Title

Migraine in post-menopausal women and the risk of invasive breast cancer

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ABSTRACT

Background: The frequency of migraine headache changes at various times of a woman's reproductive cycle. Menarche, menses, pregnancy, and perimenopause may carry a different migraine risk conceivably because of fluctuating estrogen levels, and in general migraine frequency is associated with falling estrogen levels. Given the strong relationship between endogenous estrogen levels and breast cancer risk, migraine sufferers may experience a reduced risk of breast cancer.

Methods: We combined data from two population-based case-control studies to examine the relationship between migraine and risk of postmenopausal invasive breast cancer among 1,199 ductal carcinoma cases, 739 lobular carcinoma cases, and 1,474 controls 55-79 years of age. Polytomous logistic regression was used to estimate odds ratios and 95% confidence intervals; all statistical tests were 2-sided.

Results: Women who reported a clinical diagnosis of migraine had reduced risks of ductal carcinoma (IDC) [odds ratio (OR): 0.67, 95% confidence interval (CI): 0.54-0.82] and lobular carcinoma (ILC) (OR: 0.68, 95% CI: 0.52-0.90). These associations were primarily limited to hormone receptor positive tumors as migraine was associated with a 0.65-fold (95% CI: 0.51-0.83) reduced risk of estrogen receptor (ER) positive/progesterone receptor (PR) positive ductal carcinoma. The reductions in risk observed were seen among migraine sufferers who did and did not use prescription medications for their migraines.

Conclusions: These data suggest a history of migraine is associated with a decreased risk of breast cancer, particularly among ER+/PR+ ductal and lobular carcinomas. Because this is the first study to address an association between migraine history and breast cancer risk, additional studies are needed to confirm this finding.

INTRODUCTION

Migraine is a common neurological disorder characterized by episodic attacks of moderate to severe throbbing headache which may be disabling and accompanied by nausea, vomiting, photophobia and/or phonophobia. An estimated 15-18% of the U.S. female population has either diagnosed or undiagnosed migraine, with the highest prevalence occurring in women aged 25 to 55 years (1, 2). Several observations support a relationship between female sex hormones and migraines. The prevalence of migraine in women is roughly two to three times higher than that in men. Low levels of serotonin are clearly associated with increased frequency of migraine, and estrogen positively regulates serotonin (3-5). In addition, the frequency of migraine in women varies during menarche, menses, pregnancy, and menopause, a pattern which may be attributable to fluctuating estrogen levels (3). Of particular relevance, migraines in women are often associated with estrogen withdrawal states and low serotonin levels. Migraine frequency increases immediately before or during menses when endogenous estrogen levels decline in cycling premenopausal women, and it also increases during the hormone free week of oral contraceptive use (6-8). In contrast, pregnancy, a high estrogen state, is associated with migraine remission for the majority of migraine sufferers (9), particularly in the second and third trimesters. Though not typically used as a first-line of treatment for menstrual-associated migraine, hormonal treatments, particularly those administered during the hormone-free week of OC users, may have a beneficial effect on female migraineurs unless there is a contraindication for estrogen supplementation (7). Given that lifetime estrogen exposure is correlated with breast cancer risk (10), the occurrence of migraines in women, which also has a relationship to estrogen, may be related to breast cancer risk. However, to date, no study has evaluated this potential association.

The purpose of this study is to assess the hypothesis that migraine is associated with a reduced risk of breast cancer using data from two population-based case-control studies that included postmenopausal women 55-79 years of age.

METHODS

Subjects

Women from two population-based case-control studies conducted in the Seattle-Puget Sound region in Washington state were used for this analysis. The earlier of these two studies included women aged 65-79 years diagnosed with invasive breast cancer between 1997-1999 regardless of histological type. Details of the methods used in this study have been published previously (11). The Cancer Surveillance System (CSS), a population-based cancer registry that monitors cancer incidence in western Washington, was used to ascertain cases. Of 1,210 eligible cases identified 975 (81%) were interviewed. Records from the Centers for Medicare and Medicaid Service were used to identify female controls without breast cancer from the general population of King, Pierce, and Snohomish counties who were frequency matched 1:1 to cases on 5-year age groups, year, and county of residence. Of the 1,365 eligible controls identified, 1,007 (74%) were enrolled and interviewed.

