These did not alter odds ratios and were not included in final models

Table 9.14*S* Continued

Study	Design/population	Source and definition of smoking status	Estimate of effects (95% CI)	Findings
Parrazzini et al. 1992	• Case-control study • Maternity hospital and obstetric and gynecology clinic • 120 cases, women diagnosed with ectopic pregnancy, confirmed by laparoscopy or laparotomy admitted to 2 sites • 209 controls, women who gave birth to healthy term (>37 weeks gestation) infants randomly selected days at the hospital where the cases had been identified, within 1 month of case ascertainment and with comparable age distributions between cases and controls. • Study period: 1989–1991 • Milan, Italy	Source: interview Current smoking: smoking in the preconception period	ARR* cigarettes/day: ≤ 10: 1.1 (0.5–2.3) >10: 1.9 (.1.1–3.5) ARR** cigarettes/day: ≤ 10: 0.8 (.4-1.6) >10: 1.1 (.6–2.6)	• Adjusted for age • Reference group is never smoked • Adjusted for age, education, infertility, abdominal surgery, PID/salpingitis, age at first intercourse, number of sexual partners • Test for trend was not significant • Retrospective recall of smoking after delivery from controls
Phillips et al. 1992	• Brigham and Women's Hospital • Case-control study • Three main exposures: smoking, chlamydia infection, and douching • 69 cases, women 18–40 years of age with surgically confirmed ectopic pregnancy receiving care at the study hospital • 101 controls, women with IUP pregnancy <= 14 weeks gestation receiving care from physicians at the study hospital • Excluded women with history of tubal reconstructive surgery or tubal sterilization, previous in vitro fertilization, IUD in place within 14 weeks before enrollment, inability to speak English • Study period: 1986–1987 • Boston, MA	Source: interview Current smoking: smoking during the month of conception Former smoking: smoking during the month before conception	COR Overall: 4.2 (2.1–8.2) AOR* Overall: 2.4 (1.2–5.1) Cigarettes/day: 0-10: 3.2 (1.1–8.9) 11-20: 3.2 (0.6–18.1) ≥21: 1.4 (0.4–5.3)	• Nonsmokers and former smokers combined for reference group. • Adjusted for number of previous sexual partners, prior ectopic pregnancy, and prior PID • When prior PID omitted from models as potential mediating factor, AOR = 2.7 (1.3-5.6) • When the analysis restricted to women with no previous ectopic pregnancy, AOR = 1.9 (0.9-4.1) • No increased risk for former smokers

Table 9.14*S* Continued

Study	Design/population	Source and definition of smoking status	Estimate of effects (95% CI)	Findings
Saraiya et al. 1998	• Case-control study • Inner-city hospital • 196 cases, Non-Hispanic black women, 18–44 years of age, surgically confirmed ectopic pregnancy and admitted to study hospital • 1,119 controls, Non-Hispanic black women who delivered a live or stillborn infant weighing ≥500gm at the same hospital during the same period, women who sought an induced abortion identified at the preabortion visit to the ambulatory surgical clinic of their hospital • Controls from a systematic random sample of the two groups, selected in 4:1 proportion to reflect pregnant women in the population served by the hospital (planning to complete pregnancy vs. those who don't seek to carry their pregnancy to term) • Excluded women with a history of ectopic pregnancy, tubal surgery, or current IUD use • Study period: 1988–1990 • Atlanta, GA	Source: interview Current smoking: smoked ≥ 100 cigarettes in their lifetime, smoking in the periconceptional period (in 6 months before LMP through 1 month after LMP) Never smoked: smoked < 100 cigarettes in their lifetime	COR Overall: 2.4 (1.7–3.3) AOR* Overall: 1.9 (1.4–2.7) Cigarettes/day: 1–5: 1.6 (.9–2.9) 6–10: 1.7 (1.1–2.8) 11–20: 2.3 (1.3–4.0) >20: 3.5 (1.4–8.6)	• Never and former smokers combined for reference group • Adjusted for age, previous parity, infertility, and douching • No effect modification by age, previous parity, infertility, or douching • Dose-response with smoking as continuous variable was significant (p = 0.0002) • Collected data on other variables that were not significant in final models • Education, marital status, household income, previous gravidity, former IUD use, prior pelvic surgery, history of induced abortions, history of spontaneous abortions, number of sexual partners, history of douching, history of PID, history of any STIs.
Bouyer et al. 2003	• Case-control study • 803 cases ectopic pregnancy cases included in a regional register; married or living with a partner and not using contraception • 1,683 controls deliveries to women who gave birth at the center in which the case was treated and, which occurred very shortly after treatment of the case. Excluded women with induced abortion. • Study period: 1993–2000 • Central France	Source: interview and medical records Current smoking: smoking at conception	COR Cigarettes/day: 1–9: 1.6 (1.2, 2.1) 10–19: 2.9 (2.2–3.7) ≥20: 3.7 (2.8–5.0) AOR* Cigarettes/day: 1–9: 1.7 (1.2, 2.4) 10–19: 3.1 (2.2–4.3) ≥20: 3.9 (2.6–5.9)	• Adjusted for age, prior spontaneous abortion, prior induced abortions, appendectomy, prior STDs, prior tubal surgery, prior use of IUD, history of infertility • Used random effects model to account for repeat pregnancies. • Adjusted attributable risk = 35% • Because some case women might have undergone induced abortion if their pregnancies had been intrauterine, the authors restricted cases and controls to women married or living as a couple

Table 9.14*S* Continued

Study	Design/population	Source and definition of smoking status	Estimate of effects (95% CI)	Findings
Karaer et al. 2006	• Case-control study • Zekai Tahir Burak Women Health Education and Research Hospital • 225 cases women with histopathological examination-confirmed ectopic pregnancy • 3 controls groups (combined for analysis) • 195 women with uncomplicated intrauterine pregnancy at 14 weeks gestation or less • 29 women with induced abortions • 150 nonpregnant women • Study period: 2003–2005 • Ankara, Turkey	Source: interview Current smoking: smoking at the time of conception	COR Cigarettes/day: 1–9: 1.4 (0.8–2.1) 10–19: 2.0 (1.0–3.9) >20: 3.6 (1.7–7.3) AOR* Overall: 1.7 (1.1–2.6)	• Adjusted for age, marital status, prior ectopic pregnancy, prior caesarean section, age at first intercourse, multisexual partner, vaginal douching, prior PID, prior infertility, induced conception cycle, in vitro fertilization, barrier methods, IUD • No statistical test results presented for dose-response • Did not discuss selection of control groups, distribution of women across control groups, or analysis of separate control groups
Roelands et al. 2009	• Hospital discharge data from exposure and diagnosis, prevalence of outcomes compared between smokers and nonsmokers • Representing 90% of all US hospital discharges • 21,207,981 weighted and 4,387,959 unweighted count of pregnancy-related hospital discharges (2,122 smokers with ectopic pregnancy • 11,566 nonsmokers with ectopic pregnancy) • United States	Source: ICD-9 codes from hospital discharge records: used to identify smoking status (305.1 and V15.82)	OR 5.4 (4.6–6.3) Crude	• No adjustments. • Smoking likely underreported in hospital discharge data: smoking prevalence in study population only 4%

Note: **AOR** = adjusted odds ratio; **ARR** = adjusted relative risk; **CI** = confidence interval; **COR** crude odds ratio; **HMO** = health maintenance organization; ***ICD*** = *International Classification of Diseases*; **IUD** = intrauterine device; **IUP** = intrauterine pregnancy; **LMP** = ?; **PID** = Pelvic Inflammatory Disease; **RR** = relative risk; **S.E.** = standard error; **STD** = sexually transmitted disease; **STI** = sexually transmitted infection.

Table 9.15*S* Studies on the effect of maternal active smoking on spontaneous abortion (SAB) risk

Study	Design/population	Source and definition of smoking status	Estimate of effects (95% CI)	Findings
Maconochie et al. 2007	• Nested case-control study, 2-stage postal survey • 603 cases women 18–55 years of age whose most recent pregnancy ended in first trimester miscarriage • 6,116 controls women 18–55 years of age whose most recent pregnancy progressed beyond 12 weeks • Study period: 2001	Source: survey Smoking status: smoked in first trimester of pregnancy	AOR* Cigarettes/day: <5: 0.97 (0.69–1.36) 5–10: 0.91 (0.60–1.37) 11–20: 1.68 (1.16–2.42) 21–30: 1.29 (0.56–2.99)	• Adjusted for year of conception, maternal age, previous miscarriage, previous live birth
Blohm et al. 2008	• Longitudinal study of 3 cohorts of women (born in 1962, 1972, 1982) • Followed every 5 years through questionnaires and hospital record reviews for legal abortions, miscarriages, and other pregnancy outcomes • Main outcomes assessed at 29 years of age • Study period: 1981–2001 • Götegorg, Sweden	Source: questionnaire Smoking status: no additional details provided	COR Overall: 1.8 (1.1–2.9) AOR* Not significant (data not reported)	• Adjusted for BMI, exercise, ever use of combined oral contraceptive pill • 5- and 10-year follow-up >80%
Gallicchio et al. 2009	• Design: cross-sectional survey • Women age 21–50 registered as cosmetologists (n = 350) or other (realtors, teachers, nurses, retail clerks) (n = 397) • Excludes women with hysterectomy or oophorectomy • Women asked about past pregnancies and outcomes by survey; miscarriage defined as SAB at <20 weeks gestation; data collected on up to 5 pregnancies per woman • Study period: 2005–2008 • Setting: Baltimore, MD, metropolitan region	Source: mailed survey Smoking status defined by whether women reported smoking during pregnancy	AOR* 1.53 (1.09–2.16)	• Adjusted for age, race, education, alcohol use • Used repeated measures analysis of variance to take into account multiple pregnancies per mother • Collected data on marital status, BMI, income, health insurance, hormone and oral contraceptive use, family medical history
Bhattacharya et al. 2010	• Cohort study • Data on first pregnancies abstracted from the Aberdeen Maternity and Neonatal Databank. Miscarriages identified from *ICD-9* codes (spontaneous pregnancy loss <24 or 28 weeks gestation depending on coding rules) • Study period: 1950–2000 • 22,988 women with complete data for smoking analysis • Scotland	Source: self-reported smoking status coded at first contact with hospital staff for each pregnancy	AOR* Overall: 1.13 (1.05–1.22)	• Adjusted for age, year of event • Smoking status missing for 44,237 women

Table 9.15*S* Continued

Study	Design/population	Source and definition of smoking status	Estimate of effects (95% CI)	Findings
Zhang et al. 2010	• Case-control study • 326 cases women with 3–6 miscarriages never investigated, excluded those with endocrine or metabolic disorders, autoimmune diseases, venous thrombosis, uterine abnormalities • Women controls randomly selected from 1,000 women with no history of pregnancy loss and at least 1 live birth or an ongoing pregnancy of >20 weeks • Matched to cases on age and education • Study period: 2007–2009 • 3 institutions on Guangdong Province, China	Source: questionnaire Smokers: smoking at enrollment Never smokers: smoked <100 cigarettes in past 5 years	AOR* Cigarettes/day: <10: 1.42 (0.12–17.17) 10–19: 1.62 (0.13–20.87) ≥20: 2.11 (0.09–47.66)	• *Adjusted for BMI, family history of miscarriage, smoking exposure to ETS, alcohol consumption, and coffee intake • Response rates of cases and controls differed (95% and 40%, respectively) • Smoking status at early pregnancy not clearly defined
Baba et al. 2011	• Case-control study medical record review • 430 cases of women consecutively hospitalized in the study hospital for medical procedure for early spontaneous abortion (<12 weeks gestation) • 860 controls women with term deliveries in the study hospital, randomly selected, matched to cases on age and calendar year • Study period: 2001–2005 • Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka, Japan	Source: medical records Smoking status: smokers included women who quit after becoming pregnant; no additional details provided	COR Cigarettes/day: 1–19: 1.24 (0.83–1.85) ≥20: 1.99 (1.18–3.35) *P* for trend = 0.03 AOR* Cigarettes/day: 1–19: 1.30 (0.84–2.02) ≥20: 2.39 (1.26–4.53) *P* for trend = 0.02	• Adjusted for past spontaneous abortion, induced abortion, treatment for infertility, BMI, drinking status, employment, husband's age, and husband's smoking
Campbell et al. 2011	• Cross-sectional study • Aboriginal and Torres Straight Islander women 15–44 years of age surveyed, linked to hospital records for pregnancy-related conditions from survey through 2008 (births of >20 weeks gestation, miscarriages, no elective terminations) • Study period: 1999–2008 • 16 rural and remote indigenous communities in Bowen, Cairns, and Cape York, Torres Straight, and Mount Isa Health Service Districts	Source: baseline survey, self-reported	PR 0.89 (0.52–1.53) APR* 0.94 (0.55–1.61)	• Adjusted for age and ethnicity • Smoking status at the time of the pregnancy subsequent to the survey not assessed • Also collected data on alcohol use, BMI, diet, physical activity, urine tested for STIs (Chlamydia trachomatis and Neisseria gonorroeae). SAB significantly associated with alcohol use and STIs

Note: **AOR** = adjusted odds ratio; **APR** = adjusted prevalence ratio; **BMI** = body mass index; **CI** = confidence interval; **COR** = crude odds ratio; **ETS** = environmental tobacco smoke; ***ICD*** = *International Classification of Diseases*; **PR** = prevalence ratio; **STI** = sexually transmitted infection.

Table 9.16*S* Experimental studies of the association between smoking and erectile dysfunction

Study	Design/population	Stimulus	Findings
Gilbert et al. 1986	• Humans: randomized controlled trial with 42 smokers • 18–44 years of age	Visual sexual stimulation	• High-nicotine cigarettes reduced the extent to which penile diameter increased
Glina et al. 1988	• Humans: acute experiment with 12 smokers • 22–65 years of age	Erection pharmocostimulation	• Smoking 2 cigarettes reduced intracavernous pressure measurements
Juenemann et al. 1987	• Animals: acute experiment using dogs	Cavernous nerve electrostimulation	• Inhalation of cigarette smoke reduced erectile parameters
Xie et al. 1997	• Animals: chronic experiment using rats	Cavernous nerve electrostimulation	• Inhalation of cigarette smoke did not alter erection parameters
Guay et al. 1998	• Humans: acute experiment with 10 smokers • 32–62 years of age	Sleep-related erection	• Cessation of cigarette smoking improved erectile parameters

Table 9.17*S* Cross-sectional studies of the association between smoking and the risk of erectile dysfunction

Study	Design/population	Prevalence (%) of erectile dysfunction by smoking status	*p* Value
Feldman et al. 1994[a]	• U.S. residents • 40–70 years of age • Studied during 1987–1989 • Boston, MA	• Never and former: 9.3 • Current: 11.0	>0.200
Mannino et al. 1994[a]	• U.S. veterans • 31–49 years of age • Studied during 1985–1986	• Never: 2.2 • Current: 3.7 • Former: 2.0	0.005[b]
Feldman et al. 2000[c]	• U.S. residents • 40–70 years of age • Studied during 1987–1997 • Boston, MA	• Never and former: 14.0 • Current: 24.0	0.03
Kleinman et al. 2000	• U.S. men • 40–70 years of age • Studied during 1987–1997 • Boston, MA	• Never: NR • Current: NR • Former: NR	NR
Parazzini et al. 2000[a]	• Italian men • >18 years of age • Studied during 1996–1997	• Never: 24.2 • Current: 35.6 • Former: 40.2	NR
Blanker et al. 2001[a]	• Dutch men • 50–78 years of age • Studied during 1995–1998	• Never and former: NR • Current: NR	NR
Martin-Morales et al. 2001[a]	• Spanish men • 25–70 years of age • Studied during 1998–1999	• Never and former: NR • Current: NR	NR
Bacon et al. 2003[a]	• U.S. male health professionals • 53–90 years of age • Data from 2000	• Never: NR • Current: NR • Former: NR	NR
Shiri et al. 2005	• Finnish men • 50–75 years of age • Studied during 1994–1999	• Never: 16.3 • Current: 20.9 • Former: 26.1	NR
Lam et al. 2006b	• Chinese men • Studied in 2001 • Hong Kong	• Never: 42.5 • Former: 40.8 • Current: • ≤20 cigarettes/day: 43.0 • >20 cigarettes/day: 51.2	NR
Millett et al. 2006[a]	• Australian men • 16–59 years of age • Studied during 2001–2002	• Nonsmokers: 8.8 • Current: • ≤20 cigarettes/day: 9.4 • >20 cigarettes/day: 14.7	<0.001
He et al. 2007	• Chinese men • 35–74 years of age • Studied during 2000–2001	• Smokers vs. never smokers: • 35–44 years of age: 6.4 vs. 4.6 • 45–54 years of age: 17.8 vs. 14.8 • 55–64 years of age: 44.0 vs. 35.6 • 65–74 years of age: 54.7 vs. 45.6	0.01 (overall); <0.0001 (age trend)

Table 9.17*S* Continued

Study	Design/population	Prevalence (%) of erectile dysfunction by smoking status	*p* Value
Kupelian et al. 2007	• U.S. men • 30–79 years of age • Studied during 2002–2005 • Boston, MA	• Never: NR • Never (passive): NR • Current: NR	NR

Note: **NR** = not reported.
[a]Prevalence study.
[b]Significant results.
[c]Incidence study.

Chapter 10
Other Specific Outcomes

Table 10.1*S* Summary of evidence from case-control studies on the association between smoking and age-related macular degeneration (AMD) *S-347*

Table 10.2*S* Summary of evidence from cross-sectional studies on the association between smoking and age-related macular degeneration (AMD) *S-356*

Table 10.3*S* Summary of evidence from prospective cohort studies on the association between smoking and age-related macular degeneration (AMD) *S-362*

Table 10.4*S* Summary of evidence from other types of studies on the association between smoking and age-related macular degeneration (AMD) *S-370*

Table 10.5*S* Studies on the association between active smoking and dental caries *S-374*

Table 10.6*S* Studies on exposure to tobacco smoke and dental caries *S-379*

Table 10.7*S* Studies on smoking and failure of dental implants *S-383*

Table 10.8*S* Characteristics of studies included in the meta-analysis on smoking and diabetes *S-393*

Table 10.14*S* Studies on the association between smoking and rheumatoid arthritis (RA) risk *S-400*

Table 10.15*S* Studies on the association between smoking and rheumatoid arthritis (RA) severity *S-403*

Table 10.16*S* Studies on the association between smoking and rheumatoid arthritis (RA) treatment response *S-405*

Table 10.17*S* Studies on the association between smoking and systemic lupus erythematosus (SLE) risk *S-406*

Table 10.18*S* Studies on the association between smoking and systemic lupus erythematosus (SLE) severity and manifestations *S-408*

Table 10.19*S* Studies on smoking and systemic lupus erythematosus (SLE) treatment response *S-409*

Table 10.20*S* Characteristics of the studies on the effects of current smoking on Crohn's disease or ulcerative colitis *S-410*

Table 10.21*S* Characteristics of the studies on the effects of former smoking on Crohn's disease or ulcerative colitis *S-427*

Table 10.1*S* Summary of evidence from case-control studies on the association between smoking and age-related macular degeneration (AMD)

Study	Design/population	AMD assessment/type studied	Findings (95% CI)
Maltzman et al. 1979	• 30 cases with AMD • 30 age-, gender-, and race-matched controls	Data not reported	• No association with smoking was found among the 10 AMD cases and 7 controls who reported being smokers
Hyman et al. 1983	• 162 AMD cases and 175 age-, gender-, and ophthalmologist-matched controls from 34 clinics • Baltimore, Maryland	AMD classified by physician-diagnosed drusen and vision loss due to AMD; fundus photographs used to verify classification	• Male smokers, OR = 2.6 (1.15–5.75), were more likely to have AMD than female smokers, OR = 0.84 (0.48–1.47) • Combined population of male and female smokers had nonsignificant increased odds of AMD, OR = 1.2 (0.80–1.89)
Blumenkranz et al. 1986	• 26 AMD cases (disciform scarring or CNV) • 23 age- and gender-matched controls	Fundus photographs graded to determine AMD status	• Compared with never smokers, ever smokers had nonsignificant increased odds of AMD, OR = 1.25 (0.3–4.4)
Eye Disease Case-Control Study Group 1992	• 421 NV AMD cases and 615 controls from 5 centers • United States	AMD classified by physicians if drusen in at least 1 eye, visual acuity worse than 6/6 or Amsler grid distortion, and at least 1 retinal sign of NV AMD; fundus photographs were used to verify a subset of cases and all controls	• After adjusting for age, gender, and clinic, current smokers, OR = 2.8 (1.8–4.2), and former smokers, OR = 1.5 (1.1–2.1), were more likely to have NV AMD than never smokers
Tsang et al. 1992	• Sydney Eye Hospital clinics • Participants 58–89 years of age • 80 AMD cases (23 drusen, 5 pigmentary abnormalities, 34 NV AMD, and 18 GA AMD) • 86 controls (spouses or acquaintances) • Australia	Fundus photographs graded to determine AMD status per the study's protocol	• In a comparison between AMD cases and controls, study did not observe any significant differences in mean number of packs of cigarettes smoked/day, mean pack-years, or mean years of smoking abstinence • After controlling for other cardiovascular risk factors and compared with never smoking, current smoking was associated with increased risk of AMD, OR = 2.8 (0.9–8.2)
Tamakoshi et al. 1997	• Men 50–59 years of age who attended a physical exam • 56 NV AMD cases • 82 controls • Japan	Fundus photographs and fluorescein angiography	• Compared with nonsmoking, current smoking associated with NV AMD, OR = 2.97 (1.00–8.84), but former smoking was not • Ever smokers who never used extra filters, OR = 3.07 (1.09–8.63), and who inhaled deeply, OR = 5.41 (1.52–19.31), had significant increased risks of NV AMD • A dose-response relationship was associated with years of smoking; those who smoked for >40 years had greater risk, OR = 3.79 (1.13–12.70), $p < 0.05$ • A dose-response relationship was also associated with age at starting smoking for those who began smoking before the age of 20 years, OR = 3.41 (1.20–9.73), $p < 0.05$

Table 10.1*S* Continued

Study	Design/population	AMD assessment/type studied	Findings (95% CI)
AREDS Research Group 2000	• AREDS • 4,519 participants 60–80 years of age • 1,568 large drusen cases, 1,060 intermediate drusen cases, 118 GA AMD cases, 658 advanced AMD cases, 1,115 controls	ARM Epidemiologic Study Group classification	• After adjusting for age and gender, smoking was associated with large drusen, OR = 1.25; GA AMD, OR = 1.61; and NV AMD, OR = 1.91
DeAngelis et al. 2004	• 73 sibling pairs from clinics • Index sibling had confirmed NV AMD and the age of the unaffected sibling was greater than the age at which the index sibling was diagnosed • Massachusetts	AMD diagnosed by a physician and confirmed with fundus photographs	• With each pack-year, risk of NV AMD increased by 2%, OR = 1.02 (1.01–1.04)
Zareparsi et al. 2004	• 632 AMD cases and 206 controls either recruited through the University of Michigan or self-referred and genotyped for 3 *APOE* alleles • Michigan	Fundus photographs graded according to International Classification of ARM	• Frequencies of smokers and nonsmokers were similar by *APOE* allele among AMD cases • No interaction was reported between smoking and *APOE* alleles for risk of AMD
Evans et al. 2005	• MRCTAMOPC • Participants ≥75 years of age • 516 AMD cases • 4,364 controls • United Kingdom • 4 years of follow-up	AMD cases defined as diagnosed by physician and causing visual impairment; visual impairment defined as binocular visual acuity of less than 6/18 as measured at 3 m with a Glasgow acuity chart according to the logmar scale; controls were those with binocular visual acuity of 6/6 or better	• Current smokers more likely than never smokers to have AMD with visual impairment, OR = 2.15 (1.42–3.26) • Former smokers for <5 years had increased odds of AMD with visual impairment, OR = 2.24 (1.01–4.96) • Former smokers for >20 years did not have increased odds of AMD with visual impairment, OR = 0.86 (0.65–1.14) • The number of pack-years was not significantly associated with odds of AMD with visual impairment • The study estimated smoking may contribute to 28,000 cases of AMD among elderly in the United Kingdom

Table 10.1*S* Continued

Study	Design/population	AMD assessment/type studied	Findings (95% CI)
Schmidt et al. 2005	• Duke University Eye Center and Vanderbilt University Medical Center clinics • White participants ≥55 years of age • 377 AMD cases (76 drusen >125 µm, 260 NV AMD, and 41 GA AMD) • 198 ethnically matched controls	Fundus photographs graded according to AREDS Grading System	• Compared with never smokers, ever smokers had increased odds of AMD, OR = 2.1 (1.4–3.2), and NV AMD, OR = 2.8 (1.7–4.6) • Current smokers were more likely to have AMD, OR = 5.8 (2.3–14.3), or NV AMD, OR = 10.9 (4.0–29.2) • Associations were slightly less strong among former smokers, AMD, OR = 1.9 (1.2–2.9), and NV AMD, OR = 2.5 (1.5–4.1); those smoking >33 years had increased odds of AMD, OR = 3.6 (2.1–6.3), and NV AMD, OR = 5.7 (3.0–10.7) • A dose-response relationship was observed for the number of cigarettes smoked/day and for pack-years for both AMD and NV AMD • Odds of NV AMD were greater among smokers with the *APOE-2* allele, OR = 4.6 (1.8–11.7), than among never smokers with the same genotype
Chen et al. 2006	• Clinic participants genotyped for 6 *CFH* SNPs (*rs3753394*, *rs800292*, *rs1061147*, *rs1061170*, *rs380390*, and *rs1329428*) • 163 AMD cases • 244 gender-matched controls • Hong Kong	Fundus photographs graded according to AREDS Grading System	• After adjusting for age and SNPs *rs3753394* and *rs1061170* and in a comparison with never smoking, AMD was associated with current smoking, OR = 2.97 (1.50–5.86), and former smoking, OR = 1.88 (1.11–3.18)
Khan et al. 2006	• White participants ≥50 years of age from hospital ophthalmology clinics, general practices, optometrists, and charitable societies • 435 AMD cases (106 GA AMD, 261 CNV, and 68 both GA and CNV) • 280 spouse controls	Fundus photographs graded according to International Classifications of ARM and AMD	• In comparison with never smokers (controls), no significant association for current smokers or former smokers with advanced AMD, GA AMD, or CNV; dose-response relationship reported for number of pack-years of cigarettes for GA AMD and CNV • Smoking >40 pack-years of cigarettes increased odds of AMD, OR = 2.75 (1.22–6.20), CNV, OR = 2.49 (1.06–5.82), and GA AMD, OR = 3.43 (1.28–9.20) • No association was observed for >40 pack-years of other tobacco products or the level of inhalation (not at all, a little, or deeply) and advanced AMD, GA AMD, or CNV • Those exposed to secondhand smoke were almost twice as likely to have advanced AMD, OR = 1.87 (1.03–3.40), as those not exposed, but this association was not significant for GA AMD, OR = 1.81 (0.97–3.39), or CNV, OR = 1.50 (0.69–3.27) • A dose-response relationship was reported between years since quitting smoking and odds of advanced AMD, CNV, and GA AMD

Table 10.1*S* Continued

Study	Design/population	AMD assessment/type studied	Findings (95% CI)
Schmidt et al. 2006	• Duke University and Vanderbilt University clinics • White participants ≥55 years of age • 610 AMD cases (140 drusen >125 µm, 393 NV AMD, and 77 GA AMD) • 259 family member- or age- and ethnicity-matched controls	Fundus photographs graded according to AREDS Grading System	• Effect of *Y402H* variant of the *CFH* gene similar for smokers and nonsmokers • Significant interaction reported between smoking and *rs10490942* SNP found in the *LOC387715* gene • Combination of the *TT* genotype at *rs10490924/TT* genotype at *Y402H* increased odds of AMD 10-fold among smokers compared with *(GG) rs10490924/(TT) Y402H* in nonsmokers, OR = 10.75 (3.92–29.49) • (*TT) rs10490924/(CC) Y402H* genotype increased odds of AMD even more, OR = 34.51 (11.87–100.32) • Smoking explained 20% of population's attributable risk of AMD, but combination of smoking, *LOC387715,* and *CFH* explained 61%
Seddon et al. 2006a	• 681 White male twins born between 1917–1927 and served in U.S. armed forces, obtained from National Academy of Sciences-National Research Council World War II Veteran Twin Registry • 222 AMD cases (AMD grades 3, 4, and 5) • 459 controls (AMD grades 1 and 2) • United States	Fundus photographs graded according to Clinical ARM Staging System, which is modification of AREDS Grading System	• In fully adjusted model, former smoker, OR = 1.72 (1.14–2.60), and ever smoker, OR = 1.74 (1.60–16.60), associated with AMD • Association between current smoking and AMD greater than these associations but not significant, OR = 1.91 (0.99–3.66) • For monozygotic twins alone, current smoking significantly associated with AMD, OR = 3.2; p trend = 0.01, but this association was not significant for dizygotic twins, OR = 1.3; p trend = 0.60
Seddon et al. 2006b	• White participants from AREDS • 208 AMD cases (429 NV and 145 GA) • 574 controls	Fundus photographs graded according to the Clinical ARM Grading System	• Former smokers and current smokers associated with advanced AMD, OR for former smokers = 1.8 (1.2–2.6), and OR for current smokers = 5.7 (2.6–12.4); with GA AMD, OR for former smokers = 1.84 (1.1–23.1), and OR for current smokers = 3.8 (1.3–11.6); and with NV AMD, OR for former smokers = 1.7 (1.1–2.5), and OR for current smokers = 5.9 (2.6–13.4) • Interaction between the *CFH Y402H* allele and smoking not significant; those with the *CC* or *CT* genotype had higher odds of AMD than those with *TT* genotype among both smokers and nonsmokers, but odds of AMD were higher among smokers
Sepp et al. 2006	• 443 AMD cases (265 CNV, 106 GA AMD, and 72 both CNV and GA AMD) • 262 spouse controls obtained from hospital ophthalmic clinics, general practices, optometrists, and charitable societies • East Anglia, United Kingdom	NR	• Moderate smokers (<20 pack-years), with *CC* genotype of *Y402H* variant of *CFH* gene more likely to have AMD than those with *TT* genotype, OR = 6.0 (2.6–13.9) • Risk of AMD doubled among heavy smokers (>20 pack-years), OR = 12.0 (4.0–35.7), but could be attributed to small number of heavy smokers in case and control groups • Moderate smokers with the *CT* genotype had increased odds of AMD, OR = 2.4 (1.2–4.6), but this association not significant among heavy smokers, OR = 1.9 (0.9–4.0)

Table 10.1*S* Continued

Study	Design/population	AMD assessment/type studied	Findings (95% CI)
DeAngelis et al. 2007	• 143 White, discordant sibling pairs, ≥50 years of age, from clinics • 103 cases of NV AMD • Massachusetts	Disease status determined from fundus photographs or fluorescein angiograms reviewed by 2 or more investigators	• Smokers of ≥10 pack-years more likely to have NV AMD, OR = 1.89 (1.08–3.32), than those smoking <10 pack-years • No significant interactions reported between NV AMD and *APOE* or *ELOVL4* or between smoking and *CFH CC* and *APOE* genotypes • Persons with 1 *CFH* allele had significantly increased odds of NV AMD • Odds of NV AMD increased among smokers of ≥10 pack-years when *CT* or *TT* genotype was reference group, OR = 2.92 (1.41–6.03), and the *TT* genotype alone was used as the reference group, OR = 2.95 (1.41–6.15) • Smoking ≥10 pack-years explained 28% of the total population's risk for AMD • Combination of smoking ≥10 pack-years and *CFH CC* or *CT* genotype explained 56% of the population's risk
Douglas et al. 2007	• General Practice Research Database • Participants ≥50 years of age • 18,007 AMD cases • 86,169 age-, gender-, and practice-matched controls • United Kingdom	Diagnosis of AMD validated in sample of cases by medical chart review	• After adjusting for consultation rate and in comparison with never smokers, risk of AMD elevated among current smokers, OR = 1.17 (1.11–1.23), and former smokers, OR = 1.14 (1.09–1.20)
Erie et al. 2007	• Participants ≥60 years of age, from the Mayo Clinic Department of Ophthalmology • 53 AMD cases • 53 age-matched controls • 16 Stage 3, 46 Stage 3, and 44 Stage 4 • Minnesota	Fundus photographs graded using 4-stage AMD severity scale from AREDS	• Smokers with AMD had: – 97% higher median Cd/creatinine urine level than smokers without AMD, p trend = 0.02 – 11% higher median Cd/creatinine level than never smokers with AMD, p <0.001 – 107% higher median Cd/creatinine level than never smokers without AMD, p <0.001 • Did not observe a significant difference between pack-years or years since quitting smoking between cases and controls
Francis et al. 2007	• White participants from AREDS • 530 advanced AMD cases (147 GA, 241 CNV, and 142 both GA and CNV) • 280 controls	Fundus photographs graded according to Clinical ARM Grading System	• Former smoking was associated with advanced AMD, OR = 1.8 (1.2–2.6); GA AMD, OR = 1.6 (1.0–2.7); NV AMD, OR = 2.0 (1.3–3.2); and NV AMD and GA AMD combined, OR = 2.0 (1.1–3.7) • Current smoking was also associated with advanced AMD, OR = 3.3 (1.7–6.7); GA AMD, OR = 3.7 (1.5–9.0); and NV AMD OR = 3.5 (1.6–7.7) • No significant interactions were reported between smoking and the *LOC387715 rs10490942* gene

