HHS Public Access

Author manuscript

*Breast Cancer Res Treat*. Author manuscript; available in PMC 2023 October 01.

Published in final edited form as:

*Breast Cancer Res Treat*. 2022 October ; 195(3): 353–366. doi:10.1007/s10549-022-06675-4.

# Lifetime personal cigarette smoking and risk of young-onset breast cancer by subtype among non-Hispanic Black and White women in the Young Women's Health History Study

**Ugonna Ihenacho**[1], **Ann S. Hamilton**[1], **Wendy J. Mack**[1], **Anna H. Wu**[1], **Jennifer B. Unger**[1], **Dorothy R. Pathak**[2], **Kelly A. Hirko**[2], **Richard T. Houang**[3], **Michael F. Press**[4], **Kendra L. Schwartz**[5,6], **Lydia R. Marcus**[7], **Ellen M. Velie**[7,8,*]

[1]Department of Population and Public Health Sciences, Keck School of Medicine, University of Southern California, Los Angeles, California, United States

[2]Department of Epidemiology and Biostatistics, College of Human Medicine, Michigan State University, East Lansing, Michigan, United States

[3]Center for the Study of Curriculum, College of Education, Michigan State University, East Lansing, Michigan, United States

[4]Department of Pathology, Keck School of Medicine, University of Southern California, Los Angeles, CA, United States

[5]Department of Family Medicine and Public Health Sciences, School of Medicine, Barbara Ann Karmanos Cancer Institute, Detroit, Michigan, United States

[6]Wayne State University, Detroit, Michigan, United States

[*]Address for correspondence and reprint requests: Ugonna Ihenacho, PhD, MPH; ihenacho@usc.edu.

*Author Contributions:* Dr. Ugonna Ihenacho, Dr. Ann S. Hamilton, and Dr. Ellen M. Velie developed the research concept and aims and acquired funding. Dr. Ihenacho conducted the formal analysis and wrote the original draft. Dr. Velie designed the original study. Dr. Velie and Dr. Hamilton oversaw data collection, provided supervision of the current analysis, contributed to the interpretation of analyses, and contributed to writing the original draft. Dr. Wendy J. Mack provided supervision and contributed to the formal analysis and interpretation of the current analysis. Dr. Dorothy R. Pathak contributed to designing the original study and data collection efforts, to the interpretation of the current analysis, and to the writing of the original draft. Dr. Kelly A. Hirko and Dr. Richard T. Houang contributed to the interpretation of the analysis. Dr. Kendra L. Schwartz oversaw data collection. Ms. Lydia R. Marcus contributed to the preparation of data for analysis. Dr. Anna H. Wu, Dr. Jennifer B. Unger and Dr. Michael F. Press all provided supervision and contributed to the interpretation of the analysis. All authors reviewed and edited previous versions of the manuscript. All authors read and approved the final manuscript.

*Competing Interests:* M.F.P. has a consulting or advisory role with AstraZeneca, Biocartis SA, Cepheid, Eli Lilly & Company, Merck & Company, Puma Biotechnology, and Zymeworks, He also has a private equity role with TORL Biotherapeutics LLC. All other authors have no relevant financial or non-financial interests to disclose. The authors have no relevant financial or non-financial interests to disclose.

*Ethics Approval:* This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by institutional review boards at the University of Wisconsin–Milwaukee, Michigan State University, the University of Southern California, the California Committee for the Protection of Human Subjects, Wayne State University, and the Michigan Department of Community Health. The Medical College of Wisconsin IRB deferred to the University of Wisconsin–Milwaukee IRB. The California Cancer Registry also reviewed and approved the study.

*Consent to Participate:* Written informed consent was obtained from all individual participants included in the study.

*Consent to Publish:* All participants included in the final YWHHS sample consented to having their data published in scientific publications.

[7]Joseph J. Zilber School of Public Health, University of Wisconsin-Milwaukee, Milwaukee, Wisconsin, United States

[8]Departments of Medicine and Pathology, Medical College of Wisconsin, Milwaukee, Wisconsin, United States.

## Abstract

**Purpose—**To evaluate the association between lifetime personal cigarette smoking and young-onset breast cancer (YOBC; diagnosed <50 years of age) risk overall and by breast cancer (BC) subtype, and whether risk varies by race or socioeconomic position (SEP).

**Methods—**Data are from the Young Women's Health History Study (YWHHS), a population-based case-control study of non-Hispanic Black (NHB) and White (NHW) women, ages 20–49 years (n=1,812 cases, n=1,381 controls) in the Los Angeles County and Metropolitan Detroit Surveillance, Epidemiology, and End Results (SEER) registry areas, 2010–2015. Lifetime personal cigarette smoking characteristics and YOBC risk by subtype were examined using sample-weighted, multivariable-adjusted polytomous logistic regression.

**Results—**YOBC risk associated with ever versus never smoking differed by subtype ($P_{heterogeneity}$=0.01) with risk significantly increased for Luminal A (adjusted odds ratio [aOR] 1.34; 95% confidence interval [CI] 1.06–1.68) and HER2-type (aOR 1.97; 95% CI 1.23–3.16), and no association with Luminal B or Triple Negative subtypes. Additionally, ≥30 years since smoking initiation (versus never) was statistically significantly associated with an increased risk of Luminal A (aOR 1.55; 95% CI 1.07–2.26) and HER2-type YOBC (aOR 2.77; 95% CI 1.32–5.79), but not other subtypes. Also, among parous women, smoking initiated before first full-term pregnancy (versus never) was significantly associated with an increased risk of Luminal A YOBC (aOR 1.45; 95% CI 1.11–1.89). We observed little evidence for interactions by race and SEP.

**Conclusion—**Findings confirm prior reports of a positive association between cigarette smoking and Luminal A YOBC and identify a novel association between smoking and HER2-type YOBC.

### Keywords

Breast neoplasms; cigarette smoking; young-onset breast cancer; pre-menopause; molecular subtype; health status disparities

## INTRODUCTION

Breast cancer (BC) is the most commonly diagnosed cancer among young women (<50 years) with an annual incidence in the United States (US) of 73.2 per 100,000 persons and a five-year average annual percent increase among young women of 0.5% per year from 2011–2015 [1,2]. Breast cancer etiology differs by molecular subtypes that are categorized by estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) status, and tumor grade [3]. Some evidence suggests lifetime personal cigarette smoking is associated with an increased risk of both pre- and post-menopausal BC [4–8], but it is unclear whether the association differs by tumor subtype, particularly among young women.

Racial and socioeconomic disparities in BC incidence also persist in the US [2,9–14]. Among young women (<50 years of age), non-Hispanic White (NHW) women have the highest incidence of Luminal A BC, the subtype associated with the highest survival, with an annual incidence of 44.3 per 100,000 compared to 35.8 among non-Hispanic Black [NHB] women in 2011–2013 [15]. Conversely, young NHB women have the highest incidence of TNBC, which has the poorest prognosis, with an annual incidence of 17.5 per 100,000 compared to 9.3 among NHW women in 2011–2013 [15]. Research has also shown that increased socioeconomic position (SEP) is associated with increased risk for hormone receptor positive (HR+) BC with the inverse potentially true for the more aggressive HR- BC subtypes [16,17]. Little research has evaluated whether associations between lifetime personal cigarette smoking and BC risk, overall and by tumor subtypes, vary by race or SEP.

In studies of younger women, the association between personal cigarette smoking and BC risk was not observed in several early studies [18–21], whereas several recent studies observed an association [4,5,7,8,22]. In the Nurses' Health Study (NHS), current (versus never) cigarette smoking was not associated with BC risk among young women, but smoking for 20+ years was associated with an increased risk of ER+ BC [22]. The Black Women's Health Study (BWHS) and African American Breast Cancer Epidemiology and Risk Consortium (AMBER) evaluated these associations among young black women in the US [7,23]. BWHS observed a 70% increase in premenopausal BC risk among women who initiated smoking before age 18 and smoked at least 20 pack-years compared to those who never smoked [7]. Conversely, the AMBER study observed a 20% decreased BC risk among premenopausal women who currently smoked with no differences in risk by ER status [23]. These studies did not examine BC risk associated with personal cigarette smoking by race or SEP among young women, as we are able to in the current analysis with our racially and socioeconomically diverse study population [6,7,24,25].

Thus, in this study we investigated the hypothesis that lifetime personal cigarette smoking is associated with an increased risk of young-onset BC (YOBC; diagnosed before age 50 years) and that tumor subtype differences may exist in a socioeconomically diverse population-based study of young NHB and NHW women. We further examined whether smoking-related YOBC risk is modified by race or SEP.

## METHODS

### Study population of cases and controls

Data are from a population-based case-control study of YOBC, the Young Women's Health History Study (YWHHS). A detailed description of the study was previously published [26]. Briefly, eligible participants included US-born residents of Los Angeles County (LA) or the tri-county (Oakland, Wayne and Macomb Counties) Metropolitan Detroit area (Detroit) who self-identified as female, NHB or NHW and were 20–49 years of age at the reference date. The reference date refers to the date of histologically confirmed BC diagnosis for cases and the date four months before the screening interview for controls.

Cases were identified from rapid case ascertainment protocols, which identify cases diagnosed within 3–6 months of diagnosis via pathology report screening methods [27],

as provided by the LA and Detroit Surveillance, Epidemiology, and End Results (SEER) registries. Women diagnosed with histologically confirmed incident, invasive, primary BC between 2010–2015 and who met the demographic criteria were eligible. In total, 1,812 women with invasive YOBC (n=1,130 NHW, n=682 NHB) completed an in-person interview (response rate 60%) [26].

Area-based controls were sampled from postal addresses based on the 2010 US Census and were frequency matched to cases on race, study region, and five-year age group; >24,000 households were identified and contacted through three-stage sampling [26]. In total, 1,381 control women (n=716 NHW, n=665 NHB) completed the study interview (response rate 53%) [26].

Overall, response rates were higher for NHB women than NHW women and for women in LA versus Detroit but did not differ significantly by age [26]. All analyses utilized sample weights, which account for the sampling design and adjust for non-response; for control-only analyses, results were weighted to their populations based on the 2010 US Census [26].