The more recently completed of these two studies enrolled women aged 55-74 years diagnosed with invasive breast cancer between 2000-2004. Because the purpose of this study was to evaluate the etiology of lobular carcinomas, sampling of cancer cases differed by histological type. Details of the methods used in this study were recently published (12). The CSS was used to identify cases. Of the 1,251 eligible cases identified 1,044 (83%) were subsequently enrolled in the study and interviewed including 501 ductal and 543 lobular cases. Random digit dialing was used to identify women without breast cancer from the general population who were the same

age and reference year as cases. A total of 9,876 telephone numbers were identified and 87% were successfully screened for eligibility. Of the 660 eligible controls identified, 469 (71%) were enrolled and interviewed.

Both studies used similar protocols that were approved by the Fred Hutchinson Cancer Research Center Institutional Review Board, and written informed consent was obtained from all participants. Both studies excluded all women with a prior history of in situ or invasive breast cancer. All cases and controls were interviewed in-person by a trained interviewer. Data were collected via standardized questionnaires that were very similar across the two studies. Women were asked about exposures occurring before their reference date, which for cases was defined as the date of their breast cancer diagnosis. Control reference dates were assigned based on the expected distribution of case reference dates. With respect to migraine history, women were asked about whether they were ever clinically diagnosed with migraine (yes/no), age at migraine diagnosis, ever use of prescription medications for migraine, and age of first prescription migraine medication use. Information on specific medications used to treat migraine, including name, dose, and duration was not collected. The two IDC cases, one ILC case, and two controls with an unknown history of migraine were excluded from this analysis. In addition, detailed information on other known or suspected breast cancer risk factors, including reproductive history, anthropometric characteristics, use of exogenous hormones, family history of breast cancer, and lifestyle characteristics, was collected.

Cases were classified as IDC or ILC (including both pure lobular and mixed ductal-lobular carcinomas) based on a centralized review of pathology reports conducted at the Fred Hutchinson Cancer Research Center. Since the more recently completed study only enrolled ductal and lobular cases, the 500 ductal and 542 lobular

cases were included in this analysis. Since the earlier study enrolled cases regardless of histology this analysis included the 699 ductal and 197 lobular cases enrolled, but excluded the 78 cases with other histological types of breast cancer. In total, 1,199 IDC and 739 ILC cases with a known migraine history were included in this analysis. Data on ER/PR status was also centrally ascertained through this review. The 116 (6%) cases with an unknown ER/PR status were excluded from the ER/PR analyses.

Statistical Analysis

In order to compare IDC and ILC cases to controls, polytomous logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (13). All analyses were adjusted for age (continuous) and reference year. The referent category was women with no history of migraine. Variables considered as potential confounders or effect modifiers included race, income, marital status, education, age at menarche, parity, age at first birth, type of menopause, age at menopause, duration of oral contraceptive use, use of hormone therapy, family history of breast cancer, body mass index (BMI), smoking status, and average alcohol intake. None of these variables changed our risk estimates by more than 10%, and so none were included as confounders in the final statistical models. Effect modification was assessed using likelihood ratio testing, and none of these variables were observed to be statistically significant effect modifiers (p-value for interaction<0.05). We also assessed heterogeneity across the ORs for migraine history across the two histological types of breast cancer studied by testing the null hypothesis that each of these ORs was equivalent to each other (test of homogeneity of ORs). Statistical tests were two-sided and p-values <0.05 were considered statistically significant. All analyses were conducted using Stata 9.2 (Stata Corp, College Station, TX).

RESULTS

Compared to controls, both IDC and ILC cases were more likely than controls to be current users of combined estrogen and progestin hormone therapy and have a first-degree family history of breast cancer (Table 1). ILC cases were somewhat more likely than both IDC cases and controls to be younger, more educated, and nulliparous.

