

Research Article

Relationship between Menopausal Symptoms and Risk of Postmenopausal Breast Cancer

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Abstract

Background: Prior studies indicate that women with menopausal symptoms have lower estrogen levels because they go through menopause as compared with women who do not experience them. Given the central role of hormones in the etiology of breast cancer, a link between menopausal symptoms and breast cancer is plausible. However, no prior studies have evaluated the association between menopausal symptoms and breast cancer risk.

Methods: Utilizing data from a population-based case-control study we examined associations between menopausal symptoms and risks of different histologic types of breast cancer among postmenopausal women. We calculated multivariate adjusted odds ratios (OR) using polytomous logistic regression and evaluated several potential effect modifiers.

Results: Women who ever experienced menopausal symptoms had lower risks of invasive ductal carcinoma (IDC) (OR = 0.5; 95% CI: 0.3–0.7), invasive lobular carcinoma (ILC, OR = 0.5; 95% CI: 0.3–0.8), and invasive ductal-lobular carcinoma (IDLC, OR = 0.7; 95% CI: 0.4–1.2), and these reductions in risk were independent of recency and timing of hormone therapy use, age at menopause, and body mass index. Increasing intensity of hot flashes among women who ever experienced hot flashes was also associated with decreasing risks of all three breast cancer subtypes (*P* values for trend all ≤ 0.017).

Conclusion: This is the first study to report that women who ever experienced menopausal symptoms have a substantially reduced risk of breast cancer, and that severity of hot flashes is also inversely associated with risk.

Impact: If confirmed, these findings could enhance our understanding of breast cancer etiology and factors potentially relevant to prevention. *Cancer Epidemiol Biomarkers Prev*; 20(2); 379–88. ©2011 AACR.

Introduction

Breast cancer is the most common form of cancer and the second leading cause of cancer death among women in United States (1). There is overwhelming evidence that estrogen plays a critical role in the disease's pathogenesis (2, 3). In a meta-analysis of 9 prospective studies of endogenous sex hormones and postmenopausal breast cancer, the relative risk (RR) estimates for women in the highest quintiles of total estradiol and free estradiol levels were 2.00 and 2.58, respectively, compared with women in the lowest quintiles (4). Menopausal symptoms commonly occur in peri- and postmenopausal women as endogenous estrogen and progesterone levels fluctuate and decline due to the gradual cessation of ovarian function (5). The severity and types of symptoms women

experience as they go through menopause vary considerably and can include vasomotor symptoms, urogenital atrophy symptoms, psychological changes, and insomnia. Previous research has demonstrated associations between early to late perimenopausal shifts in endogenous hormone levels and the onset of vasomotor and vaginal symptoms (6). A 7-year prospective cohort study (6) following women during the transition from perimenopause to 3 years after menopause reported a 5-fold decrease in estradiol, a similar fold increase in follicle-stimulating hormone (FSH) level, and increases in the severity of hot flashes, night sweats, and vaginal dryness. Other studies have reported that oophorectomy results in hot flashes, perspiration and atrophic vaginitis and that these symptoms are relieved by exogenous estrogen therapy (7–10). In contrast, exogenous menopausal hormone therapy (HT) has not been shown to have an effect on reducing mood changes related to menopause, and thus they may be less closely linked to hormonal changes (7–10). In the Women's Health Initiative randomized trials of estrogen plus progestin (E + P) and unopposed estrogen HT among postmenopausal women, users of both types of menopausal HT were 20% to 30% more likely than women receiving placebo to report relief of vasomotor symptoms but similar percentages of women

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treated and untreated with these hormones experienced mood changes (9, 10).

Although vasomotor menopausal symptoms are particularly influenced by hormones, no prior studies have evaluated how menopausal symptoms are related to breast cancer risk. The purpose of this study was to examine the relationship between severity of menopausal symptoms and breast cancer risk among postmenopausal women.

Methods

We utilized data from a population-based case-control study of postmenopausal breast cancer originally designed to evaluate the relationship between use of menopausal HT and risk of different histologic types of breast cancer among women aged 55 to 74 years. Our approach stratifies risk by histology given evidence suggesting that compared with invasive ductal carcinomas, invasive lobular carcinomas are more hormonally sensitive in that they are more frequently hormone receptor positive (11) and use of combined estrogen plus progestin menopausal HT is more strongly related to risk of lobular compared with ductal tumors (11, 12). Details of this study's methods have been described previously (12). In addition to collecting detailed information on HT, this study also captured detailed self-reported data on history of menopausal symptoms through a structured in-person interview as described in the following text.