Table 10.1*S* Continued

Study	Design/population	AMD assessment/type studied	Findings (95% CI)
Hughes et al. 2007	• 401 NV AMD cases • 266 age-matched controls • Northern Ireland	Fundus photographs graded according to Wisconsin ARM Grading System	• Smoking ($p < 0.001$) and history of smoking (p trend = 0.05) were associated with AMD, and this was independent of *CFH* and *LOC387715* haplotype • Interactions were not observed between smoking and *LOC387715/HTRA1* haplotype, *CFH* haplotype, or *CFH* and *LOC387715/HRTA1* haplotypes • In comparison with never smokers, odds of AMD were increased among current smokers, OR = 3.14 (1.82–5.42), and former smokers, OR = 1.46 (0.96–2.22)
Kikuchi et al. 2007	• Participants with CRP levels measured • 176 advanced AMD cases • 97 polypoidal choroidal vasculopathy cases • 262 controls • Chubu, Japan	Fundus photographs examined and graded according to Rotterdam Study classification	• NV AMD more frequently observed in smokers than nonsmokers
Mori et al. 2007	• Participants from clinics who were genotyped for 4 SNPs on *CFH* gene: *rs800292*, *rs1061170*, *rs1410996*, and *rs2274700* • 188 AMD cases • 139 controls without AMD • Japan	Fundus photographs graded according to Wisconsin ARM Grading System	• Smoking significantly associated with AMD, OR = 2.03 (1.41–2.90), but no interaction reported between smoking and 4 *CFH* SNPs that were tested: *rs800292*, *rs1061170*, *rs1410996*, and *rs2274700*
Ross et al. 2007	• Clinic-based sample participants ≥49 years of age • 103 advanced AMD cases and 137 age-matched controls from NEI study • 278 advanced AMD cases and 192 controls from AREDS • 278 AMD cases and 557 age- and gender-matched controls from BMES • All participants genotyped for *rs10490924* SNP of *LOC387715* gene	NEI and AREDS: fundus photographs graded using AREDS Grading System BMES: fundus photographs graded according to Wisconsin ARM Grading System	• Smoking associated with AMD, OR = 1.46 (1.10–2.04), based on combined dataset • No significant interactions between smoking and *LOC387715* for risk of AMD observed for either dataset – Study found increased joint effect of smoking and presence of the *T/T LOC387715* genotype on the risk of (a) AMD for AREDS+NEI dataset and (b) late AMD for BMES dataset

Table 10.1*S* Continued

Study	Design/population	AMD assessment/type studied	Findings (95% CI)
Scott et al. 2007	• Participants from clinics • 599 AMD cases (170 drusen >125 µm, 351 NV AMD, and 78 GA AMD) • 242 controls • United States	Fundus photographs graded based on modification of AREDS Grading System, using Wisconsin ARM Grading System example slides and International Classification System as guide	• Ever smoking and the *CFH T1277C* polymorphism had independent multiplicative effects on risk for AMD • Ever smoking was associated with AMD, OR = 1.57 (1.10–2.24), and NV AMD, OR = 2.90 (1.73–4.87) • Smoking >10 pack-years was associated with increased risk of AMD, OR = 1.10 (1.01–1.20), and NV AMD, OR = 1.17 (1.01–1.35) • Heavy smokers (>30 pack-years) had highest risk of AMD, OR = 2.35 (1.42–3.91), and NV AMD, OR = 4.22 (2.07–8.59) • Light smokers (<30 pack-years) not associated with AMD but increased risk of NV AMD, although not significantly, OR = 1.38 (0.74–2.55)
Spencer et al. 2007	• White participants from clinics genotyped for *CFH* gene variant *Y402H* • 584 AMD cases • 248 controls	Fundus photographs graded using modified Wisconsin ARM Grading System	• Study assessed interactions between smoking and *CAATTTAG* (*P1*) and *CGGCTTAG* (*P2*) haplotypes of the *Y402H* variant of the *CFH* gene • LRTs indicated significant interactions between smoking and *P2* haplotype (p trend = 0.008) and the pooled haplotypes (p trend = 0.032) • Possible interaction between smoking and *P2* haplotype reported to be AMD protective
Chu et al. 2008	• Participants from ophthalmic clinics of Peking Union Medical College Hospital and Beijing Tongren Hospital • 144 NV AMD cases • 126 age-, gender-, and ethnicity-matched controls • Beijing, China	Fundus photographs graded according to AREDS Research Group classification	• Ever smokers (former or current) more likely to have NV AMD than never smokers, OR = 3.54 (1.84–6.81) • Interaction between smoking and *rs1410996-AG* genotype of *CFH* gene associated with increased odds of NV AMD, OR = 7.33 (2.93–18.37) • Interaction was not significant for *rs1410996-GG* genotype, OR = 2.03 (0.65–6.34)
Goverdhan et al. 2008	• Participants ≥55 years of age recruited from Southampton Eye Unit • Genotyped for *IL* gene SNPs (*IL-β*, *IL-6*, *IL-8*, and *IL-10*) • 478 AMD cases • 555 normal controls • United Kingdom	Physician-diagnosed AMD and fluorescein angiography	• Compared with never smokers, ever smokers more likely to have AMD, p trend = 2.0 • Smoking status not associated with *IL-8* genotype status, reported to be an important risk factor for AMD

Table 10.1*S* Continued

Study	Design/population	AMD assessment/type studied	Findings (95% CI)
Kim et al. 2008b	• 244 participants ≥50 years of age from 104 discordant sibling pairs; 1 member had NV AMD and another had normal maculae and was past the age of the index patient's diagnosis • All participants were of Northern European descent and genotyped for 9 CRP SNPs	Examination of fundus photographs or fluorescein angiograms	• Compared with <10 pack-years, ≥10 pack-years was associated with increased risk of NV AMD, OR = 1.97 (1.12–3.46) • The study did not find any associations between any of 9 *CRP* SNPs and neovascularization, alone or when stratified by exposure to smoking
Seitsonen et al. 2008	• Participants from the Departments of Ophthalmology of Helsinki, Oulu, and Kuopio Universities hospitals • 332 AMD cases • 105 age-matched non-AMD controls • 350 anonymous blood donor controls	Physician-diagnosed AMD and fluorescein angiography	• Ever smokers more likely to have AMD, OR = 3.22 (1.81–6.09) than controls • Joint OR for AMD of ever smoker and carrier of risk alleles *CFH Y402H*, *LOC387715 A69S*, and *C3 R102G* was 74.3 (10.81–2,123.6) • In comparison with women who never smoked, stratified analyses revealed that women who ever smoked had increased risk of AMD, OR = 4.68 (1.95–14.12) • Effect of ever smoking was less pronounced among men, OR = 2.57 (0.99–6.86)
Tam et al. 2008	• 163 NV AMD cases • 183 gender- and age-matched controls	Fundus photographs graded according to International ARM Epidemiologic Study Group classification	• In comparison with never smokers, ever smokers had increased odds of NV AMD, OR = 1.76 (1.11–2.80); ever smokers with nonrisk genotype *GG* of *rs11200638* allele of *HTRA1* gene were more likely to have NV AMD, OR = 3.67 (1.14–11.84), than never smokers with same genotype • In comparisons with *GG* genotype reference group, ever smokers homozygous for risk genotype (*AA*) were more likely to have AMD, OR = 15.71 (5.43–45.49), as were never smokers with same *AA* genotype, OR = 14.33 (4.99–41.18)
Tuo et al. 2008	• Pooled data from clinic- and population-based samples from NEI and AREDS (Washington, DC, area), BMES (Australia), and donor eyes from MLEB • 805 AMD cases (145 NEI, 330 AREDS, 284 BMES, 46 MLEB) • 921 controls (138 NEI, 193 AREDS, 568 BMES, 22 MLEB)	NEI and AREDS: ARM Epidemiologic Study Group classification; BMES: fundus photographs; MLEB: stereoscopic macular images graded according to Minnesota Grading System, which corresponds to AREDS classification system	• For *HTRA1* promoter gene *rs11200638* nonrisk genotype *GG*, ever smokers had increased odds of AMD, OR = 1.70 (1.25–2.30), compared with never smokers and reference group, nonrisk genotype *GG* among never smokers • Compared with ever smokers with nonrisk genotype *GG*, ever smokers with risk genotype *AA* had 10 times the odds of AMD, OR = 17.71 (7.49–41.88)

Table 10.1*S* Continued

Study	Design/population	AMD assessment/type studied	Findings (95% CI)
McKay et al. 2009	• 318 NV AMD cases • 243 age-matched controls • Northern Ireland	Fundus photographs graded according to Wisconsin ARM Grading System	• Data from Hap Map Project used to determine 18 SNPs across *CC2/CFB* region and assess linkage disequilibrium among AMD cases and controls, to identify novel functional variants of these genes • After accounting for the genetic effects of variation at *CFH* and *LOC387715/HTRA1* loci and in comparison with never smokers, current smokers had increased risk of AMD: OR = 2.44 (1.31–4.56) • Association not significant when comparing former smokers with never smokers, OR = 1.51 (0.94–2.43) • Smoking did not change effect of genetic variation at *CFH* and *LOC387715/HTRA1* loci
Park et al. 2009	• 738 White participants • 439 AMD cases and 299 controls from the Mayo Clinic • Replication study of 1,541 White participants (1,241 AMD cases and 300 controls) from AREDS	Fundus photographs graded according to Wisconsin ARM Grading System	• Study used LRTs to assess interactions between complement component 3 (*C3*) SNPs (*rs1047286*, *rs11569536*, and *rs3745565*) and smoking status on AMD • No interactions between smoking and AMD for *C3* SNPs, p trend = 0.40–0.78
Wang et al. 2009b	• Vanderbilt University and Duke University clinics • 685 AMD cases • 269 independent controls	Fundus photographs graded using modification of AREDS Grading System	• LRTs used to compare full and reduced regression models to analyze interactions between smoking and SNPs on *ARMS2* (*rs10490924*) and *HTRA1* (*rs11200638*), after adjustment for *CFH* and age • Resulting LRTs were similar for 2 SNPS (*rs10490924*, LRT = 2.89; and *rs11200638*, LRT = 2.71), but the interactive effect of smoking was not significant for either polymorphism, *rs10490924* (p trend = 0.09) or *rs11200638* (p trend = 0.10)

Note: **AREDS** = Age-Related Eye Disease Study; **ARM** = age-related maculopathy; **BMES** = Blue Mountains Eye Study; **Cd** = cadmium; **CI** = confidence interval; **CNV =** choroidal neovascularization; **CRP** = C-reactive protein; **GA** = geographic atrophy; **LRTs** = likelihood ratio tests; **m** = meter; **µm** = micrometer; **MLEB** = Minnesota Lions Eye Bank; **MRCTAMPOPC** = Medical Research Council Trial of Assessment and Management of Older People in the Community; **NEI** = National Eye Institute; **NV** = neovascular; **OR** = odds ratio; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **SNPs** = single nucleotide polymorphisms.

Table 10.2*S* Summary of evidence from cross-sectional studies on the association between smoking and age-related macular degeneration (AMD)

Study	Design/population	AMD assessment/type studied	Findings (95% CI)
Paetkau et al. 1978	• Patients from University of Alberta Hospital • 114 NV AMD cases • Canada	Physician-diagnosed AMD and fluorescein angiography	• The mean age of AMD onset (accompanied by vision loss) was earlier among current smokers (64 ± 8.2 years) than former smokers (68 ± 10.0 years) ($p < 0.001$) or never smokers (71 ± 9.0 years)
West et al. 1989	• 769 watermen • 96 AMD cases (9 NV AMD or GA AMD and 87 any drusen) • Maryland	Fundus photographs graded to determine AMD status	• Compared with never smokers, ever smokers were less likely to have AMD: OR = 0.61 (0.35–1.05) • A dose-response relationship was not observed
Pauleikhoff et al. 1992	• Population-based sample • 430 participants ≥65 years of age • London, United Kingdom	Physician-diagnosed AMD and fundus photography inspection; fluorescein angiogram images graded for 25 participants	• Study did not observe any significant differences in prevalence of smoking between those with and without AMD
Vinding et al. 1992	• Population-based sample • 773 residents ≥60 years of age • 24 NV AMD and 88 GA AMD cases • Copenhagen, Demark	Macular changes, as indicated on fundus photographs and accompanied by visual acuity of 6/9 or less	• Smoking without inhaling significantly associated with NV AMD, OR = 1.2 ($p < 0.01$), and GA AMD, OR = 1.2 ($p < 0.01$) • Compared with smokers who did not inhale, smokers who inhaled had higher odds of NV AMD, OR = 2.5, and GA AMD, OR = 2.4, but these findings were not significant
Klein et al. 1993	• BMES • 4,771 White participants 43–86 years of age • 41 NV AMD and 29 GA AMD cases	Fundus photographs graded using modified Wisconsin ARM Grading System	• Smoking status, pack-years, and exposure to secondhand smoke not associated with early AMD, increased retinal pigment, or GA AMD • Compared with former smoking and never smoking, current smoking was associated with NV AMD across both genders: women, RR = 2.50 (1.01–6.20), and men, RR = 3.29 (1.03–10.50) • Significant association was observed between ever smoking and NV AMD in women, RR = 2.06 (1.03–4.100) but not in men, RR = 2.86 (0.64–12.7) • Male smokers had increased risk of RPE hyperplasia • Risk of AMD increased in both genders per 10 pack-years smoked: men, RR = 1.00 (0.88–1.16), and women, RR = 1.16 (1.04–1.30) • Smoking status and exposure to secondhand smoke were not associated with increased retinal pigment or GA AMD
Hirvela et al. 1996	• Population-based sample • 500 residents ≥70 years of age • Oulu Province, Finland	Fundus photographs graded by 2 independent readers for 83% of population, and ophthalmoscope findings used when fundi could not be seen (14% of the population)	• Study did not report association between smoking and ARM

Table 10.2*S* Continued

Study	Design/population	AMD assessment/type studied	Findings (95% CI)
Smith et al. 1996	• BMES • 3,654 participants ≥49 years of age • 72 late AMD cases (50 NV AMD and 22 GA AMD)	Modified Wisconsin ARM Grading System	• Rent smokers had increased odds of late AMD, OR = 4.46 (2.20–9.03); NV AMD, OR = 3.26 (1.45–7.33); GA AMD, OR = 4.94 (1.29–18.82); and early ARM, OR = 1.89 (1.25–2.84) • Similar associations were reported for current smokers vs. current nonsmokers, and these associations remained significant • Compared with never smoking, ever smoking was statistically associated with late AMD, OR = 1.83 (1.07–3.13), but not significantly associated with other types of AMD • Secondhand smokers had increased odds of late AMD, but association was not significant: OR = 1.42 (0.62–3.26) • For all AMD categories, associations usually higher for women than for men
Vingerling et al. 1996	• Rotterdam Study • 6,174 participants ≥55 years of age • 65 NV AMD and 36 GA AMD cases • The Netherlands	Fundus photographs graded using a modified Wisconsin ARM Grading System	• Current smoking, RR = 3.6 (1.8–7.4), and former smoking, RR = 2.1 (1.1–3.9), associated with NV AMD when never smoking was the referent • Odds of NV AMD were greater among those aged 55–84 years than among those aged≥85 years • Odds of NV AMD rose as the number of pack-years increased, but dose-response relationship was not observed between years since quitting smoking and odds of NV AMD
Klaver et al. 1997	• Rotterdam Study • 6,174 participants ≥55 years of age • 65 NV AMD and 36 GA AMD cases • The Netherlands	Fundus photographs graded using a modified Wisconsin ARM Grading System	• In comparison with never smokers, current smoking was associated with AMD in those ≥55 years of age, OR = 3.5 (1.8–7.0); 55–84 years of age, OR = 3.6 (1.6–8.0); and ≥85 years of age, OR = 5.2 (1.2–23.1) • The associations among former smokers were not significant
Delcourt et al. 1998	• 2,196 residents ≥60 years of age • 41 late AMD, 280 soft distinct drusen, 49 indistinct drusen, 200 hyperpigmentation, and 126 hypopigmentation • Sète, France	Fundus photographs graded according to International Classification of ARM and Macular Degeneration using standards from Wisconsin ARM Grading System	• After multivariate adjustment and in comparison with never smokers, current smokers, OR = 3.5 (1.0–12.2), and former smokers, OR = 2.8 (1.1–6.9) had increased odds of late AMD • Risk of late AMD increased as number of pack-years increased • Compared with never smokers, those with ≥40 pack-years had nearly 5 times the odds of late AMD: OR = 4.8 (1.8–12.9) • Risk of AMD decreased as years since quitting smoking increased • Risk of AMD among those who quit smoking >20 years earlier was not significantly different from that of never smokers, but those who quit smoking 1–9 years earlier had significant increased risk of late AMD: OR = 8.3 (2.7–25.4) • Significant associations not observed between smoking and early AMD (soft drusen, indistinct drusen, and pigmentary abnormalities)

Table 10.2*S* Continued

Study	Design/population	AMD assessment/type studied	Findings (95% CI)
Smith et al. 1998	• BMES • 3,654 participants • Provided fasting blood samples at baseline • 240 early AMD and 72 late AMD cases	Fundus photographs graded according to Wisconsin ARM Grading System	• Smoking associated with increased risk of late AMD, OR = 3.83 (2.02–7.28), and early ARM, OR = 1.75 (1.20–2.55)
Klaver et al. 1999	• Rotterdam Study • Population-based sample with baseline exam data • 1,438 participants ≥75 years of age • The Netherlands	Fundus photographs graded according to International Classification of ARM and Macular Degeneration	• Frequencies of current smokers varied by ARM stage: no ARM (12.1%); soft distinct drusen without pigmentary irregularities and GA or NV AMD (11.8%); distinct drusen with pigmentary irregularities or indistinct or reticular drusen (13.0%); indistinct or reticular drusen with pigmentary irregularities (23.3%); and GA or NV AMD (19.4%) • Frequencies of former smokers also varied by ARM stage: no ARM (25.6%); soft distinct drusen without pigmentary irregularities and GA or NV AMD (29.1%); distinct drusen with pigmentary irregularities or indistinct or reticular drusen (33.5%); indistinct or reticular drusen with pigmentary irregularities (30.2%); and GA or NV AMD (28.4%)
Klein et al. 1999	• NHANES III • 8,270 civilian noninstitutionalized participants >40 years of age • Grouped into 3 racial/ethnic groups: non-Hispanic Whites, non-Hispanic Blacks, and Mexican-Americans	Fundus photographs graded according to Wisconsin ARM Grading System	• Current smoking not significantly associated with soft drusen among non-Hispanic Whites, OR = 0.76 (0.56–1.04); non-Hispanic Blacks, OR = 1.39 (0.96–2.02); or Mexican-Americans, OR = 1.02 (0.67–1.57) • Current smoking was not significantly associated with increased retinal pigment among non-Hispanic Whites, OR = 1.44 (0.84–2.48), or non-Hispanic Blacks, OR = 1.44 (0.56–3.68), but was significantly associated among Mexican-Americans, OR = 3.84 (1.07–13.75)
Kuzniarz et al. 2002	• BMES • 2,873 participants from who completed a food frequency questionnaire at baseline	Fundus photographs graded according to Wisconsin ARM Grading System	• Any vitamin use not significantly associated with risk of early AMD for smokers, OR = 0.7 (0.4–1.3), p trend = 0.27; or nonsmokers, OR = 1.2 (0.9–1.5), p trend = 0.24 • No significant associations reported between smoking and risk of AMD when stratified by type of vitamin
Miyazaki et al. 2003	• 1,482 residents (596 men and 886 women) • Participants ≥50 years of age • 7 late ARM and 241 early ARM • Hisayama, Japan	Fundus photographs graded according to Wisconsin ARM Grading System	• Current smoking not significantly associated with ARM across genders: men, OR = 1.01 (0.65–1.55), and women, OR = 1.13 (0.46–2.77)
Weeks et al. 2004	• 530 families and 736 affected sibling pairs recruited from University of Pittsburgh • Genomewide scans performed on all participants	Physician-diagnosed AMD and fluorescein angiography	• Ordered-subset analyses revealed that the effect of smoking on the risk of AMD increased when a gene in the 10226 region was included in the analyses

Table 10.2*S* Continued

Study	Design/population	AMD assessment/type studied	Findings (95% CI)
Dandekar et al. 2006	• 711 participants of Western European origin from a medical retina clinic • 578 NV AMD	Fundus photographs graded according to International Classification of ARM and Macular Degeneration	• Current smoking associated with increased, but not significant, odds of NV AMD, OR = 1.88 (0.91–3.89) • Compared with current smoking, former smoking associated with decreased, but not significant, odds of NV AMD, OR = 0.86 (0.58–1.30) • Number of pack-years not related to odds of NV AMD, OR = 1.00 (0.99–1.01) • No association between quitting smoking for >5 years and NV AMD
Fraser-Bell et al. 2006	• Population-based sample of 5,875 Latino residents ≥40 years of age • 551 had any early AMD lesions, 421 soft indistinct drusen, 328 increased retinal pigment, 133 RPE depigmentation, and 25 any advanced AMD (17 NV AMD and 9 GA AMD), and 5,299 controls • La Puente, California	Fundus photographs graded using a modified Wisconsin ARM Grading System	• Compared with never smokers, former smokers were more likely to have early AMD lesions, OR = 1.3 (1.02–1.5), and soft indistinct drusen, OR = 1.3 (1.03–1.5); and current smokers were more likely to have increased retinal pigment, OR = 1.4 (1.01–1.9), and RPE depigmentation, OR = 1.7 (1.1–2.8) • Compared with never smokers, ever smokers had significantly increased odds of early AMD lesions, OR = 1.2 (1.0–1.4); soft indistinct drusen, OR = 1.3 (1.03–1.5); and advanced AMD, OR = 2.4 (1.0–5.4) • Because of small numbers, the risks of NV AMD, OR = 2.1 (0.8–5.6), and GA AMD, OR = 2.2 (0.6–8.5), among current smokers were not significant. • A dose-response relationship was observed among those with >5 pack-years and early AMD, OR = 1.3 (1.1–1.6). • A dose-response relationship was not significant between pack-years and advanced AMD
Wong et al. 2006	• Atherosclerosis Risk in Communities Study • Population-based sample • 10,139 participants 49–73 years of age who were genotyped for four variants of the *APOE* gene	Fundus photographs graded according to Wisconsin ARM Grading System	• No associations reported between early ARM and smoking status because the distribution of current smokers was similar between those with ARM (21.7%) and those without ARM (22.8%) (p trend = 0.58) • Similarly, the prevalence of ARM stratified by smoking status did not differ among *APOE* genotypes
Xu et al. 2006	• Beijing Eye Study • 4,376 participants ≥40 years of age • 74 AMD (61 early AMD, 9 late AMD, and 4 NV AMD) • China	Fundus photographs graded according to Wisconsin ARM Grading System	• History of smoking not significantly associated with early AMD, OR = 1.14 (0.65–2.00), or late AMD, OR = 1.01 (0.20–5.23) • Similarly, odds of AMD (early or late combined) not associated with current smoking, p trend = 0.43 (0.26–1.77), or former smoking, p trend = 0.31 (0.67–3.49) • The frequency of smokers did not vary significantly from nonsmokers by age group

Table 10.2*S* Continued

Study	Design/population	AMD assessment/type studied	Findings (95% CI)
Chakravarthy et al. 2007	• Population-based sample • 4,750 residents ≥65 years of age • 2,650 AMD, 1,733 either drusen (63–125 µm) only or pigment irregularities only, 482 drusen (>125 µm) or reticular drusen only or soft distinct drusen with pigment irregularities, 117 soft indistinct or reticular drusen with pigment irregularities • 158 NV AMD or GA AMD cases • Estonia, France, Greece, Italy, Norway, Spain, United States	Color fundus photographs taken and sent to Rotterdam grading center, where images were graded according to International Classification System for ARM	• Current smokers had significantly increased odds of NV AMD, OR = 4.81 (2.08–11.08), and GA AMD, OR = 2.56 (1.36–4.84) • Persons who had quit smoking for <20 years also had increased odds of NV AMD, OR = 2.01 (1.42–2.84), and GA AMD, OR = 2.24 (1.16–4.34) • Persons who had quit smoking for ≥20 years did not have significantly increased odds of NV or GA AMD • Current smokers, OR = 4.84 (1.92–12.21), and persons who had quit smoking for <20 years, OR = 2.58 (1.21–5.48), had increased odds of bilateral AMD vs. ARM • Study observed a reduction in odds of bilateral AMD vs. unilateral AMD among those who had quit smoking >20 years earlier: OR = 0.49 (0.34–0.71) • Dose-response patterns were reported for NV AMD and bilateral AMD but not for GA • Dose-response relationships were also observed for pack-years and NV AMD
Neuner et al. 2007	• 982 patients 60–80 years of age from the Müensteraner Altern und Retina Studie • 483 early ARM in at least 1 eye, 285 AMD in at least 1 eye • 214 controls	Trained graders used Rotterdam classification grading system to classify fundus photographs as "no AMD," "early AMD," or "late AMD"	• Compared with never smokers, current smokers had increased adjusted prevalence for ARM, OR = 2.61 (1.34–5.09), and AMD, OR = 3.94 (1.91–8.14) • Time since quitting smoking was associated with decreased odds of ARM, OR = 0.55 (0.33–0.99), and AMD, OR = 0.52 (0.30–0.90) • Smoking intensity had a nonsignificant negative association with ARM, OR = 0.85 (0.38–1.89), and a nonsignificant positive association with AMD, OR = 2.36 (0.99–5.66)
Cackett et al. 2008	• Population-based sample of 3,280 residents 40–80 years of age • 169 early AMD and 21 late AMD • Malaysia	Fundus photographs graded according to Wisconsin ARM Grading System	• Compared with ever smokers, current smokers were more likely to have late AMD, OR = 3.79 (1.40–10.23) • Compared with never smokers, the odds of late AMD were increased among current smokers, OR = 5.23 (1.47–18.66), but there was no significant increase in odds among former smokers, OR = 1.77 (0.48–6.54) • A dose-response relationship was reported for late AMD among those currently smoking >5 packs of cigarettes per week: OR = 9.35 (2.49–35.08)
Kawasaki et al. 2008	• 1,625 residents ≥35 years of age • 58 early AMD and 8 late AMD • Funagata, Japan	Fundus photographs graded according to Wisconsin ARM Grading System	• After adjusting for age and gender, current smoking was associated with late AMD: OR = 5.03 (1.00–25.47) • Association was somewhat higher in men: OR = 6.19 (1.08–35.5) • Current smoking was not significantly associated with early AMD

Table 10.2*S* Continued

Study	Design/population	AMD assessment/type studied	Findings (95% CI)
Baker et al. 2009	• Cardiovascular Health Study • Population-based sample • 2,088 participants 69–97 years of age	Fundus photographs graded according to Wisconsin ARM Grading System	• The frequency of smoking did not differ significantly between those with any type of AMD (49.3%) and those who did not have AMD (51.2%) (p trend = 0.51)

Note: **ARM** = age-related maculopathy; **BMES** = Blue Mountains Eye Study; **CI** = confidence interval; **GA** = geographic atrophy; **µm** = micrometer; **NHANESIII** = Third National Health and Nutrition Examination Survey; **NV** = neovascular; **OR** = odds ratio; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **RPE** = retinal pigment epithelium; **RR =** relative risk.