Women who reported a clinical diagnosis of migraine had a 33% reduced risk of IDC (95% confidence interval (CI): 0.54-0.82) and a 32% reduced risk of ILC (95% CI: 0.52-0.90) compared to women with no history of migraine (Table 2). These reductions in risk did not vary substantially by age at migraine diagnosis or by history of ever using prescription migraine medications. The test for homogeneity of risk across histology associated with a history of migraine suggests no difference in ORs (p=0.68).

Specifically, compared to women with no history of migraine, migraineurs had reduced risks of ER+/PR+ IDC (OR: 0.65, 95% CI: 0.51-0.83), ER+/PR- IDC (OR: 0.49, 95% CI: 0.27-0.88) and ER+/PR+ ILC (OR: 0.63, 95% CI: 0.47-0.85), but not of ER-/PR- IDC (OR: 0.87, 95% CI: 0.56-1.36) or ER+/PR- ILC (OR: 0.80, 95% CI: 0.47-1.36) (Table 3). In addition, given that the ages of the women and the type of controls differed by study, we analyzed risk of breast cancer associated with migraine history across both contributing studies separately. In the earlier of the two studies, which enrolled women 65-79 years of age, a history of migraine was associated with a 0.71-fold (95% CI: 0.53-0.94) reduced risk of IDC, but not a reduced risk of ILC (OR: 1.00, 95% CI: 0.66-1.51). In the more recently completed study, which enrolled women 55-74 years of age, a history of migraine was associated with a 0.60-fold (95% CI: 0.43-0.83) reduced risk of IDC and a 0.54-fold (95% CI: 0.39-0.75) reduced risk of ILC. Risk did not differ significantly by age at migraine diagnosis for either study.

DISCUSSION

This study has several limitations. Information on migraine history was based on self-report and thus is subject to bias. However, given the severity of migraine and its associated morbidity, it is likely that recall of migraine history will be accurate. In addition, we only captured information on migraine that was diagnosed by a physician or other health professional. It has been reported that approximately 27-59% of migraine sufferers are never clinically diagnosed (14-16). However, any misclassification resulting from this would most likely be non-differential, particularly since there are no reports in the literature on the association between migraine and breast cancer risk. Our lack of data on migraine characteristics, particularly their relationship to the menstrual period and other reproductive events, and migraine treatments is of concern since this may be relevant to breast cancer risk. Specifically, we did not collect data on the use of non-steroidal anti-inflammatory drugs (NSAIDs), which are associated with a modest reduction in breast cancer risk (17), although not all studies have observed a reduction in risk (18).

Our results suggest that a history of diagnosed migraine may be associated with a reduced risk of breast cancer in postmenopausal women, and particularly with a reduced risk of ER+/PR+ tumors. These reductions were observed in women with either IDC or ILC tumors and did not vary by history of prescription migraine medication use or age at migraine diagnosis. To our knowledge, this is the first study to address the association between a history of diagnosed migraine in women and breast cancer risk.

Based on previous studies documenting the influence of hormonal changes on migraine, it is plausible that migraine is associated with a reduced risk of IDC and ILC through hormonal pathways. Several studies have observed an association between hormonally associated events (i.e. menarche, menses, pregnancy, and menopause)

and migraine frequency and severity (3, 8, 9, 14, 19-25). Approximately 60% of female migraineurs report an association of migraine with menses, suggesting that hormonal fluctuations, particularly the withdrawal of estrogen, triggers migraine (8). Indeed, 7% to 14% of women with migraine report that their migraines exclusively occur two days before to three days after the onset of the menstrual period (20).

There are several other lines of evidence that also support the association between falling estrogen levels and migraine occurrence. Women taking oral contraceptives have more migraine headaches during their hormone-free week, particularly during the first few days of this week (26). Two studies have also shown that women with menstrual migraine treated with estradiol experience reductions in migraine frequency, duration, and severity compared to women given placebo (27, 28). Migraine frequency also decreases during pregnancy when estrogen levels substantially increase (8). In one study, 79% of women reported total migraine remission by their third trimester (29). Menopause is associated with low levels of endogenous steroid hormones. In one study, two-thirds of women with premenopausal migraine reported fewer migraines after menopause (24). Together these observations further indicate that stable endogenous estrogen levels, and perhaps the use of exogenous estrogens, are inversely associated with migraine frequency. While it may be important for future studies to measure serum hormone levels in migraineurs, given that frequent short-term fluctuating endogenous estrogen levels may be most likely to trigger migraine attacks, it is probably impractical to effectively measure endogenous hormone levels in a large group of migraineurs over a long period of time.

