Migraine history and risk of different molecular subtypes of breast cancer

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Abstract

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Background: A history of prior migraines has been found to be associated with a reduced risk of breast cancer. However, its relationship with different breast cancer subtypes defined by joint estrogen receptor (ER)/progesterone receptor (PR)/human epidermal growth factor receptor-2 (HER2) status are largely unknown.

Methods: We conducted a population-based case-case study consisting of 2,346 women aged 20 to 69 years who were first diagnosed with invasive breast cancer between 2004 and 2015. We estimated odds ratios (ORs) and 95% confidence intervals (CIs) by using polytomous logistic regression to assess the relationships between different migraine characteristics and risks of hormone positive (HR+, ER+ and/or PR+), triple negative (TN, ER-/PR-/HER2-), and HER2-overexpressing (H2E, ER-/HER2+) breast cancers.

Results: Compared to HR+ cases, history of migraine was not associated with risks of either TN or H2E breast cancers (TN: OR = 0.86, 95%CI: 0.71, 1.04; H2E: OR = 1.05, 95%CI: 0.81, 1.36).

Conclusions: No significant associations were observed between migraine history and risk of different molecular breast cancer subtypes. Further studies are needed to replicate our results.

Introduction

Migraine is a neurological disorder that is more prevalent in women than men[1]. It is well-established that certain aspects of migraine are hormonal related. For example, more than half of women report that their migraine attacks are closely related to the menstrual cycle[2] and symptoms often improve during pregnancy[3]. Additionally, migraine symptoms may worsen after menopause[4]. Evidence also suggests that migraine patients with aura have higher levels of estrogen compared to patients who experience migraines without aura[5,6]. Migraine has also been associated with obesity, as obese individuals have been observed to suffer more frequent attacks compared to those with normal weights[7,8]. Specifically, one study observed that compared to women with a BMI lower than 23 kg/m^2, women with a BMI of 35 kg/m^2 or higher have a 1.03-fold higher risk of having a migraine history[9].

Breast cancer is the most common cancer among women and many of its risk factors are hormonally related[10]. Given that both migraine and breast cancer are influenced by hormones, prior studies have evaluated the relationship between migraine history and breast cancer risk, and several have observed that migraineurs have a reduced risk of breast cancer[11,12,13]. Breast cancer is a heterogenous disease and its major subtypes are defined according to the expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) into three primary subgroups: hormone receptor positive (HR+, ER+ and/or PR+), triple negative tumors (TN, ER-/PR-/HER2-) and HER2-overexpressing tumors (H2E, ER-/HER2+)[14,15,16]. There is also some evidence to suggest that the reduction in breast cancer risk associated with a migraine history is strongest for risk of ER+/PR+ breast cancer compared with other tumor subtypes[13,12]. However, evidence regarding the impact of different migraine characteristics on the risks of different breast cancer subtypes is lacking. The aims of this study were to determine how various aspects of migraine history impact risk of different molecular subtypes of breast cancer and to further evaluate the potential effect modification by relevant risk factors.

Methods

We conducted a population-based case-case study of breast cancer details of which have been previously published[17,18,19]. Cases were identified through the Seattle-Puget Sound Surveillance, Epidemiology and End Results (SEER) population-based cancer registry. Potential cases were women age 20 to 69 years who were first diagnosed with invasive breast cancer between June 1, 2004 and June 30, 2015 in the greater Seattle-Tacoma metropolitan area (King, Pierce, and Snohomish counties). Patients with incomplete information on ER, PR, and HER2 status were excluded from the study. Of the 2,883 eligible patients, 2,346 (81.4%) subjects were enrolled. They each completed a structured interviewer-administered questionnaire which obtained data on various established/suspected breast cancer risk factors and detailed information on headache and migraine history. Of 2,346 enrolled women, 10 (0.4%) with an unknown migraine history were excluded leaving a total of 2,336 breast cancer cases in our final analytic set. This study was approved by the Fred Hutchinson Cancer Research Center's Institutional Review Board (IRB).

