Published in final edited form as:
*Cancer Causes Control*. 2014 December ; 25(12): 1707–1715. doi:10.1007/s10552-014-0479-y.

# The risk of breast cancer associated with specific patterns of migraine history

**Sarah J. Lowry**[1,2], **Kathleen E. Malone**[1,2], **Kara L. Cushing-Haugen**[1], and **Christopher I. Li**[1,2]

[1]Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N., Seattle, WA 98109

[2]Department of Epidemiology, School of Public Health and Community Medicine, University of Washington

## Abstract

**Purpose—**Studies have suggested that a history of migraines may be associated with a lower risk of some types of breast cancer, though biological mechanisms are unclear. Identifying specific characteristics of migraines which are most strongly associated with breast cancer risk could improve our understanding of this relationship.

**Methods—**We ascertained specific characteristics of women's migraine histories (severity, timing features, presence of migraine aura). We used polytomous logistic regression to estimate the risk of ER+ ductal, ER- ductal, ER+ lobular, and ER+ ductal-lobular breast cancer associated with self-reported characteristics of migraine history. 715 breast cancer cases (276 ER+ ductal, 46 ER- ductal, 191 ER+ lobular, 202 ER+ ductal-lobular) and 376 controls ages 55-74 years were included in this population-based case-control study.

**Results—**Compared to women without a migraine history, women with a >30-year history of migraines had a 60% (95% CI: 0.2-0.6) lower risk of ER+ ductal breast cancer; those who had their first migraine before age 20 had 50% lower risks of ER+ ductal and ER+ lobular breast cancer (both 95%CIs: 0.3-0.9), and women who experienced migraine with aura had 30% (95%CI 0.5-0.98) and 40% (95%CI: 0.4-0.9) lower risks of ER+ ductal and ER+ lobular breast cancer, respectively.

**Conclusion—**The lower risk of ER+ breast cancer associated with migraine appears to be limited to those women with early onset or long duration of migraine history, or those who experienced migraine with aura. This expands our understanding of the relationship between migraine and breast cancer and provides additional insight into potential underlying biological mechanisms.

### Keywords

migraine; breast cancer; case-control; hormones; estrogen; postmenopausal

Corresponding author: Sarah J. Lowry, 1100 Fairview Ave. N., M4-B874, Seattle, WA 98109, Phone: 206-667-4153; Fax: 206-667-5948; slowry@fhcrc.org.

**Disclosures:** NONE

The authors state they have no conflicts of interest.

## Introduction

Four studies have evaluated the relationship between migraine and breast cancer,[1-4] of which three observed that women with a history of migraine have an 11-33% lower risk of breast cancer.[1-3] The three studies which reported this association suggest that it is stronger for ER+/PR+ breast cancer, and that it does not vary by menopausal status, age at first migraine, use of prescription medications for migraine, use of NSAIDS, or among women who avoided migraine triggers (alcohol, smoking, exogenous hormones). [1-3] The biological mechanisms underlying the potential association between migraine and breast cancer risk are uncertain, but estrogen is known to influence risk of both breast cancer and migraine. Risk of breast cancer is higher in women with greater lifetime cumulative exposure to estrogen.[5] Estrogen, and fluctuations in estrogen levels, also appear to play a role in migraine etiology. [6,7] For example, migraines are more frequent in women than in men,[8] and among women they are more common during the years of menstruation,[8] within 2 days of the start of the menstrual cycle,[7] and, in oral contraceptive users, during the estrogen-free week.[9] In contrast, during periods of time when estrogen levels remain relatively constant, such as pregnancy when they remain at a high level and after menopause when they stay chronically low, migraines are less frequent.[10] There is evidence that both estrogen supplementation, as well as down-regulation of estrogen production and withdrawal of supplemental estrogen, can trigger migraine attacks in some women. (as reviewed by Brades, et al.[11]) However, migraines are heterogeneous and their presentation can vary in terms of symptoms, age at onset, frequency, and duration. Only one of the prior studies of migraine and breast cancer investigated relationships between specific migraine characteristics and breast cancer risk, but did not stratify these analyses by the different types of breast cancer. That study observed little evidence for an association between breast cancer overall and migraine with or without aura, or migraine frequency, and did not assess other aspects of migraine history including duration or age at first migraine.[4]

The purpose of this study was to assess whether certain migraine characteristics are more strongly associated with breast cancer risk, in order to expand our understanding of the potential link between migraine and breast cancer. To determine whether specific aspects of migraine history could help explain the link with breast cancer risk, we recontacted participants from one of the previous studies[12] to learn more specific details of their migraine experience.

## Methods

This analysis was an extension of a completed population-based study of breast cancer (Seattle area Hormone And Reproductive Epidemiology breast cancer study, or SHARE study) and details regarding the parent study's design and eligibility criteria have been published previously. [12] This study population was also included in a previous report on the association between migraine and breast cancer,[3] and for the current study, participants were recontacted to obtain more detailed information on specific aspects of migraine history (e.g. duration, timing, presence of aura, frequency, intensity).

First, we will briefly summarize methods in the original SHARE study. Cases were women diagnosed with a primary invasive ductal or lobular breast cancer between 1/1/2000 and 4/21/2004 between the ages of 55 and 74 years, using the Seattle-Puget Sound Surveillance Epidemiology and End Results (SEER) cancer registry. Of the eligible women identified, 83% were interviewed, including 524 with ductal, 324 with lobular, and 196 with mixed ductal-lobular breast cancer. Because ductal breast cancer is more common, all lobular and mixed ductal-lobular cases were included, and a randomly selected sample of ductal cases was frequency-matched 1:1 by 5-year age group to the combined group of lobular and mixed ductal-lobular cases. Population-based controls were then identified by random-digit dialing within the same 3 counties of residence as cases (King, Pierce and Snohomish), and were frequency-matched to cases on age and reference year (assigned to controls to be similar to the distribution of reference dates among cases). Women who had previously been diagnosed with breast cancer (invasive or in-situ) were excluded from the control group, as were those without a landline home phone number. Cases and controls in the original SHARE study completed an interview (between 2/2001 and 4/2005) which included questions about reproductive history, medical history, lifestyle factors including smoking and alcohol, demographic factors, and weight and height.

