Published in final edited form as:

Cancer Causes Control. 2016 November ; 27(11): 1333–1340. doi:10.1007/s10552-016-0811-9.

Menopausal vasomotor symptoms and incident breast cancer risk in the Study of Women's Health Across the Nation

Vicki Hart¹, Susan R. Sturgeon¹, Nicholas Reich¹, Lynnette Leidy Sievert², Sybil L. Crawford³, Ellen B. Gold⁴, Nancy E. Avis⁵, and Katherine W. Reeves¹

¹Department of Biostatistics and Epidemiology, University of Massachusetts Amherst, Amherst, MA

²Department of Anthropology, University of Massachusetts Amherst, Amherst, MA

³Department of Medicine, University of Massachusetts Medical School, Worcester, MA

⁴Department of Public Health Sciences, School of Medicine, University of California School of Medicine, Davis, CA

⁵Department of Social Sciences and Health Policy, Wake Forest School of Medicine, Winston-Salem, NC

Abstract

Purpose—Two case-control studies reported a 50% decreased breast cancer risk among women who experienced menopausal vasomotor symptoms (VMS), but one cohort study found no association. VMS may be triggered by declining estrogen levels during menopause, whereas elevated estrogen levels have been associated with increased breast cancer risk. VMS may thus be indicative of lower susceptibility to breast cancer.

Methods—We evaluated this relationship in the longitudinal Study of Women's Health Across the Nation (SWAN), using discrete survival analysis of approximately annual data on VMS and self-reported breast cancer occurrences for up to 13 years of follow-up in 3,098 women who were pre- or early perimenopausal at enrollment.

Results—Over an average 11.4 years of follow-up, 129 incident breast cancer cases were self-reported, and approximately 50% of participants experienced VMS. Symptomatic women had a reduced risk of breast cancer compared to non-symptomatic women (adjusted HR 0.63, 95% CI 0.39, 1.00). The association was stronger in the subgroup of women who fully transitioned to postmenopause during follow-up (N=67 cases, adjusted HR 0.45, 95% CI 0.26, 0.77).

Conclusion—VMS appeared to be a marker of reduced breast cancer risk. Future research is needed to understand the biology underlying this relationship.

Keywords

Breast cancer; vasomotor symptoms; menopause; postmenopausal

Introduction

Two recent case-control studies found an approximate 50% reduction in breast cancer risk for women who reported any menopausal vasomotor symptoms (VMS), defined as hot flashes and/or night sweats, prior to their diagnosis compared to those who did not [1, 2]. This provocative result was not supported by a recent, large, prospective cohort study [3], however. Importantly, this recent study assessed VMS at three-year intervals, which was likely insufficient for capturing true VMS occurrence [4] and therefore may have attenuated true associations. A clear inverse relationship between VMS and breast cancer risk could identify an easily measurable factor that may enhance current risk prediction methods. The inconsistent findings from previous studies warrant further prospective investigation of this relationship.

An inverse relationship between VMS and breast cancer risk is plausible, given the common hormonal mechanisms underlying both VMS and breast carcinogenesis. Many identified breast cancer risk factors are associated with an increased lifetime exposure to sex hormones, particularly estrogen, such as early menarche, lower parity, and late age at menopause [5, 6]. Further, use of certain exogenous hormone therapies has been associated with increased breast cancer risk [7]. Although we lack a complete understanding of the etiology of VMS, fluctuations and decline in endogenous sex hormones during the menopausal transition are known to contribute to the onset of VMS [8–10]. Exogenous hormone therapy is effective in relieving VMS in many women [11], further suggesting that hormone levels may be important to the management and etiology of VMS.

We prospectively investigated the association between VMS and incident breast cancer in the longitudinal Study of Women's Health Across the Nation (SWAN), a large, racially/ethnically diverse cohort of women who have been followed for up to 13 years across the menopausal transition, and on whom annual demographic and reproductive data are available. We hypothesized that menopausal VMS would be associated with reduced breast cancer risk.

Materials and Methods

Study population

The design and recruitment procedure of the SWAN cohort has been described in detail elsewhere [12]. Briefly, the study enrolled women from seven locations during 1996–1997, with some locations oversampling from specific racial/ethnic groups to create a diverse cohort. Women were aged 42–52 years at enrollment and were pre- or early perimenopausal (i.e., bleeding within the last three months) at enrollment. Women using hormone therapy or oral contraceptives in the prior three months were excluded from enrollment, as were women who were pregnant or breastfeeding or who did not have an intact uterus and at least one ovary. In total, 3,302 women were enrolled and each provided written consent at the location of recruitment. All sites obtained institutional review board approval for the study protocol. Annual follow-up visits are on-going and include clinical assessments and questionnaires. Data through follow-up visit 13 were available.

