

Original Contribution

Smoking and Risk of Breast Cancer in a Racially/Ethnically Diverse Population of Mainly Women Who Do Not Drink Alcohol

The MEC Study

Inger T. Gram*, Song-Yi Park, Laurence N. Kolonel, Gertraud Maskarinec, Lynne R. Wilkens, Brian E. Henderson†, and Loïc Le Marchand

* Correspondence to Dr. Inger T. Gram, Department of Community Medicine, Faculty of Health Sciences, UiT (University of Tromsø) The Arctic University of Norway, P.O. Box 6050 Langnes, N-9037 Tromsø, Norway (e-mail: inger.gram@uit.no).

† Deceased.

Initially submitted January 22, 2015; accepted for publication April 1, 2015.

We prospectively examined the association between smoking and the risk of breast cancer in a racially/ethnically diverse population comprising mainly women who did not drink alcohol. From 1993 to 2010, we followed 83,300 women who were enrolled in the Multiethnic Cohort Study at 45–75 years of age. We identified cancer cases via linkage to the Surveillance, Epidemiology, and End Results Program cancer registries that covered the states of Hawaii and California through December 2010. We used Cox proportional hazards models to estimate hazard ratios and 95% confidence intervals while adjusting for confounders that were decided a priori. During a mean follow-up of 15 years, 4,484 women developed invasive breast cancer. Compared with parous never smokers, women who had smoked for more than 20 pack-years and initiated smoking more than 5 years before their first childbirth had an overall risk of breast cancer that was 35% higher (hazard ratio = 1.35, 95% confidence interval: 1.13, 1.63). Among women who did not drink alcohol, the risk was 40% higher (hazard ratio = 1.40, 95% confidence interval: 1.08, 1.81). This higher risk did not significantly differ among racial/ethnic groups ($P_{\text{interaction}} = 0.82$). We found that various measures of smoking exposure were associated with a higher risk of breast cancer, especially smoking initiated many years before first childbirth, and that risk did not differ by alcohol consumption (yes vs. no) or racial/ethnic group.

breast cancer; cohort studies; confounding; ethnic differences; Multiethnic Cohort Study; alcohol abstinence; smoking; smoking duration before first childbirth

Abbreviations: CI, confidence interval; HR, hazard ratio.

Alcohol consumption is an established risk factor for breast cancer, whereas smoking is not. Results from recent cohort studies indicate that cigarette smoking, especially of long duration and when initiated before first childbirth (1–4), is an emerging risk factor for breast cancer.

In the United States, the rate of smoking among men started to decrease in the 1960s, whereas it rose among women. The decline among women did not start until the 1980s. Today, the majority of persons who try cigarettes do so by 18 years of age (87%), and nearly all do by 26 years of age (98%) (5).

There is overwhelming evidence of the harmful effects of smoking on health (5–7). Although more women than men

smoke in only 2 countries in the world, more girls than boys smoke in 24 countries (8). In a recent study in which data from 16 countries were compared, the rates of smoking among women in the United States were among the highest reported (9). Data from the Surveillance, Epidemiology, and End Results (SEER) Program show that the incidence of breast cancer rose from 1975 to 2010, with a peak around the end of the 20th century (10). This is also the period during which lung cancer incidence plateaued for US women (5). The increase in breast cancer incidence, which is also known to vary across racial/ethnic groups, cannot be fully explained by improved screening, early detection, or changes in known risk factors (10–12).

The Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk recently concluded that the relationship between smoking and breast cancer was consistent with causality (13). However, in a 2012 monograph (7), the International Agency for Research on Cancer classified cigarette smoking as possibly carcinogenic to the human breast. Likewise, in 2014, the US Surgeon General concluded that the evidence is suggestive of but not sufficient to imply a causal relationship between tobacco smoke and breast cancer (5).

The purpose of the present study was to examine the association between smoking and the risk of breast cancer in the Multiethnic Cohort (MEC) Study. This is of particular interest because the women are from a racially/ethnically diverse population and most of them did not drink alcohol.

METHODS

Study population

The MEC Study cohort consists of more than 215,000 men and women who were 45–75 years of age at the time of entry into the study and were living in California or Hawaii. The majority of the cohort members belong to 1 of 5 racial/ethnic populations: African Americans, Japanese Americans, Latinos, Native Hawaiians, and whites. The cohort has been previously described in detail (11, 14). Briefly, between 1993 and 1996, adults enrolled in the study by completing a 26-page mailed questionnaire that contained detailed questions about demographic factors, dietary habits, other lifestyle factors, prior medical conditions, and family histories of common cancers. We identified potential participants through driver's license files from the departments of motor vehicles, voter registration lists, and Health Care Financing Administration (Medicare) data files of California and Hawaii. The institutional review boards of the University of Hawaii and the University of Southern California approved the study protocol.