Data on demographic, epidemiologic, and clinical characteristics were collected through structured telephone interviews. Questions focused on exposures prior to the date of each patient's breast cancer diagnosis. In terms of migraine history, women were asked to self-report if they had ever experienced a migraine. Recognizing the potential misclassification of migraine history, each participant was asked a series of questions related to the characteristics of the headaches that they ever experienced, including duration, severity, location, and associated symptoms, and this information was combined to determine whether or not women ever experienced headaches that meet the established clinical criteria for a migraine diagnosis[20]. Specifically, we defined women as having a history of migraine without aura if they had ever experienced headaches lasting more than four hours and accompanied by moderate to severe pain intensity, nausea/vomiting and/or sensitivity to light/sound, and at least one of the following: (1) located on only one side, (2) throbbing/pounding headache, and (3) headache that was made worse by routine physical activity. Migraine with aura was further defined as headaches meeting the criteria for migraine just described but also involving visual disturbances such as flickering lights, spots, and lines or loss of vision before or during a headache. Information on age at first migraine was collected as well.

Additionally, information on a number of potential confounders and breast cancer risk factors was collected including age at breast cancer diagnosis, year of breast cancer diagnosis, race/ethnicity, education, first-degree family history of breast cancer, age at menarche, number of full-term pregnancies, menopausal status, hormonal contraceptive use, menopausal hormone use, nonsteroidal anti-inflammatory drugs (NSAIDs) use, body mass index (BMI), alcohol consumptions, and smoking history. Information on clinical tumor characteristics including histology and ER/PR/HER2 status was abstracted from pathology reports collected by the SEER registry. We classified breast cancer into three subgroups based on joint ER/PR/HER2 status: hormone receptor positive (n = 1,276), triple-negative (n = 741), and HER2-overexpressing (n = 319). Assessments by histologic type focused on ductal vs. lobular carcinomas and were restricted to HR+ tumors given that only 19 lobular carcinomas were HR- (ductal: n = 990; lobular: n = 209).

We first conducted descriptive analyses assessing demographic and relevant breast cancer risk factor distributions by breast cancer subgroups. For primary analyses, in order to evaluate the associations between migraines history and the risks of different molecular breast cancer subtypes, polytomous logistic regression was used to estimate odds ratios and 95% confidence intervals (CIs). We also evaluated association with various clinical characteristics of migraines, including migraine with/without aura and age at first migraine. In analyses by molecular subtype hormone receptor positive women served as the reference group, and in analyses by histology HR+ ductal women served as the reference group. All models were adjusted for age and year of breast cancer diagnosis. None of the other potential confounders changed the odds ratio by more than 10%, and therefore, none were adjusted for in our final models. Potential effect modification was assessed by comparing models with and without interaction terms using likelihood ratio testing. Significant interactions were found with BMI and alcohol use (p-values > 0.05; data not shown) and then stratified analyses were conducted to assess the interactions. A threshold of 0.05 was utilized to evaluate statistical significance and all analyses were performed in Stata 15 (StataCorp, College Station, TX).

Results

Compared to other subtypes, women with HR+ breast cancer were somewhat more likely to be non-Hispanic white, to be current users of hormone contraceptives and combined estrogen and progestin hormone therapy, and to consume 1 or more drinks per week (Table 1). Patients diagnosed with TN disease were more likely to have post-menopausal status, to have had used NSAIDs and to be obese. H2E cases were less likely to be nulliparous.

Overall, compared to HR+ cases, neither history of migraine, age at first migraine, nor history of migraine with aura were significantly associated with other subtypes of breast cancer risks accounting for age diagnosed with breast cancer and the year of breast cancer diagnosis (Table 2). There were also few differences in risk by histologic type. The one exception was that compared to women with HR+ ductal tumors, patients older than 20 years of age at first migraine had an increased risk of HR+ lobular breast cancer (OR = 1.47, 95% CI: 1.01 – 2.14), relative to patients without a migraine history.

