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Menopausal symptoms and the risk of young-onset breast cancer

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Summary

Background—Women with menopausal symptoms have been reported to have reduced risk of breast cancer, possibly reflecting differences in endogenous hormone levels. We examined the associations between menopausal symptoms and breast cancer in women under age 50.

Methods—We carried out a sister-controlled case-control study, the Two Sister Study, comparing 1422 women with breast cancer diagnosed before age 50 and their 1669 sisters who were free of breast cancer and had enrolled in the prospective Sister Study cohort. History and age at first occurrence of menopause-associated symptoms (e.g. hot flashes, poor sleep, or night sweats) was ascertained using computer-assisted telephone interviews. To equalize opportunity for exposure, we assessed exposures in relation to a sibship-based *index age* (the minimum of the age at diagnosis of the case sister and the age at interview of her control sister(s)), and estimated odds ratios using conditional logistic regression with adjustment for menopausal status and birth order.

Findings—Having had menopause-associated symptoms (n=706) prior to the index age was associated with reduced risk of young-onset breast cancer (odds ratio (OR), 0.49; 95% confidence interval (CI), 0.40 to 0.61). Similar results were seen for hot flashes and for “other” menopausal symptoms. The association between menopausal symptoms and breast cancer risk was somewhat stronger for estrogen receptor positive tumors than for estrogen receptor negative tumors (heterogeneity $p = 0.07$). Menopausal status, age at menopause, BMI and hormone replacement therapy did not modify the associations, but the inverse association between menopausal symptoms and breast cancer attenuated with increasing index age ($p < 0.01$).

Interpretation—Menopause-associated symptoms were associated with markedly reduced risk of young-onset breast cancer. Further studies are needed to confirm the association and elucidate possible pathways.

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Contributors

CF, LAD, DPS and CRW conceived the study design. CF and CRW did the statistical analysis. CF drafted the initial manuscript. LAD, DPS and CRW were responsible for data collection and acquired funding. All authors participated in data interpretation and in critical review of the manuscript, and had full access to the data.

Conflicts of interest

All authors declare that they have no conflicts of interest.

Introduction

Peri-menopause often brings hot flashes, night sweats, sleep disturbances, depression and other symptoms. Of these symptoms, hot flashes are the most characteristic symptom of perimenopause, with up to 75% of women experiencing them ¹. The aetiology of menopausal symptoms is complex, but they are thought to be caused by ovarian senescence and the resulting estrogen decline ². In a recent case-control study of postmenopausal women, menopausal symptoms were linked to lower risk of breast cancer, and among those with symptoms, greater severity of hot flashes was associated with lower risk ³. To date, no other epidemiologic study has evaluated the association between menopausal symptoms and risk of breast cancer.

We examined the associations between hot flashes and other menopausal symptoms and the risk of young-onset breast cancer in the Two Sister Study, a sister-based case-control study.

Methods

The study design and methods for subject selection have been described elsewhere ⁴ (<http://www.sisterstudy.org>). Briefly, case subjects were recruited through their sisters who had enrolled in the Sister Study, a prospective cohort study of 50,884 women aged 35 to 74 years residing in the United States or Puerto Rico. Sister Study participants each had a sister with breast cancer. For the retrospective Two Sister Study, Sister Study participants whose case sister had been younger than 50 at diagnosis and had been diagnosed within 4 years of being identified as eligible were contacted and asked to send a letter of invitation to their affected sister. Consenting case sisters completed the same computer-assisted telephone interviews (CATIs) on reproductive history, health conditions and life style factors as their control sisters had at the time of enrollment in the Sister Study. In addition, case sisters completed a CATI on breast cancer diagnosis and treatment and authorized release of relevant medical records. 1422 cases enrolled and 1669 corresponding control sisters were identified. A total 191 cases had more than one participating sister control. Of 1517 cases who were identified as being possibly eligible but did not participate, 91 were reported by their sister to have died. Others may also have died or been too ill to participate and some may have self-selected out because they thought they were ineligible (e.g. because of actual age at diagnosis). We were unable to compare the participating and nonparticipating cases directly, but did compare the controls who participated to those who did not participate to explore possible selection biases related to age at enrollment, race, education and other factors. During their subsequent follow up in the Sister Study five control sisters were diagnosed with breast cancer at a younger age than their sister case. As a sensitivity analysis, those control sisters were excluded.