Institutional review boards (IRB) at the University of Wisconsin–Milwaukee (UWM), Michigan State University, the University of Southern California, the California Committee for the Protection of Human Subjects, Wayne State University, the Karmanos Cancer Center, and the Michigan Department of Community Health approved the study. The study was also approved by the California Cancer Registry. The Medical College of Wisconsin IRB deferred to the UWM IRB. Informed consent was obtained from all participants.

### Tumor subtyping

Tumor subtypes were derived from pathology information provided to SEER registries on HR status (ER/PR), HER2 status, and tumor grade. Molecular subtypes were categorized as Luminal A (ER/PR+, HER2−, grade 1/2), Luminal B (ER/PR+, HER2+, any grade or ER/PR+, HER2−, grade 3+), HER2-type (ER−, PR−, HER2+), and TNBC (ER−, PR−, HER2−) [3,28].

### Smoking exposure variables

Exposure and covariate information was ascertained from in-person interviews. Lifetime personal cigarette smoking histories were obtained from questions about cigarette smoking status, average number of cigarettes smoked per day (CPD), periods of smoking cessation, and age at initiation. Smoking exposure definitions were based on the distribution of smoking among control participants or guided by categories used in the existing literature to allow comparison across studies [6,7,23,29,30]. Ever smoking was defined as having ever smoked ≥1 cigarette a day for ≥6 months. Personal smoking status was described as formerly smoked and currently smoke. Participants who reported smoking cessation ≤1 year before the study reference date were designated as currently smoke (n=73). Time since quitting was defined among women who formerly smoked as >1 but <10 years since quitting, and ≥10 years before reference date. Cut point of 10 years was chosen based on the median value among controls. We categorized the average number of lifetime CPD as <5, 5–19, ≥20 CPD. Lifetime smoking intensity in pack-years was calculated by dividing CPD

by 20 cigarettes/pack and multiplied by years of smoking history and then categorized as <5, 5–19, ≥20 pack-years. We categorized age at smoking initiation as <18, 18–24, ≥25 years and time since smoking initiated as <20, 20–29, ≥30 years. Lastly, we evaluated the timing of smoking initiation in relation to first full-term pregnancy (FFTP) among parous women and categorized it as initiated after FFTP, initiated before FFTP. Each smoking exposure used a reference category of "never smoked."

## Covariates

Covariates included sociodemographic characteristics and potential BC risk factors. Sociodemographic characteristics included age at reference date (20–29, 30–39, 40–49 years), residence in LA/Detroit, race/ethnicity (NHW, NHB), highest attained education (high school diploma or less; vocational school, associate's degree, or some college; bachelor's degree or higher), and SEP assessed by household percent poverty (HHP) in the 12 months before reference date. HHP of the federal poverty level (FPL) was calculated from self-reported gross income 12 months before reference date and the number of household members supported by that income and categorized as ≥200% of FPL, <200% of FPL [31,32]. Potential BC risk factors included first-degree family history of BC (no, yes, unknown), age at menarche (≤11, 12, 13, ≥14 years), lifetime cumulative alcohol use (0 – Abstainers, 0.1–6.9, 7–13.9, 14–27.9, ≥28 grams/day), body mass index (BMI; underweight, normal, overweight, obese; calculated from weight 12 months before reference date in kilograms/height in meters squared [$kg/m^2$]), menopausal status (premenopausal, peri-/post-menopausal), and combined parity and age at FFTP (nulliparous, 1–2 children and <25 years, 1–2 children and ≥25, 3+ children and <25 years, 3+ children and ≥25) [28,33,34].

A summary of the demographic characteristics of the YWHHS participants by case-control status has been previously published [26]. In evaluating potential covariates to include in analyses, we also evaluated their potential association with BC status and the following covariates were associated with BC status ($p<0.05$): HHP, BMI within 12 months of reference date, joint parity/age at FFTP, first-degree family history of BC, and cumulative lifetime alcohol use [26].

## Statistical analysis

Distributions of participant sociodemographic characteristics and BC risk factors with personal cigarette smoking status were reported as percentages or means with statistical comparisons evaluated by chi-square tests for categorical variables and the Wald tests for continuous variables [35]. The relative risk of YOBC, overall and by BC subtype, was estimated by the odds ratio in crude and multivariable-adjusted models [36]. Multivariable logistic regression was used to estimate adjusted odds ratios (aOR) and 95% confidence intervals (CI) for the association between lifetime personal cigarette smoking characteristics and YOBC risk overall and with polytomous logistic regression for associations by BC subtype.

Multivariable models were adjusted for study site, age, HHP, family history of BC, BMI, alcohol use, joint parity/age at FFTP, and menopausal status based on assessments for

confounding (15% change in OR) with ever smoking status and overall BC status or based on prior evidence of an association with BC. The Wald test was employed to assess heterogeneity in the OR estimates by BC subtypes. Analyses were also stratified by race (NHB and NHW) and SEP (HHP ≥200% and <200% of FPL); cross-product interaction terms of smoking exposures by each stratum (by race and by SEP, separately) were evaluated by the Wald test.

Smoking status was missing for 18 participants (14 cases and 4 controls) who were excluded from all analyses. Tumor subtype information was missing for 130 case participants who were excluded from subtype analyses. For each covariate in multivariable models, values were imputed for missing data [26] except first-degree family history of BC, where values for missing and "don't know" were combined as "unknown" (n=38).

In sensitivity analyses, we assessed two alternative models that would evaluate the effect of BMI on the association between ever smoking and personal smoking status with YOBC risk. Since BMI may mediate the association between smoking and YOBC [37], we conducted analysis with and without adjustment for BMI, and also evaluated the association between ever smoking and YOBC risk stratified by BMI (<25 and ≥25 $kg/m^2$).

All tests for significance were two-sided. We utilized sample weights to conduct weighted analyses in all assessments. Statistical interactions were assessed at a significance level of $P<0.10$ and all other tests at $P<0.05$ [38]. Analyses were conducted using Stata version 15.1 (StataCorp LLC, College Station, TX).

## RESULTS

The demographic characteristics of never, formerly, and current smoking among controls (n=1,381) are presented in Table 1. Among the sociodemographic variables, study region, age at reference year, race, HHP and education were significantly associated with smoking status ($p<0.05$). Women from LA County, younger participants (20–29 years), NHB, those with higher SEP (HHP ≥200% of FPL), and women with a bachelor's degree or higher had a higher proportion of never smoking compared to their respective counterparts. Among potential confounders, those who were premenopausal, abstained from alcohol use or were light drinkers had higher proportions of never smoking. Nulliparous participants and those with parity of 3+ and age FFTP ≥25 years were more likely to have never smoked compared to others.

Table 2 presents a summary of cigarette smoking characteristics for controls (n=1,377), all cases (n=1,798), and cases by BC subtype (n=1,670). Age at smoking initiation was significantly associated with BC status ($P=0.04$); compared to controls, a higher proportion of cases had initiated smoking at ages under 18 years or at ages ≥25 years (22.5% vs. 20.2% and 4.1% vs. 2.7%, respectively). Smoking differed significantly by BC subtype for multiple smoking characteristics: personal smoking status, age at smoking initiation, time since smoking initiated, and smoking initiation in relation to FFTP ($P\leq0.01$ for each). The highest proportions of elevated (or long-term) smoking exposure were consistently observed among cases with HER2-type YOBC.

In multivariable adjusted models, we observed a positive, significant association between ever vs. never smoking and overall YOBC risk (aOR 1.20; 95% CI 1.00–1.44) (Table 3), and also found significant heterogeneity in the association between ever smoking and YOBC risk by BC subtype ($P_{heterogeneity}$=0.01). For ever smoking compared to never smoking, we observed a significantly increased risk of Luminal A YOBC (aOR 1.34; 95% CI 1.06–1.68) and HER2-type YOBC (aOR 1.97; 95% CI 1.23–3.16), but no associations with Luminal B (aOR 1.04; 95% CI 0.78–1.39) or TNBC subtypes (aOR 0.92; 95% CI 0.68–1.25). When ever smoking was broken down by current and former status, current smoking remained statistically significantly associated with Luminal A subtype (aOR 1.36; 95% CI 1.02–1.81), while former smoking did not reach statistical significance (aOR 1.33; 95% CI 0.98–1.71). For HER2-type YOBC, the association with former smoking remained statistically significant (aOR 2.41; 95% CI 1.45–4.01), while current smoking was of similar magnitude as the Luminal A subtype, however, did not reach statistical significance (aOR 1.58; 95% CI 0.84–2.99).

Risk of HER2-type YOBC increased with each increasing category of lifetime CPD and pack-years of smoking. Older age at smoking initiation (≥25 years vs. never smoked) was associated with about a two-fold increased risk for overall YOBC (aOR 1.91; 95% CI 1.24–2.96), for Luminal A (aOR 2.25; 95% CI 1.32–3.84), and for TN YOBC (aOR 1.94; 95% CI 1.03–3.64) (Table 3). A young age at smoking initiation (<18 years vs. never smoked) was positively associated with risk of HER2-type YOBC (aOR 2.36; 95% CI 1.36–4.09). For time since smoking was initiated, risk of Luminal A YOBC consistently increased with increasing time. For HER2 type, the increase was significant for those who initiated <20 years ago and those who initiated ≥30 years ago. Among women who initiated smoking before their FFTP, compared to never smoking, there was a significant increase in risk for YOBC overall (aOR 1.25; 95% CI 1.02–1.54), for Luminal A subtype (aOR 1.45; 95% CI 1.11–1.89) and an increased, however not reaching statistical significance association for HER2 subtype (aOR 1.79; 95% CI 0.99–3.25).