The current analyses used data from the full SWAN cohort. We excluded 21 women with a history of breast cancer at enrollment and a further 183 women who did not participate in any follow-up visits beyond the baseline enrollment visit and therefore had no incident breast cancer information. Women who reported that they were pregnant or breastfeeding during the study period were excluded for those specific visits (four women, five study visits). After these exclusions, the study population included 3,098 women who contributed data from 34,905 SWAN visits.

VMS assessment

At the baseline and each follow-up visit, SWAN participants reported the frequency of VMS in the prior two weeks via a self-administered questionnaire in the language appropriate to the participant (English, Spanish, Cantonese, or Japanese). Questions related to hot flashes and night sweats were worded as follows: “Thinking back over the last two weeks, how often have you had hot flashes or flushes/night sweats?” Response categories were: not at all, 1–5 days, 6–8 days, 9–13 days, every day. Consistent with previous analyses in the SWAN cohort [13–15], women who reported any hot flashes or night sweats (versus not at all) were classified as being symptomatic of VMS at that visit. Women who reported having hot flashes or night sweats on 6 or more days in the last two weeks were classified as reporting frequent VMS at that visit [16], while women who reported having hot flashes or night sweats 1–5 days in the last two weeks were classified as having infrequent VMS at that visit.

Breast cancer assessment

SWAN participants self-reported cancer history during the baseline enrollment interview. At each subsequent follow-up, women were asked if they had been told that they had breast cancer by a health care provider since their last assessment. Responses were recorded as “Yes,” “No,” or “Don’t know.” Interviews were administered by trained personnel in the language appropriate to the participant (English, Spanish, Cantonese, or Japanese). We included self-reported breast cancer cases through July 2014. During follow-up visits 12 and 13, women who had self-reported a breast cancer diagnosis were asked to provide consent for medical record review to adjudicate these cases. A total of 80 women provided consent, among whom 76 breast cancer cases (95%) were confirmed, while 4 self-reported cases were indeterminate. Given the high rate of confirmation and the relatively small number of adjudicated cases available, we have performed our primary analyses using all self-reported cases. We also report a sensitivity analysis restricted to adjudicated breast cancer cases among participants included in this analysis (n=71).

Covariate assessment

Information on covariates was collected during the baseline and SWAN follow-up visits. Demographic and reproductive variables that were modeled using baseline values in the current analysis included: race/ethnicity, education, age at first birth, age at menarche, age at menopause (if observed), alcohol consumption, physical activity, active and passive smoking exposure, dietary fat and fiber intake, and SWAN site. Covariates that were considered time-varying and updated at each follow-up visit included: menopausal status, body mass index

(BMI), parity, family history of breast cancer, hormone therapy use, and bilateral oophorectomy and/or hysterectomy.

Menopausal status was classified in accordance with standard SWAN protocol [12]: women who had a menstrual period in the prior three months and had no change in menstrual regularity over the past year were considered premenopausal; women who had a menstrual period in the past three months but reported increased menstrual variability were considered early perimenopausal; women with no menstrual bleeding in the prior 3 months but who reported menstrual bleeding in the 3–11 months before the interview date were considered late perimenopausal; and those with no bleeding in the last 12 months were considered postmenopausal. Early and late perimenopause were collapsed into a single perimenopausal category for these analyses. Women who reported bleeding in the previous 12 months and reported hormone therapy (HT) use in the previous year were classified as unknown menopausal status due to HT use for those visits. Postmenopausal women remained classified as such if HT use was initiated after the final menstrual period. Women reporting a hysterectomy or bilateral oophorectomy were classified as surgical menopause starting at the visit at which the surgery was reported and were grouped with postmenopausal women for these analyses.