Table 10.3*S* Summary of evidence from prospective cohort studies on the association between smoking and age-related macular degeneration (AMD)

Study	Design/population	AMD assessment/type studied	Findings (95% CI)
Macular Photocoagulation Study Group 1986	• 119 eyes assigned to argon laser photocoagulation treatment with a diagnosis of NV AMD • Followed for 3 years	Angiograms showing CNV 200–2,500 µm from the foveal center; recurrence determined by angiograms and photographs	• Smokers of ≥10 cigarettes/day had higher rates of recurring CNV than smokers of <10 cigarettes/day (p <0.02)
Christen et al. 1996	• 21,157 male physicians 40–84 years of age who participated in the Physicians' Health Study • 438 AMD (268 vision loss, 27 drusen only, 63 RPE only, and 58 NV changes) • United States • Mean follow-up of 12.2 years	Self-report of AMD, with visual acuity of 20/30 or worse in at least 1 eye and confirmation by medical record review	• Compared with never smokers, current smokers who smoked >20 cigarettes/day were 2.46 times as likely to develop AMD with vision loss, RR = 2.46 (1.60–3.79) • Those smoking <20 cigarettes/day were about half as likely as those smoking >20 cigarettes/day to develop AMD with vision loss of 20/30 or greater, RR = 1.26 (0.61–2.59) • Former smoking was associated, but not significant, with AMD with vision loss, RR = 1.30 (0.99–1.70) • No association was found between being a former smoker and NV AMD, but current smokers have a nonsignificant increased risk of NV AMD, RR = 1.95 (0.89–4.24) • The risk of AMD with vision loss rose as pack-years increased (p <0.001): ≥40 pack-years, RR = 2.10 (1.50–2.93) • Former smokers who had smoked ≥20 cigarettes/day and who quit <20 years earlier had a greater risk of AMD, RR = 1.76 (1.23–2.53) than those who had smoked <20 cigarettes/day and had quit <20 years earlier, RR = 0.81 (0.39–1.67)
Seddon et al. 1996	• Nurses' Health Study • 31,843 registered nurses ≥50 years of age in 1980 • 215 AMD with vision loss worse than 20/30, 138 dry AMD, and 77 NV AMD • United States • 12 years of follow-up	Self-report of AMD with visual acuity of 20/30 or worse in at least 1 eye and confirmation by medical record review	• Compared with never smokers, current smokers were more likely to develop AMD with vision loss, RR = 1.7 (1.2–2.5) • Those who currently smoked ≥25 cigarettes/day were 2.4 times as likely as never smokers to develop AMD with vision loss, RR = 2.4 (1.4–4.0); and former smokers who used to smoke ≥25 cigarettes/day were 2 times as likely as never smokers to develop AMD, RR = 2.0 (1.2–3.4) • As the number of pack-years increased, the risk of all AMD increased (p <0.001) • Compared with never smokers, women who smoked ≥65 pack-years had 2.4 times the risk of AMD, RR = 2.4 (1.5–3.8) • This dose-response relationship was also reported for dry AMD (p <0.001), NV AMD (p trend = 0.01), and AMD with vision 20/50 or worse (p trend = 0.005) • No significant association between AMD and years since quitting smoking

Table 10.3*S* Continued

Study	Design/population	AMD assessment/type studied	Findings (95% CI)
Klein et al. 1998	• 3,583 White participants 43–86 years of age from BDES • Beaver Dam, Wisconsin • 5-year follow-up visit	Fundus photographs graded using a modified Wisconsin ARM Grading System	• After adjusting for age, vitamin use, and beer intake and compared with never smokers, the incidence of large drusen in current smokers was elevated across both genders: men, RR = 3.21 (1.09–9.45), and women, RR = 2.20 (1.04–4.66) • In similar analyses, women who were former smokers had increased incidence of large soft drusen, RR = 1.97 (1.06–3.64) • After adjusting for age, significant associations were not observed for either gender between smoking and incidence of early ARM, soft indistinct drusen, increased retinal pigment, RPE depigmentation, late ARM, or NV ARM • Among men, a dose-response relationship was reported for pack-years and incidence of ARM, OR = 2.17 (1.13–4.15), p trend = 0.01; this relationship was not observed among women • A dose-response relationship was reported between pack-years and large soft drusen for both genders (p trend = 0.01)
McCarty et al. 2001	• Population-based sample • 4,345 participants ≥40 years of age • 656 ARM and 30 AMD cases • Victoria, Australia	Fundus photographs graded according to International Classification of ARM	• After multivariate adjustment, those who smoked >40 years had increased risk of AMD, OR = 2.39 (1.02–5.57), and ARM, OR = 1.30 (1.02–1.66) • A dose-response relationship was reported between years of smoking and the risk of ARM (Mantel-Haenszel 2 = 33.6; p <0.001) but not the risk of AMD (p >0.10)
Klein et al. 2002	• BDES • Population-based sample • 3,678 White participants 43–86 years of age • Followed for 10 years	Fundus photographs graded using a modified Wisconsin ARM Grading System	• Compared with never smokers, current smokers were more likely to develop large soft drusen, RR = 2.19 (1.44–3.3) • Current smoking was not significantly associated with early ARM, pigment abnormalities, late ARM, NV ARM, or progression to total ARM • A dose-response relationship was reported between pack-years and large soft drusen • Compared with nonsmokers, those who had accumulated 15–34 pack-years, RR = 1.67 (1.08–2.58), and >35 pack-years, RR = 2.0 (1.34–2.98), were more likely to have large soft drusen • Those who had accumulated >15 pack-years had increased risk of pigment abnormalities, RR = 1.71 (1.20–2.44) • No associations for those who had <15 pack-years

Table 10.3*S* Continued

Study	Design/population	AMD assessment/type studied	Findings (95% CI)
Mitchell et al. 2002	• BMES • 2,335 participants ≥49 years of age • 1992–1994 • Participated in the 5-year visit; 26 late AMD, 13 NV AMD, and 17 GA AMD cases	Fundus photographs graded according to Wisconsin ARM Grading System	• Current smokers had an increased incidence of GA AMD, OR = 3.7 (1.0–12.9), and late lesions, OR = 2.7 (1.0–7.2) in comparison with former smokers • After adjusting for age and gender, no significant associations were reported between current smokers and late AMD or NV macular degeneration • Former smoking was not significantly associated with any form of ARM • Among women who were former and current smokers, no significant associations were reported for early or late ARM • Among men who were current smokers, significant associations were observed for GA AMD, OR = 7.3 (1.3–39.6); late lesions, OR = 6.1 (1.5–24.4); increased retinal pigment, OR = 2.8 (1.4–5.6); RPE depigmentation, OR = 3.6 (1.5–8.3); and pigment abnormalities, OR = 2.8 (1.4–5.6) • No significant associations were reported between men who were former smokers and ARM
Seddon et al. 2003	• Hospital-based sample of 261 participants ≥60 years of age with non-NV AMD and visual acuity of 20/200 or better in at least 1 eye at baseline • Mean follow-up of 4.6 years	Fundus photographs graded according to International Classification of ARM	• The study did not find any significant associations between smoking and risk of progression to AMD
Tomany et al. 2004	• 9,523 residents 43–95 years of age • 67 NV AMD, 38 GA AMD, and 102 late AMD cases • Australia, The Netherlands, United States	Fundus photographs graded according to Wisconsin ARM Grading System or International ARM Grading System	• Pooled data indicated current smokers had significant increased odds of GA, OR = 2.83 (1.15–6.93), and late AMD, OR = 2.35 (1.30–4.27), compared with nonsmokers, but significant association was not found for NV AMD, OR = 1.90 (0.88–1.14) • Current smokers were at higher risk than former smokers in the pooled analysis, but none of the associations were significant • Among the individual studies, only the data from Rotterdam indicate an increased nonsignificant 5-year incidence of AMD from smoking, OR = 1.81 (0.36–9.10) • Nonsignificant protective associations were reported from BDES, OR = 0.82 (0.21–3.23), and BMES, OR = 0.93 (0.21–4.19) • Data were not pooled because of significant differences between the studies
Clemons et al. 2005	• AREDS • 2,506 participants 55–80 years of age in the bilateral drusen group and 788 participants in the unilateral advanced AMD group • Mean follow-up of 6.3 years	Fundus photographs graded according to International Classifications of ARM and AMD	• Compared with smokers with <10 pack-years, smokers with >10 pack-years was associated with increased incidence of NV AMD, OR = 1.55 (1.15–2.09), and central GA AMD, OR = 1.82 (1.25–2.65)

Table 10.3*S* Continued

Study	Design/population	AMD assessment/type studied	Findings (95% CI)
Krishnaiah et al. 2005	• Andhra Pradesh Eye Disease Study • 3,723 participants ≥40 years of age • South India • 71 AMD detected during follow-up	Fundus photographs graded according to International Classification and Grading System	• Increased prevalence of AMD significantly associated with current cigar smoking, OR = 3.29 (1.42–7.57), and heavy cigar smoking (above the 25th percentile of pack-years), OR = 2.36 (1.17–4.71) • Compared with never smokers, current and former smokers had higher odds of prevalence of AMD, but associations were not significant
Miyazaki et al. 2005	• Hisayama Study • 961 participants ≥40 years of age, who attended the 5-year follow-up exam • 166 early AMD and 10 late AMD cases • Japan	Fundus photographs graded according to Wisconsin ARM Grading System	• After adjusting for age, smoking was associated with a significant increase in incidence of ARM (early and late combined), OR = 2.2 (1.14–4.33)
Arnarsson et al. 2006	• Reykjavik Eye Study • Population-based sample • 864 participants ≥50 years of age • Iceland	Fundus photographs graded according to Wisconsin ARM Grading System	• Smoking was not associated with risk of ARM when comparing current smokers and former smokers with never smokers and when examining the number of pack-years
Despriet et al. 2006	• Population-based sample • 5,681 residents ≥55 years of age from Rotterdam, who were genotyped for *CFH Y402H* SNPs • The Netherlands • Mean follow-up of 8 years	Fundus photographs graded according to International Classification of ARM and Macular Degeneration	• Compared with never smoking, current smoking was significantly associated with odds of AMD among noncarriers of the *Y402H* risk allele, OR = 3.36 (1.14–9.86) • This effect was 10 times as great among current smokers who were homozygous for risk allele, OR = 34.0 (13.0–88.6)
Klein et al. 2007	• Women's Health Initiative Sight Examination Study • 4,288 participants ≥63 years of age	Fundus photographs graded according to Wisconsin ARM Grading System	• Total pack-years were associated with late AMD, OR = 1.02 (1.003–1.03), but not RPE depigmentation, NV AMD, or increased retinal pigment

Table 10.3*S* Continued

Study	Design/population	AMD assessment/type studied	Findings (95% CI)
Seddon et al. 2007	• AREDS • 1,466 White participants • 281 AMD cases • Mean follow-up of 6.3 years	Fundus photographs graded using AREDS Grading System	• Compared with never smoking, ever smoking was associated with AMD progression, but not significant, OR = 1.2 (0.9–1.7) • Compared with nonsmokers with homozygous nonrisk (*TT*) genotypes, smokers had increased risk of progression to AMD, OR = 1.6 (0.8–3.3), that did not reach significance • Risk of progression to AMD increased among those with (*CC*) genotypes of the *CFH Y402H* allele: never smokers, OR = 2.8 (1.4–5.6); and ever smokers, OR = 3.8 (2.0–7.6) • This difference was less for homozygous nonrisk (*GG*) genotypes—ever smokers, OR = 1.4 (0.8–2.5)—and risk (*TT*) genotypes of the *LOC387715 A69S* allele: never smokers, OR = 4.7 (2.5–9.2) • No significant interactions were observed between smoking and genotype
Shankar et al. 2007	• 2,089 BMES participants ≥49 years of age • 10-year follow-up	Fundus photographs graded according to Wisconsin ARM Grading System	• In a comparison of those in the highest tertile of white blood cell count (>6.7 x 109 cells/L) with those in the lowest tertile (≤5.5 x 109 cells/L), the risk of incident early AMD was significantly higher among former smokers, RR = 2.22 (1.25–3.92), and never smokers, RR = 1.62 (1.04–2.52), but not among current smokers, RR = 1.85 (0.4–8.48)
Tan et al. 2007	• BMES • Population-based sample • 2,454 participants ≥49 years of age • 226 soft indistinct drusen, 266 early AMD, 409 pigment abnormalities, 43 NV AMD, 33 GA AMD, and 72 any late AMD cases • Followed for 10 years	Fundus photographs graded according to Wisconsin ARM Grading System	• Compared with never smokers, current smokers more likely to have any form of late AMD: RR = 3.9 (1.7–8.8) • Increased incidence of GA AMD was found among those who had quit smoking for <17 years before baseline, RR = 4.4 (1.2–15.8), and those who had quit smoking for ≥17 years before baseline, RR = 2.9 (0.9–9.4), although the latter finding was not significant • In comparison with never smokers, risk findings were markedly lower for current smokers, RR = 10.3 (2.7–39.1), and former smokers, RR = 3.4 (1.2–9.7) • No significant associations between time of quitting smoking and late AMD were reported. • Former and current smoking were not significantly associated with NV AMD, early AMD, soft indistinct/reticular drusen, or pigment abnormalities • No significant dose-response relationship between the number of pack-years and late AMD • In joint analyses, risk of late AMD was elevated among current smokers with low levels of high-density lipoprotein or low consumption of fish

Table 10.3*S* Continued

Study	Design/population	AMD assessment/type studied	Findings (95% CI)
Baird et al. 2008	• 233 early AMD participants • Melbourne, Australia • Average follow-up of 7 years	Macular photographs taken at baseline were graded according to International Classification for AMD Grading	• Ever smoking was associated with increased odds of AMD progression, OR = 2.28 (1.26–4.12) • Ever smokers with the *CC* risk genotype of the *Y402H CFH* gene were more likely to have AMD progression, OR = 2.39 (0.72–7.98) and increased odds of AMD than never smokers with the *CC* genotype, OR = 1.67 (0.50–5.55), although neither comparison was significant • An interaction between smoking and genotype was reported, the excess risk of AMD was estimated to be 0.45
Chang et al. 2008	• Salisbury Eye Evaluation Study • Population-based sample • 1,937 participants 65–84 years of age	Fundus photographs graded at baseline	• Compared with never smokers, current smokers more likely to progress from medium drusen to large drusen, OR = 2.7 (1.18–6.19) • Association was dose dependent: those smoking >20 cigarettes/day had a significantly increased risk of progression, OR = 3.07 (1.1–7.94) • Compared with never smokers, current smokers more likely to develop focal hyperpigmentation, OR = 1.9 (1.05–3.48) • Association was dose dependent: compared with never smokers, those smoking ≥10 cigarettes/day had twice the risk of incident focal pigmentation, OR for 10–19 cigarettes/day = 2.29 (1.00–5.25), and OR for ≥20 cigarettes/day = 2.16 (1.07–4.35) • Associations were not observed in former smokers
Complications of Age-Related Macular Degeneration Prevention Trial Research Group 2008	• ARM Degeneration Prevention Trial • 1,052 participants • 10 or more large drusen (≥125 µm) and visual acuity of 20/40 or better in each eye • CNV developed in 141 treated and 141 untreated eyes (bilaterally in 57 participants) • 5–6 years of follow-up	Fundus photographs graded according to Wisconsin ARM Grading System	• Compared with never smokers in multivariate analyses, current smokers had increased risk of CNV in treated and untreated eyes combined, RR = 1.98 (1.16–3.39) • No significant association was reported between CNV and former smoking • GA not significantly associated with current smoking in univariate analyses comparing current smokers and never smokers, OR = 1.56 (0.62–3.89)

Table 10.3*S* Continued

Study	Design/population	AMD assessment/type studied	Findings (95% CI)
Klein et al. 2008a	• Population-based sample • 4,926 White residents 43–84 years of age • 400 AMD cases (391 early AMD, 63 NV AMD, and 39 GA AMD) • Beaver Dam, Wisconsin • Up to 15 years of follow-up	Fundus photographs graded according to Wisconsin ARM Grading System	• Current smoking at baseline associated with progression of AMD, OR = 1.43 (1.05–1.94), during follow-up • Association was greater than the 15-year cumulative incidence of AMD among former smokers, OR = 1.03 (0.81–1.32) • Compared with nonsmokers, men current smokers had significantly increased odds of developing AMD, OR = 2.19 (1.30–3.69), but women current smokers did not • In men, duration of smoking, time since quitting smoking, and age at quitting smoking were significantly associated with progression of AMD • Among women, duration of smoking and age at quitting smoking were associated with progression of AMD • Compared with never smokers, current smokers at baseline were more likely to develop early AMD, OR = 1.47 (1.08–1.99) • Among men and women combined, no significant relationship was observed between smoking intensity, duration, pack-years, or time since quitting smoking and the cumulative incidence of NV AMD or GA AMD • Exposure to environmental tobacco smoke not associated with prevalence of AMD, 5-year incidence of this problem, or AMD progression in either gender
Klein et al. 2008b	• BDES • 2,119 participants 43–86 years of age • 15-year follow-up	Fundus photographs graded according to Wisconsin ARM Grading System	• After controlling for age, and compared with never smokers, current smokers had increased incidence of reticular drusen, OR = 1.9 (1.03–3.6), association was not significant when comparing former smokers with never smokers or for total pack-years • After adjusting for age and compared with never smokers, those who had accumulated >35 pack-years had an increased prevalence of reticular drusen, OR = 2.6 (1.17–5.85)
Tan et al. 2008	• BMES • 2,083 participants • Baseline data on food frequency who attended either the 5- or 10-year follow-up exam • Australia	Fundus photographs graded according to Wisconsin ARM Grading System	• When stratified by smoking status, each increase of one standard deviation in total dietary beta-carotene intake was significantly associated with increased risk of NV AMD, RR = 1.62 (1.24–2.11)
Williams 2009	• 29,532 male and 12,176 female runners • Participants ≥18 years of age • 152 incident cases of AMD • Average follow-up of 7.7 years	Self-reported, physician-diagnosed AMD	• After adjusting for age and gender, ever smokers had more AMD cases (45.23% of cases) than never smokers (39.12% of cases) • The association between running long distances and risk of AMD was not affected by smoking status (p trend = 0.63)

Table 10.3*S* Continued

Study	Design/population	AMD assessment/type studied	Findings (95% CI)
Wang et al. 2009c	• BMES • Participants ≥49 years of age • 1,791 at risk for late AMD and 1,705 at risk for early AMD • Followed for 10 years	Fundus photographs graded according to Wisconsin ARM Grading System	• Current smokers with *CFH* risk genotype (*CC/CT*) had about twice the risk of late AMD as former smokers with the risk genotype • Compared with nonsmokers without the risk genotype, current smokers with the risk genotype had 10 times the risk of late AMD • Study reported a joint effect of the *CFHCC/CT* genotype and smoking on the risk of late AMD
Yasuda et al. 2009	• Population-based sample • 1,401 residents • Participants ≥40 years of age • Hisayama, Japan	Fundus photographs graded according to International ARM Epidemiological Study Group grading protocol and grids from Wisconsin ARM Grading System	• Smoking more common among men (74.8%) than women (7.1%) • After adjusting for other risk factors and compared with never smokers, ever smokers were more likely to develop late AMD, OR = 3.98 (1.07–14.7)
Coleman et al. 2010	• Study of Osteoporotic Fractures • Women ≥65 years of age • Attended 10- and 15-year visits • Fundus images from both eyes taken at both exams	Fundus photographs graded according to Wisconsin ARM Grading System	• No association reported between early or late AMD and current smoking (yes vs. no) • Study observed a significant interaction between age at the 10-year visit and current smoking status on risk for early AMD • Current smokers aged ≥80 years were more likely to have early AMD than those aged ≤79 years who were not current smokers, OR = 5.49 (1.57–19.20)

Note: **AREDS** = Age-Related Eye Disease Study; **ARM** = age-related maculopathy; **BDES** = Beaver Dam Eye Study; **BMES** = Blue Mountains Eye Study; **CI** = confidence interval; **CNV** = choroidal neovascularization; **GA** = geographic atrophy; **L** = liter; **µm** = micrometer; **NV** = neovascular; **OR** = odds ratio**; pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **RPE** = retinal pigment epithelium; **RR =** relative risk; **SNPs** = single nucleotide polymorphisms.

Table 10.4*S* Summary of evidence from other types of studies on the association between smoking and age-related macular degeneration (AMD)

Study	Design/population	AMD assessment/type studied	Findings (95% CI)
Smith et al. 2001	• BDES (4,756) • Rotterdam Study (6,411) • BMES (3,585) • Combined population • Meta-analysis • 14,752 racially similar participants 43–99 years of age • 241 AMD cases (131 NV AMD, 79 GA AMD, and 31 both NV and GA AMD)	Fundus photographs graded according to Wisconsin ARM Grading System	• From pooled odds from all 3 studies, after adjusting for age and compared with never smokers, current smokers had increased odds of AMD, OR = 3.12 (2.10–4.64), but the odds were not significantly greater among former smokers, OR = 1.36 (0.97–1.90) • Among the 3 studies, current smokers had a greater increased risk of NV AMD, OR = 4.55 (2.74–7.54), than GA AMD alone, OR = 2.54 (1.25–5.17) • Each study reported significant increased odds of AMD among current smokers and nonsignificant increased odds of AMD among former smokers • For GA AMD among current smokers, significant increased odds were reported only in the Rotterdam Study, OR = 2.62 (1.03–6.62), and BMES, OR = 5.82 (1.27–26.71) • BDES reported a nonsignificant protective effect of current smoking, OR = 0.77 (0.09–6.34), against GA AMD • For NV AMD, the Rotterdam Study reported the highest risk among current smokers, OR = 7.07 (2.80–17.84), and BDES reported the lowest, OR = 3.32 (1.39–7.90) • Data not pooled because BDES had significantly different findings from BMES and Rotterdam Study
Seddon et al. 2004	• AREDS participants 55–80 years of age • Nested case-control • Analyzed for CRP levels • 747 cases (222 advanced AMD, 325 intermediate AMD, and 200 mild maculopathy) • 183 controls	Fundus photographs graded according to International Classification of ARM	• When compared with the lowest tertile among never smokers, the highest tertile of CRP (>4.5–117.0 mg/L), OR = 2.16 (1.33–3.49), and the second tertile of CRP (>1.7–4.5 mg/L), OR = 1.87 (1.15–3.06), were associated with increased risk of AMD for smokers • In stratified analyses, smoking increased the risk of AMD in the two lowest CRP tertiles, OR = 1.79 (1.06–3.00) and OR = 1.90 (1.12–3.22), respectively, but not in the highest CRP tertile, OR = 1.01 (0.61–1.69)
Paunksnis et al. 2005	• Cohort study • Participants 35–64 years of age • Nested case-control • 84 ARM cases and 84 controls matched for age, gender, and education level • Lithuania	Fundus photographs graded according to International Classification of ARM	• Prevalence of smoking did not differ between male ARM cases and male controls • Among women, prevalence of current smoking was significantly higher among ARM cases (17.5%) than among control cases (0%) (p trend = 0.019) • No other significant differences were reported among women

Table 10.4*S* Continued

Study	Design/population	AMD assessment/type studied	Findings (95% CI)
Conley et al. 2006	• Population-based sample • Nested case-control and meta-analysis • Participants ≥65 years of age from the CHS; 126 ARM and 1,051 controls • Participants 55–80 years of age from AREDS (a multicenter study), 1,402 ARM cases and 175 controls • Cases and controls limited to Whites who were genotyped *CFH Y402H* and *LOC387715 S69A*	CHS: physician-diagnosed AMD and fluorescein angiography AREDS: fundus photographs graded according to AREDS Grading System	• In AREDS cohort, compared with never smokers, ever smokers had increased risk of ARM for both genotypes: *CRH Y402H,* OR = 1.59 (1.13–2.23), and *LOC387715 S69A,* OR = 1.57 (1.12–2.20) • Associations were not significant in CHS cohort • No significant interactions between *Y402H* or *S69A* and smoking on the risk of ARM were detected for CHS or AREDS datasets
Schaumberg et al. 2007	• Nurses' Health Study and the Health Professionals Follow-Up Study • Nested case-control • Genotyped for the *Y402H* variant of the *CFH* gene and *LOC387715 A69S* gene • 457 AMD cases • 1,071 age- and gender-matched controls	Physician-diagnosed AMD and fluorescein angiography	• Multiplicative interaction terms not significant for the joint effects of smoking and *CFY Y402H* (p trend = 0.72) or *LOC387715 A69S* genotypes (p trend = 0.56) • For current smokers, the risk of developing AMD was significantly increased among *HH* (risk allele) *CFH Y402H* carriers, IRR = 8.69 (3.86–19.57), compared with nonsmokers without the risk allele (they had *YY*) • Current smokers with *SS* allele of the *LOC387715 A69S* gene had greater risk of developing AMD, IRR = 22.47 (4.70–107.54), than nonsmokers with the nonrisk (*AA*) genotype
Bauer et al. 2008b	• 5,040 participants from the European Eye Study • 23,000 participants from Eye Diseases Prevalence Research Group • Meta-analysis • Pooled data from other prevalence studies, including participants of White European descent	International ARM Study Group definition of AMD	• In Switzerland, 7% of late AMD cases (12% of men and 4% of women) were attributed to smoking • Using the mean prediction model, 3,800 cases of late AMD will be attributed to smoking by 2020 and 6,600 cases by 2050

Table 10.4*S* Continued

Study	Design/population	AMD assessment/type studied	Findings (95% CI)
Cong et al. 2008	• 13 studies (5 cohort and 8 case-control) obtained from PubMed and MEDLINE published from January 1966 to August 2007 and provided an RR or OR estimating the relationship between smoking and AMD risk after adjusting for potential risk factors • Meta-analysis	Definitions and grading systems varied by study	• Both types of studies associated ever smoking with AMD: cohort studies, RR = 1.61 (1.01–2.57), and case-control studies, RR = 1.76 (1.56–1.99) • Association between AMD and former smoking was inconsistent in pooled analyses for both cohort and case-control studies • In all studies, current smoking was associated with a greater risk of AMD than former smoking • Both types of studies significantly associated current smoking with AMD, cohort, RR = 2.06 (1.12–3.77), and case-control, RR = 2.38 (1.74–3.26) • Both types of studies significantly associated smoking with GA: cohort, RR = 2.79 (1.47–5.28), and case-control, RR = 1.71 (1.23–2.39); but only case-control studies significantly associated smoking with NV AMD, RR = 1.96 (1.69–2.27) • A significant association between smoking and AMD was observed among studies using hospital-based controls, RR = 1.85 (1.58–2.16), and population-based controls, RR = 1.62 (1.33–1.98)
Hogg et al. 2008	• Clinic- and community-based sample • Nested case-control • 292 cases (195 CNV and 97 non-NV AMD) • 115 controls	Fundus photographs graded according to Wisconsin ARM Grading System	• Smoking associated with NV AMD, OR = 3.71 (1.25–11.06) • Biomarkers for AMD, CRP, and ICAM1 positively associated with smoking status
Wang et al. 2008a	• BMES • Population-based sample • Nested case-control • Participants ≥49 years of age • 278 AMD cases (224 early and 54 late) • 557 controls matched on age, gender, and smoking	Fundus photographs graded according to Wisconsin ARM Grading System	• Compared with never and former smokers with the nonrisk (*GG*) genotype, the interaction between current smokers and the risk (*GT*+*TT*) genotype of the *LOC387715* gene resulted in increased odds of late AMD, OR = 6.06 (1.96–18.76) • Ever smokers with the nonrisk genotype (*GG*) had a null association with early AMD, OR = 1.01 (0.49–2.09) • Compared with never and former smokers with the same genotype, current smokers with the nonrisk (*GG*) genotype had nonsignificant increased odds of late AMD, OR = 1.21 (0.27–5.54), and current smokers with the risk genotype (*GT*+*TT*) had significant increased odds of late AMD, OR = 6.06 (1.96–18.76) • Results do not indicate an interaction between smoking and the *LOC387715* genotype
Despriet et al. 2009	• Pooled data from 6,418 participants ≥55 years of age in Rotterdam Study and case-control study • Meta-analysis • 357 AMD cases and 173 controls • The Netherlands	Fundus photographs graded according to Wisconsin ARM Grading System	• Although the *R102G* and *P314L* variants of the *C3* gene were significantly associated with AMD, no effect modification observed for smoking among the separate datasets or when datasets were combined

Table 10.4*S* Continued

Study	Design/population	AMD assessment/type studied	Findings (95% CI)
Seddon et al. 2009	• AREDS • Prospective and case-control • Incidence analysis: 1,446 participants (279 advanced AMD cases and 1,167 without signs of AMD) • Prevalence analysis: 731 participants (509 advanced AMD cases and 222 controls)	Fundus photographs graded according to clinical ARM Grading System	• Smoking independently associated with AMD and multiplicative joint effect with genotype on AMD risk • Former smoking associated with advanced AMD, OR = 1.9 (1.2–2.9) • Compared with never smokers, current smokers were more likely to have advanced AMD, OR = 3.9 (1.7–8.9); unilateral advanced AMD, OR = 3.7 (1.5–9.6); bilateral advanced AMD, OR = 4.0 (1.5–10.7); and NV AMD, OR = 4.4 (1.9–10.4) • Compared with never smokers, former smokers had increased odds of unilateral advanced AMD, OR = 2.2 (1.3–3.6); GA AMD, OR = 1.8 (1.0–3.1); and NV AMD, OR = 1.9 (1.2–3.1) • In analyses of incident cases, and compared with nonprogressing never smokers, current smokers were more likely to progress to unilateral advanced AMD, OR = 2.7 (1.1–6.7); bilateral advanced AMD, OR = 3.0 (1.4–6.3); and NV AMD, OR = 3.4 (1.4–8.7) • Overall, the incidence of advanced AMD was associated with current smoking, OR = 3.1 (1.7–5.6) • Former smoking was not significantly associated with the incidence of any form of AMD

Note: **AREDS** = Age-Related Eye Disease Study; **ARM** = age-related maculopathy; **BDES** = Beaver Dam Eye Study; **BMES** = Blue Mountains Eye Study; **CHS** = Cardiovascular Health Study; **CI** = confidence interval; **CNV** = choroidal neovascularization; **CRP** = C-reactive protein; **GA** = geographic atrophy; **IRR** = incidence rate ratio; **mg/L** = milligrams per liter; **NV** = neovascular; **OR** = odds ratio; **RR =** relative risk.

Table 10.5*S* Studies on the association between active smoking and dental caries

Study	Design/population	Findings
Bruno-Ambrosius et al. 2005	• Cohort • 162 girls • 12 years of age at baseline (7 grade) • Falkenberg, Sweden • 3-year follow-up	• Mean DMFS (±SD) increment by 8th-grade smoking status: – Smoker: 7.7 (±4.7), p <0.001 – Nonsmoker: 1.9 (±4.7) • DMFS increment ≥1 for smokers: OR = 4.1 (1.0–18.9)
Birnboim-Blau et al. 2006	• Cross-sectional • 581 male army recruits • 17–26 years of age • Israel	• DT (mean): – Smoker: 2.31 – Nonsmoker: 1.48 – p <0.0001 (t-test) • MT (mean): – Smoker: 0.40 – Nonsmoker: 0.19 – p = 0.0012 (t-test) • FT (mean): – Smoker: 2.73 – Nonsmoker: 3.57 – p = 0.0049 (t-test) • DMFT (mean): – Smoker: 5.44 – Nonsmoker: 5.25 – p = 0.6000 (t-test)
Dye et al. 2007	• Cross-sectional • Nationally	• Prevalence of dental caries: – Current smoker: 91.48% – Former smoker: 92.83% – Never smoker: 91.19% • Prevalence of untreated dental caries: – Current smoker: 39.26% – Former smoker: 19.67% – Never smoker: 20.56% • DT (mean): – Current smoker: 1.42 – Former smoker: 0.53 – Never smoker: 0.51 • MT (mean): – Current smoker: 4.12 – Former smoker: 2.30 – Never smoker: 1.83 • FT (mean): – Current smoker: 5.90 – Former smoker: 7.73 – Never smoker: 7.31 • DMFT (mean): – Current smoker: 11.44 – Former smoker: 10.55 – Never smoker: 9.65

Table 10.5*S* Continued

Study	Design/population	Findings
Ojima et al. 2007	• Cross-sectional • Nationally	• Prevalence of untreated dental caries: – Current smoker: 52.4% – Former smoker: 42.3% – Never smoker: 33.9% • AOR for untreated dental caries (adjusted for frequency of brushing, BMI, alcohol consumption, and intake of vitamins C and E): – Current smoker: 1.67 (1.28–2.20) – Former smoker: 1.25 (0.77–2.04) – Never smoker: 1.00 (reference)
Aguilar-Zinser et al. 2008	• Cross-sectional • 824 male truck drivers, 20–65 years of age (mean age = 35.5 years) • Mexico City, Mexico	• DT (mean): – Current smoker: 3.97 – Former smoker: 3.94 – Nonsmoker: 4.13 – Tukey-Kramer p trend = 0.85 • MT (mean): – Current smoker: 1.65 – Former smoker: 2.24 – Nonsmoker: 1.40 – Tukey-Kramer p trend < 0.01 • FT (mean): – Current smoker: 3.16 – Former smoker: 3.66 – Nonsmoker: 3.02 – Tukey-Kramer p trend = 0.27 • DMFT (mean): – Current smoker: 8.80 – Former smoker: 9.86 – Nonsmoker: 8.55 – Tukey-Kramer p trend = 0.01
Hamasha and Safadi 2008	• Cross-sectional • 1,096 randomly selected adults • 18–67 years of age • Irbid, Jordan	• DS (mean): – Smoker: 7.27 – Nonsmoker: 6.01 – Mann-Whitney p trend = 0.05 • MS (mean): – Smoker: 25.18 – Nonsmoker: 19.45 – Mann-Whitney p trend = 0.05 • FS (mean): – Smoker: 6.75 – Nonsmoker: 8.33 – Mann-Whitney p trend = 0.05 • DFS (mean): – Smoker: 14.02 – Nonsmoker: 14.24 – Mann-Whitney p trend = 0.05 • DMFS (mean): – Smoker: 39.20 – Nonsmoker: 33.79 – Mann-Whitney p trend = 0.05 • Smoking status was a significant (p <0.005) independent variable in a multiple linear regression model of DMFS that also included age, frequency of dental flossing, family income, urban/rural residence, education level, and frequency of toothbrushing.

