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Low level alcohol intake, cigarette smoking and risk of breast cancer in Asian-American women

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Abstract

Studies have shown that breast cancer incidence rates among Asian migrants to the United States approach U.S. incidence rates over several generations, implicating potentially modifiable exposures such as moderate alcohol use that has been linked to excess breast cancer risk in other populations. The goal of this study was to investigate the effect of alcohol intake, primarily low levels, on breast cancer risk in Asian-American women and explore whether smoking and alcohol contributed to the in breast cancer incidence rates observed among Asian migrants to the United States. Study subjects in this population-based case-control study included 597 incident cases of breast cancer of Chinese, Japanese, and Filipino ethnicity living in San Francisco-Oakland, Los Angeles, and Oahu, Hawaii and 966 population controls frequency matched on age, ethnicity, and area of residence. The fraction of smokers and drinkers was significantly higher in women born in Western compared with Eastern countries. However, breast cancer risk was not significantly associated with smoking (odds ratio (OR) = 1.2, 95% confidence interval (95% CI) = 0.9–1.6) or alcohol drinking (OR = 0.9, 95% CI = 0.7–1.1) in this population of low consumers of alcohol (median intake among drinkers in grams per day was 0.48 for cases and 0.40 for controls). These data suggest that low alcohol intake is not related to increased breast cancer risk in Asian-American women and that neither alcohol nor cigarette use contributed to the elevated risks in Asian-American women associated with migration patterns and Westernization.

Keywords

Breast cancer; Alcohol drinking; Cigarette smoking; Asian-American; Epidemiology

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Introduction

Historically, breast cancer incidence rates in the United States have been 4–7 times higher than in Asian populations [1]. This differential in rates has continued during more recent years, with age-standardized incidence rates 2–4 times higher in U.S. white women than in Asian women [2]. When Asian women migrate to the United States, their breast cancer rates rise and continue to rise in subsequent generations to the level of rates in white women living in the United States [3]. It is widely accepted that potentially modifiable exposures related to lifestyle or environment rather than genetics explain the international differences in breast cancer risk.

A previous analysis of data from this population-based study of Asian-American women [3] found a 6-fold gradient in risk for migration history, a composite measure of acculturation to Western lifestyles based on the birthplace of the subject and her grandparents, length of residence in the West (US and Europe), and urban or rural residence while in the East (Asia). Previous investigations of the data from this study explored whether the relationship between migration patterns and breast cancer risks could be explained by menstrual and reproductive factors, oral contraceptive use, weight and height, or soy intake [4–6]; but none of these factors explained a substantial fraction of the gradient in risk. In this paper, we examine the contribution of alcohol, particularly low levels of intake, and smoking to breast cancer incidence in these Asian-American women and explore whether these factors might contribute to the rapid rise in breast cancer rates observed among Asian migrants to the U.S. We consider both the strength of the association with alcohol intake and smoking and the differences in exposure by place of birth.

Materials and methods

Study participants and design

Methods for selection of cases and controls have been published in detail elsewhere [3]. In brief, all histologically confirmed cases of first primary breast cancer [International Classification of Diseases for Oncology (ICDO) site code 174] diagnosed between April 1, 1983 and June 30, 1987 among women aged 20–55 years of Chinese, Japanese, or Filipino ethnicity living in the San Francisco-Oakland Metropolitan Statistical Area (MSA), the Los Angeles MSA, or Oahu, Hawaii, at the time of diagnosis were eligible for inclusion in this study. Controls were frequency-matched, using a 2:1 ratio where possible, based on the study area-, ethnicity-, and age-specific (5-year age groups) numbers of cases anticipated. Random-digit dialing was utilized for control selection in San Francisco-Oakland and Los Angeles, whereas controls in Hawaii were obtained through the Health Surveillance Program of the Hawaii State Department of Health, which samples 2% of the households in the State annually. Participation rates were 70% for cases and 75% for controls and were similar by study area and ethnicity.

Trained interviewers successfully conducted in-person interviews with 597 cases (164 Chinese, 239 Japanese, 194 Filipino) and 966 controls (288 Chinese, 395 Japanese, 283 Filipino) in Chinese, Japanese, or English in the homes of the participants. Information was obtained on the use of alcohol and tobacco; usual adult and childhood/adolescent diet; weight, weight change, and height; reproductive, menstrual, medical, and family cancer history; socio-demographic/cultural factors; and residential history.

