Published in final edited form as:
Cancer Causes Control. 2013 January ; 24(1): 81–89. doi:10.1007/s10552-012-0092-x.

Migraine and Subsequent Risk of Breast Cancer: a Prospective Cohort Study

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Abstract

Purpose—Previous studies have suggested that migraineurs are at decreased risk for developing breast cancer. Further prospective studies are warranted to confirm these results. In addition, studies evaluating migraine characteristics (e.g. migraine subtypes and frequency) are lacking.

Methods—We conducted a prospective cohort study among 39,696 participants in the Women's Health Study who were 45 years and older at study entry. Information on migraine was self-reported with good validation rates. Incident breast cancer cases were confirmed by medical record review. We distinguished the following major endpoints: any breast cancer, a combined

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Conflict of interest: We report a full disclosure for the last 2 years for each author:
Dr. Winter has received an international postdoctoral research fellowship of the American Association of University Women and a research fellowship of the German Research Foundation (DFG).
Dr. Rexrode has received investigator-initiated research funding from the National Institutes of Health. She has also received honoria from Pfizer pharmaceuticals for contributing to a scientific advisory panel.
Dr. Lee has received investigator-initiated research funding and support from the National Institutes of Health. She has served as a consultant to, and on the Scientific Advisory Board of, Virgin HealthMiles
Dr. Buring has received investigator-initiated research funding and support from the National Institutes of Health and Dow Corning Corporation; research support for pills and/or packaging from Bayer Health Care and the Natural Source Vitamin E Association.
Dr. Tamimi has received investigator-initiated research funding from the National Institutes of Health. She has also received honoria from Pfizer pharmaceuticals for contributing to a scientific advisory panel.
Dr. Kurth has received investigator-initiated research funding from the French National Research Agency, the US National Institutes of Health, the Migraine Research Foundation, and the Parkinson's disease Foundation. He has received honoraria from the American Academy of Neurology and Merck for educational lectures, from MAP Pharmaceutical for contributing to a scientific advisory panel, and from the British Medical Journal for editorial services.

Authors' contributions
Dr. Winter: Study design, data analysis, data interpretation, writing manuscript
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endpoint of invasive and in situ cases, in situ breast cancer only and invasive breast cancer only. Cox proportional hazards models were used to calculate age- and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (95% CI).

Results—7,318 (18.4%) women reported any migraine. During a mean-follow-up time of 13.6 years, 432 in situ and 1,846 invasive breast cancer cases occurred. Migraine was not associated with breast cancer risk. The multivariable-adjusted HRs (95% CI) were 1.10 (0.99–1.22) for any breast cancer, 1.06 (0.83–1.35) for in situ breast cancer and 1.11 (0.99–1.25) for invasive breast cancer. The risk for developing breast cancer differed according to hormone receptor status with a suggestion of increased risks for hormone receptor negative tumors (HR ER−/PR−: 1.28, 95%CI: 0.96–1.71). We did not observe meaningful differences with regard to histologic subtype or according to migraine aura status or migraine attack frequency.

Conclusions—Results of our study do not support the hypothesis that migraineurs have a decreased risk for breast cancer.

Keywords

migraine; migraine subtypes; breast cancer; prospective cohort study; epidemiology

Introduction

Migraine is a primary, intermittent and often chronic headache disorder, characterized by recurrent disabling attacks of neurovascular origin. Migraine is a heterogeneous disease and several subtypes of migraine can be distinguished. The most common subtypes are migraine with aura and migraine without aura. In 1988, the International Headache Society (IHS) published the first edition of diagnostic criteria for migraine to facilitate a standardized diagnosis of this complex disorder [1]. According to data from the American Migraine Study, approximately 18% of the female population and 6% the male population suffer from migraine in the United States [2].

Since migraine predominantly affects women and the course of migraine changes over the lifespan with a decline of migraine attack frequency after the reproductive years [3], a role of estrogen in migraine pathophysiology has been hypothesized [4]. Hormonal fluctuations occurring during pregnancy and the menstrual cycle have been reported to influence the occurrence of migraine. Women in the third trimester of pregnancy, when estrogen levels are high, report remission of migraine attacks [5,6]. In addition, hormonal fluctuations, particularly a significant drop in circulating estrogen levels preceding the menses are hypothesized to be related to menstrual migraine [7].

