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Migraine and breast cancer risk: a meta-analysis of observational studies based on MOOSE compliant

Xiujuan Wu, MM, Minghao Wang, MM, Shifei Li, MM, Yi Zhang, MD*

Abstract

It has long been speculated that migraine may contribute to an increased risk of breast cancer; however, results from previous studies have been inconclusive. To definitively interrogate this issue, we performed a meta-analysis to assess the correlation between these 2 diseases.

Medline and PubMed were searched to identify relevant studies that had been published until October 2015. Based on a random effects model, relative risk (RR) and the corresponding 95% confidence interval (CI) were used to evaluate the pooled risk.

A total of 7 studies involving 17,776 cases and 162,954 participants were included. Our study revealed that there was an inverse relationship between migraine and total breast cancer risk, with RR (95%CI) was 0.78 (0.66, 0.92). In subgroup-analysis, such an inverse relationship was also identified in the ductal and lobular carcinoma, case–control studies, and the ER^+/PR^+ breast cancer. Little evidence indicative of a publication bias was uncovered.

In conclusion, our study implicates a statistically significant inverse association between migraine and the risk of breast cancer. However, larger prospective cohort studies concerning other geographic populations to assess the association between migraine and the breast cancer risk are warranted.

Abbreviations: RR = relative risk, CI = confidence interval, OR = odds ratio, ER = estrogen receptor, PR = progesterone receptor, NSAIDs = nonsteroidal anti-inflammatory drugs.

Keywords: breast cancer, meta-analysis, migraine

1. Introduction

As a common neurologic disease, migraine is clinically manifested as throbbing headache of varying intensity, often accompanied by photophobia tears, nausea, and vomiting. The incidence of migraine in women is 2–3 times higher than that in men,[1,2] which may largely result from the fluctuation of estrogen that has been shown to influence the frequency of migraine occurrences.[3] Indeed, reduced levels of estrogen as a consequence of administration of oral contraceptives or of occurrence of menstruation can significantly enhance the likelihood of migraine[4,5]; on the contrary, increased levels of estrogen resulting from pregnancy can always mitigate the intensity and sufferings of migraine.[6]

As the most common cancer among women, breast cancer represents a type of notorious estrogen-related malignancies that has adversely influenced a wide population across the globe.[7] Previous studies have demonstrated that estrogen levels appear to be associated with the risk of breast cancer. Furthermore, it has been established that exposure to higher levels of estrogen can increase the breast cancer risk.[8] Considering that estrogen seem to contribute to the pathogenesis of both migraine and breast, it has been hypothesized that migraine may be also correlated with breast cancer risk. Indeed, the past decade has witnessed an exponentially increased interest in these 2 types of disorders, and their correlation has been extensively interrogated by a large body of studies.[9–13] An inverse relationship between migraine and the risk of breast cancer has been suggested by multiple reports[9,10]; however, additional studies have contradictorily shown otherwise.[11,12] Consequently, the underlying correlation between migraine and the breast cancer risk remain to be thoroughly characterized. A potential explanation for the inconclusiveness of previous studies lies in the relatively small sample size involved in these separate studies. Given a large amount of new evidence that has recently emerged, we set out to conduct a meta-analysis to uncover the relationship between migraine and breast cancer risk.

2. Methods

2.1. Literature search

Databases from Medline and PubMed were utilized to identify published studies (until October 2015) that have investigated the relationship between migraine and the risk of breast cancer, with "migraine" and "breast cancer" as keywords. In addition,

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Breast Disease Center, Southwest Hospital, Third Military Medical University, Chongqing, China.

* Correspondence to Yi Zhang, Breast Disease Center, Southwest Hospital, Third Military Medical University, Chongqing, China (e-mail: zy53810@163.com).

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references cited within relevant reviews were retrieved, and we contacted the authors of the primary studies for additional information.

2.2. Inclusion criteria

Previous studies were included for our meta-analysis if they met the following criteria: the study comprised a case-control or cohort study design; estrogen exposure history with respect to migraine development is available; the primary outcome of interest was risk of breast cancer; the relative risk (RR) or odds ratio (OR) and the corresponding 95% confidence interval (CI) of the breast cancer associated with migraine history were reported (alternatively, they could be determined through calculation); and studies should be published in English.

