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ORIGINAL REPORT

Migraine History and Breast Cancer Risk Among Postmenopausal Women

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ABSTRACT

Purpose
Both migraine and breast cancer are hormonally mediated. Two recent reports indicate that women with a migraine history may have a lower risk of postmenopausal breast cancer than those who never suffered migraines. This finding requires confirmation; in particular, an assessment of the influence of use of nonsteroidal anti-inflammatory drugs (NSAID) is needed, because many studies indicate that NSAID use also may confer a reduction in breast cancer risk.

Methods
We assessed the relationship between self-reported history of migraine and incidence of postmenopausal breast cancer in 91,116 women enrolled on the Women's Health Initiative Observational Study prospective cohort from 1993 to 1998 at ages 50 to 79 years. Through September 15, 2005, there were 4,006 eligible patients with breast cancer diagnosed.

Results
Women with a history of migraine had a lower risk of breast cancer (hazard ratio [HR], 0.89; 95% CI, 0.80 to 98) than women without a migraine history. This risk did not vary by recent NSAID use. The lower risk was somewhat more pronounced for invasive estrogen-receptor–positive and progesterone-receptor–positive tumors (HR, 0.83; 95% CI, 0.71 to 0.97), as no reduction in risk was observed for invasive ER-negative/PR-negative tumors (HR, 1.16; 95% CI, 0.86 to 1.57), and this difference in risk estimates was borderline statistically significant ($P = .06$).

Conclusion
This study supports the hypothesis that a history of migraine is associated with a lower risk of breast cancer and that this relationship is independent of recent NSAID use.

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INTRODUCTION

Two recently published studies are the first reports that postmenopausal women with a clinical history of migraine have a 26% to 33% lower risk of invasive breast cancer than women without such a history.[1,2] A potential link between migraine history and breast cancer risk was hypothesized, because both diseases are influenced by reproductive hormones. In women, the risk of migraine changes during menarche, menses, pregnancy, and perimenopause as a result of fluctuating estrogen levels.[3] Particularly relevant to breast cancer risk is that migraines in women are often associated with declines in estrogen levels. Migraine frequency increases during menses, when endogenous estrogen levels drop sharply, and when the levels reach their lowest point in cycling premenopausal women. Specifically, approximately 60% of female migraineurs report a higher frequency and severity of migraines around the time of menses.[4,5] Similarly, migraine frequency also increases during the hormone-free week of oral contraceptive use when estrogen is withdrawn.[6] These observations suggest that marked drops in estrogen may be a migraine trigger.[7] Indeed, 4% to 14% of women with migraine report that their migraines exclusively occur 2 days before to 3 days after the onset of menses.[8-10] In contrast, two observations indicate that stable estrogen levels, whether they are high or low, are associated with a reduction in migraine frequency. First, during pregnancy, when women reach a high estrogen steady-state and do not experience monthly hormonal fluctuations, migraine frequency is reduced for almost all migraine sufferers. Approximately 11% of migraine sufferers who become pregnant experience no migraines during pregnancy, and 87% experience a reduced frequency of migraine.[11] Second, after women go through menopause and estrogen levels hold at a generally low steady-state, 67% of women

with a history of premenopausal migraine report fewer migraines.[12] Given that lifetime estrogen exposure is strongly related to breast cancer risk[13] and that hormones clearly influence migraine, a relationship between these two health problems is biologically plausible. Additionally supporting this link is the observation that migraine history was more strongly related to a lower risk of hormone-receptor–positive breast cancer than it was to risk of hormone-receptor–negative disease in the two studies that have assessed this association.[1,2]