Hormones may be relevant to the pathophysiology of migraine because of their impact on serotonin (5-HT), a central and peripheral neurotransmitter. While the mechanisms through which serotonin participates in the migraine syndrome is

incompletely understood, current evidence suggests that the triptans, specific serotonin derivatives, prevent the release of nociceptive and inflammatory peptides and cause vasoconstriction of meningeal vasculature. It also has been shown that triptans bind centrally in the brainstem as well, possibly modulating central transmission (30). Hormones and serotonin have been linked in primate studies indicating that both estrogen and progesterone increase serotonin production and transport (4, 31). Given these observations and the well established positive association between endogenous circulating hormone levels and risk of hormone receptor positive breast cancer (32-34), we hypothesized that migraine may be particularly associated with a reduced risk of hormone receptor positive tumors. Indeed, we found that a history of migraine was strongly associated with reduced risks of hormone receptor positive tumors, but not with ER-/PR- tumors.

However, it is also possible that medications used to treat or prevent migraine, rather than the occurrence of migraines itself, may be responsible for the reductions in risk we observed. In particular, several studies of non-steroidal anti-inflammatory drugs (NSAIDs) have shown that NSAID use is associated with a reduced risk of breast cancer, especially hormone receptor positive tumors (17, 35, 36). NSAIDs are a common treatment for migraine and are typically taken at the time of onset of migraine symptoms. NSAIDs likely reduce breast cancer risk through inhibition of cyclooxygenase (COX)-2, the rate-limiting enzyme in the prostaglandin pathway (37). While we could not assess the impact of use of over the counter migraine medications on our risk estimates because these data were not collected, we did find that both users and non-users of prescription migraine medications had reduced risks of breast cancer. In general, however, prescription migraine medications, including beta-blockers, calcium-channel blockers, and tricyclic antidepressants, have not been associated with

a reduced risk of breast cancer (38-42). There are no reports in the literature regarding any association between breast cancer risk and the use of other classes of migraine medications including anti-convulsants, triptans, and ergot derivatives.

In summary, this is the first study to suggest that migraine may be associated with a reduced risk of breast cancer. Migraine is primarily a premenopausal disease and the studies focusing on hormone levels in premenopausal women in relation to breast cancer are few and the evidence is mixed (43-45), thus this could expand our understanding of the impact hormonal exposures during a woman's premenopausal years can have on her risk of developing breast cancer when she is postmenopausal. Previous studies investigating the relationship between hormonally-related factors and migraine indicate this association is biologically plausible, and the reductions in risk we observed were confined to hormone receptor positive tumors, lending further support to a possible underlying hormonal mechanism. While we cannot rule out that NSAID use may be partly or entirely responsible for this reduction in breast cancer risk, two observations suggest that a history of migraine, rather than medications used for migraine, is independently related to risk. First, the association between NSAID use and breast cancer risk is modest, with a meta-analysis of six cohort studies and eight case-control studies finding that regular use of NSAIDs is associated with only an 18% (95% CI: 11%-25%) reduced risk of breast cancer (17). Here we observed that women with migraine had a 33% reduced risk of breast cancer, which is higher than the 18% reduction associated with NSAID use. Second, NSAID use for migraine is episodic. Several studies of NSAID use in relation to breast cancer risk indicate that regular use, not episodic use, is what is most strongly protective of breast cancer. Indeed, both prospective cohort and retrospective case-control studies have observed a decreased risk of breast cancer among regular NSAID users but not among non-regular NSAID

users (36, 46-49), though it should be noted that prospective data from several other large cohort studies have found no association between regular use of NSAIDs and breast cancer risk (50-53). It is uncertain if the majority of migraine sufferers would in fact be regular NSAID users. While the public health importance of these findings is currently unclear, we feel additional studies are certainly needed to clarify this issue. We are not suggesting that expensive large-scale studies are needed to confirm these data, but further work that can account for NSAID use is required to confirm and expand upon our findings given that this is the first report of this association in the literature.

