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Predictors of Vasomotor Symptoms among Breast Cancer Survivors

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Abstract

Purpose—Vasomotor symptoms (VMS) are a common side effect of breast cancer treatment, yet modifiable factors that may predict VMS among breast cancer survivors are unknown.

Methods—We estimated multivariable-adjusted odds ratios and 95% confidence intervals (aOR, 95% CI) for predictors of VMS among 3,595 breast cancer survivors enrolled in the Life and Longevity after Cancer Study (LILAC), an ancillary study of the Women's Health Initiative (WHI).

Results—VMS post-diagnosis were reported by 790 (22.0%) participants. Risk of VMS after diagnosis was positively associated with prior chemotherapy (aOR 1.80, 95% CI 1.21-2.68) and adjuvant hormone therapy (aOR 2.73, 95% CI 2.08-3.58), postmenopausal hormone therapy use (aOR 1.67, 95% CI 1.30-2.13), prior VMS (aOR 2.20, 95% CI 1.73-2.80), bilateral oophorectomy (aOR 1.77, 95% CI 1.37-2.27), and baseline antidepressant use (aOR 1.49, 1.06-2.09). VMS post-diagnosis were less likely among younger women (aOR 0.94, 95% CI 0.93-0.96), women younger at menopause (aOR 0.98, 95% CI 0.97-1.00), women with more time since diagnosis (aOR 0.92, 95% CI 0.90-0.94), and diabetics (aOR 0.45, 95% CI 0.21-0.95). Metabolic syndrome was not associated with post-diagnosis VMS (aOR 0.76, 95% CI 0.45-1.28).

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Compliance with Ethical Standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Conclusions—VMS following breast cancer diagnosis was related to a number of modifiable factors, but was unrelated to metabolic syndrome.

Implications for Cancer Survivors—Identification of factors that predispose women to VMS following a breast cancer diagnosis may allow clinicians to recognize and address VMS in the subset of women who are most likely to experience such symptoms.

Keywords

Breast cancer; vasomotor symptoms; metabolic syndrome; treatment

Introduction

Breast cancer treatments, although potentially life-saving, often have unintended, and unwanted, side effects such as vasomotor symptoms (VMS). VMS encompass hot flashes and night sweats. Hot flashes are defined as “recurrent, transient, episodes of flushing and a sensation of intense heat on the upper body and face, sometimes followed by chills,” [1] with those occurring during sleep referred to as “night sweats.” VMS are a common complaint of breast cancer survivors, with 65% of such women reporting this symptom in one study [2]. Although VMS are also experienced by approximately 50% of healthy women during peri-menopause [3], at least one study has documented that the frequency, severity, and duration of hot flashes are all increased among breast cancer survivors as compared to healthy controls [4].

VMS can have a significant, negative impact on breast cancer survivors’ quality of life [4]. Additionally, studies in healthy women have reported that VMS are related to poorer cardiovascular risk profiles [5], increased risk of subclinical cardiovascular disease [6, 7] and cardiovascular events [8], as well as decreased bone mineral density [9] and increased bone turnover [10]. Thus, VMS are not merely bothersome, but are indicative of later chronic disease risk.

While it is known that treatment with selective estrogen receptor modulators or aromatase inhibitors can cause VMS among breast cancer survivors [11], little is known about patient characteristics that may affect risk of VMS during and after treatment for breast cancer. One recent study reported that women with higher body mass index (BMI), as compared to women with low BMI, experienced more frequent and more intense hot flashes after initiating aromatase inhibitor therapy [12]. In healthy women elevated BMI [3, 13, 14], percent body fat [6], and increases in body fat [15] have been associated with greater reported VMS. Further, a recent study observed that hot flashes and night sweats were more common among women with metabolic syndrome compared to those without (75.0% vs. 60.1%, respectively, $p=0.03$) [16]. It is likely that these anthropometric and metabolic characteristics may also increase risk of VMS among breast cancer survivors, though this has not been specifically evaluated.

Identification of potentially modifiable factors that predispose women to VMS after a diagnosis of breast cancer may help women to reduce their risk of VMS, and may also allow clinicians to recognize a subset of women who are most likely to experience such side

effects of treatment. We evaluated predictors of VMS within the Life and Longevity After Cancer (LILAC) study [17], a prospective cohort of cancer survivors within the Women's Health Initiative (WHI), with a particular interest in metabolic syndrome and its components.

