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Modification of breast cancer risk according to age and menopausal status: A combined analysis of five population-based case-control studies

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Abstract

Purpose—While several risk factors for breast cancer have been identified, studies have not consistently shown whether these factors operate more strongly at certain ages or for just pre- or

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postmenopausal women. We evaluated whether risk factors for breast cancer differ according to age or menopausal status.

Methods—Data from five population-based case-control studies conducted during 1988-2008 were combined and analyzed. Cases (N=23,959) and population controls (N=28,304) completed telephone interviews. Logistic regression was used to estimate adjusted odds ratios and 95% confidence intervals and tests for interaction by age and menopausal status.

Results—Odds ratios for first-degree family history of breast cancer were strongest for younger women—reaching two-fold elevations—but were still statistically significantly elevated by 58-69% among older women. Obesity was inversely associated with breast cancer among younger women and positively associated with risk for older women (interaction $P<0.0001$). Recent alcohol intake was more strongly related to breast cancer risk among older women, although consumption of 3 or more drinks/day among younger women also was associated with elevated odd ratios ($P<0.0001$). Associations with benign breast disease and most reproductive/menstrual factors did not vary by age. Repeating analysis stratifying by menopausal status produced similar results.

Conclusions—With few exceptions, menstrual and lifestyle factors are associated with breast cancer risk regardless of age or menopausal status. Variation in the association of family history, obesity, and alcohol use with breast cancer risk by age and menopausal status may need to be considered when determining individual risk for breast cancer.

Keywords

case-control studies; breast neoplasms; alcohol drinking; obesity; risk factors; menopause; age factors

Introduction

Breast cancer has been associated with numerous risk factors in epidemiologic studies.[18] Several factors are believed to operate through sex hormone pathways, including parity, breast feeding, and age at menarche, first full-term pregnancy, and menopause. Alcohol intake is consistently related to an increase in breast cancer risk,[48] also likely through hormonal mechanisms.[15] These risk factors are modestly associated with breast cancer, increasing risk in the range of 1.2 – 1.7.[13] First degree family history of breast cancer is more strongly related to elevated risk—exceeding 2-fold— especially when more than one first degree family member has been diagnosed or the relative was diagnosed at a young age.[16] Some studies suggest that the elevated risk associated with a first degree family history of breast cancer may be limited to younger women [11] but this is not consistently seen.[5, 23]

Modification of breast cancer risk factor associations by age or menopausal status has been most consistently demonstrated for obesity, which is associated with decreased risk in younger women and increased risk in older women.[22, 30, 57] Other factors, such as oral contraceptive or postmenopausal hormone use, are related to menopausal status due to specific medication prescribing practices.[1, 47] Several other factors including menstrual and reproductive characteristics are relevant for breast cancer risk throughout life, but the

magnitude of risk may operate more strongly at one life stage than another.[29, 39] Since several studies use age 50 as a proxy for the menopausal transition, these studies are unable to evaluate which factor—age or menopausal status—is driving the modification of breast cancer risk.

Identification of risk factors specifically relevant for women at different ages is hampered by the large sample size needed to identify significant heterogeneity and the difficulty in combining results across multiple studies that have used different age categories or risk factor definitions. To overcome these limitations, we combined data from five phases of a case-control study of breast cancer conducted over two decades. Consistent protocols were used over time, facilitating combined analysis. The purpose of this analysis was to examine established breast cancer risk factors and to test for heterogeneity by age and menopausal status. We were particularly interested in identifying risk factors for younger women and determining whether patterns in risk are most strongly defined by age or menopausal status.