Breast cancer is the most common cancer among females [8]. The role of exposure to endogenous and exogenous hormone in breast cancer etiology has been discussed in detail [9,10]. Studies indicate that higher lifetime exposure to estrogens and use of postmenopausal hormone therapy increase the risk of breast cancer, particularly hormone receptor positive tumors [11].

Since estrogens may play an important role in the etiology of breast cancer and in the pathophysiological mechanisms responsible for triggering migraine attacks, an association between the two diseases has been hypothesized. Results of two case-control studies and one previously published prospective study evaluating the relationship between migraine and breast cancer suggested that a history of migraine is associated with a 10–30% risk reduction for breast cancer [12–14].

Further prospective studies evaluating the association between migraine and breast cancer are warranted to confirm these findings as they would provide novel opportunities to better understand breast cancer etiology. Additionally, studies assessing the role of migraine characteristics including migraine subtypes and frequency of migraine attacks are lacking. We therefore aimed to evaluate the association between migraine, migraine characteristics (i.e. migraine subtypes, migraine attack frequency) and incident breast cancer in a large prospective cohort study.

Materials and Methods

Study population

The Women's Health Study (WHS) was a randomized double blind placebo controlled trial to test the risks and benefits of low dose aspirin and Vitamin E in the primary prevention of cardiovascular disease (CVD) and cancer among apparently healthy women. The design, methods and results have been described in detail previously [15,16]. Briefly, a total of 39,876 US female health care professionals aged 45 years or older at study entry (1992–1995) without a history of CVD, cancer, or other major illnesses were randomly assigned to receive active aspirin (100mg on alternate days), active vitamin E (600 IU on alternate days), both active agents, or both placebos. All participants provided written informed consent, and the institutional review board of Brigham and Women's Hospital, Boston, MA, approved the WHS. Baseline information was self-reported and collected by a mailed questionnaire that asked about several cardiovascular risk factors and lifestyle variables. Twice in the first year and yearly thereafter, participants were sent follow-up questionnaires asking about study outcomes, including diagnoses of breast cancer, and other information. The trial ended in March 2004. At this time point, 89% of the initially randomized women still alive were eligible and willing to enter observational follow-up. For the purpose of this analysis, we included information from the time of randomization through March 2010.

Assessment of migraine

On the baseline questionnaire, participants were asked: “Have you ever had migraine headaches?” and “In the past year, have you had migraine headaches?” Similar to previous reports [17,18], we defined the following migraine categories: 1) no migraine history, 2) active migraine, which included women with self-reported migraine in the year prior to completing the baseline questionnaire, and 3) prior migraine, which included women who reported ever having had a migraine but none in the year prior to completing the questionnaire. Women with active migraine and prior migraine were defined as having “any history of migraine”.

Participants who reported active migraine were asked whether they had an “aura or any indication a migraine is coming.” Responses were used to classify women who reported active migraine into active migraine with aura and active migraine without aura, similar to previous studies [17,18].

In addition, active migraineurs were asked to report the frequency of migraine attacks in the past year (daily, weekly, monthly, every other month, less than 6 times per year). Because very few women reported experiencing migraine daily or weekly we defined the following attack frequency categories: at least weekly, monthly, every other month and <6 times/year.

Those participants who reported active migraine were further asked details about their migraine attacks, including attack duration of 4 to 72 hours; unilateral location and pulsating quality of pain; inhibition of daily activities; aggravation by routine physical activity; nausea or vomiting; and sensitivity to light or sound. This information allowed us to classify women according to modified 1988 IHS criteria.

In previous studies of the WHS [19,17], we have shown good agreement between our migraine classification and modified 1988 diagnostic criteria of the IHS [1]. Furthermore, another study using a subsample of the WHS showed excellent agreement between self-reported migraine and migraine classification according to the 2004 IHS diagnostic criteria [20]. Over 87% of women with active migraine could be diagnosed as migraine without aura (71.5%) or probable migraine without aura (16.2%) when applying 2004 diagnostic criteria [21].