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Table 1. Selected characteristics of controls, invasive ductal carcinoma cases, and invasive lobular carcinoma cases

	Controls	Ductal carcinoma	Lobular carcinoma
	n=1,474 (%)	n=1,199 (%)	n=739 (%)
Reference age, yrs			
55-59	137 (9.3)	140 (11.7)	162 (21.9)
60-64	121 (8.2)	125 (10.4)	139 (18.8)
65-69	442 (30.0)	341 (28.4)	189 (25.5)
70-74	478 (32.4)	380 (31.7)	195 (26.4)
75-79	296 (20.1)	213 (17.7)	54 (7.3)
Race			
White (non-Hispanic)	1346 (91.3)	1116 (93.1)	688 (93.1)
Black	45 (3.1)	22 (1.8)	16 (2.2)
Asian/Pacific Islander	38 (2.6)	35 (2.9)	11 (1.5)
Other/unknown	45 (3.0)	26 (2.2)	24 (3.2)
Education			
Less than high school	177 (12.0)	127 (10.6)	53 (7.2)
High school	520 (35.3)	403 (33.6)	221 (29.9)
Some college	467 (31.7)	407 (33.9)	238 (32.2)
College/college grad	309 (21.0)	262 (21.9)	227 (30.7)
Missing	1	0	0
Parity			
Nulliparous	130 (8.8)	126 (10.5)	99 (13.4)
Parous	1344 (91.2)	1073 (89.5)	640 (86.6)
Age at first birth, yrs			
14-19	273 (20.4)	201 (18.8)	124 (19.5)
20-24	650 (48.5)	519 (48.6)	306 (48.0)
25-29	305 (22.7)	244 (22.8)	136 (21.4)
30-42	113 (8.4)	105 (9.8)	71 (11.1)
Missing	133	130	102
Use of oral contraceptives, months			
0	907 (63.4)	721 (63.0)	339 (49.2)
6-59	297 (20.8)	219 (19.1)	193 (28.0)
60-409	227 (15.9)	204 (17.8)	157 (22.8)
Missing	43	55	50
Recency of menopausal hormone therapy (HT) use			
Never user	433 (32.4)	323 (29.9)	134 (19.3)
Former user of HT	246 (18.4)	185 (17.1)	96 (13.9)
Current EHT user	450 (33.6)	297 (27.5)	195 (28.1)
Current CHT user	209 (15.6)	276 (25.5)	268 (38.7)
Missing	136	118	46
First-degree family history of breast cancer			
No	1153 (83.4)	878 (77.3)	556 (77.3)
Yes	229 (16.6)	258 (22.7)	163 (22.7)
Missing	92	63	20
Body mass index, quartiles (kg/m^2)			
≤23.16	363 (25.4)	265 (22.6)	210 (29.0)
23.17-26.44	372 (26.1)	309 (26.4)	154 (21.3)
26.45-30.82	343 (24.0)	283 (24.1)	200 (27.6)
≥30.83	350 (24.5)	315 (26.9)	160 (22.1)
Missing	46	27	15

Abbreviations: EHT=estrogen hormone therapy, CHT=combined hormone therapy.

Table 2. Relationship between a history of migraine and risks of invasive ductal and invasive lobular breast carcinomas