Methods

Selection of cases

All female residents of Maine, Massachusetts (excluding metropolitan Boston), New Hampshire, and Wisconsin with a new diagnosis of invasive breast cancer (ICD-O version 2 C50.0-C50.9) reported to each state's cancer registry and aged <75 years at diagnosis between April 1988 and January 2008 were eligible for five consecutive phases of a case-control study collectively called the Collaborative Breast Cancer Study.[31, 33-35, 51] According to a protocol approved by the institutional review boards of the participating centers, eligibility was limited to cases with listed telephone numbers, driver's licenses verified by self-report (if less than 65 years of age), and known dates of diagnosis. Recruitment of cases differed by state (Maine, 1988-1991; New Hampshire and Massachusetts, 1988-2001; Wisconsin, 1988-2008). Age criteria also changed over time to include ages 20-74 during 1988-1991, ages 50-79 during 1992-1995, and ages 20-69 during 1997-2008. A total of 30,245 women with breast cancer were eligible for the study. Physicians refused contact with 1,069 (3.5%), 1,206 (4.0%) were deceased, 690 (2.3%) could not be located, and 3,199 (10.6%) refused to participate. Overall, 24,081 (80%) women were interviewed; 98% of cases were confirmed by positive histology according to the cancer registry reports.

Selection of controls

During 1988-2003, controls were randomly selected in each state using lists of licensed drivers (ages <65) and Medicare beneficiaries (ages ≥65). Controls of all ages were selected only from lists of licensed drivers during 2004-2008. Controls were selected at random within 5-year age strata to yield an age distribution similar to the cases enrolled in each state. Controls were required to have no personal history of breast cancer (self-reported), a listed telephone number, and a self-reported driver's license (ages <65 during 1988-2003; all ages during 2004-2008). Of the 37,069 potential controls, 434 (1.2%) were deceased, 1,336 (3.6%) could not be located, and 6,833 (18.4%) refused to participate. Interviews were obtained for 28,466 (77%) controls.

Data collection

Trained interviewers were blinded to disease status. The 40-minute telephone interview elicited information on reproductive history, alcohol consumption, smoking history, height and weight, use of oral contraceptive and postmenopausal hormones, personal and family medical history, and demographic factors. Interviews took place for cases on average about a year after diagnosis (median 1.25 years).

Statistical analysis

For each case, a reference date was defined as the registry-supplied date of invasive breast cancer diagnosis. Controls were assigned an individual reference date based on the average number of days from diagnosis to interview among cases already interviewed within each state.

A woman was defined as postmenopausal if she reported a natural menopause (no menstrual periods for at least six months for women interviewed 1988-2005, and 12 months for women interviewed 2005-2008) before the reference date. Women taking postmenopausal hormones and still having periods, and women who reported hysterectomy without bilateral oophorectomy were classified as 1) premenopausal if their reference ages were in the first decile of age at natural menopause among the controls (<41 years of age for current smokers, <43 years of age for non-smokers), 2) postmenopausal if their reference ages were in the highest decile for age at natural menopause in the control group (≥54 years of age for current smokers, ≥56 years of age for non-smokers) with age at menopause defined unknown, and 3) unknown menopausal status for intermediate ages.

Family history of breast cancer was defined as a report of breast cancer in a woman's mother or sister. Personal history of benign breast disease was defined based on a woman's report of a doctor's diagnosis of biopsied benign breast disease. Parity was defined as the number of pregnancies lasting at least 6 months.

Body mass index (BMI, kg/m^2) was based on self-reported weight 1-5 years prior (depending on recruitment period) to the reference date and tallest adult height. BMI categories were defined based on World Health Organization cut-points for underweight (<18.5 kg/m^2), normal (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obese (≥30 kg/m^2).[56] Alcohol intake was defined as the average of the sum of drinks of beer, wine and liquor per week during the 5 years prior to the reference date. Ever-use of cigarette smoking was defined as report of smoking at least 100 cigarettes; current smoking included women who smoked within the year prior to the reference date.

Logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI) adjusted for age, state, study period, and other covariates. Models were fit separately for women in four age groups: 18-39, 40-49, 50-64, and 65-79 years. In separate models including all ages, tests of interaction between age and each factor of interest were conducted by examining the change in the log-likelihood after a model was fit including a cross-product term between age (defined continuously in years) and the factor of interest as shown in Table 1. Tests were repeated in separate models with a cross-product term between each risk factor and menopausal status as a binary term (pre- and post-menopausal). Tests of

interaction involving age at first full-term pregnancy were limited to parous women. Alcohol intake was treated as a continuous variable (drinks/week) for interaction tests. Factors with significant tests of interaction (P<0.05, two-sided) were evaluated in stratified models by age or menopausal status, whichever was significant; factors with significant interaction *P*-values for both age and menopausal status were also evaluated with jointly stratified models.