Ascertainment of breast cancer

Participants were asked if they had been diagnosed with breast cancer in the past year on each follow-up questionnaire. Medical records and other relevant information were obtained for all self-reported breast cancer cases and reviewed by an Endpoints Committee of physicians to confirm the diagnosis. In addition, detailed information on breast tumor characteristics at diagnosis including estrogen and progesterone receptor status and histological grading and differentiation was extracted from the medical records. Deaths were identified through family member reports, postal authorities or a search of the National Death Index.

Only confirmed first breast cancer events were included in our analyses. We defined three main outcome events: any breast cancer which included in situ and invasive breast cancer cases, in situ breast cancer only and invasive breast cancer only.

Among invasive breast cancer cases, we further distinguished between hormone receptor status and histologic subtypes of breast cancer tumors. We classified breast cancer cases by both estrogen (ER) and progesterone status (PR) using the following categories: ER+/PR+, ER+/PR−, ER−/PR+, ER−/PR− tumors. 105 women with borderline or unknown hormone receptor status were excluded from the event categories in this subgroup analysis and censored at the time of breast cancer diagnosis.

We further defined the following histologic subtype categories: ductal, lobular, and ductal and lobular. 136 women with “other histology subtypes” were excluded from these analyses and censored at the time of breast cancer diagnosis.

Statistical methods

Of the 39,876 participants, 119 women with missing migraine information were excluded. We additionally excluded 61 women who, after being randomized, reported a cancer diagnosis that occurred prior to randomization, leaving a total of 39,696 women free of any cancer for this analysis.

Baseline characteristics of participants according to migraine status were compared using t-tests for continuous variables and chi-square tests for categorical variables.

Person-time was calculated from the date of randomization to the date of first breast cancer diagnosis, date of first any other cancer diagnosis, death from any cause or end of study, whichever occurred first.

Cox proportional hazards models were used to evaluate the association between `any migraine' status at baseline and incident breast cancer. We calculated age-and multivariable-adjusted hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs). Among invasive breast cancer cases, we further evaluated the association between any migraine status and hormone receptor status as well as histology subtype.

To determine whether the risk for developing breast cancer differs according to migraine subtypes, we calculated age-and multivariable-adjusted HRs (95%CI) for migraine subtypes (migraine with aura, migraine without aura, prior migraine, and no history of migraine) and breast cancer.

To explore whether migraine attack frequency is associated with breast cancer risk, we calculated age- and multivariable-adjusted HRs for any breast cancer according to the reported number of migraine attacks among the 5,098 active migraineurs who provided attack frequency information.

We performed additional analyses where we classified breast cancer cases by age at diagnosis (≤50 yrs versus >50 yrs) and postmenopausal status at diagnosis (premenopausal versus postmenopausal) and ran separate models for each potential outcome. 182 women with unknown postmenopausal status at breast cancer diagnosis were excluded from this analysis.

All multivariable-adjusted models were adjusted for age, body mass index (BMI) (<25, 25–29.9, ≥30 kg/m^2), alcohol consumption (rarely/never, 1–3 drinks/months 1–6 drinks/week, ≥1 drink/day), smoking status (never, past, current), postmenopausal status, age at menarche (<12, 12, 13, 14, ≥15 yrs), age at menopause (<45, 45–49, 50–54, ≥55 yrs), postmenopausal hormone use (never, past, current), age at first pregnancy lasting ≥6 months (<25, 25–30, ≥30 years), number of pregnancies lasting ≥6 months (none, 1, 2, 3, 4, 5), family history of breast cancer (yes/no), and history of benign breast disease (yes/no).

Additional adjustment for race, physical activity, oral contraceptive use, history of hysterectomy, history of bilateral oophorectomy, randomized treatment assignments, and nonsteroidal anti-inflammatory drug (NSAID) use did not change any of our effect estimates by more than 5%.

