

## **Relationship between Migraine History and Breast Cancer Risk among Premenopausal and Postmenopausal Women**

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**ABSTRACT**

Both migraine and breast cancer are hormonally mediated diseases, and it is biologically plausible that women with a history of migraine may have a reduced breast cancer risk. However, this relationship has only been assessed in a single relatively small study that was unable to assess the impact of migraine triggers, that are also well established breast cancer risk factors (e.g., use of alcohol and exogenous hormones), on the inverse association observed. Utilizing data on 4,568 breast cancer cases and 4,678 controls who participated in a multi-center population-based case-control study in the United States, we evaluated the association between migraine history and breast cancer risk using unconditional logistic regression. Migraine history data were obtained from structured in-person interviews. Women with a history of migraine had a reduced risk of breast cancer [odds ratio (OR): 0.74, 95% confidence interval (CI): 0.66-0.82]. This risk did not differ by menopausal status, age at migraine diagnosis, use of prescription migraine medications, or when analyses were restricted to women who avoided various migraine triggers (including alcohol, exogenous hormones, and smoking). These data support a previous finding that a history of migraine may be associated with a reduced risk of breast cancer. It extends the prior report in observing that this relationship holds for both premenopausal and postmenopausal women and is independent of exposure to common migraine triggers.

## INTRODUCTION

In a recent case-control study of post-menopausal women we observed that women with a history of migraine had a 33% lower risk of invasive ductal breast cancer and a 32% lower risk of invasive lobular breast cancer compared to women without such a history.(1) This was the first published report to address a potential relationship between breast cancer risk and migraine, and it was motivated by the influence reproductive hormones have on both breast cancer and migraine. The impacts of both endogenous hormone levels(2) and exogenous hormonal exposures on breast cancer(3, 4) are well established. Migraine is a neurological disorder that is 2-3 times more common in women than in men.(5, 6) This difference is likely due to the influence of estrogen, particularly acute estrogen withdrawal, on migraine onset. Among cycling premenopausal women, the frequency and intensity of migraine changes in the days immediately before and during menses when endogenous estrogen levels reach their nadir.(7) Several studies suggest that approximately 4-14% of migraines occur exclusively around the time of menses,(8-10) and an estimated 60% of female migraineurs report an increased frequency of migraines around the time of menstrual bleeding.(10) Additionally, women taking oral contraceptives experience more frequent migraines during their hormone-free week.(11) Migraine frequency also decreases during pregnancy, a time when estrogen levels increase considerably. Indeed, by the third trimester, 79% of female migraineurs report complete migraine remission. (12)

The primary motivation for this study was to evaluate the relationship between a history of migraine and risk of breast cancer in both premenopausal and postmenopausal women, and to assess the potential impact of common migraine triggers, that are also established breast cancer risk factors, on this relationship.

## METHODS

The Women's Contraceptive and Reproductive Experiences Study is a population-based case-control study that recruited women aged 35-64 years old diagnosed with invasive breast cancer between 1994-1998 from five metropolitan areas: Atlanta, Detroit, Los Angeles, Philadelphia, and Seattle. Details of the methods used in this study have been previously published.<sup>(13)</sup> Cases were ascertained through Surveillance, Epidemiology, and End Results (SEER) cancer registries at four sites (Atlanta, Detroit, Los Angeles, and Seattle) and by field center staff at one site (Philadelphia). Of 5,982 eligible cases identified, 4,575 (77%) were enrolled and interviewed. Female controls without breast cancer were identified by random digit dialing in the same areas and were frequency matched to cases on 5-year age group, race, and study site. Of the 5,956 eligible controls identified, 4,682 (79%) were enrolled and interviewed. The seven cases and four controls with an unknown history of migraine were excluded from all analyses leaving a total of 4,568 cases and 4,678 controls.

The study protocol was approved by the institutional review board of each participating center, and written informed consent was obtained from all participants. This study excluded all women with a prior history of *in situ* or invasive breast cancer. All cases and controls were interviewed in-person by trained interviewers using the same questionnaire with standardized probes. Women were asked about exposures occurring before their reference date, which for cases was defined as the date of their breast cancer diagnosis. Reference dates for controls were defined as the dates study staff first contacted a member of prospective controls' households through random digit dialing. With respect to migraine history, women were asked if "a doctor or other health professional ever told you that you had migraine headaches", age at migraine diagnosis, and ever use of prescription medications for migraine. 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 (including alcohol use and smoking), was collected.

