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Active and Passive Cigarette Smoking and Mortality among Hispanic and non-Hispanic White Women Diagnosed with Invasive Breast Cancer

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Abstract

Purpose—Women who smoke at breast cancer diagnosis have higher risk of breast cancer-specific and all-cause mortality than non-smokers; however, differences by ethnicity or prognostic factors and risk for non-cancer mortality have not been evaluated.

Methods—We examined associations of active and passive smoke exposure with mortality among Hispanic (n=1,020) and non-Hispanic White (n=1,198) women with invasive breast cancer in the Breast Cancer Health Disparities Study (median follow-up of 10.6 years).

Results—Risk of breast cancer-specific (HR=1.55, 95% CI:1.11-2.16) and all-cause (HR=1.68, 95% CI:1.30-2.17) mortality was increased for current smokers, with similar results stratified by

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ethnicity. Ever smokers had an increased risk of non-cancer mortality (HR=1.68, 95% CI: 1.12-2.51). Associations were strongest for current smokers who smoked ≥20 years, were postmenopausal, overweight/obese, or reported moderate/high alcohol consumption; however, interactions were not significant. Breast cancer-specific mortality was increased 2-fold for moderate/high recent passive smoke exposure among never smokers (HR=2.12, 95% CI: 1.24-3.63).

Conclusions—Findings support associations of active and passive smoking diagnosis with risk of breast cancer-specific and all-cause mortality, and ever smoking with non-cancer mortality, regardless of ethnicity and other factors. Smoking is a modifiable lifestyle factor and effective smoking cessation and maintenance programs should be routinely recommended for women with breast cancer.

Keywords

Breast cancer; Ethnicity; Hispanic; Native American Ancestry; Smoking; Mortality; Survival

INTRODUCTION

Despite improvements in early detection and treatment, breast cancer remains the second leading cause of cancer death for women in the US, and survival rates vary by age and race/ethnicity (1). It is important to identify modifiable lifestyle factors that contribute to breast cancer-specific mortality. Cigarette smoking is a leading preventable factor for all-cause mortality. Scientific evidence demonstrates that there is no safe level of cigarette smoke exposure, which has been linked to nearly one-third of all cancer deaths (2). Cigarette smoke contains more than 70 carcinogens that can be metabolically activated and transported to breast tissues leading to DNA damage, disruption in estrogen metabolism, and carcinogenesis (2).

While biologically plausible mechanisms exist by which active and passive cigarette smoke may induce or promote breast cancer (3), the association with breast cancer-specific mortality is not well established. Cigarette smoke is reported to induce epithelial to mesenchymal transition (4), increase metastatic potential of breast cancer cells to lymph nodes (5) and lungs (6, 7), influence aggressive tumor behavior (8, 9), and is associated with later disease stage (10), all of which adversely affect breast cancer prognosis, lower quality of life (11) and increase risk of all-cause mortality (12-16). Data for breast cancer-specific mortality, however, are inconsistent, with reports of positive (12, 17-23) or no (13, 24-28) associations. No associations have been found between passive smoke exposure and breast cancer-specific mortality (27, 29-31). Several studies have evaluated whether prognostic factors, including disease stage and body mass index (BMI) (12, 13, 16, 22, 23), modify the association of smoking with breast cancer-specific mortality, but results are conflicting. Moreover, no studies have evaluated whether smoking is associated with survival differences between Hispanic and non-Hispanic White (NHW) women with breast cancer. Risk of breast cancer-specific mortality differs between Hispanic and NHW women; associations for higher (32, 33) and reduced (34) risk have been reported. Although Hispanics reportedly have lower smoking rates (35) they are a genetically admixed population with varying proportions of Native American (NA) ancestry and we previously

reported that ethnic differences in genetic factors may influence susceptibility to carcinogens in cigarette smoke (36).

We examined whether smoking is associated with death due to breast cancer and other causes in NHW and Hispanic/NA women included in the Breast Cancer Health Disparities Study (BCHDS). We also examined potential effect modification of active and passive smoke exposure and breast cancer-specific mortality by ethnicity and other factors associated with breast cancer survival.

MATERIALS AND METHODS

Study population

The BCHDS includes participants from three population-based case-control studies: 4-Corners Breast Cancer Study (4-CBCS) (37); San Francisco Bay Area Breast Cancer Study (SFBCS) (38); and Mexico Breast Cancer Study (MBCS) (39). The BCHDS methods have been previously described (40). Briefly, in-person interviews were conducted and anthropometric measurements and blood/saliva samples collected using standard protocols, and data were harmonized across studies. The analyses were restricted to histologically confirmed first primary invasive breast cancer cases from 4-CBCS (NHWs, Hispanic/NAs) and SFBCS (Hispanics), since no survival data were available for MBCS. The 4-CBCS included women ages 25-79 years diagnosed between 10/1999-05/2004 in Arizona, Colorado, New Mexico, or Utah. The SFBCS included women ages 35-79 years from the San Francisco Bay Area (Hispanics, NHWs, and African Americans diagnosed between 04/1995-04/1999; and Hispanics diagnosed from 5/1999-4/2002). In SFBCS, smoking data were collected only for Hispanic cases diagnosed from 1999-2002. Data on survival and smoking were available for 1,860 4-CBCS cases and 417 SFBCS cases. Participants signed informed written consent prior to participation. Studies were approved by their corresponding Institutional Review Boards.