Women were asked whether they had experienced hot flashes or other menopausal symptoms (such as poor sleeping, night sweats, irritability, or depression), and they were also asked their age at first having symptoms. In the analysis the presence of any menopausal symptoms was examined; hot flashes and other “menopausal symptoms” were also examined separately. By design, case sisters were under 50 at enrollment, but their control sister could have been older. To ensure equal opportunity for exposure, symptoms were only considered if they were reported to have occurred prior to an “index” age, which was defined for each sibship as the youngest of the age of the case at diagnosis and the ages at interview of her sister control(s).

Conditional logistic regression was performed to estimate odds ratios (OR) and 95% confidence intervals (CI). We adjusted for birth order among participating sisters and menopausal status at their index age (premenopausal, premenopausal hysterectomy with

retained ovary tissue and postmenopausal). We considered as premenopausal women who were still menstruating or had been recently pregnant or nursing at the index age (1396 controls and 1269 cases). Women who at the index age had not had a period for 12 months or more and had not been recently pregnant or nursing were categorized as postmenopausal (271 controls and 153 cases). Women with premenopausal hysterectomy with retained ovary tissue were treated as distinct from pre- or post-menopause because of the potential for continued but reduced ovarian function (124 controls and 77 cases). Because early menopause is protective for breast cancer and women with early menopause are more likely to experience menopausal symptoms, we explored the impact of age at menopause by further categorizing postmenopausal women as <41 years or ≥41 years at menopause. This refinement did not alter the findings so the variable with 3 levels of menopausal status was used in the final model. Other potential confounders were considered, including age at first birth, age at menarche, parity, education, duration of breast feeding, body mass index (BMI) based on recalled weight in their 30's, hormonal birth control history, cigarette smoking and average alcohol drinking. None of these adjustments materially changed the estimate. Although the use of hormone replacement therapy (HRT) is not a good candidate for adjustment because it is potentially on the causal pathway from symptoms to breast cancer, adjustment for HRT did not change the estimate of interest and this variable was not included in the final model. To determine whether menopause-associated symptoms influenced the risk of breast cancer differently in subgroups of women, we assessed selected variables as potential effect measurement modifiers (menopausal status, BMI in 30's, HRT, index age), applying likelihood-ratio tests for heterogeneity to models that included relevant interaction terms. We carried out analyses restricted to ER+ cancer to assess specificity of the results to tumor phenotype. We also restricted analysis to invasive ductal carcinoma to enable a comparison with the results from Huang et al's study.³

Role of the funding source

Aside from receiving yearly progress reports and their original decision to approve the project, Susan G. Komen for the Cure had no other role in the design and conduct of this study, collection, analysis, and interpretation of the data, and preparation of this article. All authors had full access to the study data and the corresponding author had the final responsibility to submit for publication.

Results

Case and control sisters were similar with regard to race, education, parity, breastfeeding experience, cigarette smoking and alcohol drinking in the 10 years preceding index age, but cases reported a younger age at menarche, older age at first birth, and lower BMI in their 30's, and were more likely to report having taken hormonal birth control pills for more than 10 years and less likely to have experienced menopause before the index age (Table 1) (Fei et al. 2012). By design, the control sisters tended to be older at completion of CATI interviews than case sisters had been at diagnosis. The mean index age was 43.6 years (standard deviation [SD] = 4.1 years, range 28.4-49.9 years), and 903 families had index age equal to age at diagnosis of the case sister(s). More control sisters (35.4%) than case sisters (22%) were interviewed more than 5 years after index age.

706 women (22.9%) had ever had menopause-associated symptoms before their index age, of which 518 had had hot flashes and 565 had had other menopausal symptoms. Women who reported that they had experienced menopause-associated symptoms were more likely to have experienced menopause or had premenopausal hysterectomy with retained ovary tissue (Table 2). Hot flashes and other menopause-associated symptoms were not unique to post-menopausal women: 11.3% of premenopausal women had ever had hot flashes and

14.2% had ever had other menopausal symptoms prior to index age. Nearly 30% of women who had had hot flashes had ever taken HRT, compared to 3.6% of those who had not.