Table 10.5*S* Continued

Study	Design/population	Findings
Roberts-Thomson and Stewart 2008	• Cross-sectional • 644 randomly selected adults • 20–25 years of age • South Australia	• Precavitated DS (mean): – Current smoker: 3.07 – Not current smoker: 2.19 • Cavitated DS (mean): – Current smoker: 1.43 – Not current smoker: 0.65 – $p < 0.05$ (ANOVA) • D_3MFS (mean): – Current smoker: 6.26 – Not current smoker: 5.96 • Current smoking status was also significantly associated ($p < 0.01$) with DS in a multiple linear regression model that was adjusted for government benefits, employment status, usual reason for dental visit, public/private site for last dental visit, frequency of toothbrushing, and frequency of consuming acidic beverages
Vellappally et al. 2008	• Cross-sectional • 805 dental patients • 30–69 years of age • Kochi, India	• DT (mean): – Regular smoker: 6.44 – Occasional smoker: 3.60 – Former smoker: 5.50 – Nonsmoker: 5.10 – $p < 0.001$ (Kruskal-Wallis one-way ANOVA) • MT (mean): – Regular smoker: 1.90 – Occasional smoker: 1.57 – Former smoker: 1.62 – Nonsmoker: 1.53 – p trend = 0.529 (Kruskal-Wallis one-way ANOVA) • FT (mean): – Regular smoker: 3.29 – Occasional smoker: 1.97 – Former smoker: 3.23 – Nonsmoker: 2.33 – $p < 0.001$ (Kruskal-Wallis one-way ANOVA) • DMFT (mean): – Regular smoker: 11.63 – Occasional smoker: 7.14 – Former smoker: 10.35 – Nonsmoker: 8.96 – $p < 0.001$ (Kruskal-Wallis one-way ANOVA)
Al-Habashneh et al. 2009	• Cross-sectional • 560 periodontal patients • 16–35 years of age • Irbid, Jordan	• Chronic gingivitis, DMFT (mean): – Smoker: 8.02 – Nonsmoker: 5.39 – $p < 0.05$ (t-test) • Chronic periodontitis, DMFT (mean): – Smoker: 12.87 – Nonsmoker: 9.59 – $p < 0.05$ (t-test) • Aggressive periodontitis, DMFT (mean): – Smoker: 5.03 – Nonsmoker: 3.00 – $p < 0.05$ (t-test)

Table 10.5*S* Continued

Study	Design/population	Findings
Du et al. 2009	• Cross-sectional • 1,080 adults, 35–44 years of age • 1,080 adults, 65–74 years of age • Hubei Province, China	• Prevalence of experience with root surface caries among persons with gingival recession: – Current smoker: 38.6% – Former smoker: 30.7% – Never smoker: 29.8% • AOR for root surface caries among persons with gingival recession (adjusted for age, ethnicity, tea drinking, dental visits, and annual family income): – Current smoker: 1.76 (1.18–2.63) – Former smoker: 1.39 (1.10–1.75) – Never smoker: 1.00 (reference)
Iida et al. 2009	• Cross-sectional • Nationally representative sample • 5,110 females • 15–44 years of age • United States	• Prevalence of untreated caries: – Current smoker: 34.6% – Former smoker: 18.3% – Never smoker: 20.3% • DMFS (mean): – Current smoker: 25.5 – Former smoker: 16.5 – Never smoker: 16.1 • AOR for untreated caries (adjusted for age, race/ethnicity, country of birth, poverty status, education level, health insurance status, marital status, number of live births, BMI, alcohol consumption, time since last dental visit, and reason for last dental visit): – Current smoker: 1.82 (1.23–2.70) – Former smoker: 0.99 (0.65–1.52) – Never smoker: 1.00 (reference)
Skudutyte-Rysstad et al. 2009	• Cross-sectional • Random sample of 149 adults • 35 years of age • Oslo, Norway	• Number of sound teeth (mean): – Current smoker: 17.4 – Former smoker: 16.0 – Never smoker: 17.5 • Prevalence of decay: – Current smoker: 50% – Former smoker: 32% – Never smoker: 14% • AOR for decay (adjusted for family income, frequency of toothbrushing, pattern of dental visits, and time since last dental visit): – Current smoker: 4.5 (1.6–12.6) – Former smoker: 2.8 (1.0–8.2) – Never smoker: 1.00 (reference)
Ditmyer et al. 2010	• Case-control • Cases: 1,576 adolescents, 12–19 years of age, with ≥4 DMFT • Controls: 1,392 adolescents, 12–19 years of age, with no dental caries • Nevada	• Smoking status of adolescent cases: – Currently smoke: 372 (23.6%) – Currently do not smoke: 1,204 (76.4%) • Smoking status of adolescent controls: – Currently smoke: 215 (15.4%) – Currently do not smoke: 1,177 (84.6%) • AOR for ≥4 DMFT (adjusted for race/ethnicity, age, dental insurance status, fluoridation status, exposure to secondhand smoke, and presence of dental sealants): 1.85 (1.68–2.06)

Table 10.5*S* Continued

Study	Design/population	Findings
Kumar et al. 2010	• Cross-sectional • 345 medical students • 18–25 years of age • Udaipur, India	• DT (mean): – Smoker: 4.05 – Nonsmoker: 2.82 – p <0.0001 (t-test) • MT (mean): – Smoker: 0.27 – Nonsmoker: 0.06 – p <0.0001 (t-test) • FT (mean): – Smoker: 1.69 – Nonsmoker: 1.19 – p trend = 0.004 (t-test) • DMFT (mean): – Smoker: 6.01 – Nonsmoker: 4.08 – p <0.0001 (t-test)
Sugihara et al. 2010	• Cross-sectional • 153 adults • 60–94 years of age • Chiba, Japan	• Smoking status was not associated with the number of decayed root surfaces
Campus et al. 2011	• Cross-sectional • 762 adults • 21–32 years of age, enrolled in a military academy • Italy	• DS (mean): – Heavy smoker: 1.1 – Light smoker: 0.8 – Nonsmoker: 0.6 – p trend = 0.01 (Kruskal-Wallis) • MS (mean): – Heavy smoker: 2.5 – Light smoker: 2.5 – Nonsmoker: 2.3 – p >0.05 (Kruskal-Wallis) • FS (mean): – Heavy smoker: 7.9 – Light smoker: 7.6 – Nonsmoker: 7.4 – p >0.05 (Kruskal-Wallis) • DMFS (mean): – Heavy smoker: 11.5 – Light smoker: 11.3 – Nonsmoker: 9.9 – p trend = 0.04 (Kruskal-Wallis)

Notes: **ANOVA** = analysis of variance; **AOR** = adjusted odds ratio; **BMI** = body mass index; **CI** = confidence interval; **DFS** = decayed or filled permanent tooth surfaces; **DMFS** = decayed, missing, or filled permanent tooth surfaces; **D_3MFS** = cavitated, decayed, untreated, missing, or filled permanent tooth surfaces; **DMFT** = decayed, missing, or filled permanent teeth; **DS** = decayed permanent tooth surfaces; **DT** = decayed permanent teeth; **FS** = filled permanent tooth surfaces; **FT** = filled permanent teeth; **MS** = missing permanent tooth surfaces; **MT** = missing permanent teeth; **OR** = odds ratio; **SD** = standard deviation.

Table 10.6*S* Studies on exposure to tobacco smoke and dental caries

Study	Design/population	Findings
Williams et al. 2000	• Cross-sectional • Nationally representative sample • 749 children • 3–4.5 years of age • United Kingdom	• Prevalence of dental caries by parental smoking status: – Neither parent: 21% – Mother only: 38% (p<0.001)[a] – Father only: 25% (p not significant)[a] – Both parents: 31% (p <0.05)[a] – Either parent: 33% (p <0.001)[a] • dmft (mean) by parental smoking status: – Neither parent: 0.8 – Mother only: 1.8 – Father only: 0.8 – Both parents: 1.5 – Either parent: 1.3 • Prevalence of dental caries by household social class (nonmanual or manual occupation) and mothers' smoking status: – Nonmanual, smoker: 32% (p <0.01)[b] – Nonmanual, nonsmoker: 18% – Manual, smoker: 38% (p <0.05)[b] – Manual, nonsmoker: 26% • dmft (mean) by household social class and mothers' smoking status: – Nonmanual, smoker: 1.4 – Nonmanual, nonsmoker: 0.6 – Manual, smoker: 1.9 – Manual, nonsmoker: 1.0 • AOR for mothers' smoking and dental caries in child (adjusted for child's age and social class of head of household): 1.54 (1.07–2.21)
Aligne et al. 2003	• Cross-sectional • Nationally representative sample • 3,531 children • 4–11 years of age • United States	• Prevalence of decayed or filled tooth surfaces of deciduous teeth by serum cotinine level (ng/mL): – <0.2 (decayed): 18.2% (reference) – 0.2–10 (decayed): 31.7% (p <0.001) – <0.2 (filled): 29.2% (reference) – 0.2–10 (filled): 36.5% (p = 0.01) • Prevalence of decayed or filled tooth surfaces of permanent teeth by serum cotinine level (ng/mL): – <0.2 (decayed): 7.4% (reference) – 0.2–10 (decayed): 10.4% (p = 0.07) – <0.2 (filled): 19.7% (reference) – 0.2–10 (filled): 18.3% (p = 0.59) • AOR for decayed deciduous teeth associated with serum cotinine level (ng/mL): – <0.05: 1.0 (reference) – 0.05–<0.2: 1.3 (0.8–2.4) – 0.2–1.0: 2.2 (1.3–3.6) – >1.0: 2.3 (1.4–3.0) • AOR for filled deciduous teeth associated with serum cotinine level (ng/mL): – <0.05: 1.0 (reference) – 0.05–<0.2: 1.1 (0.7–1.8) – 0.2–1.0: 1.6 (1.0–2.4) – >1.0: 1.5 (1.0–2.3)

Table 10.6*S* Continued

Study	Design/population	Findings
Shenkin et al. 2004	• Prospective cohort • 637 children • 4–7 years of age • Iowa	• Prevalence and RR of dental caries in primary dentition by SES and presence of regular smoker in household (reference: no smoker in home): – Low SES. Smoker in home: 48%, RR = 1.50 (0.95–2.37); no smoker in home: 32% – Middle SES. Smoker in home: 52%, RR = 2.15 (1.35–3.45); no smoker in home: 24% – High SES. Smoker in home: 33%, RR = 1.66 (0.64–4.33); no smoker in home: 20% – All. Smoker in home: 44%, RR = 1.74 (1.27–2.37); no smoker in home: 25% • AOR for caries in primary dentition and presence of regular smoker in household (adjusted for age, frequency of toothbrushing, total ingested fluoride, and SES): 3.38 (1.68–6.79)
Tanaka et al. 2006	• Cross-sectional • Nationally representative sample • 925 children • 1–14 years of age • Japan	• Prevalence of decayed or filled teeth and AOR (adjusted for age, gender, region, frequency of toothbrushing, experience with topical fluoride application, and BMI) for outcome by presence of smoking in household (reference: no smoker in home): – Decayed and/or filled teeth. Smoker in home: 63.4%, AOR = 1.26 (0.93–1.69); no smoker in home: 59.6% – Decayed teeth. Smoker in home: 40.5%, AOR = 1.34 (1.02–1.76); no smoker in home: 33.6% – Filled teeth. Smoker in home: 49.1%, AOR = 1.03 (0.76–1.40); No smoker in home: 49.4%
Ayo-Yusuf et al. 2007	• Cross-sectional representative sample • 1,873 8th-grade students • 12–19 years of age • Limpopo Province, South Africa	• Prevalence and AOR for decayed second permanent molars by exposure to secondhand smoke: – Smoker in home: 23.4%, AOR = 2.02 (1.22–3.33) – No smoker in home: 12.3%, AOR = 1.00 (reference)
Saraiva et al. 2007	• Cross-sectional • Nationally representative sample • 3,189 children • 2–5.9 years of age • United States	• Prevalence and AOR for ≥1 dft by number of smokers in the home (adjusted for child's gender, age, and race/ethnicity; maternal age at birth of child; fluoride supplementation status; carbohydrate intake; education level of head of household; household income poverty ratio; frequency of dental visits; duration of bottle feeding; low birth weight; and preterm birth): – No smokers in home: 17.6%, AOR = 1.00 (reference) – 1 or 2 smokers in home: 28.6%, AOR = 1.42 (1.13–1.78) – >2 smokers in home: 24.6%, AOR = 1.39 (1.02–1.89)
Avsar et al. 2008	• Cross-sectional • 180 dental patients • 4–6 years of age • Turkey	• Prevalence of dental caries and mean dmft by status of smoking in the household: – No smoking in home: 65.6%, 4.64 – Smoking in home: 89.9%, 10.58 • Mean dmft by number of cigarettes smoked/day by members of the household: – <10 cigarettes/day: 5.20 – 10–20 cigarettes/day: 9.77 – >20 cigarettes/day: 16.77

Table 10.6*S* Continued

Study	Design/population	Findings
Hanioka et al. 2008	• Cross-sectional • 732 children • 3 years of age, attending a public health center • Hokkaido, Japan	• Adjusted mean number of decayed teeth, prevalence of decayed teeth, and AOR for having decayed teeth by smoking status of parents (adjusted for gender, order of birth, main type of drink, frequency of sugar-containing snacks, daily toothbrushing by parents, use of fluoridated toothpaste, and residential location): – Neither parent smokes: 1.2 (mean), 25.6%, AOR = 1.00 (reference) – Only father smokes: 1.6 (mean), 35.3%, AOR = 1.52 (1.01–2.30) – Only mother smokes: 2.1 (mean), 45.7%, AOR = 2.25 (1.51–3.37)
Leroy et al. 2008	• Cross-sectional • Representative samples: 1,250 children, 3 years of age; 1,283 children, 5 years of age • Flanders (Flemish Region), Belgium	• For children, 3 years of age, prevalence and AOR of experience with dental caries by family smoking status: – Current smoker: 10.3%, AOR = 1.98 (0.68–5.76) – Former smoker: 5.9%, AOR = 1.71 (0.30–9.65) – Never smoker: 4.9%, AOR = 1.00 (reference) • For children, 5 years of age, prevalence and AOR of experience with dental caries by family smoking status: – Current smoker: 41.8%, AOR = 3.36 (1.49–7.58) – Former smoker: 24.8%, AOR = 0.55 (0.19–1.65) – Never smoker: 25.2%, AOR = 1.00 (reference)
Tanaka et al. 2009	• Cross-sectional • 2,109 children • 3 years of age • Fukuoka City, Japan	• Prevalence and AOR of dental caries by exposure to secondhand smoke at home (p value for linear trend = 0.006): – Current smoker: 25%, AOR = 1.25 (1.04–1.50) – Former smoker: 24%, AOR = 1.23 (0.88–1.71) – Never smoker: 17.8%, AOR = 1.00 (reference) • Prevalence and AOR of dental caries by pack-months of exposure to secondhand smoke at home: – ≥18: 27.1%, AOR = 1.33 (1.09–1.63) – 0.1–17.9: 22.6%, AOR = 1.16 (0.93–1.44) – None: 17.8%, AOR = 1.00 (reference)
Christensen et al. 2010	• Cross-sectional • 2,168 children and adolescents • 5, 12, and 15 years of age • Denmark	• Mean number of DMFS+dmfs and AOR for DMFS+dmfs >1 by smoking status of parents/respondents: – Smoker: 2.8 (mean) (p <0.001); AOR = 1.35 (p <0.05) – Nonsmoker: 1.9 (mean) (reference)
Ditmyer et al. 2010	• Case-control • Cases: 2,115 adolescents; 12–19 years of age, with ≥4 DMFT • Controls: 2,035 adolescents; 12–19 years of age, with no dental caries • Nevada	• Number and percentage of cases and controls exposed and not exposed to secondhand smoke: – Exposed: 871 cases (41.2%); 565 controls (27.8%) – Not exposed: 1,244 cases (58.8%); 1,470 controls (72.2%) • AOR (adjusted for race/ethnicity, age, dental insurance status, fluoridation status, smoking status, and presence of dental sealants): 1.42 (1.03–1.53)

Table 10.6*S* Continued

Study	Design/population	Findings
Tanaka et al. 2010	• Cross-sectional • Representative sample • 20,703 school children • 6–15 years of age • Okinawa, Japan	• Prevalence of decayed or filled teeth and adjusted PRs by status of smoking in household (p <0.0001): – Never smoker: 79.3%, PR = 1.00 (reference) – Former smoker: 83.4%, PR = 1.03 (1.00–1.05) – Current smoker <15 cigarettes/day: 84.4%, PR = 1.04 (1.02–1.05) – Current smoker ≥15 cigarettes/day: 85.5%, PR = 1.04 (1.03–1.06) • Prevalence of decayed or filled teeth and adjusted PRs by pack-years of secondhand smoking in household (p <0.0001): – None: 79.3%, 1.00 (reference) – 0.1–2.9: 84.3%, PR = 1.03 (1.02–1.05) – 3.0–6.9: 84.1%, PR = 1.03 (1.01–1.05) – ≥7.0: 85.3%, PR = 1.04 (1.03–1.06)

Notes: **AOR** = adjusted odds ratio; **BMI** = body mass index; **CI** = confidence interval; **dft** = decayed or filled primary teeth; **dmfs** = decayed, missing, or filled primary tooth surfaces; **DMFS** = decayed, missing, or filled permanent tooth surfaces; **dmft** = decayed, missing, or filled primary teeth; **ng/mL** = nanogram per milliliter; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **PR** = prevalence ratio; **RR** = relative risk; **SES** = socioeconomic status.
[a]p value, $\chi 2$ test compared households where neither parent smoked.
[b]p value, $\chi 2$ test compared prevalence of caries among children by mother's smoking status in each stratum of social class.

Table 10.7*S* Studies on smoking and failure of dental implants

Study	Design/population	Proportion of failed implants by smoking status	Estimate of effects (95% CI)	Comments
Bain and Moy 1993	• Retrospective cohort • 540 patients • 2,194 implants • Follow-up: 81 months (maximum)	• Nonsmokers: 4.76% • Smokers: 11.28%	• Crude RR = 2.37 (1.67–3.35)[a]	Failure after prosthetic load
De Bruyn and Collaert 1994	• Retrospective cohort • 117 patients (26 smokers) • 462 implants • Follow-up: 7 years	• Total: – Nonsmokers: 1.1% – Smokers: 6.1% • Maxilla: – Nonsmokers: 1.8% – Smokers: 9.0% • Mandible: – Nonsmokers: 0.6% – Smokers: 0%	• Crude RR= 5.19 (1.55–17.40)[a] • RR adjusted for arch: 4.21 (1.19–14.85)[a]	Failures: implants removed due to mobility, fracture, or infection
Gorman et al. 1994	• Prospective randomized clinical trial • 310 patients (82 smokers) • 2,066 implants (646 in smokers)	• By implant: – Nonsmokers: 3.31% – Smokers: 6.50% • By patient: – Nonsmokers: 8.77% – Smokers: 21.95%	• By implant: crude RR = 1.96 (1.31–2.95) • By patient: crude RR = 2.50 (1.39–4.49)	Failure at time of uncovering of implants, defined as mobility, radiolucency, pain, or infection
Weyant 1994	• Prospective cohort (implant registry) • 598 patients • 2,098 implants • Follow-up: 4 years	NR		Smoking not associated with implant failure in bivariate or multivariate analyses; parameters not reported
Bain 1996	• Prospective cohort • 78 patients • 223 implants	• Nonsmokers: 5.68% • Smokers who quit smoking after placement: 11.76% • Smokers who continued to smoke: 38.46%	• Nonsmokers: Reference • Quit smoking: crude RR = 2.07 (0.69–6.22)[a] • Continued smoking: crude RR = 6.77 (2.71–16.88)[a]	Early failure only (before prosthetic loading)
Minsk et al. 1996	• Retrospective cohort • 727 implants (157 in smokers) • Follow-up: 6 years (maximum)	• Nonsmokers: 10.8% • Smokers: 9.1%	• Crude RR = 1.19 (0.71–1.99)[a]	
Wang et al. 1996	• Prospective cohort • 30 patients • 83 implants (14 in smokers) • Follow-up: 3 years	• Nonsmokers: 15.7% • Smokers: 15.4%	• Crude RR = 0.98 (0.24–3.91)[a]	

Table 10.7*S* Continued

Study	Design/population	Proportion of failed implants by smoking status	Estimate of effects (95% CI)	Comments
Lemons et al. 1997	• Prospective cohort (32 sites) • 595 patients (178 smokers) • 2,671 implants (858 in smokers) • Follow-up: 2 years (maximum)	• Nonsmokers: 2.5% • Smokers: 2.8%	• Crude RR = 1.11 (0.68–1.81)[a]	Significantly higher failure rate among smokers early in study, which may have influenced subsequent patient selection
Lindquist et al. 1997	• Prospective cohort • 45 patients (21 smokers) • 266 implants (125 in smokers) • Follow-up: 10 years	• Nonsmokers: 2.1% • Smokers: 0%	NA	All patients were edentulous
Minsk and Polson 1998	• Retrospective cohort • 116 women patients • 51–91 years of age • 450 implants (126 in smokers)	• Nonsmokers: 7.5% • Smokers: 9.5%	• Crude RR = 1.32 (0.60–2.86)[a]	
Morris and Ochi 1998	• Prospective cohort • 2,188 implants (1,005 in smokers) • Follow-up: 3 years (maximum)	• Never smokers: 6.6% • Current smokers: 8.9%	• Crude RR = 1.38 (1.00–1.80)[a]	
De Bruyn et al. 1999	• Prospective cohort • 32 patients • 85 implants • Follow-up: 7 years	• Nonsmokers: 28.1% • Smokers: 20.0%	• Crude RR = 0.71 (0.29–1.76)[a]	Data for maxillary implants only
Grunder et al. 1999	• Prospective cohort • 74 patients (19 smokers) • 219 implants (55 in smokers) • Follow-up: 34.4 months (maximum) (mean 28.5 months)	• Nonsmokers: 0% • Current smokers: 1.8%	• OR = 0.00 (0.00–7.25)[b]	
Jones et al. 1999	• Prospective cohort (within randomized clinical trial) • 63 patients (19 smokers) • 348 implants (126 in smokers) • Follow-up: 5 years	• Preloading proportion of patients with failure: – Nonsmokers: 9% – Smokers: 26% • Postloading proportion of patients with failure: – Nonsmokers: 4% – Smokers: 37% • Proportion of implants that failed: – Nonsmokers: 2.3% – Smokers: 8.7%	• Preloading failure: crude RR = 2.89 (0.87–9.61)[a] • Postloading failure: crude RR = 8.11 (1.85–35.48)[a] • Proportion of failure: crude RR = 3.79 (1.35–10.66)[a]	

Table 10.7*S* Continued

Study	Design/population	Proportion of failed implants by smoking status	Estimate of effects (95% CI)	Comments
Keller et al. 1999	• Retrospective cohort • 54 patients (8 current smokers, 20 former smokers) • 248 implants (32 in current smokers, 73 in former smokers) • Follow-up: 12 years (maximum)	• Never smoker: 15.4% • Former smoker: 5.5% • Current smoker: 21.9%	• Never smoker: crude RR = 1.00 (reference) • Former smoker: crude RR = 0.36 (0.13–1.00)[a] • Current smoker: crude RR = 1.42 (0.67–3.04)[a]	All patients received autogenous maxillary bone graft
Wilson and Nunn 1999	• Retrospective cohort • 62 patients (27 smokers) • 101 implants • Follow-up: 49 days–10.65 years	NR	• HR = 2.50 (1.12–5.56)	
Berge and Gronning-saeter 2000	• Retrospective cohort • 30 patients • 116 implants • Follow-up: 14.1 years (maximum)	NR	• HR = 4.21 (1.71–10.43)	
Lambert et al. 2000	• Prospective cohort study (within randomized clinical trial) • 2,887 implants • Follow-up: 3 years	• Current smoker: 8.9% • Former/never smoker: 6.0%	• Crude RR = 1.49 (1.14–1.95)	Smoking was a significant predictor of failure in multivariate logistic regression modeling, but parameter estimates were not reported
Olson et al. 2000	• Randomized clinical trial • 28 patients, 34–78 years of age • 116 implants (51 current smokers, 30 former smokers) • Follow-up: 5–71 months (mean 38.2 months)	• Never smoker: 0% • Former smoker: 3.3% • Current smoker: 3.9%	• Current smokers: crude RR = 3.46 (0.17–69.98) • Former smokers: crude RR = 3.48 (0.15–82.48)	
Wallace 2000	• Retrospective cohort • 56 patients (17 smokers) • 187 implants (72 in smokers) • Follow-up: 4 years (maximum)	• Nonsmoker: 6.9% • Current smoker: 16.6%	• Crude RR = 2.40 (1.03–5.58)[a]	All failures occurred within 11 months of placement
Eckert et al. 2001	• Retrospective cohort • 63 patients • 75 implants (7 in smokers) • Follow-up: up to 734 days	NR	• Current smoking: multivariate HR = 2.4 (p trend = 0.16)	
Ekfeldt et al. 2001	• Case-control • 26 cases • 25 controls	NR	• Crude OR = 1.82 (0.58–5.70)a	Cases: at least one-half of implants failed; controls: no implant failed

Table 10.7*S* Continued

Study	Design/population	Proportion of failed implants by smoking status	Estimate of effects (95% CI)	Comments
Geurs et al. 2001	• Retrospective cohort • 100 patients • 329 implants (62 in smokers) • Follow-up: 3 years	• Nonsmokers: 4.7% • Smokers: 11.3%	• Crude RR = 2.42 (1.01–5.82)[a]	All patients had sinus grafts
Mayfield et al. 2001	• Retrospective cohort • 15 patients (3 smokers) • 39 implants (7 in smokers) • Follow-up: 4–6.5 years	• Nonsmokers: 15.6% • Smokers: 28.6%	• Crude RR = 2.11 (0.51–8.81)[a]	All implants were placed in areas with osseous augmentation
Widmark et al. 2001	• Prospective cohort • 36 patients (11 smokers) • 198 implants (67 in smokers) • Follow-up: 1–5 years	• Nonsmokers: 11% • Smokers: 39%	• Crude RR = 3.63 (2.03–6.48)[a]	16 patients had bone grafts prior to implant placement
Bain et al. 2002	• Multicenter prospective cohort • 1,791 patients (333 smokers) • 4,883 implants (889 in smokers) • Follow-up: 3 years	• Nonsmokers: 5.05% • Smokers: 5.09%	• Crude RR = 1.01 (0.72–1.41)[a]	Larger proportion of smokers (13.8%) than nonsmokers (8.3%) lost to follow-up ($p < 0.0001$)
Chuang et al. 2002	• Retrospective cohort • 677 patients • 2,349 implants • Follow-up: 0.3–90.9 months (mean 23.8 months)	NR	• Current tobacco use: HR = 3.1 (1.7–5.5)[c]	
Kan et al. 2002	• Retrospective cohort • 60 patients • 228 implants (70 in smokers) • Follow-up: up to 60 months	• Nonsmokers: 7.0% • Smokers: 17.1%	• Crude RR = 2.46 (1.14–5.31)	
Kumar et al. 2002	• Retrospective cohort • 461 patients (72 smokers) • 1,183 implants (269 in smokers) • Follow-up: 12 weeks (from placement of implant until prosthetic loading)	• Nonsmokers: 1.6% • Current: 3.0%	• Crude RR = 1.81 (0.78–4.23)[a]	All smokers smoked ≥1/2 pack/day at the time of surgery
Ortorp and Jemt 2002	• Prospective cohort (within clinical trial) • 126 patients (43 smokers) • 729 implants • Follow-up: 1–3 years	• Nonsmokers: 6.0%[d] • Smokers: 23.3%[d]	• Crude RR = 3.86 (1.41–10.58)[a]	

Table 10.7*S* Continued

Study	Design/population	Proportion of failed implants by smoking status	Estimate of effects (95% CI)	Comments
Schwartz-Arad et al. 2002	• Retrospective cohort • 261 patients (89 smokers) • 959 implants (380 in smokers) • Follow-up: 6 months (minimum)	• Nonsmokers: 1.7%[a] • Smokers: 3.2%[a]	• Crude RR = 1.87 (0.82–4.28)[a]	
Karoussis et al. 2003	• Prospective cohort • 53 patients (12 smokers) • 112 implants (28 in smokers) • Follow-up: 10 years	• Nonsmokers: 3.6% • Smokers: 7.1%	• Crude RR = 2.00 (0.35–11.36)[a]	
Leonhardt et al. 2003	• Prospective cohort • 9 patients • 44 implants	• Nonsmokers: 5.6% • Smokers: 23.1%	• Crude RR = 4.15 (0.55–31.62)[a]	All patients had peri-implantitis on at least 1 implant
Rocci et al. 2003	• Prospective cohort (within randomized clinical trial) • 44 patients (12 smokers) • 121 implants • Follow-up: 1 year	• Nonsmokers: 9.4%[e] • Smokers: 33.3%[e]	• Crude RR = 3.56 (0.93–13.60)[a]	
Baelum and Ellegaard 2004	• Prospective cohort • 128 patients (90 smokers) • 258 implants • Follow-up: 10 years (maximum)	NR	• Adjusted HR = 2.6 (0.9–7.6)	All patients had history of periodontal surgery
Woo et al. 2004	• Retrospective cohort • 553 patients (57 smokers)	NR	• Current smoker vs. nonsmoker: adjusted HR = 4.4 (2.0–9.8)[c]	All patients had dentoalveolar reconstructive surgery; same patient population as Chuang and colleagues (2002)
Moheng and Feryn 2005	• Prospective cohort • 93 patients (15 smokers) • 266 implants • Follow-up: 1 year	• Nonsmokers: 3.8% • Smokers: 26.7%	• Crude RR = 6.93 (1.72–27.87)[a] • Adjusted RR = 14.4[f]	
Moy et al. 2005	• Retrospective cohort • 1,140 patients (173 smokers) • 4,680 implants • Follow-up: 20 years (maximum)	• Nonsmokers: 14.0% • Smokers: 20.2%	• Crude RR = 1.45 (1.04–2.03)[a] • Adjusted OR = 1.39 (p trend = 0.03)[g]	Implants placed over a 21-year period

Table 10.7*S* Continued

Study	Design/population	Proportion of failed implants by smoking status	Estimate of effects (95% CI)	Comments
DeLuca et al. 2006	• Retrospective cohort • 389 patients • 1,539 implants • Follow-up: 1–230 months (mean 59.8 months)	• Early failure by nonsmoker: 3.06% • Early failure by current smoker: • ≤5 cigarettes/day: 3.51% • 6–14 cigarettes/day: 4.82% • ≥15 cigarettes/day: 5.65%	• Crude RR = 1.72 (1.04–2.85)[a]	Current smoking not associated with late failure
Ellegaard et al. 2006	• 68 patients (45 smokers) • 262 implants • Follow-up: 147 months (maximum)	• 27 of 262 implants (10.3%) failed • Not reported by smoking status	• HR = 2.2 (0.8–6.1)	All patients had periodontitis and at least 1 implant placed in maxillary sinus region
Mundt et al. 2006	• Retrospective cohort • 159 patients • 663 implants (115 in current smokers, 247 in former smokers) • Follow-up: 120 months	• Never smokers: 2.0% • Former smokers: 5.7% • Current smokers: 13.9%	• Smoking duration of 10 years: adjusted HR = 1.54 (1.15– 2.06)[h]	Smoking modeled as continuous variable in Cox regression analysis
Peleg et al. 2006	• Prospective cohort • 731 patients (226 smokers) • 2,132 implants (627 placed in smokers) • Follow-up: 24–108 months (mean 69 months)	• Nonsmokers: 1.9% • Smokers: 2.6%	• Crude RR = 1.37 (0.75–2.52)[a]	All patients received sinus floor augmentation
Rao et al. 2006	• Retrospective cohort • 27 patients (16 smokers) • 131 implants (87 in smokers) • Follow-up: 5 years	• Nonsmokers: 15.9% • Smokers: 25.3%	• Crude RR = 1.59 (0.74–3.43)[a]	All patients were surgically treated for oral cancer
Roos-Jansaker et al. 2006	• Retrospective cohort • 218 patients (80 never smokers, 57 current smokers, 81 former smokers) • 1,057 implants • Follow-up: 9–14 years	• Never smokers: 6%[i] • Ever smokers: 12%[i]	• Crude RR = 1.97 (0.76–5.14)[a]	
Wagenberg and Froum 2006	• Retrospective cohort • 891 patients • 1,925 implants (323 placed in smokers)	• Nonsmokers: 3.7% • Smokers: 5.6%	• Crude RR = 1.51 (0.91–2.53)	Smokers defined as currently smoking >10 cigarettes/day

Table 10.7*S* Continued

Study	Design/population	Proportion of failed implants by smoking status	Estimate of effects (95% CI)	Comments
Al-Nawas, Hangen et al. 2007	• Retrospective cohort • 83 patients (17 smokers) • 264 implants	• Mean survival time in months (95% CI): • Nonsmokers: 50 (49–52) • Smokers: 39 (36–43)	• HR = 2.6 (1.2–5.3)	Kaplan-Meier survival estimates; Cox proportional hazards modeling
Alsaadi et al. 2007	• Retrospective cohort • 2,004 patients • 6,946 implants	• Proportion of failures by cigarettes/day: • 0: 3.28% • <10: 4.85% • 10–20: 5.31% • >20: 7.05%	• 0 cigarettes/day (reference) • <10 cigarettes/day: OR = 1.76 (0.60–5.16) • 10–20 cigarettes/day: OR = 1.90 (1.01–3.60) • >20 cigarettes/day: OR = 2.18 (1.20–3.97)	Early implant failures only (before and up to abutment connection)
Aykent et al. 2007	• Retrospective cohort • 34 patients • 106 implants • Follow-up: 1–5 years	• Nonsmokers: 2.3% • Smokers: 24.2%	NR	
Doyle et al. 2007	• Retrospective cohort • 171 patients • 196 implants (10 in smokers) • Follow-up: 1 year (minimum; maximum not reported)	• Nonsmokers: 5.0% • Smokers: 27.1%	NR	
Kinsel and Liss 2007	• Retrospective cohort • 43 patients (12 smokers) • 344 implants (95 in smokers) • Follow-up: 2–10 years	• Nonsmokers: 3.6% • Smokers: 7.4%	• Crude RR = 2.04 (0.78–5.32)[a]	All patients were edentulous
Penarrocha et al. 2007	• Retrospective cohort • 192 patients (64 smokers) • 642 implants • Follow-up: 1 year	NR	• 0 cigarettes/day (reference) • ≤10 cigarettes/day: HR = 1.68 (0.19–15.19) • >10 cigarettes/day: HR = 1.86 (0.57–6.04)	Overall survival rate: 97.13%
Sanchez-Perez et al. 2007	• Retrospective cohort • 66 patients (40 smokers) • 165 implants (95 in smokers) • Follow-up: 5 years	• Nonsmokers: 1.4% • Smokers: 15.8%	• Crude RR = 11.05 (1.50–81.71)[a]	