Methods

Study Population

The WHI enrolled postmenopausal women between ages 50 and 79 at 40 clinical centers nationwide between October 1, 1993 and December 21, 1998 [18]. The WHI consisted of a set of three clinical trials (CT; N=68,132) and an Observational Study (OS; N=93,676). Participants provided data at annual in-person clinic visits (CT) or through annual mailed questionnaires and in-person clinic visits every three years (OS). Participants were followed for up to 10 years within the WHI, and many continue follow-up in the WHI Extension Study.

All women with adjudicated, incident breast, colorectal, endometrial, ovarian, or lung cancers or with melanoma, leukemia or lymphoma during their WHI follow-up and still alive and enrolled in WHI in 2013 were invited to join LILAC. The WHI Cancer Survivor study team mailed out baseline surveys to 8,043 participants, of which 6,349 were returned (78.9%).

The present analysis included all LILAC participants with a diagnosis of invasive breast cancer (N=3,595) who completed the baseline LILAC questionnaire (mean 8.2 years post-diagnosis). Compared to WHI participants with a breast cancer diagnosis who did not enroll in LILAC (N=6,441), LILAC participants were somewhat younger (69.6 vs. 71.0 years, $p<0.001$), less likely to have diabetes at WHI enrollment (2.9% vs 6.2%, $p<0.001$), less likely to be obese prior to breast cancer diagnosis (31.7% vs 35.5%, $p<0.001$), less likely to have MetS (4.9% vs 8.9%, $p<0.001$), and more likely to have menopausal VMS pre-diagnosis at WHI enrollment (74.4% vs 70.6%, $p<0.001$).

Data Ascertainment

Data on a variety of factors were collected during the WHI main study. We utilized demographic (age, race/ethnicity, income) and reproductive/medical history (number of live births, age at menopause, oophorectomy, menopausal VMS pre-diagnosis, menopausal hormone therapy (mHT) use, antidepressant use, smoking status, hypertension, use of cholesterol-lowering medications, diabetes) data from participants' baseline questionnaires completed upon enrollment into the WHI main study. Body mass index (BMI) and waist circumference were measured at WHI clinic visits during the WHI main study (among CT participants, BMI was measured yearly and waist circumference was measured at baseline, year 1, and then every three years for a subset of participants; among OS participants, BMI and waist circumference were measured at baseline and year 3 for everyone and at year 6 for a subset). We used the BMI and waist circumference measurements from the closest WHI clinic visit prior to breast cancer diagnosis (mean 5.3 and 6.7 years pre-diagnosis for BMI and waist circumference, respectively) in our analyses. Age at breast cancer diagnosis was

obtained from medical records used to adjudicate the cancer diagnosis. Data on breast cancer treatments received were self-reported on the LILAC baseline questionnaire; women were asked to report whether or not they had been treated with chemotherapy, surgery, radiation therapy, or adjuvant hormone therapy (aHT).

LILAC participants self-reported VMS (defined as hot flashes) on the baseline LILAC questionnaire. Women were specifically asked to report VMS that occurred after their initial breast cancer treatment.

Definition of Metabolic Syndrome

Metabolic syndrome (MetS) was defined as having at least three of the following criteria at WHI enrollment: 1) waist circumference ≥ 88 cm, 2) systolic blood pressure ≥ 130 mm Hg and/or diastolic blood pressure ≥ 85 mm Hg or self-reported taking hypertension medications, 3) self-reported diabetes, and 4) high cholesterol, defined as self-report use of cholesterol-lowering medications. Data on triglycerides and high density lipoprotein cholesterol were available on only a subset of WHI participants, and fasting glucose measurements were not available. Our definition is similar to that used for analyses of MetS in the Study of Osteoporotic Fractures [19] and follows recent guidelines for the diagnosis of MetS [20].

Statistical Analysis

Multivariable logistic regression was used to identify predictors of self-reported VMS following initial treatment. Due to concerns about selection bias (i.e., LILAC participants with invasive breast cancer are not reflective of all WHI participants with invasive breast cancer) we incorporated inverse probability weights (IPWs) into our analyses [21]. These weights were constructed by fitting a logistic regression model for inclusion in LILAC including as predictors study design variables (study arm, region), demographic variables (income, education, age at diagnosis, race), smoking status, stage of cancer, self-reported VMS at baseline, BMI (normal, overweight, obese), and the different components of metabolic syndrome (diabetes, use of cholesterol-lowering medications, hypertension, waist circumference of ≥ 88 cm or greater). The inverse of the predicted probabilities from the model for inclusion into LILAC were then used as weights in the estimating equations for our multivariable logistic regression model for self-reported VMS following initial treatment.