The paucity of information regarding the association between migraine and breast cancer warrants additional assessment of this relationship. One of the limitations of the two prior studies of migraine and breast cancer was the lack of data on use of nonsteroidal anti-inflammatory drugs (NSAIDs). This is relevant, because migraine sufferers are more likely to use these medications, and they are the only type of medication commonly used to treat migraines that has been shown to be modestly related to breast cancer risk. In particular, a recent meta-analysis of studies of NSAID use and breast cancer risk observed a 12% lower risk for women classified as ever using any NSAID.[14] Similarly, in the Women's Health Initiative (WHI) Observational Study (OS) prospective cohort, regular use of any NSAID for 5 years or longer was associated with a 19% lower risk of breast cancer compared with non-NSAID users and users of NSAIDs for less than 1 year.[15] The WHI OS provides an excellent setting to evaluate the relationship between migraine and breast cancer risk because data on NSAID use and migraine history were collected, and because in this large cohort more than 4,000 patients with breast cancer have been diagnosed during cohort follow-up.

METHODS

This study utilized data collected in the WHI OS. The details of the scientific rationale, eligibility criteria, and design of the WHI OS have been published.[16] Briefly, 93,676 postmenopausal women, age 50 to 79 years, were enrolled between October 1, 1993 and December 31, 1998, through 40 clinical centers dispersed throughout the United States, and these women were not subjected to any study interventions. All exposures used in this analysis were collected at the time of entry into the WHI OS. Data were collected from participants uniformly according to standardized institutional review board–approved procedures and protocols by centrally trained study staff. All participants provided written informed consent for participation in the WHI OS at the time of enrollment.

Cohort members completed baseline self-administered questionnaires covering a wide range of topics, including demographic characteristics, medical history, reproductive history, lifestyle characteristics, and family history of various diseases. In addition, baseline height and weight were measured by study staff. With respect to our primary exposure of interest, clinical history of migraine, women were asked at baseline if they have ever been told by a doctor that they had migraine headaches. The 2,560 women with an unknown migraine history were excluded from all analyses, so a total of 91,116 included women remained. Information about migraine was not assessed in subsequent questionnaires, so all analyses were based on migraine history at baseline. Participants also were asked at baseline to provide information on all over-the-counter and prescription drugs they were currently using and the durations they had been using them. These data were queried to identify women who were using NSAIDs at baseline, including aspirin, ibuprofen, naproxen, and various less commonly used over-the-counter and prescription-only NSAIDs. Summary variables of use of any NSAID at baseline and duration of current NSAID use were computed by using this information. Only women reporting NSAID use at least two times in each of the 2 weeks preceding completion of the baseline questionnaire were recorded as current NSAID users.

The primary follow-up of WHI OS participants was through annual mailed, self-administered questionnaires. This report includes information collected on the cohort through September 15, 2005, through which 2.2% of participants had been lost to follow-up, 2.5% declined additional follow-up, and 6.7% had died. Women with breast cancer were identified from annual questionnaires. The medical records of all women reporting a breast cancer diagnosis were reviewed by a study adjudicator at the respective study centers to verify the diagnosis. For the 4,006 confirmed patients identified through September 15, 2005 in the entire cohort, information from medical records was forwarded to the WHI coordinating center for coding of breast cancer stage, estrogen receptor (ER) status, progesterone receptor (PR) status, and histology. Of the 4,006 occurrences of breast cancer, 688 were in situ, and 3,318 were invasive. Analyses were also conducted that focused on subgroups of invasive breast cancer defined by ER/PR status and histology. In the ER/PR-specific analyses, the 609 invasive occurrences with unknown ER/PR status were excluded, as were those with ER-negative/PR-positive tumors, because of insufficient statistical power (n = 40), so that a total of 2,669 invasive cases remained for inclusion in the analysis. Analyses by invasive breast cancer histology were based on occurrences classified as ductal (n = 1,916; International Classification of Disease, Oncology [ICD-O] -8500) or lobular (n = 754; ICD-O-8520 and -8522). Those with other ICD-O codes were grouped together as having other histology (n = 392), and 256 invasive occurrences had unknown histology.