By study design, women were not taking HT at baseline enrollment. At each follow-up interview, women were asked to report the use of HT or oral contraceptives since their last study visit. When possible, interviewers verified medication from the container label. Lifestyle variables, including alcohol consumption, physical activity, smoking, and dietary fat and fiber intake were assessed in accordance with previous SWAN publications [14, 16, 17]. Total alcohol consumption was categorized as: <1 drink/month, 1 drink/month – <2 drinks/week, 2+ drinks/week. Physical activity was assessed using a continuous variable that incorporated the proportion of the year in which activity was performed, a standardized intensity score, and the duration of each bout of activity. Development of the physical activity score has been described in detail in previous SWAN publications [18]. Smoking was categorized as: never smoked/no passive exposure, never smoked/with passive exposure, former smoker, current smoker. Baseline dietary fat and fiber intake were assessed using composite variables that reflected total average consumption based on a validated food frequency questionnaire [19]. At each visit a standard protocol was used for measuring height with a stadiometer and weight with a balance beam scale. BMI was computed as weight in kilograms/(height in meters)² and categorized as <25, 25–29.9, and ≥30 kg/m².

Statistical methods

After omitting study visits that occurred after a breast cancer diagnosis, a total of 31,712 observations from 3,098 participants contributed to the current analyses. Descriptive statistics included means and standard deviations for continuous variables and percentages for categorical variables. We calculated relative risks of breast cancer diagnosis for baseline covariates using discrete survival analysis.

We assessed the longitudinal association between VMS and incident breast cancer risk using discrete survival analyses. This statistical approach is appropriate for data in which the outcome is recorded at discrete time intervals (i.e., SWAN visits) and the actual date of the

outcome is unknown [20]. Women could contribute varying numbers of observations, and observations were omitted after the visit at which the event occurred or continued to the end of the study period if no event occurred. As in other survival analysis approaches, the inclusion of each interval in the dataset was conditional on the participant having “survived” past the previous intervals. To avoid temporal concerns with breast cancer treatment affecting VMS, we modeled VMS at the index visit as a predictor of self-reported breast cancer at a subsequent visit.

To differentiate between symptomatic and non-symptomatic women, we modeled any VMS at each study visit as VMS reported at that visit or any prior visit. Therefore, a woman was considered symptomatic from the first visit at which she reported any VMS. Frequent VMS was modeled similarly, meaning that a woman was considered symptomatic of frequent VMS from the first visit at which frequent VMS was reported. HT use during the study period was modeled similarly, categorizing women as ever users once HT use was reported. We developed multivariable regression models using a backward selection considering the covariates listed above. Due to the limited number of breast cancer outcomes, we developed a parsimonious model, retaining covariates only if they were significant ($p < 0.05$) in the model, or if their exclusion resulted in a change in the hazard ratio for the VMS exposure of 10% or more. Model building preceded with all eligible participants; for consistency, we report in our tables statistics for only the subsample with complete data utilized in the regression analyses ($N = 2,807$). Because HT use may act as a confounder or intermediary in the relationship between VMS and breast cancer, we repeated our analysis among women who did not ever use HT during the study period. We assessed effect modification by race/ethnicity, HT use, BMI, and menopausal status.

To assess the effect of VMS on breast cancer risk through the complete menopausal transition, we performed a secondary analysis using multivariable logistic regression of VMS during pre- or perimenopause and postmenopausal breast cancer outcomes. This analysis was restricted to women who fully transitioned to postmenopause during the study period ($N = 2,468$), including 1,348 who did so without any self-reported HT use and thus were considered to have a “clean” transition. Only VMS reported during visits at which the woman was pre- or perimenopausal and only breast cancer diagnoses reported during visits at which the woman was postmenopausal were included in this secondary analysis. Women reporting pre- or perimenopausal breast cancer were censored at the visit before their breast cancer was reported. A parsimonious multivariable logistic regression model was built for this analysis with covariate selection proceeding as described above.

Due to incomplete data collection, information from the New Jersey location was missing for SWAN visits 07, 08, 10, and 11. This affected 345 study participants, including all Hispanic women and one breast cancer case. We thus performed a sensitivity analysis by excluding all women from the New Jersey location and comparing our results to those including these participants.

We repeated all analyses using only the sub-sample of cases that were confirmed via adjudication. All analyses were performed using SAS Version 9.2 (SAS Institute, Cary, North Carolina).

Results

On average, women were approximately 46 years old at enrollment (Table 1). Over an average of 11.7 years of follow-up, 129 breast cancer cases were self-reported, 108 of which had complete data and were included in the final multivariable regression models. Women who reported a breast cancer diagnosis during follow-up were more likely to be Caucasian (53.7% vs 48.3%) and obese (38.9% vs 30.6%). Overall, any VMS were reported at 51% of SWAN visits, and the frequency of VMS increased from pre- to peri- and postmenopause (32%, 56%, 52% of visits, respectively). More African American women reported VMS than Caucasian and Hispanic women (63.2% versus 48.8% of visits, $p<0.01$), while fewer Asian women reported VMS than Caucasian and Hispanic women (40.6% versus 48.8% of visits, $p<0.01$).