Women who reported that they had experienced any menopause-associated symptoms prior to the index age were less likely to have young-onset breast cancer (odds ratio (OR), 0.49; 95% confidence interval (CI), 0.40 to 0.61) (Table 2). Inverse associations were separately observed for reported hot flashes (OR=0.47, 95% CI 0.37, 0.60) and other menopausal symptoms (OR=0.56, 95% CI 0.45, 0.70). Analysis restricted to invasive ductal carcinoma (n=1011) produced similar results (data not shown). When we subdivided breast cancers according to hormone receptor status, the reduction in breast cancer risk associated with symptoms was greater for ER+ cases than for ER- cases, but differences were statistically significant only for “other” menopausal symptoms (p for heterogeneity=0.04) and were borderline significant for the presence of any menopausal symptoms (p for heterogeneity=0.07) (Table 3).

The association between menopausal symptoms and the risk of young-onset breast cancer was not significantly modified by menopausal status at index age, BMI in the 30's, or use of HRT. But the inverse association between menopausal symptoms and breast cancer attenuated with increasing index age (p=0.0004). In exploratory analysis, the time interval between index age (either age at cancer diagnosis or age at completion of enrollment) and age at interview was found to be inversely associated with reporting of menopausal symptoms prior to index age in controls. As a sensitivity analysis, we excluded those women who were interviewed 5 years or more after the index age, and the associations remained between breast cancer risk and hot flashes (OR=0.48, 95% CI 0.35, 0.65) or other menopausal symptoms (OR=0.52, 95% CI 0.39, 0.70) (Supplemental Table 1).

The comparison of controls who were included in the analysis and those who were not included because their sister did not enroll showed they were similar in their age at enrollment, region of residence in the US, and percentage who had a mother diagnosed with breast cancer. However, included sisters were more often non-Hispanic white, more likely to have had a sister diagnosed after age 45 and more often college-educated. Exclusion of the five controls who were later diagnosed at a younger age than their case sister did not change the results.

Discussion

In this sister-based case-control study, we found that menopause symptoms were associated with reduced risk of young-onset breast cancer, and the reduction was somewhat stronger in estrogen receptor-positive tumors. The inverse associations observed were similar to the results from Huang et al's study, which is the only published study examining the association between menopausal symptoms and subsequent risk of breast cancer.³

The cases in Huang et al's study were postmenopausal women, whereas more than 90% of our cases were premenopausal at diagnosis. Huang et al also oversampled invasive lobular carcinoma and invasive ductal-lobular carcinoma. They found that menopausal symptoms were associated with reduced risk of all breast cancer subtypes. We only had 84 with lobular tumors, which did not allow us to examine lobular carcinoma separately, but the strength of the association we found was close to what they found.

Menopausal symptoms can occur at any adult age and are not necessarily specific to the peri-menopause. For example, hot flashes can occur in the last trimester of pregnancy when estrogen levels are high.¹ Hot flashes are associated with declining serum estrone and estradiol levels, but estrogen levels alone cannot explain their occurrence⁵. Although it is not clear why menopausal symptoms would be associated with reduced risk of breast cancer,

it may be due to reduced endogenous hormone levels associated with menopausal symptoms.

Breast cancer is a heterogeneous disease and ER+ and ER- tumors are believed to be etiologically somewhat different. We found a stronger association with ER+ breast cancer, and weaker (and not statistically significant) associations with ER- breast cancer, although power to detect this difference was limited because many fewer cases were ER-. The difference between ER+ and ER- tumors is consistent with a hormonal mechanism underlying the observed association of menopausal symptoms with breast cancer. Genetic factors that are involved in hormone biosynthesis and metabolism may predispose women to menopausal symptoms⁶⁻⁹ and some of these genes are also associated with risk of breast cancer, although findings have been inconsistent among studies^{10, 11}.

Our study is subject to some limitations. Young-onset breast cancer intrudes at a time of life when women may be busy with children and careers, which may discourage participation. Moreover, the participating sister whom we contacted could simply choose not to send our invitation to her case sister. Some of the 1517 nonparticipants would have been ineligible. However, although we were only informed about 91 who had died, there could have been other deaths and others who were too ill to participate.