Data on estrogen receptor (ER) status, progesterone receptor (PR) status, and histology of cases were obtained from SEER registry files (Atlanta, Detroit, Los Angeles, and Seattle) or from pathology reports, medical records, and hospital registry abstracts (Philadelphia). We excluded cases with ER-/PR+ tumors (n=185, due to insufficient statistical power) and cases with an unknown ER/PR status (n=804) from our ER/PR analyses. Histology was classified as ductal (n=3,457, ICD-O code 8500), lobular (n=535, ICD-O codes 8520 and 8522), and other (n=576, all other ICD-O codes).

Unconditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CI) comparing cases to controls.<sup>(14)</sup> We compared cases of each ER/PR status and histological type to controls using polytomous logistic regression.<sup>(15)</sup> All analyses were adjusted for age, race, and study site. The referent category was women with no history of clinically diagnosed migraine. Variables considered as potential confounders or effect modifiers included income, education, age at menarche, parity, age at first birth, type of menopause, age at menopause, duration of oral contraceptive use, use of hormone therapy, first-degree 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 (all p-values for interaction > 0.05). We also assessed heterogeneity of risk estimates associated with migraine history across breast cancer subtypes defined by ER/PR status and by histology by testing the null hypothesis that the ORs were equivalent to each other (test of homogeneity of ORs). All analyses were conducted using Stata 9.2 (Stata Corp, College Station, TX).

## RESULTS

Cases were somewhat more likely than controls to have experienced a natural menopause and to be current users of combined estrogen and progestin hormone therapy (CHT), but were otherwise comparable to controls (Table 1).

Women who reported a clinical diagnosis of migraine had a reduced risk of breast cancer (OR=0.74, 95% CI: 0.66-0.82) than women with no history of migraine (Table 2). Breast cancer risk did not differ by age at migraine diagnosis ( $p=0.84$ ) or by history of ever using prescription migraine medications ( $p=0.11$ ). This relationship was similarly observed among both premenopausal (OR=0.79, 95% CI: 0.67-0.93) and postmenopausal women (OR=0.74, 95% CI: 0.62-0.87), and among both white (OR=0.77, 95% CI: 0.68-0.88) and black (OR=0.67, 95% CI: 0.55-0.82) women. In addition, given that some migraine triggers are also related to breast cancer risk we assessed this relationship among subgroups of women including never drinkers of alcohol over the past 10 years, never smokers, never users of oral contraceptives, and never users of menopausal hormone therapy and for each of these subgroups the same association between migraine history and breast cancer was observed (OR=0.79, 95% CI: 0.68-0.92; OR=0.76, 95% CI: 0.65-0.90; OR=0.67, 95% CI: 0.52-0.87; and OR=0.76, 95% CI: 0.66-0.88, respectively).

Migraineurs had reduced risks of ER+/PR+ tumors (OR: 0.69, 95% CI: 0.60-0.80), ER+/PR- tumors (OR: 0.83, 95% CI: 0.62-1.10), and ER-/PR- tumors (OR: 0.83, 95% CI: 0.70-0.99), though the risk estimate for ER+/PR- tumors was within the limits of chance (Table 3). Statistically significant variation in these risk estimates across ER/PR subtypes was observed ( $p=0.03$ ); in particular, the risk estimate for ER+/PR+ tumors differed from that of ER-/PR- tumors ( $p=0.04$ ). In contrast, associations between migraine and breast cancer did not vary by histological type; compared to non-migraineurs women with a history of migraine had similarly reduced risks of both ductal (OR=0.74, 95% CI: 0.66-0.83) and lobular (OR=0.73, 95% CI: 0.57-0.93) carcinomas ( $p$ -value for test of homogeneity of risk across histologies=0.89).



## DISCUSSION

Our study found that a history of a clinical diagnosis of migraine is associated with a 26% reduced risk of breast cancer among both premenopausal and postmenopausal women. This result is consistent with the 33% reduction in risk of invasive ductal breast carcinomas observed in the only other published study to assess this relationship.(1) In the data presented here, the association between migraine and breast cancer did not vary substantially by age at migraine diagnosis, but there was some suggestion that risks were lower among women who had used prescription migraine medications. Although we did not assess migraine severity, use of prescription medications may be a proxy for more severe disease, or this observation could also reflect a reduction in risk associated with use of these medications. The lack of a significant effect among women not using medication may also be the result of exposure misclassification since the proportion of women reporting a history of migraine who actually only suffered non-migraine headaches may be higher among the non-medication users compared to the users. However, more detailed studies are needed to carefully assess how factors such as migraine severity, frequency, and/or intensity and use of specific migraine treatments may be related to breast cancer risk.