Exposure assessment

Smoking measures included: ever smoking (≥100 cigarettes with at least one cigarette/day for ≥six months), never, current, or former smoking during the referent year (calendar year pre-diagnosis); intensity (cigarettes/day); duration (years smoked); pack-years (intensity times duration); and recency (years since quitting for former smokers). Passive smoke exposure, collected in 4-CBCS only, was defined as the number of hours/week exposed both inside and outside the home during the referent year and at ages 15, 30, and 50 years. Long-term passive smoke exposure was based on average exposure at ages 15 and 30 years and during the referent year for women aged <50 years; and at ages 15, 30, and 50 years and during the referent year for women aged ≥50 years (36).

Covariates

Women who reported having periods during the referent year were classified as premenopausal. Women were considered postmenopausal if they reported a natural menopause, taking hormone therapy, or still having periods but were above the 95th percentile of age for ethnicity of those who reported having a natural menopause within their

study center. BMI was calculated as self-reported weight (kg) during the referent year, divided by measured height squared (m^2). Grams of alcohol intake was based on self-reported consumption over the lifetime, with the exception of a subset of SFBCS cases for whom it was consumption during the referent year. Physical activity was based on hours of vigorous intensity activity/week during the referent year. Education was categorized as completion of high school or less or some college/graduate school. Ethnicity was based on self-report in both studies; a few women self-identified as NA and were combined with Hispanic women (37). NA ancestry was based on 104 ancestry informative markers to distinguish European and NA ancestry (40), genotyped using a multiplexed bead array assay (GoldenGate chemistry, Illumina, San Diego, California) following Whole Genome Amplification.

Tumor characteristics and survival

Statewide cancer registries provided information on disease stage, ER/PR status (determined by diagnosing pathologists), months of survival post-diagnosis, and primary cause of death. Survival data were through December 2011 for Utah, Colorado, and California, and through 2010 for Arizona and New Mexico. Surveillance Epidemiology and End Results (SEER) summary disease stage was categorized as local, regional, or distant.

Statistical analysis

Genetic admixture, the proportion of an individual's genome originating from one of two original founding populations (European and NA), was inferred using STRUCTURE 2.0, a multilocus genetic model-based clustering algorithm (41). Categorization of NA ancestry was based on the distribution of NA ancestry in control women (40). Two categories were used for the present analyses: low (<29%) versus moderate/high (≥29%). Descriptive statistics were calculated for potential confounders: t-tests and chi-square tests were used to compare smoking status categories. Other smoking measures were defined as cigarettes/day (<20, ≥20); duration (<20, ≥20 years); pack-years (<20, ≥20, <35, ≥35); recency (<20, ≥20 years); and passive smoke exposure hours: average long-term (none, low (1-8), moderate/high (>9)), and recent (none, low (1-10), moderate/high (>10)). Passive smoke exposure categories were based on distribution of exposure hours and events; three strata best fit the data and allowed sufficient power for assessing associations.

Associations between smoking and breast cancer-specific, non-cancer, and all-cause mortality were evaluated using multivariable Cox proportional hazards models (PHREG). Hazard ratios (HR) and 95% confidence intervals (CI) were estimated with months post-diagnosis as the time scale with the following referent groups: never smokers for active smoking analyses and no active/no passive smokers for passive smoking analyses. Covariates were retained in the final models for the three mortality outcomes if in the breast cancer-specific analysis the univariable p-values were ≤0.20, and if adjustment produced a change of ≥10% in the HR for smoking, allowing for direct comparison of results across all analyses. Age and study center were matching variables and included in all models. Physical activity, menopausal status, NA ancestry, and ER/PR status were excluded from final models. Participants were censored if they were lost to follow-up; or died of causes not

related to the outcomes. Those with unspecified cause of death were censored at death date; sensitivity analysis indicated that their inclusion did not meaningfully alter estimates.