BMI modified the relationship between migraine history and risk of different molecular subtypes of breast cancer. Among patients with a BMI lower than 25 kg/m^2, compared with HR+ cases, patients with a history of migraine had a decreased odds of TN breast cancer (Table 3, OR = 0.60, 95% CI: 0.42 – 0.85) that appeared to be largely confined to women with a history of migraine without aura (OR = 0.45, 95% CI: 0.28, 0.72). There was also some evidence that this inverse association was stronger for women who experienced their first migraine at age 20 or later (P-trend = 0.004). There were no associations between any aspect of migraine history and risk of TN breast cancer among women with a BMI >25 kg/m^2. Among women with a BMI lower than 25 kg/m^2, a history of migraine with aura was associated with a decreased odds of H2E breast cancer (OR = 0.50, 95% CI: 0.25 – 0.99), but among women with a BMI of 30 kg/m^2 or greater, a history of migraine with aura was associated with an increased odds of H2E breast cancer (OR = 1.90, 95% CI: 1.07, 3.38).

Among patients who consumed less than 1 drink per week, compared with HR+ cases, patients with history of migraine had an increased odds of H2E breast cancer (OR = 1.54, 95% CI: 1.02 – 2.31). Among women who consumed more than 7 drinks per week migraineurs had a decreased odds of H2E breast cancer (OR = 0.40, 95% CI: 0.19 – 0.87).

Discussion

In this study, we did not observe an overall relationship between migraine history and risk of different breast cancer subtypes defined by either joint ER/PR/HER2 status or histology. These null results are in line with findings from previous studies which indicated that hormone receptor status did not significantly impact the relationship between migraine and breast cancer risk[21, 22]. However, some studies reported that migraineurs had a more pronounced reduction in risk of ER+/PR+ breast cancer compared to other tumor subtypes[13,12,11], indicating hormones could play an important role in both triggering migraines and resulting in breast cancer[11,23]. Shi, et al., on the other hand, suggested the reason for the hormone-differentially associations is that hormone receptors may tend to be expressed among some women based on genetic

predisposition, which is related to both migraine and breast cancer mechanism[21]. While there is some inconsistency in the existing literature, our case-case study design provides more robust evidence regarding these relationships given its larger numbers of both TN and H2E patients.

There was though some evidence that both BMI and alcohol modify the relationships between migraine history and risk of different molecular subtypes of breast cancer. Compared to women diagnosed with HR+ disease, migraine history was associated with a reduced risk of TN breast cancer among lean women (BMI <25). A history of migraines was associated with an increased risk of H2E breast cancer among never/infrequent consumers of alcohol (<1 drink/week) and a decreased risk of H2E breast cancer among regular consumers of alcohol (>7 drinks/week). The potential biological mechanisms underlying these associations are unknown. It is important to note that many migraineurs avoid drinking given its association with migraine[24,25]. There is also evidence that alcohol consumption is more strongly related with HR+ breast cancer than it is with H2E breast cancer[26,27]. To our knowledge, this is the first study that observed significant interactions between BMI and alcohol use and the relationship between migraine history and breast cancer subtypes. Further studies are needed to confirm and better understand these relationships.

Our study has several strengths and limitations that are important to acknowledge. Our case-only study design reduced the potential for recall bias. Given all the subjects were breast cancer cases, it is less likely for different groups of patients to answer the questions differentially. As for the limitations, in this study, the hormone-positive subtype group was considered as the reference group when estimating the risk estimates. We do not have a disease-free control group to compare with because of the case-case study design. Further, the existing literature on the relationship between migraine and breast cancer risk is mixed. Differentiated by study design, case-control studies have found generally observed an inverse relationship, however, cohort studies have generally reported no associations. Lastly, the generalizability of our findings is somewhat limited by the fact that our study population predominantly consists of non-Hispanic White women.

In conclusion, this study did not observe a significant relationship between migraine history and risk of breast cancer subtypes though these associations may be modified by BMI and alcohol consumption. However, given the limited existing evidence, additional studies are needed to confirm our findings.