Common triggers for migraines are use of exogenous hormones, alcohol consumption, and smoking, and each of these exposures is related to breast cancer risk, with the evidence related to exogenous hormones and alcohol use being particularly strong. Given that use of both exogenous hormones and alcohol have been consistently positively related to breast cancer risk,(1, 3, 16), one potential explanation for the relationship between migraine is simply that migraine sufferers are less likely to use exogenous hormones and alcohol and this conveys a lower risk of breast cancer. However, we observed the same relationship between migraine and breast cancer when our analyses were restricted to never users of oral contraceptives, never users of menopausal hormone therapy, women who reported no alcohol consumption over the past 10 years, and never smokers. Thus, differences in these characteristics between

migraineurs and women without migraines did not explain the relationship between migraine history and breast cancer risk.

Since NSAIDs are associated with a reduced risk of breast cancer, it is also possible that the relationship between migraine and breast cancer is an artifact of more frequent NSAID use among migraineurs. While this may explain part of the association it is unlikely to explain it entirely. The recent meta-analysis of studies of NSAID use and breast cancer risk observed only a 12% reduction in risk for women classified as ever using any NSAID, and the magnitude of this relationship did not vary when results were restricted to women with high NSAID intake.<sup>(17)</sup> The magnitude of this risk is less than half that observed with migraine history. In addition, many classes of medications are prescribed for both migraine prevention and treatment of acute attacks. NSAIDs are just one of these types of medications and the only one possibly shown to be related to breast cancer risk (various antidepressants and antihypertensives, which are sometimes used to treat migraine, have not been consistently associated with breast cancer risk across several studies). Since many classes of drugs can be used for migraine, it is unclear what proportion of migraineurs actually use NSAIDs at a level which biologically could confer a reduced risk of breast cancer. Nevertheless, further studies are needed to assess the impact of NSAID use on the relationship between migraine and breast cancer.

The primary motivation for considering a potential link between migraine and breast cancer is that both diseases are hormonally related. The majority of established risk factors for sporadic breast cancer have a hormonal component and, as a result of hormonal changes, migraine attacks can be triggered (such as with drops in estrogen occurring during the natural menstrual cycle) or suppressed (such as during the third trimester of pregnancy when estrogen levels reach a high steady state).<sup>(7-12)</sup> However, the precise biology and hormonal pathways of migraine relevant to a potential reduction in breast cancer risk are poorly understood. Migraine is also a heterogeneous disease; not all are associated with hormonal changes. Thus, further studies assessing whether the types and triggers of migraine are associated with breast

cancer risk could provide further insight into the biology underlying the relationship between migraine and breast cancer.

It is also important to acknowledge the limitations of this study. Information on clinical diagnosis of migraine, including age at diagnosis and use of prescription migraine medications, was based on patient recall and is subject to bias. We expect that recall of history of a clinical diagnosis of migraine will be reasonably accurate given the typical severity of migraine symptoms precipitating a clinical diagnosis. Misclassification remains an issue in that migraine could have been diagnosed in women who do not actually meet established clinical criteria for such a diagnosis; alternatively, they could have been undiagnosed. The latter situation is likely of greater concern since approximately 27-59% of migraine sufferers are never clinically diagnosed.(5, 18, 19) However, this type of misclassification would most likely be non-differential, primarily because there were no published reports of the relationship between migraine and breast cancer during the time this study was conducted. We should also note that this study did not collect data on the timing, frequency, or intensity of migraine headaches, or information on specific medications used to treat migraines, all of which may be relevant to breast cancer risk. Perhaps most importantly, data on the use of non-steroidal anti-inflammatory drugs (NSAIDs), medications commonly used by migraineurs and which are associated with an approximately 12% reduced risk of breast cancer risk,(17) were not collected.