Participants

Women 55 to 74 years of age with no history of *in situ* or invasive breast cancer when diagnosed with invasive breast cancer between January 1, 2000, and March 31, 2004, were eligible as cases. Invasive lobular carcinoma (ILC) and invasive ductal-lobular carcinoma (IDLC) cases were oversampled such that all women diagnosed with these two histologic types of breast cancer over the study period were eligible. A random sample of invasive ductal carcinoma (IDC) cases were selected with the goal of matching this group 1:1 with the combined ILC and IDLC cases. The Cancer Surveillance System, the population-based tumor registry that serves the Seattle-Puget Sound region of Washington State and participates in the Surveillance, Epidemiology, and End Results program of the National Cancer Institute, was used to identify these women. Of 1,251 eligible cases identified, 1,044 (83%) were interviewed, including 524 IDC cases, 324 ILC cases, and 196 IDLC cases. Histologic classifications were based on a centralized review of both pathology reports and available tumor tissue specimens.

Controls were women without a history of breast cancer who were identified by random-digit dialing from the general population of female residents of King, Pierce, and Snohomish counties, using the Mitosky-Waksberg method with a clustering factor of 5 (18). Controls were frequency matched 1:1 within 5-year age groups, based

on the age distributions of the ILC and IDLC cases combined using 1-step recruitment. A total of 9,876 telephone numbers were either verified as residential or presumed to be residential. Thirteen percent of these could not be successfully screened for study eligibility, due to varied reasons: always answered by machine, respondents refusing answering screening questions, and language or communication barriers. Six hundred sixty eligible controls were identified, and 469 of these were interviewed (71%).

Seventeen women (5 IDC, 2 ILC, 5 IDLC cases, and 5 controls) were excluded from the overall analyses because they had missing data on menopausal symptoms. In addition, 59 women with missing data for confounders of the relationship between menopausal symptoms and breast cancer risk (duration of HT use and type of menopause) were excluded. So, the total numbers of women included in this analysis were 449 controls, 494 IDC cases, 307 ILC cases, and 187 IDLC cases.

Exposure assessment

Cases and controls were interviewed in-person and all questions were limited to exposures that occurred before each participant's reference date. The reference dates for cases were their diagnosis dates, and controls were assigned reference dates to reflect the distribution of case reference dates. Participants were asked about their reproductive history, menstruation and menopause history, hormone medication history, body size, medical history, family history of cancer, and history of alcohol consumption. In addition, information on type and intensity of all menopausal symptoms experienced before reference date was collected. Participants were asked whether they ever experienced one or more menopausal symptoms listed in separate questions, including hot flashes; sweating (including night sweats); vaginal dryness; bladder problems; irregular or heavy menstrual bleeding; depression, anxiety, or emotional distress; and insomnia. Women were also asked to report the severity of all symptoms they experienced (mild, moderate, or severe). Women who experienced hot flashes were also asked an additional series of questions that included: "On average, how many minutes did these episodes last?" "How often did these occur in a typical week?" "For how many total weeks or months did you have them?" and Whether or not perspiration and/or awakening accompanied them.

In our main analysis, the reference exposure category consisted of women who never experienced menopausal symptoms. This group of women was compared with women who ever experienced menopausal symptoms of any type, and those who ever experienced menopausal symptoms were further stratified by specific type of symptom experienced (including vasomotor symptoms, urogenital atrophy symptoms, and mood changes/insomnia), number of menopausal symptoms experienced (1, 2, ≥ 3), and number of severe menopausal

symptoms experienced (1, 2, ≥ 3). Vasomotor symptoms included symptoms related to the dilation or constriction of blood vessels close to the skin, such as hot flushes and night sweats. Urogenital atrophy symptoms included vaginal dryness, irregular or heavy menstrual bleeding, and bladder control problems. Mood changes/insomnia included depression, anxiety, emotional distress, and sleep disturbances.

With the additional information collected on hot flushes we further characterized severity of hot flushes according to both perspiration and awakening. Specifically, we assessed risks associated with hot flash duration and intensity (3 mutually exclusive levels: hot flushes without perspiration or awakening, hot flushes with perspiration but not awakening, and hot flushes with awakening regardless of perspiration).

Statistical analysis

Polytomous logistic regression was performed to calculate odds ratios (OR) and their associated 95% CI to compare IDC, ILC, and IDLC cases to controls. All analyses were conducted using Stata/SE version 10.0 (StataCorp LP). We also calculated 2-sided *P* values for the comparison between ILC and IDLC risk estimates versus IDC risk estimates using polytomous logistic regression models that treated IDC group as the reference category and excluded the controls.

All models were adjusted for age (5-year categories) and reference year (continuous). Several additional variables were evaluated as potential confounders, including education, first-degree family history of breast cancer (yes/no), type of menopause [natural, induced, simple hysterectomy (hysterectomy without a bilateral oophorectomy)], age at menopause, parity, age at first use of HT (<45, 45–54, and ≥ 55 years), timing of first use of HT in relation to age at menopause (before menopause, in the same year of menopause, 1–4 years after menopause, 5 years or longer after menopause), duration of HT use, recency of HT use (never users, former users, current estrogen only users, and current E + P users), body mass index (BMI) 1 year prior to reference date (quartiles of control population), recency of alcohol consumption (never users, former users, and current users), and the number of drinks per week consumed among current drinkers (<1, 1–4, 5–9, ≥ 10). Only type of menopause and duration of HT use changed our risk estimates by more than 10% when included in our statistical models, and thus were the only 2 confounders added to our final multivariate adjusted statistical models along with age and year of diagnosis.

