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Smoking and Breast Cancer Risk by Race/Ethnicity and Estrogen and Progesterone Receptor Status: The Multiethnic Cohort (MEC) Study

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Abbreviations: BMI: body mass index; CI: confidence interval; ER+: Estrogen receptor positive, ER–: Estrogen receptor negative; HR: hazard ratio; MEC: Multiethnic Cohort; PR+: Progesterone receptor positive; PR–: Progesterone receptor negative; SD: standard deviation;

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Abstract;

Background. The purpose of this study was to examine if the smoking-related higher breast cancer risk was similar for the five race/ethnicity groups in the MEC and by estrogen (ER) and progesterone (PR) receptor status.

Methods: From 1993 to 2013, we followed 67,313 women who were enrolled in the Multiethnic Cohort study at 45–75 years of age. We identified breast cancer cases and tumor receptor status via linkage to the Hawaii and California Surveillance, Epidemiology, and End Results Program cancer registries through December 2013. We used Cox proportional hazards regressions to estimate multivariable-adjusted hazard ratios with 95% confidence intervals (CI).

Results: During a mean follow-up of 16.7 years, we identified 4,230 incident, invasive breast cancer cases. Compared with parous never smokers, parous ever smokers who had smoked more than five years before their first live childbirth had a higher risk of breast cancer overall of 31% (95% CI: 1.14-1.51). This higher risk was 51% (95% CI: 1.05-2.16) for African Americans, 66% (95% CI: 1.10-2.50) for Native Hawaiians, 42% (95% CI: 1.13-1.78) for Whites, 37% (95% CI: 1.17-1.61) for ER+ tumors and 33% (95% CI: 1.11-1.59) for PR+ tumors. No difference was suggested by racial/ethnic groups ($P_{heterogeneity}$ = 0.15) or tumor receptor status ($P_{heterogeneity}$ = 0.60 by ER status and 0.95 by PR status).

Conclusions: We find that the higher breast cancer risk related to smoking is similar across racial/ethnic groups and by ER and PR receptor status, indicating that breast cancer should be considered as a smoking related cancer.

Key words: Breast cancer; cohort studies; ethnic differences; ER positive tumors; hormone receptor tumors; Multiethnic Cohort Study; non-alcohol drinkers; PR positive tumors; smoking; smoking duration before first childbirth

Key Messages

- Smoking is not an established risk factor for breast cancer.
- Our main findings suggest that the smoking related breast cancer risk is similar across racial/ethnic groups and by estrogen and progesterone receptor status, indicating that breast cancer is a smoking related cancer.
- The results of the present study, together with those from other recent cohort studies, support the notion that women who start smoking as teenagers and continue until they get pregnant years later, have a higher risk of breast cancer.
- Public health agencies reviewing the smoking and breast cancer data should reconsider the available evidence and update their conclusions.
- Breast cancer prevention messages should address smoking by adolescent girls.

Introduction

Smoking is not an established risk factor for breast cancer, but increasing evidence supports an association especially for women who initiated smoking before first childbirth (1-10). In contrast to the developed world, tobacco consumption is increasing in the developing world and more women are initiating smoking in their teens than in previous generations (11;12). We previously reported that risk of breast cancer in the Multiethnic Cohort (MEC) study (13) was directly associated with various measures of active smoking. The magnitude of the association among women who did not drink alcohol was similar to that in the overall study population, indicating that confounding by alcohol did not explain the smoking-breast cancer association.

Differences in risk by race/ethnicity have not been addressed in detail with regard to the smoking and breast cancer association. Most recent cohort studies reporting on this subject included only African Americans (14), Japanese (15) or only Whites (16-21) or mostly (22-27). Moreover, the 2014 US Surgeon General's report raised the possibility of differences in the risk associated with smoking by hormone receptor status (4). This topic has been examined in several recent cohort studies (14;18-24;26), but the results have remained inconsistent.

The purpose of this study was to examine if the smoking-related higher breast cancer risk was similar for the five race/ethnicity groups in the MEC and by estrogen (ER) and progesterone (PR) receptor status.

Methods

Study population

The MEC study consists of more than 215,000 men and women who were aged 45-75 years and living in California and Hawaii at time of cohort entry. It comprises mainly five racial/ethnic populations: African Americans, Japanese Americans, Latinos, Native Hawaiians, and Whites. The cohort has been previously described in detail (28;29). Briefly, between 1993 and 1996, participants enrolled in the study by completing a 26-page mailed questionnaire asking detailed information about demographic factors, dietary habits, other lifestyle factors, prior medical conditions, and family history of common cancers. We identified potential participants through driver's license files from the state Department of Motor Vehicles, voter registration lists, and Health Care Financing Administration (Medicare) data files. The Institutional Review Boards of the University of Hawaii and the University of Southern California approved the study.

Altogether, 96,137 postmenopausal women returned the questionnaire. Women who did not belong to one of the five targeted racial/ethnic groups (N=5,506), who had a prior breast cancer based on questionnaire reports or information from tumor registry linkages (N=5,455), or who had missing information on alcohol intake (N=3,588), smoking status (N=1,698) were excluded. As the result, 79,890 participants remained for this analysis.

