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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 as they go through menopause compared to 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% confidence interval (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.

Keywords

menopausal symptoms; hot flashes; breast cancer; ductal; lobular

INTRODUCTION

Breast cancer is the most common form of cancer and the second leading cause of cancer death among women in U.S. [1]. There is overwhelming evidence that estrogen plays a critical role in the disease's pathogenesis [2,3]. In a meta-analysis of nine 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 to 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 three years after menopause reported a five-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 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 hormone therapy among postmenopausal women, users of both types of menopausal hormone therapy were 20–30% more likely than women receiving placebo to report relief of vasomotor symptoms, but similar percentages of women 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 hormone therapy (HT) and risk of different histologic types of breast cancer among women aged 55 to 74. Our approach stratifies risk by histology given evidence suggesting that compared to 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 hormone therapy is more strongly related to risk of lobular compared to ductal tumors [12]. Details of this study’s methods have been described previously [12]. In addition to collecting detailed information on hormone therapy, this study also captured detailed self-reported data on history of menopausal symptoms through a structured in-person interview as described below.

Participants

Women 55 to 74 years of age with no prior 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. 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 prior 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 (20). Controls were frequency matched 1:1 within 5-year age groups based on the age distributions of the invasive lobular carcinoma (ILC) and invasive ductal-lobular carcinoma (IDLC) cases combined using one-step recruitment. 9,876 telephone numbers were either verified as residential or presumed to be residential. 13% 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. 660 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 hormone therapy 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 if 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 to 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 flashes 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 flashes we further characterized severity of hot flashes according to both perspiration and awakening. Specifically, we assessed risks associated with hot flash duration and intensity (three mutually exclusive levels: hot flashes without perspiration or awakening, hot flashes with perspiration but not awakening, and hot flashes with awakening regardless of perspiration).

Statistical Analysis

Polytomous logistic regression was performed to calculate odds ratios (OR) and their associated 95% confidence intervals (95% CI) to compare IDC, ILC and IDLC cases to controls. All analyses were conducted using Stata/SE version 10.0 (StataCorp LP, College Station, TX). We also calculated two sided *p*-values for the comparison between ILC and IDLC risk estimates vs. 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 (<45y, 45–54y, ≥55y), 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, five 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, 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 >10% when included in our statistical models, and thus were the only two confounders added to our final multivariate adjusted statistical models along with age and year of diagnosis.

We also evaluated recency of hormone therapy 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 two 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 three 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 hormone therapy compared to controls. ILC and IDLC cases tended to have a lower BMI and were more frequently current E+P users compared to IDC cases and controls.

Among controls, compared to 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 hormone therapy (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 non-significant 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, though trends with increasing numbers of severe menopausal symptoms experienced were not significant. 40% 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 three 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+ vs. ER- disease (data not shown, all *p*-values for comparison of ER+ vs. 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 hormone therapy use, age at first use of any type of menopausal hormone therapy, timing of first use of hormone therapy in relation to age at menopause, age at menopause, timing of age at reference in relation to age at menopause, or body mass index (all *p*-values for interaction were >0.4, Table 4). Specifically, the same inverse association between ever having experienced menopausal symptoms and breast cancer risk was consistently observed among never vs. current menopausal hormone therapy 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 to women who only experienced hot flashes without perspiration (all *p*-values for heterogeneity of ORs across the three 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 <0.001–0.017) were statistically significant across the three 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 >0.05.

DISCUSSION

Before interpreting the results of our study, it is important to first describe its limitations. While 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 themselves. Also, the resulting misclassification of exposure is likely to be non-differential 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 two most common histologic types of breast cancer. In addition, we observed that women who ever had menopausal symptoms also had a 70% lower risk of IDLC, though 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 three histologic subtypes of breast cancer studied. In particular, women who experienced severe hot flashes with awakening had lower risks of breast cancer compared to women who experienced menopausal symptoms other than hot flashes with awakening and also compared to 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. While vasomotor symptoms are more clearly linked to hormonal changes, psychological symptoms are not [6–10], but the high proportions of women who reported more than one 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, et al. [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 35–40% lower estradiol levels compared to 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. While 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 which 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 55–74 years of age at diagnosis suggesting that the

hormonal changes that occur with menopause that take place five 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.