A total of 99,817 postmenopausal women returned the questionnaire. We excluded women who did not belong to 1 of the 5 targeted racial/ethnic groups listed above ($n = 6,443$), who had prior breast cancer as determined from questionnaire reports or information from tumor registry linkages ($n = 4,683$), or who had missing information on alcohol consumption ($n = 3,676$) or smoking status ($n = 1,715$). The cohort comprised the 83,300 remaining women.

Data collection

At baseline, participants reported whether they had smoked at least 20 packs of cigarettes in their lifetime, for how many years they smoked cigarettes, the average number of cigarettes smoked per day, and the number of years since they stopped smoking. Based on the answer to the question, "What is the total number of years you have smoked?" we computed age at smoking initiation as the age at questionnaire completion minus the number of years for which the participant smoked for current smokers and as the age at questionnaire completion minus the sum of the number of years for which the participant smoked and the number of years since smoking cessation for former smokers. We also calculated pack-years of smoking as the 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 the age in years at the birth of the first child minus the age at smoking initiation.

The baseline questionnaire included questions about years of education, current height and weight for the calculation of body mass index (weight (kg)/height (m)²), age at and type of menopause, postmenopausal hormone therapy use, and alcohol consumption during the past year. We calculated mean alcohol intake in grams per day based on the amounts of pure alcohol in different beverages and their usual portion sizes. Women who reported consuming alcohol less than once per month had their consumption set to 0. We used level of education as a proxy for socioeconomic status. We classified women who did not report their menopausal status and were older than 55 years of age at cohort entry as postmenopausal (13.3% of the total sample of 83,300).

We identified incident cancer cases via linkage to the Surveillance, Epidemiology, and End Results Program cancer registries for Hawaii and California. Because migration outside the catchment area was low (<5% in the first 10 years), few incident cases are likely to have been missed. We identified deaths through linkage to death certificate files in Hawaii and California and to the National Death Index. Ascertainment of cases and their vital statuses was complete through December 31, 2010.

We calculated person-years from the start of follow-up (date of returned questionnaire) to the date of diagnosis of invasive breast cancer, death from any cause, or the end of follow-up (December 31, 2010), whichever occurred first. We included only cases of breast cancer that were coded with *International Classification of Diseases, Tenth Revision*, code C50; cases with hematopoietic and lymphoid tumors in the breast were excluded based on their histologic codes.

Statistical analysis

We calculated crude breast cancer incidence rates per 100,000 person-years truncated to ages 45–85 years by dividing the number of cases by the total number of person-years in that exposure category. The rates were then age-adjusted using the 2000 US standard population (15). We used the Cox proportional hazards regression model with age as the underlying time scale to estimate multivariate-adjusted hazard ratios and 95% confidence intervals for the associations between breast cancer and different measures of smoking exposure. Smoking exposure was defined using smoking status at cohort entry (never, former, current, or ever); for women who had ever smoked, further exposures were defined using age at smoking initiation (<20, 20–24, or ≥25 years), smoking duration (≤20, 21–30, or >30 years), number of cigarettes smoked per day (≤10, 11–20, or >20); and number of pack-years of smoking (≤10, 11–20, or >20). Never smokers were the reference group.

For parous women, we estimated breast cancer risk by category of age at smoking initiation in relation to first childbirth (after or within 1 year before first childbirth, 1–5 years before, or >5 years before) compared with parous never smokers overall and stratified by accumulated number of pack-years of smoking (≤10, 11–20, or >20). We determined associations for the entire study population and for only those who did not drink alcohol.

We included covariates that could potentially confound the association between smoking and breast cancer; these covariates were decided a priori based on established risk factors and previous findings in the Multiethnic Cohort Study (11). We included the following variables in the final multivariate models: ethnicity (African American, Native Hawaiian, Japanese, Latina, or white), age at cohort entry (continuous), family history of breast cancer (no, yes, or missing), educational level (≤ 12 years, ≥ 13 years, or missing), body mass index (< 25 , 25.0–29.9, ≥ 30 , or missing), age at menarche (≤ 12 years, 13–14 years, ≥ 15 years, or missing), age at first childbirth (no children, ≤ 20 years, 21–30 years, ≥ 31 years, or missing), number of children for parous women (1, 2–3, ≥ 4 , or missing), type of menopause (natural, oophorectomy, or hysterectomy); age at menopause (for natural menopause, < 45 years, 45–49 years, 50–54 years, or ≥ 55 years; for oophorectomy, < 45 years, 45–49 years, or ≥ 50 years; or missing), postmenopausal hormone replacement therapy use (no current estrogen use, past estrogen use with or without progestin use, current estrogen use without progestin use, current estrogen use with past or current progestin use, or missing), and alcohol consumption (continuous; measured as grams of ethanol per day). Tests for linear trends were conducted by including an ordinal exposure variable with equally spaced scores in models. We created separate models that included and excluded never smokers.