For breast cancer-specific mortality, likelihood-ratio tests were used to assess two-way interactions between current smoking and ethnicity, NA ancestry, menopausal status, overweight/obese (BMI <25, ≥25 kg/m^2), ER/PR status (positive, negative), disease stage (local, regional/distant), long-term alcohol consumption (none/low <5gm/day, moderate/high ≥5gm/day), and time since diagnosis (≤5, >5 years). 'Time since diagnosis' describes the short (0-5 years) and long-term (5+ years) survival by smoking status post-diagnosis. Chi-square (X^2) test Wald-p-values for interaction terms are reported. An adjusted breast cancer survival curve, based on PHREG model estimates of the survival function for ethnicity and smoking status was plotted. P-values or p-trend <0.05 were deemed statistically significant. The proportional hazards assumption was tested graphically and statistically using an interaction of main effects and covariates with the log of survival time (42). All analyses, with the exception of all-cause mortality, met the proportional hazards assumption. Age and stage appeared to be time dependent; therefore models for all-cause mortality that included time interaction terms for both were evaluated. Differences between the models with the additional time interaction terms and standard model were not meaningful; hence, we present only the results from the more widely used models. Analyses were based on 2,218 invasive cases (4-CBCS n=1,812; SFBCS n=406) with complete exposure data for significant covariates and active smoking, and 1,804 (4-CBCS only) for passive smoke exposure. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Approximately 60% of cases were never smokers, 26.8% were former smokers, and 13.4% were current smokers (Table 1). A higher proportion of current smokers were younger (mean 52.6 years) at diagnosis compared to never (mean 54.5 years) and former (mean 56 years) smokers; reported higher long-term alcohol consumption (34.9% *vs.* 12.8% and 30.6%, respectively); were less likely to be overweight/obese (54.7% *vs.* 66.3% and 60%, respectively); and were deceased by the end of follow-up (27.8% *vs.* 18.9% and 18.7%, respectively). Hispanic/NA women reported never smoking (66.1%) more frequently than NHW women (54%). Passive smoke exposure was reported by 48% of current, 32% of former, and 15% of never smokers. The median follow-up for all women was 10.6 years. Of 445 deaths, 243 (54.6%) were attributable to breast cancer (60.1% never; 19.7% former; and 20.2% current smokers).

Mortality outcomes: ever smokers

Risk of breast-cancer-specific (HR=1.55, 95% CI:1.11-2.16) and all-cause (HR=1.68, 95% CI:1.30-2.17) mortality was significantly increased for current compared to never smokers (Table 2). Non-cancer mortality (HR=1.68, 95% CI:1.12-2.51) was significantly increased among ever smokers. No significant associations were observed for smoking intensity and duration among ever smokers with breast cancer-specific mortality. Risk of non-cancer mortality was significantly increased for women who smoked ≥20 cigarettes/day (HR=1.86),

≥20 years (HR=1.79), or ≥35 (HR=2.46) pack-years. Similarly, all-cause mortality was significantly higher for women who smoked ≥20 years (HR=1.47) and ≥35 pack-years (HR=1.82). Although risk of breast cancer-specific mortality was reduced among those who quit ≥20 years prior to their diagnosis, the association was not significant due to small numbers (n=16).

Mortality outcomes: current smokers

Breast cancer-specific mortality was significantly increased among current smokers who smoked ≥20 years (HR=1.60, 95% CI:1.11-2.30) or <20 cigarettes/day (HR=1.69, 95% CI: 1.14-2.50) (Table 3). Breast cancer-specific mortality differed between ethnic and smoking status groups (p=0.01); however, none of the pair-wise comparisons were statistically significant after adjustment for multiple comparisons (Figure 1). When stratified, both NHW and Hispanic/NA current smokers had an increased risk of breast cancer-specific mortality (HR=1.51 and HR=1.58, respectively), although results were non-significant (Table 4). Results were similar by proportion of NA ancestry. Stronger associations were found among current smokers who were postmenopausal (HR=1.65, 95% CI:1.02-2.64), overweight/obese (HR=1.74, 95% CI:1.13-2.69), moderate/high alcohol consumers (HR=2.91, 95% CI: 1.37-6.18), and >5 years post-diagnosis (HR=1.75, 95% CI:1.12-2.72) (Table 4). There were no significant interactions for any of these factors or tumor characteristics (Table 4).

Mortality outcomes: passive smokers

Moderate/high passive smoke exposure during the referent year was significantly associated with breast cancer-specific mortality among all women (HR=1.54 95% CI:1.04-2.26) and never smokers (HR=2.12 95% CI:1.24-3.63), and all-cause mortality among never smokers (HR=1.83, 95% CI:1.17-2.88) (Table 2). The associations between long-term passive exposure and breast cancer-specific, all-cause, and non-cancer mortality were non-significant.

DISCUSSION

Our results suggest that women who smoked regularly at the time of breast cancer diagnosis had a significantly increased risk of breast cancer-specific (HR=1.5) and all-cause (HR=1.6) mortality compared to women who never smoked. Breast cancer-specific mortality was significantly higher among current smokers who reported smoking for ≥20 years (HR=1.6). Hispanic/NA and NHW women had comparable elevated risk estimates. Although interactions were not statistically significant, the association of current smoking with breast cancer-specific mortality was stronger among women who were postmenopausal, overweight/obese, and long-term alcohol consumers.