Women were excluded from analysis if the interviewers reported that the data were unreliable (38 cases, 37 controls) or if women reported a personal history of ovarian cancer (84 cases, 124 controls). Thus, 23,959 cases and 28,305 controls were included in analysis. Analysis for alcohol intake and benign breast disease included fewer women due to changes in the questionnaire that prevented standardized assessment across all study instruments; sample sizes are indicated in Table 1.

Results

On average, cases and controls were 58.0 and 57.0 years of age, respectively. Slightly fewer cases (25.6%) than controls (27.2%) were premenopausal. The majority of cases were diagnosed with localized breast cancer (61.8%). About 40.1% of the cases reported that diagnosis occurred as a result of a screening mammogram rather than as a result of symptoms (36.2%) or an unrelated medical test (6.8%); 16.9% of cases had unknown method of detection.

Overall odds ratios of breast cancer are shown in Table 1 along with *P*-values testing effect modification by age and menopausal status. Odds ratios of breast cancer did not appear to vary significantly by age or menopausal status for benign breast disease, age at menarche, and age at first full term pregnancy.

A family history of breast cancer was more strongly associated with breast cancer among younger women, although odds ratios were significantly elevated in all age groups (*P*=0.01; Table 2). Odds ratios of breast cancer associated with at least one first-degree relative with breast cancer was 2.28 among women aged <40, 1.92 among women aged 40-49, 1.58 for women aged 50-64, and 1.69 among women 65-79 years of age.

While the relations between breast cancer risk and most reproductive and menstrual factors were similar across age groups, parity was significantly associated with reduced breast cancer risk only in women ≥40 years of age (*P*=0.0001; Table 2). Conversely, odds ratios associated with use of oral contraceptives were elevated for women of all ages but confidence intervals excluded one only for women aged 50 to 64 (*P*<0.0001). Analysis of time since use of oral contraceptives was limited by few current users; only about 6% of women used oral contraceptives within five years (data not shown).

Modifiable factors were more strongly associated with breast cancer risk in certain age groups (Table 1 and 2). Compared to “normal” BMI, an elevated BMI was associated with 11-30% reduced risk in women <50, whereas overweight and obesity in women aged ≥50 had an 8-49% increased risk of breast cancer (*P*<0.0001). Results suggested that current smoking was inversely associated with breast cancer among younger women and positively associated with risk among older women (*P*=0.03). Consumption of greater amounts of

alcohol was consistently associated with increased risk of breast cancer among older women, but the results were largely null for women <50 years of age (P=0.0002).

The relation between breast cancer and three factors—family history of breast cancer, body mass index, and alcohol intake—were significantly modified by both age and menopausal status (Table 1 and 3). Family history of breast cancer was most strongly associated with breast cancer risk for premenopausal women less than age 40 (OR 2.25, 95% CI 1.75-2.89; Table 4), although the risk of breast cancer associated with a family history of breast cancer was significantly elevated in all strata defined jointly according to age and menopausal status. Conversely, the association between body mass index and cancer risk depended on both age and menopausal status with, at the extremes, a negative association for premenopausal women aged <40 (OR 0.97, 95% CI 0.96-0.99 per 1 kg/m^2) and a positive association for postmenopausal women aged ≥70 (OR 1.04, 95% CI 1.03-1.05 per 1 kg/m^2). Results suggest that increasing consumption of alcohol is associated with greater risk of breast cancer for all women, although odds ratio estimates were not statistically significant for some age categories among premenopausal women (Table 4).

Finally, results suggest that the relation between breast cancer and one factor—duration of breast feeding—was modified by menopausal status but not age. In particular, the odds ratio for breast feeding >12 months was 0.76 (95% CI 0.69, 0.85; Table 3) among premenopausal women; the odds ratio was null for postmenopausal women (OR 1.01, 95% CI 0.93, 1.09).

Discussion

In this large study including data from a series of five case-control studies, some associations between established risk factors and breast cancer risk were not modified by age or menopausal status including benign breast disease, age at menarche, and age at first full term pregnancy. Conversely, other factors were modified by age or menopausal status or both, including family history, parity, breast feeding, body mass index, cigarette smoking and alcohol intake.