For each of the 5 racial/ethnic groups, we estimated breast cancer risk for women who had ever smoked compared with those who had never smoked with adjustment for the applicable covariates described above. Likewise, for parous women, we estimated risk by smoking initiation in relation to first childbirth, with the corresponding parous never smokers serving as the reference group. We tested for heterogeneity in the association of breast cancer risk with smoking variables by race/ethnicity using the Wald test of cross-product terms. We performed the analyses using SAS, version 9.2 (SAS Institute Inc., Cary, North Carolina) and considered 2-sided P values < 0.05 as statistically significant.

RESULTS

At cohort entry, the mean age of the participants was 61.6 years. Of these women, 44.6% reported at baseline that they had ever smoked (14.2% were current smokers and 30.4% were former smokers), and 63.2% reported that they did not drink alcohol. During the more than 1.3 million person-years of observation (mean follow-up time was 14.6 years), we ascertained 4,484 incident cases of invasive breast cancer. The annual age-adjusted incidence rate per 100,000 person-years truncated to ages 45–85 was 288.6 for all women, 292.7 for ever smokers, and 284.6 for never smokers.

Table 1 shows that ever smokers were younger at cohort entry and at diagnosis, were more likely to have higher education, were younger at first childbirth and at natural menopause, were more likely to be ever users of postmenopausal hormone therapy, and were more likely to consume alcohol than were never smokers (Table 1). Web Table 1 (available at <http://aje.oxfordjournals.org/>) shows these and some additional characteristics by race/ethnicity. The age-adjusted breast

cancer incidence rates (per 100,000 persons) for ever smokers and never smokers were highest for Native Hawaiians (375 and 356, respectively) and lowest for Latinas (199 and 195, respectively).

Overall, the mean age at initiation of smoking was 30 years. Twenty-six percent of ever smokers started to smoke before their first childbirth, with a mean smoking duration of 5 years before first childbirth. Table 2 shows that the proportion of women who reported being ever smokers ranged from 56% for African Americans, Native Hawaiians, and whites to 36% for Latinas and 30% for Japanese Americans. Native Hawaiians and whites reported the youngest age at smoking initiation, the highest numbers of cigarettes smoked per day, the longest smoking duration, and therefore the highest numbers of pack-years of smoking. The proportion of women who started to smoke before their first childbirth ranged from more than 30% for Native Hawaiians, Japanese Americans, and whites to less than 20% for African Americans and Latinas (Table 2).

Table 3 shows that ever smokers had a higher, but not statistically significantly higher, risk of breast cancer than did never smokers; overall, the risk was 4% (hazard ratio (HR) = 1.04, 95% confidence interval (CI): 0.98, 1.11), and for women who did not drink alcohol, the risk was 3% (HR = 1.03, 95% CI: 0.95, 1.12). For ever smokers overall, significant associations with breast cancer risk were observed for age at smoking initiation ($P_{\text{trend}} = 0.006$), smoking duration ($P_{\text{trend}} = 0.022$), number of cigarettes smoked daily ($P_{\text{trend}} = 0.025$), and pack-years of smoking ($P_{\text{trend}} = 0.006$) when never smokers were included as a separate exposure category. When we excluded never smokers, we found significant associations for age at smoking initiation ($P_{\text{trend}} = 0.013$) and pack-years of smoking ($P_{\text{trend}} = 0.025$). For women who did not drink alcohol, age at smoking initiation ($P_{\text{trend}} = 0.025$), number of cigarettes smoked per day ($P_{\text{trend}} = 0.045$), and pack-years of smoking ($P_{\text{trend}} = 0.005$) showed significant associations when we excluded never smokers (Table 3).

Table 4 shows the risk of breast cancer among parous women compared with that among parous never smokers, stratified by pack-years and duration of smoking before first childbirth. Parous women who smoked for more than 5 years before their first childbirth had a statistically significantly higher risk of breast cancer compared with the reference group; the risk was 21% higher for all women (HR = 1.21, 95% CI: 1.05, 1.39) and 24% higher (HR = 1.24, 95% CI: 1.01, 1.51) for women who did not drink alcohol. Parous women who were heavy smokers (i.e., > 20 pack-years) and who began smoking more than 5 years before their first childbirth had a statistically significantly higher risk of breast cancer compared with the corresponding reference group. Overall, the risk was 35% (HR = 1.35, 95% CI: 1.13, 1.63), and for women who did not drink alcohol, the risk was 40% (HR = 1.40, 95% CI: 1.08, 1.81). In comparison, the corresponding hazard ratios for parous heavy smokers who started smoking within 1 year of or after their first childbirth were not significantly higher for all women (HR = 1.08, 95% CI: 0.93, 1.25) or for those who did not drink alcohol (HR = 1.18, 95% CI: 0.97, 1.43) (Table 4). The trend tests were not statistically significant when never smokers were excluded; however, for all ever smokers, P_{trend} was 0.02 (Table 4).