Data analysis

Alcohol drinkers were defined as study participants who reported drinking beer; American, European, Japanese (e.g., sake or plum wine), or Chinese (e.g., rice wine) wine; or liquor (Western-type, Philippine, strong Philippine, strong Chinese, or strong Japanese) at least once

a year. For drinkers, usual weekly consumption of alcoholic beverages was estimated by summing the contribution from each type of alcohol, where one drink was considered equivalent to 12 oz of beer, 4 oz of any type of wine, or 1 1/2 oz of any type of liquor. The number of grams of ethanol consumed per day was estimated by multiplying the number of drinks of each specific type of alcohol consumed per week by the appropriate number of grams of ethanol per drink and then summing across the types of alcohol and dividing by seven. The grams of ethanol attributed to a 12 oz serving of beer, 4 oz serving of American or European wine, 4 oz serving of Chinese or Japanese wine, and 1.5 oz serving of any type of liquor, were 13 g, 11 g, 18 g, and 15 g, respectively.

Cigarette smokers were defined as study participants who reported smoking cigarettes regularly for six months or longer and ex-smokers were defined as cigarette smokers who had not smoked for the last two years. Questions were asked about the age at first and last use as well as about the number of years they had smoked and usual number of cigarettes smoked.

Adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated using unconditional logistic regression [7]. In the tests for linear trend, categorical variables were entered as continuous variables in the logistic models, with each study participant whose level fell in a particular category assigned the median value for that variable among control subjects whose level fell in that category. General linear models were used to compare the means of continuous drinking and smoking variables by birthplace while also controlling for age (5-year groups), study area, and ethnicity. Pearson's correlation coefficient was utilized to measure the strength of the linear relationship between continuous variables. All statistical tests were two-sided, and SAS software was used for the analysis [8].

All logistic models included the selection factors--age (<40, 40–44, 45–49, 50+ years), study area (Los Angeles, San Francisco-Oakland, Oahu), and ethnicity (Chinese, Japanese, Filipino)--as well as accepted breast cancer risk factors--age at menarche (<12, 12–13, 14–15, 16+ years), age at first live birth (never pregnant; no live births; <21, 21–25, 26–30, 31–35, 36+ years at first live birth), number of live births (never pregnant; no live births; 1, 2, 3, 4+ live births), menopausal status (premenopausal; postmenopausal including natural and surgical), age at menopause (premenopausal; 28–47, 48–50, 51+ years at menopause), family history of breast cancer (yes, no), and history of benign breast disease (yes, no). Alcohol and tobacco use were also adjusted for migration history, a composite index of acculturation to Western lifestyles based on the birthplace of the subject and her grandparents, [East (China, Taiwan, Hong Kong, Macao, Japan, the Philippines, Southeast Asia, the Malaysian Peninsula, Singapore, and India) and West (countries in North America and Europe, Australia, and New Zealand)], subject's length of residence in the West (<8, 8+ years), and urban or rural residence while in the East [3]. Risks were calculated for all subjects combined and separately by place of birth (East and West), menopausal status, and family history of breast cancer. Two subjects, born in Mauritius and Trinidad, Tobago, were excluded from the place of birth analysis.

Results

Use of alcoholic beverages was reported by 59.8% of the cases and 60.6% of the controls whose drinking habits were recorded by interviewers (OR = 0.9) (Table 1). However, total consumption was low, with only 5% percent of the cases and 4% of the controls reporting 1 or more drinks per day and only 1.5% of the cases and 2% of the controls reporting 2 or more drinks per day. The median number of drinks per week among the women who did consume alcohol was 0.25 for cases and 0.23 for controls. The median grams of ethanol consumed per day among drinkers were 0.48 for cases and 0.40 for controls. Patterns of breast cancer risk by number of drinks per week and grams of ethanol per day were similar, with non-statistically significant increased risks of 1.5 for intermediate levels of intake (2.5–7.0 drinks/week; 5–9.99

g ethanol/day) and 1.3 for higher intake, compared with never drinkers. For the few women with the highest intake (14+ drinks/week or 20+ g ethanol/day), there was a non-statistically significant reduction in breast cancer risk compared to never drinkers. Similar patterns were observed for both premenopausal (424 cases, 662 controls) and postmenopausal (165 cases, 299 controls) women, for women with (117 cases, 92 controls) and without (480 cases, 874 controls) a family history of breast cancer, and for women born in the East (325 cases, 563 controls) and born in the West (272 cases, 401 controls) (data not shown). Additional adjustment for number of drinks/week and grams of ethanol/day as well as for migration history resulted in modest (<10%) reductions in risk. Additional adjustment of the two alcohol intake exposures for number of cigarettes smoked per day did not change the alcohol associations.