Data collection

At baseline, participants reported whether they had ever smoked at least 20 packs of cigarettes in their lifetime, the number of years they smoked cigarettes, the average number of cigarettes smoked per day during the period when they smoked, and the number of years since they quit smoking. We computed age at smoking initiation as age at questionnaire completion minus years smoking for current smokers, or as age at questionnaire completion minus the sum of

years smoking and years since quitting for former smokers. We also calculated pack-years as number of cigarettes smoked per day, divided by 20 and multiplied by the duration of smoking in years. For parous smokers, we calculated "years of smoking before first childbirth" as age at their first child's birth minus age at smoking initiation.

The baseline questionnaire asked about years of education, height and current weight for calculating body mass index (BMI, kg/m^2), age at and type of menopause, ever use of postmenopausal hormone therapy, and alcohol consumption during the past year. We calculated mean alcohol intake in g/day based on the alcohol content of different beverages and usual portion sizes.

We identified invasive incident cancer cases by linkage to the Surveillance, Epidemiology, and End Results Program cancer registries covering Hawaii and California. We classified breast cancer cases according to the organ site code (C50) in the International Classification of Diseases, Tenth Revision and according to estrogen and progesterone tumor receptor status categories (ER+, ER–, PR+, PR–) based on information from the registries. We identified deaths by linkage to death certificate files in Hawaii and California and to the National Death Index. Case ascertainment and vital status were complete through December 31, 2013. We calculated person-years from the start of follow-up to the date of invasive breast cancer diagnosis, death, or the end of follow-up (December 31, 2013), whichever occurred first.

Statistical analysis.

We calculated age-adjusted breast cancer incidence rates per 100,000 person-years, truncated to ages 45-85 years, weighted by the age distribution of the 2000 US standard population (30). We used Cox proportional hazards regression to model time to breast cancer, with age as the underlying time scale. Hazard ratios (HRs) with 95% confidence intervals (CIs) were computed for the associations with different measures of smoking exposure [smoking status at

cohort entry (never, former, current, ever); and among ever smokers, age at smoking initiation (<20, 20-24, ≥25 years), smoking duration (≤20, 21-30, ≥31 years), number of cigarettes smoked per day (≤10, 11-20, ≥21) and number of pack-years (≤10, 11-20, ≥21)], with never smokers as the reference group. We included as covariates [race/ethnicity (African American, Native Hawaiian, Japanese, Latina, and white, adjusted as a strata variable), age at cohort entry (continuous), family history of breast cancer (no, yes,), education (≤12; >12 years;), BMI (<25; 25–<30; ≥30 kg/m^2,), age at menarche (≤12; 13–14; ≥15 years;), age at first childbirth (no children; ≤20; 21–30; ≥31 years;), number of children for parous women (1; 2–3; ≥4;), age at and type of menopause (natural: age <45, 45–<50, 50–<55, ≥55 years; oophorectomy: age <45, 45–<50, ≥50 years; hysterectomy: age <45, 45–<50, ≥50 years,), postmenopausal hormone therapy (no current estrogen use; past estrogen use with or without progestin; current estrogen use without progestin; current estrogen use with past/current progestin;), and alcohol consumption (continuous as ethanol g/day). The proportional hazards assumption was tested using Schoenfeld residuals and was found to hold (31;32).

We conducted tests for linear trends by including an ordinal exposure variable with equally spaced scores in models and never smokers as the first category. We assessed heterogeneity in the association of breast cancer risk with smoking variables by race/ethnicity by testing the vector of parameters for the pairwise product terms between smoking and race against zero using a Wald test (31). For parous women, we estimated breast cancer risk by smoking initiation in relation to first childbirth (after or <1 year before first childbirth, 1-5 years before, >5 years before), compared with parous never smokers overall and stratified by the five racial/ethnic groups, adjusting for the applicable covariates described above. We repeated these multivariable analyses with three categories of smoking exposure (never, initiation at time of /after first birth, initiation before first birth). We then performed competing risk analysis using cause-specific models for time to receptor status breast cancer outcomes, with

censoring at diagnosis for any breast cancer cases with a receptor status other than that being considered (32-34). The receptor status outcomes considered were ER+ and ER–, PR+ and PR–, and a combination of positive and negative hormone receptor statuses as the outcomes. Cases with missing information on both ER and PR status (N=466) were excluded from these analyses. In order to compare the parameters by tumor receptor status, an augmented data approach as described in Lunn and McNeil (35) was implemented that computes simultaneous models for breast cancer of each receptor status type. Heterogeneity by tumor receptor status categories is assessed by a Wald test comparing the interaction between tumor receptor event type and smoking exposures, using robust variance estimates.

The primary analysis used a complete case approach which excluded women with missing data on any of the covariates (N=12,577), leaving 67,313 women for the multivariable analyses. The analyses were also rerun using multiple imputation models and 5 iterations, assuming the missing data were missing completely at random, conditional on age and ethnicity (36). The results of the complete case (excluding altogether 28,824 women) and multiple imputation models (excluding altogether 16,247 women) were very similar. We present the complete case analysis in the main tables and figure and in Supplementary tables S1 & S2.The imputation results are available in Supplemental tables S3-S5 .