2.3. Study selection

Initially, we reviewed the titles and abstracts to identify potential studies to be included in our meta-analysis. For those that were difficult to determine with titles and abstracts only, full-text assessment was conducted. All published studies were reviewed and evaluated by 2 authors. All discrepancies were resolved by discussion. Because the data included in this study were retrieved from the literature, ethical approval from ethics committees was not needed.

2.4. Data extraction and validity assessment

The following information was collected from the included studies: the last name of the first author, publication year, country, mean age of the participants, sample size, RR (OR) and the corresponding 95% CI of the breast cancer associated with history of migraine.

The key components of study design, including selection of patient populations, ascertainment of exposure factors and clinical outcome and duration of follow-up examination, were used to estimate the quality of primary studies, instead of the aggregate scores.[14]

2.5. Statistical analysis

All analyses were performed using stata 12.0 (StataCorp., College Station, Texas). The combined RR and the corresponding 95% CI was used to measure the association between migraine and the risk of breast cancer by assuming a random-effects model that takes into account within-study and between- study variation.[15] Homogeneity test was performed with the use of Q and I^2 statistics and subgroup analysis carried out to identify, if any, the source of heterogeneity and the effect of potential factors on the overall risk estimate. Additionally, a sensitivity analysis was used to investigate the influence of a single study on the overall risk estimate by omitting one study in turn. Publication bias was determined by Begg and Egger test. P value less than 0.05 was considered as statistically significant in our study.

3. Results

A total of 203 potential articles from PubMed and Medline were initially identified, most of which were, however, excluded primarily because they were reduplicated, review articles, reports, not relevant to our analysis, or chiefly animal studies. The exclusion led to 7 studies (4 case–control and 3 cohort studies) involving 17,776 breast cancer cases and 162,954 participants to be ultimately selected for our subsequent analysis.[9–13,16,17]

Table 1 summarizes the general characteristics for the 7 studies that were included in our meta-analysis. They were published between 2008 and 2015 in English. Among these 7 studies,

Table 1

The characteristics of the included studies.

Study, y	Population	Study design	Age range	Sample Size (n) case–control or participants	Adjusted RR (95%CI)	ER/PR status	Migraine medications use	Variables used in multivariate model
Mathes et al (2008)	American	Case–control	55–79	1938/1474	Post. 0.67 (0.57, 0.80)	Yes	Yes	Age, reference year
Li et al (2009)	American	Case–control	35–64	4568/4678	All. 0.74 (0.66, 0.82)	Yes	Yes	Age, race, study site
Li et al (2010)	American	Cohort	50–79	4006/91116	Post. 0.89 (0.80, 0.98)	Yes	Yes	Age, race, hysterectomy, menopausal hormones and NSAID use, alcohol consumption, smoking, coffee consumption
Winter et al (2013)	American	Cohort	>45	2278/39696	All. 1.10 (0.99, 1.22)	Yes	No	Age, BMI, smoking, alcohol consumption, postmenopausal status, age at menarche, age at menopause, postmenopausal hormone, NO. of pregnancies, age at first pregnancy, family history of BC history of benign breast disease
Lowry et al (2014)	American	Case–control	55–74	715/376	All.0.62 (0.49, 0.78)	Yes	No	Age, county of residence, reference year, BMI
Winter et al (2014)	American	Cohort	25–42	3924/116430	All. 0.96 (0.88, 1.04)	Yes	No	Age, BMI, family history of breast cancer, parity, age at first birth, breastfeeding, NSAID use, oral contraceptive use, age at menarche, smoking status, alcohol, menopausal status, Estrogen and progesterone use and other hormone use
Ghorbani et al (2015)	Iranian	Case–control	20–60	347/300	0.51 (0.40, 0.66)	No	No	No

BMI = body mass index, CI = confidence interval, No = no statement, NSAID = nonsteroidal anti-inflammatory drug, RR = relative risk, Yes = reported.