A backward selection methodology was used to select the predictors for our multivariable logistic regression model. Factors related to our outcome at the 0.2 significance level based on univariate analyses were considered for inclusion in our models. The initial model also included an interaction between treatment type (chemotherapy and hormone therapy) to allow the associations to vary with number of treatment types. Since only 2609 of 3,595 (73%) breast cancer participants in LILAC had complete data on all factors in our initial model for backward selection, multiple imputation was used to impute missing covariate data. Multiple imputation provides unbiased estimates of covariate effects in regression models when the reason for missingness is related to the observed data whereas an analysis of just the complete cases may result in substantial bias [22]. Since the missingness pattern

was not monotone, a fully conditional specification (FCS) imputation procedure was used [23]. At each step of backward selection, potential predictors were eliminated based on the p-value ($p < 0.10$ criterion) obtained by combining the estimates from 30 imputed datasets [24]. The initial model containing all predictors significant at the 0.2 level based on univariate analyses had an average quasi-AIC (QIC) of 8092.00 across the 30 imputed data sets. After sequential elimination of predictors that were insignificant at the 0.1 level, the fit actually improved: average QIC = 8047.43.

Results

Approximately 1 in 5 breast cancer survivors (22.0%) reported experiencing VMS following their diagnosis (Table 1). Women who reported VMS were slightly younger at diagnosis and more likely to have regional disease and estrogen receptor (ER) positive disease compared to women without VMS. Additionally, treatment with chemotherapy or adjuvant hormone therapy was more common among women reporting VMS following diagnosis. Time since diagnosis was significantly less among women reporting VMS compared to those not reporting VMS after diagnosis. Furthermore, 39.1% of those who reported VMS were surveyed within five years of their initial cancer diagnosis compared to 32.2% among those who did not report VMS ($p < 0.001$). Metabolic syndrome and its components were less prevalent among women with VMS compared to those without, and women with VMS were more likely to be nulliparous, have an earlier age at menopause, have had a bilateral oophorectomy, and be current smokers. Also, women with VMS were more likely to have self-reported mHT and VMS at WHI baseline and to currently use antidepressants.

In multivariable analyses, the strongest predictor of VMS following breast cancer diagnosis was treatment type (Table 2). Women who received chemotherapy (OR 1.80, 95% CI 1.21-2.68) or aHT (OR 2.73, 95% CI 2.08-3.58) had approximately a two-fold higher risk of VMS compared to women receiving neither chemotherapy nor aHT. VMS at WHI baseline was also strongly predictive of VMS after diagnosis (OR 2.20, 95% CI 1.73-2.80). Other statistically significant risk factors were bilateral oophorectomy (OR 1.77, 95% CI 1.30-2.13), mHT use at WHI baseline (OR 1.67, 95% CI 1.30-2.09), and antidepressant use (OR 1.49, 95% CI 1.06-2.09). Women with diabetes (OR 0.45, 95% CI 0.21-0.95) were less likely to report post-diagnosis VMS, as were women with a younger age at menopause (OR 0.98, 95% CI 0.97-1.00) and a younger age at diagnosis (OR 0.94, 95% CI 0.93-0.96). Time since diagnosis also was negatively associated with self-reported VMS (OR 0.92, 95% CI 0.90-0.94). When we restricted the analytic sample to women whose baseline LILAC questionnaire was completed within 5 years of their cancer diagnosis, treatment type, oophorectomy status, antidepressant use, and diabetes were no longer significantly associated with VMS (data not shown), but ER+ status was more strongly associated with VMS (OR 2.86, 95% CI 1.24-6.60). Similar associations were observed for mHT at WHI baseline, VMS at WHI baseline, age at menopause, and age at diagnosis as were observed within the full sample.

When MetS was evaluated as a single exposure in multivariable analyses, we observed no association between presence of MetS and VMS following diagnosis (Table 3). Additionally, the number of MetS components was not related to post-diagnosis VMS. Similar results

were obtained when restricting analyses to women whose cancer diagnosis was within 5 years of their LILAC baseline questionnaire.