In models stratified by race, ever (vs. never) smoking was associated with increased overall YOBC risk in NHW women (aOR 1.39; 95% CI 1.06–1.82), but not in NHB women (aOR 0.96; 95% CI 0.70–1.31) (Table 4). Among NHW women, a significantly increased overall YOBC risk was observed for both, former smoking (aOR 1.40; 95% CI 1.02–1.93), and current smoking (aOR 1.38; 95% CI 1.0–1. 90). Among NHW women, an increased risk was also observed for initiating smoking before age 18 years (aOR 1.60; 95% CI 1.18–2.17), for time since smoking was initiated for ≥30 years (aOR 1.78; 95% CI 1.18–2.70), and for smoking initiated before first full term pregnancy (aOR 1.47; 95% CI 1.08–2.00). There was no evidence for statistical interactions of the above associations by race ($P_{interaction}$>0.17 for each). On the other hand, we did observe a possible interaction of lifetime smoking pack-years with overall YOBC risk by race ($P_{interaction}$=0.09). Lifetime smoking pack-years (compared to never smoking) was associated with an increased risk of overall YOBC among NHW women, which reached statistical significance only for the 5–19 lifetime pack years, (aOR 1.72; 95% CI 1.18–2.17). Such pattern was not observed for NHB women – though risk was nonsignificantly increased in NHB women who smoked ≥20 pack-years (aOR 1.44; 95% CI 0.73–2.84).

In models stratified by SEP (HHP ≥200% and <200% of FPL) we observed a possible interaction in personal smoking status (current, former vs. never) and overall YOBC risk ($P_{interaction}$=0.07) (Table 4). Among women with lower SEP (HHP <200% FPL), risk of overall YOBC was increased for women that had formerly vs. never smoked (aOR 1.80; 95 % CI 1.08–3.01). Conversely, within the group with higher SEP (HHP ≥200% FPL), comparing current vs. never smoked, we observed an increased risk of overall YOBC (aOR 1.46; 95% CI 1.01–2.12).

In our additional analyses stratified by adult BMI, the highest risk of HER2-type YOBC was observed among women who ever (versus never) smoked with a BMI <25 kg/m$^2$ (aOR 2.20; 95% CI 1.15–4.22). In sensitivity analyses, aORs were little changed and almost all were slightly lower in models without adjusting for BMI (data not shown).

## DISCUSSION

In this large population-based study of YOBC, we found that various aspects of personal cigarette smoking, including ever smoking, increased intensity of smoking (CPD), increased pack-years of smoking, and longer duration since smoking initiated and before FFTP, were associated with an increased risk for YOBC overall, Luminal A and HER2-type YOBC. Ever vs. never smoking was associated with 34% increased odds of Luminal A BC and 97% increased odds of HER2-type BC. We also observed little evidence for interactions by race and SEP, however, ever (versus never) smoking was significantly associated with an increased risk of overall YOBC among NHW, but not among NHB women – potentially because of the low prevalence of smoking among NHB women. Also, some differences in the association between smoking and YOBC risk by SEP were observed where risk associated with formerly (versus never) smoking was significant only for poorer (HHP <200% FPL) women and risk associated with currently smoking was significant only for wealthier (HHP ≥200% FPL) women.

Previous studies have evaluated the association between smoking and BC risk by subtype among women of all ages, and many, as we did, have identified a positive association between smoking and risk of Luminal A or HR+ BC [6,22,23,39–44]. Risk for BC in relation to several risk factors has been shown to vary by age or menopausal status, and given the different hormonal milieu, may also vary for smoking status [45–47]. Few studies with information on tumor subtypes have reported associations between personal cigarette smoking and BC risk among younger or premenopausal women [22,23,42,43]. Our finding of a 45% increased odds for Luminal A BC (all ER+ tumors) associated with smoking prior to FFTP was consistent with a similar study in the Seattle area of young women (<45 years of age) that reported a 40% increased odds of ER+ BC with smoking initiated before FFTP [42]. Similar to the Seattle study, we did not observe a consistently increasing risk with increasing lifetime-pack-years for overall BC risk, although we did observe increased risk for the category of 5–19 pack years for overall and Luminal A YOBC [42]. We also observed increased risk for lifetime pack-years of <5 and ≥20 for HER2 type BC. The Seattle study did not include assessment of HER2-type YOBC. Findings in our study are also consistent with two case-control studies comparing smoking to never smoking that observed about a 30%–170% increased odds of YOBC [42,43].

Our observation that ever smoking was associated with a 97% higher odds of HER2-type YOBC is novel. Three previous BC studies have evaluated personal cigarette smoking and risk of HER2-subtype, and none reported a positive association between smoking and HER2-subtype in any age group [48–50]. Two of these other studies, however, were case-only studies comparing risk in HER2 type to Luminal A or ER+ BC and we observed that both groups were at increased risk relative to our controls unaffected by BC. Also, the other study was a case-control study of only women ages 50–69 years and risk may differ with our population of only women <50 years of age. Inclusion of HER2-type BC in population-based epidemiologic studies is still a relatively new and evolving field as HER2 protein expression was often underreported in the pathology reports of cases diagnosed before 2005 and routine reporting of HER2 status was not available in SEER cancer registries until 2010 [2,51].

Our finding of a significant positive association between former smoking and HER2-type YOBC risk was unexpected but may be explicable through BMI's known association with smoking [52,53]. Smoking is associated with lower BMI and studies have shown that HER2-type YOBC may be more common among women with normal vs. obese BMI [54]. Within our subgroup analysis, ever smoking was associated with the highest risk for HER2-type YOBC among women with a BMI <25 $kg/m^2$. The association between smoking and HER2-type YOBC risk warrants further evaluation with consideration of lower BMI as a possible explanation for the association. As more studies have information on HER2-type BC status these hypotheses can be investigated further.

We did not observe strong evidence of a statistical interaction for several smoking characteristics by race or SEP. Many of the characteristics had a trend for increased risk among NHW, but not NHB participants. Higher rates of smoking among NHW women, and its association with Luminal A BC may be contributing to this observation of an association of smoking only among NHW women [15,55,56]. We also observed a suggested difference in personal smoking status (former, current vs. never) by SEP where for most characteristics the magnitude of the association was higher among women with a higher SEP (HHP ≥200% FPL), although a significant statistical interaction was not observed. Given sample size and the lower prevalence of smoking, particularly among NHB women, we may have been underpowered to detect significant associations in each subgroup of stratified analyses.

The public health significance of smoking is well established, but evidence for an association between smoking and BC in young women is still developing [57,58]. Heavy smoking is associated with increased androgen levels among premenopausal and postmenopausal women and with increased estradiol levels among postmenopausal women [45,46]. One primary proposed biologic pathway for smoking to affect BC carcinogenesis is through impaired hormone receptor binding [57]. Since ER+ and PR+ BC subtypes are hormone dependent, there may be factors affecting hormone levels or receptor binding at play [47,57,59]. A second potential mechanism is via the formation of deoxyribonucleic acid (DNA) adducts, which may contribute to unregulated cell growth or carcinogenic proliferation [57]. The increased risk of HER2-type BC associated with personal cigarette smoking may involve the formation of smoking-related DNA adducts that contribute to the mutation and over-expression of the HER2 protein, leading to impaired tumor suppression

and carcinogenesis [57]. Previous studies, such as the Long Island Breast Cancer Study, identified a positive association between smoking and DNA adduct formation in normal breast tissues [60]. A Spanish follow-up study found a 60% increased risk of BC with increasing DNA adduct concentration in white blood cells (relative risk [RR] 1.61; 95% CI 1.29–2.01) [61]. Additionally, these investigators also detected a significant interaction with smoking such that the RR associated with an effect of DNA adducts on BC risk among former and current smokers compared to never smokers were 2.89 (95% CI 1.42–5.86) and 2.19 (95% CI 1.22–3.93), respectively [61]. ER status was evaluated in this Spanish study, but HER2 status was not considered [61]. Except for smoking initiation after FFTP, we observed suggestive and statistically significant positive associations between various indicators of smoking exposure with HER2-type BC ranging from aORs of about 1.40 to 3.40. Additional studies are needed with an evaluation of the association between DNA adduct concentration and BC risk among populations that include women with YOBC and with assessments by subtype, including HER2-type BC.

This study had many strengths. Bias in assessing cancer diagnoses was minimized by using the population-based SEER registry for case ascertainment and for BC subtyping. Additionally, the area-based sampling approach utilized to identify and recruit a population-based sample of controls reduces risk of selection bias, particularly given that sample weights were applied to account for sampling and nonresponse bias. The study included a large population-based sample of NHB women who were underrepresented in previous studies and was able to evaluate risk by SEP. Also, only one other study has explored the association between smoking and HER2-type BC subtype in young women – and the study was a case-only analysis [49].

Limitations include concerns about differential misclassification of exposures that may occur in a case-control study based on self-reported recall. However, in-home interviews conducted with life history calendar memory prompts and interviewer quality control measures were applied equally to cases and controls to prompt memory and minimize recall bias [26]. Also, participants who had quit smoking ≤1 year of the reference date were captured as currently smoking to minimize differential misclassification of smoking potentially associated with health concerns related to a subsequent diagnosis of YOBC. Another limitation is a lack of information on other combustible tobacco products and e-cigarette use, which could underestimate the true association. We do not expect this to have meaningfully impacted our results, however, because of the low prevalence of other combustible tobacco products and e-cigarette use reported in national surveys conducted in similar time periods; in 2009–2010, 3.1% of women ages 18+ years used cigar, cigarillo, or small cigars [62], and in 2013–2014, only 1.5% of women ages 18–44 years used e-cigarettes exclusively and 6.1% used both e-cigarette and cigarettes [63]. Last, as in all observational studies, unmeasured confounding may contribute to observed findings, but all known BC risk factors were adjusted for in analyses [64].

Another potential limitation could be that multiple models were used to examine associations of interest based on a priori hypotheses related to risk of BC by subtype, race, and SEP, which contributed to small cell counts; this stratification, particularly given a lower prevalence of smoking exposures, may have reduced the power to detect an association [65].

For example, despite the large sample of NHB women included in this study, given the prevalence of smoking is lower among NHB, in models stratified by race we had reduced power to observe a significant effect. Still the consistency of the results is suggestive of an association that warrants further evaluation in larger studies or in populations with a higher prevalence of lifetime cigarette smoking. These findings may also not be generalizable to women living outside of LA County and Metropolitan Detroit (Oakland, Wayne and Macomb counties), however both regions include populations residing in urban, suburban and rural areas that are likely to be representative of other regions in the US [66]. Last, as in all observational studies, unmeasured confounding may contribute to some bias in the results [64].