The lack of association between ever smoking and breast cancer-specific mortality agrees with Calle et al (18), but contrasts with three studies reporting increased risk (HR range: 1.26-1.40) (16, 27, 43). We found a positive association between ever smoking and all-cause mortality, similar to previous reports (14, 16). We also observed a significant relationship between increasing pack-years of smoking and non-cancer mortality, similar to a previous report (23). While a positive association between current smoking and death from ‘other

causes' was reported previously, other cancers were included as events (12, 23). Smoking affects CVD and pulmonary mortality by impairing immune function and exacerbating comorbid conditions (2). It is unclear whether these pathways affect breast cancer survival also (25).

Six studies have reported that current smoking is associated with risk of breast cancer-specific mortality (12, 18-23), in which the prevalence of current smoking varied from 4.6% (28) to 39.5% (23), and mean follow-up time was ≥5 years. Also, the proportion of deaths ranged widely from 0.15% (18) to 45.3% (25). In the present study, 13.4% (n=298) of women reported current smoking and 16.4% (n=49) of them died of breast cancer. A recent meta-analysis (17), reported a significant summary estimate for breast cancer-specific mortality for current smokers (HR=1.33, 95% CI:1.12-1.58) (12, 13, 16, 19, 21, 22, 24, 25, 27). Additionally, several studies have reported an association between current smoking and all-cause mortality (12, 13, 17, 20, 22-25) with estimates ranging from 1.16 (25) to 2.63 (12).

We did not find an association between former smoking and risk of breast cancer-specific mortality, possibly due to reduced power or to behavioral changes that decreased mortality risk. Few studies have reported a significant association, even considering time from cessation to diagnosis (20, 24, 26, 28). Results are conflicting, with HRs ranging from 0.46 in British (24) to 4.79 in Japanese (26) women. However, Pierce et al. (20) found a dose-response relationship, with the highest risk of death associated with ≥35 pack-years of smoking (HR=1.61, 95% CI: 1.28-2.03), and Saquib et al. (28) reported an increased risk among those who had smoked ≥20 pack-years (HR=1.62, 95% CI:1.11-2.37).

Some previous studies reported increased risk of breast cancer death among smokers who were premenopausal (12, 22), had ER positive tumors (12, 13), were older at diagnosis (16), or overweight/obese (12, 13, 23). The increased risk in current smokers who were overweight/obese, postmenopausal could be due to increased bioavailable estrogen and IGF-1, which stimulate cell proliferation (44). Increased risk in moderate/high alcohol consumers could be due to interference with estrogen pathways via ethanol metabolism (45). Synergistic effects on mortality in these subgroups are therefore plausible.

It has been suggested that including women exposed to passive smoke in the never smoking referent group attenuates risk estimates (46). We compared results for analyses using a no active smoking vs. a no active/no passive smoking referent group. HRs for current smoking with breast cancer-specific and all-cause mortality increased by only 12% and 6%, respectively, when based on a no active/no passive smoking referent group. However, CIs overlapped and statistical power was reduced due to the use of a smaller referent group (n=321) (3). Moreover, women who have never been exposed to passive smoke may differ in many ways from those who have been exposed.

Four reports (27, 29-31) evaluating the relationship between passive smoke exposure and breast cancer-specific mortality reported no significant associations with a spouse who smoked, exposure in the home or workplace, or by intensity and duration; however, none evaluated passive smoke exposure at multiple time periods to estimate lifestyle exposure.

We found a significant association of breast cancer-specific mortality with recent passive smoke exposure, but not with average long-term exposure. However, we did not have data for exposure source, duration, dosage, or changes in intensity over time, which could measure cumulative exposure to passive smoking, as included in the 2014 Surgeon General's Report (3) and 2007 California Environmental Protection Agency Report (46).

Smoking may affect breast cancer-specific mortality by several mechanisms. Compounds contained in cigarette smoke reach breast tissue and activate genotoxic metabolites that damage DNA, form DNA adducts, disrupt hormone metabolism, and impair immune function (2). Cigarette smoke may influence the metastatic potential of cancer cells, cell adhesiveness, and stimulate tumor angiogenesis and growth. Smoking is associated with less favorable prognostic markers that affect tumor behavior (5-8), including increased frequency and larger metastases to lymph nodes and lungs (5-8), increased risk for ER/PR negative tumors (9), and regional stage disease (10). Pierce et al. recently reported that former and current smoking increases risk of breast cancer recurrence by 37% and 41%, respectively (20). Similarly, Bishop and colleagues found that recurrence was 6.7 times higher for current smokers at the time of a partial mastectomy and radiation therapy compared to nonsmokers (47). Furthermore, Peppone et al. found that smoking is associated with a higher symptom burden during and after treatment, which may influence completion of treatment regimens (48).