Cigarette smoking was reported by 27.1% of the cases and 24.6% of the controls whose smoking history was recorded by interviewers, for a non-significant elevated risk of 1.2 (Table 2). Compared with the risk for never smokers, risk was not increased for current smokers (OR=0.9) but was statistically significantly elevated for ex-smokers (OR = 1.6), particularly those who had quit for 2–19 years (OR=1.7). However, risk was not significantly elevated for subjects who quit smoking 20 or more years earlier (OR = 1.1) and no pattern was observed with age at which smoking stopped. Quitting smoking can lead to weight gain, and we have previously reported that among these Asian-American women, recent relative weight and recent weight gain were both strong predictors of increased breast cancer risk [5].

However, the increased risk among ex-smokers was not explained by either recent relative weight (weight in current decade/height^{1.5}) or recent weight change. In fact, among the controls, a substantially greater percentage of current smokers (14.2%) reported losing weight over the past decade than of never smokers (9.6%) or ex-smokers (8.7%). Compared with never smokers, a significantly increased risk (OR = 2.9, 95% CI=1.1–7.9) was observed for the small number of women (11 cases, 9 controls) who smoked during adolescence (before age 16) but not for women who started smoking before their first childbirth (data not shown). There were no consistent gradients in risk with either intensity or duration of cigarette smoking. There was little variation by menopausal status in the associations between smoking patterns and breast cancer risk. Additional control for migration history reduced smoking-associated risks slightly, with decreases in risk for ever smokers (OR=1.1, 95% CI=0.8–1.4) and ex-smokers (OR=1.4, 95% CI=1.0–2.0). Addition of the number of drinks per week to the smoking-pattern models did not alter any of the associations with breast cancer risk.

To evaluate whether exposure patterns to alcohol and tobacco were consistent with the elevated risk of breast cancer among women born in the West, we calculated the percent consumers and mean intake among consumers for drinking and smoking by birthplace among the study controls (Table 3). The percentage of drinkers was significantly greater among controls born in the West compared with those born in the East (70.1% vs. 53.8%; $P = .01$); however, there were no significant differences among drinkers in the mean weekly consumption of alcoholic beverages or the daily intake of ethanol by place of birth. Among controls, significantly fewer smokers were born in the East than in the West (13.8% vs. 40.1%; $P < .001$), but mean cigarette smoking intensity and duration among smokers were similar for Western and Asian-born women.

Table 4 presents the risk of breast cancer by migration history. Migration history categories are ordered by decreasing risk of breast cancer, from the most acculturated (the women born in the West with 1–4 grandparents born in the West) to the least acculturated (the women born in the East with all 4 grandparents born in the East who always lived in a rural area in the East and who had lived in the West less than 8 years). Breast cancer risk was significantly lower in the least acculturated women; the multivariate OR was 0.2 (95% CI = 0.1 – 0.4). However, the gradient in risk by migration history was not noticeably altered when the model was further

adjusted for weekly intake of alcohol beverages ($X^2 = 7.50$, $df=6$, $P = 0.28$) or daily use of cigarettes ($X^2 = 1.80$, $df=5$, $P = 0.88$).

Discussion

In this population of Asian-American women with breast cancer, we assessed the impact on breast cancer risk of two common modifiable exposures, alcohol and tobacco use, to determine whether they partially explained the 6-fold gradient in risk by acculturation in this migrant population. Alcohol consumption is an accepted risk factor for breast cancer. Several pooled and meta-analyses, as well as most recent studies, have found evidence of a dose-response relationship that appears at modest intake (approximately 1 drink per day), with risk increasing 3% – 12% for each 10 g of alcohol (approximately one drink) consumed per day [9–19]. Questions still remain, however, about the shape of the dose-response curve, especially at low levels of intake (< 1 drink per day) [14,15].