Our results indicate several characteristics of personal cigarette smoking were associated with an increased risk for YOBC. Further research to confirm these findings and to understand potential biological mechanisms for an increased risk of smoking and Luminal A and HER2-type YOBCs is warranted. Our results suggest that as new combustible tobacco products are developed, particularly targeted to younger populations, future studies are strongly needed to investigate associations between the use of these tobacco products and YOBC risk. In sum, based on these findings and consistent with other studies, efforts to prevent smoking initiation and encourage smoking cessation early in life are necessary to reduce the risk of adverse health outcomes, including YOBC.

## ACKNOWLEDGEMENTS

This work was supported by the National Cancer Institute (grant R01CA136861 to E.M.V.); the Tobacco-Related Disease Research Grants Program Office of the University of California (grant T29DT0375 to U.I.); the Breast Cancer Research Foundation, (grant BCRF-19-132 and BCRF-20-132 to M.F.P.); the Tower Cancer Research Foundation (006886-0001 to M.F.P.); and a gift from Dr. Richard Balch (to M.F.P.). The collection of cancer incidence data from California used in this study was supported by the California Department of Public Health pursuant to California Health and Safety Code Sect. 103885; Centers for Disease Control and Prevention's (CDC) National Program of Cancer Registries, under cooperative agreement 5NU58DP006344; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contract HHSN2612018000032I awarded to the University of California, San Francisco, contract HHSN261201800015I awarded to the University of Southern California, and contract HHSN261201800009I awarded to the Public Health Institute. The ideas and opinions expressed herein are those of the authors and do not necessarily reflect the opinions of the funders or their contractors and subcontractors. We thank Mr. Darek Lucas for his data management support and Ms. Denise Modjeski for her administrative support in this research.

## Data Availability Statement:

The datasets generated and/or analyzed for this study are not publicly available because main study findings are in process of being analyzed but are available from the corresponding author on reasonable request.

## Abbreviations:

| | |
|---|---|
| **AMBER** | African American Breast Cancer Epidemiology and Risk Consortium |
| **aOR** | adjusted odds ratio |
| **BC** | breast cancer |
| **BMI** | body mass index |

| | |
|---|---|
| **BWHS** | Black Women's Health Study |
| **CI** | confidence interval |
| **CPD** | cigarettes per day |
| **Detroit** | Metropolitan Detroit |
| **ER** | estrogen receptor |
| **FFTP** | first full-term pregnancy |
| **FPL** | federal poverty level |
| **HER2** | human epidermal growth factor receptor 2 |
| **het** | heterogeneity |
| **HHP** | household poverty level |
| **HR** | hormone receptor |
| **int** | interaction |
| **IRB** | institutional review board |
| **kg/m$^2$** | kilograms per meters squared |
| **LA** | Los Angeles County |
| **NHB** | non-Hispanic Black |
| **NHS** | Nurses' Health Study |
| **NHW** | non-Hispanic White |
| **PR** | progesterone receptor |
| **SEP** | socioeconomic position |
| **SEER** | Surveillance, Epidemiology, and End Results |
| **TNBC** | triple negative breast cancer |
| **US** | United States |
| **UWM** | University of Wisconsin–Milwaukee |
| **YOBC** | young-onset breast cancer |
| **YWHHS** | Young Women's Health History Study |
| **(−)** | negative |
| **(+)** | positive |

## REFERENCES


1. Ward EM, Sherman RL, Henley SJ, Jemal A, Siegel DA, Feuer EJ, Firth AU, Kohler BA, Scott S, Ma J, Anderson RN, Benard V, Cronin KA (2019) Annual Report to the Nation on the Status of Cancer, Featuring Cancer in Men and Women Age 20–49 Years. J Natl Cancer Inst 111:1279–1297. 10.1093/jnci/djz106 [PubMed: 31145458]
2. DeSantis CE, Ma J, Gaudet MM, Newman LA, Miller KD, Goding Sauer A, Jemal A, Siegel RL (2019) Breast cancer statistics, 2019. CA Cancer J Clin 69:438–451. 10.3322/caac.21583 [PubMed: 31577379]
3. Provenzano E, Ulaner GA, Chin SF (2018) Molecular Classification of Breast Cancer. PET Clin 13:325–338. 10.1016/j.cpet.2018.02.004 [PubMed: 30100073]
4. Reynolds P (2013) Smoking and breast cancer. J Mammary Gland Biol Neoplasia 18:15–23. 10.1007/s10911-012-9269-x [PubMed: 23179580]
5. Kispert S, McHowat J (2017) Recent insights into cigarette smoking as a lifestyle risk factor for breast cancer. Breast Cancer (Dove Med Press) 9:127–132. 10.2147/BCTT.S129746 [PubMed: 28331363]
6. Xue F, Willett WC, Rosner BA, Hankinson SE, Michels KB (2011) Cigarette smoking and the incidence of breast cancer. Arch Intern Med 171:125–133. 10.1001/archinternmed.2010.503 [PubMed: 21263102]
7. Rosenberg L, Boggs DA, Bethea TN, Wise LA, Adams-Campbell LL, Palmer JR (2013) A prospective study of smoking and breast cancer risk among African-American women. Cancer Causes Control 24:2207–2215. 10.1007/s10552-013-0298-6 [PubMed: 24085586]
8. Morabia A, Bernstein MS, Bouchardy I, Kurtz J, Morris MA (2000) Breast cancer and active and passive smoking: the role of the N-acetyltransferase 2 genotype. Am J Epidemiol 152:226–232. 10.1093/aje/152.3.226 [PubMed: 10933269]
9. Danforth DN Jr. (2013) Disparities in breast cancer outcomes between Caucasian and African American women: a model for describing the relationship of biological and nonbiological factors. Breast Cancer Res 15:208. 10.1186/bcr3429 [PubMed: 23826992]
10. National Cancer Institute Surveillance Research Program National Cancer Institute SEER*Stat software. https://seer.cancer.gov/seerstat version 8.3.6
11. Liu L, Deapen D, Bernstein L (1998) Socioeconomic status and cancers of the female breast and reproductive organs: a comparison across racial/ethnic populations in Los Angeles County, California (United States). Cancer Causes Control 9:369–380. 10.1023/a:1008811432436 [PubMed: 9794168]
12. Borugian MJ, Spinelli JJ, Abanto Z, Xu CL, Wilkins R (2011) Breast cancer incidence and neighbourhood income. Health Rep 22:7–13.
13. Vainshtein J (2008) Disparities in breast cancer incidence across racial/ethnic strata and socioeconomic status: a systematic review. J Natl Med Assoc 100:833–839. 10.1016/s0027-9684(15)31378-x [PubMed: 18672561]
14. Vona-Davis L, Rose DP (2009) The influence of socioeconomic disparities on breast cancer tumor biology and prognosis: a review. J Womens Health (Larchmt) 18:883–893. 10.1089/jwh.2008.1127 [PubMed: 19514831]
15. Shoemaker ML, White MC, Wu M, Weir HK, Romieu I (2018) Differences in breast cancer incidence among young women aged 20–49 years by stage and tumor characteristics, age, race, and ethnicity, 2004–2013. Breast Cancer Res Treat. 10.1007/s10549-018-4699-9
16. Akinyemiju TF, Pisu M, Waterbor JW, Altekruse SF (2015) Socioeconomic status and incidence of breast cancer by hormone receptor subtype. Springerplus 4:508. 10.1186/s40064-015-1282-2 [PubMed: 26405628]
17. Andaya AA, Enewold L, Horner MJ, Jatoi I, Shriver CD, Zhu K (2012) Socioeconomic disparities and breast cancer hormone receptor status. Cancer Causes Control 23:951–958. 10.1007/s10552-012-9966-1 [PubMed: 22527173]
18. Smith SJ, Deacon JM, Chilvers CE (1994) Alcohol, smoking, passive smoking and caffeine in relation to breast cancer risk in young women. UK National Case-Control Study Group. Br J Cancer 70:112–119. 10.1038/bjc.1994.258 [PubMed: 8018520]

19. Field NA, Baptiste MS, Nasca PC, Metzger BB (1992) Cigarette smoking and breast cancer. Int J Epidemiol 21:842–848. 10.1093/ije/21.5.842 [PubMed: 1468843]

20. Adami HO, Lund E, Bergstrom R, Meirik O (1988) Cigarette smoking, alcohol consumption and risk of breast cancer in young women. Br J Cancer 58:832–837. 10.1038/bjc.1988.320 [PubMed: 3224085]

21. London SJ, Colditz GA, Stampfer MJ, Willett WC, Rosner BA, Speizer FE (1989) Prospective study of smoking and the risk of breast cancer. J Natl Cancer Inst 81:1625–1631. 10.1093/jnci/81.21.1625 [PubMed: 2795691]

22. Al-Delaimy WK, Cho E, Chen WY, Colditz G, Willet WC (2004) A prospective study of smoking and risk of breast cancer in young adult women. Cancer Epidemiol Biomarkers Prev 13:398–404. [PubMed: 15006915]

23. Park SY, Palmer JR, Rosenberg L, Haiman CA, Bandera EV, Bethea TN, Troester MA, Viscidi E, Kolonel LN, Olshan AF, Ambrosone CB (2016) A case-control analysis of smoking and breast cancer in African American women: findings from the AMBER Consortium. Carcinogenesis 37:607–615. 10.1093/carcin/bgw040 [PubMed: 27207658]

24. Bao Y, Bertoia ML, Lenart EB, Stampfer MJ, Willett WC, Speizer FE, Chavarro JE (2016) Origin, Methods, and Evolution of the Three Nurses' Health Studies. Am J Public Health 106:1573–1581. 10.2105/AJPH.2016.303338 [PubMed: 27459450]

25. Palmer JR, Ambrosone CB, Olshan AF (2014) A collaborative study of the etiology of breast cancer subtypes in African American women: the AMBER consortium. Cancer Causes Control 25:309–319. 10.1007/s10552-013-0332-8 [PubMed: 24343304]