We observed that symptomatic women had a 37% reduced risk of breast cancer compared to non-symptomatic women (adjusted HR = 0.63, 95% CI 0.39–1.00) (Table 2). This association was modified by race/ethnicity ($p_{\text{interaction}}=0.07$). After stratification, we found that the relationship between VMS and breast cancer risk was most strongly negative and statistically significant among Caucasian women (adjusted HR = 0.42, 95% CI 0.23–0.78) (Table 2) and attenuated and non-significant among African American and Asian women. We observed no significant interaction of the protective relation of VMS with breast cancer by menopausal status (postmenopausal: adjusted HR=0.47, 95% CI 0.22, 1.00; perimenopausal: adjusted HR=1.33, 95% CI 0.60, 2.93; premenopausal: adjusted HR=0.08, 95% CI 0.01, 0.74; unknown: adjusted HR=0.63, 95% CI 0.11, 3.76; $p=0.23$), hormone use (never: adjusted HR=0.65, 95% CI 0.38, 1.12; ever: adjusted HR=0.55, 95% CI 0.22, 1.40; $p=0.75$), or BMI ($<30\text{kg/m}^2$: adjusted HR=0.54, 95% CI 0.30, 0.99; 30 kg/m^2 : adjusted HR=0.73, 95% CI 0.34, 1.57; $p=0.88$). We found similar results when looking at infrequent and frequent VMS separately compared to none, although confidence intervals were wider due to smaller numbers of breast cancer cases in each group. Similar associations were observed when analyses were restricted to adjudicated cases, with any VMS reducing breast cancer risk by 46% overall (adjusted HR = 0.54, 95% CI 0.28–1.02) and 58% among Caucasians (adjusted HR = 0.37, 95% CI 0.16–0.85).

In the secondary analysis of pre- and perimenopausal VMS and postmenopausal breast cancer ($N=2,003$ women, 67 cases), we observed that symptomatic women had a significant 55% reduction in risk of postmenopausal breast cancer compared to non-symptomatic women (adjusted HR = 0.45, 95% CI 0.26–0.77) (Table 3). We observed no significant interaction of this protective relation by race/ethnicity (White: adjusted HR=0.30, 95% CI 0.15, 0.57; African American: adjusted HR=1.68, 95% CI 0.21, 13.24; Asian: adjusted HR 0.63, 95% CI 0.18, 2.19; Hispanic: adjusted HR=not estimable; $p=0.30$), HT use (never: adjusted HR=0.50, 95% CI 0.23, 1.10; ever: adjusted HR=0.38, 95% CI 0.18, 0.82; $p=0.73$), or BMI ($<30\text{ kg/m}^2$: adjusted HR=0.38, 95% CI 0.20, 0.74; 30 kg/m^2 : adjusted HR=0.57, 95% CI 0.22, 1.49; $p=0.68$). Among women who transitioned to postmenopause with no use of HT ($N=1,220$, 33 cases), results were similar although non-significant (adjusted HR = 0.50, 95% CI 0.23–1.10) (Table 3). Again, associations were consistent when restricting to adjudicated cases, with significant reductions in risk associated with any VMS overall

(adjusted HR = 0.45, 95% CI 0.26–0.77) and among women without use of HT (adjusted HR = 0.50, 95% CI 0.23, 1.10).

Results of our analysis did not change after exclusion of women from the New Jersey location. We have therefore presented results from the full study population.

Discussion

Our findings are consistent with two case-control studies that both concluded an approximate 50% reduction in risk for women who experienced any VMS at any point during the menopausal transition [1, 2]. However, a recent prospective investigation observed no association between VMS and breast cancer risk [3]. This study followed 11,297 women with a mean age of 47.6 years at enrollment for an average of 13.7 years. During follow-up, 34% reported hot flashes, 26% reported night sweats, and 348 incident breast cancer cases were recorded. Participants were surveyed at three-year intervals and asked to report VMS in the past 12 months; thus VMS reporting was not captured for two out of every three years, and women could contribute a maximum of six observations. It is likely that some short-term VMS were not captured due to the infrequency of the data collection in this study [4]. This may explain why the percentage of women reporting VMS was considerably lower than general estimates of 50–80% [16, 21, 22], and may have contributed to the observed null findings. In contrast, our study participants provided annual assessments of VMS over the past two weeks. Although some VMS may still have been missed, this protocol was more likely to capture VMS at least once during each menopausal stage, and allowed for up to 13 observations per woman.