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Table 1. Distribution of demographic and risk factors by breast cancer subtype (n = 2,336)

	Hormone receptor positive n=1,276 N (%)	Triple-negative n=741 N (%)	HER2-overexpressing n=319 N (%)
Age at breast cancer diagnosis, years			
< 40	108 (8.5%)	67 (9.0%)	29 (9.1%)
40 - 49	386 (30.3%)	185 (25.0%)	74 (23.2%)
50 - 59	494 (38.7%)	283 (38.2%)	136 (42.6%)
60 - 69	288 (22.6%)	206 (27.8%)	80 (25.1%)
Year of breast cancer diagnosis			
2004 - 2006	194 (15.2%)	136 (18.4%)	55 (17.2%)
2007 - 2008	175 (13.7%)	125 (16.9%)	48 (15.0%)
2009 - 2010	242 (19.0%)	146 (19.7%)	52 (16.3%)
2011 - 2012	314 (24.6%)	163 (22.0%)	82 (25.7%)
2013 - 2015	351 (27.5%)	171 (23.1%)	82 (25.7%)
Race/Ethnicity			
Non-Hispanic white	1,078 (84.5%)	615 (83.0%)	263 (82.4%)
other	198 (15.5%)	126 (17.0%)	56 (17.6%)
Education			
High school or less	438 (34.4%)	268 (36.3%)	113 (35.5%)
College or bachelor's degree	671 (52.7%)	371 (50.2%)	161 (50.6%)
Master's or higher degree	165 (13.0%)	100 (13.5%)	44 (13.8%)
Missing	2	2	1
First-degree family history of breast cancer			
Yes	316 (25.2%)	171 (23.5%)	65 (20.7%)
No	937 (74.8%)	557 (76.5%)	249 (79.3%)
Missing	23	13	5
Age at menarche, years			
< 12	233 (18.3%)	154 (20.8%)	67 (21.1%)
12 - 13	747 (58.6%)	428 (57.8%)	181 (56.9%)
>= 14	295 (23.1%)	159 (21.5%)	70 (22.0%)
Missing	1	0	1
Number of full-term pregnancies			
0	314 (24.6%)	179 (24.2%)	72 (22.6%)
1	219 (17.2%)	134 (18.1%)	58 (18.2%)
2	503 (39.4%)	268 (36.2%)	117 (36.7%)
>= 3	240 (18.8%)	160 (21.6%)	72 (22.6%)
Menopausal status			
Pre-menopausal	504 (40.6%)	224 (31.2%)	101 (32.6%)
Peri-menopausal	121 (9.8%)	65 (9.0%)	36 (11.6%)
Post-menopausal	616 (49.6%)	430 (59.8%)	173 (55.8%)
Missing	35	22	9
Recency of hormonal contraceptive use at diagnosis			
Never	1,050 (82.4%)	636 (85.9%)	279 (87.5%)

Former	72 (5.6%)	42 (5.7%)	19 (6.0%)
Current	153 (12.0%)	62 (8.4%)	21 (6.6%)
Missing	1	1	0
Recency of menopausal hormone use at diagnosis			
Never	1,083 (84.9%)	608 (82.2%)	267 (83.7%)
Former	54 (4.2%)	66 (8.9%)	23 (7.2%)
Current estrogen alone	64 (5.0%)	50 (6.8%)	22 (6.9%)
Current estrogen + progestin	74 (5.8%)	16 (2.2%)	7 (2.2%)
Missing	1	1	0
NSAIDs use at breast cancer diagnosis			
Yes	356 (27.9%)	229 (31.1%)	87 (27.4%)
No	918 (72.1%)	508 (68.9%)	230 (72.6%)
Missing	2	4	2
Body mass index, kg/m^2			
< 25	527 (41.3%)	230 (31.1%)	123 (38.6%)
25 – 29.9	352 (27.6%)	232 (31.4%)	115 (36.1%)
>= 30	397 (31.1%)	278 (37.6%)	81 (25.4%)
Missing	0	1	0
Alcohol use, drinks/week			
< 1	419 (32.8%)	274 (37.0%)	133 (41.7%)
1 - 7	609 (47.7%)	327 (44.1%)	138 (43.3%)
> 7	248 (19.4%)	140 (18.9%)	48 (15.0%)
Smoking status at breast cancer diagnosis			
Never	771 (62.2%)	431 (60.4%)	189 (61.0%)
Former	125 (10.1%)	78 (10.9%)	34 (11.0%)
Current	344 (27.7%)	205 (28.7%)	87 (28.1%)
Missing	36	27	9