We evaluated whether the association between any migraine and breast cancer was modified by age at baseline (<55, 55–64, 65–75, ≥75), BMI (<25, 25–29.9, ≥30kg/m^2), smoking status (never, past, current), physical activity (rarely/never, 1/week, 1–3 times/week, ≥4 times/week) oral contraceptive use (yes/no), postmenopausal hormone use (never, past, current), and NSAID use (yes/no). Effect modification was tested by including an interaction term for migraine and the potential effect modifier to the outcome model.

The proportional hazards assumption was tested by including an interaction term for migraine status and logarithm of follow-up time for any breast cancer in age-adjusted models. We found no statistically significant violation.

A missing value indicator was incorporated in the outcome models for covariates if the number of participants with missing information was greater or equal to 100. We assigned participants with missing values to the covariate reference category if the number of missing information was less than 100.

For all analyses, we used SAS (version 9.1.3, SAS Institute Inc. Cary, NC). All p-values were 2-tailed and p-value <0·05 was considered statistically significant.

Results

Of the 39,696 participants, 7,318 (18.4%) women reported any migraine.

In Table 1, baseline characteristics of participants according to any migraine status are presented. Migraineurs had a mean age of 53.6 years and were younger than women without

migraine. Women with any history of migraine were also more likely to rarely/never drink alcohol, to never smoke cigarettes, to be premenopausal at baseline, to currently use postmenopausal hormones and to report a history benign breast disease compared to women without migraine.

During a mean follow-up time of 13.6 years, 432 in situ and 1,846 invasive breast cancer cases were confirmed. In Table 2, age- and multivariable-adjusted HRs (95% CI) for breast cancer according to any migraine status are presented. Any migraine status was not associated with risk of any breast cancer (adjusted HR: 1.10, 95% CI: 0.99–1.22), in situ breast cancer (adjusted HR: 1.06, 95% CI: 0.83–1.35), or invasive breast cancer (adjusted HR: 1.11, 95% CI: 0.99–1.25).

Of the 1,846 invasive breast cancer cases, 1,237 were classified as ER+/PR+; 213 were ER +/PR− 28 were ER−/PR+ and 263 were ER−/PR−. Compared to women without migraine, women who reported any migraine had an increased, but not statistically significant, multivariable-adjusted HR for ER−/PR− tumors (HR: 1.28, 95% CI: 0.96–1.71). We found no association between any migraine history and histology subtypes.

In Table 3, age- and multivariable-adjusted HRs for breast cancer according to migraine subtypes are presented. The risk for developing any breast cancer did not substantially differ according to migraine subtypes. The highest effect estimates were observed for migraineurs without aura (HR: 1.14, 95% CI: 0.98–1.33). In subgroup analyses, migraineurs without aura had a HR of 1.21 (1.03–1.43) for invasive breast cancer.

In Table 4, age-and multivariable-adjusted HRs for breast cancer according to migraine frequency are shown. Of the 5,164 active migraineurs, 5,098 reported their migraine attack frequency. Compared to women with a migraine attack frequency of <6 times/year, migraineurs who reported an attack frequency of every other month, monthly and ≥weekly had multivariable-adjusted HRs of 1.01 (0.69–1.48), 1.05 (0.78–1.40) and 0.84 (0.48–1.47), respectively, for developing breast cancer.

In Table 5, age and multivariable-adjusted Hrs for breast cancer classified according to age at diagnosis and menopausal status at diagnosis are presented. Migraineurs had a non-significant increase in their multivariable-adjusted risk for developing breast cancer at ≤50 years (HR: 1.69, 95%CI: 1.00–2.87) and premenopausal breast cancer (HR: 1.38, 95% CI: 0.92–2.06) (Table 5).

The associations between any migraine and any breast cancer were not significantly modified by age at baseline (p for interaction: 0.41), BMI (p for interaction: 0.84), smoking status (p for interaction: 0.23), physical activity (p for interaction: 0.43) oral contraceptive use (p for interaction: 0.50), postmenopausal hormone use (p for interaction: 0.16) and NSAID use (p for interaction: 0.71).