Statistical Analysis

Cox regression was used to calculate hazard ratios (HRs) and 95% CIs as measures of the association between migraine history and breast cancer risk. Time to breast cancer was computed from date of enrollment to date of first breast cancer diagnosis, and times for women without breast cancer were censored by date of last study follow-up or by September 15, 2005, whichever occurred first. All analyses were adjusted for age in years at enrollment (as a linear continuous term) and ethnicity (as a categoric term) through stratification of the baseline hazard rates in the Cox model, and women with no history of clinically diagnosed migraine served as the reference category. To additionally control for age at enrollment, we also adjusted all models for age at enrollment as a categoric variable (in 5-year categories). Variables considered potential confounders or effect modifiers included the following baseline characteristics: income, parity, use of menopausal hormone therapy, hysterectomy status, recent timing and duration of NSAID use, current use of migraine specific prescription medications, body mass index (BMI), smoking status, alcohol intake, and average number of cups of regular coffee consumed. Although several of these potential confounders have been associated with breast cancer risk, none of them changed our risk estimates by more than 10%. However, we do present risk estimates from models adjusted simply for age and ethnicity and risk estimates from models additionally adjusted for the following baseline characteristics according to the way they are categorized in Table 1: hysterectomy history, use of menopausal hormones, NSAID use/duration, alcohol consumption, smoking status, and consumption of caffeinated coffee. Effect modification was assessed by using likelihood ratio testing, and none of these variables were observed to be statistically significant effect modifiers (all P for interaction $> .05$). Given the particular interest in the role of NSAID use, results stratified by NSAID use at enrollment are presented. All analyses were conducted by using Stata 9.2 (Stata Corp, College Station, TX).

RESULTS

Compared with women without a history of migraine, women with a clinical history of migraine as a group were slightly younger, more frequently non-Hispanic white, more likely to have used oral contraceptives and unopposed estrogen postmenopausal hormone therapy at enrollment, more likely to have had a hysterectomy, more commonly regular users of NSAIDs for 3 years or longer at the time of enrollment, and less likely to consume seven or more alcoholic beverages per week at baseline (Table 1). The two groups of women were

Table 1. Distribution of Demographic and Lifestyle Characteristics Among Women With and Without a Clinical History of Migraine

Characteristic	History of Migraine: No (n = 80,652) No.	%	Yes (n = 10,464) No.	%
Age at enrollment, years				
50-59	24,608	30.5	4,225	40.4
60-69	35,709	44.3	4,373	41.8
70-79	20,335	25.2	1,866	17.8
Race/Ethnicity				
Non-Hispanic white	67,066	83.2	9,122	87.2
African American	6,766	8.4	565	5.4
Hispanic white	2,927	3.6	390	3.7
Asian/Pacific Islander	2,415	3.0	195	1.9
American Indian/Alaska Native	345	0.4	59	0.6
Other	1,133	1.4	133	1.3
Oral contraceptive use, years				
Never	49,019	60.8	5,553	53.1
< 5	17,445	21.6	2,963	28.3
≥ 5	14,165	17.6	1,946	18.6
Missing	23		2	
Hormone therapy use				
Never	33,464	41.5	3,346	32.0
Former	11,923	14.8	1,622	15.5
Current unopposed estrogen user	19,363	24.0	3,377	32.3
Current estrogen and progestin user	15,827	19.6	2,102	20.1
Missing	75		17	
History of a hysterectomy at baseline				
No	47,657	59.1	5,270	50.4
Yes	32,924	40.9	5,182	49.6
Missing	71		12	
Body mass index quartiles, kg/m^2				
< 23.21	19,986	25.1	2,601	25.1
23.21-26.09	19,898	25.0	2,639	25.5
26.10-30.03	19,957	25.0	2,571	24.8
≥ 30.04	19,866	24.9	2,547	24.6
Missing	945		106	
Regular use of any NSAID at baseline, years				
No	53,237	66.0	6,204	59.3
Yes	27,414	34.0	4,260	40.7
< 3	12,610	15.6	1,713	16.4
≥ 3	14,804	18.4	2,547	24.3
Missing	1		—	
Current alcohol use				
Never	8,944	11.2	1,122	10.8
Former drinker	14,723	18.4	2,292	22.0
Current drinker				
< 7 drinks per week	45,954	57.3	6,038	58.0
≥ 7 drinks per week	10,497	13.1	950	9.1
Missing	484		62	
Smoking status				
Never	40,483	50.8	5,313	51.5
Former	34,155	42.9	4,441	42.8
Current	4,987	6.3	594	5.8
Missing	1,027		140	
No. of cups of regular coffee consumed per day				
0	34,514	43.6	4,578	44.6
1	13,862	17.5	1,727	16.8
2	23,177	29.3	2,958	28.8
≥ 3	7,576	9.6	999	9.7
Missing	1,523		202	