Familial breast cancer often is diagnosed in women at a younger age and accounts for a higher proportion of breast cancer in younger than older women.[8, 9, 12, 16, 45] Although breast cancer risk associated with a family history is greatest in very young women, odds ratios for a positive family history consistently exceed 1.50 for ages >50 and support a role for hereditary breast cancer at least through age 80. Even though the prevalence of a positive family history of breast cancer tends to increase with age and may reflect a greater proportion of indolent disease in older women, family history appears to persist as a significant risk factor at all ages.[43]

Several studies have observed that full-term pregnancies are associated with a temporary increase in breast cancer risk followed by a life-long reduction in risk within 15 to 30 years.[10, 24] Pregnancy-associated breast cancer may be driven by stimulated cell division from elevated sex hormones during pregnancy [24]. In our study, null odds ratio estimates of breast cancer associated with parity were observed for women <40 years of age. Women with greater parity also tend to have longer lifetime durations of breast feeding. In our

analysis, breast feeding was significantly associated with reduced risk of breast cancer only among premenopausal women. However, we have previously reported reduced risk of postmenopausal breast cancer using data from one of the five case-controls studies included in this analysis [32]. Furthermore, a large combined analysis of 47 epidemiologic studies reported that lactation was associated with reduced breast cancer risk regardless of menopausal status [14]. Differences between study results may be due to stronger associations with breast cancer risk among women who have lactated for longer durations, exclusively (without supplementation by infant formula), or first lactated at younger ages. While greater parity and longer durations of breast feeding may be effective for reducing incidence of breast cancer of all ages, they are not realistic intervention approaches for breast cancer prevention; however, better understanding of the mechanism behind these associations with breast cancer may provide opportunities to reduce the burden of cancer in the future [14].

Our observation that obesity is inversely related with breast cancer before age 50—largely reflecting premenopausal breast cancer—and positively related with breast cancer after age 50 is concordant with the majority of studies on this topic.[30, 44, 54, 58] The average age at natural menopause of women in the U.S. and Europe is in the range of 48-52,[19, 20, 49] and has increased somewhat among more recent birth cohorts.[38] In a previous analysis, we showed that menopausal status more so than age modified the relation between body mass index and breast cancer risk.[55] This updated, larger analysis appears to confirm that while age statistically modifies the association between body mass and breast cancer risk, menopausal status appears to more clearly separate reduced from elevated risk of breast cancer.

Current smoking appeared to be associated with modest increased risk among older but not younger women. However, a combined analysis of data from 53 studies demonstrated that any apparent increased breast cancer risk associated with smoking is likely attributable to confounding effects of alcohol consumption [17]. While our estimates for smoking were adjusted for alcohol intake, the associations for these behaviors are difficult to disentangle.

Many studies show a positive association between intake of alcoholic beverages and breast cancer risk, as summarized in several meta-analyses and combined analyses of individual data.[17, 21, 27, 46, 48, 58] Alcohol intake appears to increase risk of breast cancer both before and after age 50, but we found that risk may be greatest for heavy consumers after age 50. While this observation could reflect that older women are particularly susceptible to increased estrogen levels resulting from alcohol, a rationale may alternatively involve residual confounding by other behaviors common in heavy consumers of alcohol, such as smoking and physical inactivity; we did not adjust for physical activity since this factor was elicited with different questions in each phase of the study, preventing a combined analysis. A re-analysis of data from 53 studies found a non-significantly higher increase in breast cancer risk for each 10g of alcohol consumed daily among women aged ≥50 (7.7%, SE 1.0) than among women <50 (6.2%, SE 1.2).[17] However, meta-analyses conducted by the World Cancer Research Fund did not reveal heterogeneity according to menopausal status. [58] Misclassification of alcohol intake may be common in women with the heaviest consumption, and in our study, confidence intervals around odds ratio estimates are widest

for women reporting >21 drinks each week. Nevertheless, reproducibility studies of self-reported alcohol intake have reported reasonably reliable correlations (range, 0.62 to 0.80) for both general samples of adults and for alcoholics.[28]