For the present report, in order to investigate whether certain aspects of migraine history are more strongly associated with breast cancer risk, we recontacted women from the original SHARE study to obtain more detailed information on their headache histories. Of the original 1,513 participants who had consented to be recontacted for a future study, 380 of 469 controls (81%) and 763 of 1,044 cases (73%) were successfully re-interviewed (9/2008 to 1/2011), this time about specific migraine characteristics. The difference in response rates was primarily attributable to the higher number of deaths in the cases compared to controls (14% vs. 6% respectively) as refusal rates were similar in both groups (13% for controls and 12% for cases). The interview was conducted by telephone and lasted approximately 30 minutes. It was structured to be identical for all women regardless of whether or not they reported a history of migraine in the original SHARE interview. In the follow-up interview, we assessed multiple measures of migraine history including self-reported history, as well as an evaluation of whether the types of headaches women experienced met the established clinical criteria for migraine. The self-reported migraine variable allows for comparability with prior studies, most of which have used self-report. The clinical definition is thought to be more accurate, as approximately 50% of migraine sufferers are unaware that their headaches meet the clinical criteria for migraine.[13] (Additionally, approximately 50% of migraine sufferers have never been clinically diagnosed with migraine.[14]) We also wanted to compare the two measures (self-report vs. clinical definition).

In the follow-up questionnaire, we ascertained self-report of migraine with the question, "*Before (REFDATE) did you ever have a migraine?*". For ascertainment of clinically defined migraine, participants were asked to provide detailed information on headache history, including information on the severity, duration and timing of headaches; any accompanying symptoms such as nausea or vomiting, visual disturbances, or sensitivity to light or sound; use of both prescription and over-the-counter medications to prevent or treat migraines; and family history of migraine. We defined women as having experienced a

history of migraine without aura if they had ≥5 attacks, lasting at least 4 hours, with moderate or severe pain intensity, and **either** (A) nausea/vomiting during a headache **or** (B) sensitivity to light or sound during a headache, **AS WELL AS** (C) had at least one of the following: headache located on one side of the head, headache that was made worse by routine physical activity, and throbbing or pounding headache. This definition is slightly more stringent than established clinical criteria, in that a history of moderate to severe headache pain was required instead of optional.[15] Migraine with aura was defined as at least 2 headaches accompanied by any visual disturbances such as flickering lights, spots, and lines or loss of vision before or during a headache, not attributed to other disorders. We asked a series of specific questions for each criterion to ascertain detailed migraine histories, such as "*Before (REFDATE) did you ever have a headache?*", "*Did you ever have a moderate to severe headache?*" and,"*Did you ever experience nausea or vomiting when you had a headache?*" etc. We also asked specific questions about the timing and severity of migraines, for example, "*How old were you when you first had a (moderate or severe headache/migraine)?*" and, "*When you were (AGE), on average, how many (moderate/severe headaches/migraines) did you have per week, month, or year?*" and "*On a scale of 0-10, on average how painful were these (headaches/migraines)? 0 = no pain at all, and 10 = pain as bad as it can be*." and, "*How old were you when the frequency or severity of your (headaches/migraines) changed from what you just told me?*" If a subject's migraine frequency or severity changed over time, we collected data on each time period, and used the responses to establish the lifelong history of each subject's migraine experience. We also ascertained menstrual migraines (i.e. all migraines occur within 2 days before or after the 1$^{st}$ day of menstruation) as well as menstrually related migraines (i.e. migraines occur both at menstruation and at other times), and then combined women from these 2 groups for analyses of menstrual/menstrually-related migraines.

We defined case groups as ER+ ductal, ER- ductal, ER+ lobular, and ER+ mixed ductal-lobular because only a subset of ductal cases were included in the sample, and therefore we could not focus on all ER+ or all ER- cases. ER- lobular and ER- mixed ductal-lobular cases were not included in subtype analyses because there were only 12 such cases total.

Polytomous logistic regression was used to calculate relative risks (RRs) and 95% confidence intervals (CIs) to estimate the risks of ER+ ductal (n=276), ER+ lobular (n=191), ER- ductal (n=46), and ER+ mixed ductal-lobular (n=202) breast cancer associated with various aspects of migraine history. Analyses include 376 controls and 715 cases, as we excluded cases not in one of the breast cancer subgroups listed above (n=37), as well as subjects missing data on clinical criteria for migraine (1 control, 4 cases), or on confounders which were included in the models (3 controls, 7 cases). We adjusted for an a *priori* set of confounders in all analyses, including age, county of residence, reference year, and body mass index (BMI). Several other variables, when adjusted for, did not change the main effect estimates by 10% or more, and thus were not included in the model (alcohol use, smoking, number of pregnancies, age at first pregnancy, OC use, HRT use, and ages at menopause and menarche). Secondary analyses were conducted adjusting only for age, for the sake of comparability with other studies.[4] Confounding variables were categorized as shown in Table 1. Information on these factors was collected during the original SHARE

study. We also conducted some analyses stratified by smoking vs non-smoking, and by alcohol use, to assess potential effect modification by smoking and by alcohol use. All analyses were performed using Stata 12 (StataCorp, College Station, TX).