We also evaluated recency of HT use, age at first use of HT, timing of first use of HT in relation to age at menopause, age at menopause, timing of age at reference in relation to the age at menopause, and BMI as potential effect modifiers of the relationship between menopausal symptoms and breast cancer risk, given that these factors are each hormonally related, potentially associated with menopausal symptoms, and independently related to

breast cancer risk. Interactions between these factors and menopausal symptoms were evaluated through stratified analyses, and 2-sided *P* values for interactions using Wald's test were performed.

Results

ILC and IDLC cases were somewhat more likely than controls and IDC cases to be college graduates (Table 1). Higher proportions of all 3 case groups had a first-degree family history of breast cancer, were nulliparous, experienced a natural menopause, had a later age at menopause, and a later age at first use of HT compared with controls. ILC and IDLC cases tended to have a lower BMI and were more frequently current E + P users compared with IDC cases and controls.

Among controls, compared with women who never experienced menopausal symptoms those that did were somewhat younger, less likely to have a first-degree family history of breast cancer, and somewhat more likely to be in the highest BMI quartile, to have had a natural menopause, to have a later age at menopause, and to be current users of combined estrogen and progestin menopausal HT (Table 2).

Compared with women who never had menopausal symptoms, women who ever had menopausal symptoms had reduced risks of IDC and ILC (OR = 0.5; 95% CI: 0.3–0.7 and OR = 0.5; 95% CI: 0.3–0.8, respectively), and a nonsignificant reduced risk of IDLC (OR = 0.7; 95% CI: 0.4–1.2; Table 3). Risks of ILC and IDLC decreased with increasing number of menopausal symptoms experienced (*P* for trend = 0.049 and *P* for trend = 0.028, respectively), but not for IDC (*P* for trend = 0.126). Risk estimates were similar when the analysis was restricted to history of menopausal symptoms reported to be severe, although trends with increasing numbers of severe menopausal symptoms experienced were not significant. Forty percent to 60% lower risks of IDC and ILC were observed among women who ever had vasomotor symptoms, urogenital atrophy symptoms, or emotional changes, and insomnia. For each of these symptoms 20% to 30% lower risks of IDLC were also observed, but all of these risk estimates were within the limits of chance. However, none of the risk estimates in Table 3 were statistically different across the 3 histology case groups (all *P* values were between 0.134 and 0.941). Similarly, in an analysis of our IDC group stratified by ER status, none of these relationships were statistically different when comparing risks of ER⁺ versus ER⁻ disease (data not shown, all *P* values for comparison of ER⁺ versus ER⁻ ORs were between 0.284 and 0.840).

The relationship between history of menopausal symptoms and breast cancer risk was not modified to any appreciable degree by recency of HT use, age at first use of any type of menopausal HT, timing of first use of HT in relation to age at menopause, age at menopause, years between age at menopause and reference age, or BMI (all *P* values for interaction were >0.4; Table 4). Specifically,