26. Velie EM, Marcus LR, Pathak DR, Hamilton AS, DiGaetano R, Klinger R, Gollapudi B, Houang R, Carnegie N, Olson LK, Allen A, Zhang Z, Modjesk D, Norman G, Lucas DR, Gupta S, Rui H, Schwartz K (2021) Theory, methods, and operational results of the Young Women's Health History Study: a study of young-onset breast cancer incidence in Black and White women. Cancer Causes Control. 10.1007/s10552-021-01461-x

27. Tucker TC, Durbin EB, McDowell JK, Huang B (2019) Unlocking the potential of population-based cancer registries. Cancer 125:3729–3737. 10.1002/cncr.32355 [PubMed: 31381143]

28. Tamimi RM, Colditz GA, Hazra A, Baer HJ, Hankinson SE, Rosner B, Marotti J, Connolly JL, Schnitt SJ, Collins LC (2012) Traditional breast cancer risk factors in relation to molecular subtypes of breast cancer. Breast Cancer Res Treat 131:159–167. 10.1007/s10549-011-1702-0 [PubMed: 21830014]

29. Gram IT, Park SY, Kolonel LN, Maskarinec G, Wilkens LR, Henderson BE, Le Marchand L (2015) Smoking and Risk of Breast Cancer in a Racially/Ethnically Diverse Population of Mainly Women Who Do Not Drink Alcohol: The MEC Study. Am J Epidemiol 182:917–925. 10.1093/aje/kwv092 [PubMed: 26493265]

30. Catsburg C, Miller AB, Rohan TE (2015) Active cigarette smoking and risk of breast cancer. Int J Cancer 136:2204–2209. 10.1002/ijc.29266 [PubMed: 25307527]

31. United States Census Bureau (2020) Poverty Thresholds. https://www.census.gov/data/tables/time-series/demo/income-poverty/historical-poverty-thresholds.html. Accessed November 18, 2020

32. Fass S (2009) Measuring Poverty in the United States. National Center for Children in Poverty. http://www.nccp.org/publication/measuring-poverty-in-the-united-states/. Accessed November 18, 2020

33. Rojas K, Stuckey A (2016) Breast Cancer Epidemiology and Risk Factors. Clin Obstet Gynecol 59:651–672. 10.1097/GRF.0000000000000239 [PubMed: 27681694]

34. Barnard ME, Boeke CE, Tamimi RM (2015) Established breast cancer risk factors and risk of intrinsic tumor subtypes. Biochim Biophys Acta 1856:73–85. 10.1016/j.bbcan.2015.06.002 [PubMed: 26071880]

35. Lee ES, Forthofer RN (2006) Conducting Survey Data Analysis. In: Analyzing Complex Survey Data, 2nd edn. SAGE Publications, Inc., Thousand Oaks, California, pp 50–78

36. Rothman KJ, Greenland S, Lash TL (2008) Modern epidemiology. Wolters Kluwer Health/Lippincott Williams & Wilkins, Philadelphia

37. den Tonkelaar I, Seidell JC, van Noord PA, Baanders-van Halewijn EA, Ouwehand IJ (1990) Fat distribution in relation to age, degree of obesity, smoking habits, parity and estrogen use:

a cross-sectional study in 11,825 Dutch women participating in the DOM-project. Int J Obes 14:753–761. [PubMed: 2228408]

38. Selvin S (2004) Statistical analysis of epidemiologic data. Oxford University Press, New York;
39. Butler EN, Tse CK, Bell ME, Conway K, Olshan AF, Troester MA (2016) Active smoking and risk of Luminal and Basal-like breast cancer subtypes in the Carolina Breast Cancer Study. Cancer Causes Control 27:775–786. 10.1007/s10552-016-0754-1 [PubMed: 27153846]
40. Ellingjord-Dale M, Vos L, Vik Hjerkind K, Hjartaker A, Russnes HG, Tretli S, Hofvind S, Dos-Santos-Silva I, Ursin G (2018) Number of Risky Lifestyle Behaviors and Breast Cancer Risk. JNCI Cancer Spectr 2:pky030. 10.1093/jncics/pky030
41. Kabat GC, Kim M, Phipps AI, Li CI, Messina CR, Wactawski-Wende J, Kuller L, Simon MS, Yasmeen S, Wassertheil-Smoller S, Rohan TE (2011) Smoking and alcohol consumption in relation to risk of triple-negative breast cancer in a cohort of postmenopausal women. Cancer Causes Control 22:775–783. 10.1007/s10552-011-9750-7 [PubMed: 21360045]
42. Kawai M, Malone KE, Tang MT, Li CI (2014) Active smoking and the risk of estrogen receptor-positive and triple-negative breast cancer among women ages 20 to 44 years. Cancer 120:1026–1034. 10.1002/cncr.28402 [PubMed: 24515648]
43. Morabia A, Bernstein M, Ruiz J, Heritier S, Diebold Berger S, Borisch B (1998) Relation of smoking to breast cancer by estrogen receptor status. Int J Cancer 75:339–342. 10.1002/(sici)1097-0215(19980130)75:3<339::aid-ijc2>3.0.co;2-3 [PubMed: 9455790]
44. Nishino Y, Minami Y, Kawai M, Fukamachi K, Sato I, Ohuchi N, Kakugawa Y (2014) Cigarette smoking and breast cancer risk in relation to joint estrogen and progesterone receptor status: a case-control study in Japan. Springerplus 3:65. 10.1186/2193-1801-3-65 [PubMed: 24516791]
45. Endogenous Hormones Breast Cancer Collaborative Group, Key TJ, Appleby PN, Reeves GK, Roddam AW, Helzlsouer KJ, Alberg AJ, Rollison, Dorgan JF, Brinton LA, Overvad K, Kaaks R, Trichopoulou A, Clavel-Chapelon F, Panico S, Duell EJ, Peeters PH, Rinaldi S, Fentiman IS, Dowsett M, Manjer J, Lenner P, Hallmans G, Baglietto L, English DR, Giles GG, Hopper JL, Severi G, Morris HA, Hankinson SE, Tworoger SS, Koenig, Zeleniuch-Jacquotte A, Arslan AA, Toniolo P, Shore RE, Krogh, Micheli A, Berrino F, Barrett-Connor E, Laughlin GA, Kabuto M, Akiba S, Stevens RG, Neriishi K, Land CE, Cauley JA, Lui LY, Cummings SR, Gunter MJ, Rohan TE, Strickler HD (2011) Circulating sex hormones and breast cancer risk factors in postmenopausal women: reanalysis of 13 studies. Br J Cancer 105:709–722. 10.1038/bjc.2011.254 [PubMed: 21772329]
46. Endogenous Hormones Breast Cancer Collaborative Group, Key TJ, Appleby PN, Reeves GK, Travis RC, Alberg AJ, Barricarte A, Berrino F, Krogh V, Sieri S, Brinton LA, Dorgan JF, Dossus L, Dowsett M, Eliassen AH, Fortner RT, Hankinson SE, Helzlsouer KJ, Hoff man-Bolton J, Comstock GW, Kaaks R, Kahle LL, Muti P, Overvad K, Peeters PH, Riboli E, Rinaldi S, Ro/llison DE, Stanczyk FZ, Trichopoulos D, Tworoger SS, Vineis P(2013) Sex hormones and risk of breast cancer in premenopausal women: a collaborative reanalysis of individual participant data from seven prospective studies. Lancet Oncol 14:1009–1019. 10.1016/S1470-2045(13)70301-2 [PubMed: 23890780]
47. Verkasalo PK, Thomas HV, Appleby PN, Davey GK, Key TJ (2001) Circulating levels of sex hormones and their relation to risk factors for breast cancer: a cross-sectional study in 1092 pre- and postmenopausal women (United Kingdom). Cancer Causes Control 12:47–59. 10.1023/a:1008929714862 [PubMed: 11227925]
48. Ellingjord-Dale M, Vos L, Hjerkind KV, Hjartaker A, Russnes HG, Tretli S, Hofvind S, Dos-Santos-Silva I, Ursin G (2017) Alcohol, Physical Activity, Smoking, and Breast Cancer Subtypes in a Large, Nested Case-Control Study from the Norwegian Breast Cancer Screening Program. Cancer Epidemiol Biomarkers Prev 26:1736–1744. 10.1158/1055-9965.EPI-17-0611 [PubMed: 28877889]
49. Baglia ML, Cook LS, Mei-Tzu C, Wiggins C, Hill D, Porter P, Li CI (2018) Alcohol, smoking, and risk of Her2-overexpressing and triple-negative breast cancer relative to estrogen receptor-positive breast cancer. Int J Cancer 143:1849–1857. 10.1002/ijc.31575 [PubMed: 29708591]
50. Turkoz FP, Solak M, Petekkaya I, Keskin O, Kertmen N, Sarici F, Arik Z, Babacan T, Ozisik Y, Altundag K (2013) Association between common risk factors and molecular subtypes in breast cancer patients. Breast 22:344–350. 10.1016/j.breast.2012.08.005 [PubMed: 22981738]