Similar to a large cohort study of women in the United Kingdom [19], we found no excess breast cancer risk associated with low levels of alcohol intake (< 5 g per day) in our study of Asian American women. But, we did find higher than expected risks (1.3–1.5) among women reporting recent alcohol intake of 5 – 20 g/day. However, these risk estimates have wide confidence intervals and are not statistically significant due to the relatively small number of users who drank one drink or more per week. Few studies that estimate breast cancer risk by quantity of alcohol intake in Asian or Asian-American populations have been published; those we have found were conducted in Japan. A recently published systematic review of cohort and case-control studies in Japanese populations that evaluated the relationship between alcohol drinking and breast cancer risk reported that results from both types of studies were inconsistent and often limited by study methodology [20]. The authors stated that lack of information precluded evaluating the dose-response relationship for alcohol.

The metabolism of alcohol differs in Asian and White populations. This may explain why the elevation in breast cancer risk associated with moderate drinking is unusually high in our Asian-American women. The enzyme alcohol dehydrogenase (ADH) oxidizes ethanol to acetaldehyde, which is oxidized to acetic acid by aldehyde dehydrogenase (ALDH). Two of the three common ADH genes, *ADH1B* and *ADH1C*, have polymorphisms (*ADH1B*2*; *ADH1C*1*) that code for more active enzymes, increase acetaldehyde production, and are more prevalent in Asian populations [21,22]. In addition, a polymorphism in the ALDH gene (*ALDH2*2*) that codes for an essentially inactive form of ALDH is found in Asian but not White populations [21,22]. These three polymorphisms, which would increase the acetaldehyde in circulation, are believed to be responsible for the flushing, discomfort, and nausea associated with heavy drinking in susceptible Asian individuals and the relatively low alcohol intake and low prevalence of alcoholism in Asian populations [23,24]. Acetaldehyde, a known mutagen and carcinogen, may explain why alcohol intake increases the risk of breast cancer [25,26]. Asian women who drank even small quantities of alcohol would receive greater exposure to acetaldehyde, compared with White women with similar or somewhat higher intake, which could explain the high, though not significant, risk of breast cancer we observed at modest levels of alcohol intake among the Asian-American women in our study. We were surprised that among the Asian-American women with the very highest intakes, 20+ g of alcohol/day, breast cancer risk dropped, but this estimate has wide confidence intervals and could be an unstable result based on small numbers. However, if this observation were accurate, it is conceivable that these women may be exposed to lower levels of acetaldehyde despite their higher alcohol consumption because they lack the polymorphisms that increase acetaldehyde levels and thus inhibit heavy drinking.

Other mechanisms, in addition to acetaldehyde production, have been proposed to explain why breast cancer risk is elevated at modest levels of alcohol consumption [19,27]. It is plausible that these mechanisms of action could be influenced by the genetic differences in alcohol metabolism in Asian populations. The low percentage of Asian-American women in our study drinking 5+ g of alcohol/day (7.6% of controls) and the relatively high percentage of women characterizing themselves as never drinking (39.1% of controls) are consistent with other reports of alcohol use in Asian populations [20].

Over the years, smoking has been postulated to increase the risk of breast cancer. While most epidemiologic studies have not supported an overall association, some questions, such as the influence of early initiation and long duration, remain unanswered [28,29]. Also, recent evidence suggests that cigarette smoking is associated with an increased breast cancer risk among Caucasian and African American women with *N-acetyltransferase 2 (NAT2)* slow acetylation genotypes which result in slow clearance of aromatic amines, a major class of tobacco carcinogens [30]. However, we lacked the genotype data to evaluate such a finding in our study population. Among the Asian-American women in our study, we found no statistically significant increase in risk with ever having smoked and no consistent or significant trends in risk with duration or frequency of cigarette use. However, we did find a statistically significant elevation in risk among ex-smokers who had quit from 2–19 years and consistent with other reports [31–35], we did find an increased risk associated with initiation of smoking during adolescence, a time when breasts are developing and breast cancer risk may be altered [36,37]. The results of our smoking analysis agree with a collaborative reanalysis of pooled data from 53 epidemiologic studies that found no increased breast cancer risk among ever or current smokers that did not drink [14].