Discussion

Among this population of breast cancer survivors on average 8 years post-diagnosis, approximately 22% reported experiencing a new case of hot flashes after completing their initial breast cancer treatment. This prevalence is substantially lower than that reported in other studies of breast cancer survivors [25-29], and likely reflects the extended time since breast cancer diagnosis in our cohort, although changes in breast cancer treatment practices over time also may contribute. Consistent with prior research, we identified chemotherapy and aHT as strong predictors of VMS after diagnosis [26, 28, 30]. Diagnosis with ER positive disease and mHT prior to diagnosis also were strongly predictive of VMS following breast cancer treatment. Women who experienced VMS during the menopausal transition had twice the odds of self-reporting VMS post-treatment, and age at menopause and at diagnosis were both negatively associated with VMS post-treatment.

Interestingly, we did not observe a statistically significant positive association between MetS, number of MetS components, and individual components of MetS and reported VMS post-treatment, though there was a suggestion of an inverse relationship. These findings were contrary to our hypothesis, which was based on findings in cohorts of healthy women [16, 31-33]. Additionally, one prior study of breast cancer patients reported that obese women had an increased risk of severe hot flashes following treatment [25]. This study included women who recently completed treatment and who were, on average, younger than LILAC participants, however, which might account for the difference in our reported results. Also, BMI was measured after diagnosis and treatment, while we utilized pre-diagnostic measurements. Given that weight gain is a common side effect of breast cancer treatment, it is possible that the findings of the previous study are confounded with weight gain. Also, our study only included data on the incidence of VMS, and lacked information on the severity, which was where a significant positive relationship between BMI and VMS was observed in the Carpenter *et al* study.

Menopausal VMS are believed to be due to the substantial declines in estrogen levels experienced as women transition through menopause. A similar mechanism of estrogen withdrawal would explain why breast cancer survivors experience such symptoms associated with adjuvant hormonal therapy such as selective estrogen receptor modulators and aromatase inhibitors. Because adipose tissue is known to be a source of estrogen, which is especially relevant in postmenopausal women, it had been believed that healthy, obese women would be less likely to experience VMS compared to normal weight women. However, epidemiologic studies observed the exact opposite, with BMI positively associated with VMS in multiple studies [6, 15, 34-36]. Likewise, MetS has been associated with increased risk of VMS during the menopausal transition among healthy women [16]. Our finding that BMI, MetS, and MetS components are not associated with VMS following breast cancer treatment is surprising. We considered that perhaps the extended time between breast cancer diagnosis and recruitment for LILAC may have led to a selection bias that impacted our results. In fact, we observed that, among women diagnosed with incident,

invasive breast cancer during WHI enrollment, those who enrolled in LILAC tended to be younger and with a lower prevalence of obesity, diabetes, and MetS compared to those who did not enroll. Additionally, LILAC participants were more likely to report menopausal VMS at WHI enrollment than WHI cancer survivors who did not enroll in LILAC. Such a selection bias may have led to an underestimation of our effect estimate, and could explain the null associations we report. However, we statistically adjusted for such a selection bias using inverse probability weighting. The null associations remained even after such adjustment, which suggests that selection bias is not an important factor in our reported associations.

We also observed a borderline significant decrease in VMS associated with use of cholesterol-lowering medications, which were most likely statin medications. Statins have known anti-inflammatory properties [37], and decreases in inflammation may in turn help to reduce VMS [38]. In the Study of Women's Health Across the Nation (SWAN), a cohort of healthy women transitioning through menopause, however, VMS have been associated with elevated lipid profiles [32]. Likewise, menopausal VMS have been associated with insulin resistance [33]. Differences between these findings in our own may relate to our use of proxy measures for high cholesterol and diabetes as opposed to the biological measurements utilized in SWAN. Alternatively, these differences may indicate that the mechanisms underlying menopausal hot flashes and those occurring after breast cancer diagnosis are different. Further research is needed to understand the physiological basis for VMS following breast cancer treatment.