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

similar to each other with respect to BMI, smoking status, and consumption of caffeinated coffee.

Women with a migraine history had a lower risk of developing breast cancer (multivariate adjusted HR, 0.89; 95% CI, 0.80 to 0.98) than women without a migraine history (Table 2). This association was similar for risks of both in situ and invasive breast cancer and did not vary by histology among invasive occurrences. There was some suggestion that this lower risk was more pronounced among older than younger women, but the interaction with age was not statistically significant (P for interaction = .08; 50 to 59 years of age at enrollment data: HR, 0.93; 95% CI, 0.78 to 1.11; 60 to 69 years of age at enrollment data: HR, 0.94; 95% CI, 0.81 to 1.10; and 70 to 79 years of age at enrollment data: HR, 0.69; 95% CI, 0.53 to 0.90). The lower risk was somewhat more pronounced for invasive ER-positive/PR-positive tumors (HR, 0.83; 95% CI, 0.71 to 0.97), as no reduction in risk was observed for invasive ER-negative/PR-negative tumors (HR, 1.16; 95% CI, 0.86 to 1.57), and this difference in risk estimates was borderline statistically significant ($P = .06$).

Risks of breast cancer overall, invasive breast cancer, and invasive ER-positive/PR-positive breast cancer did not vary appreciably by current use of NSAIDs at baseline, even among current users for 3 years or longer (Table 3). Risks also were similar when current use of aspirin and ibuprofen were assessed separately (data not shown). In addition, given that some migraine triggers also are related to breast cancer risk, we assessed the relationship between migraine and risk of ER-positive/PR-positive invasive breast cancer among subgroups of women, including never drinkers of alcohol during the past 10 years, never users of oral contraceptives, and never users of menopausal hormone therapy. We focused on this patient subtype, because this was the subtype most strongly related to migraine history. Within each of these exposure categories, the direction and magnitude of the association between migraine history and ER-positive/PR-positive invasive breast cancer was similar to the overall risk estimate (never drinkers data: HR, 0.79; 95% CI, 0.46 to 1.34; never users of oral contraceptives data: HR, 0.84; 95% CI, 0.69 to 1.04; and never users of menopausal hormone therapy data: HR, 0.86; 95% CI, 0.64 to 1.15). The relationship between migraine and breast cancer also did not vary when analyses were stratified by caffeine consumption, another migraine trigger, as measured by daily consumption of caffeinated coffee.

DISCUSSION

Consistent with two recently published, population-based, case-control studies in entirely different populations,[1,2] we estimate that migraine history is associated with a 10% lower risk of invasive breast cancer overall and a 17% lower risk of ER-positive/PR-positive invasive breast cancer. The magnitude of the lower risk we observed is more modest than the 26% to 33% lower risk of postmenopausal breast cancer observed previously,[1,2] and this could be due to greater misclassification of migraine history and nondifferential bias toward the null. Specifically, WHI data were based on self-reported answers to a lengthy self-administered questionnaire, and data were collected in person by trained interviewers in the two prior studies, in which participants were additionally probed regarding age at migraine diagnosis and if they had every used any prescription medications to treat their migraines. As a result, there is likely to be greater misclassification