## Results

Controls, ER+ ductal cases, ER+ lobular cases, and ER+ mixed ductal-lobular cases were similar with respect to a number of demographic characteristics and breast cancer risk factors including age, education, race, OC and HRT use (Table 1). In contrast, compared to these four groups the ER- ductal cases were somewhat more likely to be younger, less educated, and non-white, to have used oral contraceptives, and never to have used menopausal hormone therapy. ER+ ductal, ER+ lobular, and ER+ mixed ductal-lobular cases were more likely to be nulliparous, current users of estrogen plus progestin menopausal hormone therapy, and to consume at least 7 alcoholic beverages weekly, compared to controls and ER- ductal cases.

We assessed breast cancer risk in relation to two measures of migraine history (Table 2): self-reported migraine, as well as whether self-reported symptoms met the clinical criteria for migraine. Prior literature suggests that 50% of migraineurs are not aware their headaches are migraines,[13] and that migraine is undiagnosed in ∼50% of migraine sufferers.[14] Self-reported and clinically defined migraine measures were moderately correlated (kappa = 0.49).

After adjusting for age, county of residence, reference year, and BMI, women who met the clinical criteria for migraine had a lower risk of ER+ ductal (RR: 0.7, 95% CI: 0.5-1.0) and suggested lower risk of ER+ lobular (RR: 0.8, 95% CI: 0.5-1.1), but not ER- ductal (RR: 1.4, 95% CI: 0.8-2.6) or ER+ mixed ductal-lobular (RR: 1.0, 95% CI: 0.7-1.4) breast cancer (Table 3). Self-reported history of migraine was associated with an even lower risk of ER+ ductal (RR: 0.6, 95% CI: 0.4-0.9) and ER+ lobular (RR: 0.5, 95% CI: 0.3-0.8), and a statistically nonsignificant lower risk of ER+ mixed ductal-lobular (RR: 0.7, 95% CI: 0.5-1.1) and ER- ductal breast cancer (RR: 0.7, 95% CI: 0.3-1.5).

Women who experienced migraine without aura did not have an altered risk of any type of breast cancer, whereas women who had ever experienced migraine with aura had a lower risk of ER+ ductal and lobular breast cancers ($RR_{ductal}$: 0.7, 95% CI: 0.5-0.98, and $RR_{lobular}$: 0.6, 95% CI: 0.4-0.9; Table 4). Additionally, women who experienced their first migraine before the age of 20 had a lower risk of ER+ ductal and ER+ lobular (RR: 0.5, 95% CI: 0.3-0.9 for both), and there was a suggestion of a reduced risk of ER+ mixed ductal-lobular that was within the limits of chance (RR: 0.6, 95% CI: 0.3-1.1). However, no statistically significant trends with respect to age at first migraine and risk of any subtype of breast cancer were observed. Reductions in risks of ER+ ductal, ER+ lobular, and potentially ER+ mixed ductal-lobular breast cancer were also observed among women with a 30-year or longer history of migraines (RR: 0.4, 95% CI 0.2-0.6; RR: 0.5, 95% CI 0.3-0.9; and RR: 0.7, 95% CI: 0.4-1.1, respectively), and statistically significant trends with duration were observed. Women who experienced menstrual or menstrually-related migraine prior to the age of 20 also had a 60% lower risk of ER+ ductal (95% CI 0.2-0.8) breast cancer, and also

reductions in risks of ER+ lobular and ER+ mixed ductal-lobular (both: RR: 0.5, 95% CI 0.2-1.2) that were within the limits of chance. No substantive differences in breast cancer risk were associated with migraine frequency or severity for any type of breast cancer.

## Discussion

We observed that women with a longer history (≥30 years) of migraines, or a history of migraine before age 20, had a 50-60% lower risk of some ER+ breast cancers compared to women without a history of migraine. Migraine with aura was also associated with a 30-40% lower risk of ER+ breast cancer. Although these findings were based on small numbers of women, taken together the pattern is of interest, particularly if it is repeated in future studies. Three of four prior studies of the association between migraine and breast cancer, including the original study upon which these new data are based,[1-3] observed a lower risk of ER+, but not ER-, breast cancer among women with a history of migraine. The other study did not observe a relationship between migraine and breast cancer risk.[4] The latter study evaluated risk associated with migraine with and without aura and found that migraine with aura was not associated with breast cancer risk, and that migraine without aura was associated with a 20% greater risk of breast cancer.[4] The present study is the first to assess risk of different histologic subtypes of breast cancer associated with a multitude of migraine characteristics including migraine duration and intensity, history of menstrual migraine, experience of migraine with aura, and age at migraine onset. This study is also unique as it is one of the first to evaluate history of headaches meeting the clinical criteria for migraine (most prior studies were based simply on self-reported migraine history). We observed a lower risk of ER+ breast cancers (ductal as well as lobular) among postmenopausal women who had either had their first migraine before age 20, had experienced migraines for 30 years or more, and/or had ever experienced migraine with aura.

The biological mechanisms which could explain an association between both early onset migraine (before age 20) and long duration of migraine history (≥30 years) and ER+ breast cancer risk (but not ER-breast cancer risk) are uncertain. Estrogen could play a role, as it is associated with both migraine timing (in the short term) and breast cancer risk (in the long term). Short-term fluctuations in estrogen levels, whether positive or negative, are believed to trigger migraines (as reviewed by Brandes, et al.[11]), whereas a higher cumulative exposure to estrogen over a woman's lifetime is associated with higher breast cancer risk. To tie together lifetime cumulative estrogen exposure and short-term fluctuations in estrogen, there is evidence that higher lifetime cumulative exposure to estrogen is inversely associated with a lifetime history of greater fluctuations in estrogen. In particular, women who experienced early menarche (age <12 years) have higher levels of estradiol during and after adolescence, and smaller fluctuations (they have higher levels of estradiol during the lower-estrogen (luteal) but not the higher-estrogen (follicular) phase of the menstrual cycle), compared to women with late menarche (age >14 years).[16]