We found that the inverse relationship between VMS and breast cancer risk was strongest among Caucasian women and weaker among African American and Asian women. After stratification, the number of breast cancer cases in each racial/ethnic subgroup available for multivariable analysis was limited (58, 26, and 23 cases for Caucasian, African American, and Asian, respectively). Thus, low statistical power may have contributed to the attenuated results among African American and Asian women. However, the association between VMS and breast cancer risk was strengthened among Caucasian women, despite the limited number of cases. Race/ethnicity may influence self-reporting of VMS. African American women tend to report more frequent [16] and severe symptoms than Caucasian women [23, 24]. In contrast, Asian women have demonstrated less self-reporting of VMS than Caucasian women in some studies [25]. Consistent with these findings and previous analysis of SWAN VMS data [16], African American women in our study reported more VMS and Asian women reported fewer VMS than Caucasian women. Our findings suggest a differential effect of VMS on breast cancer risk by race/ethnicity, but it is unclear if this is due to true physiological differences, a lack of statistical power after stratification, or racial/ethnic variation in the self-reporting of VMS.

The association between VMS and breast cancer risk may be related to common hormonal etiologies. VMS are hypothesized to be associated with declining levels of estradiol (E2) and increased follicle stimulating hormone (FSH) during the menopausal transition; a positive relationship between E2 and breast cancer, and inverse relationships between FSH and sex

hormone binding globulin (SHBG) and breast cancer are generally supported in the literature [26]. Additional non-hormonal mechanisms also may link VMS to breast cancer. While VMS have been associated with estrogen fluctuations during the menopausal transition [27], these alone cannot account for the onset of symptoms. All women experience a decline in estrogen during menopause, but not all women experience VMS. Non-hormonal mechanisms such as changes in skin vasculature and central nervous system regulation have been hypothesized to trigger VMS [10, 28]. It is possible that non-hormonal mechanisms that are important in both the onset of VMS and breast carcinogenesis could explain our results. Future analyses are needed to definitively determine the role of endogenous hormones in mediating the observed relationship between VMS and breast cancer.

Our study was strengthened by the large, prospective, multi-racial/ethnic SWAN cohort with annual assessment of demographic, reproductive, and clinical factors over up to 13 years of follow-up. The results of our study must be interpreted within the context of its limitations, however. Both VMS and breast cancer information were self-reported. Previous analyses in the SWAN cohort using our definition of VMS have found significant associations between VMS and lower bone mineral density, insulin resistance, and subclinical cardiovascular disease [13–15]. Because efforts to adjudicate breast cancer cases began very late in the SWAN follow-up, only 80 of 129 self-reported cases provided consent for medical record retrieval. Among this subgroup, the confirmation rate (95%) was very high and no self-reported cases were definitively determined to not be breast cancer cases, though 4 were indeterminate. Self-report of breast cancer also has been shown to be valid in other large epidemiologic studies [29, 30]. However, we cannot rule out the self-reported cases as a possible explanation for differences between our analysis and previous studies, which ascertained cases from cancer registries. We analyzed all self-reported breast cancer cases to improve power, and associations were consistent when restricting to adjudicated cases. The consistency of our findings despite this limited statistical power overall and for racial/ethnic subgroups suggests that the observed association between VMS and breast cancer risk may be robust.

Establishing VMS as a risk marker for incident breast cancer has considerable public health implications. VMS are easily reportable without invasive or expensive procedures. An association between self-reported VMS and breast cancer risk could provide additional insight to clinicians on the individual breast cancer risk of their patients. However, a better understanding of the mechanisms underlying this association is needed before VMS may be suggested as an enhancement to current risk prediction tools. This result strongly justifies the need for future investigations to examine the biological mechanisms linking the onset of VMS to breast cancer etiology.

Acknowledgments

Financial support: The Study of Women's Health Across the Nation (SWAN) has grant support from the National Institutes of Health (NIH), DHHS, through the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR) and the NIH Office of Research on Women's Health (ORWH) (Grants U01NR004061; U01AG012505, U01AG012535, U01AG012531, U01AG012539, U01AG012546, U01AG012553, U01AG012554, U01AG012495). The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the NIA, NINR, ORWH or the NIH.