Table 1. Distribution of selected characteristics among controls and cases

Characteristics	Controls (n = 449)	Ductal (n = 494)	Lobular (n = 307)	Ductal-lobular (n = 187)
	n (%)	n (%)	n (%)	n (%)
Age, y				
55–59	130 (28.9)	137 (27.7)	90 (29.3)	64 (34.2)
60–64	117 (26.1)	126 (25.5)	78 (25.4)	49 (26.2)
65–69	109 (24.3)	123 (24.9)	77 (25.1)	41 (21.9)
70–74	93 (20.7)	108 (21.9)	62 (20.2)	33 (17.7)
Race/ethnicity				
Non-Hispanic White	404 (90.0)	447 (90.5)	287 (93.5)	169 (90.4)
African American	8 (1.8)	10 (2.0)	8 (2.6)	4 (2.1)
Asian/Pacific Islander	9 (2.0)	15 (3.0)	3 (1.0)	6 (3.2)
Native American	10 (2.2)	12 (2.5)	3 (1.0)	1 (0.5)
Hispanic White	18 (4.0)	10 (2.0)	6 (1.9)	7 (3.8)
Education				
Less than high school	23 (5.1)	35 (7.1)	19 (6.2)	7 (3.7)
High school graduate	120 (26.7)	135 (27.3)	79 (25.7)	43 (23.0)
Some college/technical school	173 (38.6)	176 (35.6)	96 (31.3)	70 (37.5)
College graduate	133 (29.6)	148 (30.0)	113 (36.8)	67 (35.8)
First-degree family history of breast cancer				
No	365 (84.3)	368 (78.6)	229 (76.3)	138 (75.4)
Yes	68 (15.7)	100 (21.4)	71 (23.7)	45 (24.6)
Missing	16	26	7	4
Number of pregnancies resulting in a live birth				
None	35 (7.8)	65 (13.2)	44 (14.3)	29 (15.6)
1	41 (9.2)	58 (11.7)	34 (11.1)	20 (10.7)
2	156 (34.7)	137 (27.7)	97 (31.6)	60 (32.3)
≥3	217 (48.3)	234 (47.4)	132 (43.0)	77 (41.4)
Missing	0	0	0	1
BMI, kg/m ²				
<23.4	112 (25.1)	123 (25.1)	90 (29.6)	59 (31.9)
23.4–26.4	115 (25.7)	120 (24.5)	61 (20.1)	45 (24.3)
26.5–31.0	111 (24.8)	118 (24.1)	93 (30.6)	48 (26.0)
≥31.1	109 (24.4)	129 (26.3)	60 (19.7)	33 (17.8)
Missing	2	4	3	2
Recency of alcohol consumption				
Never users	169 (38.0)	168 (35.1)	102 (33.6)	68 (37.2)
Former users	68 (15.3)	68 (14.2)	35 (11.5)	30 (16.4)
Current users	208 (46.7)	243 (50.7)	167 (54.9)	85 (46.4)
<1 drinks/day	43 (20.7)	54 (22.2)	30 (18.0)	17 (20.0)
≥1 drink/day	165 (79.3)	189 (77.8)	137 (82.0)	68 (80.0)
Missing	4	15	3	4
Type of menopause				
Natural	258 (57.5)	333 (67.4)	205 (66.8)	132 (70.6)
Induced	76 (16.9)	61 (12.4)	41 (13.3)	30 (16.0)
Simple hysterectomy	115 (25.6)	100 (20.2)	61 (19.9)	25 (13.4)
Age at menopause, y				
<45	56 (17.7)	48 (12.7)	17 (7.6)	11 (7.5)
45–54	202 (63.7)	242 (64.2)	154 (68.4)	101 (68.2)
≥55	59 (18.6)	87 (23.1)	54 (24.0)	36 (24.3)
Missing	132	117	82	39

(Continued on the following page)

Table 1. Distribution of selected characteristics among controls and cases (Cont'd)

Characteristics	Controls (n = 449)	Ductal (n = 494)	Lobular (n = 307)	Ductal-lobular (n = 187)
	n (%)	n (%)	n (%)	n (%)
Years between age at menopause and reference age				
<8	81 (25.6)	94 (25.0)	59 (26.2)	43 (29.1)
8–14	82 (25.9)	126 (33.4)	81 (36.0)	53 (35.8)
15–21	80 (25.2)	97 (25.7)	53 (23.6)	40 (27.0)
≥22	74 (23.3)	60 (15.9)	32(14.2)	12 (8.1)
Age at first use of any type of menopausal HT, y				
<45	105 (28.8)	82 (21.4)	40 (15.5)	27 (16.6)
45–54	202 (55.5)	239 (62.4)	169 (65.8)	108 (66.2)
≥55	57 (15.7)	62 (16.2)	48 (18.7)	28 (17.2)
Missing	85	111	50	24
Timing of first use of HT in relation to age at menopause				
Before menopause	78 (31.5)	96 (34.2)	67 (35.8)	43 (33.3)
Same year as menopause	103 (41.7)	95 (33.8)	62 (33.2)	47 (36.4)
1–4 y after menopause	34 (13.8)	60 (21.3)	40 (21.4)	26 (20.2)
≥5 y after menopause	32 (13.0)	30 (10.7)	18 (9.6)	13 (10.1)
Missing	202	213	120	58
Recency of menopausal HT use				
Never	87 (19.4)	117 (23.8)	51 (16.6)	25 (13.4)
Former	125 (27.8)	102 (20.7)	54 (17.6)	34 (18.2)
Current unopposed estrogen	142 (31.6)	121 (24.6)	80 (26.1)	42 (22.4)
Current E + P	95 (21.2)	152 (30.9)	122 (39.7)	86 (46.0)
Missing	0	2	0	0
Duration of HT use, y				
Never	87 (19.4)	117 (23.8)	51 (16.6)	25 (13.4)
<1	35 (7.8)	34 (6.7)	19 (6.2)	12 (6.4)
1–4	75 (16.7)	68 (13.8)	44 (14.3)	32 (17.1)
5–9	87 (19.4)	71 (14.4)	70 (22.8)	34 (18.2)
10–14	53 (11.8)	94 (19.0)	61 (19.9)	50 (26.7)
≥15	112 (24.9)	110 (22.3)	62 (20.2)	34 (18.2)

the same inverse association between ever having experienced menopausal symptoms and breast cancer risk was consistently observed among never versus current menopausal HT users, across various ages at menopause, and also across quartiles of BMI.

Risks of ILC and IDLC were lower among women who experienced hot flashes with perspiration or hot flashes with awakening compared with women who only experienced hot flashes without perspiration [all *P* values for heterogeneity of ORs across the 3 hot flash intensity categories were <0.05, except for the OR for IDC, comparing hot flashes with perspiration, but not awakening vs. hot flashes without perspiration or awakening (OR = 0.8; 95% CI: 0.5–1.3); Table 5]. The *P* values for trend (range from <0.001 to 0.017) were statistically significant across the 3 intensity categories with the hot flashes without perspiration/awakening as the reference category. However, duration of hot flashes did not further alter risks as all of the *P* values for trend based on duration of hot flashes experienced were more than 0.05.