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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 (years)				
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/m²)				
<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)

Characteristics	Controls (n=449)	Ductal (n=494)	Lobular (n=307)	Ductal-lobular (n=187)
	n (%)	n (%)	n (%)	n (%)
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 (years)				
<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
Age at first use of any type of menopausal hormone therapy (years)				
<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 hormone therapy 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 years after menopause	34 (13.8)	60 (21.3)	40 (21.4)	26 (20.2)
≥5 years after menopause	32 (13.0)	30 (10.7)	18 (9.6)	13 (10.1)
Missing	202	213	120	58
Recency of menopausal hormone therapy 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 estrogen+progestin	95 (21.2)	152 (30.9)	122 (39.7)	86 (46.0)
Missing	0	2	0	0
Timing of age at reference in relation to age at menopause (years)				
<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)
Missing	132	117	82	39
Duration of hormone therapy use (years)				
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)

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 (years)			
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/m²)			
<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 (years)			
<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 hormone therapy 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 estrogen+progestin	5 (9.8)	50 (23.4)	39 (21.7)
Duration of hormone therapy use(years)			
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)

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 (%)
≥15	18 (35.3)	43 (20.1)	49 (27.2)

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 (%)	n (%)	OR [‡] (95%CI)	n (%)	OR [‡] (95%CI)	n (%)	OR [‡] (95%CI)	n (%)	OR [‡] (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)	25 (13.4)	1.0 (ref)
Ever had menopausal symptoms	398 (88.6)	398 (80.6)	0.5 (0.3–0.7) [†]	251 (81.8)	0.5 (0.3–0.8) [†]	162 (86.6)	0.7 (0.4–1.2)	162 (86.6)	0.7 (0.4–1.2)
Number of menopausal symptoms experienced									
1	59 (13.1)	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)	32 (17.1)	1.1 (0.5–2.2)
2	114 (25.4)	119 (24.1)	0.5 (0.3–0.7) [†]	69 (22.5)	0.4 (0.3–0.7) [†]	49 (26.2)	0.7 (0.4–1.3)	49 (26.2)	0.7 (0.4–1.3)
≥3	225 (50.1)	207 (41.9)	0.4 (0.3–0.7) [†]	130 (42.4)	0.4 (0.3–0.7) [†]	81 (43.3)	0.6 (0.3–1.0)	81 (43.3)	0.6 (0.3–1.0)
<i>P</i> for trend		0.126		0.049		0.028		0.028	
Ever had severe menopausal* symptoms	180 (100)	166 (100)	0.5(0.3–0.7) [†]	115 (100)	0.5(0.3–0.8) [†]	71 (100)	0.8(0.4–1.5)	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	96	1.0 (ref)	56	1.0 (ref)	25	1.0 (ref)	25	1.0 (ref)
1	83 (46.1)	81 (48.8)	0.5 (0.3–0.8) [†]	52 (45.2)	0.5 (0.3–0.9) [†]	42 (59.1)	0.9 (0.5–1.7)	42 (59.1)	0.9 (0.5–1.7)
2	55 (30.6)	48 (28.9)	0.4 (0.2–0.7) [†]	30 (26.1)	0.4 (0.2–0.8) [†]	19 (26.8)	0.6 (0.3–1.3)	19 (26.8)	0.6 (0.3–1.3)
≥3	42 (23.3)	37 (22.3)	0.4 (0.2–0.8) [†]	33 (28.7)	0.6 (0.3–1.1)	10 (14.1)	0.4 (0.2–0.9) [†]	10 (14.1)	0.4 (0.2–0.9) [†]
<i>P</i> for trend		0.296		0.877		0.070		0.070	
Ever had vasomotor symptoms	355 (89.2)	355 (89.2)	0.5 (0.3–0.7) [†]	225 (89.6)	0.5 (0.3–0.8) [†]	141 (87.0)	0.7 (0.4–1.2)	141 (87.0)	0.7 (0.4–1.2)
Ever had urogenital atrophy symptoms	257 (64.6)	244 (61.3)	0.4 (0.3–0.7) [†]	148 (59.0)	0.5 (0.3–0.7) [†]	100 (61.7)	0.7 (0.4–1.2)	100 (61.7)	0.7 (0.4–1.2)
Ever had emotional changes or insomnia	170 (42.7)	175 (44.0)	0.5 (0.3–0.8) [†]	108 (43.0)	0.5 (0.3–0.8) [†]	71 (43.8)	0.8 (0.4–1.4)	71 (43.8)	0.8 (0.4–1.4)