We performed the analyses using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

During a mean follow-up of 16.7 years, we identified 4,230 incident, invasive breast cancer cases with at least one tumor hormone receptor type ascertained. Table 1 shows that the age-adjusted incidence rates for breast cancer ranged from 403 among Native Hawaiians to 217 per 100,000 person-years (truncated to ages 45-85) among Latinas. African Americans,

Native Hawaiians and Whites were more likely to be ever smokers than Japanese Americans and Latinas (Table 1).

Table 2 shows that compared with never smokers, ever smokers had a 9% higher breast cancer risk (95% CI: 1.02-1.16). The results did not suggest risk differences across the five racial/ethnic groups for ever versus never smokers ($P_{heterogeneity} = 0.65$). We observed direct associations with breast cancer risk overall, for smoking duration ($P_{trend} < 0.001$), number of cigarettes smoked daily ($P_{trend} = 0.004$), and number of pack-years ($P_{trend} <0.001$) and an inverse association for age at smoking initiation ($P_{trend} <0.001$). When we restricted the analyses to parous women, ever smokers who had smoked more than five years before their first live childbirth had a higher risk of breast cancer overall of 31% (95% CI: 1.14-1.51) compared with never smokers. This higher risk was 51% (95% CI: 1.05-2.16) for African Americans, 66% (95% CI: 1.10-2.50) for Native Hawaiians, and 42% (95% CI: 1.13-1.78 for Whites. Similar results were found for all five racial/ethnic groups ($P_{heterogeneity} = 0.15$). (Table 2).

As shown in Supplementary Table S1, the distribution of tumors by receptor status was similar for ever smokers compared to all cases and by racial/ethnic group. Native Hawaiians were more likely to be diagnosed with ER+ and PR+ tumors, and less likely to be diagnosed with ER– and PR– tumors. The opposite was true for African Americans (Supplementary Table S1).

Table 3 shows that compared with never smokers, ever smokers had an eight or nine % higher breast cancer risk for all four tumor subtypes, with corresponding CI's all including the null value. We observed positive trends for higher breast cancer risk with duration of smoking ER+ ($P_{trend} = 0.01$) and PR+ ($P_{trend} = 0.02$) tumors, for number of cigarettes per day for PR+ ($P_{trend} = 0.04$) tumors, and for pack-years for ER+ ($P_{trend} = 0.013$), and PR+ ($P_{trend} = 0.01$)

tumors. Similarly, we found an inverse association for age at smoking initiation and both ER+ (P_{trend} <0.001) and PR+ (P_{trend} <0.001) tumors.

When we restricted the analyses to parous women, women who initiated smoking >5 years before their first childbirth had a higher risk for all four hormone receptor categories: for ER+ tumors 37% (95% CI: 1.17,1.61), for ER– 44% (95% CI: 1.02-2.04, $P_{heterogeneity}$ = 0.60), for PR+ 33 % (95% CI: 1.11-1.59), and for PR– 60% (95% CI: 1.23-2.08, $P_{heterogeneity}$ = 0.95) (Table 3).

Supplementary Table S2 shows that when we stratified according to race/ethnicity and hormone receptor status; whites who had smoked >5 years before their first birth, had a higher risk of similar magnitude for ER+ 51% (95% CI: 1.18-1.94) and PR+ 52% (95% CI: 1.15-2.01) (Supplementary Table S2). The results did not suggest differences in the smoking and breast cancer risk associations across the five race/ethnic subgroups ($P_{heterogeneity}$ = 0.27 for ER+, 0.32 for PR+, 0.33 for ER+/PR+ and 0.09 for ER+/PR– tumors) for smoking initiation before first childbirth among parous ever smokers

Figure 1 (a-f) displays the association for ever compared with never parous smokers by two categories of smoking initiation (after or at the time of, and before first child birth), for all invasive cases and according to six (ER+, ER–, PR+, PR–, ER+/PR+, ER–/PR–) hormone receptor tumor categories overall and stratified by race/ethnic groups. The figure shows that for those who started before first live birth the association with breast cancer risk shows similar patterns for both positive and negative hormone receptor tumors overall and when stratified by race/ethnicity (Fig 1 (a-f).

Discussion

In this prospective study with three additional years of incident breast cancer cases, we confirm our previous findings showing that various measures of smoking exposure, i.e., age at smoking initiation, smoking duration, number of cigarettes/day, pack-years and smoking before first child birth, are associated with an elevated breast cancer risk for all five racial/ethnic groups. Among parous women, the magnitude of the higher breast cancer risk for those who initiated smoking before first birth was very consistent across racial/ethnic groups, except for Latinas for whom no association was observed. Furthermore, we show that these associations seem to be of similar magnitude by ER and PR status.

Past cohort studies that included only Whites all found a positive association with either active (17;20;21), or active and passive (16;18;19) smoking and breast cancer risk. A past study in African Americans (14) found a higher breast cancer risk for both active and passive smoking, while a study in Japanese (15) reported a higher risk for passive, but not for active smoking. Also, the Sister cohort study conducted in the US and Puerto Rico reported a higher risk for passive, but not active smoking (27).