51. Epidemiology Surveillance and Results End (SEER) Program (n.d.) Breast Subtype (2010+). National Cancer Institute, DCCPS, Surveillance Research Program. https://seer.cancer.gov/seerstat/databases/ssf/breast-subtype.html. Accessed June 25, 2020
52. Audrain-McGovern J, Benowitz NL (2011) Cigarette smoking, nicotine, and body weight. Clin Pharmacol Ther 90:164–168. 10.1038/clpt.2011.105 [PubMed: 21633341]
53. Graff-Iversen S, Hewitt S, Forsen L, Grotvedt L, Ariansen I (2019) Associations of tobacco smoking with body mass distribution; a population-based study of 65,875 men and women in midlife. BMC Public Health 19:1439. 10.1186/s12889-019-7807-9 [PubMed: 31675936]
54. Gershuni V, Li YR, Williams AD, So A, Steel L, Carrigan E, Tchou J (2017) Breast cancer subtype distribution is different in normal weight, overweight, and obese women. Breast Cancer Res Treat 163:375–381. 10.1007/s10549-017-4192-x [PubMed: 28293912]
55. Jamal A, Phillips E, Gentzke AS, Homa DM, Babb SD, King BA, Neff LJ (2018) Current Cigarette Smoking Among Adults - United States, 2016. MMWR Morb Mortal Wkly Rep 67:53–59. 10.15585/mmwr.mm6702a1 [PubMed: 29346338]
56. Nighbor TD, Doogan NJ, Roberts ME, Cepeda-Benito A, Kurti AN, Priest JS, Johnson HK, Lopez AA, Stanton CA, Gaalema DE, Redner R, Parker MA, Keith DR, Quisenberry AJ, Higgins ST (2018) Smoking prevalence and trends among a U.S. national sample of women of reproductive age in rural versus urban settings. PLoS One 13:e0207818. 10.1371/journal.pone.0207818 [PubMed: 30485376]
57. U.S. Department of Health and Human Services (2010) How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General. 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, Atlanta (GA)
58. U.S. Department of Health and Human Services (2014) The Health Consequences of Smoking-50 Years of Progress: A Report of the Surgeon General. Atlanta (GA)
59. Yager JD, Davidson NE (2006) Estrogen carcinogenesis in breast cancer. N Engl J Med 354:270–282. 10.1056/NEJMra050776 [PubMed: 16421368]
60. Faraglia B, Chen SY, Gammon MD, Zhang Y, Teitelbaum SL, Neugut AI, Ahsan H, Garbowski GC, Hibshoosh H, Lin D, Kadlubar FF, Santella RM (2003) Evaluation of 4-aminobiphenyl-DNA adducts in human breast cancer: the influence of tobacco smoke. Carcinogenesis 24:719–725. 10.1093/carcin/bgg013 [PubMed: 12727801]
61. Agudo A, Peluso M, Munnia A, Lujan-Barroso L, Barricarte A, Amiano P, Navarro C, Sanchez MJ, Quiros JR, Ardanaz E, Larranaga N, Tormo MJ, Chirlaque MD, Rodriguez-Barranco M, Sanchez-Cantalejo E, Cellai F, Bonet C, Sala N, Gonzalez CA (2017) Aromatic DNA adducts and breast cancer risk: a case-cohort study within the EPIC-Spain. Carcinogenesis 38:691–698. 10.1093/carcin/bgx047 [PubMed: 28535209]
62. King BA, Dube SR, Tynan MA (2012) Current tobacco use among adults in the United States: findings from the National Adult Tobacco Survey. Am J Public Health 102:e93–e100. 10.2105/AJPH.2012.301002 [PubMed: 22994278]
63. Do EK, Nicksic NE, Clifford JS, Hayes A, Fuemmeler BF (2020) Perceived harms of and exposure to tobacco use and current tobacco use among reproductive-aged women from the PATH study. Women & Health 60:1040–1051. 10.1080/03630242.2020.1789261
64. Howards PP (2018) An overview of confounding. Part 1: the concept and how to address it. Acta Obstet Gynecol Scand 97:394–399. 10.1111/aogs.13295 [PubMed: 29341103]
65. Nemes S, Jonasson JM, Genell A, Steineck G (2009) Bias in odds ratios by logistic regression modelling and sample size. BMC medical research methodology 9:56–56. 10.1186/1471-2288-9-56 [PubMed: 19635144]
66. Herb J, Wolff R, McDaniel P, Holmes M, Lund J, Stitzenberg K (2021) Rural representation of the surveillance, epidemiology, and end results database. Cancer Causes Control 32:211–220. 10.1007/s10552-020-01375-0 [PubMed: 33392903]

**Table 1.**

Characteristics of the control participants in the Young Women's Health History Study by personal cigarette smoking status (n=1,381), 2010–2015[a]

| | Total Population | Never Smoked | Formerly Smoked | Currently Smoke | *P*-value [b] |
|---|---|---|---|---|---|
| | N (W%) | N (W%) | N (W%) | N (W%) | |
| Total | 1377 (100%)[c] | 898 (67.8%) | 171 (11.5%) | 308 (20.8%) | |
| Study Site | | | | | <0.001 |
| Metropolitan Detroit | 715 (59.4) | 432 (61.9) | 94 (12.6) | 189 (25.5) | |
| Los Angeles County | 662 (40.6) | 466 (76.4) | 77 (9.8) | 119 (13.8) | |
| Age at reference year, years (weighted mean (weighted 95% CI)) | 34.3 (33.2–35.4) | 33.5 (32.1–34.8) | 37.6 (35.3–39.9) | 35.3 (34.0–36.6) | 0.002 |
| Age at reference year, years | | | | | 0.01 |
| 20–29 | 246 (36.6) | 184 (76.3) | 8 (5.2) | 54 (18.5) | |
| 30–39 | 481 (30.1) | 309 (63.5) | 63 (14.2) | 109 (22.3) | |
| 40–49 | 650 (33.3) | 405 (62.2) | 100 (16.0) | 145 (21.8) | |
| Race | | | | | <0.001 |
| Non-Hispanic White | 714 (65.5) | 436 (65.2) | 131 (15.0) | 147 (19.8) | |
| Non-Hispanic Black | 663 (34.5) | 462 (72.5) | 40 (4.9) | 161 (22.6) | |
| Household poverty level | | | | | <0.001 |
| ≥200% of federal poverty level | 719 (54.3) | 507 (73.7) | 119 (13.9) | 93 (12.4) | |
| <200% of federal poverty level | 616 (42.8) | 367 (60.0) | 49 (8.9) | 200 (31.1) | |
| Missing | 42 (2.9) | 24 (70.2) | 3 (4.9) | 15 (24.9) | |
| Education | | | | | <0.001 |
| High school diploma or less | 291 (17.9) | 167 (57.6) | 25 (9.5) | 99 (32.9) | |
| Vocational school, associate degree, or some college | 559 (42.9) | 335 (62.6) | 72 (12.0) | 152 (25.4) | |
| Bachelor's degree or higher | 527 (39.2) | 396 (78.0) | 74 (11.8) | 57 (10.2) | |
| Body mass index, kg/m$^2$ | | | | | 0.59 |
| Underweight: <18.5 | 38 (4.5) | 22 (69.7) | 3 (3.0) | 13 (27.2) | |
| Normal: 18.5–24.9 | 491 (39.2) | 319 (71.0) | 69 (11.0) | 103 (18.0) | |
| Overweight: 25–29.9 | 380 (28.0) | 251 (65.0) | 39 (12.5) | 90 (22.5) | |
| Obese: ≥30 | 468 (28.3) | 306 (65.7) | 60 (12.4) | 102 (21.8) | |
| Age at menarche | | | | | 0.11 |
| ≤11 | 400 (30.6) | 266 (68.9) | 42 (7.3) | 92 (23.8) | |
| 12 | 424 (31.8) | 263 (64.9) | 57 (14.6) | 104 (20.6) | |
| 13 | 303 (21.6) | 196 (67.2) | 39 (11.0) | 68 (21.8) | |
| ≥14 | 250 (16.0) | 173 (72.0) | 33 (14.2) | 44 (13.9) | |

| | Total Population | Never Smoked | Formerly Smoked | Currently Smoke | *P*-value [b] |
|---|---|---|---|---|---|
| | N (W%) | N (W%) | N (W%) | N (W%) | |
| Menopausal status | | | | | 0.001 |
| Premenopausal | 1,222 (92.2) | 815 (69.0) | 154 (11.4) | 253 (19.6) | |
| Peri-/Post-menopausal | 155 (7.8) | 83 (53.6) | 17 (12.4) | 55 (34.0) | |
| Joint parity & age (in years) at first full-term pregnancy status | | | | | <0.001 |
| Nulliparous | 402 (39.2) | 277 (75.4) | 46 (9.5) | 79 (15.1) | |
| 1–2, <25 | 298 (19.4) | 181 (61.4) | 28 (7.6) | 89 (31.0) | |
| 1–2, ≥25 | 320 (21.3) | 224 (67.0) | 52 (17.5) | 44 (15.5) | |
| 3+, <25 | 272 (15.1) | 151 (53.6) | 29 (11.2) | 92 (35.3) | |
| 3+, ≥25 | 85 (4.9) | 65 (78.5) | 16 (18.1) | 4 (3.3) | |
| History of breast cancer among first-degree relative | | | | | 0.18 |
| No | 1,195 (88.3) | 788 (69.0) | 150 (11.5) | 257 (19.5) | |
| Yes | 116 (7.5) | 74 (60.0) | 12 (11.8) | 30 (28.3) | |
| Unknown | 66 (4.2) | 36 (55.9) | 9 (11.3) | 21 (32.8) | |
| Lifetime alcohol use status, g/day | | | | | <0.001 |
| 0 (Abstainers) | 429 (29.3) | 344 (81.6) | 28 (4.6) | 57 (13.9) | |
| 0.1–6.9 | 414 (31.5) | 290 (71.1) | 56 (11.4) | 68 (17.5) | |
| 7–13.9 | 221 (15.7) | 133 (65.9) | 31 (13.1) | 57 (21.0) | |
| 14–27.9 | 190 (14.6) | 97 (58.7) | 37 (16.1) | 56 (25.2) | |
| ≥28 | 123 (8.9) | 34 (28.6) | 19 (24.5) | 70 (47.0) | |

Abbreviations: CI, confidence interval; g, grams; kg, kilograms; m, meter; W, sample-weighted.

[a] n=4 participants missing smoking status are not included. All values are absolute frequencies and sample-weighted row percentages unless otherwise specified.

[b] Estimated for 3-category personal smoking status (never, formerly, currently smoke). Missing categories are not included in chi-square p-value estimates.

[c] Absolute frequencies and sample-weighted column percentages are presented for the total population.