Table 1. Selected Characteristics of Postmenopausal Women, by Smoking Status at Baseline,^a the Multiethnic Cohort Study, 1993–2010

Characteristic	Ever Smokers (n = 37,124)		Never Smokers (n = 46,176)	
	%	Mean (SD)	%	Mean (SD)
Age at cohort entry, years		60.8 (7.9)		62.3 (7.9)
Age at diagnosis, years		69.2 (8.4)		70.9 (8.4)
Family history of breast cancer	11.9		11.2	
Body mass index ^b		26.9 (6.0)		26.2 (5.5)
≥13 years of education	52.9		48.5	
Age at menarche, years		13.1 (1.7)		13.2 (1.7)
Parous women	87.1		88.1	
No. of children ^c		3.3 (1.7)		3.4 (1.7)
Age at first childbirth, years ^c		22.3 (4.6)		23.5 (4.6)
Ever use of postmenopausal hormone therapy	57.0		53.7	
Age at menopause, years ^d		48.3 (5.2)		49.0 (5.1)
Menopause type ^e				
Natural	60.1		64.0	
Oophorectomy	19.4		17.5	
Hysterectomy	20.5		18.5	
Women who did not drink alcohol	53.6		70.8	
Alcohol consumption ^f		14.5 (26.4)		7.5 (16.3)

Abbreviation: SD, standard deviation.

^a Baseline information was collected from 1993 to 1996. A total of 83,300 women from the Multiethnic Cohort Study were eligible for this analysis.^b Weight (kg)/height (m)².^c Among parous women.^d Natural menopause. Information was available for 55.7% of ever smokers and 58.4% of never smokers.^e Information was available for 92.6% of ever smokers and 91.3% of never smokers.^f Among women who consumed alcohol; expressed in grams per day.**Table 2.** Distribution of Various Measures of Smoking by Race/Ethnicity Among Postmenopausal Women at Baseline,^a the Multiethnic Cohort Study, 1993–2010

Smoking Exposure	Race									
	African American (n = 17,215)		Native Hawaiian (n = 5,471)		Japanese American (n = 22,506)		Latina (n = 18,309)		White (n = 19,799)	
	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)
Current smoker	19.8		22.1		8.4		10.3		17.1	
Ever smoker	55.9		55.6		30.4		35.7		56.0	
Age at smoking initiation, years ^b		31.8 (11.4)		27.2 (10.3)		30.6 (10.2)		33.0 (11.6)		27.7 (9.7)
Smoking duration, years ^b		22.9 (12.4)		23.7 (12.1)		21.0 (12.5)		18.8 (12.9)		23.4 (12.7)
No. of cigarettes smoked per day ^b		11.3 (6.6)		14.0 (7.6)		12.3 (6.8)		9.1 (6.1)		15.8 (8.4)
Pack-years of smoking ^b		14.4 (12.6)		18.3 (14.9)		14.6 (13.2)		10.1 (11.4)		20.9 (17.1)
Smokers who started to smoke before the first childbirth ^c	18.9		30.6		30.1		17.2		33.7	
Years of smoking before first childbirth ^c		5.1 (4.1)		5.2 (4.1)		5.5 (4.2)		5.4 (4.4)		5.6 (4.3)

Abbreviation: SD, standard deviation.

^a Baseline information was collected from 1993 to 1996. A total of 83,300 women from the Multiethnic Cohort Study were eligible for this analysis.^b Among ever smokers.^c Among parous women who started smoking before first childbirth.

Table 3. Multivariate-Adjusted Hazard Ratios^a for Breast Cancer by Measures of Smoking Among Postmenopausal Women, the Multiethnic Cohort Study, 1993–2010

Smoking Exposure	All Women (n = 83,300)			Women Who Did Not Drink Alcohol (n = 52,610)		
	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI
Smoking status						
Never	2,469	1.00	Referent	1,705	1.00	Referent
Former	1,413	1.03	0.96, 1.10	740	1.04	0.96, 1.14
Current	602	1.07	0.98, 1.18	266	1.01	0.88, 1.15
Ever	2,015	1.04	0.98, 1.11	1,006	1.03	0.95, 1.12
Ever smokers ^b						
Age at smoking initiation, years						
≥25	1,198	1.01	0.94, 1.08	600	0.97	0.89, 1.07
20–24	411	1.15	1.03, 1.28	208	1.24	1.07, 1.44
<20	358	1.15	1.02, 1.29	165	1.11	0.94, 1.31
P_{trend}^c			0.006			0.046
P_{trend}^d			0.013			0.025
Smoking duration, years						
≤20	885	1.00	0.92, 1.08	440	0.97	0.87, 1.08
21–30	484	1.16	1.05, 1.28	244	1.15	1.00, 1.31
>30	608	1.07	0.98, 1.18	296	1.10	0.97, 1.24
P_{trend}^c			0.022			0.065
P_{trend}^d			0.120			0.085
No. of cigarettes smoked per day						
≤10	993	1.01	0.94, 1.09	505	0.99	0.89, 1.09
11–20	662	1.11	1.01, 1.21	318	1.08	0.96, 1.23
>20	336	1.09	0.97, 1.23	169	1.20	1.02, 1.41
P_{trend}^c			0.025			0.039
P_{trend}^d			0.170			0.045
Pack-years of smoking						
≤10	769	1.00	0.92, 1.08	380	0.96	0.86, 1.07
11–20	641	1.08	0.98, 1.18	316	1.05	0.93, 1.18
>20	551	1.14	1.04, 1.26	274	1.22	1.07, 1.39
P_{trend}^c			0.006			0.014
P_{trend}^d			0.025			0.005