In the MEC, four out of five tumors were hormone receptor positive, and the associations with smoking for this type of tumor were more consistent than for those with hormone receptor negative tumors, possibly because of the smaller number of cases for the latter. In EPIC (18), we found the strongest association with smoking for ER+/PR– breast tumors, as was reported in the US (24) and in Denmark (20). In all of these three cohorts, the vast majority of breast cancer cases were also either ER or PR positive tumors (18;20;24). In the present study, we used the same categories of smoking exposure as in our recent report from the Norwegian Woman and Cancer study (19). In that study, we found associations between smoking before first birth, and a higher breast cancer risk for both ER and PR positive and

negative hormone receptor tumors. Also, the Dutch study reported similar associations for the smoking and breast cancer associations for the different hormone receptor subtypes (21).

The two US studies (23) (14) study, as well as the previously mentioned pooled analysis (26), reported a smoking-related higher n breast cancer risk with ER+, but not with ER–, tumors. In all three studies (14;23;26), >80% of the tumors were estrogen receptor positive, like in the present study. The pooled analysis, including data from 14 cohort studies, had over 36 000 invasive breast cancer cases, of which 5000 were ER–. Such a sample size would have been sufficient to detect a modest higher risk with smoking in ER-tumors. We may have lacked power to detect a difference in association by ER status.

Our study has several major strengths. It focuses on the smoking-related risk of breast cancer in a multi-ethnic population, in which close to 90% of tumors were classified according to ER and PR status. In addition, all women were postmenopausal, the majority was non-drinkers of alcohol and we were able to adjust for most established breast cancer risk factors.

The main limitation of this study is that despite more than 4,000 incident postmenopausal breast cancer cases, the numbers of cases were relatively small for important subset analyses. The low proportion of ever smokers among Latinas and Japanese Americans, the late age of smoking initiation for African Americans, Japanese Americans and Latinas, and the low proportion of women who started to smoke before their first childbirth particularly among African Americans and Latinas reduced the power to examine these associations in more detail. Nevertheless, our study displays also strong positive associations for several of these subgroup analyses.

In a report from the Norwegian Women and Cancer Study, with a similar follow-up time as in the present study, we found that one in three deaths among middle-aged Norwegian women were smoking related (37). Smokers in the present study may have died from different causes

of smoking related deaths, before they were diagnosed with breast cancer . The reduction in life expectancy associated with smoking may conceal or obscure the association between the different measures of smoking exposure and breast cancer risk.

The association between active smoking and breast cancer risk became stronger when women exposed to passive smoking were excluded from the reference group in six cohort studies (14-16;18;19;27). Thus, our risk estimates may have been attenuated since women exposed to passive smoking could not be excluded from our reference group due to the lack of information on this potential risk factor. Our main findings suggest that the higher breast cancer risk related to smoking is similar across racial/ethnic groups and for estrogen and progesterone receptor status, indicating that breast cancer is a smoking related cancer. The previously cited expert reports (1-4) have described the biological mechanisms by which smoking may be a cause of breast cancer. All four conclude that these mechanisms provide plausibility to the causal nature of a smoking-breast cancer association (1-4). The results of the present study, together with those from other recent cohort studies, support the notion that women who starts smoking as teenagers and continue until they get pregnant years later, are at a higher risk of breast cancer. Public health agencies reviewing the smoking and breast cancer data should reconsider the available evidence and update their conclusions. Breast cancer prevention messages should address smoking by adolescent and young women.

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Supplementary Data

Supplementary data are available at *IJE* online.

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Conflict of interest: None declared. This work was mainly carried out while Professor Gram was a Visiting Scholar in the Epidemiology Program, University of Hawaii Cancer Center, Honolulu, Hawaii.

Disclosure of Potential Conflicts of Interest

No Potential Conflicts of Interest were disclosed

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Table 1. Distribution of selected characteristics given as %[a] and mean (SD)[b] for postmenopausal women at baseline in 1993-1996, by race/ethnicity and breast cancer status in the Multiethnic Cohort Study, followed to 2013 (N=67,313)