Table 2. Risk of Breast Cancer Associated With Migraine History

Breast Cancer Type	No. of Incident Cases Without a Migraine History	No. of Incident Cases With a Migraine History	Adjusted for Age and Race/Ethnicity		Multivariate Adjusted Analysis*	
			HR	95% CI	HR	95% CI
Any breast cancer	3,595	411	0.89	0.80 to 0.98†	0.89	0.80 to 0.98†
In situ breast cancer	623	65	0.80	0.62 to 1.03	0.81	0.62 to 1.05
Invasive breast cancer	2,972	346	0.91	0.81 to 1.01	0.90	0.80 to 1.01
ER/PR status						
ER and PR positive	1,693	185	0.85	0.73 to 0.99†	0.83	0.71 to 0.97†
ER positive and PR negative	361	42	0.89	0.65 to 1.23	0.92	0.66 to 1.28
ER and PR negative	335	53	1.22	0.91 to 1.63	1.16	0.86 to 1.57
Histology						
Ductal	1,709	207	0.94	0.81 to 1.08	0.91	0.79 to 1.06
Lobular	678	76	0.87	0.69 to 1.10	0.88	0.69 to 1.13
Other	359	33	0.73	0.51 to 1.05	0.72	0.50 to 1.04

Abbreviations: HR, hazard ratio; ER, estrogen receptor; PR, progesterone receptor.
*Multivariate adjusted HRs are adjusted for age, race/ethnicity, and the following baseline characteristics: hysterectomy, use of menopausal hormones, nonsteroidal anti-inflammatory drug use/duration, alcohol consumption, smoking status, and regular coffee consumption. The 3,333 women missing data for one or more of the covariates adjusted for in the multivariate models were excluded from these analyses.
†$P < .05$.

of migraine history in WHI, but this misclassification is nondifferential, which means that women who were or were not diagnosed with breast cancer could be assumed to be equally likely to have migraine history misclassified. It is well established that this type of misclassification results in an attenuation of the estimated size of the true association.[17] However, a unique strength of WHI was its collection of detailed covariate data, including data on NSAID use, which was lacking in the prior studies. Here, we find that the reduction in risk associated with migraine history did not vary by NSAID use.

Additionally, common triggers for migraines are use of exogenous hormones and alcohol consumption. Given that both of these exposures are positively related to breast cancer risk across numerous studies,[1,18,19] one potential explanation for the relationship between migraine and breast cancer is simply that migraine sufferers may be less likely to use exogenous hormones and alcohol and that this conveys a lower risk of breast cancer (though in this cohort migraine sufferers were actually more likely to use oral contraceptives and unopposed estrogen hormone therapy). 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, and never drinkers, similar to the only prior study that also stratified its analyses by these factors.[2]

Table 3. Risk of Breast Cancer Associated With Migraine History Stratified by NSAID Use

NSAID Use Category	No. of Incident Cases Without a Migraine History	No. of Incident Cases With a Migraine History	Adjusted for Age and Race/Ethnicity		Multivariate Adjusted Analysis*	
			HR	95% CI	HR	95% CI
Not currently using NSAIDs						
Any breast cancer	2,355	247	0.90	0.79 to 1.03	0.89	0.78 to 1.02
Invasive breast cancer	1,930	211	0.94	0.82 to 1.09	0.93	0.80 to 1.07
ER- and PR-positive invasive breast cancer	1,080	105	0.83	0.68 to 1.02	0.79	0.64 to 0.98†
Current NSAID users						
Any breast cancer	1,241	164	0.86	0.73 to 1.02	0.88	0.74 to 1.04
Invasive breast cancer	1,042	135	0.85	0.71 to 1.02	0.87	0.72 to 1.04
ER- and PR-positive invasive breast cancer	613	80	0.87	0.69 to 1.10	0.88	0.69 to 1.12
Current NSAID users for < 3 years						
Any breast cancer	586	57	0.74	0.56 to 0.97†	0.74	0.56 to 0.97†
Invasive breast cancer	488	52	0.81	0.60 to 1.07	0.81	0.60 to 1.08
ER- and PR-positive invasive breast cancer	276	34	0.95	0.66 to 1.35	0.96	0.66 to 1.39
Current NSAID users for ≥ 3 years						
Any breast cancer	655	107	0.96	0.78 to 1.18	0.98	0.79 to 1.21
Invasive breast cancer	554	83	0.89	0.70 to 1.12	0.91	0.72 to 1.15
ER- and PR-positive invasive breast cancer	337	46	0.81	0.60 to 1.11	0.83	0.61 to 1.14