Biologically, it is plausible that estrogen could play a role in associations between ER+ breast cancer and migraine with aura as well. Migraine with aura occurs more frequently at times in the menstrual cycle when estrogen levels are high.[6,17,7] Estrogen acts on the brain through several pathways,[11,18,19,10] increasing cortical and neuronal excitability,

[20,21] and increasing the amplitude and rate of repetition of cortical spreading depression (CSD),[22] which is thought to cause, or be equivalent to, migraine with aura.[23-25,10] CSD is defined as alternating waves of neural excitation and suppression that spread across cortical tissue in the brain.[20] As is thought to be the case with migraines, CSD has been shown via in-vitro studies to be triggered by fluctuations in estrogen levels, whether increasing[20] or decreasing estrogen.[26] However, the relevance of this link between estrogen and migraine with aura to the observed relationship between migraine with aura and risk of some types of breast cancer is unknown. Lifetime patterns of estrogen exposure are just one possible explanation for a link between migraines and breast cancer risk. If these findings are replicated in future studies this could motivate specific biological studies to characterize underlying biological mechanisms.

An alternate explanation for a lower risk of ER+ breast cancer in women with a history of migraines could be that such women are more likely to avoid migraine triggers (i.e. alcohol, cigarette smoking, poor sleep, stress), some of which are also risk factors for breast cancer. Such behaviors might be expected to lower the risk of ER+ breast cancer, as alcohol[27,28] and smoking[29] have been found to be associated with ER+, and not ER- breast cancer. The data used in the previous study[4] are consistent with this hypothesis, in that alcohol and smoking were less common among migraineurs. In our study migraineurs were more likely to be non-drinkers compared to non-migraineurs (53% vs. 46%) and less likely to be heavier drinkers compared to non-migraineurs (22% vs 30% consumed ≥4 drinks per week). Rates of smoking were similar among migraineurs and non-migraineurs. However, tests for interaction between clinical migraine and either smoking ($p=0.78$) or alcohol ($p=0.55$) were not statistically significant and adjusting for these factors did not impact the direction or magnitude of our risk estimates.

A potential limitation of this study is the possibility of exposure misclassification via recall or reporting bias. However, if women diagnosed with breast cancer were somehow more likely to remember or report a migraine history (or a more severe one) compared to controls, this would result in a positive association, not the inverse relationship we observed. Sample size was also a limitation particularly with respect to the small number of ER- cancer (only 46 ER- ductal cases) included in this study. This limited our statistical power and our ability to make any strong inferences with respect to the relationship between migraine and risk of ER- breast cancer. Based on the characteristics of our study population, these findings may be less generalizable to younger women, non-white women, and those with advanced or aggressive breast cancer at diagnosis. The limitations of our study are balanced by several key strengths. This study is population-based and collected detailed information on, and assessed multiple measures of, migraine history. We were able to identify a sizeable number of participants who experienced headaches meeting the clinical criteria for migraine who were not aware that their headaches were migraines.

Our results further characterize the potential reduction in risk of breast cancer associated with migraine history as we observed that it may be confined to migraineurs with early onset migraine, a long history of migraines, and a history of migraine with aura. Additional research is needed to confirm these findings and to explore the potential biological links between migraine history and a reduced risk of ER+ breast cancer.

## Acknowledgments

We would like to thank several people who contributed to this work, including Kassidy Benoscek, David Grogan, Carolyn Howard, Dick Jacke, Rob McKenna, Anne Oswald, Georgene Ranney, April Reitan, LJ Sweetland, Mei-Tzu Tang, Camille Taylor, and Sarah Taylor. This study was supported by two grants from the National Cancer Institute: NCI: R03-CA135688 and NCI: R01-CA85913, and the manuscript was supported by training grant: 2T32CA009168-36.

## References

1. Li CI, Mathes RW, Bluhm EC, Caan B, Cavanagh MF, Chlebowski RT, Michael Y, O'Sullivan MJ, Stefanick ML, Prentice R. Migraine history and breast cancer risk among postmenopausal women. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010; 28(6):1005–1010.10.1200/JCO.2009.25.0423 [PubMed: 20100960]
2. Li CI, Mathes RW, Malone KE, Daling JR, Bernstein L, Marchbanks PA, Strom BL, Simon MS, Press MF, Deapen D, Burkman RT, Folger SG, McDonald JA, Spirtas R. Relationship between migraine history and breast cancer risk among premenopausal and postmenopausal women. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2009; 18(7):2030–2034.10.1158/1055-9965.EPI-09-0291
3. Mathes RW, Malone KE, Daling JR, Davis S, Lucas SM, Porter PL, Li CI. Migraine in postmenopausal women and the risk of invasive breast cancer. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2008; 17(11):3116–3122.10.1158/1055-9965.EPI-08-0527
4. Winter AC, Rexrode KM, Lee IM, Buring JE, Tamimi RM, Kurth T. Migraine and subsequent risk of breast cancer: a prospective cohort study. Cancer causes & control : CCC. 2013; 24(1):81–89.10.1007/s10552-012-0092-x [PubMed: 23143336]
5. Dumitrescu RG, Cotarla I. Understanding breast cancer risk -- where do we stand in 2005? Journal of cellular and molecular medicine. 2005; 9(1):208–221. [PubMed: 15784178]
6. Bousser MG. Estrogens, migraine, and stroke. Stroke; a journal of cerebral circulation. 2004; 35(11 Suppl 1):2652–2656.10.1161/01.STR.0000143223.25843.36
7. MacGregor EA. Oestrogen and attacks of migraine with and without aura. Lancet neurology. 2004; 3(6):354–361.10.1016/S1474-4422(04)00768-9
8. Buse DC, Loder EW, Gorman JA, Stewart WF, Reed ML, Fanning KM, Serrano D, Lipton RB. Sex Differences in the Prevalence, Symptoms, and Associated Features of Migraine, Probable Migraine and Other Severe Headache: Results of the American Migraine Prevalence and Prevention (AMPP) Study. Headache. 201310.1111/head.12150
9. Allais G, Castagnoli Gabellari I, De Lorenzo C, Mana O, Benedetto C. Oral contraceptives in migraine therapy. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2011; 32(Suppl 1):S135–139.10.1007/s10072-011-0538-z
10. Sacco S, Ricci S, Degan D, Carolei A. Migraine in women: the role of hormones and their impact on vascular diseases. The journal of headache and pain. 2012; 13(3):177–189.10.1007/s10194-012-0424-y [PubMed: 22367631]
11. Brandes JL. The influence of estrogen on migraine: a systematic review. JAMA : the journal of the American Medical Association. 2006; 295(15):1824–1830.10.1001/jama.295.15.1824
12. Li CI, Malone KE, Porter PL, Lawton TJ, Voigt LF, Cushing-Haugen KL, Lin MG, Yuan X, Daling JR. Relationship between menopausal hormone therapy and risk of ductal, lobular, and ductal-lobular breast carcinomas. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2008; 17(1):43–50.10.1158/1055-9965.EPI-07-0558
13. Bigal M, Krymchantowski AV, Lipton RB. Barriers to satisfactory migraine outcomes. What have we learned, where do we stand? Headache. 2009; 49(7):1028–1041.10.1111/j.1526-4610.2009.01410.x [PubMed: 19389137]