	African American (N=12,776)		Native Hawaiian (N=4,286)		Japanese American (N=19,043)		Latina (N=14,371)		White (N=16,837)	
	Cases	Noncases	Cases	Noncases	Cases	Noncases	Cases	Noncases	Cases	Noncases
No. of participants	754	12,022	375	3,911	1,306	17,737	667	13,704	1,128	15,709
Age at cohort entry, y[b]	63.0 (7.4)	62.8 (7.8)	58.9 (7.4)	59.1 (8.0)	62.6 (7.1)	63.2 (7.6)	61.1 (6.7)	60.7 (6.8)	61.7 (7.6)	61.3 (8.0)
Person-years of follow-up	7,790	207,873	3,883	69,225	13,064	331,685	6,848	254,293	11,007	284,427
Follow-up years[b]	9.3 (5.7)	16.3 (5.8)	9.3 (5.5)	16.7 (5.1)	9.0 (5.5)	17.7 (4.1)	9.3 (5.6)	17.6 (4.4)	8.8 (5.4)	17.1 (4.8)
Incidence/100,000[c]	247.5		402.6		325.8		216.8		288.0	
Age at diagnosis, y[b]	72.9 (8.5)		68.7 (8.3)		72.1 (8.6)		70.8 (8.3)		71.0 (8.5)	
Family history of breast cancer[a]	17.2	10.7	18.1	13.1	15.1	10.2	15.4	8.4	18.0	11.8
Current smoker[a]	18.0	20.0	20.5	22.5	6.6	8.4	11.5	10.4	15.3	16.6
Ever smoker[a]	56.2	56.3	55.7	55.8	30.9	30.5	36.4	36.2	57.4	55.7
Age at smoking initiation, y[b, d]	31.6 (11.2)	31.5 (11.1)	26.6 (11.1)	27.3 (10.3)	30.3 (9.8)	30.7 (10.1)	31.9 (10.6)	33.1 (11.4)	27.8 (9.9)	27.8 (9.6)
Smoking duration, y[b, d]	22.3 (12.6)	23.4 (12.3)	23.9 (11.8)	23.9 (12.1)	19.7 (12.3)	21.0 (12.5)	20.1 (12.3)	18.7 (12.9)	23.5 (12.6)	23.5 (12.8)
No. of cigarettes smoked/day[b, d]	10.9 (6.3)	11.4 (6.6)	14.8 (7.7)	14.0 (7.6)	12.2 (6.5)	12.3 (6.9)	10.0 (6.5)	9.2 (6.2)	15.3 (8.3)	15.8 (8.4)
Pack-years of smoking[b, d]	14.0 (12.5)	14.8 (12.8)	19.5 (15.1)	18.4 (14.9)	13.9 (12.7)	14.7 (13.3)	11.5 (11.5)	10.1 (11.5)	20.4 (17.1)	20.9 (17.3)
Smokers who started to smoke before the first childbirth[a, d, e]	21.9	19.2	35.1	30.1	35.3	30.1	13.9	17.2	36.9	33.4
Years of smoking before first childbirth[b, d, e]	5.7 (3.9)	5.1 (4.2)	5.7 (5.0)	5.1 (4.1)	5.8 (3.8)	5.4 (4.2)	5.4 (5.2)	5.5 (4.5)	6.2 (4.3)	5.5 (4.3)
Body mass index (kg/m^2) [b]	29.0 (5.4)	28.8 (5.7)	29.3 (6.2)	28.2 (6.1)	24.3 (3.9)	23.4 (3.7)	28.1 (5.2)	27.8 (5.1)	25.7 (4.9)	25.7 (5.2)
≥13 years of education[a]	65.8	59.0	41.9	41.1	59.6	52.9	32.8	27.7	69.1	68.2
Age at menarche, y[b]	13.1 (1.6)	13.2 (1.7)	12.8 (1.7)	12.9 (1.7)	13.1 (1.6)	13.3 (1.7)	13.3 (1.7)	13.2 (1.7)	13.1 (1.7)	13.1 (1.6)
Parous women[a]	85.8	86.6	90.7	93.1	84.9	87.1	89.2	91.7	83.1	84.2
Number of children[b, e]	3.2 (1.8)	3.4 (1.9)	4.0 (1.8)	4.0 (1.8)	2.7 (1.1)	2.8 (1.2)	3.9 (1.8)	4.1 (1.9)	2.8 (1.4)	3.0 (1.5)
Age at first childbirth, y[b, e]	21.8 (4.6)	21.4 (4.6)	21.6 (4.0)	21.6 (3.8)	25.7 (4.2)	25.2 (4.1)	22.6 (4.7)	22.1 (4.5)	24.0 (4.5)	23.4 (4.4)
Ever postmenopausal hormone therapy use[a]	49.7	46.0	54.9	51.7	67.0	59.2	52.8	47.7	72.3	66.5
Age at menopause, y[b, f]	48.7 (5.4)	48.3 (5.4)	48.6 (5.3)	48.1 (5.4)	50.2 (4.5)	49.7 (4.7)	48.5 (5.4)	48.0 (5.3)	49.4 (4.8)	48.7 (5.0)
Menopause type[a]										
Natural	56.1	55.5	72.0	65.9	72.7	71.3	69.3	68.7	69.6	65.7
Oophorectomy	21.9	23.0	17.9	22.7	17.5	18.4	14.5	15.2	16.8	20.8
Hysterectomy	22.0	21.5	10.1	11.4	9.9	10.2	16.2	16.1	13.6	13.5
Nondrinkers[a]	63.3	63.4	65.1	64.6	78.1	79.2	60.9	64.7	35.2	40.9
Alcohol consumption, g/day[g]										

	African American (N=12,776)		Native Hawaiian (N=4,286)		Japanese American (N=19,043)		Latina (N=14,371)		White (N=16,837)	
	Cases	Noncases	Cases	Noncases	Cases	Noncases	Cases	Noncases	Cases	Noncases
Mean (SD)	14.7 (28.1)	12.1 (27.7)	11.5 (20.7)	12.4 (27.1)	6.6 (12.3)	6.1 (11.7)	7.2 (15.2)	7.1 (17.3)	17.6 (24.3)	15.4 (24.2)
Median (min, max)	4.1 (0.4, 208)	3.3 (0.0, 392)	3.9 (0.2, 154)	3.7 (0.0, 403)	1.6 (0.4, 106)	1.7 (0.2, 248)	2.4 (0.4, 186)	2.2 (0.0, 328)	9.8 (0.4, 263)	6.6 (0.2, 428)

[a] Values are percents.
[b] Values are means (standard deviations).
[c] Rates, truncated to ages 45-85, were adjusted to the 2000 US standard population.
[d] Among ever smokers.
[e] Among parous women.
[f] Natural menopause.
[g] Among drinkers.