Discussion

In this large, prospective cohort study of female health professionals aged ≥45 years at baseline, any history of migraine was not associated with breast cancer risk. This lack of association did not differ according to migraine attack frequency. When we restricted our outcome to invasive cancer only, we found a suggestion of increased risk among migraineurs without aura. The risk for developing invasive breast cancer varied according to hormone receptor status with a suggestion of increased risk for hormone receptor negative tumors. We did not observe meaningful differences with regard to histologic subtypes.

Two case-control and one prospective cohort study evaluating the association between migraine and breast cancer have been published to date [12–14]. Contrary to our findings, migraine was associated with a decreased risk for breast cancer in all three studies.

In the first case-control study, Mathes et al. combined data from two different population-based case-control studies [14]. The first population consisted of 975 women with invasive breast cancer aged 65–79 years who were identified using the Cancer Surveillance System, a cancer registry in western Washington, and 1,007 matched controls. Using the same cancer registry, 1,251 women aged 55 to 74 with ductal and lobular invasive breast cancer were recruited for the second population and matched with 496 controls from the general population, identified through random digit dialing. All cases and controls were interviewed in person and participants were asked whether they were ever clinically diagnosed with migraine. A history of migraine was associated with a decreased multivariable-adjusted OR of 0.67 (0.54–0.82) for ductal carcinomas and 0.68 (0.52–0.90) for lobular carcinomas in this study among postmenopausal women [14].

In the second case-control study among pre-and postmenopausal women, Li et al. evaluated the association between migraine and breast cancer among 4,575 women aged 35–64 years with invasive breast cancer, ascertained through Surveillance, Epidemiology, and End Results cancer registries in Atlanta, Detroit, Los Angeles and Seattle, and 4,678 age- race- and study-site-matched controls identified through random digit dialing [13]. Information on migraine history and other comorbidities was assessed by standardized interviews and migraine diagnosis was based upon a self-reported doctor diagnosis. Women with a history of migraine had an adjusted OR of 0.74 (95%CI: 0.66–0.82) for any breast cancer.

In the prospective cohort study among 91,116 postmenopausal women participating in the Women's Health Initiative Observational Study (WHI OS), women with a history of migraine had a multivariable-adjusted HR of 0.89 (0.80–0.98) for any breast cancer, 0.81 (0.62–1.05) for in situ breast cancer and 0.90 (0.80–1.01) for invasive breast cancer [12]. Differences in the study composition and migraine ascertainment between the WHI and our study could account for the different findings. In the WHI OS, women were asked if they have ever been told by a doctor that they had migraine headaches. In our study, we asked women to report if they ever had a migraine headache. The prevalence of self-reported clinician diagnosis of migraine was 11.5% in the WHI OS which is lower than the migraine prevalence of 18.4% in our cohort. Furthermore, the participants of the WHI OS were older (50 to 79 years) and postmenopausal at enrollment, contrary to our population which also included premenopausal women. Age and postmenopausal status are factors that may influence migraine prevalence and breast cancer incidence.

Ethnic differences and variation in socioeconomic status may have also contributed to the contradictory results. The WHS participants are predominately white health professionals while ethnically more diverse populations with a broader SES status range were included in the other studies.

Our data suggests that the risk for developing breast cancer differs according to hormone receptor status. While we did not observe an overall decreased risk for any breast cancer and hormone receptor positive tumors as reported in previous studies [12,13], we found a suggestion that migraineurs had increased risk of ER−/PR− tumors in our cohort (HR: 1.28, 95% CI: 0.96–1.71). This finding may contribute to the recently generated hypotheses concerning hormone receptor defined breast tumor etiology. There is increasing evidence that hormone receptor expression may represent distinct breast cancer phenotypes with different epidemiological risk factor sets [22]. While several traditional breast cancer risk factors, particularly reproductive factors, have been linked with hormone receptor positive

tumors, information on predictors for hormone receptor negative tumors are inconclusive [11]. However, conclusions should be drawn carefully since the effect estimate is modest and statistically insignificant.