* Thirty women (13 controls, 12 IDC cases, and 5 ILC cases) had missing data on intensity of menopausal symptoms and excluded from the analysis.

[†] *p*-value <0.05.[‡] All odds ratios (OR) are adjusted for age, year, duration of hormone therapy use, and the type of menopause.

Table 4

Relationship between menopausal symptoms and breast cancer risk stratified by hormone therapy use, age at menopause, and body mass index

	Ductal cases (n=494)		Lobular cases (n=307)		Ductal-lobular cases (n=187)	
	Ever had menopausal symptoms	OR* (95% CI)	Ever had menopausal symptoms	OR* (95% CI)	Ever had menopausal symptoms	OR* (95% CI)
Overall		0.5 (0.3-0.7) [†]		0.5 (0.3-0.8) [†]		0.7 (0.4-1.2)
Recency of hormone therapy use						
Never users	0.8	0.5 (0.3-0.9) [†]	0.5	0.6 (0.3-1.3)	0.9	0.7 (0.3-1.7)
Former users		0.5 (0.3-0.7) [†]		0.5 (0.3-0.9) [†]		0.7 (0.4-1.3)
Current estrogen only users		0.5 (0.3-0.8) [†]		0.5 (0.3-0.8) [†]		0.7 (0.4-1.3)
Current estrogen+progestin users		0.5 (0.2-0.9) [†]		0.4 (0.2-0.9) [†]		0.7 (0.3-1.9)
Age at first use of any type of menopausal hormone therapy (years)						
<45	0.4	0.3(0.1-1.0)	0.7	0.7(0.1-3.7)	0.6	0.5(0.1-3.4)
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) [†]		0.6(0.3-0.9) [†]		0.8(0.4-1.6)
Timing of first use of hormone therapy in relation to age at menopause						
Before menopause	0.6	0.3(0.1-1.7)	0.8	0.5(0.1-2.8)	0.9	0.8(0.1-5.8)
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) [†]		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	0.6	0.4 (0.1-1.2)	0.7	0.7 (0.1-3.2)	0.8	0.7 (0.1-4.1)
45-49		0.4 (0.2-0.9) [†]		0.6 (0.2-1.7)		0.7 (0.2-2.5)
50-54		0.5 (0.3-0.8) [†]		0.5 (0.3-1.0)		0.8 (0.4-1.7)
55+		0.6 (0.3-0.9) [†]		0.5 (0.3-0.8) [†]		0.9 (0.4-1.8)
Timing of age at reference in relation to age at menopause (years)						
<8	0.8	0.6 (0.2-1.9)	0.7	0.4 (0.1-1.4)	0.9	0.8 (0.2-3.7)
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) [†]		0.7 (0.3-1.4)

	Ductal cases (n=494)		Lobular cases (n=307)		Ductal-lobular cases (n=187)	
	OR* (95% CI)	P for interaction	OR* (95% CI)	P for interaction	OR* (95% CI)	P for interaction
22+	0.5 (0.3–0.8) [†]		0.5 (0.3–0.9) [†]		0.7 (0.3–1.4)	
Body mass index, quartiles (kg/m²)						
<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) [†]		0.5 (0.3–0.9) [†]		0.9 (0.5–1.6)	
31.1+	0.4 (0.3–0.7) [†]		0.5 (0.3–0.8) [†]		0.6 (0.3–1.2)	

* All odds ratios (OR) are adjusted for age, year, duration of hormone therapy use, and the type of menopause.