The diagnosis of breast cancer has changed over the course of the study. Detection by mammography has increased, and the distribution of histologic subtypes also changed in conjunction with earlier detection.[25] Evaluation of breast cancer risk factors according to histologic subtype or method of tumor detection suggests that hormone-related factors may be more strongly associated with lobular breast cancer and disease detected by mammography as compared with ductal and symptomatic breast cancer.[36, 37, 50] We were unable to evaluate risk factors defined by estrogen receptor (ER) status or other tumor markers such as human epidermal growth factor receptor 2 (HER2). Several other studies have evaluated the relations between risk factors and breast cancer risk according to ER and HER2 as well as other tumor factors, revealing potential differences.[2, 4, 26, 40-42, 53, 54] Since breast tumors are more likely to be ER positive with increasing age,[3] our results may reflect different distributions of tumor subtypes in older as compared with younger women.

While we investigated most factors that have been identified to play important roles in breast cancer risk, information on some factors was not available. Breast density is increasingly identified as a strong risk factor for breast cancer beyond its inverse correlation with obesity and potential masking of cancer detection by mammography.[6, 7] Conclusions from our study are also limited by the composition of the study population. Due to delays in reporting of cases to their tumor registries, cases were approached on average one year after diagnosis. For this reason, more advanced cases of breast cancer are under-represented; in our data, 2.2% of cases were diagnosed with distant-staged breast cancer, whereas 5.6% of invasive breast cancer cases diagnosed during 1998-2008 (ages 40-79 years) to SEER registries were diagnosed with distant disease.[52] In addition, the vast majority—96%—of the cases and controls self-reported white race. While this study sample was not racially diverse, the study reflects the underlying populations of the four states in which these women lived and conclusions from the analysis remain internally valid.

Overall, many menstrual, reproductive, and lifestyle factors are associated with breast cancer risk regardless of age or menopausal status. Indeed, reproductive risk factors that are established in the first three or four decades of life including ages at menarche and first full-term pregnancy are consistently associated with breast cancer of all ages. Conversely, variation in the association of family history of breast cancer, obesity, and alcohol use with breast cancer risk by age and menopausal status may need to be considered in personalized risk assessments.

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Abbreviations

BI-RADS	Breast Imaging-Reporting and Data System
BMI	body mass index
CI	confidence interval
ER	estrogen receptor
HER2	human epidermal growth factor receptor 2
ICD-O	International Classification of Diseases-Oncology
OR	odds ratio
SE	standard error

SEER Surveillance, Epidemiology and End-Results

Table 1

Odds Ratios for Breast Cancer According to Risk Factors, Collaborative Breast Cancer Study, 1988-2008

Characteristic	Cases (n=23,959) %	Controls (n=28,304) %	Odds Ratio[a]	95% CI[a]	Effect Modification P-value with Age[b]	Effect Modification P-value with Menopausal Status[c]
First degree family history of breast cancer						
None	78.2	85.8	1		0.01	0.001
1	17.3	11.5	1.61	1.53-1.69		
2	2.2	0.9	2.44	2.10-2.84		
≥ 3	0.3	0.1	3.04	1.97-4.69		
Unknown	2.0	1.7				
None	78.2	85.8	1		0.001	0.001
1, diagnosed < 50 yr	5.0	3.1	1.74	1.59-1.90		
1, diagnosed 50-59 yr	4.0	2.7	1.61	1.46-1.78		
1, diagnosed ≥ 60 yr	7.9	5.4	1.55	1.44-1.66		
≥ 2, diagnosed <50 yr	1.4	0.6	2.62	2.16-3.17		
≥ 2, diagnosed ≥50 yr	1.1	0.5	2.49	2.02-3.07		
Unknown	2.5	2.0				
Benign breast disease	n=14,144 [h]	n=15,830 [h]				
Never	72.0	79.7	1		0.14	0.15
Ever	26.0	18.5	1.61	1.53-1.71		
Unknown	2.0	1.8				
Age at menarche						
≤ 12	43.9	41.5	1		0.42	0.75
13	27.2	27.2	0.94	0.90-0.98		
14	15.1	16.0	0.88	0.84-0.93		
≥ 15	11.4	13.2	0.80	0.76-0.85		
Unknown	2.4	2.2				
Parity						
Nulliparous	13.5	12.0	1		0.0001	0.11
Parous	85.7	87.4	0.84	0.80-0.89		
Unknown	0.8	0.7				