This study has some limitations. Smoking exposure was limited to prior to diagnosis with no follow-up for change in status. Data were self-reported with potential recall bias. Statistical power was limited for detection of effect modifiers further categorized by smoking intensity and duration. Thirty-five percent of cases were missing smoking data, however 99.6% of these were SFBCS participants (diagnosed between 1995-1999) who were not asked about smoking habits, suggesting less potential for differential bias than if they had refused to respond. Data for treatment, mode of detection, tumor characteristics (lymph node involvement, histological grade, HER2/neu status), response to treatment, and screening history by smoking status were unavailable. It is possible that current smokers received less aggressive, interrupted/incomplete treatments because of poor general health (48), which can differently impact survival outcomes and findings should be interpreted with caution. We were, however, able to evaluate multiple other covariates including demographic, behavioral, and tumor prognostic markers such as stage and ER/PR status.

There are several strengths to our study. This study is the first to evaluate whether associations between smoking and breast cancer-specific mortality differ by Hispanic/NA and NHW ethnicity and by proportion of NA ancestry. We had a relatively long follow-up time (median=10.6 years); thus, our analyses included women with local and regional stage disease, while studies with shorter follow-up (5-6 years) mainly reflect mortality in women with distant stage disease. We ascertained vital status from state-wide tumor registries and the National Death Index, which reduced potential misclassification of cause of death. We were able to evaluate passive smoke exposure inside and outside of the home for various ages in the subset of women from 4-CBCS; although, there is potential recall bias of passive smoke exposure at age of 15 among a mostly postmenopausal group. Lastly, while other

studies use the definition ‘100 cigarettes in a lifetime’, we defined regular use of cigarettes as ‘at least 1 cigarette/day for 6 months or longer.’

Our results strongly suggest that active and passive smoking around the time of breast cancer diagnosis is associated with increased risk of breast cancer-specific and all-cause mortality. A history of ever smoking is associated with increased risk of non-cancer mortality, which is primarily attributed to cardiovascular and pulmonary diseases. Lastly, the association between current smoking and breast cancer-specific mortality did not differ by ethnicity, which suggests that smoking does not explain differences in breast cancer survival observed between NHW and Hispanic/NA women. More research is needed on the association of smoking with breast cancer-specific mortality in ethnically diverse populations and subgroups, and how changes in smoking habits following diagnosis impact breast cancer outcome. Ten to 20% of women smoke post-breast cancer diagnosis (49, 50), with the highest proportion (43%) among women aged 18-40 years (50). Smoking at breast cancer diagnosis is a major modifiable risk factor for poorer outcomes, and effective smoking cessation and maintenance programs should be routinely recommended for women with breast cancer.

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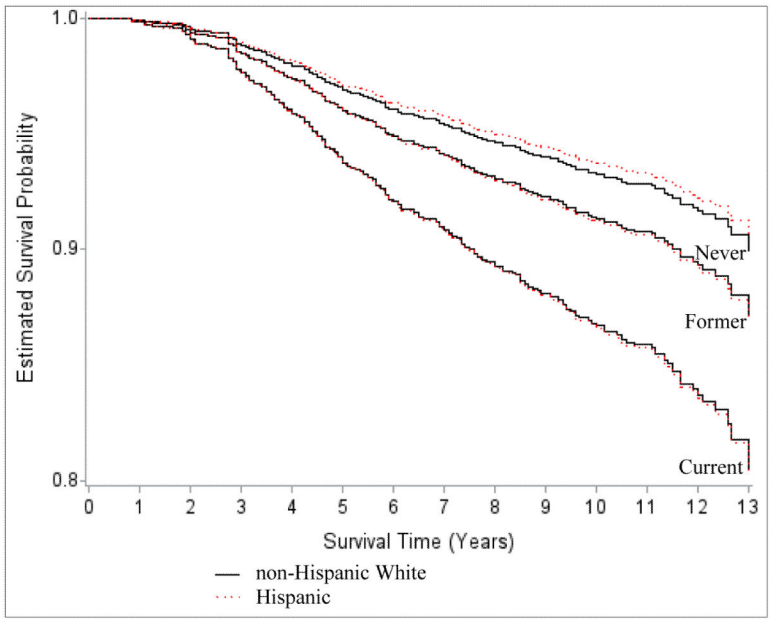

Figure 1. Adjusted breast cancer survival by ethnicity and cigarette smoking status

Log-rank p-value=0.01; Wald p=0.01; Adjusted for age, study, body mass index, stage, alcohol consumption, and education

Sidak multiple comparisons adjusted Log-rank pair-wise p-values: Within Hispanic women: current vs. former, p= 0.22; current vs. never, p=0.99; former vs. never, p= 0.99.

Within non-Hispanic women: current vs. former, p= 0.10; current vs. never, p=0.96; former vs. never, p= 0.99

Table 1

Study Characteristics by Smoking Status among Women Diagnosed with Invasive Breast Cancer, the Breast Cancer Health Disparities Study.