Table 2. Relationship between history of migraine and risk of breast cancer subtypes by joint ER/PR/HER2 receptor and histology*

	Hormone receptor positive n=1,276	Triple-negative n=741		HER2-overexpressing n=319	
	N (%)	N (%)	Adjusted OR (95% CI)	N (%)	Adjusted OR (95% CI)
History of migraine					
No	816 (64.0)	503 (67.9)	1.00 (ref)	201 (63.0)	1.00 (ref)
Yes	460 (36.1)	238 (32.1)	0.86 (0.71, 1.04)	118 (37.0)	1.05 (0.81, 1.36)
Age at first migraine, years					
Never had migraine	816 (68.5)	503 (72.0)	1.00 (ref)	201 (68.6)	1.00 (ref)
< 20	142 (11.9)	72 (10.3)	0.85 (0.63, 1.16)	27 (9.2)	0.78 (0.50, 1.21)
>= 20	234 (19.6)	124 (17.7)	0.88 (0.68, 1.12)	65 (22.2)	1.14 (0.83, 1.57)
p for trend			0.153		0.648
History of migraine with aura					
Never had migraine	816 (64.0)	503 (67.9)	1.00 (ref)	201 (63.0)	1.00 (ref)
Migraine with aura	213 (16.7)	116 (15.6)	0.89 (0.69, 1.15)	58 (18.2)	1.11 (0.79, 1.54)
Migraine without aura	247 (19.4)	122 (16.5)	0.83 (0.65, 1.06)	60 (18.8)	0.89 (0.72, 1.38)

	HR+ Ductal n=990	HR+ Lobular n=209	
	N (%)	N (%)	Adjusted OR (95% CI)
History of migraine			
No	635 (64.1)	133 (63.6)	1.00 (ref)
Yes	355 (35.9)	76 (36.4)	1.04 (0.76, 1.44)
Age at first migraine, years			
Never had migraine	635 (69.0)	133 (67.2)	1.00 (ref)
< 20	117 (12.7)	14 (7.1)	0.61 (0.33, 1.09)
>= 20	168 (18.3)	51 (25.8)	1.47 (1.01, 2.14)+
p for trend			0.137
History of migraine with aura			

Never had migraine	635 (64.1)	133 (63.7)	1.00 (ref)
Migraine with aura	170 (17.2)	32 (15.3)	0.93 (0.61, 1.44)
Migraine without aura	185 (18.7)	44 (21.1)	1.13 (0.78, 1.69)

[*] All models adjusted for age at breast cancer diagnosis and the year of breast cancer diagnosis

[+] P- value < 0.05

Table 3. Adjusted odds ratio for history of migraine by BMI and alcohol use*

		Hormone receptor positive n=1,276	Triple-negative n=741		HER2-overexpressing n=319	
		N (%)	N (%)	Adjusted OR (95% CI)	N (%)	Adjusted OR (95% CI)
BMI						
< 25						
	History of migraine					
	No	331 (62.8)	170 (73.9)	1.00 (ref)	87 (70.7)	1.00 (ref)
	Yes	196 (37.2)	60 (26.1)	0.60 (0.42, 0.85)+	36 (29.3)	0.70 (0.45, 1.07)
	Age at first migraine, years					
	Never had migraine	331 (67.1)	170 (77.3)	1.00 (ref)	87 (77.0)	1.00 (ref)
	< 20	62 (12.6)	23 (10.5)	0.81 (0.48, 1.38)	5 (4.4)	0.34 (0.13, 0.88)+
	>= 20	100 (20.3)	27 (12.3)	0.51 (0.32, 0.81)+	21 (18.6)	0.76 (0.45, 1.30)
	p for trend			0.004+		0.170
	History of migraine with aura					
	Never had migraine	331 (62.8)	170 (73.9)	1.00 (ref)	87 (70.7)	1.00 (ref)
	Migraine with aura	81 (15.4)	34 (14.8)	0.81 (0.52, 1.27)	11 (8.9)	0.50 (0.25, 0.99)+
	Migraine without aura	115 (21.8)	26 (11.3)	0.45 (0.28, 0.72)+	25 (20.3)	0.85 (0.51, 1.40)
25 – 29.9						
	History of migraine					
	No	236 (67.1)	158 (68.1)	1.00 (ref)	71 (61.7)	1.00 (ref)
	Yes	116 (32.9)	74 (31.9)	0.96 (0.67, 1.38)	44 (38.3)	1.27 (0.81, 1.99)
	Age at first migraine, years					
	Never had migraine	236 (72.0)	158 (73.8)	1.00 (ref)	71 (66.4)	1.00 (ref)
	< 20	35 (10.7)	15 (7.0)	0.61 (0.32, 1.18)	14 (13.1)	1.36 (0.68, 2.75)
	>= 20	57 (17.4)	41 (19.2)	1.09 (0.69, 1.74)	22 (20.6)	1.31 (0.74, 2.32)
	p for trend			0.988		0.314
	History of migraine with aura					