**Table 2.**

Cigarette smoking characteristics of women in the Young Women's Health History Study by breast cancer status and subtype (n=3,193)[a]

| | Breast Cancer Status | | *P*-value | Breast Cancer Subtype[b] | | | | *P*-value |
|---|---|---|---|---|---|---|---|---|
| | Control | Case | | Luminal A | Luminal B | HER2-type | TNBC | |
| | N (W%) | N (W%) | | N (W%) | N (W%) | N (W%) | N (W%) | |
| Total | 1,377 (50.1%) | 1,798 (49.9%) | | 691 (21.1%) | 564 (15.3%) | 104 (2.6%) | 311 (7.5%) | |
| Ever smoking status | | | 0.56 | | | | | 0.01 |
| Never smoked | 898 (63.4) | 1,149 (62.2) | | 429 (60.4) | 379 (65.8) | 52 (46.4) | 210 (65.9) | |
| Ever smoked | 479 (36.6) | 649 (37.8) | | 262 (39.6) | 185 (34.2) | 52 (53.6) | 101 (34.1) | |
| Personal smoking status | | | 0.14[d] | | | | | 0.01[d] |
| Never smoked | 898 (63.4) | 1,149 (62.2) | | 429 (60.4) | 379 (65.8) | 52 (46.4) | 210 (65.9) | |
| Formerly smoked | 171 (15.3) | 299 (18.3) | | 118 (19.1) | 93 (17.4) | 27 (27.4) | 37 (13.4) | |
| ≥10 years since quitting[c] | 95 (10.2) | 181 (11.7) | | 79 (13.1) | 52 (10.6) | 13 (14.7) | 21 (7.7) | |
| <10 years since quitting[c] | 76 (5.0) | 116 (6.5) | | 39 (6.0) | 40 (6.7) | 14 (12.7) | 15 (5.3) | |
| Currently smoke | 308 (21.3) | 350 (19.6) | | 144 (20.5) | 92 (16.8) | 25 (26.2) | 64 (20.7) | |
| Average number of cigarettes per day | | | 0.90 | | | | | 0.06 |
| Never smoked | 898 (63.4) | 1,149 (62.2) | | 429 (60.4) | 379 (65.8) | 52 (46.4) | 210 (65.9) | |
| <5 | 125 (8.1) | 161 (9.0) | | 58 (8.7) | 53 (9.3) | 9 (9.3) | 26 (8.1) | |
| 5–19 | 236 (17.4) | 301 (17.4) | | 128 (19.4) | 87 (16.2) | 24 (21.8) | 39 (13.2) | |
| ≥20 | 118 (11.1) | 184 (11.3) | | 76 (11.5) | 44 (8.5) | 18 (21.3) | 35 (12.4) | |
| Missing | 0 (0) | 3 (0.2) | | 0 (0) | 1 (0.1) | 1 (1.2) | 1 (0.4) | |
| Lifetime smoking pack-years | | | 0.60 | | | | | 0.07 |
| Never smoked | 898 (63.4) | 1,149 (62.2) | | 429 (60.4) | 379 (65.8) | 52 (46.4) | 210 (65.9) | |
| <5 | 226 (13.8) | 250 (14.3) | | 92 (14.2) | 81 (15.0) | 18 (18.0) | 37 (11.5) | |
| 5–19 | 186 (14.7) | 286 (16.2) | | 123 (17.9) | 80 (13.9) | 21 (20.4) | 40 (13.5) | |
| ≥20 | 67 (8.1) | 107 (7.0) | | 47 (7.5) | 21 (4.8) | 12 (14.0) | 22 (8.4) | |
| Missing | 0 (0) | 6 (0.3) | | 0 (0) | 3 (0.4) | 1 (1.2) | 2 (0.7) | |

| | Breast Cancer Status | | *P*-value | Breast Cancer Subtype[b] | | | | *P*-value |
|---|---|---|---|---|---|---|---|---|
| | Control | Case | | Luminal A | Luminal B | HER2-type | TNBC | |
| | N (W%) | N (W%) | | N (W%) | N (W%) | N (W%) | N (W%) | |
| Age smoking initiated, years | | | 0.04 | | | | | 0.009 |
| Never smoked | 898 (63.4) | 1,149 (62.2) | | 429 (60.4) | 379 (65.8) | 52 (46.4) | 210 (65.9) | |
| <18 | 233 (20.2) | 370 (22.5) | | 154 (24.0) | 102 (19.9) | 33 (34.9) | 56 (19.4) | |
| 18–24 | 207 (13.7) | 204 (11.1) | | 81 (11.2) | 62 (10.9) | 14 (14.7) | 29 (9.7) | |
| ≥25 | 39 (2.7) | 74 (4.1) | | 27 (4.4) | 20 (3.2) | 5 (4.0) | 16 (5.0) | |
| Missing | 0 (0) | 1 (0.05) | | 0 (0) | 1 (0.2) | 0 (0) | 0 (0) | |
| Time since smoking initiated, years | | | 0.58 | | | | | 0.003 |
| Never smoked | 898 (63.4) | 1,149 (62.2) | | 429 (60.4) | 379 (65.8) | 52 (46.4) | 210 (65.9) | |
| <20 | 201 (6.9) | 152 (7.1) | | 47 (5.3) | 47 (7.2) | 12 (10.3) | 33 (10.1) | |
| 20–29 | 187 (18.2) | 328 (17.4) | | 139 (19.0) | 101 (16.9) | 21 (20.4) | 43 (13.4) | |
| ≥30 | 91 (11.5) | 168 (13.3) | | 76 (15.3) | 36 (9.9) | 19 (23.0) | 25 (10.6) | |
| Missing | 0 (0) | 1 (0.05) | | 0 (0) | 1 (0.2) | 0 (0) | 0 (0) | |
| Smoking initiation timing - FFTP[e] | | | 0.05 | | | | | 0.008 |
| Never smoked | 621 (63.9) | 837 (62.5) | | 315 (60.0) | 258 (65.4) | 42 (49.5) | 158 (68.8) | |
| After FFTP | 94 (7.0) | 73 (4.8) | | 26 (4.1) | 21 (5.1) | 4 (5.1) | 14 (5.6) | |
| Before FFTP | 259 (29.0) | 394 (32.6) | | 170 (35.8) | 108 (29.6) | 33 (45.4) | 52 (25.1) | |
| Missing | 1 (0.1) | 2 (0.1) | | 0 (0) | 0 (0) | 0 (0) | 1 (0.4) | |

Abbreviations: FFTP, first full-term pregnancy; HER2, human epidermal growth factor receptor 2; TNBC, triple negative breast cancer; W, sample-weighted.

[a] n=18 participants (14 cases and 4 controls) missing smoking status are not included. All values are absolute frequencies and sample-weighted column percentages.

[b] n=128 cases missing breast cancer subtype not included in analyses by breast cancer subtype·

[c] Among n=543 participants who formerly smoked; time since smoking cessation missing for n=2.

[d] Estimated for 3-category personal smoking status (never, former, current).

[e] Among n=2,213 parous women.

**Table 3.**

Multivariable-adjusted odds ratios and 95% CI[a] for the association of personal cigarette smoking history and risk of breast cancer overall and by tumor subtype

| | Overall (N controls=1,377; N cases=1,798) | Luminal A (N controls=1,377; N cases = 691) | Luminal B (N controls=1,377; N cases = 564) | HER2-type (N controls=1,377; N cases = 104) | TNBC (N controls=1,377; N cases = 311) | |
|---|---|---|---|---|---|---|
| | **Adjusted OR (95% CI)** | **Adjusted OR (95% CI)** | **Adjusted OR (95% CI)** | **Adjusted OR (95% CI)** | **Adjusted OR (95% CI)** | $P_{het}$ |
| Ever smoking status | | | | | | 0.01 |
| Never smoked | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | |
| Ever smoked | 1.20 (1.00–1.44) | 1.34 (1.06–1.68) | 1.04 (0.78–1.39) | 1.97 (1.23–3.16) | 0.92 (0.68–1.25) | |
| Personal smoking status | | | | | | 0.03[c] |
| Never smoked | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | |
| Formerly smoked | 1.27 (0.98–1.64) | 1.33 (0.98–1.79) | 1.15 (0.78–1.70) | 2.41 (1.45–4.01) | 0.90 (0.61–1.34) | |
| ≥10 years since quitting[b] | 1.17 (0.84–1.63) | 1.28 (0.86–1.89) | 1.05 (0.67–1.65) | 1.95 (1.05–3.61) | 0.77 (0.42–1.42) | |
| <10 years since quitting[b] | 1.45 (0.99–2.11) | 1.42 (0.89–2.27) | 1.40 (0.84–2.33) | 3.40 (1.52–7.62) | 0.98 (0.53–1.78) | |
| Currently smoke | 1.13 (0.92–1.40) | 1.36 (1.02–1.81) | 0.93 (0.69–1.25) | 1.58 (0.84–2.99) | 0.94 (0.63–1.40) | |
| Average number of cigarettes per day | | | | | | 0.09 |
| Never smoked | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | |
| <5 | 1.22 (0.90–1.65) | 1.25 (0.83–1.88) | 1.16 (0.74–1.82) | 1.60 (0.80–3.22) | 1.01 (0.58–1.74) | |
| 5–19 | 1.16 (0.91–1.48) | 1.37 (1.03–1.83) | 1.04 (0.71–1.51) | 1.69 (0.94–3.04) | 0.74 (0.49–1.12) | |
| ≥20 | 1.23 (0.93–1.63) | 1.35 (0.92–1.98) | 0.91 (0.57–1.46) | 2.64 (1.38–5.02) | 1.12 (0.73–1.72) | |
| Lifetime smoking pack-years | | | | | | 0.07 |
| Never smoked | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | |
| <5 | 1.12 (0.88–1.44) | 1.17 (0.86–1.60) | 1.08 (0.75–1.55) | 1.81 (1.09–3.01) | 0.82 (0.53–1.28) | |
| 5–19 | 1.32 (1.00–1.73) | 1.59 (1.14–2.22) | 1.09 (0.75–1.60) | 1.93 (0.93–4.02) | 0.88 (0.57–1.37) | |
| ≥20 | 1.08 (0.76–1.53) | 1.23 (0.77–1.96) | 0.76 (0.41–1.42) | 2.28 (1.05–4.93) | 1.11 (0.61–2.02) | |
| Age smoking initiated, years | | | | | | 0.24 |
| Never smoked | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | |
| <18 | 1.33 (1.05–1.67) | 1.51 (1.14–2.00) | 1.14 (0.80–1.63) | 2.36 (1.36–4.09) | 0.94 (0.65–1.37) | |