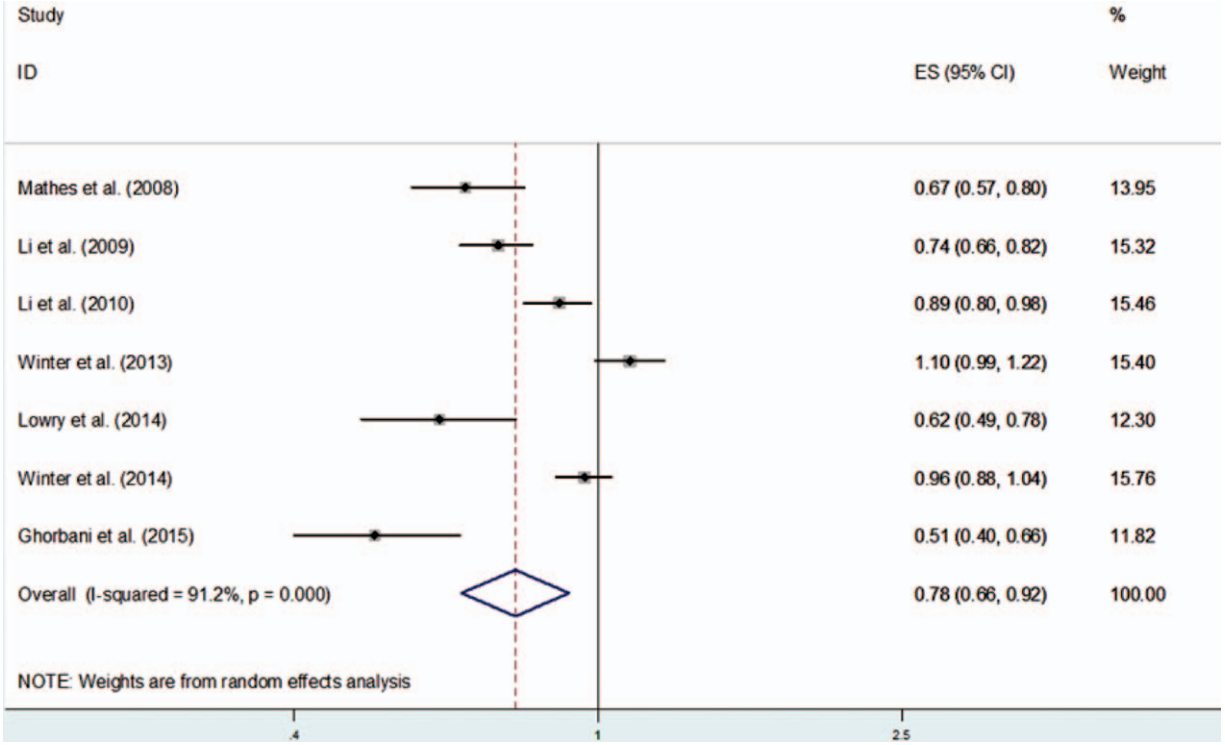

Figure 1. Forest plot for the relationship between migraine and total breast cancer risk.

5 showed that migraine was associated with reduced risk of breast cancer risk,[9–11,13,17] whereas the other 2 contradictorily implicated no correlation between migraine and breast cancer risk.[12,16] Six of them were based on the Americans,[9–13,16] and 1 was among Iranians.[17] All the RRs were based on the multivariable adjusted, except for one that did not report values. All studies were evaluated and classified with our criteria as high quality.

Figure 1 presents the analysis results that uncovered the relationship between migraine and total breast cancer risk. Based on a random-effects model, we revealed a statistically significant inverse relationship between migraine and total breast cancer risk, with RR (95%CI) being 0.78(0.66, 0.92; $P<0.05$). However, the evidence suggestive of significant heterogeneity was also found among these studies ($I^2=91.2\%$; $P=0.000$).

Table 2 summarizes the results of subgroups analyses. Based on the histological classification of breast cancer, we divided these studies into 3 subgroups, and our results demonstrated that migraine not only reduced the risk of ductal carcinoma, but also alleviated that of lobular carcinoma, with RR (95%CI) being 0.77 (0.62, 0.97) and 0.72 (0.61, 0.87), respectively. Notably, the correlation between migraine and breast cancer risk appeared to be study design dependent as the inverse relationship was detected only in case–control studies, but not in cohort counterparts, as evidenced by RR (95%CI) of 0.65 (0.56, 0.75) and 0.98 (0.87, 1.10), respectively. With respect to ER/PR

Table 2

Subgroup analysis of the association between migraine and breast cancer risk.