Characteristic	Cases (n=23,959) %	Controls (n=28,304) %	Odds Ratio[a]	95% CI[a]	Effect Modification P-value with Age[b]	Effect Modification P-value with Menopausal Status[c]
Parity						
0	13.5	11.9	1		0.06	0.33
1	11.2	10.1	0.99	0.92-1.07		
2	29.2	27.2	0.94	0.90-1.00		
≥ 3	45.4	50.2	0.75	0.71-0.80		
Unknown	0.8	0.7				
Age at first full term pregnancy (years)						
< 22	29.8	34.5	1.00		0.30 [d]	0.26 [d]
22-24	23.2	24.3	1.12	1.07-1.17		
25-29	22.5	20.6	1.30	1.24-1.36		
≥ 30	10.2	8.0	1.52	1.43-1.63		
Nulliparous	13.5	12.0	1.37	1.29-1.45		
Unknown	0.9	0.7				
Breastfeeding (parous women only)						
Never	49.4	49.3	1		0.94	0.87
Ever	50.6	50.7	0.97	0.94, 1.01		
Breastfeeding duration (parous women only)						
Never	49.4	49.3	1		0.75	0.04
≤ 12 months	36.3	35.8	0.98	0.94-1.03		
> 12 months	14.1	14.7	0.95	0.89-1.00		
Unknown	0.2	0.2				
Oral contraceptive use[e]						
Never	54.9	54.7	1.00		<0.0001	0.19
Ever	44.1	44.3	1.05	1.01-1.10		
Unknown	1.1	1.0				
Body mass index (kg/m^2)						
< 18.5 (underweight)	1.8	2.4	0.79	0.70-0.90	<0.0001	<0.0001
18.5 –24.9 (normal)	46.8	48.9	1			
25 –29.9 (overweight)	30.0	29.3	1.02	0.98-1.06		
≥ 30 (obese)	19.2	17.2	1.09	1.03-1.14		

Characteristic	Cases (n=23,959) %	Controls (n=28,304) %	Odds Ratio[a]	95% CI[a]	Effect Modification P-value with Age[b]	Effect Modification P-value with Menopausal Status[c]
Unknown	2.2	2.2				
Smoking status[g]						
Never	49.0	49.1	1		0.03	0.38
Former	30.3	28.8	1.04	1.00-1.08		
Current	19.8	21.3	0.96	0.91-1.00		
Unknown	0.9	0.8				
Recent alcohol consumption (drinks/week)	n=18,895 [h]	n=23,028 [h]				
Never	10.2	11.7	1.00		0.0002	0.0004
Former	9.4	8.8	1.16	1.07-1.27		
< 7	63.0	64.8	1.11	1.04-1.19		
7-13	9.6	8.8	1.25	1.15-1.37		
≥ 14	6.0	4.2	1.65	1.48-1.83		
Unknown	1.8	1.8				

[a] Odds ratios are age-adjusted for age, state of residence, and study period.

[b] Age defined continuously (per year)

[c] Excludes women with unknown menopausal status

[d] Parous women only

[e] Odds ratio adjusted for residuals of time since last use regressed on age (instead of adjusted for age).

[f] Excludes women who never used oral contraceptive.

[g] Odds ratios are age-adjusted for age, state of residence, study period, body mass index, and alcohol consumption.

[h] Sample sizes are shown when a reduced number of women are included in the analysis.