Discussion

Before interpreting the results of our study, it is important to first describe its limitations. Although our response rates were reasonably high, 83% for cases and 71% for controls, selection bias remains a potential concern. Bias could result if the women who refused to participate were different from those who did participate with respect to their histories of menopausal symptoms. However, the comparisons across case groups are unlikely to be affected by such differences, given that it is unlikely that the proportions of menopausal symptoms among the cases not interviewed would differ considerably by case type. All exposure data were based on self-report, so recall bias is another concern. Women with mild menopausal symptoms, women who experienced short-term menopausal symptoms, or women who experienced symptoms a long time prior to interview may be less likely to report their symptoms. However, there is really no better source of information on menopausal symptoms than women

Table 2. Distribution of selected characteristics by history of menopausal symptoms among controls

Characteristics	Never had menopausal symptoms (n = 51)	Ever had menopausal symptoms, but not severe symptoms (n = 214)	Ever had severe symptoms (n = 180)
	n (%)	n (%)	n (%)
Age, y			
55–59	12 (23.5)	54 (25.2)	63 (35.0)
60–64	6 (11.8)	59 (27.6)	50 (27.8)
65–69	14 (27.4)	51 (23.8)	44 (24.4)
70–74	19 (37.3)	50 (23.4)	23 (12.8)
First-degree family history of breast cancer			
No	37 (80.4)	173 (82.8)	152 (87.4)
Yes	9 (19.6)	36 (17.2)	22 (12.6)
BMI, kg/m ²			
<23.4	13 (25.5)	55 (25.9)	44 (24.4)
23.4–26.4	14 (27.5)	62 (29.3)	37 (20.6)
26.5–31.0	17 (33.3)	50 (23.6)	44 (24.4)
≥31.1	7 (13.7)	45 (21.2)	55 (30.6)
Recency of alcohol consumption			
Never users	21 (41.2)	69 (32.7)	77 (43.0)
Former users	8 (15.7)	33 (15.6)	26 (14.5)
Current users	22 (43.1)	109 (51.7)	76 (42.5)
<1 drinks/day	6 (27.3)	23 (21.1)	14 (18.4)
≥1 drink/day	16 (72.7)	86 (78.9)	62 (81.6)
Type of menopause			
Natural	22 (43.1)	136 (63.6)	98 (54.5)
Induced	16 (31.4)	26 (12.1)	33 (18.3)
Simple hysterectomy	13 (25.5)	52 (24.3)	49 (27.2)
Age at menopause, y			
<45	9 (26.5)	19 (12.3)	28 (22.0)
45–54	20 (58.8)	109 (70.8)	73 (57.5)
≥55	5 (14.7)	26 (16.9)	26 (20.5)
Recency of menopausal HT use			
Never	15 (29.4)	48 (22.4)	24 (13.3)
Former	15 (29.4)	58 (27.1)	50 (27.8)
Current unopposed estrogen	16 (31.4)	58 (27.1)	67 (37.2)
Current E + P	5 (9.8)	50 (23.4)	39 (21.7)
Duration of HT use, y			
Never	15 (29.4)	48 (22.4)	24 (13.3)
<1	4 (7.8)	20 (9.4)	12 (6.7)
1–4	9 (17.7)	31 (14.5)	32 (17.8)
5–9	3 (5.9)	46 (21.5)	38 (21.1)
10–14	2 (3.9)	26 (12.1)	25 (13.9)
≥15	18 (35.3)	43 (20.1)	49 (27.2)

themselves. Also, the resulting misclassification of exposure is likely to be nondifferential and to bias the risk estimates toward the null because menopausal symptoms are not an established risk factor for breast cancer. Another issue is that menopausal symptoms have a diverse etiology and we were unable to measure factors like endogenous hormone levels. Thus, we cannot separate the potentially independent role of menopausal symptoms themselves from the impact of endogenous hormone levels.

No prior studies have specifically investigated the relationship between breast cancer risk and menopausal symptoms among postmenopausal women, and thus our results require confirmation. Here, we show that compared with women who never had menopausal symptoms, those who reported ever experiencing symptoms had half the risk of both IDC and ILC, the 2 most common histologic types of breast cancer. In addition, we observed that women who ever had menopausal symptoms also had a 70% lower risk