References

1. Fei C, DeRoo LA, Sandler DP, et al. Menopausal symptoms and the risk of young-onset breast cancer. *Eur J Cancer*. 2013; 49:798–804. [PubMed: 23021929]
2. Huang Y, Malone KE, Cushing-Haugen KL, et al. Relationship between menopausal symptoms and risk of postmenopausal breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2011; 20:379–88. [PubMed: 21212063]
3. Johanneke van den Berg M, Mishra GD, van der Schouw YT, et al. Vasomotor menopausal symptoms are not associated with incidence of breast cancer in a population-based cohort of mid-aged women. *Eur J Cancer*. 2014; 50:824–30. [PubMed: 24361228]
4. Crawford S, Avis N, Kelsey J, et al. Is annual measurement of hot flashes sufficiently frequent in perimenopause? [abstract]. *Menopause*. 2004; 11:682.
5. Collaborative Group on Hormonal Factors in Breast Cancer. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. *Lancet Oncol*. 2012; 13:1141–51. [PubMed: 23084519]
6. Hankinson SE. Endogenous hormones and risk of breast cancer in postmenopausal women. *Breast Dis*. 2005; 24:3–15. [PubMed: 16917136]
7. Gompel A, Santen RJ. Hormone therapy and breast cancer risk 10 years after the WHI. *Climacteric*. 2012; 15:241–9. [PubMed: 22612610]
8. Al-Azzawi F, Palacios S. Hormonal changes during menopause. *Maturitas*. 2009; 63:135–7. [PubMed: 19372016]
9. Alexander C, Cochran CJ, Gallicchio L, et al. Serum leptin levels, hormone levels, and hot flashes in midlife women. *Fertil Steril*. 2010; 94:1037–43. [PubMed: 19476935]
10. Freedman RR. Pathophysiology and treatment of menopausal hot flashes. *Semin Reprod Med*. 2005; 23:117–25. [PubMed: 15852197]
11. MacLennan AH. Evidence-based review of therapies at the menopause. *Int J Evid Based Healthc*. 2009; 7:112–23. [PubMed: 21631851]
12. Sowers, M., Crawford, S., Sternfeld, B., et al. SWAN: A multicenter, multiethnic, community-based cohort study of women and the menopausal transition. In: Lobo, R.Kelsey, J.Marcus, R., Lobo, AR., editors. *Menopause: biology and pathology*. New York: Academic Press; 2000. p. 175-88.
13. Crandall CJ, Zheng Y, Crawford SL, et al. Presence of vasomotor symptoms is associated with lower bone mineral density: a longitudinal analysis. *Menopause*. 2009; 16:239–46. [PubMed: 19002017]
14. Thurston RC, El Khoudary SR, Sutton-Tyrrell K, et al. Vasomotor symptoms and insulin resistance in the study of women's health across the nation. *J Clin Endocrinol Metab*. 2012; 97:3487–94. [PubMed: 22851488]
15. Thurston RC, Sutton-Tyrrell K, Everson-Rose SA, et al. Hot flashes and subclinical cardiovascular disease: findings from the Study of Women's Health Across the Nation Heart Study. *Circulation*. 2008; 118:1234–40. [PubMed: 18765392]
16. Gold EB, Colvin A, Avis N, et al. Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: study of women's health across the nation. *Am J Public Health*. 2006; 96:1226–35. [PubMed: 16735636]
17. Butler LM, Gold EB, Conroy SM, et al. Active, but not passive cigarette smoking was inversely associated with mammographic density. *Cancer Causes Control*. 2010; 21:301–11. [PubMed: 19915951]
18. Conroy SM, Butler LM, Harvey D, et al. Physical activity and change in mammographic density: the Study of Women's Health Across the Nation. *Am J Epidemiol*. 2010; 171:960–8. [PubMed: 20354074]
19. Block G, Hartman AM, Dresser CM, et al. A data-based approach to diet questionnaire design and testing. *American journal of epidemiology*. 1986; 124:453–69. [PubMed: 3740045]
20. Allison, PD. *Survival analysis using SAS: A practical guide*. 2. Cary, NC: SAS Institute; 2010.