	Never had migraine	236 (67.1)	158 (68.1)	1.00 (ref)	71 (61.7)	1.00 (ref)
	Migraine with aura	54 (15.34)	35 (15.1)	0.98 (0.61, 1.58)	23 (20.0)	1.43 (0.81, 2.54)
	Migraine without aura	62 (17.6)	39 (16.8)	0.95 (0.60, 1.50)	21 (18.3)	1.12 (0.63, 2.00)
>= 30						
	History of migraine					
	No	249 (62.7)	174 (62.6)	1.00 (ref)	41 (53.1)	1.00 (ref)
	Yes	148 (37.3)	104 (37.4)	1.00 (0.72, 1.38)	38 (46.9)	1.58 (0.96, 2.59)
	Age at first migraine, years					
	Never had migraine	249 (67.1)	174 (65.9)	1.00 (ref)	43 (58.9)	1.00 (ref)
	< 20	45 (12.1)	34 (12.9)	1.11 (0.67, 1.82)	8 (11.0)	1.09 (0.47, 2.52)
	>= 20	77 (20.8)	56 (21.2)	1.02 (0.68, 1.53)	22 (30.1)	1.76 (0.98, 3.18)
	p for trend			0.800		0.099
	History of migraine with aura					
	Never had migraine	249 (62.7)	174 (62.6)	1.00 (ref)	43 (53.1)	1.00 (ref)
	Migraine with aura	78 (19.7)	47 (16.9)	0.85 (0.56, 1.29)	24 (29.6)	1.90 (1.07, 3.38)$^{+}$
	Migraine without aura	70 (17.6)	57 (20.5)	1.17 (0.78, 1.76)	14 (17.3)	1.22 (0.62, 2.40)

		Hormone receptor positive n=1,276	**Triple-negative n=741**		**HER2-overexpressing n=319**	
		N (%)	**N (%)**	**Adjusted OR (95% CI)**	**N (%)**	**Adjusted OR (95% CI)**
Alcohol use, drinks/week						
< 1						
	History of migraine					
	No	278 (66.4)	187 (68.3)	1.00 (ref)	75 (56.4)	1.00 (ref)
	Yes	141 (33.7)	87 (31.8)	0.94 (0.68, 1.31)	58 (43.6)	1.54 (1.02, 2.31)$^{+}$
1-7						
	History of migraine					
	No	385 (63.2)	221 (67.6)	1.00 (ref)	88 (63.8)	1.00 (ref)
	Yes	224 (36.8)	106 (32.4)	0.85 (0.63, 1.13)	50 (36.2)	0.98 (0.66, 1.44)
> 7						
	History of migraine					

No	153 (61.7)	95 (67.9)	1.00 (ref)	38 (79.2)	1.00 (ref)
Yes	95 (38.3)	45 (32.1)	0.75 (0.47, 1.19)	10 (20.8)	0.40 (0.19, 0.87)[+]

[*] All models adjusted for age at breast cancer diagnosis and the year of breast cancer diagnosis

[+] P- value < 0.05