Table 3. Menopausal symptoms and risk of breast cancer by histologic type

	Controls (n = 449)		Ductal cases (n = 494)		Lobular cases (n = 307)		Ductal-lobular cases (n = 187)	
	n (%)	OR ^c (95% CI)	n (%)	OR ^c (95% CI)	n (%)	OR ^c (95% CI)	n (%)	OR ^c (95% CI)
Never had menopausal symptoms	51 (11.4)	1.0 (ref)	96 (19.4)	1.0 (ref)	56 (18.2)	1.0 (ref)	25 (13.4)	1.0 (ref)
Ever had menopausal symptoms	398 (88.6)	0.5 (0.3-0.7) ^b	398 (80.6)	0.5 (0.3-0.7) ^b	251 (81.8)	0.5 (0.3-0.8) ^a	162 (86.6)	0.7 (0.4-1.2)
Number of menopausal symptoms experienced								
1	59 (13.1)	0.6 (0.4-1.0)	72 (14.6)	0.6 (0.4-1.0)	52 (16.9)	0.7 (0.4-1.3)	32 (17.1)	1.1 (0.5-2.2)
2	114 (25.4)	0.5 (0.3-0.7) ^b	119 (24.1)	0.5 (0.3-0.7) ^b	69 (22.5)	0.4 (0.3-0.7) ^b	49 (26.2)	0.7 (0.4-1.3)
≥3	225 (50.1)	0.4 (0.3-0.7) ^b	207 (41.9)	0.4 (0.3-0.7) ^b	130 (42.4)	0.4 (0.3-0.7) ^b	81 (43.3)	0.6 (0.3-1.0)
P for trend		0.126		0.126		0.049		0.028
Ever had severe menopausal ^a symptoms	180 (100)	0.5 (0.3-0.7) ^b	166 (100)	0.5 (0.3-0.7) ^b	115 (100)	0.5 (0.3-0.8) ^b	71 (100)	0.8 (0.4-1.5)
Number of severe menopausal symptoms among women who ever experienced a menopausal symptom								
Never had menopausal symptoms	51	1.0 (ref)	96	1.0 (ref)	56	1.0 (ref)	25	1.0 (ref)
1	83 (46.1)	0.5 (0.3-0.8) ^b	81 (48.8)	0.5 (0.3-0.8) ^b	52 (45.2)	0.5 (0.3-0.9) ^b	42 (59.1)	0.9 (0.5-1.7)
2	55 (30.6)	0.4 (0.2-0.7) ^b	48 (28.9)	0.4 (0.2-0.7) ^b	30 (26.1)	0.4 (0.2-0.8) ^b	19 (26.8)	0.6 (0.3-1.3)
≥3	42 (23.3)	0.4 (0.2-0.8) ^b	37 (22.3)	0.4 (0.2-0.8) ^b	33 (28.7)	0.6 (0.3-1.1)	10 (14.1)	0.4 (0.2-0.9) ^b
P for trend		0.296		0.296		0.877		0.070
Ever had vasomotor symptoms	355 (89.2)	0.5 (0.3-0.7) ^b	355 (89.2)	0.5 (0.3-0.7) ^b	225 (89.6)	0.5 (0.3-0.8) ^b	141 (87.0)	0.7 (0.4-1.2)
Ever had urogenital atrophy symptoms	257 (64.6)	0.4 (0.3-0.7) ^b	244 (61.3)	0.4 (0.3-0.7) ^b	148 (59.0)	0.5 (0.3-0.7) ^b	100 (61.7)	0.7 (0.4-1.2)
Ever had emotional changes or insomnia	170 (42.7)	0.5 (0.3-0.8) ^b	175 (44.0)	0.5 (0.3-0.8) ^b	108 (43.0)	0.5 (0.3-0.8) ^b	71 (43.8)	0.8 (0.4-1.4)

^aThirty women (13 controls, 12 IDC cases, and 5 ILC cases) had missing data on intensity of menopausal symptoms and excluded from the analysis.^bP < 0.05.^cAll OR are adjusted for age, year, duration of HT use, and the type of menopause.

Table 4. Relationship between history of ever having experienced menopausal symptoms and breast cancer risk stratified by HT use, age at menopause, and body mass index