This study provides support for our initial report that migraine is associated with a reduced risk of breast cancer and confirms that this relationship is somewhat stronger for hormone receptor positive tumors.(1) It also expands our knowledge of this association by demonstrating that this relationship holds for both premenopausal and postmenopausal women and also among women who are not exposed to a variety of common migraine triggers including exogenous hormones, alcohol, and smoking. However, further work is needed to resolve what accounts for this relationship; such as whether it is a consequence of factors like more frequent NSAID use among migraineurs, or if there are different hormonal milieus or sensitivities in

migraineurs compared to women who do not suffer from migraines that convey a lower risk of breast cancer.

**Table 1. Selected characteristics of breast cancer cases and population-based controls**

<b>Characteristic</b>	<b>Controls n=4,678 (%)</b>	<b>Cases n=4,568 (%)</b>
<b>Reference age, years</b>		
35-39	666 (14.2)	688 (15.1)
40-44	832 (17.8)	756 (16.5)
45-49	857 (18.3)	780 (17.1)
50-54	823 (17.6)	843 (18.5)
55-59	801 (17.1)	770 (16.9)
60-64	699 (14.9)	731 (16.0)
<b>Race</b>		
White	3,018 (64.5)	2,947 (64.5)
Black	1,660 (35.5)	1,621 (35.5)
<b>Menopausal status</b>		
Premenopausal	2,060 (50.4)	2,112 (52.4)
Natural menopause	1,120 (27.4)	1,219 (30.2)
Surgical menopause	561 (13.7)	402 (10.0)
Simple hysterectomy	346 (8.5)	301 (7.5)
Uncertain/Missing	591	534
<b>Use of oral contraceptives, years</b>		
Never	989 (21.2)	1,042 (22.9)
<1.0	829 (17.7)	787 (17.3)
1.0-4.9	1,290 (27.6)	1,210 (26.5)
≥5.0	1,564 (33.5)	1,521 (33.4)
Missing	6	8
<b>Recency of menopausal hormone therapy (HT) use</b>		
Never user	2,727 (59.2)	2,831 (62.5)
Former user of HT	562 (12.1)	432 (9.5)
Current EHT user	776 (16.7)	600 (13.3)
Current CHT user	553 (11.9)	665 (14.7)
Missing	40	40
<b>Body mass index 5 years prior to reference date, quartiles (kg/m<sup>2</sup>)</b>		
≤21.60	1,119 (24.0)	1,143 (25.1)
21.61-24.32	1,134 (24.3)	1,179 (25.9)
24.33-28.31	1,184 (25.4)	1,130 (24.9)
≥28.32	1,221 (26.2)	1,094 (24.1)
Missing	20	22
<b>Alcohol consumption, average number of drinks/week over the past 10 years</b>		
None	2,294 (49.1)	2,181 (47.9)
<1.0	615 (13.2)	592 (13.0)
1.0-2.9	657 (14.1)	643 (14.1)
3.0-6.9	592 (12.7)	584 (12.8)
≥7.0	511 (10.9)	554 (12.2)
Missing	9	14

Table 1, continued.

Characteristic	Controls n=4,678 (%)	Cases n=4,568 (%)
<b>Current smoking status</b>		
Never	2,101 (44.9)	2,094 (45.8)
Former	1,468 (31.4)	1,494 (32.7)
Current	1,107 (23.7)	980 (21.5)
Missing	2	0

Table 2. Relationship between self-reported history of migraine and breast cancer risk

	Controls (n=4,678) n (%)	Cases (n=4,568) n (%)	OR* (95% CI)
<b>Never diagnosed with migraine</b>	3,759 (80)	3,870 (85)	1.00 (ref)
<b>Ever diagnosed with migraine</b>	919 (20)	698 (15)	0.74 (0.66-0.82) <sup>†</sup>
<b>Age at migraine diagnosis, yrs</b>			
<20	201 (4)	166 (4)	0.81 (0.65-1.00) <sup>†</sup>
20-39	513 (11)	365 (8)	0.69 (0.60-0.80) <sup>†</sup>
≥40	205 (4)	167 (4)	0.78 (0.64-0.97) <sup>†</sup>
	p-value for difference across age categories <sup>‡</sup> = 0.84		
<b>Ever use of prescription migraine medications</b>			
No	201 (4)	176 (4)	0.85 (0.69-1.05)
Yes	717 (15)	519 (11)	0.70 (0.62-0.79) <sup>†</sup>
	p-value for difference across medication categories <sup>‡</sup> = 0.11		

\* Odds ratios (OR) and 95% confidence intervals (CI) are adjusted for age, race, and study site.