[†] p-value <0.05.

Table 5

History of hot flashes and the risk of breast cancer by histologic types

Hot flashes	Controls (n=449)		Ductal cases (n=494)		Lobular cases (n=307)		Ductal-lobular cases (n=187)	
	n (%)	OR [‡] (95%CI)	n (%)	OR [‡] (95%CI)	n (%)	OR [‡] (95%CI)	n (%)	OR [‡] (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)
Experienced menopausal symptoms, but never hot flashes	55 (12.2)	0.5 (0.3–0.9) [‡]	61 (12.3)	0.5 (0.3–0.9) [‡]	45 (14.7)	0.7 (0.4–1.2)	27 (14.4)	0.9 (0.4–2.0)
Ever experienced hot flashes *	343 (76.4)	3.37 (68.2)	337 (68.2)	0.5 (0.3–0.7) [‡]	206 (67.1)	0.5 (0.3–0.7) [‡]	135 (72.2)	0.7 (0.4–1.2)
Ever had hot flashes without perspiration or awakening	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) [§]								
<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)	
Ever had hot flashes with perspiration, but not awakening	132 (100)	147 (100)	0.5 (0.3–0.8) [‡]	72 (100)	0.4 (0.3–0.7) [‡]	56 (100)	0.7 (0.3–1.3)	
Duration of hot flashes with perspiration but not awakening (months) [§]								
<12	48 (36.4)	57 (38.8)	0.6 (0.3–1.0) [‡]	29 (40.3)	0.4 (0.2–0.8) [‡]	20 (35.7)	0.6 (0.3–1.3)	
12–35	43 (32.6)	48 (32.6)	0.5 (0.3–0.9) [‡]	21 (29.2)	0.4 (0.2–0.8) [‡]	18 (32.2)	0.6 (0.3–1.4)	
≥36	41 (31.0)	42 (28.6)	0.5 (0.3–0.9) [‡]	22 (30.5)	0.5 (0.3–1.0) [‡]	18 (32.1)	0.8 (0.3–1.8)	
Ever had hot flashes with awakening	147 (100)	114 (100)	0.4 (0.2–0.6) [‡]	79 (100)	0.3 (0.2–0.6) [‡]	40 (100)	0.5 (0.3–1.1)	
Duration of hot flashes with awakening (months) [§]								
<12	34 (23.1)	36 (31.6)	0.5 (0.3–0.9) [‡]	25 (31.6)	0.5 (0.2–1.0) [‡]	13 (32.5)	0.8 (0.3–2.1)	
12–35	56 (38.1)	32 (28.1)	0.3 (0.2–0.5) [‡]	22 (27.8)	0.2 (0.1–0.5) [‡]	15 (37.5)	0.5 (0.2–1.2)	
≥36	57 (38.8)	46 (40.3)	0.4 (0.2–0.6) [‡]	32 (40.6)	0.3 (0.2–0.7) [‡]	12 (30.0)	0.4 (0.2–1.0)	
P for trend in hot flash intensity[¶]			0.007		0.017		<0.001	

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

[‡] p-value <0.05.

[‡] Odds ratios (OR) are adjusted for age, year, duration of hormone therapy use, and the type of menopause.

[§] All p-values for trend in duration of hot flashes were >0.05.

[¶] p-value for trend across the three categories of hot flash intensity.