	All women		Never smokers		Former smokers		Current smokers		
	n=2,218		n=1,325 (59.7%)		n=595 (26.8%)		n= 298 (13.4%)		p-value[a]
Median follow-up, years, IQR[b]	10.6	3.4	10.6	3.2	10.7	3.3	10.4	4.4	0.26
Age at diagnosis, mean, SD	54.5	11.0	54.2	11.2	56	10.7	52.6	10.2	<0.0001
Study, n %									
4-CBCS	1812	81.7	1057	79.8	508	85.4	247	82.9	0.03
SFBCS	406	18.3	268	20.2	87	14.6	51	17.1	
Self-reported ethnicity, n %									
NHW	1198	54.0	651	49.1	372	62.5	175	58.7	<0.0001
Hispanic/NA	1020	46.0	674	50.9	223	37.5	123	41.3	
Native American ancestry[c], n %									
Low	1055	47.6	593	44.8	319	53.6	143	48.0	<0.0001
Moderate/High	671	30.2	464	35.0	133	22.4	74	24.8	
Missing	492	22.2	268	20.2	143	24.0	81	27.2	
Menopausal status[d], n %[c]									
Premenopausal	815	36.7	501	37.8	200	33.6	114	38.3	0.54
Postmenopausal	1372	61.9	803	60.6	391	65.7	178	59.7	
Missing	31	1.4	21	1.6	4	0.7	6	2.0	
Body mass index, kg/m^2, n %									
<25	820	37.0	447	33.7	238	40.0	135	45.3	<0.0001
≥25	1398	63.0	878	66.3	357	60.0	163	54.7	
Education, n %									
High school or less	930	41.9	574	43.3	224	37.7	132	44.3	0.50
Some college/graduate school	1288	58.1	751	56.7	371	62.4	166	55.7	
Alcohol consumption n %									
None/Low	1762	79.4	1155	87.2	413	69.4	194	65.1	<0.0001
Moderate/High	456	20.6	170	12.8	182	30.6	104	34.9	
Passive smoke exposure hours[e]									
None	377	17.0	321	24.2	41	6.9	15	5.0	<0.0001
Low	526	23.7	341	25.7	133	22.3	52	17.4	
Moderate	468	21.1	241	18.2	167	28.1	60	20.1	
High	433	19.5	154	11.6	161	27.1	118	39.6	
Missing	414	18.7	268	20.2	93	15.6	53	17.8	
Time since diagnosis, n %									
≤5 years	274	12.3	155	11.7	77	12.9	42	14.1	0.21
>5 years	1944	87.7	1170	88.3	518	87.1	256	85.9	
Stage, n %									

	All women		Never smokers		Former smokers		Current smokers		
	n=2,218		n=1,325 (59.7%)		n=595 (26.8%)		n= 298 (13.4%)		p-value[a]
Local	1403	63.3	821	62.0	397	66.7	185	62.1	
Regional	787	35.5	485	36.6	191	32.1	111	37.3	0.31
Distant	28	1.3	19	1.4	7	1.2	2	0.7	
ER status[f], n %									
Positive	1372	61.9	826	62.3	356	59.8	190	63.8	0.63
Negative	408	18.4	246	18.6	113	19.0	49	16.4	
Missing	438	19.7	253	19.1	126	21.2	59	19.8	
PR status[f], n %									
Positive	1198	54.0	726	54.8	310	52.1	162	54.4	0.81
Negative	582	26.2	346	26.1	159	26.7	77	25.8	
Missing	438	19.7	253	19.1	126	21.2	59	19.8	
Vital status, n %									
Alive	1773	79.9	1074	81.1	484	81.3	215	72.2	0.005
Deceased	445	20.1	251	18.9	111	18.7	83	27.8	
Cause of death[g], n %									
Breast cancer	243	54.6	146	58.2	48	43.2	49	59.0	
Other cancer	54	12.1	27	10.8	14	12.6	13	15.7	0.99
Non-cancer	102	22.9	52	20.7	37	33.3	13	15.7	
Unspecified	46	10.3	26	10.4	12	10.8	8	9.6	

Abbreviations: 4-CBCS- 4-Corners Breast Cancer Study; ER-Estrogen receptor; PR-Progesterone receptor; SFBCS-San Francisco Bay Area Breast Cancer Study. Note: column percentages may not total 100% due to rounding.

[a]For tests of differences by cigarette status, p-value from t-tests for continuous variables and Mantel-Haenszel Chi square p-values for categorical variables are reported.

[b]Chi-square p-value was derived using a non-parametric Kruskal-Wallis test to evaluate differences in the median follow-up times

[c]Data for Native American ancestry are available for 1,726 of the 2,218 cases included in this analysis.

[d]Data for menopausal status are available for 2,187 of the 2,218 cases included in this analysis.