Table 2. Multivariable adjusted hazard ratios (HR) and 95% confidence intervals (CI) for breast cancer by race/ethnicity according to different measures of smoking exposures, the Multiethnic Cohort Study, 1993-2013[a]

Smoking exposures	All women (N=67,313)		African American (N=12,776)		Native Hawaiian (N=4,286)		Japanese American (N=19,043)		Latina (N=14,371)		White (N=16,837)		$P_{heterogeneity}$[b]
	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	
Common reference group													
Never smokers	2303	1.00 (ref)	330	1.00 (ref)	166	1.00 (ref)	903	1.00 (ref)	424	1.00 (ref)	480	1.00 (ref)	
Smoking status													
Former	1378	1.08 (1.01-1.16)	288	1.12 (0.96-1.32)	132	1.08 (0.86-1.37)	317	1.05 (0.92-1.20)	166	0.98 (0.82-1.17)	475	1.13 (0.99-1.28)	
Current	549	1.11 (1.00-1.22)	136	1.09 (0.89-1.34)	77	1.05 (0.79-1.39)	86	0.89 (0.71-1.12)	77	1.28 (1.00-1.64)	173	1.20 (1.00-1.43)	0.45
Ever	1927	1.09 (1.02-1.16)	424	1.11 (0.96-1.29)	209	1.07 (0.87-1.32)	403	1.01 (0.90-1.14)	243	1.06 (0.90-1.24)	648	1.14 (1.01-1.29)	0.65
Ever smokers													
Smoking duration, y													
≤20	855	1.04 (0.96-1.13)	182	1.11 (0.93-1.34)	78	1.05 (0.80-1.39)	208	1.04 (0.89-1.21)	119	0.91 (0.74-1.12)	268	1.06 (0.91-1.24)	
21-30	460	1.20 (1.08-1.33)	105	1.22 (0.97-1.52)	52	0.96 (0.70-1.32)	93	1.04 (0.83-1.29)	64	1.68 (1.29-2.20)	146	1.25 (1.03-1.50)	
≥31	581	1.12 (1.02-1.24)	127	1.07 (0.87-1.32)	75	1.21 (0.91-1.61)	95	0.94 (0.76-1.16)	53	1.09 (0.82-1.45)	231	1.23 (1.05-1.44)	
P_{trend}		<0.001		0.26		0.30		0.82		0.07		0.004	0.26
Number of cigarettes													
≤10/day	961	1.07 (0.99-1.15)	259	1.15 (0.98-1.36)	81	0.96 (0.73-1.26)	211	0.99 (0.85-1.16)	165	0.98 (0.82-1.18)	245	1.15 (0.99-1.35)	
11-20/day	626	1.13 (1.03-1.24)	123	1.08 (0.87-1.33)	79	1.14 (0.87-1.50)	145	1.08 (0.91-1.30)	52	1.33 (1.00-1.78)	227	1.13 (0.97-1.33)	
≥21/day	316	1.12 (0.99-1.26)	33	0.98 (0.68-1.40)	48	1.27 (0.91-1.76)	43	0.90 (0.66-1.23)	19	1.29 (0.81-2.05)	173	1.17 (0.98-1.40)	
P_{trend}		0.004		0.53		0.13		0.89		0.11		0.045	0.63
Pack-years													
≤10	748	1.05 (0.96-1.14)	178	1.16 (0.97-1.40)	56	0.91 (0.67-1.24)	169	0.98 (0.83-1.16)	127	0.93 (0.76-1.13)	218	1.14 (0.97-1.34)	
11-20	602	1.11 (1.01-1.21)	135	1.02 (0.83-1.25)	78	1.14 (0.86-1.50)	141	1.05 (0.87-1.25)	68	1.31 (1.01-1.69)	180	1.12 (0.95-1.34)	
≥21	531	1.19 (1.08-1.32)	95	1.21 (0.96-1.53)	70	1.20 (0.90-1.60)	84	1.01 (0.80-1.27)	38	1.50 (1.08-2.10)	244	1.21 (1.03-1.42)	
P_{trend}		<0.001		0.19		0.16		0.77		0.01		0.02	0.45
Age at smoking initiation, y													
≥25	1150	1.05 (0.98-1.13)	278	1.10 (0.93-1.29)	95	0.98 (0.76-1.26)	262	1.00 (0.87-1.15)	163	1.01 (0.84-1.22)	352	1.09 (0.95-1.25)	
20-24	398	1.19 (1.07-1.33)	75	1.18 (0.91-1.52)	49	1.15 (0.83-1.60)	82	1.09 (0.87-1.38)	47	1.50 (1.11-2.04)	145	1.17 (0.97-1.41)	
<20	340	1.20 (1.06-1.35)	59	1.21 (0.91-1.61)	61	1.26 (0.93-1.72)	50	0.95 (0.71-1.27)	24	0.98 (0.65-1.49)	146	1.33 (1.10-1.61)	
P_{trend}		<0.001		0.09		0.13		0.90		0.22		0.003	0.55