14. Cady R, Dodick DW. Diagnosis and treatment of migraine. Mayo Clinic proceedings Mayo Clinic. 2002; 77(3):255–261.10.4065/77.3.255
15. Headache Classification Subcommittee of the International Headache S. The International Classification of Headache Disorders. Cephalalgia : an international journal of headache (2nd). 2004; 24(Suppl 1):9–160. [PubMed: 14979299]
16. Bernstein L. Epidemiology of endocrine-related risk factors for breast cancer. Journal of mammary gland biology and neoplasia. 2002; 7(1):3–15. [PubMed: 12160084]
17. Calhoun AH. Current topics and controversies in menstrual migraine. Headache. 2012; 52(Suppl 1):8–11.10.1111/j.1526-4610.2012.02130.x [PubMed: 22540198]
18. Brandes JL. Migraine in women. Continuum. 2012; 18(4):835–852.10.1212/01.CON.0000418646.70149.71 [PubMed: 22868545]
19. Greco R, Tassorelli C, Mangione AS, Smeraldi A, Allena M, Sandrini G, Nappi G, Nappi RE. Effect of sex and estrogens on neuronal activation in an animal model of migraine. Headache. 2013; 53(2):288–296.10.1111/j.1526-4610.2012.02249.x [PubMed: 22913654]
20. Eikermann-Haerter K, Kudo C, Moskowitz MA. Cortical spreading depression and estrogen. Headache. 2007; 47(Suppl 2):S79–85.10.1111/j.1526-4610.2007.00818.x [PubMed: 17850538]
21. Shyti R, de Vries B, van den Maagdenberg A. Migraine genes and the relation to gender. Headache. 2011; 51(6):880–890.10.1111/j.1526-4610.2011.01913.x [PubMed: 21631474]
22. Sachs M, Pape HC, Speckmann EJ, Gorji A. The effect of estrogen and progesterone on spreading depression in rat neocortical tissues. Neurobiology of disease. 2007; 25(1):27–34.10.1016/j.nbd.2006.08.013 [PubMed: 17008106]
23. Chauvel V, Vamos E, Pardutz A, Vecsei L, Schoenen J, Multon S. Effect of systemic kynurenine on cortical spreading depression and its modulation by sex hormones in rat. Experimental neurology. 2012; 236(2):207–214.10.1016/j.expneurol.2012.05.002 [PubMed: 22587906]
24. Pietrobon D, Moskowitz MA. Pathophysiology of migraine. Annual review of physiology. 2013; 75:365–391.10.1146/annurev-physiol-030212-183717
25. Vecchia D, Pietrobon D. Migraine: a disorder of brain excitatory-inhibitory balance? Trends in neurosciences. 2012; 35(8):507–520.10.1016/j.tins.2012.04.007 [PubMed: 22633369]
26. Kudo, CHK.; Moskowitz, MA.; Ayata, C. Estrogen modulates the susceptibility to cortical spreading depression, in vivo; Paper presented at the Society for Neuroscience; Atlanta, GA. October 17, 2006; 2006.
27. Li CI, Chlebowski RT, Freiberg M, Johnson KC, Kuller L, Lane D, Lessin L, O'Sullivan MJ, Wactawski-Wende J, Yasmeen S, Prentice R. Alcohol consumption and risk of postmenopausal breast cancer by subtype: the women's health initiative observational study. Journal of the National Cancer Institute. 2010; 102(18):1422–1431.10.1093/jnci/djq316 [PubMed: 20733117]
28. Coronado GD, Beasley J, Livaudais J. Alcohol consumption and the risk of breast cancer. Salud publica de Mexico. 2011; 53(5):440–447. [PubMed: 22218798]
29. Kabat GC, Kim M, Phipps AI, Li CI, Messina CR, Wactawski-Wende J, Kuller L, Simon MS, Yasmeen S, Wassertheil-Smoller S, Rohan TE. Smoking and alcohol consumption in relation to risk of triple-negative breast cancer in a cohort of postmenopausal women. Cancer causes & control : CCC. 2011; 22(5):775–783.10.1007/s10552-011-9750-7 [PubMed: 21360045]