| | Overall (N controls=1,377; N cases=1,798) | Luminal A (N controls=1,377; N cases = 691) | Luminal B (N controls=1,377; N cases = 564) | HER2-type (N controls=1,377; N cases = 104) | TNBC (N controls=1,377; N cases = 311) | |
|---|---|---|---|---|---|---|
| | **Adjusted OR (95% CI)** | **Adjusted OR (95% CI)** | **Adjusted OR (95% CI)** | **Adjusted OR (95% CI)** | **Adjusted OR (95% CI)** | $P_{het}$ |
| 18–24 | 0.90 (0.70–1.17) | 0.95 (0.69–1.31) | 0.83 (0.57–1.20) | 1.40 (0.69–2.82) | 0.71 (0.45–1.12) | |
| ≥25 | 1.91 (1.24–2.96) | 2.25 (1.32–3.84) | 1.44 (0.74–2.79) | 2.25 (0.75–6.76) | 1.94 (1.03–3.64) | |
| Time since smoking initiated, years | | | | | | 0.09 |
| Never smoked | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | |
| <20 | 1.23 (0.93–1.64) | 1.20 (0.82–1.75) | 1.01 (0.66–1.53) | 2.02 (1.06–3.84) | 1.23 (0.80–1.92) | |
| 20–29 | 1.09 (0.86–1.38) | 1.26 (0.95–1.66) | 1.01 (0.72–1.40) | 1.55 (0.87–2.77) | 0.77 (0.52–1.14) | |
| ≥30 | 1.38 (1.00–1.90) | 1.55 (1.07–2.26) | 1.12 (0.66–1.90) | 2.77 (1.32–5.79) | 0.95 (0.54–1.67) | |
| Smoking initiation timing - first full-term pregnancy[d] | | | | | | 0.15 |
| Never smoked | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | |
| After FFTP | 0.90 (0.59–1.37) | 0.90 (0.51–1.60) | 0.96 (0.50–1.85) | 0.91 (0.26–3.18) | 0.67 (0.33–1.36) | |
| Before FFTP | 1.25 (1.02–1.54) | 1.45 (1.11–1.89) | 1.13 (0.82–1.58) | 1.79 (0.99–3.25) | 0.82 (0.55–1.22) | |

Abbreviations: BC, breast cancer; BMI, body mass index; CI, confidence interval; ref, reference; FFTP, first full-term pregnancy; FPL, federal poverty level; HER2, human epidermal growth factor receptor 2; het, heterogeneity; HHP, household poverty; N, no; OR, odds ratio; ref, reference; TNBC, triple negative breast cancer; Y, yes.

[a]Estimation of BC risk overall or by cancer subtype was relative to controls for all analyses. Adjusted for study site (Detroit, Los Angeles); age at diagnosis (continuous); HHP (≥200%, <200% of FPL); first-degree family history of BC (Y, N, unknown); BMI 12 months before reference date (underweight, normal, overweight, obese); lifetime alcohol use (0, 0.1–6.9, 7–13.9, 14–27.9 and ≥28 grams/day); parity/age at FFTP (nulliparous, 1–2 children and <25 years, 1–2 children and ≥25, 3+ children and <25 years, 3+ children and ≥25); menopausal status (premenopausal, peri-/post-menopausal).

[b]Among participants who formerly smoked.

[c]Estimated for 3-category personal smoking status (never, former, current).

[d]Among parous women.

**Table 4.**

Multivariable-adjusted odds ratios and 95% CI[a] for the association of personal cigarette smoking history and risk of breast cancer by race and SEP

| | Non-Hispanic White (N controls=716; N cases = 1,130) | Non-Hispanic Black (N controls=665; N cases = 682) | | HHP ≥200%[b] (N controls=721; N cases = 1,222) | HHP <200%[b] (N controls=617; N cases = 517) | |
|---|---|---|---|---|---|---|
| | **Adjusted OR (95% CI)** | **Adjusted OR (95% CI)** | $P_{int}$ | **Adjusted OR (95% CI)** | **Adjusted OR (95% CI)** | $P_{int}$ |
| Ever smoking status | | | 0.17 | | | 0.76 |
| Never smoked | 1.00 (ref) | 1.00 (ref) | | 1.00 (ref) | 1.00 (ref) | |
| Ever smoked | 1.39 (1.06–1.82) | 0.96 (0.70–1.31) | | 1.28 (0.97–1.68) | 1.08 (0.79–1.47) | |
| Personal smoking status | | | 0.31[d] | | | 0.07[d] |
| Never smoked | 1.00 (ref) | 1.00 (ref) | | 1.00 (ref) | 1.00 (ref) | |
| Formerly smoked | 1.40 (1.02–1.93) | 1.13 (0.68–1.88) | | 1.18 (0.86–1.62) | 1.80 (1.08–3.01) | |
| ≥10 years since quitting[c] | 1.29 (0.87–1.92) | 0.94 (0.49–1.82) | | 1.10 (0.72–1.66) | 1.47 (0.72–3.04) | |
| <10 years since quitting[c] | 1.60 (1.00–2.55) | 1.31 (0.62–2.80) | | 1.32 (0.82–2.12) | 2.04 (1.02–4.08) | |
| Currently smoke | 1.38 (1.00–1.90) | 0.89 (0.63–1.27) | | 1.46 (1.01–2.12) | 0.88 (0.63–1.23) | |
| Average number of cigarettes per day | | | 0.36 | | | 0.27 |
| Never smoked | 1.00 (ref) | 1.00 (ref) | | 1.00 (ref) | 1.00 (ref) | |
| <5 | 1.47 (0.95–2.28) | 0.80 (0.51–1.24) | | 1.51 (0.99–2.31) | 0.87 (0.51–1.49) | |
| 5–19 | 1.32 (0.93–1.86) | 1.00 (0.66–1.54) | | 1.12 (0.78–1.61) | 1.21 (0.84–1.74) | |
| ≥20 | 1.43 (0.98–2.07) | 1.07 (0.60–1.92) | | 1.36 (0.86–2.15) | 1.01 (0.64–1.59) | |
| Lifetime smoking pack-years | | | 0.09 | | | 0.98 |
| Never smoked | 1.00 (ref) | 1.00 (ref) | | 1.00 (ref) | 1.00 (ref) | |
| <5 | 1.20 (0.88–1.65) | 0.97 (0.64–1.48) | | 1.17 (0.85–1.60) | 1.04 (0.66–1.63) | |
| 5–19 | 1.72 (1.18–2.51) | 0.81 (0.54–1.22) | | 1.42 (0.98–2.07) | 1.24 (0.85–1.82) | |
| ≥20 | 1.20 (0.77–1.88) | 1.44 (0.73–2.84) | | 1.21 (0.67–2.18) | 0.86 (0.48–1.55) | |
| Age smoking initiated, years | | | 0.61 | | | 0.43 |
| Never smoked | 1.00 (ref) | 1.00 (ref) | | 1.00 (ref) | 1.00 (ref) | |
| <18 | 1.60 (1.18–2.17) | 1.03 (0.69–1.53) | | 1.46 (1.03–2.07) | 1.14 (0.77–1.68) | |
| 18–24 | 1.00 (0.69–1.45) | 0.75 (0.50–1.11) | | 0.90 (0.62–1.30) | 0.91 (0.60–1.38) | |

| | Non-Hispanic White (N controls=716; N cases = 1,130) | Non-Hispanic Black (N controls=665; N cases = 682) | | HHP ≥200%[b] (N controls=721; N cases = 1,222) | HHP <200%[b] (N controls=617; N cases = 517) | |
|---|---|---|---|---|---|---|
| | **Adjusted OR (95% CI)** | **Adjusted OR (95% CI)** | ***P*** **int** | **Adjusted OR (95% CI)** | **Adjusted OR (95% CI)** | ***P*** **int** |
| ≥25 | 2.23 (0.99–5.04) | 1.44 (0.78–2.63) | | 2.69 (1.22–5.93) | 1.25 (0.64–2.45) | |
| Time since smoking initiated, years | | | 0.36 | | | 0.91 |
| Never smoked | 1.00 (ref) | 1.00 (ref) | | 1.00 (ref) | 1.00 (ref) | |
| <20 | 1.35 (0.90–2.04) | 0.99 (0.64–1.54) | | 1.39 (0.89–2.18) | 1.08 (0.68–1.71) | |
| 20–29 | 1.21 (0.88–1.67) | 0.99 (0.69–1.43) | | 1.16 (0.81–1.65) | 0.95 (0.67–1.36) | |
| ≥30 | 1.78 (1.18–2.70) | 0.83 (0.47–1.48) | | 1.44 (0.92–2.27) | 1.29 (0.74–2.25) | |
| Smoking initiation timing – FFTP[e] | | | 0.41 | | | 0.62 |
| Never smoked | 1.00 (ref) | 1.00 (ref) | | 1.00 (ref) | 1.00 (ref) | |
| After FFTP | 1.16 (0.44–3.07) | 0.72 (0.46–1.11) | | 1.15 (0.54–2.47) | 0.78 (0.45–1.34) | |
| Before FFTP | 1.47 (1.08–2.00) | 1.06 (0.71–1.58) | | 1.26 (0.92–1.72) | 1.22 (0.84–1.76) | |

Abbreviations: BC, breast cancer; BMI, body mass index; CI, confidence interval; FFTP, first full-term pregnancy; FPL, federal poverty level; HHP, household poverty; int, interaction; N, no; OR, odds ratio; ref, reference; Y, yes.

[a]Estimation of BC risk was relative to controls for all analyses. Adjusted for study site (Detroit, Los Angeles); age at diagnosis (continuous); HHP (≥200%, <200% of FPL); first-degree family history of BC (Y, N, unknown); BMI 12 months before reference date (underweight, normal, overweight, obese); lifetime alcohol use (0, 0.1–6.9, 7–13.9, 14–27.9 and ≥28 grams/day); parity/age at FFTP (nulliparous, 1–2 children and <25 years, 1–2 children and ≥25, 3+ children and <25 years, 3+ children and ≥25); menopausal status (premenopausal, peri-/post-menopausal).

[b]n=116 participants (73 cases 43 controls) were missing information on HHP and did not contribute to analyses stratified by HHP.

[c]Among participants who formerly smoked.

[d]Interaction term by 3-category personal smoking status (never, former, current).

[e]Among parous women.