[e]Exposure to passive smoke is based on data available from 4-CBCS for 1,804 of the 2,218 cases included in this analysis; this variable captures long-term exposure to passive smoke and was based on the average of exposure hours/week reported for ages 15 and 30 years and during the referent year for women <50 years of age; and at ages 15, 30, and 50 years and during the referent year for women ≥50 years of age.

[f]Data for ER/PR status are available for 1,780 of the 2,218 cases included in this analysis.

[g]Non-cancer deaths included: cardiovascular diseases (CVD) (32%); pulmonary diseases (21%); renal failure/kidney diseases (9%); diabetes-related illnesses (7%); and other conditions (31%).

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Table 2

Associations Between Active and Passive Smoking History and Breast Cancer-specific, Non-cancer, and All-cause Mortality among Women Diagnosed with Invasive Breast Cancer, the Breast Cancer Health Disparities Study.

	Breast cancer mortality (243 events)				Non-cancer mortality (102 events)				All-cause mortality (445 events)			
	Events	**Total**	**HR**	**95% CI**	**Events**	**Total**	**HR**	**95% CI**	**Events**	**Total**	**HR**	**95% CI**
Active smoke exposure[a]												
Never smokers	146	1325	1.00	Referent	52	1325	1.00	Referent	251	1325		
Smoking status												
Ever	97	893	1.05	0.81, 1.38	50	893	1.68	1.12, 2.51	194	893	1.21	0.99, 1.47
Former	48	595	0.79	0.57, 1.11	37	595	1.68	1.08, 2.60	111	595	1.00	0.79, 1.26
Current	49	298	1.55	1.11, 2.16	13	298	1.68	0.90, 3.13	83	298	1.68	1.30, 2.17
Cigarettes/day												
<20	66	565	1.1	0.81, 1.48	27	565	1.37	0.86, 2.19	114	565	1.13	0.90, 1.42
≥20	31	324	0.98	0.65, 1.46	20	324	1.86	1.07, 3.23	77	324	1.29	0.99, 1.69
p_{trend}			0.89				0.02				0.06	
Duration, years												
<20	42	416	0.91	0.64, 1.30	14	416	1.29	0.71, 2.35	64	416	0.92	0.69, 1.22
≥20	55	465	1.24	0.90, 1.72	33	465	1.79	1.14, 2.81	126	465	1.47	1.14, 1.79
p_{trend}			0.30				0.01				0.01	
Pack-years												
<35	74	677	1.05	0.78, 1.40	29	677	1.33	0.84, 2.10	133	677	1.11	0.90, 1.38
≥35	15	135	1.43	0.82, 2.49	14	135	2.46	1.32, 4.59	45	135	1.82	1.30, 2.54
p_{trend}			0.33				0.008				0.003	
Recency, years												
<20	32	342	0.92	0.62, 1.38	14	342	1.34	0.72, 2.47	62	342	1.08	0.81, 1.44
≥20	16	251	0.65	0.38, 1.10	21	251	1.78	1.06, 3.01	47	251	0.92	0.67, 1.27
p_{trend}			0.15				0.03				0.88	
Long-term passive smoke exposure[b]												
All women												
None	45	377	1.00	Referent	18	377	1.00	Referent	74	377	1.00	Referent

	Breast cancer mortality (243 events)				Non-cancer mortality (102 events)				All-cause mortality (445 events)			
	Events	**Total**	**HR**	**95% CI**	**Events**	**Total**	**HR**	**95% CI**	**Events**	**Total**	**HR**	**95% CI**
Low	55	526	0.97	0.65, 1.45	18	526	0.59	0.30, 1.15	94	526	0.85	0.62, 1.16
Moderate/high	104	901	1.09	0.75, 1.59	37	901	0.64	0.35, 1.18	192	901	0.95	0.71, 1.27
p_{trend}			0.59				0.22				0.95	
Never smokers												
None	36	321	1.00	Referent	14	321	1.00	Referent	59	321	1.00	Referent
Low	34	341	1.00	0.62, 1.62	9	341	0.49	0.21, 1.16	58	341	0.92	0.63, 1.33
Moderate/high	51	395	1.34	0.86, 2.09	12	395	0.54	0.24, 1.22	78	395	1.08	0.76, 1.54
p_{trend}			0.18				0.14				0.64	
Recent passive smoke exposure[c]												
All women												
None	123	1266	1.00	Referent	50	1266	1.00	Referent	227	1266	1.00	Referent
Low	42	291	1.38	0.96, 1.99	13	291	1.49	0.80, 2.79	65	291	1.49	0.80, 2.79
Moderate/high	39	247	1.54	1.04, 2.26	10	247	1.32	0.65, 2.67	68	247	1.32	0.65, 2.67
p_{trend}			0.02				0.27				0.27	
Never smokers												
None	79	816	1.00	Referent	28	816	1.00	Referent	139	816	1.00	Referent
Low	24	152	1.43	0.89, 2.31	4	152	1.13	0.39, 3.31	32	152	1.29	0.86, 1.93
Moderate/high	18	89	2.12	1.24, 3.63	3	89	1.27	0.37, 4.34	24	89	1.83	1.17, 2.88
p_{trend}			0.004				0.67				0.01	

Abbreviations: 4-CBCS-4-Corners Breast Cancer Study; SFBCS-San Francisco Bay Area Breast Cancer Study

Note: p-value for trend is the linear trend of the hazard ratios further categorized by smoking measures of intensity and duration; never smokers are the referent group for all active smoke exposure analyses and are included in the p-trend calculation.