Although we were not able to directly compare participating and non-participating cases to assess selection bias, the participating index controls were similar to the nonparticipating controls in their age at enrollment, the region of the US where they lived and the fraction who had a mother diagnosed with breast cancer. However, participants were more likely to have had a sister diagnosed between 45 and 50, more often non-Hispanic white and more often college-educated. The latter two factors are typically associated with participation; the slightly older ages at diagnosis could reflect selection for reduced childcare responsibilities. Despite these small differences, our design relies on within-family case-control comparisons and thus provides internal validity.

Our study relied on self-reported measures of menopausal symptoms. These measures are subject to biases in retrospective reporting as well as effects of mood, intervening experiences, and expectations. For example, sternal skin conductance monitors have been used to collect objective data on hot flash frequency and comparisons of objective and subjective measures indicate substantial underreporting in self-reported data of hot flash frequency⁵. We found that women who were interviewed longer after index age were less likely to report that they had had symptoms prior to index age. The concern is more relevant for controls who tended to have longer intervals. However, any resulting bias from interval-associated under-reporting should have produced an attenuation of the estimated odds ratio toward 1, since more controls than cases reported having had symptoms prior to the index age. Thus, we may be slightly understating the protective association with symptom history. To reduce the possible effect of recall bias, we carried out a sensitivity analysis that restricted to those who were interviewed within 5 years since index age and found the associations were similar.

In conclusion, our results suggest that menopausal symptoms are inversely associated with the risk of breast cancer in women under 50 and that these associations are stronger for ER+ cancer. Further studies are warranted to confirm the finding, and if confirmed to identify an underlying biological mechanism and elucidate possible pathways that might link determinants of menopausal symptoms to determinants of young-onset breast cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of participant sisters in the Two Sister Study

Characteristic	Control sisters (n = 1669)	Case sisters (n = 1422)
Race, No. (%)		
Non-Hispanic white	1487 (89.1)	1253 (88.1)
Others	182 (10.9)	169 (11.9)
Education, No. (%)		
High school or less	217 (13.0)	177 (12.4)
Some college	533 (31.9)	410 (28.8)
Bachelor degree	525 (31.5)	480 (33.8)
Master or doctoral degree	394 (23.6)	355 (25.0)
Age at menarche [‡] , mean (SD), y	12.8 (1.5)	12.6 (1.5)
Nulliparous, No. (%)	358 (21.5)	304 (21.4)
Age at first birth among parous women, mean (SD), y	26.8 (5.4)	27.7 (5.2)
Total duration of breastfeeding, mean (SD), weeks	46.3 (70.8)	44.5 (64.4)
Cigarette smoking [‡] , No. (%)		
Never-smoker	1044 (62.6)	859 (60.4)
<1 pack-year	148 (8.9)	157 (11.0)
1–10 pack-years	235 (14.1)	217 (15.3)
10 pack-years	240 (14.4)	189 (13.3)
Alcohol drinking in the 10 years preceding index age [‡] , No. (%)		
Non-drinker	317 (19.3)	263 (18.6)
0.1–<5 g/d	821 (50.1)	725 (51.2)
5–<10 g/d	241 (14.7)	205 (14.5)
10 g/d	261 (15.9)	222 (15.7)
Body mass index at ages 30–39 y [‡]		
Underweight and normal (<25.0 kg/m ²)	1210 (72.7)	1035 (73.1)
Overweight (25.0–29.9 kg/m ²)	312 (18.7)	283 (20.0)
Obesity (≥ 30.0 kg/m ²)	143 (8.6)	98 (6.9)
Use of hormonal birth control [‡] , No. (%)		
Never user	163 (9.8)	135 (9.5)
<10 y	889 (53.4)	700 (49.3)
10 y	590 (35.4)	568 (40.0)
Unknown duration	24 (1.4)	17 (1.2)
Hormone replacement therapy [‡] , No. (%) [†]		
Never user	1499 (89.9)	1346 (94.8)
Estrogen only	113 (6.8)	50 (3.5)
Combined estrogen and progesterone	55 (3.3)	24 (1.7)
Menopausal status [‡] , No. (%)		
Premenopausal	1396 (83.7)	1269 (89.2)

Characteristic	Control sisters (n = 1669)	Case sisters (n = 1422)
Postmenopausal	147 (8.8)	76 (5.3)
Premenopausal hysterectomy, with retained ovarian tissue	124 (7.4)	77 (5.4)
Interval between interview and index age, y		
<1	587 (35.2)	0 (0)
1-<5	491 (29.4)	1110 (78.1)
5-<10	423 (25.3)	270 (19.0)
10	168 (10.1)	42 (3.0)

All time-varying variables (parity, age at first birth among parous women, total duration of breastfeeding, use of hormonal birth control, cigarette smoking, alcohol drinking and menopausal status) were defined in reference to the index age; index age was defined as the minimum of age at diagnosis for the case sister and the age(s) at interview of her control sister(s).