Our results should be considered in the context of a few additional limitations. Data on VMS were self-reported and retrospective and lacked information on duration or severity. Though women were instructed to report only those VMS occurring since completion of their treatment, it is possible that some misclassification of exposure occurred, which may have caused non-differential misclassification and biased our results toward finding no association. Additionally, we observed a positive association between antidepressant use and VMS following diagnosis, which likely reflects antidepressants being used to treat VMS. It may be that antidepressant users are especially prone to experiencing VMS, and depression and antidepressant use have a complicated, likely bidirectional relationship with body weight and MetS; thus our adjustment for antidepressant use in multivariable models is critical for capturing the independent effect of MetS on VMS. Unfortunately, we lacked data on alternative treatments for VMS (e.g. natural supplements, relaxation techniques) and therefore were unable to adjust for the use of such treatments in our analyses. Also, our measures of MetS components were taken from data collected at WHI enrollment. It is possible that MetS status at the time of diagnosis is more relevant to likelihood of experiencing VMS after treatment, but we were unable to evaluate this in the present study. We utilized BMI measurements as near to the time of diagnosis as possible, but these were still an average of 5.3 years prior to diagnosis; thus measurement error related to the classification of obesity at diagnosis also might have impacted our results.

Our study has many strengths, however. This is the largest study to date to evaluate predictors of VMS in breast cancer survivors. The one prior study that specifically examined metabolic and demographic predictors of VMS in breast cancer survivors included only 114

women [25]. Also, we took advantage of the vast data available through WHI to access prospective data on MetS, which avoids any potential impact of breast cancer treatment on MetS and its components. We also had available to us self-reported data on breast cancer treatment, which allowed us to adjust for these important factors in our analysis.

Data on metabolic predictors of VMS following treatment are very limited, and additional research is warranted given the contrasting results of the two existing studies. It is possible that the mechanisms relating metabolic characteristics to VMS in healthy women differ from those that operate in women with a history of breast cancer, but this will require confirmation from other studies in breast cancer survivors. Given that hot flashes are associated with an increased risk of discontinuing aHT [39], it is important to understand which factors might increase or decrease one's risk of VMS following breast cancer treatment. Although VMS are common among breast cancer survivors, clinicians may want to be especially vigilant in inquiring about VMS with breast cancer survivors who have received prior chemotherapy or prior aromatase inhibitor therapy, experienced VMS prior to breast cancer diagnosis, or have a history of bilateral oophorectomy before their cancer diagnosis. Such information may help clinicians to effectively counsel their patients and treat their VMS in order to avoid negative effects of VMS on quality of life and discontinuation of potentially life-saving treatment.

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Table 1

Descriptive characteristics of study population by vasomotor symptoms post-treatment for breast cancer (N=3,595)

	No VMS N=2,805	VMS N=790	P value ¹
Age at diagnosis, years; Mean (SD)	70.0 (7.6)	67.7 (7.4)	<0.001
White race; N (%)	2543 (90.9)	707 (89.5)	0.317
Household income; N (%)	394 (14.7)	122 (16.1)	0.005
100,000+	394 (14.7)	122 (16.1)	
50,000-99,999	959 (35.9)	317 (41.9)	
<50,000	1322 (49.4)	318 (42.0)	
College Graduate; N (%)	1477 (52.3)	397 (50.5)	0.288
Study arm; N (%)			<0.001
Observational Study	1540 (54.9)	448 (56.7)	
E+P control	127 (4.5)	21 (2.7)	
E+P intervention	170 (6.1)	21 (2.7)	
E-alone control	72 (2.6)	14 (1.8)	
E-alone intervention	70 (2.5)	9 (1.1)	
Other Clinical Trial	826 (29.4)	277 (35.1)	
Stage at diagnosis; N (%)			0.060
Localized	2207 (78.9)	594 (76.1)	
Regional	580 (20.7)	180 (23.0)	
Distant	9 (0.3)	7 (0.9)	
Estrogen Receptor Positive; N (%)	2302 (86.2)	694 (91.6)	<0.001
Chemotherapy; N(%)	767 (27.5)	267 (34.1)	0.002
Radiation therapy; N (%)	1949 (70.0)	557 (71.1)	0.388
Adjuvant hormone therapy; N (%)	1765 (63.5)	641 (81.7)	<0.001
BMI category; N (%)			0.003
<25 kg/m ²	936 (33.5)	294 (37.3)	
25-<30 kg/m ²	945 (33.8)	276 (35.0)	
>=30 kg/m ²	916 (32.7)	218 (27.7)	
Waist circumference; Mean (SD)	86.5 (13.7)	85.0 (12.5)	0.004
Hypertension; N (%)			0.031
Never	1382 (50.9)	408 (52.8)	
Past	43 (1.6)	20 (2.6)	
Untreated hypertension	714 (26.3)	202 (26.1)	
Treated hypertension	574 (21.2)	143 (18.5)	
High cholesterol; N(%)	311 (11.8)	60 (8.0)	<0.001
Diabetes; N (%)	95 (3.4)	10 (1.3)	0.001
Metabolic syndrome; N (%)	148 (5.4)	25 (3.2)	0.003
Number of metabolic syndrome components; N (%)			0.001
0	900 (34.4)	290 (38.8)	