Migraine is a heterogeneous disease and there is an ongoing debate whether migraine with aura and migraine without aura are two distinct diseases [23]. Several population-based studies suggested that migraineurs with and without aura differ with regard to comorbid conditions, particularly cardiovascular disease [17,24]. Our data do not indicate that the risk for any breast cancer differ according to migraine subtypes. When we restricted our analysis to incident invasive breast cancer, we found a suggestion for an increased risk among migraineurs without aura. However, this modest positive association in a subgroup analysis should be interpreted carefully and needs to be replicated in future studies.

Migraine attack frequency can be envisioned as one potential marker for disease severity. We found no evidence that migraine attack frequency has an effect on breast cancer risk among women with active migraine.

Our study has several strengths including the large number of participants, the large number of outcome events, the prospective study design and standardized assessment of migraine and good validation of our migraine information according to IHS criteria. Furthermore, incident breast cancer cases were confirmed by medical record review. In addition, information on a variety of covariates was available allowing us to adjust for potential confounders.

The following limitations should be considered when interpreting our results. First, information on migraine was self-reported and we cannot rule out misclassification. However, we have shown excellent agreement between self-reported migraine and the 2004 IHS diagnostic criteria in a previously published study of the WHS [21]. Second, due to the observational study design, residual and unmeasurable confounding remains possible. Third, the limited number of cases in subgroup analyses results in limited power and our subgroup results should be interpreted cautiously. Lastly, our cohort consists mainly of white female health professionals which may limit the generalizability to other populations.

In summary, the findings from this large prospective study of middle-aged pre-and postmenopausal female health professionals, migraine was not associated with incident breast cancer. The risk for developing breast cancer did not substantially differ according to migraine status and was not related to migraine attack frequency. Results of our study do not support the hypothesis that migraineurs have a decreased risk of breast cancer.

Acknowledgments

We are indebted to the participants in the Women's Health Study for their outstanding commitment and cooperation, to the entire Women's Health Study staff for their expert and unfailing assistance.

Funding: This study was supported in part by a research fellowship of the German Research Foundation (DFG) to Dr. Winter. The Women's Health Study is supported by grants from the National Heart, Lung, and Blood Institute (HL-043851 and HL-080467); and the National Cancer Institute (CA-47988). The sponsors of the study played no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

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Table 1

Baseline characteristics according to migraine status (n=39,696)

	No history of migraine	Any history of migraine	
	n=32,378	n=7,318	p-value
Demographic information			
Mean age, years (SD)	54.8 (7.2)	53.6 (6.4)	<0.01
Race,%			
White	30,469 (94.9)	6,848 (94.5)	0.21
Life style variables,%			
BMI (kg/m^2)			0.07
<25	16,196 (51.1)	3,571 (49.9)	
25–29.9	9,809 (30.9)	2,223 (31.0)	
≥30	5,718 (18.0)	1,367 (19.1)	
Alcohol consumption			<0.01
Rarely/never	14,403 (44.5)	3,496 (47.8)	
1–3 drinks/month	4,167 (12.9)	1,055 (14.4)	
1–6 drinks/week	10,341 (32.0)	2,175 (29.7)	
≥1 drink/day	3,458 (10.7)	592 (8.1)	
Smoking Status			<0.01
Never	16,362 (50.6)	3,903 (53.4)	
Past	11,703 (36.2)	2,490 (34.1)	
Current	4,286 (13.3)	916 (12.5)	
Physical activity			<0.01
Rarely/never	12,378 (38.3)	2,832 (38.7)	
<1/week	6,276 (19.4)	1,624 (22.2)	
1–3 times/week	10,184 (31.5)	2,164 (29.6)	
≥4 times/week	3,526 (10.9)	694 (9.5)	
Reproductive history,%			
Age at menarche, years			0.05
<12	7,915 (24.5)	1,797 (24.6)	
12	9,147 (28.3)	2,096 (28.7)	
13	9,366 (29.0)	2,037 (27.9)	
14	3,458 (10.7)	759 (10.4)	
≥15	2,452 (7.6)	620 (8.5)	
Age at menopause, years			<0.01
< 45	4,365 (25.7)	1,119 (32.1)	
45– <50	5,380 (31.6)	1,095 (31.4)	
50– <55	6,128 (36.0)	1,054 (30.2)	
≥55	1,134 (6.7)	217 (6.2)	
Postmenopausal status at baseline			<0.01