Table 10.7*S* Continued

Study	Design/population	Proportion of failed implants by smoking status	Estimate of effects (95% CI)	Comments
Sanna et al. 2007	• Retrospective cohort • 30 patients (13 smokers) • 212 implants (96 in smokers) • Follow-up: 5 years (maximum) (mean 2.2 years)	• Nonsmokers: 0.8% • Smokers: 8.3%	• Crude RR = 9.92 (1.26–77.91)[a]	All patients had at least 1 edentulous arch; substantial loss to follow-up: >50% after 18 months
Stavropoulos et al. 2007	• Clinical trial • 26 patients (9 smokers) • 26 implants (9 placed in smokers) • Follow-up: 1 year	• Nonsmokers: 17.6% • Smokers: 33.3%	• Crude RR = 1.89 (0.47–7.52)[a]	
Alsaadi et al. 2008a	• Prospective cohort • 283 patients • 720 implants	• Nonsmokers: 1.12% • Smokers: 5.56%	• Crude RR = 4.68 (1.52–14.46)[a]	Early implant failures only (before and up to abutment connection)
Alsaadi et al. 2008b	• Retrospective cohort • 412 patients (61 smokers) • 1,514 implants • Follow-up: 2 years	• Proportion of failures by cigarettes/day: • 0: 6.20% • <10: 10.14% • 10–20: 14.55% • >20: 6.06%	• 0 cigarettes/day (reference) • <10 cigarettes/day: OR = 1.39 (0.38–5.09) • 10–20 cigarettes/day: OR = 2.92 (0.97–8.77) • >20 cigarettes/day: OR = 1.21 (0.39–3.73)	
Anitua et al. 2008	• Retrospective cohort • 1,060 patients • 5,787 implants • Follow-up: 5-years	• Nonsmokers: 0.7% • Smokers: 1.1%	• p trend = 0.013	Failure rates based on life-table analysis
Balshe et al. 2008	• Retrospective cohort • 593 patients (104 smokers) received 2,182 smooth surface implants • 905 patients (95 smokers) received 2,425 rough-surface implants • Follow-up: 5 years (maximum)	• Smooth surface: • Nonsmokers: 3.9% • Smokers: 14.0% • Rough surface: • Nonsmokers: 5.7% • Smokers: 3.6%	• Smooth surface: HR = 3.1 (1.6–5.9) • Rough surface: HR = 0.8 (0.3–2.1)	Kaplan-Meier estimates for survival rates; Cox proportional hazards estimates adjusted for age and gender
Blake et al. 2008	• Retrospective cohort • 43 patients • Follow-up: 8–10 years	• Nonsmokers: 6.9% • Smokers: 7.8%	• Crude RR = 1.13 (0.44–2.92)[a]	All patients underwent osseous reconstruction prior to implant placement

Table 10.7*S* Continued

Study	Design/population	Proportion of failed implants by smoking status	Estimate of effects (95% CI)	Comments
Holahan et al. 2008	• Retrospective cohort • Females ≥50 years of age • 192 patients (24 smokers) • 646 implants (83 in smokers) • Follow-up: 10 years (maximum)	• Nonsmokers: 4.9% • Smokers: 12.0%	• HR = 2.6 (1.20–5.63)	
Levin et al. 2008	• Retrospective cohort • 64 patients (6 current smokers) • 64 implants • Follow-up: 5–14 years	• Nonsmokers: 6.1% • Smokers: 16.75	• Crude RR = 2.72 (0.33–22.19)[a]	
Machtei et al. 2008	• Retrospective cohort • 56 patients (15 smokers) • 79 implants (15 in smokers) • Follow-up: 7–78 months	• Nonsmokers: 15.6% • Smokers: 20.0%	• Crude RR = 1.28 (0.40–4.09)[a]	All subjects had history of chronic periodontitis and previous failed implants
Sverzut et al. 2008	• Retrospective cohort • 650 patients (76 smokers) • 1,628 implants (197 in smokers) • Follow-up: 249 days (mean)	• Nonsmokers: 3.0% • Smokers: 3.6%	• HR = 1.24 (0.56–2.76)[h]	
Tawil et al. 2008	• Prospective cohort • 90 patients • 499 implants • Follow-up: 1–12 years (mean 42.4 months)	• Diabetes: • Nonsmokers: 0% • Smokers: 3.5% • No diabetes: • Nonsmokers: 1.4% • Smokers: 0%	• RR = 2.63 (0.39–17.50)[a,j]	45 subjects had type 2 diabetes; 45 patients without diabetes served as controls
Koldsland et al. 2009	• Retrospective cohort • 109 patients (59 current and former smokers) • 374 implants • Follow-up: 1.1–16 years	• Never smokers: 2.0%[k] • Ever smokers: 15.3%[k]	• Crude RR = 7.63 (1.00–58.15)	
Nystrom et al. 2009a	• Prospective cohort • 45–68 years of age • 44 patients (12 smokers) • 334 implants (89 in smokers) • Follow-up: 9–14 years (mean 11 years)	• Nonsmokers: 6.5% • Smokers: 12.4%	• Crude RR = 1.89 (0.91–3.92)[a]	All patients received maxillary bone grafts; nonsmokers included 5 former smokers

Table 10.7*S* Continued

Study	Design/population	Proportion of failed implants by smoking status	Estimate of effects (95% CI)	Comments
Nystrom et al. 2009b	• Prospective cohort • 38–70 years of age • 26 patients (6 smokers) • 167 implants (36 in smokers) • Follow-up: 11–16 years (mean 13 years)	• Nonsmokers: 14.5% • Smokers: 13.9%	• Crude RR = 0.96 (0.38–2.39)[a]	All patients received maxillary reconstructive surgery, including osteotomy and bone grafts; nonsmokers included 4 former smokers
Torres et al. 2009	• Randomized clinical trial • 87 patients (31 smokers) • 282 implants (110 placed in smokers) • Follow-up: 24 months	• Nonsmokers: 1.2% • Smokers: 4.5%	• Crude RR = 3.91 (0.77–19.80)[a]	All patients received anorganic bovine bone, either alone or in combination with platelet-rich plasma, for sinus augmentation prior to implant placement; smoking defined as smoking >10 cigarettes/day
Vandeweghe and De Bruyn 2011	• Retrospective cohort • 329 patients (41 smokers) • 712 implants (104 placed in smokers) • Follow-up: 6–28 months	• Nonsmokers: 1.2% • Smokers: 4.8%	• Crude RR = 4.18 (1.35–12.91)	

Notes: **CI** = confidence interval; **HR** = hazard ratio; **NA** = not available; **NR** = not reported; **OR** = odds ratio; **RR** = relative risk.
[a]Calculation based on reported data.
[b]Calculation based on reported data using exact confidence limits.
[c]Parsimonious multivariate model.
[d]Proportion of persons with implant failure; unable to calculate proportion of failed implants by smoking status.
[e]Proportion of patients with implant loss; proportion of implants lost by smoking status was not reported and could not be calculated.
[f]Confidence interval was not reported; model included type of restoration and type of implant.
[g]Confidence interval was not reported.
[h]95% confidence interval was calculated from reported data.
[i]Proportion of patients with implant loss; proportion of implants lost by smoking status was not reported.
[j]Mantel-Haenszel adjusted for diabetes status.
[k]Proportion of persons with implant failure; proportion of implants failed was not reported.

Table 10.8*S* Characteristics of studies included in the meta-analysis on smoking and diabetes

Study	Design/population	Male (%)	Diabetes incidence by smoking status, number/total			Factors adjusted in study
			Current smoker	Never smoker	Former smoker	
Keen et al. 1982	• The Bedford Survey • 241 participants • 36 cases	52.7	9/71	27/170	NA	Age, BMI, gender, diet, glucose, insulin, systolic blood pressure, urinary albumin excretion, tolbutamide
Rimm et al. 1995	• Health Professionals Follow-up Study • 39,745 participants • 492 cases	100	65/3,585	188/19,386	239/16,774	Age, BMI, heredity, physical activity, alcohol consumption
Kawakami et al. 1997	• Japanese cohort of male employees • 2,312 participants • 41 cases	100	NR/1,420	NR/583	NR/309	Age, BMI, heredity, education, physical activity, alcohol consumption, occupation, type of work shift
Njolstad et al. 1998	• Cardiovascular disease study • 11,654 participants • 162 cases	52.3	67/5,921	95/5,733	NA	Age, ethnicity, physical activity, blood pressure, total cholesterol, triglycerides, HDL cholesterol, antihypertensive treatment, height, glucose
Sugimori et al. 1998	• MHTS database • 2,573 participants • 296 cases	71.9	181/1,413	115/1,160	NA	Age, BMI, heredity, blood pressure, alcohol consumption, eating breakfast, dairy intake, total cholesterol, fasting glucose, uric acid
Uchimoto et al. 1999	• Osaka Health Survey • 6,250 participants • 450 cases	100	302/3,880	79/1,302	69/1,068	Age, BMI, heredity, physical activity, alcohol consumption, total cholesterol, triglycerides, HDL cholesterol, fasting plasma glucose, hematocrit
Manson et al. 2000	• Physicians' Health Study • 21,068 participants • 770 cases	100	127/2,229	323/10,511	320/8,258	Age, BMI, physical activity, alcohol consumption, blood pressure, total cholesterol, parental history of MI before 60 years of age, treatment assignment
Nakanishi et al. 2000	• Japanese male office workers • 1,266 participants • 54 cases	100	42/646	7/407	5/213	Age, BMI, heredity, physical activity, alcohol consumption, blood pressure, total cholesterol, triglycerides, HDL cholesterol, fasting plasma glucose, uric acid, hematocrit
Strandberg and Salomaa 2000	• Helsinki Businessmen Study • 1,802 participants • 94 cases	100	40/550	25/608	29/644	BMI, blood pressure, triglycerides

Table 10.8*S* Continued

Study	Design/population	Male (%)	Diabetes incidence by smoking status, number/total			Factors adjusted in study
			Current smoker	Never smoker	Former smoker	
Hu et al. 2001	• Nurses' Health Study • 84,941 participants • 3,283 cases	0	620/NR	1,446/NR	1217/NR	Age, heredity, study period, menopausal status, use of postmenopausal hormone therapy
Wannamethee et al. 2001	• British Regional Heart Study • 6,397 male participants • 256 cases	100	127/2,942	47/1,541	82/1,914	Age, BMI, education, physical activity, alcohol consumption, antihypertensive treatment, preexisting CHD
Will et al. 2001	• Cancer Prevention Study I • 275,190 female participants • 10,634 cases	100	5,411/147,863	2,602/64,192	2,621/63,162	Age, BMI, ethnicity, education, physical activity, alcohol consumption, diet
Will et al. 2001	• Cancer Prevention Study I • 434,637 participants • 14,763 cases	0	3,250/126,722	10,710/281,868	803/26,047	Age, BMI, ethnicity, education, physical activity, diet, alcohol consumption
Montgomery and Ekbom 2002	• British National Child Development Study • 4,917 participants • 28 cases	NR	15/1,666	13/3,251	NA	Gender, BMI, maternal smoking during pregnancy, age mother left school, birth weight, birth mother's age, family social class at birth
Bonora et al. 2004	• The Bruneck Study • 837 participants • 64 cases	50	14/NR	50/NR	NA	Age, gender
Carlsson et al. 2004	• Nord-Trondelag Health Study • 38,706 participants • 738 cases	46.9	170/12,813	365/17,353	203/8,540	Age, BMI, gender
Eliasson et al. 2004	• Northern Sweden MONICA Study • 1,275 participants • 27 cases	100	8/235	7/761	12/279	Age, duration of follow-up, annual percentage weight gain between baseline and follow-up
Sairenchi et al. 2004	• Japanese who underwent health checkups • 39,528 male participants • 3,702 cases	100	1,831/NR	748/NR	1,125/NR	Age, BMI, heredity, blood pressure, total cholesterol, triglycerides, HDL cholesterol, antihypertensive treatment, fasting glucose status
Sairenchi et al. 2004	• Japanese who underwent health checkups • 88,613 female participants • 4,286 cases	0	196/NR	4,067/NR	23/NR	Age, BMI, heredity, blood pressure, total cholesterol, triglycerides, HDL cholesterol, antihypertensive treatment, fasting glucose status

Table 10.8*S* Continued

Study	Design/population	Male (%)	Diabetes incidence by smoking status, number/total			Factors adjusted in study
			Current smoker	Never smoker	Former smoker	
Foy et al. 2005	• Insulin Resistance Atherosclerosis Study • 906 participants • 156 cases	43.3	32/128	60/424	56/354	Age, BMI, gender, ethnicity, waist-to-hip ratio, physical activity, alcohol consumption, triglycerides, HDL cholesterol, clinic, glucose tolerance status, hypertension, ethnicity by clinic
Lyssenko et al. 2005	• Botnia Study, Western Finland • 2,115 participants • 127 cases • Finland	45.7	NR/799	NR/1,277	NA	BMI
Patja et al. 2005	• 4 surveys in Finland • 41,372 participants • 3,110 cases	47.7	799/12,498	1,567/22,957	404/5,917	Age, BMI, gender, education, physical activity, alcohol consumption, coffee consumption, blood pressure, study year
Tenenbaum et al. 2005	• Bezafibrate Infarction Prevention Study • 630 participants • 98 cases	89.2	18/78	32/195	48/357	Age, BMI, gender, blood pressure, total cholesterol, triglycerides, presence of NYHA III functional class, glucose, previous MI, peripheral vascular disease, anginal syndrome, bezafibrate treatment
Waki et al. 2005	• JPHC-based prospective study on cancer and cardiovascular diseases, males • 12,913 participants • 703 cases	100	365/6,702	150/3,227	188/2,972	Age, BMI, heredity, physical activity, alcohol consumption, blood pressure
Waki et al. 2005	• JPHC Study, females • 15,980 participants • 480 cases	0	26/661	436/15,099	18/219	Age, BMI, heredity, physical activity, alcohol consumption, blood pressure
Harding et al. 2006	• EPIC-Norfolk • 24,518 participants • 464 cases	45	49/1,358	130/3,989	285/5,965	Age, BMI, gender, heredity, physical activity, alcohol intake
Houston et al. 2006	• CARDIA Study • 4,572 participants • 764 cases	44.7	NA/1,386	NA/2,565	NA/621	Age, gender, ethnicity, education, waist circumference, physical activity, diet, alcohol consumption, blood pressure, triglycerides, CRP, insulin concentration, health insurance

Table 10.8*S* Continued

Study	Design/population	Male (%)	Diabetes incidence by smoking status, number/total			Factors adjusted in study
			Current smoker	Never smoker	Former smoker	
Meisinger et al. 2006	• MONICA/KORA Augsburg Cohort Study • 5,470 males participants • 409 cases	100	145/1,713	89/1,669	175/2,088	Age, BMI, heredity, education, physical activity, alcohol consumption, blood pressure, total cholesterol, triglycerides, HDL cholesterol, survey
Meisinger et al. 2006	• MONICA/KORA Augsburg Cohort Study • 5,422 females participants • 263 cases	0	42/1,153	179/3,282	42/987	Age, BMI, heredity, education, physical activity, alcohol consumption, blood pressure, total cholesterol, triglycerides, HDL cholesterol, survey
Burke et al. 2007	• Australian aboriginal cohort • 463 participants • 103 cases • Australia	50.2	34/185	76/266	1/13	Age, gender, waist girth, location, alcohol and processed meat consumption, physical activity
Cugati et al. 2007	• Blue Mountains Eye Study • 2,123 participants • 165 cases	41.5	27/257	138/1,866	NA	Age, BMI, gender, heredity, fasting plasma glucose level, serum cholesterol level, serum HDL cholesterol level, serum triglycerides, hypertension
Dehghan et al. 2007	• Rotterdam Study • 6,935 participants • 645 cases	39.4	NR/1,535	NR/5,400	NA	Age, BMI, waist circumference, heredity, CRP
Holme et al. 2007	• Oslo Study • 6,382 participants • 584 cases	100	262/2,801	135/1,602	187/1,979	Age, BMI, education, leisure- time physical activity, glucose, triglycerides, treated hypertension, systolic blood pressure
Hur et al. 2007	• Korea Medical Insurance Corporation Study • 27,635 participants • 1,170 cases	100	NR/14,457	NR/5,701	NR/7,477	Age, baseline BMI, weight change, heredity, physical activity, alcohol consumption, baseline fasting glucose
Mozaffarian et al. 2007	• Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico-Prevenzione Study • 8,291 participants • 998 cases • Italy	87	NR/3,699	NR/1,670	NR/2,922	Age, BMI, gender, duration and severity of MI, blood pressure, intermittent claudication, use of antiplatelet medication, exercise stress test, exercise capacity, coffee consumption, wine consumption, cheese consumption, Mediterranean diet score

Table 10.8*S* Continued

Study	Design/population	Male (%)	Diabetes incidence by smoking status, number/total			Factors adjusted in study
			Current smoker	Never smoker	Former smoker	
Onat et al. 2007	• Turkish Adult Risk Factor Study • 3,026 participants • 204 cases	49.5	NR/1,181	NR/1,790	NR/414	Age, BMI, income bracket, physical activity grade
Schulze et al. 2007	• EPIC-Potsdam Study • 25,167 participants • 849 cases	38.7	NR	NR	NR	Age, waist circumference, height, moderate alcohol drinking, physical activity, red meat, whole-grain bread and coffee consumption, history of hypertension
Hayashino et al. 2008	• HIPOP-OHP Study • 6,498 participants • 229 cases	79.1	NR/2,900	NR/2,129	b/779	Age, BMI, gender, heredity, physical activity, alcohol consumption, hypertension, health promotion intervention, sweetened beverage, vegetable, care about fat intake or not
Lyssenko et al. 2008	• Malmö Preventive Project • 16,061 participants • 2,063 cases	NR	NR/5,981	NR/10,080	NA	Age, BMI, gender, heredity, blood pressure, triglycerides, fasting plasma glucose
Magliano et al. 2008	• Australian Diabetes, Obesity and Lifestyle Study • 5,842 participants • 224 cases	45.7	35/659	116/3,475	73/1,708	Age, gender, heredity, waist circumference, education level, physical activity category, hypertension, fasting plasma glucose, triglycerides
Nagaya et al. 2008	• Nagoya City University, Japan (follow-up study) • 16,829 participants • 869 cases • Japan	100	445/8,807	193/3,882	231/4140	Age, alcohol consumption, physical activity, education
Nichols et al. 2008	• Kaiser Permanente Northwest • 46,578 participants • 1,854 cases	40.4	NR/9,502	NR/37,076	NA	Age, BMI, gender, fasting glucose, blood pressure, HDL, LDL, triglycerides, hypertension, cardiovascular diseases
Park et al. 2008	• Korean men • 1,717 participants • 50 cases	100	34/970	9/439	7/308	Age, BMI, heredity, alcohol consumption, physical activity, baseline fasting plasma glucose and hemoglobin levels
Chien et al. 2009	• Chin-Shan Community Cardiovascular Cohort • 2,960 participants • 548 cases	46.0	172/931	353/1,897	23/132	Age, BMI, white blood cell count, triacylglycerol, HDL-cholesterol and fasting glucose

Table 10.8*S* Continued

Study	Design/population	Male (%)	Diabetes incidence by smoking status, number/total			Factors adjusted in study
			Current smoker	Never smoker	Former smoker	
Cho et al. 2009	• South Korean community-based study • 3,048 participants • 329 cases	100	155/1,419	51/646	123/983	Age, heredity, rural or urban area, waist, body fat, physical activity, alcohol drinking, income, education, WBC, HDL cholesterol, triglyceride, ALT, hs-CRP, systolic blood pressure, HOMAIR, HOMA-beta
Cullen et al. 2009	• Iowa Women's Health Study • 36,839 participants • 3,281 cases • Iowa	0	402/5,303	2,215/24,265	664/7,271	Waist-to-hip ratio, marital status, educational status, physical activity, hypertension, use of hormone replacements, use of vitamin supplements, dietary and nutrient consumption (intake of calories, fat, cholesterol, carbohydrates, fruit and vegetables, red meat, whole grains, vitamin E, dairy products, alcohol)
Hippisley-Cox et al. 2009	• Study of the QDScore in England and Wales • 1,257,618 participants • 43,165 cases • United Kingdom	100	NR/349,294	NR/908,324	NA	Age, BMI, and their fractional polynomial terms, heredity, treated hypertension, use of corticosteroids, diagnosed CVD, social deprivation, ethnicity
Hippisley-Cox et al. 2009	• England and Wales QDScore • 1,283,135 participants • 34,916 cases • United Kingdom	0	NR/298,455	NR/984,680	NA	Age, BMI, and their fractional polynomial terms, heredity, treated hypertension, corticosteroids use, diagnosed CVD, social deprivation, ethnicity
Mozaffarian et al. 2009	• Cardiovascular Health Study • 4,883participants • 337 cases	41.4	NR/569	135/2,279	NR/2,035	Age, gender, race, BMI, waist, education, annual income, physical activity, dietary score, alcohol consumption
Laaksonen et al. 2010	• Mini-Finland Health Survey and Health 2000 Survey • 8,627 participants • 226 cases	44.7	55/1,962	112/4,733	59/1,896	Age, gender

Table 10.8*S* Continued

Study	Design/population	Male (%)	Diabetes incidence by smoking status, number/total			Factors adjusted in study
			Current smoker	Never smoker	Former smoker	
Yeh et al. 2010	• ARIC Study • 10,892 participants • 1,254 cases	61.9	NR/2,579	NR/4,900	NR/2,910	Age, BMI, waist circumference, physical activity, race, gender, ARIC Study center, level of education, triglyceride level, HDL level, systolic blood pressure

Notes: **ALT** = alanine transaminase; **ARIC** = Atherosclerosis Risk in Communities Study; **BMI** = body mass index; **CARDIA** = Coronary Artery Risk Development in Young Adults; **CHD** = coronary heart disease; **CRP** = C-reactive protein; **CVD** = cardiovascular diseases; **EPIC** = European Prospective Investigation into Cancer and Nutrition; **HDL** = high density lipoprotein; **HIPOP-OHP** = High-Risk and Population Strategy for Occupational Health Promotion Study; **HOMA-beta** = homeostasis model assessment–beta cell function; **HOMA-IR** = homeostasis model assessment–insulin resistance; **hsCRP =** high sensitivity C-reactive protein; **JPHC** = Japan Public Health Center; **KORA** = Cooperative Research in the Region of Augsburg; **LDL =** low density lipoprotein; **M** = male; **MHTS** = Multiphasic Health Testing Services; **MI =** myocardial infarction; **MONICA** = Monitoring of Trends and Determinants in Cardiovascular Diseases; **NA** = not applicable; **NR** = not reported; **NYHA III** = New York Heart Association functional class III; **WBC** = white blood cells.

Table 10.14*S* Studies on the association between smoking and rheumatoid arthritis (RA) risk

Study	Design/ population	Tobacco exposure	Outcome	Findings
Heliövaara et al. 1993	• 512 incident RA cases	Never smokers, ex-smokers, current smokers	Diagnosis of RA	• RR of seropositive RA was 2.6 (95% CI, 1.3–5.3) in male ex-smokers and 3.8 (95% CI, 2.0–6.9) in current smokers, in comparison with the men who had never smoked
Voigt et al. 1994	• 349 incident RA cases • 1,457 random controls	Ever, never, pack-years	Diagnosis of RA	• Women with ≥20 pack-years of smoking, RR = 1.5 (95% CI, 1.0–2.0) compared with never smokers
Silman et al. 1996	• 79 monozygotic and 71 same-sex dizygotic twin pairs who were discordant for RA	Never, ever, pack-years	Diagnosis of RA	• Strong association between ever smoking and RA in the monozygotic pairs, OR = 12.0 (95% CI, 1.78–513), with a similar trend observed in the dizygotic pairs, OR = 2.5 (95% CI, 0.92–7.87)
Symmons et al. 1997	• 165 early (<1 year) RA cases • 165 controls	Never, current, past	Diagnosis of RA	• History of having ever smoked was associated with a higher risk of developing RA, OR = 1.66 (95% CI, 0.95–3.06)
Karlson et al. 1999	• 377,481 women	Never, ever, pack-years	Diagnosis of RA, RF status	• In age-adjusted analysis, compared with women who never smoked, the RR of developing RA was 1.01 (95% CI, 0.95–1.08) among past smokers and RR = 1.22 (95% CI, 1.16–1.28) among current smokers
Uhlig et al. 1999	• 361 recently diagnosed RA cases compared to 5,851 random controls	Never, current, past	Diagnosis of RA, RF status	• Current smoking was an overall risk factor, OR = 1.46 (95% CI, 1.10–1.94), in men, OR = 2.38 (95% CI, 1.45–3.92), especially in men with seropositive RA, OR = 4.77 (95% CI, 2.09–10.90)
Criswell et al. 2002	• 31,336 women without history of RA	Never, current, past, pack-years	Diagnosis of RA	• Compared with women who had never smoked, women who were current smokers, RR = 2.0 (95% CI, 1.3–2.9) or who had quit ≤10 years before study baseline, RR = 1.8 (95% CI, 1.1–3.1) were at increased risk of RA, but women who had quit >10 years before baseline were not at increased risk, RR = 0.9 (95% CI, 0.5–2.6)
Padyukov et al. 2004	• 858 RA cases • 1,048 controls	Current, former, nonsmoker	*HLA–DRB1* genotyping for *SE* alleles	• RR of RF-seropositive RA = 2.8 (95% CI, 1.6–4.8) in never smokers with *SE* genes, RA = 2.4 (95% CI, 1.3–4.6) in current smokers without *SE* genes, and RA = 7.5 (95% CI, 4.2–13.1) in current smokers with *SE* genes • Smokers carrying 2 *SE* genes, RR of RF-seropositive RA = 15.7 (95% CI, 7.2–34.2) • Interaction between smoking and SE genes was significant with AP = 0.4 (95% CI, 0.2–0.7) for smoking and any *SE*, AP = 0.6 (95% CI, 0.4–0.9) for smoking and 2 *SE*

Table 10.14*S* Continued

Study	Design/ population	Tobacco exposure	Outcome	Findings
Costenbader et al. 2006	• 680 women with incident RA and 103,818 women	Never, ever, current, past, pack-years	Diagnosis of RA	• RR of RA was significantly elevated among current, RR = 1.43 (95% CI, 1.16–1.75) and past smokers, RR =1.47 (95% CI, 1.231.76), compared with never smokers • Risk of RA was significantly elevated with 10 pack-years or more of smoking and increased linearly with increasing pack-years (P trend <.01).
Klareskog et al. 2006	• 930 RA cases • 1,126 controls	Never, ever, pack-years	*HLA–DRB1* genotyping for *SE* alleles, anti-ccp antibodies in serum and BAL cells	• In smokers, increased risk of anti-ccp positive RA in *SE*-negative individuals, RR = 1.5 (95% CI, 0.8–2.6), 1 *SE* copy increased RR = 6.5 (95% CI, 3.8–11.4) and 2 *SE* copies increased RR = 21.0 (95% CI, 11.0–40.2) • In nonsmokers, RR was 3.3 (95% CI, 1.8–5.9) with 1 *SE* copy and 5.4 (95% CI 2.7–10.8) with 2 *SE* copies
Pedersen et al. 2006	• 515 new (<5 yrs) RA cases • 769 controls	Never, former, current, pack-years	Diagnosis of RA	• Tobacco smoking, OR = 1.65 (95% CI, 1.03–2.64; for >20 vs. 0 pack-years) was selectively associated with risk of anti-CCP-positive RA
Costenbader et al. 2008	• 437 women with incident RA and age matched, healthy women	Never, ever, pack-years	Diagnosis of RA	• *PTPN22* was associated with increased RA risk, pooled OR in multivariable dominant model = 1.46 (95% CI, 1.02–2.08) • Significant multiplicative interaction between *PTPN22* and smoking for more than 10 pack-years was observed (P = 0.04).
Karlson et al. 2010	• 439 RA cases • 439 controls	Never, ever, pack-years	High-resolution *HLA-DRB1* genotyping for *SE* alleles	• Strong additive interaction, AP = 0.50 (p <0.001) and significant multiplicative interaction (p = 0.05) were found between heavy smoking and any *HLA-SE* in seropositive RA risk • Highest risk was in heavy smokers with double copy *HLA-SE*, OR = 7.47 (95% CI, 2.77– 20.11)
Keenan et al. 2010	• 549 RA cases • 549 controls	Ever smoker, Heavy smoker (>10 pack-years)	Genotyping for *GSTM1-null* and *GSTT1-null,* and alleles for *GSTP1* and *HMOX1*	• For the risk of all RA, multiplicative (p = 0.05) and additive, AP = 0.53 (P = 0.0005) interactions between the *GSTT1-null* polymorphism and ever smoking and multiplicative interactions (P = 0.05) between *HMOX1* and ever smoking were observed
Mikuls et al. 2010	• 605 AA RA cases • 255 AA healthy controls	Current, former, never, pack-years	*SE* status	• Significant additive interaction between *SE* status and heavy smoking (≥10 pack-years) in RA risk, AP =0.58 (p = 0.007) with an AP = 0.47 (p = 0.006) between *SE* status and ever smoking
Bergström et al. 2011	• 290 incident RA cases	Current smoker, smoker for >10 years, smoker of >20 cigarettes/ day	Diagnosis of RA	• Current smoking associated with RA, OR = 1.79 (95% CI, 1.32–2.42)

Table 10.14*S* Continued

Study	Design/ population	Tobacco exposure	Outcome	Findings
de Hair et al. 2012	• 55 persons at risk for developing RA followed for average of 13 months	Ever smoker, never smoker	Diagnosis of RA	• Smoking was associated with development of RA, HR = 9.6 (95% CI, 1.3–73.0)
Mikuls et al. 2012	• 727 AA early RA (<2 yrs) cases compared to 262 AA non-RA controls	Current, former, never, heavy smoker ≥10 pack-years	Genotyping for drug-metabolizing enzymes, Diagnosis of RA	• Significant additive interactions between heavy smoking and *NAT2* SNPs *rs9987109* (Padditive = 0.000003) and *rs1208* (Padditive = 0.00001) • Attributable proportion due to interaction ranged from 0.61–0.67
Nielsen et al. 2012	• 9,712 people without RA	Pack-years	RF status, Development of RA	• High (>100 IU/mL) RF positivity was associated with 10-year risk of developing RA, HR = 39 (95% CI, 18–85), especially if smoker
Too et al. 2012	• 1,076 RA cases and 1,612 matched controls	Ever, never	Genotyping for *SE,* anti-ccp antibodies, diagnosis of RA	• *SE* alleles and smoking were associated with increased risk of developing anti-ccp positive RA, OR *SE* alleles = 4.7 (95% CI, 3.6–6.2) • OR smoking = 4.1 (95% CI, 1.9–9.2)
Bergström et al. 2013	• 172 RA cases compared to age and sex matched controls	Current regular smoker, occasional smoker, former smoker, never smoker	Diagnosis of RA	• Ever smoking increased likelihood of having RA, OR = 2.02 (95% CI, 1.31–3.12)

Note: **AA** = African American; **Anti-ccp** = anticyclic citrullinated peptide; **AP** = attributable proportion; **BAL** = bronchoalveolar lavage; **CI** = confidence interval; **HR** = hazard ratio; **IU/mL** = international units per milliliter; **OR** = odds ratio; **RF** = rheumatoid factor; **RR** = relative risk; **SE** = standard error; **SNPs** = single nucleotide polymorphisms.