Smoking exposures	All women (N=67,313)		African American (N=12,776)		Native Hawaiian (N=4,286)		Japanese American (N=19,043)		Latina (N=14,371)		White (N=16,837)		$P_{heterogeneity}$ [b]
	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	
Smoking initiation in relation to first childbirth for parous women													
Never[c]	2006	1.00 (ref)	303	1.00 (ref)	151	1.00 (ref)	775	1.00 (ref)	385	1.00 (ref)	392	1.00 (ref)	
During/after	1141	1.04 (0.96-1.12)	267	0.99 (0.84-1.17)	128	1.03 (0.81-1.31)	217	0.94 (0.81-1.10)	178	1.08 (0.90-1.30)	351	1.12 (0.97-1.30)	
≤5 years before	203	1.03 (0.89-1.19)	30	0.97 (0.66-1.42)	26	0.99 (0.65-1.51)	50	0.98 (0.73-1.31)	13	0.80 (0.46-1.39)	84	1.16 (0.91-1.47)	
>5 years before	242	1.31 (1.14-1.51)	37	1.51 (1.05-2.16)	31	1.66 (1.10-2.50)	59	1.22 (0.93-1.60)	10	0.63 (0.33-1.19)	105	1.42 (1.13-1.78)	
P_{trend}		0.002		0.18		0.08		0.52		0.45		0.002	0.15

[a] Adjusted for age at cohort entry, race/ethnicity where applicable, body mass index, family history of breast cancer, age at first birth, number of children, age at menarche, age at and type of menopause, hormone replacement therapy, alcohol intake, and education.

[b] P for heterogeneity across race/ethnicity

[c] Parous never smokers as reference group.

Table 3. Multivariable adjusted hazard ratios (HR) and 95% confidence intervals (CI) for ER+, ER–, PR+,PR– breast cancer according to different measures of smoking exposures, the Multiethnic Cohort Study, 1993-2013[a]