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; HR, hazard ratio; ER, estrogen receptor; PR, progesterone receptor.
*Multivariate adjusted HRs are adjusted for age, race/ethnicity, and the following baseline characteristics: hysterectomy, use of menopausal hormones, alcohol consumption, smoking status, and regular coffee consumption. The 3,332 women with a known NSAID use history but with missing data for one or more of the covariates adjusted for in the multivariate models were excluded from these analyses.
†$P < .05$.

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; as a result of hormonal changes, migraine attacks can be triggered (eg, with declines in estrogen occurring during the natural menstrual cycle) or suppressed (eg, during the third trimester of pregnancy when estrogen levels reach a high steady-state).[6-11] Interestingly, in both this study and the two prior studies evaluating the relationship between migraine and breast cancer, a history of migraine appeared to more strongly related to risk of ER-positive/PR-positive breast cancer, supporting a hormonal basis for this relationship.[1,2] 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, additional studies assessing whether the types and triggers of migraine are associated with breast cancer risk could provide greater insight into the biology underlying the relationship between migraine and breast cancer and specifically into the influence of migraine on risk of ER-positive/PR-positive breast tumors.

It is important to acknowledge the limitations of this study. Information on clinical diagnosis of migraine was based solely on participant recall and is subject to potential bias. Underreporting of migraine is of particular concern, because an estimated 27% to 59% of migraine sufferers are never clinically diagnosed[20-22] and, alternatively, because some diagnosed patients may not have suffered headaches that met established clinical criteria for a migraine diagnosis. Although the extent of this type of misclassification is unknown, it is most likely nondifferential, given the prospective nature of this study. Another potential limitation of this study is that migraine history was only ascertained at baseline, so women diagnosed with migraine after baseline were all classified as not having a migraine history. However, a recent report on the cumulative lifetime migraine incidence among women in the United States indicates that 97% of women ever clinically diagnosed with migraine are diagnosed before age 50 years,[23] and all women enrolled on the WHI OS were 50 years of age or older, which thus limited the impact of the resulting misclassification. The WHI OS did not collect information on the timing, frequency, or intensity of migraine headaches, so the impact of these factors on breast cancer risk could not be assessed. Lastly, although some data on NSAID use were available, duration was only known for women who reported currently using NSAIDs at study enrollment. However, on the basis of a recent meta-analysis of studies evaluating the relationship between NSAID use and breast cancer risk, it is unclear the extent to which duration of use is related to the overall 12% reduced risk of breast cancer risk associated with any NSAID intake.[14] In an analysis that used WHI OS data, though, only NSAID use for 5 years or longer was associated with a lower risk of breast cancer.[15]

This study provides support for two initial reports from case-control studies that migraine is associated with a lower risk of breast cancer. All three studies also consistently observed that this relationship is somewhat stronger for hormone-receptor–positive tumors.[1,2] Here, we expand our knowledge of this association by demonstrating that this relationship is independent of NSAID use and exposure to common migraine triggers, including exogenous hormones and alcohol. However, additional work is needed to resolve what accounts for this relationship, such as differences in hormonal milieus or sensitivities in migraineurs compared with women who do not suffer from migraines, to convey a lower risk of breast cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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