Table 10.15*S* Studies on the association between smoking and rheumatoid arthritis (RA) severity

Study	Population	Tobacco exposure	Outcome	Findings
Saag et al. 1997	• 336 RA patients	Current, former, never, pack-years	Larsen score, RF positivity, and presence of nodules	• Pack-years of cigarette smoking was significantly associated with RF positivity, radiographic erosions, and nodules
Wolfe 2000	• 610 RA patients	Nonsmoker, former, smoker, pack-years	Complete joint examination, health status questionnaires, RF values, Larsen score, nodules	• RF concentration and nodule formation were linearly related to the number of years smoked • Nonlinear relationships were found between smoking and Larsen score and pulmonary illness
Mattey et al. 2002	• 164 women with established RA	Past, current, never, pack-years	HAQ score, Larsen's score	• Ever having smoked was associated with a worse radiographic and functional outcome than was never having smoked • Both past and current smoking were associated with increased disease severity
Turesson et al. 2003	• 609 RA patients	Ever, never	Presence of extra-articular disease	• Main predictor of severe extra-articular manifestations was smoking at RA diagnosis
Papadopoulos et al. 2005	• 293 early RA (<2 years) patients	Current, ex-smokers, nonsmokers	DAS-28, Larsen's score, presence of nodules	• Smoker patients had higher DAS-28, and higher Larsen's score as compared to nonsmokers at diagnosis and at follow-up • Smokers more frequently had rheumatoid nodules than the ex-smokers and nonsmokers
Nyhall-Wahlin et al. 2006	• 112 patients with RA nodules	Current, former, nonsmoker	Presence of nodules	• Strong association between smoking and rheumatoid nodules in early seropositive rheumatoid arthritis
Finckh et al. 2007	• 2,004 RA patients	Nonsmoker, smoker, pack-years	Ratingen score	• Radiographic joint damage progressed at a similar rate in current smokers and nonsmokers • Smoking intensity was associated with a significant inverse dose-response • Heavy smokers (>1 pack-day) progressed significantly less than nonsmokers or moderate smokers
Mikuls et al. 2008	• 300 African American early RA (<2 years) patients	Current, former, never, pack-years	IgA RF serum concentration, nodules	• Current smokers were approximately twice as likely as never smokers to have higher IgA-RF concentrations and nodules
Kim et al. 2008c	• 405 RA patients	Smoker (past or current), nonsmoker	Presence of extra-articular disease	• Smoking was closely associated with extra-articular manifestation
Naranjo et al. 2010	• 7,307 RA patients	Never, former, current	DAS-28, RF, nodules, erosions	• Ever smokers were more likely to be RF-positive • Rheumatoid nodules were more frequent in ever smokers • Erosive arthritis and extra-articular disease were similar in all smoking categories • Mean DAS28 was similar in nonsmokers vs. those who had ever smoked

Table 10.15*S* Continued

Study	Population	Tobacco exposure	Outcome	Findings
Ruiz-Esquide et al. 2011	• 156 early RA (<2 years) patients	Never, ever, past, current	Disease activity (EULAR), Larsen score,	• No difference in disease activity between smokers and nonsmokers • Current smoking associated with radiographic progression of disease
Andersson et al. 2012	• 1,460 early RA (<2 years) patients	Smoker, nonsmoker, pack-years	Disease activity (EULAR response), comorbidities, death	• No difference in EULAR responses between smoking groups but high risk of cardiovascular mortality and morbidity in smokers with RA
Moura et al. 2012	• 262 RA patients	Smoker, nonsmoker	Presence of extra-articular disease	• Current smoking correlated with presence of extra-articular disease
Söderlin et al. 2013	• 1,421 RA patients	Secondhand smoke	Disease activity (EULAR response)	• No association between secondhand exposure and disease activity

Note: **DAS-28** = disease activity scale 28; **EULAR** = European League Against Rheumatism; **HAQ** = health assessment questionnaire; **IgA** = immunoglobulin A; **RF** = rheumatoid factor; **RR** = relative risk; **SE =** standard error.

Table 10.16*S* Studies on the association between smoking and rheumatoid arthritis (RA) treatment response

Study	Population	Tobacco exposure	Outcome	Findings
Hyrich et al. 2006	• 2,879 patients receiving infliximab or etanercept	Current smoker	EULAR disease response	• Current cigarette smoking was associated with lower response rate among patients receiving infliximab, OR = 0.77 (95% CI, 0.60–0.99)
Inokuma et al. 2008	• 5,043 RA patients on leflunomide	Smoking history	Leflunomide lung injury	• Smoking is a risk factor for developing leflunomide-associated lung injury, OR = 3.12
Westhoff et al. 2008	• 896 early RA patients	Never, quit before RA onset, smoked continuously, pack-years	Drug need	• Current RF+ smokers had taken more DMARD combinations (35.8%) or biologics (14.9%) than RF+ previous smokers (29.9% and 11.2%, respectively) and RF+ never smokers (20.3% and 8.1% respectively), p = 0.022 for DMARDs and p = 0.105 for biologics
Mattey et al. 2009	• 154 RA patients starting anti-TNF drug	Never, past, current, pack-years	EULAR disease response	• Increasing trend of no response with increasing pack-years at 3 and 12 months (p trend = 0.008 and 0.003, respectively) • DAS28 was inversely associated with number of pack-years (r = –0.28; p = 0.002)
Abhishek et al. 2010	• 395 RA patients starting their first anti-TNF drug	Current, ex-smoker, nonsmoker	EULAR disease response	• Current smoking reduced the chance of achieving at least a moderate response on the EULAR response criteria when compared with nonsmokers, AOR = 0.20 (95% CI, 0.05–0.83; p = 0.03)
Saevarsdottir et al. 2011	• 535 early RA patients starting MTX and anti-TNF drug	Current, past, never	EULAR disease response	• Compared with never smokers, current smokers were less likely to achieve a good response at 3 months following the start of MTX (27% vs. 36%; P = 0.05) and at 3 months following the start of anti-TNF drugs (29% vs. 43%; p = 0.03)
Canhão et al. 2012	• 617 RA patients starting their first anti-TNF drug	Ever, never	EULAR disease response	• Smoking was negatively associated with good disease response, OR = 0.98 (95% CI, 0.55–1.71; p = 0.009)
Khan et al. 2012	• 150 RA patients receiving rituximab	Current, previous, never	DAS28 score	• Never smokers had the highest falls in DAS28 scores (mean 2.72, SD 0.94) • Previous smokers had fewer falls (mean 1.49, SD 0.92) • Current smokers the least falls (mean 0.63, SD 1.09; p<0.001 by one-way analysis of variance)
Soderlin et al. 2012	• 934 RA patients starting their first anti-TNF drug	Current, previous, never, pack-years	EULAR disease response	• Current smoking was predictive of poor response, OR = 0.53 (95% CI, 0.32–0.87; p = 0.012)

Note: **AOR** = adjusted odds ratio; **CI** = confidence interval; **DAS-28** = disease activity scale 28; **DMARD** = Disease-Modifying Antirheumatic Drug; **EULAR** = European League Against Rheumatism; **MTX** = methotrexate; **OR** = odds ratio; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **RF** = rheumatoid factor; **SD** = standard deviation; **TNF** = tumor necrosis factor.

Table 10.17*S* Studies on the association between smoking and systemic lupus erythematosus (SLE) risk

Study	Population	Tobacco exposure	Outcome	Findings
Nagata et al. 1995	• 282 female SLE cases • 292 controls	Never, past, current	Diagnosis of SLE	• Risk of SLE was significantly increased for current smokers, age-adjusted OR = 2.31 (95% CI, 1.34–3.97)
Sanchez-Guerrero et al. 1996	• 106,391 women	Never, past, current, pack-years	Diagnosis of SLE	• Age-adjusted RR of SLE showed no relation to smoking status: compared with never smokers, current smokers RR = 1.09 (95% CI, 0.66–1.80) and past smokers RR = 0.91 (95% CI, 0.54–1.55)
Hardy et al. 1998	• 150 SLE cases • 300 controls	Never, ex-smoker, current	Diagnosis of SLE	• Current smokers had a significantly increased risk of development of SLE compared with never smokers, OR = 1.95 (95% CI, 1.14–3.31)
Cooper et al. 2001	• 265 SLE cases • 355 controls	Never, former, current	Diagnosis of SLE	• No association with smoking history and risk of developing SLE, OR = 1.1 (95% CI, 0.7–1.7) for current smokers, or former smokers, OR = 0.6 (95% CI, 0.4–1.0), compared to never smokers
Ghaussy et al. 2001	• 125 SLE cases • 125 controls	Never, ex-smoker, current	Diagnosis of SLE	• Smoking before SLE diagnosis and ex-smoking before SLE diagnosis significantly increased the risk of development of SLE, OR = 6.69 (95% CI, 2.59–17.28; p <0.001) OR = 3.62 (95% CI, 1.22–10.70; p = 0.02, respectively)
Bengtsson et al. 2002	• 85 SLE cases • 205 controls	Nonsmoker, smoker, pack-years	Diagnosis of SLE	• Suggested association with increased SLE risk was seen for smoking, OR = 1.8 (95% CI, 0.9–3.6)
Formica et al. 2003	• 67 new female SLE cases compared to matched survey participants	Never, past, current, pack-years	Diagnosis of SLE	• IRR for current and past smoking = 1.6 (95% CI, 0.8–3.3) • Risk was greater for women who began smoking before age 19 years, IRR = 1.9 (95% CI, 1.0–3.6)
Miot et al. 2005	• 57 DLE cases • 215 healthy controls	Nonsmokers, smokers	Diagnosis of DLE	• Higher smoking prevalence noted in DLE cases (84.2%) than controls (33.5%), and the adjusted OR was 14.4 (95% CI, 6.2–33.8; multiple logistic regression, p <0.01)
Cooper et al. 2010	• 258 SLE cases • 263 controls	Never, former, current	Diagnosis of SLE	• Smoking status not associated with SLE risk, OR = 1.2 (95% CI, 0.7–2.3) for former smokers and OR = 0.8, (95% CI, 0.6–1.2) for current smokers, compared to never smokers
Kiyohara et al. 2012a	• 171 female SLE cases • 492 healthy controls	Nonsmokers, former, current	Diagnosis of SLE	• Compared with nonsmoking, current smoking was significantly associated with increased risk of SLE, OR = 3.06 (95% CI, 1.86–5.03)
Kiyohara et al. 2012b	• 151 female SLE cases • 21 female controls	Nonsmokers, former, current	Diagnosis of SLE, genotyping for *CYP1A1 rs4646903* and *GSTM1*	• Smokers with *CC* genotype of *CYP1A1 rs4646903* were significantly associated with increased risk of SLE, OR = 9.72 (95% CI, 2.73–34.6) • Smokers with combined *CYP1A1 rs4646903/ GSTM1* 'at-risk' genotype were significantly associated with increased risk of SLE, OR = 17.5 (95% CI, 3.20–95.9)

Table 10.17*S* Continued

Study	Population	Tobacco exposure	Outcome	Findings
Ekblom-Kullberg et al. 2013	• 223 SLE cases • 1,538 controls	Never, ever, past, current, daily, occasional	Diagnosis of SLE	• In women with a history of daily smoking for more than 1 year, OR for SLE = 1.45 (95% CI, 1.07–1.97), in current daily smokers as compared to never smokers, OR = 1.55 (1.00–2.40), and in ex-smokers vs. never smokers OR = 1.80 (1.15–2.83) • Number of men with SLE, who smoked >100 cigarettes during their lifetime was higher than in male controls (p = 0.026)

Note: **CI** = confidence interval; **DLE** = discoid lupus erythematosus; **IRR** = incidence rate ratio; **OR** = odds ratio; **RR** = relative risk.

Table 10.18*S* Studies on the association between smoking and systemic lupus erythematosus (SLE) severity and manifestations

Study	Population	Tobacco exposure	Outcome	Findings
Ward and Studenski1992	• 160 adults with SLE nephritis	Nonsmoker, former, current	Development of ESRD	• Smoking status at onset of nephritis was strongly associated with differences in time to development of ESRD with a median time of developing ESRD at 146 months for smokers and 273 months for nonsmokers
Ghaussey et al. 2003	• 111 SLE cases	Never, ex-smoker, current	SLEDAI	• Current smokers demonstrated significantly higher SLEDAI scores than ex-smokers and never smokers
Calvo-Alén et al. 2005	• 570 SLE cases	Never, ever	Presence of thrombotic event	• Smoking is a significant risk factor for thrombosis
Freemer et al. 2006	• 410 SLE cases	Never, former, current	Serum dsDNA antibodies	• Significantly higher risk of dsDNA seropositivity in current smokers than former or never smokers
Kaiser et al. 2009	• 1930 SLE cases	Never, ever	Presence of thrombotic event	• Smoking was a significant risk factor for thrombosis
Turchin et al. 2009	• 276 SLE cases	Never, past, current	Cumulative cutaneous damage scores	• Current smoking is associated with scarring and active lupus rash
Barta et al. 2010	• 181 women with SLE	Never, past, current	Health related quality of life	• Smokers more likely to have poor health related quality of life compared to nonsmokers
Piette et al. 2012	• 218 CLE or SLE cases	Never, past, current	Disease severity, response to treatment, quality of life	• Current smokers with SLE had worse disease and worse quality of life than nonsmokers
Bourré-Tessier et al. 2013	• 1,346 SLE cases	Never, ever, past, current, pack-years	SLEDAI-2K, cutaneous ACR criteria	• Current smoking was associated with active rash, as recorded by the SLEDAI-2K, OR = 1.63 (95% CI, 1.07–2.48) for current vs. noncurrent smokers, and OR = 1.68 (95% CI, 1.08–2.60) for current vs. never smokers • Ever smoking was associated with the presence of cutaneous ACR criteria, OR = 1.50 (95% CI, 1.22–1.85) • Association driven by discoid rash, OR = 2.36 (95% CI, 1.69–3.29) and photosensitivity, OR = 1.47 (95% CI, 1.11–1.95) • Higher pack-years was associated with the presence of active rash among current smokers, RR/5 pack-years = 1.17 (95% CI, 1.06–1.29).

Note: **ACR** = American College of Radiology; **CI** = confidence interval; **CLE** = cutaneous lupus erythematosus; **dsDNA** = double-stranded DNA; **ESRD** = end stage renal disease; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **OR** = odds ratio; **RR** = relative risk; **SLEDAI** = systemic lupus erythematosus disease activity index.

Table 10.19*S* Studies on smoking and systemic lupus erythematosus (SLE) treatment response

Study	Population	Tobacco Exposure	Outcome	Findings
Wahie et al. 2011	• 200 cases with DLE (11 with SLE) on hydroxychloroquine	Nonsmoker, smoker	Clinical response to hydroxychloroquine	• No significant difference in response rate between nonsmokers compared with smokers (OR = 0.78; 95% CI: 0.43–1.45; p = 0.27)
Jewell and McCauliffe 2000	• 61 cases (47 DLE, 14 SCLE)	Nonsmoker, ex-smoker, smoker, pack-years	Skin disease response to therapy	• A significant difference (p <.0002) in antimalarial response rate was observed for smokers (40%) vs. nonsmokers (90%)

Note: **CI** = confidence interval; **CLE** = cutaneous lupus erythematosus; **DLE** = discoid lupus erythematosus; **ESRD** = end stage renal disease; **OR** = odds ratio; **pack-years** = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day; **SCLE** = subacute cutaneous lupus erythematosus.

Table 10.20*S* Characteristics of the studies on the effects of current smoking on Crohn's disease or ulcerative colitis

Study	Design/Population	Current smoking definition	Number of cases analyzed in current smoking comparison	Type of effect estimate[a]	Findings/ Effect estimates (95% CI)	Adjustments for current smoking effect estimate
Mayberry et al. 1978	• Case control • Prevalent Crohn's disease • United Kingdom	Current at questionnaire	100 cases	OR	• Current smoking: 1.08 (0.62–1.89)	
Harries et al. 1982	• Case control • Prevalent Crohn's disease • United Kingdom	Current at questionnaire	101 cases	OR	• Current smoking: 1.15 (0.71–1.89)	
Thornton et al. 1985	• Case control • Prevalent Crohn's disease • 28 cases • United Kingdom	Current at symptom onset	28 cases	OR	• Current smoking: 5.70 (1.81–17.97)	
Franceschi et al. 1987	• Case control • Prevalent Crohn's disease • 109 cases • Italy	Current at time of diagnosis		OR	• Current smoking: 4.20 (2.30–7.70)	Age, gender, education or social class, former smoking, body mass index, other
Funakoshi et al. 1987	• Case control • Prevalent Crohn's disease • 25 cases • Japan	Current at symptom onset		OR	• Current smoking: 0.53 (0.19–1.41)	Age
Sorensen et al. 1987	• Case control • Prevalent Crohn's disease • 106 cases • Denmark	Smoking, otherwise undefined		OR	• Current smoking: 1.34 (0.72–2.48)	
Tobin et al. 1987	• Case control • Prevalent Crohn's disease • 115 cases • United Kingdom	Current at symptom onset (6 months before symptom onset)		OR	• Current smoking: 2.90 (1.80–4.90)	Age, gender, location, region or center
Katschinski et al. 1988	• Case control • Prevalent Crohn's disease • 104 cases • United Kingdom	Current at questionnaire		OR	• Current smoking: 1.80 (1.04–3.20)	Diet

Table 10.20*S* Continued

Study	Design/Population	Current smoking definition	Number of cases analyzed in current smoking comparison	Type of effect estimate[a]	Findings/ Effect estimates (95% CI)	Adjustments for current smoking effect estimate
Lindberg et al. 1988	• Case control • Prevalent Crohn's disease • 141 cases • Sweden	Current at time of diagnosis		OR	• Current smoking: 2.20 (1.30–3.50)	Age, gender, location, center or region
Duclos et al. 1990	• Case control • Prevalent Crohn's disease • 151 cases • France	Current at questionnaire		OR	• Current smoking: 1.59 (0.90–2.83)	
Persson et al. 1993	• Case control • Prevalent Crohn's disease • 51 cases • Sweden	Current at questionnaire		OR	• Current smoking: 1.30 (0.70–2.70)	Age, other
Tragnone et al. 1993	• Prospective cohort • Incident Crohn's disease • 35 cases • Italy	Current at time of diagnosis		OR	• Current smoking: 1.55 (0.70–3.45)	
Martinez Salmeron et al. 1994	• Case control • Prevalent Crohn's disease • 30 cases • Spain	Ever at diagnosis		OR	• Current smoking: 1.14 (0.41–3.17)	
Reif et al. 1995	• Case control • Prevalent Crohn's disease • 33 cases • Israel	Current at questionnaire		OR	• Current smoking: 0.24 (0.07–0.92)	
Breslin et al. 1997	• Case control • Prevalent Crohn's disease • 111 cases • Ireland	Current at questionnaire		OR	• Current smoking: 1.11 (0.68–1.81)	
Fich et al. 1997	• Case control • Prevalent Crohn's disease • 91 cases • Israel	Current at questionnaire		OR	• Current smoking: 1.05 (0.57–1.96)	

Table 10.20*S* Continued

Study	Design/Population	Current smoking definition	Number of cases analyzed in current smoking comparison	Type of effect estimate[a]	Findings/ Effect estimates (95% CI)	Adjustments for current smoking effect estimate
Corrao et al. 1998	• Case control • Incident Crohn's disease • 194 cases • Italy	Current at questionnaire		OR	• Current smoking: 1.70 (1.10–2.60)	Age, location, region or center, oral contraceptives or hormone replacement therapy, breastfeeding
Thompson et al. 1998	• Case control • Prevalent Crohn's disease • 291 cases • United Kingdom	Current (unclear–says during last week but not sure of reference)		OR	• Current smoking: 1.29 (0.95–1.75)	Age, gender, location, region or center
Genser et al. 1999	• Case control • Prevalent Crohn's disease • 24 cases • Austria	Current at questionnaire		OR	• Current smoking: 2.00 (0.68–5.85)	
Koutroubakis et al. 1999	• Case control • Prevalent Crohn's disease • 63 cases • Greece	Current at questionnaire		OR	• Current smoking: 1.63 (0.82–3.23)	
Brignola et al. 2000	• Case control • Prevalent Crohn's disease • 636 cases • Italy	Current at time of diagnosis		OR	• Current smoking: 2.28 (1.50–3.48)	
Reif et al. 2000	• Case control • Prevalent Crohn's disease • 208 cases • Israel	Current at questionnaire		OR	• Current smoking: 0.96 (0.63–1.46)	Age, gender, education or social class, location, region or center
Lopez Ramos et al. 2001	• Case control • Prevalent Crohn's disease • 134 cases • Spain	Current at time of diagnosis		OR	• Current smoking: 2.75 (1.80–4.27)	Age, gender, education or social class, tonsillectomy or appendectomy, oral contraceptives or hormone replacement therapy

Table 10.20*S* Continued

Study	Design/Population	Current smoking definition	Number of cases analyzed in current smoking comparison	Type of effect estimate[a]	Findings/ Effect estimates (95% CI)	Adjustments for current smoking effect estimate
Herrlinger et al. 2002	• Case control • Prevalent Crohn's disease • 35 cases • Germany	Smoking, otherwise undefined		OR	• Current smoking: 0.84 (0.32–2.24)	
Lakatos et al. 2004	• Case control • Prevalent Crohn's disease • 202 cases • Hungary	Current at time of diagnosis		OR	• Current smoking: 1.72 (1.26–2.36)	
Van Kruiningen et al. 2005	• Case control • Prevalent Crohn's disease • 21 cases • Belgium	Ever		OR	• Current smoking: 2.80 (1.47–5.34)	
Firouzi et al. 2006	• Case control • Prevalent Crohn's disease • 46 cases • Iran	Current at time of diagnosis (assumed at diagnosis because surgery history taken prior to diagnosis)		OR	• Current smoking: 0.43 (0.16–1.16)	Age, gender, tonsillectomy or appendectomy, non-steroidal anti-inflammatory drugs, oral contraceptives or hormone replacement therapy
Jones et al. 2006	• Case control • Prevalent Crohn's disease • 5 cases • United Kingdom	Current at questionnaire		OR	• Current smoking: 2.66 (0.05–26.99)	
Lerebours et al. 2007	• Case control • Prevalent Crohn's disease • 165 cases • France	Current at questionnaire		OR	• Current smoking: 3.93 (2.45–6.32)	Age, gender, education or social class, other
Sonntag et al. 2007	• Case control • Prevalent Crohn's disease • 1,096 cases • Germany	Ever at time of questionnaire		OR	• Current smoking: 1.40 (1.10–1.80)	Gender, tonsillectomy or appendectomy, non-steroidal anti-inflammatory drugs, other

Table 10.20*S* Continued

Study	Design/Population	Current smoking definition	Number of cases analyzed in current smoking comparison	Type of effect estimate[a]	Findings/ Effect estimates (95% CI)	Adjustments for current smoking effect estimate
Tuvlin et al. 2007	• Case control • Prevalent Crohn's disease • 351 cases • United States	Current at time of diagnosis		OR	• Current smoking: 1.27 (1.00–1.60)	
Okazaki et al. 2008	• Case control • Prevalent Crohn's disease • 213 cases • Canada	Ever at time of questionnaire		OR	• Current smoking: 2.06 (1.35–3.14)	Age, gender, race or ethnicity, location, region or center, family history of inflammatory bowel disease, genes
Carlens et al. 2010	• Prospective cohort • Incident Crohn's disease • 628 cases • Sweden	Ever smoker		HR	• Current smoking: 1.50 (1.20–1.80)	Age, location, region or center, other
de Silva et al. 2010	• Nested case control • Prevalent Crohn's disease • 74 cases • Denmark	Current at recruitment		OR	• Current smoking: 1.89 (1.11–3.19)	
Gearry et al. 2010	• Case control • Prevalent Crohn's disease • 638 cases • New Zealand	Current at time of diagnosis		OR	• Current smoking: 1.99 (1.48–2.68)	Age, gender, race or ethnicity, education or social class, family history of inflammatory bowel disease
Morgan et al. 2010	• Case control • Prevalent Crohn's disease • 238 cases • New Zealand	Current at time of diagnosis		OR	• Current smoking: 2.36 (1.65–3.39)	
Andersen et al. 2011	• Case control • Prevalent Crohn's disease • 282 cases • Denmark	Current at time of diagnosis		OR	• Current smoking: 1.30 (0.95–1.77)	

Table 10.20*S* Continued

Study	Design/Population	Current smoking definition	Number of cases analyzed in current smoking comparison	Type of effect estimate[a]	Findings/ Effect estimates (95% CI)	Adjustments for current smoking effect estimate
Hansen et al. 2011	• Case control • Prevalent Crohn's disease • 123 cases • Denmark	Current time of questionnaire		OR	• Current smoking: 2.35 (1.33–4.15)	Age, gender, race or ethnicity, location, region or center, tonsillectomy or appendectomy, oral contraceptives or hormone replacement therapy, coffee or tea, diet
Osterman et al. 2011	• Nested case control • Prevalent Crohn's disease • 7,716 cases • United Kingdom	Current, undefined		OR	• Current smoking: 1.20 (1.15–1.26)	
Pugazhendhi et al. 2011	• Case control • Prevalent Crohn's disease • 200 cases • India	≥10 cigarettes or a packet of bidi/week prior to onset of illness		OR	• Current smoking: 0.75 (0.43–1.32)	
van der Heide et al. 2011	• Case series • Prevalent Crohn's disease • 104 cases • Netherlands	Current at time of diagnosis		OR	• Current smoking: 1.29 (1.07–1.51)	
Benjamin et al. 2012	• Case control • Prevalent Crohn's disease • 101 cases • United Kingdom	Current at questionnaire		OR	• Current smoking: 2.52 (1.06–5.96)	
Castiglione et al. 2012	• Case control • Prevalent Crohn's disease • 468 cases • Italy	Smoking, otherwise undefined		OR	• Current smoking: 1.40 (1.08–1.80)	
Habashneh et al. 2012	• Case control • Prevalent Crohn's disease • 56 cases • Jordan	Current at questionnaire		OR	• Current smoking: 1.16 (0.59–2.27)	

Table 10.20*S* Continued

Study	Design/Population	Current smoking definition	Number of cases analyzed in current smoking comparison	Type of effect estimate[a]	Findings/ Effect estimates (95% CI)	Adjustments for current smoking effect estimate
Kayahan et al. 2012	• Case control • Prevalent Crohn's disease • 20 cases • Turkey	Any tobacco use in the past 30 days at time of questionnaire		OR	• Current smoking: 0.61 (0.16–2.34)	
Chan et al. 2013	• Nested case control • Incident Crohn's disease • 75 cases • Europe	Current at recruitmen		OR	• Current smoking: 1.98 • (1.13–3.48)	Age, gender, location, region or center
Vessey et al. 1986	• Prospective cohort • Incident Crohn's disease, females • 17 cases • United Kingdom	Current at recruitment		RR	• Current smoking: 3.26 (1.21–8.81)	
Logan and Kay 1989	• Prospective cohort • Incident Crohn's disease • Females • 42 cases • United Kingdom	Current at recruitment		RR	• Current smoking: 1.83 (0.99–3.34)	
Sandler et al. 1992	• Case control • Prevalent Crohn's disease, females • 167 cases • United States	Current at time of diagnosis		OR	• Current smoking: 1.62 (0.73–3.62)	
Katschinski et al. 1993	• Case control • Prevalent Crohn's disease • Females • 79 cases • Germany	Current at time of diagnosis		OR	• Current smoking: 3.00 (1.30–6.80)	Age, oral contraceptives or hormone replacement therapy
Boyko et al. 1994	• Case control • Prevalent Crohn's disease • Females • 78 cases • United States	Current at symptom onset		OR	• Current smoking: 2.36 (1.34–4.17)	

Table 10.20*S* Continued

Study	Design/Population	Current smoking definition	Number of cases analyzed in current smoking comparison	Type of effect estimate[a]	Findings/ Effect estimates (95% CI)	Adjustments for current smoking effect estimate
Higuchi et al. 2012	• Prospective cohort • Incident Crohn's disease • Females • 219 cases • United States	Current at recruitment		HR	• Current smoking: 1.90 (1.42–2.53)	Age, gender, body mass index, oral contraceptives or hormone replacement therapy
Harries et al. 1982	• Case control • Prevalent ulcerative colitis disease • 111 cases • United Kingdom	Current at questionnaire		OR	• Current smoking: 0.14 (0.08–0.25)	
Jick and Walker 1983	• Case control • Prevalent ulcerative colitis disease • 189 cases • United States	Current at time of hospitalization		OR	• Current smoking: 0.31 (0.22–0.43)	Age, gender, location, region or center
Logan et al. 1984	• Case control • Prevalent ulcerative colitis disease • 115 cases • United Kingdom	Current at time of diagnosis		OR	• Current smoking: 0.17 (0.08–0.34)	Age, gender, location, region or center
Stermer et al. 1985	• Case control • Prevalent ulcerative colitis disease • 93 cases • Israel	Smoking, otherwise undefined		OR	• Current smoking: 0.53 (0.30–0.94)	
Thornton et al. 1985	• Case control • Prevalent ulcerative colitis disease • 16 cases • United Kingdom	Current at symptom onset		OR	• Current smoking: 0.52 (0.13–2.01)	
Boyko et al. 1987	• Nested case control • Prevalent ulcerative colitis disease • 161 cases • United States	Current at time of diagnosis		OR	• Current smoking: 0.70 (0.40–1.20)	Age, gender, alcohol, coffee or tea

Table 10.20*S* Continued

Study	Design/Population	Current smoking definition	Number of cases analyzed in current smoking comparison	Type of effect estimate[a]	Findings/ Effect estimates (95% CI)	Adjustments for current smoking effect estimate
Franceschi et al. 1987	• Case control • Prevalent ulcerative colitis disease • 124 cases • Italy	Current at time of diagnosis		OR	• Current smoking: 0.50 (0.30–1.00)	Age, gender, education or social class, former smoking, body mass index, other
Funakoshi et al. 1987	• Case control • Prevalent ulcerative colitis disease • 105 cases • Japan	Current at symptom onset		OR	• Current smoking: 0.50 (0.29–0.84)	Age
Tobin et al. 1987	• Case control • Prevalent ulcerative colitis disease • 90 cases • United Kingdom	Current at symptom onset (6 months before symptom onset)		OR	• Current smoking: 0.17 (0.08–0.36)	Age, gender, location, region or center
Lindberg et al. 1988	• Case control • Prevalent ulcerative colitis disease • 252 cases • Sweden	Current at time of diagnosis		OR	• Current smoking: 0.70 (0.40–0.97)	Age, gender, location, region or center
Lorusso et al. 1989	• Case control • Prevalent ulcerative colitis disease • 84 cases • Italy	Current at questionnaire		OR	• Current smoking: 0.23 (0.07–0.83)	Age, gender, location, region or center, education or social class
Higashi et al. 1991	• Case control • Prevalent ulcerative colitis disease • 43 cases • Japan	Current at symptom onset		OR	• Current smoking: 0.80 (0.18–3.41)	
Samuelsson et al. 1991	• Case control • Prevalent ulcerative colitis disease • 167 cases • Sweden	Current at questionnaire		OR	• Current smoking: 0.53 (0.29–0.94)	Age, gender, location, region or center, former smoking, diet, other

Table 10.20*S* Continued

Study	Design/Population	Current smoking definition	Number of cases analyzed in current smoking comparison	Type of effect estimate[a]	Findings/ Effect estimates (95% CI)	Adjustments for current smoking effect estimate
Sandler et al. 1992	• Case control • Prevalent ulcerative colitis disease • 130 cases • United States	Current at time of diagnosis		OR	• Current smoking: 0.87 (0.48–1.55)	Age, gender, education or social class
Persson et al. 1993	• Case control • Prevalent ulcerative colitis disease • 66 cases • Sweden	Current at questionnaire		OR	• Current smoking: 0.90 (0.50–1.80)	Age, other
Srivasta et al. 1993	• Case control • Prevalent ulcerative colitis disease • 83 cases • United Kingdom	Current at questionnaire		OR	• Current smoking: 0.46 (0.28–0.74)	Age, gender
Tragnone et al. 1993	• Prospective cohort • Incident ulcerative colitis • 54 cases • Italy	Current at time of diagnosis		OR	• Current smoking: 1.54 • CI: 0.77–3.10	
EGRCIBD-Japan 1994	• Case control • Prevalent ulcerative colitis disease • 101 cases • Japan	Current at time of diagnosis, ≥20 cigarettes/ day		OR	• Current smoking: 0.70 (0.20–2.00)	Age, gender, location, region or center, alcohol
Martinez Salmeron et al. 1994	• Case control • Prevalent ulcerative colitis disease • 63 cases • Spain	Ever at diagnosis		OR	• Current smoking: 0.31 (0.13–0.71)	
Nakamura and Labarthe 1994	• Case control • Prevalent ulcerative colitis disease • 300 cases • Japan	Current at symptom onset		OR	• Current smoking: 0.30 (0.18–0.50)	Age, gender, alcohol

Table 10.20*S* Continued

Study	Design/Population	Current smoking definition	Number of cases analyzed in current smoking comparison	Type of effect estimate[a]	Findings/ Effect estimates (95% CI)	Adjustments for current smoking effect estimate
Rutgeerts et al. 1994	• Case control • Prevalent ulcerative colitis disease • 174 cases • Belgium	Current at questionnaire		OR	• Current smoking: 0.34 • CI: 0.19–0.59	Gender
Silverstein et al. 1994	• Case control • Prevalent ulcerative colitis disease • 200 cases • United States	Current at questionnaire		OR	• Current smoking: 0.23 • CI: 0.09–0.61	Age, gender, education or social class, other
Reif et al. 1995	• Case control • Prevalent ulcerative colitis disease • 46 cases • Israel	Current at questionnaire		OR	• Current smoking: 1.14 (0.50–2.61)	
Breslin et al. 1997	• Case control • Prevalent ulcerative colitis disease • 104 cases • Ireland	Current at questionnaire		OR	• Current smoking: 0.16 (0.08–0.31)	
Fich et al. 1997	• Case control • Prevalent ulcerative colitis disease • 71 cases • Israel	Current at questionnaire		OR	• Current smoking: 0.34 (0.21–0.54)	Age, gender
Minocha and Raczkowski 1997	• Case control • Prevalent ulcerative colitis disease • 177 cases • United States	Current at questionnaire		OR	• Current smoking: 0.73 (0.68–0.79)	Age, gender, race or ethnicity, tonsillectomy or appendectomy, former smoking
Corrao et al. 1998	• Case control • Incident ulcerative colitis disease • 409 cases • Italy	Current at questionnaire		OR	• Current smoking: 0.90 (0.70–1.20)	Age, location, region or center, oral contraceptives or hormone replacement therapy, breastfeeding