Table 2

Multivariable-adjusted Odds Ratios of Breast Cancer According to Age Group, Collaborative Breast Cancer Study, 1988-2008

	Women ages 18 to 39 (1,324 cases/ 2,038 controls)		Women ages 40 to 49 (4,315 cases/ 5,241 controls)		Women ages 50 to 64 (10,913 cases/ 13,053 controls)		Women ages 65 to 79 (7,407 cases/ 7,972 controls)	
Characteristic	**Odds Ratio[a]**	**95% CI[a]**	**Odds Ratio[a]**	**95% CI[a]**	**Odds Ratio[a]**	**95% CI[a]**	**Odds Ratio[a]**	**95% CI[a]**
Family history of breast cancer								
None	1		1.00		1		1	
Any	2.28	1.78, 2.92	1.92	1.70, 2.16	1.58	1.47, 1.69	1.69	1.55, 1.84
1	2.09	1.63, 2.69	1.80	1.59, 2.04	1.52	1.41, 1.63	1.58	1.44, 1.73
2	11.60	2.55, 52.82	4.44	2.73, 7.23	2.08	1.67, 2.59	2.43	1.92, 3.10
≥ 3	b	b	3.76	1.01, 14.01	2.55	1.36, 4.76	3.25	1.62, 6.51
Parity								
0	1		1		1		1	
1	1.10	0.81, 1.48	0.90	0.76, 1.08	0.73	0.65, 0.84	0.87	0.75, 1.01
2	0.91	0.70, 1.18	0.83	0.72, 0.96	0.73	0.65, 0.80	0.84	0.74, 0.96
≥ 3	1.14	0.19, 6.73	0.71	0.61, 0.81	0.60	0.55, 0.66	0.76	0.68, 0.86
Oral contraceptive use								
Never	1		1		1		1	
Ever	1.12	0.93-1.34	1.07	0.97-1.17	1.08	1.02-1.14	1.05	0.94-1.16
Body mass index (kg/m^2)								
< 18.5 (underweight)	0.79	0.53, 1.18	0.92	0.71, 1.21	0.73	0.59, 0.91	0.77	0.61, 0.96
18.5 - 24.9 (normal)	1		1		1		1	
25 - 29.9 (overweight)	0.74	0.61, 0.90	0.89	0.81, 0.99	1.08	1.01, 1.15	1.16	1.07, 1.25
≥ 30 (obese)	0.70	0.54, 0.90	0.79	0.70, 0.89	1.16	1.09, 1.25	1.49	1.36, 1.64
Smoking status								
Never	1		1		1		1	
Former	1.00	0.83, 1.22	1.06	0.96, 1.17	1.06	1.00, 1.13	1.05	0.97, 1.13
Current	0.84	0.69, 1.01	0.97	0.87, 1.07	0.99	0.92, 1.06	1.12	1.01, 1.23
Recent alcohol consumption (drinks/week)								
Never	1		1		1		1	
< 3	1.09	0.86-1.38	1.04	0.92-1.18	0.96	0.90-1.03	1.10	1.01-1.19

	Women ages 18 to 39 (1,324 cases/ 2,038 controls)		Women ages 40 to 49 (4,315 cases/ 5,241 controls)		Women ages 50 to 64 (10,913 cases/ 13,053 controls)		Women ages 65 to 79 (7,407 cases/ 7,972 controls)	
Characteristic	**Odds Ratio[a]**	**95% CI[a]**	**Odds Ratio[a]**	**95% CI[a]**	**Odds Ratio[a]**	**95% CI[a]**	**Odds Ratio[a]**	**95% CI[a]**
3-6	1.22	0.93-1.60	1.10	0.95-1.28	1.05	0.96-1.15	1.20	1.07-1.35
7-13	1.25	0.89-1.76	1.13	0.94-1.35	1.12	1.00-1.24	1.17	1.03-1.33
14-20	0.91	0.48-1.71	1.19	0.89-1.57	1.19	1.02-1.39	1.70	1.40-2.06
21-27	2.54	1.08-5.97	1.66	0.99-2.77	1.79	1.38-2.31	2.38	1.61-3.51
28-34	1.35	0.37-4.93	1.31	0.64-2.66	1.51	1.00-2.29	2.04	1.12-3.72
≥ 35	2.17	0.77-6.09	0.94	0.53-1.68	1.97	1.33-2.93	2.32	1.30-4.12

Abbreviation: CI, confidence interval.

[a] Odds ratios are adjusted for age, state of residence, study period, and all the other factors shown in Table 1.