	Ever had menopausal symptoms					
	Ductal (n = 494)		Lobular (n = 307)		Ductal-lobular (n = 187)	
	OR ^a (95% CI)	P for interaction	OR ^a (95% CI)	P for interaction	OR ^a (95% CI)	P for interaction
Overall	0.5 (0.3–0.7) ^b		0.5 (0.3–0.8) ^b		0.7 (0.4–1.2)	
Recency of HT use						
Never users	0.5 (0.3–0.9) ^b	0.8	0.6 (0.3–1.3)	0.5	0.7 (0.3–1.7)	0.9
Former users	0.5 (0.3–0.7) ^b		0.5 (0.3–0.9) ^b		0.7 (0.4–1.3)	
Current estrogen only users	0.5 (0.3–0.8) ^b		0.5 (0.3–0.8) ^b		0.7 (0.4–1.3)	
Current E + P users	0.5 (0.2–0.9) ^b		0.4 (0.2–0.9) [†]		0.7 (0.3–1.9)	
Age at first use of any type of menopausal HT (years)						
<45	0.3 (0.1–1.0)	0.4	0.7 (0.1–3.7)	0.7	0.5 (0.1–3.4)	0.6
45–54	0.4 (0.2–0.8) [†]		0.6 (0.3–1.6)		0.6 (0.2–1.9)	
≥55	0.5 (0.3–0.8) ^b		0.6 (0.3–0.9) ^b		0.8 (0.4–1.6)	
Timing of first use of HT in relation to age at menopause						
Before menopause	0.3 (0.1–1.7)	0.6	0.5 (0.1–2.8)	0.8	0.8 (0.1–5.8)	0.9
Same year as menopause	0.4 (0.1–1.2)		0.5 (0.1–1.6)		0.8 (0.2–3.0)	
1–4 years after menopause	0.5 (0.2–0.9) ^b		0.5 (0.3–1.1)		0.8 (0.4–1.9)	
≥5 years after menopause	0.6 (0.3–1.1)		0.6 (0.3–1.2)		0.8 (0.3–2.1)	
Age at menopause						
<45	0.4 (0.1–1.2)	0.6	0.7 (0.1–3.2)	0.7	0.7 (0.1–4.1)	0.8
45–49	0.4 (0.2–0.9) ^b		0.6 (0.2–1.7)		0.7 (0.2–2.5)	
50–54	0.5 (0.3–0.8) ^b		0.5 (0.3–1.0)		0.8 (0.4–1.7)	
55+	0.6 (0.3–0.9) ^b		0.5 (0.3–0.8) ^b		0.9 (0.4–1.8)	
Years between age at menopause and reference age						
<8	0.6 (0.2–1.9)	0.8	0.4 (0.1–1.4)	0.7	0.8 (0.2–3.7)	0.9
8–14	0.5 (0.2–1.3)		0.4 (0.2–1.0)		0.7 (0.3–2.1)	
15–21	0.5 (0.3–0.9)		0.4 (0.2–0.8) ^b		0.7 (0.3–1.4)	
22+	0.5 (0.3–0.8) ^b		0.5 (0.3–0.9) ^b		0.7 (0.3–1.4)	
BMI, quartiles, kg/m ²						
<23.4	0.7 (0.3–1.6)	0.4	0.7 (0.2–2.0)	0.6	1.7 (0.4–6.7)	0.7
23.4–26.4	0.6 (0.3–1.1)		0.6 (0.3–1.2)		1.2 (0.5–3.0)	
26.5–31.0	0.5 (0.3–0.8) ^b		0.5 (0.3–0.9) ^b		0.9 (0.5–1.6)	
31.1+	0.4 (0.3–0.7) ^b		0.5 (0.3–0.8) ^b		0.6 (0.3–1.2)	

^aAll odds ratios (OR) are adjusted for age, year, duration of HT use, and the type of menopause.

^bP < 0.05.

of IDLC, although this reduction in risk was within the limits of chance. The magnitude of the risk reduction also tended to increase as the number of menopausal symptoms women experienced increased, but did not appear to be influenced by menopausal symptom type. However, we did have more detailed information on hot flashes, and increasing intensity of hot flashes was associated with progressively lower risks of all 3 histologic subtypes of breast cancer studied. In particular, women who experienced severe hot flashes with awakening had lower risks of breast cancer compared with women who experienced menopausal symptoms other than hot flashes with awakening and also compared with women who had hot flashes without perspiration.

A plausible biologic explanation for our findings is that menopausal symptoms are a surrogate marker for hormonal changes that are relevant to the etiology of breast cancer. Changes in endogenous sex hormones, and the magnitude of these changes, have been linked to menopausal symptoms (5), and thus the sharper or more pronounced hormonal changes that women who experience more intense menopausal symptoms experience may be related to breast cancer risk. A challenge in this study though was efforts to evaluate the impact of different types of menopausal symptoms separately. Although vasomotor symptoms are more clearly linked to hormonal changes, psychological symptoms are not (6–10, 14), but the high proportions of women who reported more than