**Table 1**

**Selected characteristics of controls, ER+ ductal, ER- ductal, ER+ lobular, and ER+ mixed ductal-lobular cases**

| | Controls (n=376) | | ER+ ductal (n=276) | | ER- ductal (n=46) | | ER+ lobular(n=191) | | ER+ ductal/lobular (n=202) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) |
| **Age at reference date** | | | | | | | | | | |
| 55-59 years | 110 | 29% | 87 | 32% | 16 | 35% | 57 | 30% | 66 | 33% |
| 60-64 years | 106 | 28% | 71 | 26% | 13 | 28% | 56 | 29% | 60 | 30% |
| 65-69 years | 84 | 22% | 65 | 24% | 13 | 28% | 46 | 24% | 41 | 20% |
| 70-74 years | 76 | 20% | 53 | 19% | 4 | 9% | 32 | 17% | 35 | 17% |
| **Education** | | | | | | | | | | |
| <High school | 18 | 5% | 13 | 5% | 3 | 7% | 7 | 4% | 5 | 2% |
| High school graduate | 91 | 24% | 75 | 27% | 16 | 35% | 47 | 25% | 51 | 25% |
| Some college or technical school | 150 | 40% | 89 | 32% | 22 | 48% | 64 | 34% | 64 | 32% |
| College graduate | 117 | 31% | 99 | 36% | 5 | 11% | 73 | 38% | 82 | 41% |
| **Reference year** | | | | | | | | | | |
| 2000 | 87 | 23% | 56 | 20% | 16 | 35% | 38 | 20% | 47 | 23% |
| 2001 | 84 | 22% | 61 | 22% | 6 | 13% | 51 | 27% | 56 | 28% |
| 2002 | 86 | 23% | 74 | 27% | 12 | 26% | 51 | 27% | 61 | 30% |
| 2003 | 79 | 21% | 74 | 27% | 9 | 20% | 38 | 20% | 35 | 17% |
| 2004 | 40 | 11% | 11 | 4% | 3 | 7% | 13 | 7% | 3 | 1% |
| **Race/Ethnicity** | | | | | | | | | | |
| Non-Hispanic White | 339 | 90% | 247 | 89% | 38 | 83% | 178 | 93% | 187 | 93% |
| Other Race | 37 | 10% | 29 | 11% | 8 | 17% | 13 | 7% | 15 | 7% |
| **Oral contraceptive use** | | | | | | | | | | |
| Never used | 127 | 34% | 101 | 37% | 11 | 24% | 58 | 31% | 66 | 33% |
| <4 months | 19 | 5% | 20 | 7% | 4 | 9% | 15 | 8% | 15 | 7% |
| ≥4 months | 230 | 61% | 155 | 56% | 31 | 67% | 117 | 62% | 120 | 59% |
| Missing | 0 | | 0 | | 0 | | 1 | | 1 | |
| **Hormone therapy use** | | | | | | | | | | |
| Never use | 85 | 23% | 79 | 29% | 16 | 35% | 32 | 17% | 35 | 17% |
| Former use | 83 | 22% | 37 | 13% | 6 | 13% | 31 | 16% | 27 | 13% |

| | Controls (n=376) | | ER+ ductal (n=276) | | ER- ductal (n=46) | | ER+ lobular(n=191) | | ER+ ductal/lobular (n=202) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) |
| Current use of estrogen alone | 128 | 34% | 62 | 22% | 12 | 26% | 52 | 27% | 46 | 23% |
| Current estrogen+ progestin use | 80 | 21% | 98 | 36% | 12 | 26% | 76 | 40% | 94 | 47% |
| **Body mass index, kg/m$^2$** | | | | | | | | | | |
| ≤24.9 | 113 | 30% | 96 | 35% | 17 | 37% | 70 | 37% | 70 | 35% |
| 25.0-29.9 | 141 | 38% | 87 | 32% | 16 | 35% | 61 | 32% | 75 | 37% |
| 30.0-39.9 | 108 | 29% | 71 | 26% | 13 | 28% | 51 | 27% | 47 | 23% |
| ≥40.0 | 14 | 4% | 22 | 8% | 0 | 0% | 9 | 5% | 10 | 5% |
| **Age at menarche, yrs** | | | | | | | | | | |
| ≤11 | 83 | 22% | 53 | 19% | 13 | 28% | 41 | 22% | 52 | 26% |
| 12-13 | 212 | 56% | 169 | 61% | 17 | 37% | 103 | 54% | 105 | 52% |
| ≥14 | 81 | 21% | 54 | 20% | 16 | 35% | 47 | 24% | 44 | 22% |
| Missing | 0 | | 0 | | 0 | | 0 | | 1 | |
| **Age at menopause, yrs** | | | | | | | | | | |
| ≤44 | 41 | 16% | 20 | 9% | 5 | 18% | 7 | 5% | 13 | 8% |
| 45-49 | 59 | 23% | 53 | 24% | 6 | 21% | 40 | 30% | 31 | 20% |
| 50-52 | 74 | 29% | 73 | 33% | 8 | 29% | 39 | 29% | 49 | 32% |
| 53-55 | 50 | 19% | 46 | 21% | 5 | 18% | 30 | 23% | 42 | 27% |
| ≥56 | 37 | 14% | 28 | 13% | 4 | 14% | 17 | 13% | 20 | 13% |
| Missing | 115 | | 56 | | 18 | | 58 | | 47 | |
| **First-degree family history of breast cancer** | | | | | | | | | | |
| No | 301 | 83% | 206 | 78% | 39 | 89% | 142 | 76% | 154 | 77% |
| Yes | 61 | 17% | 59 | 22% | 5 | 11% | 46 | 25% | 46 | 23% |
| Missing | 14 | | 11 | | 2 | | 3 | | 2 | |
| **Parity** | | | | | | | | | | |
| Nulliparous | 30 | 8% | 46 | 17% | 2 | 4% | 30 | 16% | 28 | 14% |
| Parous | 346 | 92% | 230 | 83% | 44 | 96% | 161 | 84% | 174 | 86% |
| **Age at first full-term pregnancy, yrs** | | | | | | | | | | |
| <20 | 64 | 18% | 48 | 21% | 10 | 23% | 31 | 19% | 34 | 20% |
| 20-24 | 173 | 50% | 110 | 48% | 18 | 41% | 72 | 45% | 79 | 45% |
| 25-29 | 83 | 24% | 47 | 20% | 10 | 23% | 42 | 26% | 33 | 19% |