Both alcohol and cigarette use were significantly higher in Asian-American women born in the West than in those born in the East, with the percentage of ever drinkers 30.3% higher and the percentage of ever smokers 190% higher. Among drinkers and smokers, the frequency of use did not vary substantially by place of birth. However, because the influence of alcohol and cigarettes on breast cancer risk was modest, these factors explain little of the 6-fold gradient in breast cancer risk associated with migration history and acculturation.

A limitation on estimating the influence of moderate to heavy intake of alcohol in this Asian population is the small percentage of subjects who drank 5 or more grams of alcohol per day. Also no information was available on different patterns of alcohol use that may have occurred over their lifetime. Strengths of this migrant study are that it is population-based and included a wide range of lifestyles and acculturation in Asian-American women. Also, this is the first study to examine the role of smoking and alcohol consumption, particularly low levels of intake, with data collected consistently from Asian-American women from the general population.

In conclusion, low alcohol intake was not related to increased breast cancer risk and neither alcohol nor cigarette use contributed to the striking increase in breast cancer risk with acculturation in these Asian-American women. In previous analyses we found that this increase also was not due to differences in menstrual or reproductive factors, anthropometry, or dietary intake of soy [4–6]. However, in previous analyses of this case-control dataset, we were able to demonstrate that breast cancer incidence in Asian migrants to the United States has approached that of U.S. White women [3]. Recent analyses have confirmed this finding in Japanese- and Filipino-American women [38–40]. Thus, modifiable factors associated with Westernization are likely to play a major role in breast cancer etiology, and continued research is necessary to elucidate the responsible lifestyle and environmental exposures.

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Abbreviations

OR	Odds ratio
CI	Confidence interval
MSA	Metropolitan statistical area
ICDO	International Classification of Diseases for Oncology
SD	Standard deviation
ADH	Alcohol dehydrogenase
ALDH	Aldehyde dehydrogenase
g	Grams

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Table 1

Association of alcoholic beverage use with breast cancer in Asian-American women

	Cases	Controls	Multivariate OR ^{a,b}	95% CI	Test for trend among drinkers
Drank alcohol					
Never drank	234	375	1.0	Ref	
Ever drank	357	585	0.9	0.7–1.2	
Drinks per week					
None	234	375	1.0	Ref	
<1	250	435	0.9	0.7–1.1	
1–2.5	42	77	0.9	0.6–1.4	
2.51–6.99	34	31	1.5	0.9–2.7	
7–13.99	22	22	1.3	0.7–2.5	
≥14	9	20	0.6	0.3–1.5	P = 0.95
Grams of ethanol per day					
None	324	375	1.0	Ref	
<1	216	394	0.8	0.6–1.1	
1–4.99	77	118	1.0	0.7–1.5	
5–9.99	30	27	1.5	0.8–2.7	
10–19.99	22	24	1.3	0.7–2.4	
≥20	12	22	0.8	0.4–1.6	P = 0.86

^aExcludes six cases and six controls with unknown drinking habits

^bAdjusted for age, study area, ethnicity, age at menarche, age at first live birth, number of live births, menopausal status, age at menopause, family history of breast cancer, and history of benign breast disease in an unconditional logistic model

Table 2

Association of cigarette smoking with breast cancer in Asian-American women

	Cases	Controls	Multivariate OR ^{a,b}	95% CI	Test for trend
Smoked cigarettes cigarettes					
Never smoked	429	722	1.0	Ref	
Ever smoked	162	238	1.2	0.9–1.6	
Current smoker ^c	70	135	0.9	0.6–1.3	
Ex-smoker	92	103	1.6	1.1–2.2	
Years since quitting smoking					
Never smoked	429	722	1.0	Ref	
2–9 years	37	40	1.7	1.0–2.9	
10–19 years	35	38	1.7	1.0–2.9	
≥20 years	19	25	1.1	0.6–2.1	P = 0.22 ^d
Age stopped smoking					
Never smoked	429	722	1.0	Ref	
< 30 years	26	32	1.5	0.9–2.8	
30–39 years	32	35	1.6	1.0–2.8	
≥40 years	33	36	1.5	0.9–2.6	P = 0.76 ^d
Age started smoking					
Never smoked	429	722	1.00	Ref	
< 16 years	11	9	2.92	1.1–7.9	
16–18 years	40	58	1.18	0.7–1.9	
19–21 years	56	85	1.03	0.7–1.5	
≥22 years	55	86	1.20	0.8–1.8	P = 0.81 ^e
Cigarettes smoked per day					
Never smoked	429	722	1.0	Ref	
< 10 per day	58	85	1.2	0.8–1.7	
10–19 per day	47	64	1.3	0.9–2.1	
20 per day	41	64	1.2	0.8–1.9	
≥21 per day	16	25	0.9	0.5–1.9	P = 0.51 ^e
Years smoked cigarettes					