Abbreviations: CI, confidence interval; HR, hazard ratio.

^a Adjusted for race/ethnicity, age at cohort entry, body mass index, family history of breast cancer, age at first childbirth, number of children, age at menarche, age at and type of menopause, postmenopausal hormone therapy use, alcohol consumption, and educational level.^b Never smokers were used as the reference group.^c Including never smokers.^d Excluding never smokers.

The results did not suggest differences in the associations of smoking and breast cancer risk by race/ethnicity (for smoking status, $P_{\text{interaction}} = 0.82$; for smoking duration before first childbirth, $P_{\text{interaction}} = 0.36$; data not shown). For the latter association, Native Hawaiians (HR = 1.66, 95% CI: 1.10, 2.50) and Latinas (HR = 0.72, 95% CI: 0.40, 1.29) who had smoked for more than 5 years before their first childbirth represented the range of the estimates (data not shown).

DISCUSSION

In the present prospective study, we found that the risk of breast cancer was associated with the various measures of smoking exposure (age at smoking initiation, duration of smoking in years, daily number of cigarettes smoked, and lifetime cigarette use in pack-years) and that the magnitude of the association in the overall study population was similar to that in the subgroup of women who did not drink alcohol. Among

Table 4. Multivariate-Adjusted Hazard Ratios^a for Breast Cancer Among Parous Postmenopausal Women According to Number of Pack-Years and Duration of Smoking Before First Childbirth, the Multiethnic Cohort Study, 1993–2010

Timing and Duration of Smoking ^b by Pack-Years of Smoking	All Women (n = 70,921)			Women Who Did Not Drink Alcohol (n = 45,376)		
	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI
Never smokers ^c	2,139	1.00	Referent	1,495	1.00	Referent
Ever smokers						
After or <1 year before ^d	1,181	1.02	0.95, 1.10	619	1.02	0.93, 1.13
1–5 years before	219	1.07	0.93, 1.24	101	1.04	0.84, 1.27
>5 years before	233	1.21	1.05, 1.39	112	1.24	1.01, 1.51
<i>P</i> _{trend} ^d			0.014			0.076
<i>P</i> _{trend} ^e			0.020			0.089
≤10 Pack-years						
After or <1 year before ^d	674	1.02	0.93, 1.11	343	0.97	0.86, 1.10
1–5 years before	45	0.84	0.62, 1.13	21	0.78	0.51, 1.21
>5 years before	37	0.90	0.65, 1.25	18	0.99	0.62, 1.58
<i>P</i> _{trend} ^d			0.560			0.420
<i>P</i> _{trend} ^e			0.200			0.620
11–20 Pack-years						
After or <1 year before ^d	284	1.07	0.94, 1.21	153	1.10	0.92, 1.30
1–5 years before	58	1.06	0.81, 1.38	28	1.04	0.72, 1.52
>5 years before	65	1.22	0.95, 1.57	31	1.14	0.80, 1.64
<i>P</i> _{trend} ^d			0.088			0.270
<i>P</i> _{trend} ^e			0.075			0.520
>20 Pack-years						
After or <1 year before ^d	214	1.08	0.93, 1.25	117	1.18	0.97, 1.43
1–5 years before	113	1.21	1.00, 1.47	50	1.16	0.87, 1.54
>5 years before	131	1.35	1.13, 1.63	63	1.40	1.08, 1.81
<i>P</i> _{trend} ^d			<0.001			0.003
<i>P</i> _{trend} ^e			0.081			0.320

Abbreviations: CI, confidence interval; HR, hazard ratio.

^a Adjusted for race/ethnicity, age at cohort entry, body mass index, family history of breast cancer, age at first childbirth, number of children, age at menarche, age at and type of menopause, postmenopausal hormone therapy use, alcohol consumption, and educational level.^b Relative to first childbirth.^c Includes only parous never smokers.^d Including never smokers.^e Excluding never smokers.

parous women, those who began smoking more than 5 years before their first childbirth had a statistically significantly higher risk of breast cancer than did never smokers. Interestingly, the difference in risk for heavy smokers (>20 pack-years) appeared to be greater for parous women who began smoking more than 5 years before their first childbirths than for those who began smoking after or within 1 year before first childbirth. We found similar associations among women who did not drink alcohol. We did not observe any difference by race/ethnicity, but our sample size for these ethnic-specific analyses was limited.

