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 effect of migraine triggers, which 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 multicenter 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.

Introduction

In a recent case-control study of postmenopausal 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 with 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 effects of both endogenous hormone levels (2) and exogenous hormonal exposures on breast cancer (3, 4) are well-established. Migraine is a neurologic disorder that is twice to thrice 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% to 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 effect of common migraine triggers, which are also established breast cancer risk factors, on this relationship.

Materials and Methods

The Women’s Contraceptive and Reproductive Experiences Study is a population-based case-control study that recruited women ages 35 to 64 years diagnosed with invasive breast cancer between 1994 to 1998 from five metropolitan areas: Atlanta, Detroit, Los Angeles, Philadelphia, and Seattle. Details of the methods used in this study have been previously published (13). Cases were ascertained through Surveillance, Epidemiology, and End Results 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 invasive breast cancer between 1994 to 1998 from five metropolitan areas: Atlanta, Detroit, Los Angeles, Philadelphia, and Seattle. Details of the methods used in this study have been previously published (13). Cases were ascertained through Surveillance, Epidemiology, and End Results 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.

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estimates by >10%, and so none were included as con-
founders in the final statistical models. Effect modifi-
cation was assessed using likelihood ratio testing, and
none of these variables were observed to be statistically
significant effect modifiers (all Pinteraction > 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).

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 with
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 pre-
menopausal (OR, 0.79; 95% CI, 0.67-0.93) and postmen-
opausal 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 men-
opausal hormone therapy, and for each of these sub-
groups, 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), although the risk estimate for ER+/PR−
tumors was within the limits of chance (Table 3). Stat-
istically 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
histologic type; compared with nonmigraineurs 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 ob-
servation 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 because the pro-
portion of women reporting a history of migraine who
actually only suffered nonmigraine headaches may be
higher among the nonmedication users compared with
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

| Table 2. Relationship between self-reported history of migraine and breast cancer risk |
|---------------------------------|-----------------|----------------|
|                                | Controls (n = 4,678) | Cases (n = 4,568) | OR* (95% CI) |
| Never diagnosed with migraine | 3,759 (80)        | 3,870 (85)       | 1.00 (Reference) |
| Ever diagnosed with migraine  | 919 (20)          | 698 (15)         | 0.74 (0.66-0.82)$^*$ |
| Age at migraine diagnosis, years |
| <20                            | 201 (4)           | 166 (4)          | 0.81 (0.65-1.00)$^*$ |
| 20-39                          | 513 (11)          | 365 (8)          | 0.69 (0.60-0.80)$^*$ |
| ≥40                            | 205 (4)           | 167 (4)          | 0.78 (0.64-0.97)$^*$ |
| Ever use of prescription migraine medications |
| No                             | 201 (4)           | 176 (4)          | 0.85 (0.69-1.05)$^*$ |
| Yes                            | 717 (15)          | 519 (11)         | 0.70 (0.62-0.79)$^*$ |

$^*$ORs and 95% CIs are adjusted for age, race, and study site.
$^!P < 0.05.$

$^?$P values are from tests for homogeneity of the odds ratios.
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.

Because nonsteroidal anti-inflammatory drugs (NSAID) 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. Although 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 (17). 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). Because many classes of drugs can be used for migraine, it is unclear what proportion of migraineurs actually use NSAIDs at a level that biologically could confer a reduced risk of breast cancer. Nevertheless, further studies are needed to assess the effect of NSAID use on the relationship between migraine and breast cancer.

### Table 3. Relationship between self-reported clinical history of migraine and risk of breast cancer by ER/PR status and histology

<table>
<thead>
<tr>
<th>Controls (n = 4,678)</th>
<th>ER+/PR+ (n = 2,128)</th>
<th>ER+/PR− (n = 369)</th>
<th>ER−/PR− (n = 1,082)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n (%)</strong></td>
<td><strong>n (%)</strong></td>
<td><strong>OR</strong> (95% CI)</td>
<td><strong>n (%)</strong></td>
</tr>
<tr>
<td><strong>Never diagnosed with migraine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3,759 (80)</td>
<td>1,814 (85)</td>
<td>1.00 (Reference)</td>
<td>307 (83)</td>
</tr>
<tr>
<td><strong>Ever diagnosed with migraine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>919 (20)</td>
<td>314 (15)</td>
<td>0.69 (0.60-0.80)</td>
<td>62 (17)</td>
</tr>
<tr>
<td><strong>Age at migraine diagnosis, years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>201 (4)</td>
<td>64 (3)</td>
<td>0.66 (0.50-0.88)</td>
<td>15 (4)</td>
</tr>
<tr>
<td>20-39</td>
<td></td>
<td></td>
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<tr>
<td>513 (11)</td>
<td>166 (8)</td>
<td>0.65 (0.54-0.79)</td>
<td>29 (8)</td>
</tr>
<tr>
<td>≥40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>205 (4)</td>
<td>84 (4)</td>
<td>0.81 (0.62-1.05)</td>
<td>18 (5)</td>
</tr>
</tbody>
</table>

**P value for difference across age categories**

| **Ever use of prescription migraine medications** | | | | | | |
| No | | | | | | |
| 201 (4) | 73 (3) | 0.74 (0.56-0.98) | 21 (6) | 1.27 (0.80-2.03) | 33 (3) | 0.70 (0.48-1.02) |
| Yes | | | | | | |
| 717 (15) | 240 (11) | 0.67 | 41 (11) | 0.70 (0.50-0.98) | 148 (14) | 0.87 (0.72-1.06) |

**P value for difference across medication categories**

<table>
<thead>
<tr>
<th>Controls (n = 4,678)</th>
<th>Ductal carcinoma (n = 3,457)</th>
<th>Lobular carcinoma (n = 353)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n (%)</strong></td>
<td><strong>n (%)</strong></td>
<td><strong>OR</strong> (95% CI)</td>
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<tr>
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<td>3,759 (80)</td>
<td>2,929 (85)</td>
<td>1.00 (Reference)</td>
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<tr>
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<tr>
<td>201 (4)</td>
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<td>0.86 (0.69-1.07)</td>
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<tr>
<td>513 (11)</td>
<td>271 (8)</td>
<td>0.68 (0.58-0.79)</td>
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<tr>
<td>≥40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>205 (4)</td>
<td>123 (4)</td>
<td>0.77 (0.62-0.97)</td>
</tr>
</tbody>
</table>

**P value for difference across age categories**

| **Ever use of prescription migraine medications** | | | | | | |
| 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) | 60 (11) | 0.68 (0.51-0.90) |

**P value for difference across medication categories**

*ORs and 95% CIs are adjusted for age, race, and study site.*

† P < 0.05.

‡ P values are from tests for homogeneity of the odds ratios.
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; refs. 7-12). 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 because approximately 27% to 59% of migraine sufferers are never clinically diagnosed (5, 18, 19). However, this type of misclassification would most likely be nondifferential, 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 NSAIDs, medications commonly used by migraineurs and which are associated with an ~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 such as more frequent NSAID use among migraineurs, or if there are different hormonal milieu or sensitivities in migraineurs compared with women who do not suffer from migraines that convey a lower risk of breast cancer.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Acknowledgments
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References
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