	Cases	Controls	Multivariate OR ^{a,b}	95% CI	Test for trend
Never smoked	429	722	1.0	Ref	
< 10 years	42	60	1.3	0.8–2.1	
10–19 years	38	60	1.1	0.7–1.7	
20–29 years	56	71	1.4	0.9–2.0	
≥ 29 years	25	47	0.9	0.5–1.6	P = 0.26 ^e

^aExcludes six cases and six controls with unknown smoking habits

^bAdjusted for age, study area, ethnicity, age at menarche, age at first live birth, number of live births, menopausal status, age at menopause, family history of breast cancer, and history of benign breast disease in an unconditional logistic model

^cCurrent smoker includes those who quit 0–1 years ago

^dP for trend among ex-smokers

^eP for trend among current and ex-smokers

Table 3

Consumption of alcohol and tobacco by place of birth, based on data from Asian-American women selected as controls

	Birthplace		P value ^a
	West	East	
Total number of controls	401	563	
Ever consumed			
Alcoholic beverages (%)	70.1%	53.8%	0.010
Cigarettes (%)	40.1%	13.8%	<0.001
Mean intake among consumers			
Alcoholic drinks per week ^b	1.7	2.0	0.31
Grams of ethanol per day ^b	21.3	26.7	0.21
Cigarettes per day ^c	13.9	13.0	0.79
Years smoked cigarettes ^c	18.6	19.1	0.98

^a Adjusted for age, study area, and ethnicity

^b Based on 281 controls born in the West and 303 born in the East who consumed alcohol

^c Based on 161 controls born in the West and 77 born in the East who used cigarettes

Table 4
Association of migration history and breast cancer risk in Asian-American women

Migration history: place of birth of study participants and grandparents, residence in East, years lived in West ^e		Cases	Controls	Multivariate adjusted OR ^{b,c}	95% CI	Multivariate + alcohol adjusted OR ^{b,c,d}	95% CI	Multivariate + smoking adjusted OR ^{b,c,e}	95% CI
W//1-4W	48	57	1.0	Ref	Ref	1.0	Ref	1.0	Ref
W//4E	186	284	0.6	0.4-1.0	0.4-1.0	0.6	0.4-1.0	0.6	0.4-1.0
E//4E, urban in East, 8+ years in West	146	208	0.5	0.3-0.9	0.3-0.9	0.5	0.3-0.9	0.5	0.3-0.9
E//4E, rural in East, 8+ years in West	48	79	0.4	0.2-0.8	0.2-0.8	0.4	0.2-0.8	0.5	0.2-0.9
E//4E, urban in East, < 8 years in West	52	107	0.4	0.2-0.7	0.2-0.7	0.4	0.2-0.7	0.4	0.2-0.7
E//4E, rural in East, < 8 years in West	11	48	0.2	0.1-0.4	0.1-0.4	0.2	0.1-0.4	0.2	0.1-0.5
P value for additional variable							P=0.28		P=0.88

^a Birthplace of subject and birthplace of grandparents was categorized as West (W) or East (E). For example W//1-4W includes all subjects born in the West, 1-4 of whose grandparents were also born in the West. Residence while in the East was categorized as always urban or always rural. Excludes 106 cases and 183 controls with unclear migration history or a migration history that did not fit any of the designated categories

^b All risks relative to 1.0 for migration history W//1-4 W

^c Adjusted for age, study area, ethnicity, age at menarche, age at first live birth, number of live births, menopausal status, age at menopause, family history of breast cancer, and history of benign breast disease in an unconditional logistic model

^d Additionally adjusted for number of drinks of alcoholic beverages per week in an unconditional logistic model

^e Additionally adjusted for number of cigarettes per day in an unconditional logistic model