Our overall results agree with those from 11 recent cohort studies, the majority of which comprised predominately non-

Hispanic whites (1–4, 16–22). However, to our knowledge, the present study is the first in which the association between smoking and breast cancer risk has been examined in detail in a cohort in which the majority of women did not drink alcohol. Because alcohol is an established risk factor for breast cancer, some of the previous cohort studies (1, 3, 4, 17, 21, 22) examined the issue of confounding. There was a suggestion of a higher risk of breast cancer in female smokers who did not drink alcohol than in never smokers who abstained in the California Teachers Study (21), our own study of Scandinavian women (1), the update of the Canadian National Breast Screening Study (17), our recent Norwegian study comprising more than 300,000 women (3), the Black Women's Health Study

(22) (including close to 60,000 African Americans), and the European Prospective Investigation Into Cancer and Nutrition cohort (with >300,000 women from 10 European countries) (4). In only 2 of these studies (4, 21) did the association between smoking and breast cancer risk among women who did not drink alcohol reach statistical significance. Our finding that the associations between smoking and risk of breast cancer were of a similar magnitude for women who did not drink alcohol and for the entire population provides strong confirmatory evidence against confounding by alcohol use.

In our stratified analyses, we tried to disentangle the associations with breast cancer of lifetime dose of smoking (measured in pack-years) from those of timing of initiation (measured as duration of smoking before first childbirth). The results suggest that for heavy exposures, the timing of smoking initiation appears to be the most important contributor to the positive association between smoking and risk of breast cancer in the entire cohort as well as for women who did not drink alcohol.

Likewise, in the Nurses' Health Study (19), which included more than 8,700 cases, and the European Prospective Investigation Into Cancer and Nutrition cohort (4), which included more than 9,800 cases, investigators found a strong association between number of pack-years of smoking before the first childbirth and risk of breast cancer after stratifying the analyses by pack-years. In our cohort study from Norway, which included approximately 7,500 cases, there was a dose-response relationship between number of years of smoking before the first childbirth and breast cancer risk even in women in the lowest category of cigarettes smoked per day at enrollment (<10 cigarettes per day) (3). In another report using data from the same cohort, the results showed that smoking for several years before first childbirth increased the risk of breast cancer regardless of educational level (23). In the study by Rosenberg et al. (22), premenopausal women who had smoked for more than 20 pack-years or for more than 5 years before their first childbirth had a significant doubling in breast cancer risk compared with never smokers, whereas postmenopausal women with the same smoking history did not have a higher risk.

The results of the present study, together with those from other recent cohort studies, support an association between different measures of smoking exposure, especially before first childbirth, and risk of breast cancer. As early as 1978, the biologic plausibility of an association between cigarette smoking and breast cancer was suggested, when metabolites from tobacco smoke were detected in the breast fluid of female smokers (24, 25). Later, it was shown that smoke contains more than 20 substances that induce mammary cancers in rodents and that these compounds are also found in human breast tissue (26). In 1982, Russo et al. (27, 28) hypothesized that mammary tissue is more susceptible to carcinogenic exposures between menarche and the last trimester of the first pregnancy, when breast cells become fully differentiated.

The biologic plausibility of a causal role of smoking in breast cancer was extensively studied in the 3 previously described agency expert-panel reviews (5, 7, 13). They all concluded that sufficient evidence of the biologic mechanisms by which cigarette smoking might cause invasive breast cancer has been identified. Therefore, there is strong support for the biological plausibility of the association in the present study. The possibility that cigarette smoking acts at a relatively

early stage in the carcinogenic process and thereby increases the risk of ductal carcinoma in situ of the breast was examined in but not supported by the results from the Women's Health Initiative Clinical Trial (29).

Our study has several major strengths. It focuses on the smoking-related risk of breast cancer in a population in which the majority did not drink alcohol. In addition, we were able to adjust for most established risk factors for breast cancer, including body mass index, family history of breast cancer, age at menarche, age at first childbirth, age at and type of menopause, use of postmenopausal hormone therapy, educational level, and alcohol consumption. The smoking histories were obtained at enrollment and thus were unlikely to be subject to differential recall bias. Few women start to smoke after age 50 years (5), and the mean age at enrollment for the Multiethnic Cohort Study was older than 60 years. Thus, it is unlikely that smoking status changed for never smokers during study follow-up. Furthermore, the internal validity of the smoking exposure (30, 31) and the breast cancer outcome (11, 32) variables have been demonstrated. We also consider it a strength that all of the women were postmenopausal and that the rates of women who had ever undergone mammographic screening were higher than 90% with relatively small differences by race/ethnicity, which reduced detection bias (33).