Table 10.20*S* Continued

Study	Design/Population	Current smoking definition	Number of cases analyzed in current smoking comparison	Type of effect estimate[a]	Findings/ Effect estimates (95% CI)	Adjustments for current smoking effect estimate
Koutroubakis et al. 1999	• Case control • Prevalent ulcerative colitis disease • 97 cases • Greece	Current at questionnaire		OR	• Current smoking: 0.64 (0.37–1.12)	
Reif et al. 2000	• Case control • Prevalent ulcerative colitis disease • 192 cases • Israel	Current at questionnaire		OR	• Current smoking: 0.39 (0.24–0.62)	Age, gender, education or social class, location, region or center
Lopez Ramos et al. 2001	• Case control • Prevalent ulcerative colitis disease • 153 cases • Spain	Current at time of diagnosis		OR	• Current smoking: 0.34 (0.18–0.57)	Age, gender, education or social class, tonsillectomy or appendectomy, oral contraceptives or hormone replacement therapy
Naganuma et al. 2001	• Case control • Prevalent ulcerative colitis disease • 325 cases • Japan	Smoking, otherwise undefined		OR	• Current smoking: 0.80 (0.57–1.12)	
Uzan et al. 2001	• Case control • Prevalent ulcerative colitis disease • 150 cases • France	Current at time of diagnosis		OR	• Current smoking: 0.66 • CI: 0.38–1.15	Age, gender, location, region or center, tonsillectomy or appendectomy

Table 10.20*S* Continued

Study	Design/Population	Current smoking definition	Number of cases analyzed in current smoking comparison	Type of effect estimate[a]	Findings/ Effect estimates (95% CI)	Adjustments for current smoking effect estimate
Herrlinger et al. 2002	• Case control • Prevalent ulcerative colitis disease • 31 cases • Germany	Smoking, otherwise undefined		OR	• Current smoking: 0.94 (0.34–2.56)	
Abraham et al. 2003	• Case control • Prevalent ulcerative colitis disease • 72 cases • Australia	Current at time of diagnosis		OR	• Current smoking: 0.41 (0.19–0.87)	
Florin et al. 2004	• Case control • Prevalent ulcerative colitis disease • 294 cases • Australia	Ever at diagnosis		OR	• Current smoking: 0.95 • CI: 0.74–1.24	
Lakatos et al. 2004	• Case control • Prevalent ulcerative colitis disease • 468 cases • Hungary	Current at time of diagnosis		OR	• Current smoking: 0.31 (0.23–0.42)	
Firouzi et al. 2006	• Case control • Prevalent ulcerative colitis disease • 382 cases • Iran	Current at time of diagnosis (assumed at diagnosis because surgery history taken prior to diagnosis)		OR	• Current smoking: 0.18 (0.11–0.28)	Age, gender, tonsillectomy or appendectomy, non-steroidal anti-inflammatory drugs, oral contraceptives or hormone replacement therapy
Jones et al. 2006	• Case control • Prevalent ulcerative colitis disease • 12 cases • United Kingdom	Current at questionnaire		OR	• Current smoking: 0.01 (0.01–3.42)	

Table 10.20*S* Continued

Study	Design/Population	Current smoking definition	Number of cases analyzed in current smoking comparison	Type of effect estimate[a]	Findings/ Effect estimates (95% CI)	Adjustments for current smoking effect estimate
Brant et al. 2007	• Case control • Prevalent ulcerative colitis disease • 121 cases • Canada	Current (unclear)		OR	• Current smoking: 1.20 (0.60–2.40)	Age, gender, race or ethnicity, location, region or center, family history of inflammatory bowel diseases, former smoking
Jiang et al. 2007	• Case control • Prevalent ulcerative colitis disease • 155 cases • China	Current at time of diagnosis		OR	• Current smoking: 0.31 (0.16–0.58)	Age, gender, race or ethnicity, location, region or center, family history of inflammatory bowel diseases, former smoking, tonsillectomy or appendectomy, alcohol, coffee or tea, diet
Lerebours et al. 2007	• Case control • Prevalent ulcerative colitis disease • 72 cases • France	Current at questionnaire		OR	• Current smoking: 0.42 (0.19–0.93)	Age, gender, education or social class, other
Sonntag et al. 2007	• Case control • Prevalent ulcerative colitis disease • 763 cases • Germany	Ever at time of questionnaire		OR	• Current smoking: 0.96 (0.74–1.24)	Gender, tonsillectomy or appendectomy, family history of inflammatory bowel disease, other
Tuvlin et al. 2007	• Case control • Prevalent ulcerative colitis disease • 309 cases • United States	Current at time of diagnosis		OR	• Current smoking: 0.57 (0.42–0.76)	

Table 10.20*S* Continued

Study	Design/Population	Current smoking definition	Number of cases analyzed in current smoking comparison	Type of effect estimate[a]	Findings/ Effect estimates (95% CI)	Adjustments for current smoking effect estimate
Sicilia et al. 2008	• Case control • Prevalent ulcerative colitis disease • 142 cases • Spain	Current at questionnaire		OR	• Current smoking: 0.33 (0.21–0.51)	
Carlens et al. 2010	• Prospective cohort • Incident ulcerative colitis disease • 1014 cases • Sweden	Ever smoker		OR	• Current smoking: 1.30 (1.10–1.50)	Age, location, center or region, other
de Silva et al. 2010	• Nested case control • Prevalent ulcerative colitis disease • 175 cases • Denmark	Current at recruitment		OR	• Current smoking: 1.35 (0.95–1.93)	
Gearry et al. 2010	• Case control • Prevalent ulcerative colitis disease • 653 cases • New Zealand	Current at time of diagnosis		OR	• Current smoking: 0.67 (0.48–0.94)	Age, gender, race or ethnicity, education or social class, family history of inflammatory disease
Andersen et al. 2011	• Case control • Prevalent ulcerative colitis disease • 312 cases • Denmark	Current at time of diagnosis		OR	• Current smoking: 0.34 (0.25–0.47)	
Hansen et al. 2011	• Case control • Prevalent ulcerative colitis disease • 144 cases • Denmark	Current at time of diagnosis		OR	• Current smoking: 0.43 (0.26–0.91)	Age, gender, race or ethnicity, location, region or center, tonsillectomy or appendectomy, oral contraceptives or hormone replacement therapy, coffee or tea, diet

Table 10.20*S* Continued

Study	Design/Population	Current smoking definition	Number of cases analyzed in current smoking comparison	Type of effect estimate[a]	Findings/ Effect estimates (95% CI)	Adjustments for current smoking effect estimate
Osterman et al. 2011	• Nested case control • Prevalent ulcerative colitis disease • 12,155 cases • United Kingdom	Current, undefined		OR	• Current smoking: 0.60 (0.58–0.62)	
van der Heide et al. 2011	• Case control • Prevalent ulcerative colitis disease • 132 cases • Netherlands	Current at time of diagnosis		OR	• Current smoking: 0.61 (0.46–0.77)	
Castiglione et al. 2012	• Case control • Prevalent ulcerative colitis disease • 527 cases • Italy	Smoking, otherwise undefined		OR	• Current smoking: 0.38 (0.28–0.51)	
Habashneh et al. 2012	• Case control • Prevalent ulcerative colitis disease • 72 cases • Jordan	Current at questionnaire		OR	• Current smoking: 0.28 (0.14–0.55)	
Kayahan et al. 2012	• Case control • Prevalent ulcerative colitis disease • 19 cases • Turkey	Any tobacco use in the past 30 days at time of questionnaire		OR	• Current smoking: 0.14 (0.02–1.18)	
Chan et al. 2013	• Nested case control • Prevalent ulcerative colitis disease • 177 cases • Europe	Current at recruitment		OR	• Current smoking: 1.37 (0.95–1.98)	Age, gender, location, region or center
Vessey et al. 1986	• Prospective cohort • Incident ulcerative colitis disease • Females • 26 cases • United Kingdom	Current at recruitment		RR	• Current smoking: 0.66 (0.28–1.56)	

Table 10.20*S* Continued

Study	Design/Population	Current smoking definition	Number of cases analyzed in current smoking comparison	Type of effect estimate[a]	Findings/ Effect estimates (95% CI)	Adjustments for current smoking effect estimate
Logan and Kay 1989	• Prospective cohort • Incident ulcerative colitis disease • Females • 55 cases • United Kingdom	Current at recruitment		RR	• Current smoking: 1.14 (0.90–1.44)	
Lashner et al. 1990	• Case control • Prevalent ulcerative colitis disease • Females • 41 cases • United States	Current at questionnaire		OR	• Current smoking: 0.33 (0.06–1.67)	Age, gender, oral contraceptives or hormone replacement therapy
Boyko et al. 1994	• Case control • Prevalent ulcerative colitis disease • Females • 152 cases • United States	Current at symptom onset		OR	• Current smoking: 0.91 (0.60–1.39)	
Higuchi et al. 2012	• Prospective cohort • Incident ulcerative colitis disease • Females • 233 cases • United States	Current at recruitment		HR	• Current smoking: 0.86 (0.61–1.20)	Age, gender, body mass index, oral contraceptives or hormone therapy
Lee et al. 1996	• Case control • Prevalent ulcerative colitis disease • 54 cases • United Kingdom	Ever at time of questionnaire		OR	• Current smoking: 0.66 (0.25–1.73)	

Source: Epidemiology Group of the Research Committee of Inflammatory Bowel disease in Japan 1994 (EGRCIBD).
Notes: **CI** = Confidence interval; **HR** = hazard ratio; **OR** = odds ratio; **RR** = relative risk.
[a]As reported in text or calculated with information provided by author.

Table 10.21*S* Characteristics of the studies on the effects of former smoking on Crohn's disease or ulcerative colitis

Study	Design/Population	Effect estimate (CI)	Adjustments for current smoking effect estimate
Harries et al. 1982	• Case control • Prevalent Crohn's disease • 80 cases • United Kingdom	• Former smoking: 1.63 (0.93–2.88)	
Thornton et al. 1985	• Case control • Prevalent Crohn's disease • 9 cases • United Kingdom	• Former smoking: 5.43 (0.42–69.67)	
Franceschi et al. 1987	• Case control • Prevalent Crohn's disease • 44 cases • Italy	• Former smoking: 3.50 (1.50–8.00)	Age, gender, education or social class, body mass index, other
Funakoshi et al. 1987	• Case control • Prevalent Crohn's disease • 20 cases • Japan	• Former smoking: 0.82 (0.04–15.37)	
Tobin et al. 1987	• Case control • Prevalent Crohn's disease • 68 cases • United Kingdom	• Former smoking: 3.58 (1.82–7.06)	
Lindberg et al. 1988	• Case control • Prevalent Crohn's disease • 53 cases • Sweden	• Former smoking: 1.90 (0.80–4.30)	Age, gender, location, region or center
Persson et al. 1993	• Case control • Prevalent Crohn's disease • 38 cases • Sweden	• Former smoking: 1.20 (0.50–3.10)	Age, other
Tragnone et al. 1993	• Prospective cohort • Incident Crohn's disease • 23 cases • Italy	• Former smoking: 1.03 (0.26–4.19)	
Reif et al. 1995	• Case control • Prevalent Crohn's disease • 30 cases • Israel	• Former smoking: 2.06 (0.47–8.96)	
Breslin et al. 1997	• Case control • Prevalent Crohn's disease • 79 cases • Ireland	• Former smoking: 0.81 (0.44–1.50)	
Fich et al. 1997	• Case control • Prevalent Crohn's disease • 61 cases • Israel	• Former smoking: 0.64 (0.21–1.93)	

Table 10.21*S* Continued

Study	Design/Population	Effect estimate (CI)	Adjustments for current smoking effect estimate
Corrao et al. 1998	• Case control • Incident Crohn's disease • 147 cases • Italy	• Former smoking: 1.70 (0.90–3.30)	Age, gender, location, region or center
Koutroubakis et al. 1999	• Case control • Prevalent Crohn's disease • 41 cases • Greece	• Former smoking: 2.59 (0.92–7.31)	
Reif et al. 2000	• Case control • Prevalent Crohn's disease • 197 cases • Israel	• Former smoking: 1.19 (0.75–1.90)	Age, gender, education or social class, location, region or center
Lopez Ramos et al. 2001	• Case control • Prevalent Crohn's disease • 134 cases • Spain	• Former smoking: 0.23 (0.07–0.74)	Age, gender, education or social class, tonsillectomy or appendectomy, oral contraceptives or hormone replacement therapy
Jones et al. 2006	• Case control • Prevalent Crohn's disease • 6 cases • United Kingdom	• Former smoking: 4.35 (0.39–30.41)	
Tuvlin et al. 2007	• Case series • Prevalent Crohn's disease • 142 cases • United States	• Former smoking: 0.89 (0.48–1.64)	
Carlens et al. 2010	• Prospective cohort • Incident Crohn's disease • 228 cases • Sweden	• Former smoking: 1.30 (1.00–1.80)	Age, location, region or center, other
Gearry et al. 2010	• Case control • Prevalent Crohn's disease • 638 cases • New Zealand	• Former smoking: 0.91 (0.65–1.27)	Age, gender, race or ethnicity, education or social class, family history of inflammatory bowel disease
Andersen et al. 2011	• Case control • Prevalent Crohn's disease • 160 cases • Denmark	• Former smoking: 0.84 (0.57–1.23)	
Hansen et al. 2011	• Case control • Prevalent Crohn's disease • 123 cases • Denmark	• Former smoking: 0.63 (0.31–1.29)	Age, gender, race or ethnicity, location, region or center, tonsillectomy or appendectomy, oral contraceptives or hormone replacement therapy, coffee or tea, diet
Habashneh et al. 2012	• Case control • Prevalent Crohn's disease • 28 cases • Jordan	• Former smoking: 1.37 (0.39–4.79)	

Table 10.21*S* Continued

Study	Design/Population	Effect estimate (CI)	Adjustments for current smoking effect estimate
Vessey et al. 1986	• Prospective cohort • Incident Crohn's disease • Females • 7 cases • United Kingdom	• Former smoking: 0.79 (0.10–6.52)	
Lashner et al. 1989	• Prospective cohort • Prevalent Crohn's disease • Females • 32 cases • United States	• Former smoking: 2.50 (0.51–12.20)	Age, gender
Sandler et al. 1992	• Case control • Prevalent Crohn's disease • Females • 102 cases • United States	• Former smoking: 1.42 (0.70–2.89)	
Katschinski et al. 1993	• Case control • Prevalent Crohn's disease • Females • 43 cases • Germany	• Former smoking: 0.69 • (0.11–4.40)	Age, oral contraceptives or hormone replacement therapy
Boyko et al. 1994	• Case Control • Prevalent Crohn's disease • Females • 52 cases • United States	• Former smoking: 1.65 (0.75–3.61)	
Higuchi et al. 2012	• Prospective cohort • Incident Crohn's disease • Females • 261 cases • United States	• Former smoking: 1.35 (1.05–1.73)	Age, gender, body mass index, oral contraceptives or hormone replacement therapy
Harries et al. 1982	• Case Control • Prevalent ulcerative colitis • Females • 174 cases • United Kingdom	• Former smoking: 1.50 (0.94–2.40)	
Jick and Walker 1983	• Case control • Prevalent ulcerative colitis • 176 cases • United States	• Former smoking: 1.16 (0.77–1.76)	Age, gender, location, region or center
Logan et al. 1984	• Case Control • Prevalent ulcerative colitis • 103 cases • United Kingdom	• Former smoking: 1.69 (0.99–2.90)	Age, gender, location, region or center
Thornton et al. 1985	• Case Control • Prevalent ulcerative colitis • 26 cases • United Kingdom	• Former smoking: 9.92 (1.89–51.93)	

Table 10.21*S* Continued

Study	Design/Population	Effect estimate (CI)	Adjustments for current smoking effect estimate
Boyko et al. 1987	• Nested case control • Prevalent ulcerative colitis • 167 cases • United States	• Former smoking: 2.00 (1.10–3.80)	Age, gender, alcohol, coffee or tea
Franceschi et al. 1987	• Case control • Prevalent ulcerative colitis • 98 cases • Italy	• Former smoking: 2.70 (1.50–4.90)	Age, gender, education or social class, body mass index, other
Funakoshi et al. 1987	• Case control • Prevalent ulcerative colitis • 92 cases • Japan	• Former smoking: 0.89 (0.37–2.16)	Age
Tobin et al. 1987	• Case control • Prevalent ulcerative colitis • 126 cases • United Kingdom	• Former smoking: 1.17 (0.67–2.04)	
Lindberg et al. 1988	• Case control • Prevalent ulcerative colitis • 151 cases • Sweden	• Former smoking: 2.30 (1.40–3.90)	Age, gender, location, region or center
Lorusso et al. 1989	• Case control • Prevalent ulcerative colitis • 84 cases • Italy	• Former smoking: 2.30 (0.50–10.00)	Age, gender, education or social class
Higashi et al. 1991	• Case control • Prevalent ulcerative colitis • 35 cases • Japan	• Former smoking: 0.50 (0.02–6.98)	
Samuelsson et al. 1991	• Case control • Prevalent ulcerative colitis • 167 cases • Sweden	• Former smoking: 0.76 (0.35–1.63)	Age, gender, location, diet, other
Sandler et al. 1992	• Case control • Prevalent ulcerative colitis • 133 cases • United States	• Former smoking: 1.31 (0.68–2.52)	Age, gender, education or social class
Persson et al. 1993	• Case control • Prevalent ulcerative colitis • 56 cases • Sweden	• Former smoking: 1.50 (0.70–3.40)	Age, other
Srivasta et al. 1993	• Case series • Prevalent ulcerative colitis • 108 cases • United Kingdom	• Former smoking: 0.86 (0.55–1.32)	Age, gender

Table 10.21*S* Continued

Study	Design/Population	Effect estimate (CI)	Adjustments for current smoking effect estimate
Tragnone et al. 1993	• Prospective cohort • Incident ulcerative colitis • 41 cases • Italy	• Former smoking: 5.10 (1.60–16.90)	Age, gender
EGRCIBD-Japan 1994	• Case control • Prevalent ulcerative colitis • 61 cases • Japan	• Former smoking: 2.40 (1.00–6.00)	Age, gender, location, region or center, alcohol
Nakamura and Labarthe 1994	• Case control • Prevalent ulcerative colitis • 336 cases • Japan	• Former smoking1.67 (0.97–2.88)	Age, gender, alcohol
Rutgeerts et al. 1994	• Case control • Prevalent ulcerative colitis • 174 cases • Belgium	• Former smoking: 0.26 (0.12–0.53)	
Silverstein et al. 1994	• Case control • Prevalent ulcerative colitis • 200 cases • United States	• Former smoking1.37 (0.49–3.83)	Age, gender, education or social class, other
Reif et al. 1995	• Case control • Prevalent ulcerative colitis • 41 cases • Israel	• Former smoking: 1.17 (0.36–3.78)	
Breslin et al. 1997	• Case control • Prevalent ulcerative colitis • 164 cases • Ireland	• Former smoking1.58 (0.97–2.59)	
Fich et al. 1997	• Case control • Prevalent ulcerative colitis • 64 cases • Israel	• Former smoking: 1.32 (0.54–3.23)	
Minocha and Raczkowski 1997	• Case control • Prevalent ulcerative colitis • 150 cases • United States	• Former smoking: 0.88 (0.80–0.97)	Age, gender, race or ethnicity, tonsillectomy or appendectomy, former smoking
Corrao et al. 1998	• Case control • Incident ulcerative colitis • 457 cases • Italy	• Former smoking: 3.00 (2.10–4.30)	Age, location, region or center, oral contraceptives or hormone replacement therapy, breastfeeding
Koutroubakis et al. 1999	• Case control • Prevalent ulcerative colitis • 101 cases • Greece	• Former smoking: 2.54 (1.27–5.08)	

Table 10.21*S* Continued

Study	Design/Population	Effect estimate (CI)	Adjustments for current smoking effect estimate
Reif et al. 2000	• Case control • Prevalent ulcerative colitis • 239 cases • Israel	• Former smoking: 1.73 (1.14–2.65)	Age, gender, education or social class, location, region or center
Lopez Ramos et al. 2001	• Case control • Prevalent ulcerative colitis • 153 cases • Spain	• Former smoking: 1.03 (0.63–1.67)	Age, gender, education or social class, tonsillectomy or appendectomy, oral contraceptives or hormone replacement therapy
Abraham et al. 2003	• Case control • Prevalent ulcerative colitis • 90 cases • Australia	• Former smoking: 3.45 (1.62–7.35)	
Jones et al. 2006	• Case control • Prevalent ulcerative colitis • 18 cases • United Kingdom	• Former smoking: 4.38 (1.34–12.66)	
Brant et al. 2007	• Case control • Prevalent ulcerative colitis • 121 cases • Canada	• Former smoking: 1.90 (1.10–3.30)	Age, gender, race or ethnicity, location, region or center, family history of inflammatory bowel disease
Jiang et al. 2007	• Case control • Prevalent ulcerative colitis • 152 cases • China	• Former smoking: 6.24 (1.75–22.20)	Age, gender, family history of inflammatory bowel disease, tonsillectomy or appendectomy, alcohol, coffee or tea, diet
Tuvlin et al. 2007	• Case series • Prevalent ulcerative colitis • 205 cases • United States	• Former smoking: 1.50 (0.86–2.64)	
Sicilia et al. 2008	• Case control • Prevalent ulcerative colitis • 167 cases • Spain	• Former smoking: 1.10 (0.68–1.79)	
Carlens et al. 2010	• Prospective cohort • Incident ulcerative colitis • 427 cases • Sweden	• Former smoking: 1.50 (1.20–1.80)	Age, location, region or center, other
Gearry et al. 2010	• Case control • Prevalent ulcerative colitis • 653 cases • New Zealand	• Former smoking: 1.53 (1.14–2.25)	Age, gender, race or ethnicity, education or social class, family history of inflammatory bowel disease
Andersen et al. 2011	• Case control • Prevalent ulcerative colitis • 409 cases • Denmark	• Former smoking: 1.73 (1.33–2.25)	

Table 10.21*S* Continued

Study	Design/Population	Effect estimate (CI)	Adjustments for current smoking effect estimate
Hansen et al. 2011	• Case control • Prevalent ulcerative colitis • 144 cases • Denmark	• Former smoking: 0.94 (0.51–1.74)	Age, gender, race or ethnicity, location, region or center, tonsillectomy or appendectomy, oral contraceptives or hormone replacement therapy, coffee or tea, diet
Vessey et al. 1986	• Prospective cohort • Incident ulcerative colitis • Females • 24 cases • United Kingdom	• Former smoking: 0.47 (0.18–1.25	
Lashner et al. 1990	• Case control • Prevalent ulcerative colitis • Females • 43 cases • United States	• Former smoking: 3.59 (0.64–20.00	Age, gender, oral contraceptives or hormone replacement therapy
Boyko et al. 1994	• Case control • Incident ulcerative colitis • Females • 163 cases • United States	• Former smoking: 2.20 (1.40–3.44	
Higuchi et al. 2012	• Prospective cohort • Incident t ulcerative colitis • Females • 357 cases • United States	• Former smoking: 1.56 (1.26–1.93	Age, gender, body mass index, oral contraceptives or hormone replacement therapy
Lee et al. 1996	• Case control • Prevalent ulcerative colitis • Males • 61 cases • United Kingdom	• Former smoking: 1.78 (0.71–4.45	

Source: Epidemiology Group of the Research Committee of Inflammatory Bowel Disease in Japan 1994 (EGRCIBD).
Note: **CI** = confidence interval.

Chapter 11
General Morbidity and All-Cause Mortality

Table 11.1*S* Studies on the association between smoking and all-cause mortality *S-437*

Table 11.2*S* Studies on the association between smoking and poor general health *S-439*

Table 11.3*S* Studies on the association between smoking and relative risk of poor functional status *S-441*

Table 11.4*S* Studies on the association between smoking and SF-36 or SF-12 scores *S-444*

Table 11.5*S* Studies on the association between smoking and other measures of health and function *S-446*

Table 11.6*S* Studies on the association between smoking and hospitalizations *S-448*

Table 11.7*S* Studies on the association between smoking and outpatient visits *S-450*

Table 11.8*S* Studies on the association between smoking and nursing home stays *S-451*

Table 11.9*S* Studies on the association between smoking and costs *S-452*

Table 11.10*S* Annual per capita spending on health care, by smoking status and age group (2008 dollars) *S-453*

Table 11.11*S* Studies on the association between smoking and workplace absenteeism (days absent) *S-454*

Table 11.12*S* Studies on the association between smoking and relative risk of workplace absenteeism *S-456*

Table 11.1*S* Studies on the association between smoking and all-cause mortality

Study	Design/population	Results (rate ratio 95% CI)			Findings	Comments
		Current smoker	Former smoker	Never smoker		
Sakata et al. 2012	• 27,311 men and 40,662 women born before 1945 who were atomic bomb survivors or residents of Hiroshima and Nagasaki, Japan • Smoking status obtained during 1963–1992 • Mortality status available through 2008	**Years of age started smoking** • Men born <1920: – <20: 1.66 (1.54–1.79) – 20–29: 1.42 (1.34–1.51) – ≥30: 1.17 (1.07–1.29) – Unknown: 2.85 (2.48–3.28) – All ages: 1.46 (1.38–1.54) • Men born 1920–1945: – <20: 2.21 (1.97–2.48) – 20–29: 1.71 (1.53–1.91) – ≥30: 1.48 (1.07–2.05) – Unknown: 2.04 (1.74–2.39) – All ages: 1.89 (1.70–2.10) • Women born <1920: – <20: 1.54 (1.21–1.95) – 20–29: 1.53 (1.38–1.70) – ≥30: 1.26 (1.16–1.36) – Unknown: 1.78 (1.65–1.91) – All ages: 1.51 (1.43–1.58) • Women born 1920–1945: – <20: 2.61 (1.98–3.44) – 20–29: 2.01 (1.79–2.25) – ≥30: 1.40 (1.22–1.62) – Unknown: 1.94 (1.67–2.27) – All ages: 1.81 (1.67–1.96)	**Years of age quit smoking** • Men born <1920: – <25: 1.19 (0.84–1.68) – 25–34: 1.13 (0.94–1.36) – 35-44: 1.09 (0.95–1.24) – 45–54: 1.11 (1.00–1.22) – 55–64: 1.23 (1.12–1.34) – ≥65: 1.45 (1.33–1.59) – Unknown: 1.51 (1.28–1.78) • Men born 1920–1945: – <25: 0.91 (0.58–1.42) – 25–34: 0.83 (0.66–1.05) – 35–44: 1.21 (1.02–1.44) – 45–54: 1.43 (1.23–1.68) – 55–64: 1.73 (1.45–2.06) – ≥65: 1.72 (1.16–2.57) – Unknown: 2.14 (1.70–2.69) • Women born <1920: – <25: 0.89 (0.29–2.75) – 25-34: 1.16 (0.81–1.65) – 35-44: 1.04 (0.80–1.36) – 45-54: 0.93 (0.78–1.11) – 55-64: 1.22 (1.06–1.40) – ≥65: 1.31 (1.15–1.48) – Unknown: 1.45 (1.27–1.66) • Women born 1920–1945: – <25: 1.54 (0.64–3.70) – 25-34: 1.21 (0.81–1.81) – 35-44: 1.27 (0.95–1.70) – 45-54: 1.59 (1.26–2.00) – 55-64: 1.49 (1.15–1.92) – ≥65: 1.94 (1.15–3.29) – Unknown: 1.55 (1.23–1.95)	1.0 (ref) 1.0 (ref)	• Risk of death increased with younger age of smoking initiation, irrespective of period of birth or gender • Quitting smoking at earlier age reduced risk of death	Rate ratios presented for current vs. never smokers and for former vs. never smokers, within strata of age started/quit smoking, period of birth, and gender

Table 11.1*S* Continued

Study	Design/population	Results (rate ratio 95% CI)			Findings	Comments
		Current smoker	Former smoker	Never smoker		
Thun et al. 2013	• CPS-I (1959–1965; 183,060 men, 355,922 women • CPS-II (1982–1988, 293,592 men, 452,893 women) • 5 pooled contemporary cohort studies of NIH–AARP, the ACS CPS-II Nutrition Cohort (a subset of the original CPS-II mortality study), WHI, NHS, and HPFS (2000-2010; 421,702 men, 535,054 women), 55 years of age or older during follow-up	• Men – CPS-I: 1.76 (1.71–1.81) – CPS-II: 2.33 (2.26–2.40) – Contemporary: 2.80 (2.72–2.88) • Women – CPS-I: 1.35 (1.30–1.40) – CPS-II: 2.08 (2.02–2.14) – Contemporary: 2.76 (2.69–2.84)	• Men – CPS-I: 1.28 (1.23–1.34) – CPS-II: 1.42 (1.38–1.45) – Contemporary: 1.47 (1.45–1.50) • Women – CPS-I: 1.33 (1.23–1.43) – CPS-II: 1.33 (1.29–1.37) – Contemporary: 1.45 (1.43–1.48)	1.0 (ref) 1.0 (ref) 1.0 (ref) 1.0 (ref) 1.0 (ref) 1.0 (ref)	• Absolute risks of death from smoking continue to increase among female smokers • Increased risks now nearly identical for men and women, as compared with persons who have never smoked	Adjusted for age, race, and educational level

Note: **ACS** = American Cancer Society; **CI** = confidence interval; **CPS** = Cancer Prevention Study; **HPFS** = Health Professional Follow-up Study; **NIH-AARP** = National Institutes of Health-AARP; **NHS** = Nurses' Health Study; **WHI** = Women's Health Initiative.

Table 11.2*S* Studies on the association between smoking and poor general health

Study	Design/population	Results: Current smoker	Results: Former smoker	Results: Never smoker	Findings	Comments
Johnson and Richter 2002	• 7,844 adolescents 12–17 years of age • United States	Mean self-rated health on a scale of 1 (poor) to 5 (excellent)			• Smokers had worse self-rated health than never smokers (p <0.01)	Adjusted for gender, age, and family income
		• Total: – ≥6 days/month: 3.85 – 1–5 days/month: 3.98	• Total: 4.14	Total: 4.26		
Ostbye et al. 2002	• Health and Retirement Study (7,845 persons 51–64 years of age) • AHEAD (5,037 persons ≥70 years of age) • Longitudinal studies from 1992/1993–1998 • United States	OR (95% CI) for self-reported poor or fair health			• Current smoking—particularly heavy smoking—increases risk of fair or poor health • Former smokers who have quit within the last 15 years also have an increased risk of fair or poor health • Long-term quitters (>15 years) have a risk that's similar to never smokers	Adjusted for exercise, BMI, alcohol consumption, age, race, gender, marital status, and education
		• 51–64 years of age: – Heavy: 2.06 (1.80–2.36) – Light: 1.47 (1.24–1.73) • ≥70 years of age: – 1.55 (1.29–1.87)	• Time since quit: – <3 years: 1.99 (1.60–2.48) – 3–15 years: 1.28 (1.11–1.48) – >15 years: 1.07 (0.91–1.25) – 1.13 (1.01–1.27)	1.0 (ref) 1.0 (ref)		
Arday et al. 2003	• 134,309 elderly (≥65 years of age) and 8,640 disabled (<65 years of age) Medicare managed care enrollees	OR (95% CI) for fair or poor health			• Among disabled, current daily smokers were more likely than never smokers to report fair or poor health • Among elderly, both current and former smokers were more likely than never smokers to report fair or poor health	Adjusted for age, gender, race/ethnicity, and education
		• Disabled: – Daily: 1.58 (1.25–2.00) – Some days: 1.51 (0.97–2.34) • Elderly: – Daily: 1.53 (1.41–1.66) – Some days: 1.40 (1.21–1.63)	• Disabled: – ≤12 months: 1.41 (0.90–2.20) – >12 months: 1.20 (0.97–1.47) • Elderly: – ≤12 months: 2.72 (2.27–3.25) – >12 months: 1.26 (1.20–1.34)	1.0 (ref) 1.0 (ref)		
Strine et al. 2005	• BRFSS • 2001–2002 • 82,918 respondents • ≥18 years of age • United States	OR (95% CI) for fair or poor general health			• Current and former smokers were more likely than never smokers to report fair or poor health	Adjusted for age, gender, race/ethnicity, education, employment status, and marital status
		• Total: 1.7 (1.5–1.9)	• Total: 1.4 (1.3–1.6)	1.0 (ref)		

Table 11.2*S* Continued

Study	Design/population	Results: Current smoker	Results: Former smoker	Results: Never smoker	Findings	Comments
McClave et al. 2009	• BRFSS • 2006 • 17,800 participants in 4 states • ≥18 years of age • United States	OR (95% CI) for fair or poor general health			• Frequency of fair or poor health did not vary significantly by smoking status	Adjusted for age, race/ethnicity, gender, education, marital status, employment status, chronic disease, and health care coverage
		• Total: – Nonquitter: 1.0 (ref) – Unsuccessful quitter: 1.3 (0.8–2.1)	• Total: 1.1 (0.7–1.7)	1.1 (0.7–1.7)		
Caldeira et al. 2012	• 1,253 U.S. college students	Probability of fair or poor health status			• Compared with those who did not smoke during college, those who smoked at a high, stable level were more likely to report their health as fair or poor ($p < 0.05$)	Adjusted for gender, race, and neighborhood income
		• Total smoked at high level throughout college: 0.28		Did not smoke during college: 0.11		
Wang et al. 2012	• 36,225 adolescents • Mean 15 years of age • Hong Kong	OR (95% CI) for poor self-rated health			• Current and former smokers were more likely than never smokers to report their health as fair or poor	Adjusted for gender, age, parental education, housing type, secondhand smoke exposure, ever drinking, physical activity, illicit drug use, and school clustering effect
		• Total: 1.52 (1.38–1.67) • Boys: 1.31 (1.13–1.53) • Girls: 1.75 (1.53–2.00)	• Total: 1.43 (1.19–1.71) • Boys: 1.43 (1.12–1.83) • Girls: 1.42 (1.08–1.85)	1.0 (ref) 1.0 (ref) 1.0 (ref)		

Note: **AHEAD** = Asset and Health Dynamics among the Oldest Old Survey; **BMI** = body mass index; **BRFSS** = Behavioral Risk Factor Surveillance System; **CI** = confidence interval; **OR** = odds ratio.