	No history of migraine	Any history of migraine	
	n=32,378	**n=7,318**	**p-value**
Premenopausal	8,881 (27.5)	2,050 (28.1)	
Postmenopausal	17,890 (55.4)	3,679 (50.4)	
Biological uncertain	4,264 (13.2)	1,262 (17.3)	
Unclear/subject unsure	1,287 (4.0)	311 (4.3)	
Ever used postmenopausal hormones[a]			<0.01
Never	15,799 (48.9)	3,212 (44.0)	
Past	3,298 (10.2)	768 (10.5)	
Current	13,220 (40.9)	3,320 (45.5)	
Number of pregnancies lasting ≥6 months			0.13
none	4,125 (12.8)	890 (12.2)	
1	2,898 (9.0)	696 (9.5)	
2	9,504 (29.5)	2,188 (30.0)	
3	7,772 (24.1)	1,790 (24.5)	
4	4,460 (13.8)	1,002 (13.7)	
≥5	3,485 (10.8)	728 (10.0)	
Age at first pregnancy lasting ≥6 months, years			<0.01
<25	17,015 (59.0)	4,151 (62.9)	
25–30	7,996 (27.7)	1,632 (24.7)	
≥30	3,306 (11.5)	670 (10.2)	
Other covariates,%			
Family history of breast cancer	1,950 (6.2)	424 (6.0)	0.46
History of benign breast disease	10,889 (33.6)	2,726 (37.3)	<0.01

Percentages may not add up to 100% because of rounding or missing values

[a]Women who reported ever having used postmenopausal hormones of any kind

Table 2

Age- and multivariable-adjusted[a] HRs (95% CI) for breast cancer according to any migraine history (n=39,696)

	No migraine (n=32,378)		Any migraine (n=7,318)		
				Age-adjusted	Multivariable-adjusted
	No of cases	HR (95% CI)	No of cases	HR (95% CI)	HR (95% CI)
Any breast cancer (n=2,278)	1,841	1.00	437	1.08 (0.97, 1.20)	1.10 (0.99, 1.22)
In situ breast cancer (n=432)	351	1.00	81	1.03 (0.81, 1.32)	1.06 (0.83, 1.35)
Invasive breast cancer (n=1,846)	1,490	1.00	356	1.09 (0.97, 1.22)	1.11 (0.99, 1.25)
ER/PR status					
ER+/PR+ (n=1,237)	1,018	1.00	219	0.99 (0.85, 1.14)	1.01 (0.87, 1.17)
ER+/PR− (n=213)	170	1.00	43	1.17 (0.84, 1.64)	1.19 (0.85, 1.66)
ER−/PR+ (n=28)	22	1.00	6	1.17 (0.47, 2.90)	1.17 (0.47, 2.91)
ER−/PR− (n=263)	203	1.00	60	1.30 (0.97, 1.73)	1.28 (0.96, 1.71)
Histology					
Ductal (n=1,356)	1,090	1.00	266	1.11 (0.97, 1.26)	1.12 (0.98, 1.29)
Lobular (n=206)	173	1.00	33	0.90 (0.62, 1.31)	0.91 (0.63, 1.33)
Ductal and lobular (n=148)	122	1.00	26	0.98 (0.64, 1.50)	1.01 (0.66, 1.55)

[a]Multivariable models were adjusted for age, BMI, alcohol consumption, smoking status, postmenopausal status, age at menarche, age at menopause, postmenopausal hormone use, hormone replacement therapy use, number of pregnancies, age at first pregnancy, family history of breast cancer, history of benign breast disease

Table 3

Age and multivariable-adjusted[a] HRs (95% CIs) for breast cancer according to migraine subtypes (n=39,696)