The main limitation of the present study is the fact that despite close to 4,500 incident cases of postmenopausal breast cancer, the numbers of cases were small for important subset analyses, for example, after stratification by both race/ethnicity and years of smoking before first childbirth among parous women. Also, we did not assess lifetime drinking patterns. However, current alcohol intakes were likely to reflect lifetime habits in this cohort because drinking rates have been traditionally low in most of these racial/ethnic groups based on cultural patterns (32).

If a large proportion of participants had gaps in their smoking histories, our results could be attenuated and possibly dose-response biased toward a threshold association. If they did not include the gap years in the total number of years smoked, our estimate of age at smoking initiation would have been too high and the number of years smoked before first birth too low, which would lead to heavily exposed women being misclassified as moderately exposed. If they did include the gap years, the hazard ratio estimates for duration of smoking and number of pack-years might be attenuated and, in a similar way, indicate a threshold rather than a dose-response association, because women who were moderately exposed would have been misclassified into a heavier exposure group.

Several factors reduce the power of our study to examine these associations in more detail: 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. Because of the reduction in life expectancy associated with smoking, part of the association between the different measures of smoking exposure and risk of breast cancer may be concealed by competing causes of death. In another cohort study with a follow-up duration similar to that in the present study, we found that

1 in 3 deaths among middle-aged Norwegian women could have been prevented if the women did not smoke (34). In 3 of the previously described cohort studies (1, 4, 22), the association between active smoking and risk of breast cancer became stronger when women exposed to passive smoking were excluded from the reference group. Thus, our risk estimates might have been attenuated because passive smokers were in the reference group.

In conclusion, we found that various measures of smoking exposure were associated with a higher risk of breast cancer, especially smoking initiated many years before first childbirth. The results were similar after stratifying by drinking status and racial/ethnic group.

ACKNOWLEDGMENTS

Author affiliations: Department of Community Medicine, Faculty of Health Sciences, UiT The Arctic University of Norway, Tromsø, Norway (Inger T. Gram); Cancer Epidemiology Program, University of Hawai'i Cancer Center, Honolulu, Hawaii (Song-Yi Park, Laurence N. Kolonel, Gertraud Maskarinec, Lynne R. Wilkens, Loïc Le Marchand); and Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California (Brian E. Henderson).

This work was supported by the US Public Health Service and the National Cancer Institute (grant R37 CA54281 for The Multiethnic Cohort Study and grant UM1 CA164973 for the Multiethnic Cohort infrastructure). The tumor registries were supported by National Cancer Institute contracts N01-PC-35137 and N01-PC-35139. This work was mainly carried out while Professor Gram was a Visiting Scholar in the Cancer Epidemiology Program, University of Hawaii Cancer Center, Honolulu, Hawaii.

The funders had no input into the study design; data collection, analysis, and interpretation; the writing of the report; or the decision to submit the article for publication. Researchers were independent of influence from study funders.

Conflict of interest: none declared.