[b] Too few participants within the age stratum to estimate the odds ratio and confidence interval.

[c] Odds ratio also adjusted for residuals of time since last use regressed on age (instead of adjusted for age).

Table 3

Multivariable-adjusted Odds Ratios (OR) of Breast Cancer According to Menopausal Status, Collaborative Breast Cancer Study, 1988-2008

	Premenopausal (6,135 cases/7,697 controls)		Postmenopausal (16,517 cases/19,088 controls)	
Characteristic	**Odds Ratio[a]**	**95% CI[a]**	**Odds Ratio[a]**	**95% CI[a]**
Family history of breast cancer				
None	1		1	
Any	1.83	1.65, 2.03	1.62	1.53, 1.71
1	1.72	1.55, 1.91	1.54	1.45, 1.63
2	4.56	3.00, 6.95	2.21	1.87, 2.61
≥ 3	2.63	0.65, 10.70	3.04	1.90, 4.86
Breastfeeding duration (parous women only)				
Never	1		1	
≤ 12 months	0.90	0.82, 0.98	0.96	0.91, 1.01
> 12 months	0.76	0.69, 0.85	1.00	0.93, 1.09
Body mass index (kg/m^2)				
< 18.5 (underweight)	0.88	0.70, 1.11	0.75	0.64, 0.88
18.5 – 24.9 (normal)	1		1	
25 – 29.9 (overweight)	0.91	0.84, 0.99	1.11	1.06, 1.17
≥ 30 (obese)	0.78	0.70, 0.86	1.32	1.24, 1.40
Recent alcohol consumption (drinks/week)				
Never	1		1	
< 3	1.06	0.95-1.17	1.03	0.97-1.09
3-6	1.12	0.99-1.27	1.13	1.05-1.22
7-13	1.15	0.99-1.34	1.16	1.07-1.26
14-20	1.23	0.98-1.56	1.40	1.24-1.59
21-27	1.94	1.26-2.97	2.02	1.62-2.52
28-34	1.29	0.75-2.22	1.71	1.19-2.46
≥ 35	1.28	0.75-2.18	2.01	1.44-2.79

Abbreviation: CI, confidence interval.

[a]Odds ratios are adjusted for age, state of residence, study period, and all the other factors shown in Table 1.

Table 4

Multivariable-adjusted Odds Ratios (OR) of Breast Cancer within strata defined by Age and Menopausal Status, Collaborative Breast Cancer Study, 1988-2008

			Family history of breast cancer (any versus none)		Body mass index (continuous per 1 kg/m^2)		Alcohol intake (continuous per 1 drink per day)	
Characteristic	**Cases**	**Controls**	**OR** [a]	**95% CI** [a]	**OR** [a]	**95% CI** [a]	**OR** [a]	**95% CI** [a]
Premenopausal								
Age <40	1,264	1,969	2.25	1.75-2.89	0.97	0.96-0.99	1.11	1.01-1.22
Age 40-44	1,519	1,904	1.86	1.52-2.29	0.98	0.97-1.00	0.99	0.95-1.04
Age 45-49	1,766	2,061	1.74	1.45-2.10	0.98	0.97-1.00	1.04	0.95-1.14
Age ≥50	1,586	1,763	1.67	1.39-2.02	0.99	0.98-1.00	1.17	1.05-1.30
Postmenopausal								
Age <55	2,000	2,571	1.68	1.43-1.99	1.00	0.99-1.01	1.11	1.04-1.20
Age 55-59	3,163	3,904	1.43	1.26-1.62	1.02	1.01-1.03	1.14	1.07-1.22
Age 60-64	3,956	4,651	1.61	1.43-1.80	1.02	1.01-1.03	1.11	1.04-1.17
Age 65-69	4,200	5,024	1.64	1.47-1.82	1.03	1.02-1.04	1.13	1.07-1.20
Age ≥70	3,198	2,938	1.78	1.55-2.03	1.04	1.03-1.05	1.25	1.15-1.36

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Odds ratios are adjusted for age, state of residence, study period, family history of breast cancer, body mass index, alcohol intake, age at menarche, parity, age at first pregnancy, oral contraceptive use, and smoking status.