21. Avis NE, Crawford SL, McKinlay SM. Psychosocial, behavioral, and health factors related to menopause symptomatology. *Womens Health*. 1997; 3:103–20. [PubMed: 9332153]
22. Freeman EW, Sammel MD, Lin H, et al. The role of anxiety and hormonal changes in menopausal hot flashes. *Menopause*. 2005; 12:258–66. [PubMed: 15879914]
23. Avis NE, Stellato R, Crawford S, et al. Is there a menopausal syndrome? Menopausal status and symptoms across racial/ethnic groups. *Soc Sci Med*. 2001; 52:345–56. [PubMed: 11330770]
24. Grisso JA, Freeman EW, Maurin E, et al. Racial differences in menopause information and the experience of hot flashes. *J Gen Intern Med*. 1999; 14:98–103. [PubMed: 10051780]
25. Brown DE, Sievert LL, Morrison LA, et al. Do Japanese American women really have fewer hot flashes than European Americans? The Hilo Women's Health Study. *Menopause*. 2009; 16:870–6. [PubMed: 19367185]
26. Key T, Appleby P, Barnes I, et al. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. *J Natl Cancer Inst*. 2002; 94:606–16. [PubMed: 11959894]
27. Freedman RR, Blacker CM. Estrogen raises the sweating threshold in postmenopausal women with hot flashes. *Fertil Steril*. 2002; 77:487–90. [PubMed: 11872200]
28. Berendsen HH. The role of serotonin in hot flushes. *Maturitas*. 2000; 36:155–64. [PubMed: 11063896]
29. Bergmann MM, Calle EE, Mervis CA, et al. Validity of self-reported cancers in a prospective cohort study in comparison with data from state cancer registries. *American journal of epidemiology*. 1998; 147:556–62. [PubMed: 9521182]
30. Stavrou E, Vajdic CM, Loxton D, et al. The validity of self-reported cancer diagnoses and factors associated with accurate reporting in a cohort of older Australian women. *Cancer Epidemiol*. 2011; 35:e75–80. [PubMed: 21474409]

Table 1

Selected characteristics measured at baseline by breast cancer diagnosis status (N=2,807)

	No breast cancer diagnosis N = 2699	Breast cancer diagnosis N = 108
General characteristics		
Age, years: mean (std)	46.4 (2.7)	46.7 (2.8)
BMI, kg/m ² : mean (std)	28.0 (7.1)	28.8 (8.0)
Underweight/normal: < 25	1,123 (41.6)	43 (39.8)
Overweight: 25 – < 30	718 (26.6)	22 (20.4)
Obese: 30+	827 (30.6)	42 (38.9)
Race/ethnicity		
Caucasian	1,303 (48.3)	58 (53.7)
African-American	749 (27.8)	26 (24.1)
Asian	481 (17.8)	23 (21.3)
Hispanic	166 (6.2)	1 (0.9)
Education level		
< High school	156 (5.8)	3 (2.8)
High school	451 (16.7)	13 (12.0)
College graduate	857 (31.8)	32 (29.6)
Post-college	567 (21.0)	27 (25.0)
Family history of breast cancer (mother or sister)	296 (11.0)	20 (18.5)
Physical activity score (tertiles)		
<7.1	973 (36.1)	36 (33.3)
7.1 – <8.5	783 (29.0)	32 (29.6)
8.5+	869 (32.2)	36 (33.3)
Alcohol consumption (past year)		
Non-drinkers	1,327 (49.4)	48 (44.4)
Drinkers	1,362 (50.7)	60 (55.6)
Smoking status		
Never smoked/no passive exposure	794 (29.7)	31 (29.3)
Never smoked/passive exposure	769 (28.7)	36 (34.0)
Former smoker	698 (26.1)	23 (21.7)
Current smoker	415 (15.5)	16 (15.1)
Reproductive history		
Menopausal status at baseline		
Premenopausal	1,442 (53.4)	54 (50.0)
Early perimenopausal	1,201 (44.5)	53 (49.1)
Age at menarche (years)		
< 12	631 (23.6)	35 (32.4)
12	720 (26.7)	27 (25.0)
13	739 (27.4)	26 (24.1)
14+	584 (21.8)	24 (22.2)