REFERENCES

- Gram IT, Braaten T, Terry PD, et al. Breast cancer risk among women who start smoking as teenagers. *Cancer Epidemiol Biomarkers Prev*. 2005;14(1):61–66.
- Gaudet MM, Gapstur SM, Sun J, et al. Active smoking and breast cancer risk: original cohort data and meta-analysis. *J Natl Cancer Inst*. 2013;105(8):515–525.
- Bjerkaas E, Parajuli R, Weiderpass E, et al. Smoking duration before first childbirth: an emerging risk factor for breast cancer? Results from 302,865 Norwegian women. *Cancer Causes Control*. 2013;24(7):1347–1356.
- Dossus L, Boutron-Ruault MC, Kaaks R, et al. Active and passive cigarette smoking and breast cancer risk: results from the EPIC cohort. *Int J Cancer*. 2014;134(8):1871–1888.
- US Department of Health and Human Services. *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General*. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, Office on Smoking and Health; 2014.
- World Health Organization. *WHO Global Report on Mortality Attributable to Tobacco*. Geneva, Switzerland: World Health Organization; 2012.
- International Agency for Research on Cancer. *International Agency for Research on Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol 100 E.: A Review of Human Carcinogens: Personal Habits and Indoor Combustions*. Lyon, France: International Agency for Research on Cancer; 2012.
- Eriksen MP, Mackay J, Schluger N, et al. *The Tobacco Atlas*. 5th ed. Atlanta, GA: American Cancer Society; 2015.
- Giovino GA, Mirza SA, Samet JM, et al. Tobacco use in 3 billion individuals from 16 countries: an analysis of nationally representative cross-sectional household surveys. *Lancet*. 2012;380(9842):668–679.
- Howlader N, Noone AM, Krapcho M, et al. *SEER Cancer Statistics Review, 1975–2011*. Bethesda, MD: National Cancer Institute; 2014.
- Pike MC, Kolonel LN, Henderson BE, et al. Breast cancer in a multiethnic cohort in Hawaii and Los Angeles: risk factor-adjusted incidence in Japanese equals and in Hawaiians exceeds that in whites. *Cancer Epidemiol Biomarkers Prev*. 2002;11(9):795–800.
- Maskarinec G, Zhang Y, Takata Y, et al. Trends of breast cancer incidence and risk factor prevalence over 25 years. *Breast Cancer Res Treat*. 2006;98(1):45–55.
- Johnson KC, Miller AB, Collishaw NE, et al. Active smoking and secondhand smoke increase breast cancer risk: the report of the Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk (2009). *Tob Control*. 2011;20(1):e2.
- Kolonel LN, Henderson BE, Hankin JH, et al. A multiethnic cohort in Hawaii and Los Angeles: baseline characteristics. *Am J Epidemiol*. 2000;151(4):346–357.
- Klein RJ, Schoenborn CA. Age adjustment using the 2000 projected U.S. population. *Healthy People 2010 Stat Notes*. 2001;(20):1–10.
- Olson JE, Vachon CM, Vierkant RA, et al. Prepregnancy exposure to cigarette smoking and subsequent risk of postmenopausal breast cancer. *Mayo Clin Proc*. 2005;80(11):1423–1428.
- Cui Y, Miller AB, Rohan TE. Cigarette smoking and breast cancer risk: update of a prospective cohort study. *Breast Cancer Res Treat*. 2006;100(3):293–299.
- Ha M, Mabuchi K, Sigurdson AJ, et al. Smoking cigarettes before first childbirth and risk of breast cancer. *Am J Epidemiol*. 2007;166(1):55–61.
- Xue F, Willett WC, Rosner BA, et al. Cigarette smoking and the incidence of breast cancer. *Arch Intern Med*. 2011;171(2):125–133.
- Nyante SJ, Gierach GL, Dallal CM, et al. Cigarette smoking and postmenopausal breast cancer risk in a prospective cohort. *Br J Cancer*. 2014;110(9):2339–2347.
- Reynolds P, Hurley S, Goldberg DE, et al. Active smoking, household passive smoking, and breast cancer: evidence from the California Teachers Study. *J Natl Cancer Inst*. 2004;96(1):29–37.
- Rosenberg L, Boggs DA, Bethea TN, et al. A prospective study of smoking and breast cancer risk among African-American women. *Cancer Causes Control*. 2013;24(12):2207–2215.
- Bjerkaas E, Parajuli R, Engeland A, et al. Social inequalities and smoking-associated breast cancer—results from a prospective cohort study. *Prev Med*. 2015;73:125–129.

24. Petrakis NL, Gruenke LD, Beelen TC, et al. Nicotine in breast fluid of nonlactating women. *Science*. 1978;199(4326):303–305.
25. Petrakis NL, Maack CA, Lee RE, et al. Mutagenic activity in nipple aspirates of human breast fluid. *Cancer Res*. 1980;40(1):188–189.
26. Hecht SS. Tobacco smoke carcinogens and breast cancer. *Environ Mol Mutagen*. 2002;39(2-3):119–126.
27. Russo J, Tay LK, Russo IH. Differentiation of the mammary gland and susceptibility to carcinogenesis. *Breast Cancer Res Treat*. 1982;2(1):5–73.
28. Russo J, Moral R, Balogh GA, et al. The protective role of pregnancy in breast cancer. *Breast Cancer Res*. 2005;7(3):131–142.
29. Kabat GC, Kim M, Kakani C, et al. Cigarette smoking in relation to risk of ductal carcinoma in situ of the breast in a cohort of postmenopausal women. *Am J Epidemiol*. 2010;172(5):591–599.
30. Haiman CA, Stram DO, Wilkens LR, et al. Ethnic and racial differences in the smoking-related risk of lung cancer. *N Engl J Med*. 2006;354(4):333–342.
31. Nomura AM, Wilkens LR, Henderson BE, et al. The association of cigarette smoking with gastric cancer: the Multiethnic Cohort Study. *Cancer Causes Control*. 2012;23(1):51–58.
32. Park SY, Kolonel LN, Lim U, et al. Alcohol consumption and breast cancer risk among women from five ethnic groups with light to moderate intakes: the Multiethnic Cohort Study. *Int J Cancer*. 2014;134(6):1504–1510.
33. Edwards QT, Li AX, Pike MC, et al. Ethnic differences in the use of regular mammography: the Multiethnic Cohort. *Breast Cancer Res Treat*. 2009;115(1):163–170.
34. Gram IT, Sandin S, Braaten T, et al. The hazards of death by smoking in middle-aged women. *Eur J Epidemiol*. 2013;28(10):799–806.