[a] Active smoking estimates adjusted for age, study, ethnicity, stage, body mass index, alcohol consumption, and education; estimates by intensity and duration are among ever smokers; recency is defined as time since quitting smoking among former smokers only

[b] Exposure to passive smoke is based on data available from 4-CBCS for 1,804 of the 2,218 cases included in this analysis; this variable captures long-term exposure to passive smoke and was based on the average of exposure hours/week reported for ages 15 and 30 years and during the referent year for women <50 years of age; and at ages 15, 30, and 50 years and during the referent year for women ≥50 years of age. Estimates are adjusted for 4-CBCS study sites, age, ethnicity, stage, body mass index, alcohol consumption, cigarette pack-years (included in model with everyone), and education

[c] Exposure to passive smoke is based on data available from 4-CBCS for 1,804 of the 2,218 cases included in this analysis; this variable captures recent exposure to passive smoke and was based on the average of exposure hours/week during the referent year. Estimates are adjusted for 4-CBCS study sites, age, ethnicity, stage, body mass index, alcohol consumption, cigarette pack-years (included in model with everyone), and education.

Table 3

Risk of Breast Cancer-specific Mortality Stratified by Smoking Intensity and Duration among Current Smokers, the Breast Cancer Health Disparities Study.

	Breast cancer-specific mortality			
	Events	**Total**	**HR[a]**	**95% CI**
Never smokers	146	1325	1.00	Referent
Current smokers	49	298	1.55	1.11, 2.16
Cigarettes/day				
<20	33	176	1.69	1.14, 2.50
≥20	16	121	1.31	0.77, 2.22
Duration, years				
<20	8	47	1.33	0.64, 2.76
≥20	41	250	1.60	1.11, 2.30
Pack-years				
<20	25	133	1.52	0.98, 2.37
≥20	22	157	1.44	0.90, 2.29

[a] Adjusted for age, study, ethnicity, stage, body mass index, alcohol consumption, and education.

Table 4

Risk of Breast Cancer-specific Mortality among Current Smokers Stratified by Socio-demographic and Prognostic Factors, the Breast Cancer Health Disparities Study.

	Never Smokers		Current vs. Never Smokers				
	Events	Total	Events	Total	HR	95% CI[a]	p-value[b]
Self-reported ethnicity							
NHW	70	651	29	175	1.51	0.96, 2.38	0.98
Hispanic/NA	76	674	20	123	1.58	0.94, 2.64	
Native American ancestry							
Low	57	593	21	143	1.49	0.88, 2.52	0.92
Moderate/High	47	464	13	74	1.69	0.87, 3.27	
Menopausal status							
Premenopausal	67	501	20	114	1.41	0.82, 2.42	0.89
Postmenopausal	76	803	26	178	1.65	1.02, 2.64	
Body mass index, kg/m^2							
<25	48	447	21	135	1.33	0.77, 2.29	0.44
≥25	98	878	28	163	1.74	1.13, 2.69	
Alcohol consumption							
None/Low	134	1155	31	194	1.36	0.91, 2.02	0.15
Moderate/High	12	170	18	104	2.91	1.37, 6.18	
Time since diagnosis							
≤5 years	69	155	19	42	1.40	0.79, 2.48	0.68
>5 years	77	1170	30	256	1.75	1.12, 2.72	
SEER Summary Stage							
Local	47	821	17	185	1.66	0.94, 2.94	0.85
Regional/Distant	99	504	32	113	1.53	1.00, 2.34	
ER status							
Negative	34	246	10	49	1.58	0.75, 3.30	0.86
Positive	85	826	29	190	1.55	1.00, 2.42	
PR status							
Negative	43	346	16	77	1.72	0.94, 3.15	0.31
Positive	76	726	23	162	1.38	0.85, 2.26	

Abbreviations: SEER-Surveillance Epidemiology & End Results; ER-Estrogen receptor; PR-Progesterone receptor

[a] Adjusted for age, study, ethnicity, stage, body mass index, alcohol consumption, and education. When modification by a specific factor was evaluated, that factor was not included as a covariate in the multivariable model;

[b] p -value for interaction term. P-values for likelihood ratio tests (difference in Chi-square test statistics for the models) were not significant.