	No breast cancer diagnosis N = 2699	Breast cancer diagnosis N = 108
Age at first birth (years)		
No children	473 (17.5)	24 (22.2)
< 20	422 (15.6)	9 (8.3)
20 – 29	1260 (46.7)	46 (42.6)
30+	544 (20.2)	29 (26.9)
Number of live births		
0	473 (17.5)	24 (22.2)
1	454 (16.8)	20 (18.5)
2	920 (34.1)	38 (35.2)
3+	850 (31.5)	26 (24.1)
Hormone therapy use before baseline (ever)	186 (6.9)	11 (10.2)
Oral contraceptive use before baseline (ever)	1,983 (73.5)	77 (71.3)

Table 2
Adjusted hazard ratios (HR) and 95% confidence intervals (CI) for the risk of breast cancer diagnosis

	N (events)	Woman-Intervals	Age-adjusted		Multivariable Adjusted ^a	
			HR	95% CI	HR	95% CI
All women (N=3,098)	108	29,113				
Non-symptomatic (no VMS)	29	6,872	Ref	Ref	Ref	Ref
Symptomatic (any VMS)	79	22,241	0.88	0.57, 1.35	0.63	0.39, 1.00
Ever, infrequent (1–5 times in past two weeks)	55	16,517	0.83	0.52, 1.32	0.60	0.37, 0.98
Ever, frequent (6+ times in past two weeks)	24	5,724	1.03	0.59, 1.82	0.71	0.39, 1.28
White women (N=1,468)	58	14,394				
Non-symptomatic (no VMS)	20	3,614	Ref	Ref	Ref	Ref
Symptomatic (any VMS)	38	10,727	0.65	0.37, 1.12	0.42	0.23, 0.78
Ever, infrequent (1–5 times in past two weeks)	28	7,932	0.66	0.37, 1.17	0.43	0.23, 0.82
Ever, frequent (6+ times in past two weeks)	10	2,795	0.62	0.29, 1.34	0.39	0.17, 0.90
African-American Women (N=882)	26	8,028				
Non-symptomatic (no VMS)	5	1,305	Ref	Ref	Ref	Ref
Symptomatic (any VMS)	21	6,674	0.87	0.33, 2.30	0.80	0.28, 2.31
Ever, infrequent (1–5 times in past two weeks)	12	4,727	0.70	0.25, 2.00	0.68	0.22, 2.09
Ever, frequent (6+ times in past two weeks)	9	1,947	1.27	0.42, 3.83	1.05	0.32, 3.44
Asian woman (N=520)	23	5,775				
Non-symptomatic (no VMS)	4	1,724	Ref	Ref	Ref	Ref
Symptomatic (any VMS)	19	4,049	2.25	0.76, 6.67	1.63	0.52, 5.15
Ever, infrequent (1–5 times in past two weeks)	15	3,247	2.20	0.73, 6.67	1.60	0.41, 5.16
Ever, frequent (6+ times in past two weeks)	4	802	2.49	0.61, 10.09	1.78	0.41, 7.70

VMS, vasomotor symptoms

^a Adjusted for age, SWAN visit number, SWAN site, age at first birth, BMI, first degree family history of breast cancer, and hormone therapy or oral contraceptive use during the study period

Table 3

Adjusted odds ratios (OR) and 95% confidence intervals (CI) for the risk of postmenopausal breast cancer diagnosis among women who naturally transitioned to postmenopausal during the study period.

	N (events)	Age-Adjusted		Multivariable Adjusted ^a	
		OR	95% CI	OR	95% CI
All women (N=2,003)	67				
Non-symptomatic (no VMS)	21	Ref	Ref	Ref	Ref
Symptomatic (any VMS)	46	0.43	0.25, 0.72	0.45	0.26, 0.77
Ever, infrequent (1–5 times in past two weeks)	16	0.48	0.27, 0.86	0.39	0.20, 0.75
Ever, frequent (6+ times in past two weeks)	30	0.35	0.18, 0.68	0.50	0.28, 0.90
No HT use during the study period (N=1,220)	33				
Non-symptomatic (no VMS)	10	Ref	Ref	Ref	Ref
Symptomatic (any VMS)	23	0.45	0.21, 0.97	0.50	0.23, 1.10
Ever, infrequent (1–5 times in past two weeks)	9	0.47	0.21, 1.07	0.47	0.19, 1.21
Ever, frequent (6+ times in past two weeks)	14	0.42	0.17, 1.06	0.52	0.22, 1.23

HT, Hormone therapy; VMS, vasomotor symptoms

^a Adjusted for age at enrollment, SWAN site, age at first birth, BMI at baseline, family history of breast cancer, and hormone therapy or oral contraceptive use during study period