*Missing data: household income per person (n=81), age at menarche (n=1), parity (n=1), duration of breastfeeding (n=3), body mass index at age 30 (n=10), hormonal birth control (n=5), smoking (n=2), alcohol drinking (n=36), menopausal status (n=2).

Table 2

Menopausal symptoms by menopausal status at index age for case and control sisters in the Two Sister Study

Menopausal status	<u>Menopausal symptoms in controls</u>		<u>Menopausal symptoms in cases</u>	
	No n (%)	Yes n (%)	No n (%)	Yes n (%)
Premenopausal	1109 (91.2)	284 (63.4)	1082 (93.0)	186 (72.4)
Postmenopausal	38 (3.1)	109 (24.3)	26 (2.2)	50 (19.5)
Premenopausal hysterectomy, with retained ovary tissue	69 (5.7)	55 (12.3)	56 (4.8)	21 (8.2)

Table 3

Adjusted odds ratios for young-onset breast cancer associated with menopause-associated symptoms

Characteristics [†]	Control (n=1669)	Cases (n=1422)	OR (95% CI) [‡]
	No. (%)	No. (%)	
Had any menopause symptoms prior to index age			
No	1217 (73.0)	1164 (81.9)	1.00
Yes	449 (27.0)	257 (18.1)	0.49 (0.40, 0.61)
Had hot flashes prior to index age			
No	1311 (79.1)	1244 (87.8)	1.00
Yes	346 (20.9)	172 (12.2)	0.47 (0.37, 0.60)
Had other symptoms related to menopause prior to index age			
No	1310 (78.9)	1200 (84.9)	1.00
Yes	351 (21.1)	214 (15.1)	0.56 (0.45, 0.70)

Missing data: Hot flashes (n=18), other symptoms (n=16), any menopausal symptoms (n=4) Other menopause symptoms: poor sleeping, night sweats, irritability, or depression, etc.

[†] Menopause symptoms were defined as ever prior to index age; menopause symptoms reported as first occurring after index age were not treated as relevant.

[‡] Adjusted for birth order and menopausal status at index age (premenopausal, postmenopausal, premenopausal hysterectomy with retained ovary tissue)

Adjusted odds ratios for young-onset breast cancer associated with menopause-associated symptoms, stratified by ER status

Table 4

Characteristics [†]	ER+		ER-		p for heterogeneity	
	Control (n=1285)		Cases (n=1095)			OR (95% CI) [‡]
	No. (%)	Cases (n=296)	No. (%)	Cases (n=296)		
Had any menopause-associated symptoms prior to index age						
No	929 (72.5)	908 (83.0)	1.00	263 (75.1)	230 (77.7)	
Yes	353 (27.5)	186 (17.0)	0.44 (0.35, 0.57)	87 (24.9)	66 (22.3)	
Had hot flashes prior to index age						
No	1005 (78.8)	974 (89.3)	1.00	278 (80.1)	242 (82.3)	
Yes	271 (21.2)	117 (10.7)	0.40 (0.30, 0.54)	69 (19.9)	52 (17.7)	
Had other menopause-associated symptoms prior to index age						
No	1001 (78.3)	934 (85.8)	1.00	282 (81.0)	240 (81.1)	
Yes	278 (21.7)	154 (14.2)	0.49 (0.37, 0.63)	66 (19.0)	56 (18.9)	

Missing data: ER+: Hot flashes (n=13), other symptoms (n=13), any menopausal symptoms (n=4)

ER-: Hot flashes (n=5), other symptoms (n=2)

Other menopause symptoms: poor sleeping, night sweats, irritability, or depression, etc

[†] Menopause symptoms were defined as ever prior to index age; menopause symptoms reported as first occurring after index age were not treated as relevant.

[‡] Adjusted for birth order and menopausal status at index age (premenopausal, postmenopausal, premenopausal hysterectomy with retained ovary tissue)