| | Controls (n=376) | | ER+ ductal (n=276) | | ER- ductal (n=46) | | ER+ lobular(n=191) | | ER+ ductal/lobular (n=202) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** |
| ≥30 | 26 | 7% | 25 | 11% | 6 | 14% | 16 | 10% | 28 | 16% |
| **Alcohol use, drinks/week** | | | | | | | | | | |
| <1.0 | 232 | 62% | 157 | 57% | 28 | 61% | 89 | 48% | 130 | 65% |
| 1.0-6.9 | 86 | 23% | 59 | 22% | 10 | 22% | 60 | 32% | 35 | 18% |
| ≥7.0 | 55 | 15% | 58 | 21% | 8 | 17% | 38 | 20% | 35 | 18% |
| Missing | 3 | | 2 | | 0 | | 4 | | 2 | |
| **Smoking status** | | | | | | | | | | |
| Never | 186 | 50% | 134 | 49% | 19 | 41% | 92 | 48% | 111 | 55% |
| Former | 155 | 41% | 120 | 43% | 20 | 43% | 82 | 43% | 78 | 39% |
| Current | 35 | 9% | 22 | 8% | 7 | 15% | 17 | 9% | 13 | 6% |

Table 2

**Correlation between two measures of migraine history**

| | | Self-reported migraine: | | | |
|---|---|---|---|---|---|
| | | **No** | **Yes** | **Unknown** | **Total** |
| **Met clinical criteria for migraine:** | No | 667 | 23 | 1 | 691 |
| | Yes | 209 | 190 | 1 | 400 |
| | Total | 876 | 213 | 2 | 1,091 |
| | | | | *Kappa: 0.49* | |

**Table 3**

**Risks of ER+ ductal, ER- ductal, ER+ lobular, and ER+ mixed ductal-lobular breast cancer associated with two definitions of migraine history**

| | Controls (n=376) | | ER+ ductal cases (n=276) | | | | ER- ductal cases (n=46) | | | | ER+ lobular cases (n=191) | | | | ER+ mixed ductal-lobular cases(n=202) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | OR[a] | 95% CI | n | % | OR[a] | 95% CI | n | % | OR[a] | 95% CI | n | % | OR[a] | 95% CI |
| **Met clinical criteria for migraine** | | | | | | | | | | | | | | | | | | |
| No | 228 | 61 | 189 | 69 | 1.0 | (ref) | 24 | 52 | 1.0 | (ref) | 127 | 67 | 1.0 | (ref) | 123 | 61 | 1.0 | (ref) |
| Yes | 148 | 39 | 87 | 32 | 0.7 | (0.5-1.0)* | 22 | 48 | 1.4 | (0.8-2.6) | 64 | 34 | 0.8 | (0.5-1.1) | 79 | 39 | 1.0 | (0.7-1.4) |
| **Self-report of migraine** | | | | | | | | | | | | | | | | | | |
| No | 282 | 75 | 231 | 84 | 1.0 | (ref) | 36 | 78 | 1.0 | (ref) | 165 | 86 | 1.0 | (ref) | 162 | 80 | 1.0 | (ref) |
| Yes | 94 | 25 | 44 | 16 | 0.6 | (0.4-0.9)* | 10 | 22 | 0.7 | (0.3-1.5) | 26 | 14 | 0.5 | (0.3-0.8)* | 39 | 19 | 0.7 | (0.5-1.1) |

[a] All models are adjusted for the following variables, categorized as in Table 1: age, county of residence, reference year, body mass index.

* P-value <0.05.

**Table 4**

**Risks of ER+ ductal, ER- ductal, ER+ lobular, and ER+ mixed ductal-lobular breast cancer associated with various migraine characteristics among women meeting the clinical criteria for migraine**