	No migraine history	Active migraine with aura	Active migraine without aura	Prior migraine
	(n=32,378)	**(n=2,057)**	**(n=3,107)**	**(n=2,154)**
Any breast cancer (n=2,278)	n=1,841	n=117	n=190	n=130
Age-adjusted	1.00	1.05 (0.87, 1.27)	1.12 (0.97, 1.31)	1.04 (0.87, 1.24)
Multivariable-adjusted	1.00	1.07 (0.89, 1.29)	1.14 (0.98, 1.33)	1.07 (0.89, 1.28)
In situ breast cancer (n=432)	n=351	n=23	n=28	n=30
Age-adjusted	1.00	1.06 (0.70, 1.62)	0.85 (0.58, 1.25)	1.27 (0.88, 1.84)
Multivariable-adjusted	1.00	1.08 (0.71, 1.65)	0.86 (0.59, 1.27)	1.32 (0.91, 1.92)
Invasive breast cancer (n=1,846)	n=1,490	n=94	n=162	n=100
Age-adjusted	1.00	1.05 (0.85, 1.30)	1.19 (1.01, 1.40)	0.99 (0.81, 1.21)
Multivariable-adjusted	1.00	1.07 (0.87, 1.32)	1.21 (1.03, 1.43)	1.01 (0.83, 1.24)

[a]Multivariable models were adjusted for age, BMI, alcohol consumption, smoking status, postmenopausal status, age at menarche, age at menopause, postmenopausal hormone use, hormone replacement therapy use, number of pregnancies, age at first pregnancy, family history of breast cancer, and history of benign breast disease

Table 4

Age- and multivariable-adjusted[a] HRs (95%CI) for breast cancer according to migraine frequency (n=5,098)

	<6 times/year	Every other months	Monthly	≥Weekly
	(n=3,305)	(n=515)	(n=1,008)	(n=270)
Any breast cancer (n=300)	n=194	n=31	n=62	n=13
Age-adjusted	1.00	1.03 (0.71, 1.51)	1.08 (0.81. 1.43)	0.84 (0.48, 1.48)
Multivariable-adjusted	1.00	1.01 (0.69, 1.48)	1.05 (0.78, 1.40)	0.84 (0.48, 1.47)

[a]Multivariable models were adjusted for age, BMI, alcohol consumption, smoking status, postmenopausal status, age at menarche, age at menopause, postmenopausal hormone use, hormone replacement therapy use, number of pregnancies, age at first pregnancy, family history of breast cancer, history of benign breast disease

Table 5

Age- and multivariable-adjusted[a] HRs (95% CI) for breast cancer classified according to age at diagnosis and menopausal status at diagnosis (n=39,696)

	No migraine (n=32,378)		Any migraine (n=7,318)		
				Age-adjusted	Multivariable-adjusted
	No of cases	HR (95% CI)	No of cases	HR (95% CI)	HR (95% CI)
Age at diagnosis					
≥ 50 yrs (n=66)	46	1.00	20	1.63 (0.96, 2.75)[c]	1.69 (1.00, 2.87)[e]
> 50 yrs (n=2,212)	1,795	1.00	417	1.06 (0.96, 1.18)[c]	1.08 (0.97, 1.20)[e]
Postmenopausal status at diagnosis[b]					
Premenopausal (n=133)	101	1.00	32	1.22 (0.82, 1.82)[d]	1.38 (0.92, 2.06)[f]
Postmenopausal (n=1,963)	1,595	1.00	368	1.08 (0.96, 1.21)[d]	1.10 (0.98, 1.23)[f]

All p-value for heterogeneity were calculated using the Cochran's Q-Test.

[a]Models were adjusted for age, BMI, alcohol consumption, smoking status, postmenopausal status, age at menarche, age at menopause, postmenopausal hormone use, hormone replacement therapy use, number of pregnancies, age at first pregnancy, family history of breast cancer, history of benign breast disease

[b]182 women had dubious/unknown postmenopausal status and only contributed person-time

[c]p for heterogeneity: 0.12

[d]p for heterogeneity: 0.54

[e]p for heterogeneity: 0.10

[f]p for heterogeneity: 0.29