Group	No. of study	RR (95% CI)	*P* for heterogeneity	I^2
Histology				
Ductal carcinoma	7	0.77 (0.62, 0.97)	0.000	92.8%
Lobular carcinoma	7	0.72 (0.61, 0.87)	0.045	53.3%
Study design				
Cohort	3	0.98 (0.87, 1.10)	0.015	76.1%
Case–control	4	0.65 (0.56, 0.75)	0.045	62.7%
ER/PR status				
ER^+/PR^+	5	0.83 (0.70, 0.98)	0.000	83.4%
ER^+/PR^-	5	0.86 (0.69, 1.07)	0.108	47.3%
ER^-/PR^-	5	0.99 (0.83, 1.18)	0.081	51.8%
Migraine medications				
Yes	3	0.75 (0.66, 0.86)	0.179	38.8%
No	3	0.76 (0.63, 0.92)	0.042	63.4%
Postmenopausal Women	3	0.88 (0.68, 1.12)	0.000	91.4%

ER= estrogen receptor, No = no statement, PR= progesterone receptor, Yes = reported.

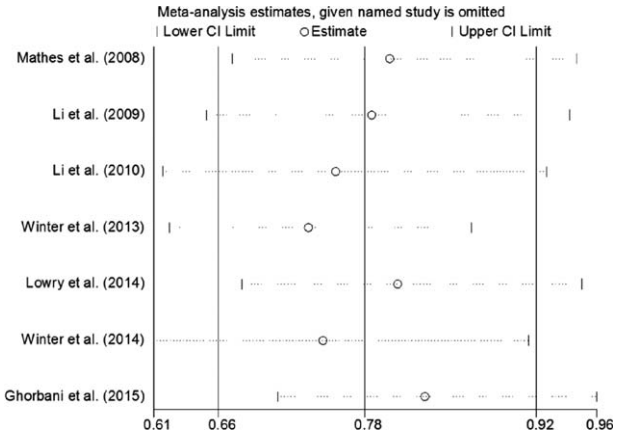

Figure 2. Forest plot for sensitivity analysis.

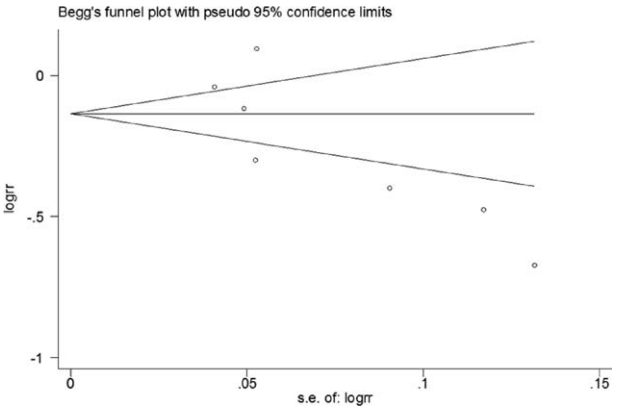

Figure 3. Forest plot for Publication bias.

status, our results only supported an significantly inverse association between migraine and the risk of the ER+/PR+ breast cancer, as identified with RR (95%CI) being 0.83 (0.70, 0.98). Intriguingly, this inverse association was not linked to the administration of migraine medications. In addition, this inverse association was not found among the postmenopausal women, RR (95%CI) was 0.88 (0.68, 1.12).

In addition, sensitivity analysis was conducted to assess the influence of each individual study on combined RR by removing one study at a time. Our results showed that the combined RRs were essentially unaltered as no single study significantly changed the combined results, which together indicated statistical stability and reliability of our analysis results. Figure 2 presented the results of sensitivity analysis.

Furthermore, Begg funnel plot showed a low probability of publication bias (Fig. 3), which is in line with Egger regression test that indicated little evidence of publication bias ($P = 0.051$).

4. Discussion

In the present study, 7 studies were identified and included from PubMed and Medline for a meta-analysis that concerns the association between migraine and the risk of breast cancer. Our analysis demonstrated a significantly inverse relationship between migraine and the total risk of breast cancer. Notably, such an inverse relationship was identified in the case–control studies, ductal and lobular carcinoma, and ER^+/PR^+ breast cancer. The evidence indicative of strong heterogeneity was positively detected among all 7 studies, which could be explained by the differences in ages, study design, adjustment for confounding factors, and other unknown factors.