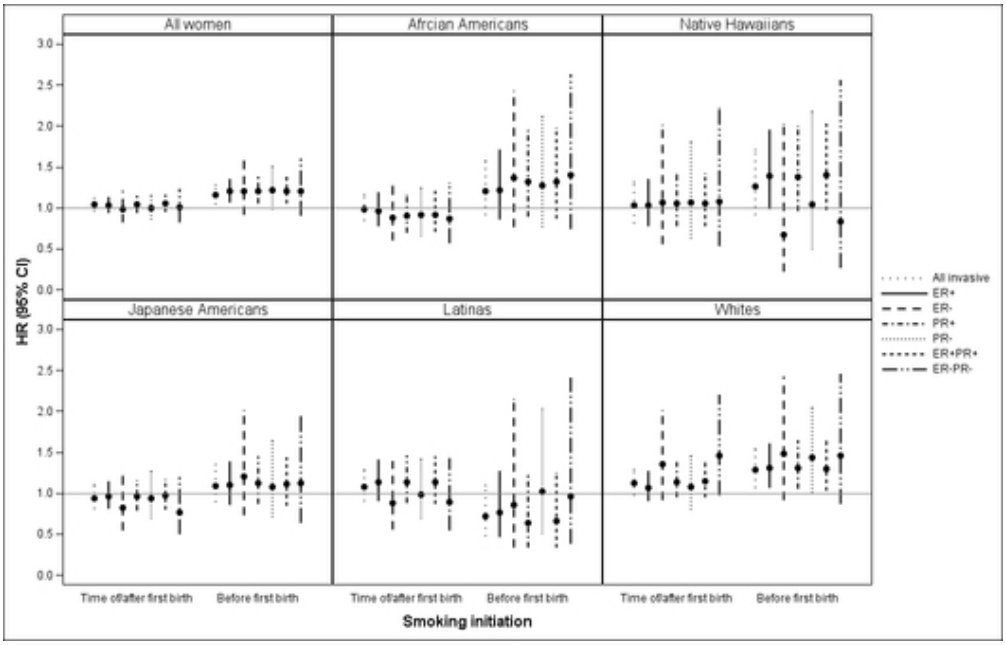
Smoking exposures	ER-positive (N=3,095)		ER-negative (N=659)		$P_{heterogeneity}$[b]	PR-positive (N=2,502)		PR-negative (N=1,063)		$P_{heterogeneity}$[b]
	Cases	HR (95% CI)	Cases	HR (95% CI)		Cases	HR (95% CI)	Cases	HR (95% CI)	
Common reference group										
Never smokers	1695	1.00 (ref)	358	1.00 (ref)		1366	1.00 (ref)	581	1.00 (ref)	
Smoking status										
Former	1020	1.09 (1.00-1.18)	206	1.06 (0.89-1.27)		838	1.11 (1.02-1.21)	329	1.04 (0.91-1.20)	
Current	380	1.06 (0.94-1.19)	95	1.13 (0.89-1.43)	0.65	298	1.03 (0.90-1.17)	153	1.19 (0.99-1.43)	0.42
Ever	1400	1.08 (1.00-1.16)	301	1.08 (0.92-1.27)	0.97	1136	1.09 (1.00-1.18)	482	1.08 (0.96-1.23)	0.86
Ever smokers										
Smoking duration, y										
≤20	627	1.04 (0.95-1.14)	130	1.01 (0.82-1.24)		509	1.05 (0.94-1.16)	212	1.03 (0.87-1.21)	
21-30	337	1.19 (1.06-1.35)	77	1.27 (0.99-1.64)		283	1.24 (1.09-1.41)	113	1.18 (0.96-1.45)	
≥31	415	1.10 (0.98-1.23)	88	1.09 (0.86-1.39)		328	1.08 (0.95-1.22)	147	1.14 (0.94-1.37)	
P_{trend}		0.01		0.20	0.78		0.02		0.09	0.84
Number of cigarettes										
≤10/day	712	1.10 (1.00-1.20)	144	0.99 (0.82-1.21)		568	1.10 (0.99-1.21)	238	1.04 (0.89-1.21)	
11-20/day	437	1.07 (0.96-1.19)	105	1.23 (0.98-1.54)		353	1.07 (0.95-1.20)	169	1.22 (1.02-1.45)	
≥21/day	237	1.10 (0.95-1.26)	46	1.11 (0.81-1.53)		204	1.15 (0.99-1.34)	66	0.96 (0.74-1.25)	
P_{trend}		0.07		0.16	0.68		0.04		0.28	0.69
Pack-years										
≤10	553	1.06 (0.96-1.17)	109	0.96 (0.78-1.20)		439	1.05 (0.94-1.17)	188	1.04 (0.88-1.23)	
11-20	447	1.12 (1.00-1.24)	98	1.13 (0.90-1.42)		371	1.15 (1.02-1.29)	149	1.08 (0.90-1.30)	
≥21	373	1.12 (1.00-1.26)	82	1.23 (0.96-1.58)		304	1.13 (0.99-1.28)	129	1.18 (0.97-1.44)	
P_{trend}		0.01		0.09	0.62		0.01		0.10	0.95
Age at smoking initiation, y										
≥25	806	1.02 (0.93-1.11)	191	1.12 (0.93-1.34)		647	1.02 (0.93-1.12)	298	1.08 (0.94-1.25)	
20-24	307	1.23 (1.09-1.40)	52	0.98 (0.73-1.32)		258	1.27 (1.11-1.46)	81	0.97 (0.76-1.23)	
<20	261	1.23 (1.07-1.41)	51	1.14 (0.83-1.54)		211	1.21 (1.04-1.41)	90	1.27 (1.01-1.61)	
P_{trend}		<0.001		0.42	0.29		<0.001		0.11	0.49
Smoking initiation in relation to first child birth for parous women										
Never[c]	1459	1.00 (ref)	324	1.00 (ref)		1172	1.00 (ref)	517	1.00 (ref)	

Smoking exposures	ER-positive (N=3,095)		ER-negative (N=659)		$P_{heterogeneity}$ [b]	PR-positive (N=2,502)		PR-negative (N=1,063)		$P_{heterogeneity}$ [b]
	Cases	HR (95% CI)	Cases	HR (95% CI)		Cases	HR (95% CI)	Cases	HR (95% CI)	
During/after	810	1.03 (0.94-1.12)	182	0.99 (0.82-1.20)		658	1.04 (0.94-1.15)	283	0.99 (0.85-1.15)	
≤5 years before	155	1.05 (0.89-1.24)	32	1.01 (0.70-1.47)		133	1.10 (0.91-1.32)	45	0.90 (0.66-1.23)	
>5 years before	191	1.37 (1.17-1.61)	39	1.44 (1.02-2.04)		149	1.33 (1.11-1.59)	73	1.60 (1.23-2.08)	
P_{trend}		0.001		0.15	0.60		0.004		0.03	0.95

[a] After excluding 466 (11.0 %) cases with missing on both ER and PR status. Adjusted for age at cohort entry, race/ethnicity, body mass index, family history of breast cancer, age at first birth, number of children, age at menarche, age at and type of menopause, hormone replacement therapy, alcohol intake, and education.

[b] P for heterogeneity between receptor status in a competing risk model.

[c] Parous never smokers as reference group.



Multivariate adjusted hazard ratios (HR) and 95% confidence intervals (CI) for breast cancer among parous ever smokers according to timing of smoking initiation in relation to first childbirth (at time of/after first birth and before first birth) by tumor receptor status and ethnicity, the Multiethnic Cohort Study, 1993-2013 [a.] a All women (total n= 79,890) and 5 racial/ethnic groups for all invasive breast cancer cases (n=4,918)

44x28mm (300 x 300 DPI)