Table 5. History of hot flashes and risk of breast cancer by histologic type

Hot flashes	Controls (n = 449)		Ductal cases (n = 494)		Lobular cases (n = 307)		Ductal-lobular cases (n = 187)	
	n (%)	n (%)	OR ^c (95% CI)	n (%)	OR ^c (95% CI)	n (%)	OR ^c (95% CI)	
Never had menopausal symptoms	51 (11.4)	96 (19.4)	1.0 (ref)	56 (18.2)	1.0 (ref)	25 (13.4)	1.0 (ref)	
Experienced menopausal symptoms, but never hot flashes	55 (12.2)	61 (12.3)	0.5 (0.3–0.9) ^b	45 (14.7)	0.7 (0.4–1.2)	27 (14.4)	0.9 (0.4–2.0)	
Ever experienced hot flashes ^a	343 (76.4)	337 (68.2)	0.5 (0.3–0.7) ^b	206 (67.1)	0.5 (0.3–0.7) [†]	135 (72.2)	0.7 (0.4–1.2)	
<i>Ever had hot flashes without perspiration or awakening</i>	39 (100)	51 (100)	0.6 (0.3–1.1)	36 (100)	0.8 (0.4–1.5)	31 (100)	1.5 (0.7–3.2)	
Duration of hot flashes without perspiration or awakening (months) ^d								
<12	17 (43.6)	21 (41.2)	0.5 (0.2–1.1)	15 (41.7)	0.6 (0.3–1.6)	10 (32.3)	1.0 (0.3–3.0)	
≥12	22 (56.4)	30 (58.8)	0.7 (0.3–1.3)	21 (58.3)	0.9 (0.4–2.0)	21 (67.7)	1.8 (0.7–4.2)	
<i>Ever had hot flashes with perspiration, but not awakening</i>	132 (100)	147 (100)	0.5 (0.3–0.8) ^c	72 (100)	0.4 (0.3–0.7) ^c	56 (100)	0.7 (0.3–1.3)	
Duration of hot flashes with perspiration but not awakening (months) ^d								
<12	48 (36.4)	57 (38.8)	0.6 (0.3–1.0) ^c	29 (40.3)	0.4 (0.2–0.8) ^c	20 (35.7)	0.6 (0.3–1.3)	
12–35	43 (32.6)	48 (32.6)	0.5 (0.3–0.9) ^c	21 (29.2)	0.4 (0.2–0.8) ^c	18 (32.2)	0.6 (0.3–1.4)	
≥36	41 (31.0)	42 (28.6)	0.5 (0.3–0.9) ^c	22 (30.5)	0.5 (0.3–1.0) ^c	18 (32.1)	0.8 (0.3–1.8)	
<i>Ever had hot flashes with awakening</i>	147 (100)	114 (100)	0.4 (0.2–0.6) ^c	79 (100)	0.3 (0.2–0.6) ^c	40 (100)	0.5 (0.3–1.1)	
Duration of hot flashes with awakening (months) ^d								
<12	34 (23.1)	36 (31.6)	0.5 (0.3–0.9) ^c	25 (31.6)	0.5 (0.2–1.0) ^c	13 (32.5)	0.8 (0.3–2.1)	
12–35	56 (38.1)	32 (28.1)	0.3 (0.2–0.5) ^c	22 (27.8)	0.2 (0.1–0.5) ^c	15 (37.5)	0.5 (0.2–1.2)	
≥36	57 (38.8)	46 (40.3)	0.4 (0.2–0.6) ^c	32 (40.6)	0.3 (0.2–0.7) ^c	12 (30.0)	0.4 (0.2–1.0)	
<i>P for trend in hot flash intensity^f</i>			0.007		0.017		<0.001	

^aTwenty-five controls, 25 IDC, 19 ILC, and 8 IDLC cases who experienced hot flashes had missing data on the intensity of hot flashes.

^b $P < 0.05$.

^cOR are adjusted for age, year, duration of HT use, and the type of menopause.

^eAll P values for trend in duration of hot flashes were more than 0.05.

^f P value for trend across the 3 categories of hot flash intensity.

1 type menopausal symptom limited our statistical power for evaluating the effects of individual symptoms (e.g., only 3 controls and 13 cases reported having "only" experienced emotional changes or insomnia related to menopause). We did however observe that increases in intensity of hot flashes were inversely associated with risks of IDC, ILC, and IDLC. Several studies provided evidence that there might be a correlation between intensity of hot flashes and hormonal levels, especially FSH and estrogen levels (15–17). In the population-based, cross-sectional study by Guthrie and colleagues (15), a negative linear relationship was observed between estradiol levels and hot flash frequency. They found that women who experienced hot flashes several times a day had 35% to 40% lower estradiol levels compared with women who did not experience hot flashes or who only experienced them a few times in last 2 weeks. Thus, the hormonal milieu of women who experience menopausal symptoms and intense hot flashes in particular may be sufficiently different from women who do not experience menopausal symptoms to convey a lower risk of breast cancer.

Although we could not assess levels of specific hormones at the time women experienced menopausal symptoms, our observation that this association was not modified by various hormone-related factors that were available for analysis in this study, including recency and timing of HT use, age at menopause, and BMI, suggests that menopausal symptoms and what they represent hormonally may be independently related to breast cancer risk. Nevertheless, the biology underlying menopausal symptoms and the specific hormonal aspects related to them that may impact the pathogenesis of breast cancer remain unclear.

In this study we made the novel observation that women who ever experienced menopausal symptoms have a lower risk of postmenopausal breast cancer and that hot flash intensity is also inversely related to risk. The natural patterns of menopausal symptoms are highly variable across women, and the factors that are involved in their pathogenesis are complex. An interesting feature of menopausal symptoms as an exposure is that their median age of onset is about 50 and the symptoms can last for months or years (13). All women included in this study were 55 to 74

years of age at diagnosis suggesting that the hormonal changes that occur with menopause that take place 5 years or earlier still appear to impact breast cancer risk. So if our observations are confirmed, a greater understanding of the biological consequences of the hormonal fluctuations that occur during menopause and their relationship to breast cancer risk would be warranted.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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