It must be noted that, although our results indicate a strong association between migraine and reduced risk of breast cancer, the underlying mechanism remains largely unclear. One potential mechanistic speculation may concern the contributing role of estrogen in the pathogenesis of both types of diseases. This is supported by a large amount of evidence that has shown the pathological relevance of hormones to increasing the risk of breast cancer as well as the causal relationship between hormonal decline and migraine.[18–20] Increased exposure to estrogen is a defining risk of breast cancer[21]; however, a short-term transient decline of estrogen levels is believed to induce migraine.[22] It is anticipated that those women who have a history of exposure to high levels of estrogen are less likely to experience great fluctuations in estrogen. Therefore, the frequency of migraine may be correlated with decreased risk of breast cancer. In addition, high levels of serotonin is linked to increased risk of breast cancer[23]; in contrast, low levels of serotonin can increase the frequency of migraine.[24] Combined together, these results lead to our speculation that increased frequency of migraine is related to reduced risk of breast cancer that may function through a yet fully characterized serotonin-mediated mechanism.

A second mechanistic explanation may lie in the observation that patients with migraine tend to avoid risk factors that contribute to the initiation and development of breast cancer, including smoking and alcohol consumption. Indeed, numerous studies have shown that consumption of beer and wine represents an important risk factor for breast cancer.[25,26] Furthermore, the risk of breast cancer in women with a smoking history is 4.02 times higher than that in nonsmoking women.[27] However, patients with migraine tend to limit or avoid alcohol consumption and smoking because this will induce and aggravate the symptoms of migraine.[28,29] By reducing the chance of becoming exposed to these risk factors for breast cancer, this may partially explain why a migraine history is correlated with decreased risk of breast cancer.

In addition, treatment for migraine commonly involves the use of nonsteroidal anti-inflammatory drugs (NSAIDs), which have been consistently shown to confer reduced predisposition for breast cancer initiation and development.[30,31] This may provide another possible explanation that underlies the association between migraine and decreased breast cancer risk.

It should be pointed out that our results need to be interpreted with precautions, particularly with respect to the evidence derived from case–control studies. In these case–control studies, breast cancer cases were identified through cancer registries, whereas control patients selected randomly. It is entirely possible that these breast cancer patients may have an underestimated migraine history, and/or control patients have an overreported migraine history. Additionally, undefined confounding and selection bias may potentially be present that have influenced the results.

Our results revealed an inverse relationship only between migraine and ER^+/PR^+ breast cancer risk. This is consistent with several previous studies,[9,10,12,16] in which this inverse relationship was also identified. They further demonstrated that the relationship function through a hormone-based mechanism; however, the precise biological and pathological underpinnings remain to be fully characterized. It is well known that migraine is a heterogeneous disease that cannot be entirely explained by

hormonal changes. Thus, additional studies focusing on the types and triggers of migraine may provide better explanations for the association between migraine and ER^+/PR^+ breast cancer risk.[12]

As a highly debated unanswered question, the correlation between migraine and the risk of breast cancer has been controversial for many years. Because of the insufficient statistical power that each individual study entails, we conducted a meta-analysis to include multiple independent studies to identify this association. Our investigation covers a larger sample size, thereby enhancing the statistical persuasion that led to more reliable results and better-corroborated conclusions. Moreover, the strategy we utilized to identify the significant inverse association between migraine and breast cancer risk may serve as an available guide for future epidemiologic investigations. However, several potential limitations of the present approach should be considered. Foremost, the majority of these studies have a case–control design, and the information regarding migraine history was based on self-report; thus, the recall bias after diagnosis of breast cancer cannot be excluded. Second, given that about 27% to 59% of patients with migraine are never clinically diagnosed,[32] we could not evaluate the relationship between migraine history and breast cancer risk among these individuals. Furthermore, the evidence for significant heterogeneity was found, which may result from distinct study designs and status of hormone receptor status. However, significant evidence of heterogeneity also exists among the cohort studies. Other uncontrolled and unmeasured factors may equally influence the heterogeneity. For example, the information concerning variables, such as nutrition, lifestyle, and family history, was not reported in the original studies. In addition, although there was little evidence of publication bias among these studies, the number of studies available for our meta-analysis was very limited. Finally, most of the included studies were conducted in Americans, and additional studies focusing on other geographic populations are much needed to verify the results.

In conclusion, this meta-analysis strongly implicates a significantly inverse association between migraine and the risk of breast cancer. However, larger prospective cohort studies concerning other geographic populations to assess the association between migraine and the breast cancer risk are warranted.

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