	Controls (n=1,474)	Ductal carcinoma (n=1,199)		Lobular carcinoma (n=739)	
	n (%)	n (%)	OR* (95% CI)	n (%)	OR* (95% CI)
Never diagnosed with migraine	1,202 (82)	1,037 (87)	1.00 (ref)	630 (85)	1.00 (ref)
Ever diagnosed with migraine	272 (19)	162 (14)	0.67 (0.54-0.82)†	109 (15)	0.68 (0.52-0.90)†
Age at migraine diagnosis, yrs					
<20	73 (5)	32 (3)	0.50 (0.33-0.76)†	23 (3)	0.55 (0.33-0.91)†
20-39	110 (8)	80 (7)	0.83 (0.62-1.13)	48 (7)	0.77 (0.53-1.12)
≥40	89 (6)	50 (4)	0.62 (0.43-0.89)†	36 (5)	0.62 (0.41-0.95)†
p-value for difference across age categories			0.52		0.85
Ever use of prescription migraine medications					
No	127 (9)	67 (6)	0.58 (0.43-0.79)†	53 (7)	0.65 (0.46-0.93)†
Yes	144 (10)	92 (8)	0.73 (0.56-0.97)†	55 (8)	0.69 (0.49-0.97)†
p-value for difference across medication categories			0.25		0.98

* Odds ratios adjusted for age and reference year.
† p<0.05.

Table 3. Relationship between a history of migraine and risks of invasive ductal and invasive lobular breast carcinomas by joint estrogen receptor/progesterone receptor status

	Ductal carcinoma						
	Controls (n=1,474)	ER+/PR+ (n=855)		ER+/PR- (n=133)		ER-/PR- (n=147)	
	No (%)	No (%)	OR* (95% CI)	No (%)	OR* (95% CI)	No (%)	OR* (95% CI)
Never diagnosed with migraine	1202 (82)	739 (87)	1.00 (ref)	120 (90)	1.00 (ref)	121 (82)	1.00 (ref)
Ever diagnosed with migraine	272 (19)	114 (13)	0.65 (0.51-0.83)†	13 (10)	0.49 (0.27-0.88)†	26 (18)	0.87 (0.56-1.36)
Age at migraine diagnosis, years							
<20	73 (5)	26 (3)	0.56 (0.35-0.88)†	2 (2)	0.28 (0.07-1.16)	3 (2.0)	0.37 (0.11-1.19)
20-39	110 (8)	57 (7)	0.82 (0.59-1.15)	6 (5)	0.56 (0.24-1.30)	15 (10)	1.24 (0.70-2.21)
≥40	89 (6)	31 (4)	0.53 (0.35-0.81)†	5 (4)	0.57 (0.23-1.44)	8 (5)	0.82 (0.39-1.74)
p-value for difference across age categories			0.80		0.43		0.37
Ever use of prescription migraine medications							
No	127 (9)	47 (6)	0.56 (0.39-0.79)†	6 (5)	0.48 (0.21-1.11)	11 (8)	0.79 (0.41-1.51)
Yes	144 (10)	65 (8)	0.72 (0.53-0.98)†	6 (5)	0.43 (0.19-1.00)†	15 (10)	0.95 (0.54-1.67)
p-value for difference across medication categories			0.27		0.85		0.66

	Lobular carcinoma				
	Controls (n=1,474)	ER+/PR+ (n=560)		ER+/PR- (n=110)	
	No (%)	No (%)	OR* (95% CI)	No (%)	OR* (95% CI)
Never diagnosed with migraine	1202 (82)	481 (86)	1.00 (ref)	92 (84)	1.00 (ref)
Ever diagnosed with migraine	272 (19)	78 (14)	0.63 (0.47-0.85)†	18 (16)	0.80 (0.47-1.36)
Age at migraine diagnosis, years					
<20	73 (5)	19 (4)	0.59 (0.34-1.03)	3 (3)	0.50 (0.15-1.65)
20-39	110 (8)	34 (7)	0.73 (0.47-1.13)	6 (6)	0.70 (0.30-1.66)
≥40	89 (6)	23 (5)	0.50 (0.30-0.82)†	9 (8)	1.10 (0.53-2.29)
p-value for difference across age categories			0.60		0.20
Ever use of prescription migraine medications					
No	127 (5)	35 (6)	0.57 (0.38-0.86)†	10 (9)	0.91 (0.46-1.81)
Yes	144 (10)	42 (8)	0.68 (0.46-1.00)	8 (7)	0.70 (0.33-1.49)
p-value for difference across medication categories			0.53		0.60

* Odds ratios adjusted for age and reference year.
† p<0.05