Table 11.3*S* Studies on the association between smoking and relative risk of poor functional status

Study	Design/population	Results: Current smoker	Results: Former smoker	Results: Never smoker	Findings	Comments
Ostbye et al. 2002	• Health and Retirement Study • 7,845 persons 51–64 years of age • United States	OR (95% CI) for disability (self-reported limited ability to work because of impairment or health problems)			• Current smokers were more likely than never smokers to report limited ability to work • Former smokers were also at increased risk of limited ability to work, with the exception of long-term (>15 years) quitters	Adjusted for exercise, BMI, alcohol consumption, age, race, gender, marital status, and education
		• Total – Heavy: 2.23 (1.84–2.71) – Light: 1.73 (1.37–2.18)	• Time since quit: – <3 years: 2.45 (1.81–3.33) – 3–15 years: 1.49 (1.21–1.84) – >15 years: 1.07 (0.84–1.37)	1.0 (ref)		
Atkinson et al. 2005	• 558 community-dwelling older women with moderate to severe disability • Mean age at baseline was 78 years • Followed for 3 years • United States	OR (95% CI) for experiencing both cognitive and physical decline. Physical decline based on walking speed. Mental decline based on MMSE			• Compared with never smokers, current smokers had a more than 5-fold increase in risk of cognitive and physical decline • Risk among former smokers was similar to that of never smokers	Adjusted for age, race, education, number of diseases, pulmonary disease, hemoglobin, baseline walking speed, baseline MMSE score, baseline instrumental activities of daily living, and baseline activities of daily living
		• Total: 5.66 (1.49–21.54)	• Total: 1.38 (0.48–4.00)	1.0 (ref)		
Sulander et al. 2005	• 11,793 people between 65–79 years of age • Finland	OR (95% CI) for worse functional status. Functional status scored as 0–5 (higher score reflecting worse status) based on sum of five activities of daily living: use of stairs, walking outside, bathing, dressing, and eating			• Current and former smokers had worse functional status than never smokers	Adjusted for age, alcohol, diet, physical activity, BMI, time period, occupation, and marital status
		• Men: 2.05 (1.62–2.61) • Women: 1.99 (1.47–2.68)	• Men: 1.26 (1.05–1.52) • Women: 1.67 (1.30–2.16)	1.0 (ref) 1.0 (ref)		

Table 11.3*S* Continued

Study	Design/population	Results: Current smoker	Results: Former smoker	Results: Never smoker	Findings	Comments
Myint et al. 2007	• EPIC study • 16,678 participating men and women • 40–79 years of age at baseline (1993–1997)	OR (95% CI) for poor physical functional health (bottom 20% of population)			• Current and former smokers have worse physical and mental function than never smokers	Adjusted for age, BMI, social class, education level, prevalent illness, alcohol intake, and physical activity
		• Men: 1.85 (1.49–2.30) • Women: 1.56 (1.30–1.87)	• Men: 1.18 (1.02–1.35) • Women: 1.16 (1.03–1.30)	1.0 (ref) 1.0 (ref)		
		OR (95% CI) for poor mental functional health (bottom 20% of population)				
		• Men: 1.38 (1.12–1.70) • Women: 1.77 (1.51–2.07)	• Men: 1.18 (1.02–1.35) • Women: 1.16 (1.03–1.30)	1.0 (ref) 1.0 (ref)		
Liao et al. 2011	• Taiwan Longitudinal Study in Aging • 1989–2003 • 3,187 men and women ≥60 years of age without functional disability at baseline	Hazard ratio (95% CI) for functional disability. Functional disability defined as difficulty taking a bath or walking 200–300 meters independently			• Current and former smokers had a higher risk of functional disability than never smokers	Adjusted for alcohol, sleep, exercise, gender, marital status, education, and time-varying disease status
		• Total: 1.45 (1.27–1.65)	• Total: 1.23 (1.05–1.44)	1.0 (ref)		

Table 11.3*S* Continued

Study	Design/population	Results: Current smoker	Results: Former smoker	Results: Never smoker	Findings	Comments
Vogl et al. 2012	• Health Survey for England data • 13,241 adults ≥16 years of age • 2006 • English general population	OR for problems with mobility			• Compared with never smokers, current heavy smokers scored worse on each of the 5 measures of health-related quality of life • Current moderate smokers scored worse than never smokers on all of the measures except problems with usual activity • Ex-regular smokers scored worse than never smokers on problems with mobility, pain/discomfort, and anxiety depression	Adjusted for age, gender, BMI, cardiovascular disease, number of limiting conditions, alcohol intake, physical activity, ethnicity, marital status, education, economic status, household income and size, and social capital
		• Total – Heavy: 1.67[a] – Moderate: 1.55[a] – Light: 1.13	• Total – Ex-regular: 1.18[a] – Ex-occasional: 0.99	1.00 (ref)		
		OR for problems with self-care				
		• Total – Heavy: 1.70[a] – Moderate: 1.45[a] – Light: 1.25	• Total – Ex-regular: 1.11 – Ex-occasional: 0.88	1.00 (ref)		
		Odds ratio for problems with usual activity				
		• Total – Heavy: 1.42[a] – Moderate: 1.37 – Light: 0.95	• Total – Ex-regular: 1.11 – Ex-occasional: 1.12	1.00 (ref)		
		Odds ratio for problems with pain/discomfort				
		• Total – Heavy: 1.46[a] – Moderate: 1.36[a] – Light: 1.34[a]	• Total – Ex-regular: 1.28[a] – Ex-occasional: 1.07	1.00 (ref)		
		Odds ratio for problems with anxiety/depression				
		• Total – Heavy: 1.86[a] – Moderate: 1.49[a] – Light: 1.43[a]	• Total – Ex-regular: 1.16[a] – Ex-occasional: 1.11	1.00 (ref)		

Note: **BMI** = body mass index; **CI** = confidence interval; **EPIC** = European Prospective Investigation into Cancer; **MMSE** = Mini-mental state examination; **OR** = odds ratio.
[a]Indicates $p<0.05$ relative to never smokers.

Table 11.4*S* Studies on the association between smoking and SF-36 or SF-12 scores[a]

Study	Design/population	Results			Findings	Comments
		Current smoker	Former smoker	Never smoker		
Mulder et al. 2001	• 9,660 men and women 20–59 years of age without a history of tobacco-related chronic disease • The Netherlands	PCS score			• PCS was higher among never smokers than among former (p <0.05) and current (p <0.001) smokers • MCS was lower among current smokers than among former and never smokers (p <0.0001)	Adjusted for age, gender, education level, and town
		• Total: 51.4	• Total: 51.6	• Total: 52.0		
		MCS score				
		• Total: 46.9	• Total: 49.2	• Total: 49.3		
Arday et al. 2003	• 134,309 elderly (≥65 years of age) and 8,640 disabled (<65 years of age) Medicare managed care enrollees	PCS score			• Compared with never smokers, all smoking groups had worse PCS scores (p ≤0.03) • Among disabled, current smokers—but not former smokers—had worse MCS scores than never smokers (p ≤0.01) • Among elderly, current smokers and more recent quitters had worse MCS scores than never smokers (p <0.01)	Adjusted for age, gender, race, education
		• Disabled • Daily: 29.4 • Some days: 27.5 • Elderly • Daily: 40.4 • Some days: 41.2	• Disabled: • ≤12 months quit: 29.2 • >12 months quit: 29.6 • Elderly • ≤12 months quit: 37.3 • >12 months quit: 40.8	31.8 42.4		
		MCS score				
		• Disabled – Daily: 39.0 – Some days: 40.4 • Elderly – Daily: 51.3 – Some days: 51.3	• Disabled – ≤12 months quit: 43.8 – >12 months quit: 43.9 • Elderly – ≤12 months quit: 49.3 – >12 months quit: 52.8	43.5 53.0		
Borzecki et al. 2005	• 1,242 male veterans • Mean 63 years of age • United States	Regression coefficients for the effect of smoking on PCS score at baseline			• Current smokers did not have statistically significantly worse PCS or MCS than never smokers • Former smokers had worse PCS than never smokers (p <0.05) in the cross-sectional analysis	Adjusted for age, marital status, education, employment, living alone, comorbidity, alcohol use, exercise, BMI, seat belt use, and cholesterol screening
		• Total: -1.40	• Total: -1.52	Ref		
		Regression coefficients for the effect of smoking on MCS score at baseline				
		• Total: -0.49	• Total: 0.84	Ref		

Table 11.4*S* Continued

Study	Design/population	Results: Current smoker	Results: Former smoker	Results: Never smoker	Findings	Comments
Laaksonen et al. 2006	• 8,970 employees of the city of Helsinki • 40–60 years of age	PCS score			• Heavy current smokers had worse PCS and MCS than never smokers • Former smokers and never smokers had similar PCS and MCS	Adjusted for age and occupational class
		• Men – Heavy: 48.9 – Moderate: 50.1 • Women – Heavy: 47.8 – Moderate: 48.8	• Men: 50.5 • Women: 48.6	• Women: 50.7 • Women: 48.6		
		MCS score				
		• Men – Heavy: 50.3 – Moderate: 50.1 • Women – Heavy: 49.4 – Moderate: 51.4	• Men: 52.1 • Women: 51.8	• Men: 52.0 • Women: 52.1		
Strandberg et al. 2008	• 26-year follow-up study of 1,658 White men • Finland	Compared with men who were never smokers in 1974, men who smoked more than 20 cigarettes/day in 1974 had a statistically significantly worse PCS score in 2000; there was a graded deterioration in PCS score with increasing number of cigarettes smoked daily; the relationship between smoking and the MCS score was not statistically significant			• After 26 years of follow-up, heavy smokers had worse PCS than never smokers	Age-adjusted
Sarna et al. 2008	• Nurses' Health Study cohorts • 158,736 women between 29 and 71 years of age	Regression coefficients (SE) for the effects of smoking on PCS			• Current smokers had worse PCS and MCS than never smokers ($p < 0.001$) • Former smokers had worse MCS than never smokers ($p < 0.001$)	Adjusted for age, BMI, physical activity, living alone, and comorbidity
		• Total: -0.55 (0.06)	• Total: -0.08 (0.05)	Ref		
		Regression coefficients (SE) for the effects of smoking on mental component summary score (MCS)				
		• Total: -2.0 (0.07)	• Total: -0.32 (0.05)	Ref		
Pisinger et al. 2009	• 9,322 men and women between 30 and 60 years of age • Denmark	At baseline, PCS score and MCS score were highest in never smokers and lowest in daily smokers			• Smokers had worse PCS and MCS than never smokers ($p < 0.001$)	Adjusted for gender, age, employment status, and length of vocational training

Note: **BMI** = body mass index; **MCS** = mental component summary score; **PCS** = physical component summary score; **SE** = standard error.
[a]Measures of functional health and well-being; higher scores indicate better function.

Table 11.5*S* Studies on the association between smoking and other measures of health and function

Study	Design/population	Results: Current smoker	Results: Former smoker	Results: Never smoker	Findings	Comments
Ostbye et al. 2002	• Health and Retirement Study (845 persons 51–64 years of age) • AHEAD (5,037 persons ≥70 years of age) • Longitudinal studies from 1992/1993–1998 • United States	OR (95% CI) for difficulty walking several blocks • 51–64 years of age – Heavy: 2.37 (2.05–2.74) – Light: 1.68 (1.41–2.00) • ≥70 years of age: – 2.06 (1.69–2.49)	• Time since quit: – <3 years: 2.08 (1.65–2.62) – 3–15 years: 1.34 (1.16–1.56) – >15 years: 1.09 (0.93–1.29) • ≥1.30 (1.15–1.48)	1.0 (ref) 1.0 (ref)	• Current smokers were more likely than never smokers to have difficulty walking a short distance • Former smokers were also more likely to report difficulty, although the effect varied with time since quitting; long-term quitters had a risk that was similar to never smokers	Adjusted for exercise, BMI, alcohol consumption, age, race, gender, marital status, and education
Woods et al. 2005	• 28,181 WHI observational study participants • Women 65–79 years of age and free of frailty at baseline • United States • 3 years of follow-up	OR (95% CI) for incident frailty by baseline smoking status Frailty defined as a score of 3 or higher based on the following: poor-self reported physical function (2 points), exhaustion (1 point), low physical activity (1 point), and unintentional weight loss (1 point) • Total: 2.90 (2.35–3.57)	• Total: 1.12 (1.02–1.23)	1.0 (ref)	• Current and former smokers were more likely than never smokers to develop frailty	Adjusted for age, income, education, ethnicity, BMI, alcohol, hormone therapy, self-reported health, disability, living alone, and comorbid conditions
Heikkinen et al. 2008	• 8,028 persons ≥30 years of age • Mean: 51 years of age among men and 54 among women • Survey conducted 2000–2001 • Finland	Overall quality of life Respondents were asked to rate on a scale of 0 (worst) to 10 (best) how good their present life as a whole had been within the last 30 days • Men daily smokers: 7.35 • Women daily smokers: 7.58	• Men daily smokers: 7.66 • Women daily smokers: 7.67	• Men daily smokers: 7.63 • Women daily smokers: 7.75	• Daily smokers reported worse overall quality of life than never smokers among both men ($p < 0.001$) and women ($p = 0.004$) • Former smokers and never smokers had similar quality of life	Adjusted for age, education, and health-related quality of life
McClave et al. 2009	• BRFSS • 2006 • 17,800 participants in 4 states • ≥18 years of age • United States	OR (95% CI) for life dissatisfaction • Total – Nonquitter: 1.0 (ref) – Unsuccessful quitter: 0.7 (0.4–1.3)	• Total: 0.5 (0.3–0.9)	• Total: 0.4 (0.2–0.7)	• Compared with current smokers who have not recently tried to quit, former smokers and never smokers are less likely to report life dissatisfaction	Adjusted for age, race/ethnicity, gender, education, marital status, employment status, chronic disease, and health care coverage

Table 11.5*S* Continued

Study	Design/population	Results: Current smoker	Results: Former smoker	Results: Never smoker	Findings	Comments
Hardy et al. 2010	• 9,563 community-dwelling Medicare beneficiaries ≥65 years of age	• Current smokers were more likely than never smokers to have difficulty walking ¼ mile or to be unable to walk ¼ mile • Former smokers did not differ statistically significantly from never smokers in their ability to walk a short distance			• Current smokers were more likely than never smokers to have difficulty walking a short distance or to be unable to walk a short distance ($p < 0.05$)	Adjusted for age, gender, race, marital status, income, education, insurance status, chronic conditions, and BMI
Piper et al. 2012	• 1,504 participants in a smoking cessation trial • Average 45 years of age • United States	• During 3 years of follow-up, successful quitters experienced less of a decline in global quality of life than continuing smokers • Mean (SD) change in QOLI total at 3 years was -0.24 (1.40) in quitters and -0.47 (1.40) in continuing smokers			• Smokers who quit reported better quality of life than smokers who did not quit ($p = 0.02$)	
Sabia et al. 2012	• Whitehall II Study • 5,100 men and women 42–63 years of age at baseline • Followed for a median of 16.3 years • Free of cancer, coronary artery disease, and stroke at baseline	OR (95% CI) for successful aging Successful aging defined as good cognitive, physical, respiratory, and cardiovascular functioning, and absence of disability, mental health problems, and chronic disease			• Never smokers were more likely than ever smokers to experience successful aging	Adjusted for alcohol consumption, physical activity, daily consumption of fruits and vegetables, age, gender, education, and marital status
		• Ever-smokers formed the reference group		• Total: 1.29 (1.11–1.49)		

Note: **AHEAD =** Asset and Health Dynamics among the Oldest Old Survey; **BMI** = body mass index; **BRFSS** = Behavioral Risk Factor Surveillance System; **CI** = confidence interval; **MCS** = mental component summary score; **OR** = odds ratio; **QOLI** = Quality of Life Inventory; **SD** = standard deviation; **WHI** = Women's Health Initiative.

Table 11.6*S* Studies on the association between smoking and hospitalizations

Study	Design/population	Results: Current smoker	Results: Former smoker	Results: Never smoker	Findings	Comments
Robbins et al. 2000	• 87,991 men and women serving on active duty in the U.S. Army during 1987–1998 • Average at baseline was 28.5 years of age	Rate ratio (95% CI) for hospitalization not due to injury or pregnancy			• Among both men and women, current and former smokers were more likely to be hospitalized than never smokers	Adjusted for age, race, military rank, alcohol consumption, exercise frequency, and overweight
		• Men: 1.30 (1.24–1.35) • Women: 1.25 (1.14–1.37)	• Men: 1.20 (1.14–1.26) • Women: 1.13 (1.01–1.26)	1.0 (ref) 1.0 (ref)		
Johnson and Richter 2002	• 7,844 adolescents 12–17 years of age • United States	Mean number of overnight hospital stays			• Frequent smokers reported more overnight hospital stays than less frequent smokers, former smokers, or never smokers ($p < 0.01$)	Adjusted for gender, age, and family income
		• Total – 6 or more days/month: 0.22 – 1–5 days/month: 0.04	• Total: 0.05	0.07		
Ostbye et al. 2002	• Health and Retirement Study (7,845 persons 51–64 years of age) • AHEAD (5,037 persons ≥70 years of age) • Longitudinal studies from 1992/1993–1998 • United States	OR (95% CI) for hospitalization in previous year			• Current smokers and more recent quitters were more likely to be hospitalized than never smokers • Long-term quitters (>15 years) and never smokers had a similar likelihood of hospitalization	Adjusted for exercise, BMI, alcohol consumption, age, race, gender, marital status, and education
		• 51–64 years of age – Heavy: 1.41 (1.24–1.59) – Light: 1.35 (1.16–1.56) • ≥70 years of age: – 1.28 (1.08–1.52)	• Time since quit: – <3 years: 1.46 (1.20–1.78) – 3–15 years: 1.22 (1.08–1.38) – >15 years: 0.96 (0.85–1.09) • 1.16 (1.04–1.29)	1.0 (ref) 1.0 (ref)		
Kahende et al. 2009	• NHANES • 1999–2004 • 15,332 adults ≥18 years of age • United States	OR for a hospitalization within the last year			• Current smokers, recent quitters (<2 years), and long-term quitters (≥10 years) were each more likely than never smokers to be hospitalized	Adjusted for gender, race/ethnicity, age, education, poverty level, and health insurance
		• Total: 1.20 (1.06–1.37)	• Total: – <2 years since quit: 2.49 (1.86–3.34) – 2–4 years since quit: 1.39 (0.98–1.97 – 5–9 years since quit: 1.17 (0.86–1.59) – ≥10 years since quit: 1.22 (1.02–1.46)	1.0 (ref)		

Table 11.6*S* Continued

Study	Design/population	Results			Findings	Comments
		Current smoker	Former smoker	Never smoker		
Woodruff et al. 2010	• 5,503 female U.S. Navy recruits • Mean 19.7 years of age at entry	Percent hospitalized; excludes pregnancy-related hospitalizations			• Likelihood of hospitalization did not vary by smoking status • Duration of hospitalization was longest among current smokers	Adjusted for time in service, education, race, and regular/reserve status
		• Daily smoker: 13	• Former or nondaily smoker: 12	• Never smoker: 14		
		Average duration of hospitalization (days)				
		• Daily smoker: 5.7	• Former or nondaily smoker: 5.1	• Never smoker: 5.2		

Note: **AHEAD =** Asset and Health Dynamics among the Oldest Old Survey; **BMI** = body mass index; **CI** = confidence interval; **NHANES** = National Health and Nutrition Examination Survey; **OR** = odds ratio.

Table 11.7*S* Studies on the association between smoking and outpatient visits

Study	Design/population	Results: Current smoker	Results: Former smoker	Results: Never smoker	Findings	Comments
Borzecki et al. 2005	• 1,397 male veterans • United States	Regression coefficient for the effect of smoking on physician visits			• Current smokers had fewer outpatient visits than never smokers ($p < 0.05$)	Adjusted for age, marital status, education, employment, live alone, other insurance, disability, comorbidity, alcohol, exercise, BMI, seat belt use, and cholesterol screening
		Total: -0.30	Total: -0.05	Ref		
Kahende et al. 2009	• NHANES • 1999–2004 • 15,332 adults ≥18 years of age • United States	OR for at least 1 outpatient visit within the last year			• The frequency of at least 1 outpatient visit was similar in current and never smokers • Current smokers and former smokers were more likely than never smokers to have multiple (≥4) outpatient visits • Multiple outpatient visits were most common among recent quitters	Adjusted for gender, race/ethnicity, age, education, poverty level, and health insurance
		• Total: 0.94 (0.81–1.13)	• <2 years since quit: 1.75 (1.15–2.65) • 2–4 years since quit: 1.15 (0.76–1.75) • 5–9 years since quit: 1.47 (0.90–2.40) • ≥10 years since quit: 1.75 (1.42–2.14)	1.0 (ref)		
		OR for 4 or more outpatient visits within the last year				
		• Total: 1.18 (1.06–1.33)	• <2 years since quit: 1.65 (1.29–2.12) • 2–4 years since quit: 1.59 (1.17–2.18) • 5–9 years since quit: 1.34 (1.02–1.74) • ≥10 years since quit: 1.17 (1.04–1.32)	1.0 (ref)		

Note: **BMI** = body mass index; **NHANES** = National Health and Nutrition Examination Survey; **OR** = odds ratio.

Table 11.8*S* Studies on the association between smoking and nursing home stays

Study	Design/population	Results			Findings	Comments
		Current smoker	Former smoker	Never smoker		
Ostbye et al. 2002	• AHEAD (5,037 persons ≥70 years of age) • Longitudinal study from 1993–1998 • United States	OR (95% CI) for stay in a nursing home, convalescent home, or other long-term care health facility in the previous year			• Current smokers were more likely than never smokers to have a stay in a nursing home, convalescent home, or other long-term care facility	Adjusted for exercise, BMI, alcohol consumption, age, race, gender, marital status, and education
		• ≥70 years of age: – 1.68 (1.08–2.63)	• ≥70 years of age: – 1.16 (0.85–1.58)	1.0 (ref)		
Valiyeva et al. 2006	• NHANES I Epidemiologic Follow-up Study (NHEFS) • 6,462 people who were 45–74 years of age at baseline (1971–1975) • Followed until 1992	RR (95% CI) of a nursing home admission			• Current smokers were more likely than people who did not smoke at baseline to be admitted to a nursing home	Adjusted for age, gender, race, BMI, major diagnoses at baseline, physical activity, blood pressure, cholesterol level, and diabetes
		• 45–65 years of age at baseline: – 1.56 (1.23–1.99)	Reference group did not smoke at baseline			
		• 65–74 years of age at baseline: – 1.32 (1.08–1.61)	Reference group did not smoke at baseline			

Note: **AHEAD** = Asset and Health Dynamics among the Oldest Old Survey; **BMI** = body mass index; **CI** = confidence interval; **NHANES** = National Health and Nutrition Examination Survey; **OR** = odds ratio; **RR** = relative risk.

Table 11.9*S* Studies on the association between smoking and costs

Study	Design/population	Results			Findings	Comments
		Current smoker	Former smoker	Never smoker		
CBO 2012	• Medical Expenditure Panel Survey Data for 2000–2008 from the • 1998–2007 from the National Health Interview Survey • ≥18 years of age	Annual per capita spending on health care (in 2008 dollars) for former smokers, by time since quit			• Spending tended to be highest among former smokers followed by current smokers. • Never smokers had the lowest spending in each age group except the oldest	
		• 18–24 years of age: 2,010 • 25–44 years of age: 2,850 • 45–64 years of age: 5,540 • 65–74 years of age: 7,940 • ≥75 years of age: 8,750	• 18–24 years of age: – <5 years: 2000 – 5–14 years: NA – ≥15 years: NA • 25–44 years of age: – <5 years: 3,090 – 5–14 years: 2,920 – ≥15 years: 3,330 • 45–64 years of age: – <5 years: 7,650 – 5–14 years: 6,580 – ≥15 years: 6,290 • 65–74 years of age: – <5 years: 11,250 – 5–14 years: 9,760 – ≥15 years: 9,330 • ≥75 years of age: – <5 years: 15,530 – 5–14 years: 12,280 – ≥15 years: 11,770	1,870 2,570 5,040 7,790 9,810		

Note: **CBO** = Congressional Budget Office; **NA** = not available.

Table 11.10*S* Annual per capita spending on health care, by smoking status and age group (2008 dollars*)

	18–24 years	25–44 years	45–64 years	65–74 years	≥75 years
People who have never smoked	1,870	2,570	5,040	7,790	9,810
Current or former smokers	2,010	2,940	6,170	9,230	11,580
Current smokers	2,010	2,850	5,540	7,940	8,750
Former smokers					
For <5 years	2,000	3,090	7,650	11,250	15,530
For 5–14 years	n.a.	2,920	6,580	9,760	12,280
For ≥15 years	n.a.	3,330	6,290	9,330	11,770

Source: Congressional Budget Office 2012.
Note: **n.a.** = not available (because of a lack of data to produce precise estimates). Based on data for 2000 to 2008 from the Medical Expenditure Panel Survey and for 1998 to 2007 from the National Health Interview Survey.
*The numbers shown here are rounded to the nearest $10.

Table 11.11*S* Studies on the association between smoking and workplace absenteeism (days absent)*

Study	Design/population	Results			Findings	Comments
		Current smoker	Former smoker	Never smoker		
Halpern et al. 2001	• 292 U.S. airline employees • Mean ranged from 37 years of age among never smokers to 44 years of age among former smokers	Mean (SD) absenteeism days caused by sickness during 4-month study period			• Absenteeism varied by smoking status (p = 0.0001)	
		• Total: 3.99 (4.86)	• Total: 2.40 (3.54)	• Total: 1.33 (2.20)		
Tsai et al. 2003	• 2,203 employees of a U.S. chemical and refinery facility • Ages ranged from <30 to >60	Mean number of days lost per employee/year			• Current smokers missed more days than never smokers (p-value NR)	
		• Total: 6.4	• Total: 4.8	• Total: 3.5		
Tsai et al. 2005	• 2,550 regular employees at U.S. petrochemical facility • Average 46 years of age at end of study	Mean number of days lost per employee/year			• Among both men and women, current smokers lost almost twice as many days as never smokers (p <0.05)	
		• Men: 13.3 • Women: 23.3 • Total: 14.3	• Men: 8.7 • Women: 12.5 • Time since quitting – 1–9 years: 11.0 – 10–19 years: 8.8 – ≥20 years: 7.9	• Men: 7.0 • Women: 12.3 • Total: 7.6		

Note: **NR** = not reported; **SD** = standard deviation.
*Absenteeism includes any absence during a specified time period, any short-term absence, any long-term absence, or total days lost.

Table 11.12*S* Studies on the association between smoking and relative risk (RR) of workplace absenteeism*

Study	Design/population	Results			Findings	Comments
		Current smoker	Former smoker	Never smoker		
Morikawa et al. 2004	• 2,504 male Japanese factory workers, 35–55 years of age • 6,290 male British civil service workers, 35–55 years of age	HR (95% CI) for first long-term (>7 days) sickness absence			• Current and former smokers were each more likely than never smokers to have a long-term sickness absence	Age-adjusted
		• Japan: 1.43 (1.17–1.75) • Britain: 1.51 (1.35–1.67)	• Japan: 1.39 (1.07–1.80) • Britain: 1.11 (1.02–1.21)	1.0 (ref) 1.0 (ref)		
Sindelar et al. 2005	• 383,778 full-time U.S. workers • 18–64 years of age	OR for absence in the last week			• Current and former smokers were each more likely than never smokers to have an absence (p = 0.000 for each group) • Although risk of an absence appeared to be highest among recent quitters, each group of former smokers was more likely than never smokers to have an absence (p <0.05 for each group)	Adjusted for age, education, race, ethnicity, marital status, number of children, occupation, industry, metropolitan statistical area, state, and month and year
Labriola et al. 2006	• 3,792 Danish employees • 18–64 years of age at start of study	OR for >6 days of absence of previous year			• Current and former smokers were each more likely than never smokers to have more than 6 days of absence in the previous year	Adjusted for age, gender, health status, BMI, and employer and job characteristics
		• Total: 1.61 (1.32–1.96)	• Total: 1.32 (1.03–1.68)	1.0 (ref)		
Christensen et al. 2007	• 5,020 Danish employees • 18–69 years of age	HR for long-term sickness absence (8 consecutive weeks)			• Among current smokers, only heavy smoking significantly increased risk of long-term absence • Former smoking increased risk of a long-term absence among women only	Adjusted for age, family status, SES, education, work environment, and diagnosed disease; adjustment for diagnosed disease may lead to underestimation of the smoking effect
		• Men – ≥15 cigarettes: 1.55 (1.00–2.40) – <15 cigarettes: 0.92 (0.50–1.73)	• Men: 1.36 (0.85–2.19)	1.0 (ref)		
		• Women – ≥15 cigarettes: 2.05 (1.36–3.08) – <15 cigarettes: 1.21 (0.74–1.98)	• Women: 1.61 (1.07–2.42)	1.0 (ref)		

Table 11.12*S* Continued

Study	Design/population	Results: Current smoker	Results: Former smoker	Results: Never smoker	Findings	Comments
Laaksonen et al. 2009	• 5,470 female and 1,464 male Finnish city employees • 40–60 years of age	RR for 1–3 day sickness absence			• Heavy current smoking increased the risk of both short- and longer-term absences in men and women • Lighter current smoking was linked with short-term absences in women, and with longer-term absences in men and women • The increase in absences among former smokers was only statistically significant in women	Adjusted for age and occupational class
		• Men – >20 cigarettes: 1.71 (1.39–2.11) – ≤20 cigarettes: 1.63 (1.34–1.98)	• Men: 1.12 (0.94 to 1.33)	1.0 (ref)		
		• Women – >20 cigarettes: 1.50 (1.37–1.64) – ≤20 cigarettes: 1.23 (1.13–1.34)	• Women: 1.18 (1.10–1.27)	1.0 (ref)		
		RR for ≥4 day sickness absence				
		• Men – >20 cigarettes: 1.66 (1.31–2.10) – ≤20 cigarettes: 1.23 (0.96–1.57)	• Men: 1.10 (0.90–1.34)	1.0 (ref)		
		• Women: – >20 cigarettes: 1.49 (1.34–1.65) – ≤20 cigarettes: 1.32 (1.20–1.46)	• Women: 1.18 (1.08–1.29)	1.0 (ref)		

Note: **BMI** = body mass index; **CI** = confidence interval; **HR** = hazard ratio; **OR** = odds ratio; **SES** = socioeconomic status.
*Absenteeism includes any absence during a specified time period, any short-term absence, any long-term absence, or total days lost.