| | Controls (n=376) | | ER+ ductal cases (n=276) | | | | ER- ductal cases (n=46) | | | | ER+ lobular cases (n=191) | | | | ER+ mixed ductal-lobular cases(n=202) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | OR[a] | 95% CI | n | % | OR[a] | 95% CI | n | % | OR[a] | 95% CI | n | % | OR[a] | 95% CI |
| **History of migraine with aura** | | | | | | | | | | | | | | | | | | |
| Never had migraine | 228 | 61 | 189 | 69 | 1.0 | (ref) | 24 | 52 | 1.0 | (ref) | 127 | 67 | 1.0 | (ref) | 123 | 61 | 1.0 | (ref) |
| Migraine without aura | 47 | 13 | 28 | 10 | 0.7 | (0.4-1.3) | 9 | 20 | 2.0 | (0.8-4.6) | 31 | 16 | 1.2 | (0.7-2.0) | 25 | 12 | 1.0 | (0.6-1.7) |
| Migraine with aura | 100 | 27 | 57 | 21 | 0.7 | (0.5-1.0)* | 13 | 28 | 1.2 | (0.6-2.4) | 33 | 17 | 0.6 | (0.4-0.9)* | 54 | 27 | 1.0 | (0.7-1.5) |
| **Age at first migraine, yrs** | | | | | | | | | | | | | | | | | | |
| Never had migraine | 228 | 61 | 189 | 70 | 1.0 | (ref) | 24 | 52 | 1.0 | (ref) | 127 | 68 | 1.0 | (ref) | 123 | 62 | 1.0 | (ref) |
| <20 | 52 | 14 | 22 | 8 | 0.5 | (0.3-0.9)* | 5 | 11 | 0.9 | (0.3-2.5) | 14 | 8 | 0.5 | (0.3-0.9)* | 16 | 8 | 0.6 | (0.3-1.1) |
| ≥20 | 93 | 25 | 61 | 22 | 0.8 | (0.5-1.2) | 17 | 37 | 1.7 | (0.9-3.4) | 46 | 25 | 0.9 | (0.6-1.4) | 61 | 31 | 1.2 | (0.8-1.8) |
| *p for trend* | | | | | *0.25* | | | | *0.26* | | | | *0.06* | | | | *0.06* | |
| **Number of years suffered migraines** | | | | | | | | | | | | | | | | | | |
| Never had migraine | 228 | 61 | 189 | 70 | 1 | (ref) | 24 | 52 | 1 | (ref) | 127 | 68 | 1.0 | (ref) | 123 | 62 | 1.0 | (ref) |
| <30 | 75 | 20 | 61 | 23 | 1.0 | (0.7-1.5) | 17 | 37 | 2.2 | (1.1-4.3) | * 40 | 21 | 1.0 | (0.6-1.5) | 53 | 27 | 1.3 | (0.9-2.0) |
| ≥30 | 69 | 19 | 21 | 8 | 0.4 | (0.2-0.6) * | 5 | 11 | 0.7 | (0.3-1.9) | 20 | 11 | 0.5 | (0.3-0.9)* | 24 | 12 | 0.7 | (0.4-1.1) |
| *p for trend* | | | | | *0.003* | | | | *0.03* | | | | *0.03* | | | | *0.05* | |
| **Average number of migraines per year** | | | | | | | | | | | | | | | | | | |
| Never had migraine | 228 | 62 | 189 | 70 | 1.0 | (ref) | 24 | 53 | 1.0 | (ref) | 127 | 68 | 1.0 | (ref) | 123 | 62 | 1.0 | (ref) |
| <12 | 81 | 22 | 50 | 19 | 0.7 | (0.5-1.1) | 15 | 33 | 1.8 | (0.9-3.7) | 40 | 21 | 0.9 | (0.6-1.4) | 46 | 23 | 1.0 | (0.7-1.6) |
| ≥12 | 61 | 17 | 31 | 12 | 0.6 | (0.4-1.0) | 6 | 13 | 0.9 | (0.4-2.4) | 20 | 11 | 0.6 | (0.4-1.1) | 30 | 15 | 0.9 | (0.6-1.6) |
| *p for trend* | | | | | *0.65* | | | | *0.68* | | | | *0.08* | | | | *0.35* | |
| **Average level of migraine pain** | | | | | | | | | | | | | | | | | | |
| Never had migraine | 228 | 61 | 189 | 70 | 1.0 | (ref) | 24 | 53 | 1.0 | (ref) | 127 | 68 | 1.0 | (ref) | 123 | 61 | 1.0 | (ref) |
| ≤7 | 76 | 20 | 49 | 18 | 0.7 | (0.5-1.1) | 10 | 22 | 1.3 | (0.6-2.8) | 35 | 19 | 0.8 | (0.5-1.3) | 43 | 21 | 1.0 | (0.7-1.6) |
| >7 | 68 | 18 | 33 | 12 | 0.6 | (0.4-1.0)* | 11 | 24 | 1.5 | (0.7-3.2) | 25 | 13 | 0.7 | (0.4-1.1) | 35 | 17 | 1.0 | (0.6-1.6) |
| *p for trend* | | | | | *0.51* | | | | *0.41* | | | | *0.82* | | | | *0.46* | |

*Cancer Causes Control*. Author manuscript; available in PMC 2015 December 01.

| | Controls (n=376) | | ER+ ductal cases (n=276) | | | | ER- ductal cases (n=46) | | | | ER+ lobular cases (n=191) | | | | ER+ mixed ductal-lobular cases(n=202) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | OR[a] | 95% CI | n | % | OR[a] | 95% CI | n | % | OR[a] | 95% CI | n | % | OR[a] | 95% CI |
| **History of menstrual or menstrually-related migraine** | | | | | | | | | | | | | | | | | | |
| Never had migraine | 228 | 63 | 189 | 70 | 1.0 | (ref) | 24 | 56 | 1.0 | (ref) | 127 | 69 | 1.0 | (ref) | 123 | 62 | 1.0 | (ref) |
| Non-menstrual/non-menstrually-related only | 87 | 24 | 58 | 21 | 0.8 | (0.5-1.2) | 16 | 37 | 1.8 | (0.9-3.6) | 39 | 21 | 0.8 | (0.5-1.3) | 48 | 24 | 1.0 | (0.7-1.6) |
| History of menstrual or menstrually-related migraine | 49 | 14 | 25 | 9 | 0.6 | (0.4-1.0) | 3 | 7 | 0.5 | (0.1-1.8) | 19 | 10 | 0.7 | (0.4-1.2) | 27 | 14 | 1.0 | (0.6-1.7) |
| **Age at first menstrual/menstrually-related migraine, yrs** | | | | | | | | | | | | | | | | | | |
| <20 | 27 | 10 | 9 | 4 | 0.4 | (0.2-0.8)* | N/A | N/A | N/A | N/A | 8 | 6 | 0.5 | (0.2-1.2) | 7 | 5 | 0.5 | (0.2-1.2) |
| ≥20 | 21 | 8 | 16 | 8 | 1.0 | (0.5-1.9) | N/A | N/A | N/A | N/A | 11 | 8 | 1.0 | (0.4-2.1) | 20 | 13 | 1.9 | (1.0-3.7) |

[a] All models are adjusted for the following variables, categorized as in Table 1: age, county of residence, reference year, body mass index.

* P-value <0.05.