<sup>†</sup> p<0.05.

<sup>‡</sup> P-values are from tests for homogeneity of the odds ratios.

**Table 3. Relationship between self-reported clinical history of migraine and risk of breast cancer by estrogen receptor (ER)/progesterone receptor (PR) status and histology**

	<b>Controls</b>							
	<b>(n=4,678)</b>	<b>ER+/PR+ (n=2,128)</b>		<b>ER+/PR- (n=369)</b>		<b>ER-/PR- (n=1,082)</b>		
	<b>n (%)</b>	<b>n (%)</b>	<b>OR* (95% CI)</b>	<b>n (%)</b>	<b>OR* (95% CI)</b>	<b>n (%)</b>	<b>OR* (95% CI)</b>	
<b>Never diagnosed with migraine</b>	3,759 (80)	1,814 (85)	1.00 (ref)	307 (83)	1.00 (ref)	901 (83)	1.00 (ref)	
<b>Ever diagnosed with migraine</b>	919 (20)	314 (15)	0.69 (0.60-0.80) <sup>†</sup>	62 (17)	0.83 (0.62-1.10)	181 (17)	0.83 (0.70-0.99) <sup>†</sup>	
<b>Age at migraine diagnosis, yrs</b>								
<20	201 (4)	64 (3)	0.66 (0.50-0.88) <sup>†</sup>	15 (4)	0.96 (0.56-1.64)	40 (4)	0.81 (0.57-1.15)	
20-39	513 (11)	166 (8)	0.65 (0.54-0.79) <sup>†</sup>	29 (8)	0.72 (0.48-1.06)	107 (10)	0.86 (0.69-1.08)	
≥40	205 (4)	84 (4)	0.81 (0.62-1.05)	18 (5)	0.95 (0.58-1.57)	34 (3)	0.77 (0.53-1.12)	
p-value for difference across age categories			0.28		0.96		0.86	
<b>Ever use of prescription migraine medications</b>								
No	201 (4)	73 (3)	0.74 (0.56-0.98) <sup>†</sup>	21 (6)	1.27 (0.80-2.03)	33 (3)	0.70 (0.48-1.02)	
Yes	717 (15)	240 (11)	0.68 (0.58-0.79) <sup>†</sup>	41 (11)	0.70 (0.50-0.98) <sup>†</sup>	148 (14)	0.87 (0.72-1.06)	
p-value for difference across medication categories			0.67		0.04		0.28	

  

	<b>Controls</b>		<b>Ductal carcinoma</b>		<b>Lobular carcinoma</b>	
	<b>(n=4,678)</b>	<b>(n=3,457)</b>	<b>n (%)</b>	<b>OR* (95% CI)</b>	<b>n (%)</b>	<b>OR* (95% CI)</b>
<b>Never diagnosed with migraine</b>	3,759 (80)	2,929 (85)	1.00 (ref)		453 (85)	1.00 (ref)
<b>Ever diagnosed with migraine</b>	919 (20)	528 (15)	0.74 (0.66-0.83) <sup>†</sup>		82 (15)	0.73 (0.57-0.93) <sup>†</sup>
<b>Age at migraine diagnosis, yrs</b>						
<20	201 (4)	134 (4)	0.86 (0.69-1.07)		12 (2)	0.51 (0.28-0.92) <sup>†</sup>
20-39	513 (11)	271 (8)	0.68 (0.58-0.79) <sup>†</sup>		43 (8)	0.70 (0.51-0.98) <sup>†</sup>
≥40	205 (4)	123 (4)	0.77 (0.62-0.97) <sup>†</sup>		27 (5)	0.99 (0.65-1.49)
p-value for difference across age categories			0.51			0.06
<b>Ever use of prescription migraine medications</b>						
No	201 (4)	131 (4)	0.84 (0.67-1.05)		21 (4)	0.87 (0.55-1.38)
Yes	717 (15)	395 (11)	0.71 (0.62-0.81) <sup>†</sup>		60 (11)	0.68 (0.51-0.90) <sup>†</sup>
p-value for difference across medication categories			0.20			0.47

\* Odds ratios (OR) and 95% confidence intervals (CI) are adjusted for age, race, and study site.

<sup>†</sup> p<0.05.

<sup>‡</sup> p-values are from tests for homogeneity of the odds ratios.

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