	No VMS N=2,805	VMS N=790	P value ¹
1	933 (35.6)	279 (37.3)	
2	643 (24.5)	155 (20.7)	
3+	144 (5.5)	24 (3.2)	
Number of live births; N (%)			<0.001
0	365 (13.1)	120 (15.3)	
1	255 (9.2)	66 (8.4)	
2-4	1855 (66.6)	551 (70.2)	
5+	311 (11.2)	48 (6.1)	
Age at menopause; Mean (SD)	49.2 (5.7)	47.7 (6.1)	<0.001
Oophorectomy; N (%)			<0.001
No/Don't Know	2195 (78.9)	553 (70.5)	
Unilateral	206 (7.4)	57 (7.3)	
Bilateral	382 (13.7)	174 (22.2)	
Smoking status			0.176
Never	1376 (49.6)	356 (45.6)	
Past	1256 (45.3)	372 (47.7)	
Current	140 (5.1)	52 (6.7)	
Ever used postmenopausal hormone therapy; N (%)	1894 (70.0)	663 (86.1)	<0.001
Current antidepressant use; N (%)	142 (5.1)	63 (8.0)	0.043
Vasomotor symptoms at WHI baseline; N (%)	1864 (71.3)	638 (85.1)	<0.001

^aP value from unadjusted odds ratio calculated using inverse probability weighting to account for probability of enrollment into LILAC. Results in this table are from complete case analyses and thus frequencies may not add up to listed column totals for no VMS and VMS.

Table 2

Multivariable odds ratios for post-diagnosis vasomotor symptoms, N=3,595

	OR (95% CI)
Years Since Diagnosis	0.92 (0.90-0.94)
Study Arm	
Observational Study	1 (ref)
E+P control	0.98 (0.59-1.65)
E+P intervention	0.67 (0.41-1.11)
E-alone control	0.73 (0.39-1.35)
E-alone intervention	0.39 (0.18-0.82)
Other Clinical Trial	1.19 (0.98-1.45)
BMI category	
<25 kg/m ²	1 (ref)
25-<30 kg/m ²	0.94 (0.76-1.15)
30 kg/m ²	0.79 (0.63-0.99)
Hypertension (treated or untreated) ¹	1.19 (0.99-1.42)
Diabetes ¹	0.45 (0.21-0.95)
Breast cancer treatment	
Chemotherapy vs. No chemotherapy or aHT	1.80 (1.21-2.68)
Chemotherapy + aHT vs. aHT only	1.02 (0.82-1.28)
aHT only vs. No chemotherapy or aHT	2.73 (2.08-3.58)
Chemotherapy + aHT vs. chemotherapy only	1.55 (1.08-2.20)
Age at diagnosis ²	0.94 (0.93-0.96)
Age at menopause ²	0.98 (0.97-1.00)
VMS at WHI baseline ¹	2.20 (1.73-2.80)
Oophorectomy	
No/don't know	1 (ref)
Unilateral	0.96 (0.68-1.35)
Bilateral	1.77 (1.37-2.27)
mHT at WHI baseline ¹	1.67 (1.30-2.13)
Antidepressant use ¹	1.49 (1.06-2.09)
Smoking status	
Never	1 (ref)
Past	1.06 (0.88-1.28)
Current	1.41 (0.96-2.08)

^aComparing "yes" to "no"^bPer 1 year increase

Abbreviations: aHT, adjuvant hormone therapy; BMI, body mass index; mHT, menopausal hormone therapy; WHI, Women's Health Initiative

Table 3Multivariable associations between metabolic syndrome and post-diagnosis vasomotor symptoms^a

	OR (95% CI)
Metabolic syndrome	
No	1 (ref)
Yes	0.76 (0.45-1.28)
Number of metabolic syndrome components	
0	1 (ref)
1	1.11 (0.90-1.37)
2	1.14 (0.86-1.50)
3+	0.84 (0.48-1.46)

^aAdjusted for study arm, BMI, breast cancer treatment, ER status, age at diagnosis, age at menopause, VMS at WHI baseline, oophorectomy, mHT at WHI baseline, antidepressant use, smoking status