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History of hot flashes and aortic calcification among postmenopausal women

Rebecca C. Thurston, PhD^{a,b}, Lewis H. Kuller, MD, DrPH^b, Daniel Edmundowicz, MD, MS^c, and Karen A. Matthews, PhD^{a,b}

^a University of Pittsburgh School of Medicine, Department of Psychiatry

^b University of Pittsburgh Graduate School of Public Health, Department of Epidemiology

^c Cardiovascular Institute, University of Pittsburgh School of Medicine

Abstract

Objective—Menopausal hot flashes are considered largely a quality of life issue. However, emerging research also links hot flashes to cardiovascular risk. In some investigations, this risk is particularly apparent among women using hormone therapy. The study aim is to ask whether a longer history of reported hot flashes over the study period was associated with greater aortic and coronary artery calcification. Interactions with hormone therapy use are examined in an exploratory fashion.

Methods—Participants included 302 women participating in the Healthy Women Study, a longitudinal study of cardiovascular risk during the peri- and post-menopause initiated in 1983. Hot flashes (any/none) were assessed when women were 1, 2, 5, and 8 years postmenopausal. Electron beam tomography measures of coronary artery calcification and aortic calcification were completed in 1997–2004. Associations between the number of visits reporting hot flashes, divided by the number of visits attended and aortic or coronary artery calcification (transformed) were examined in linear regression models. Interactions by hormone therapy use were evaluated.

Results—Among women using hormone therapy, a longer history of reporting hot flashes was associated with increased aortic calcification, controlling for traditional cardiovascular risk factors ($b=2.87$, $SE=1.21$, $p<0.05$). There were no significant associations between history of hot flashes and coronary artery calcification.

Conclusions—Among postmenopausal women using hormone therapy, a longer history of reporting hot flashes measured prospectively was associated with increased aortic calcification, controlling for traditional cardiovascular risk factors. Hot flashes may signal adverse cardiovascular changes among certain postmenopausal women.

Keywords

hot flashes; hot flushes; aortic calcification; coronary calcification; hormone therapy; atherosclerosis

Introduction

Approximately 75% of midlife women experience hot flashes at some point during the menopausal transition.¹ The majority of women experience hot flashes for the several years around the final menstrual period. However, hot flashes can persist for decades. Among

Corresponding Author: Rebecca C. Thurston, PhD, 3811 O'Hara St., Pittsburgh, PA 15213, (412) 648-9087, (412) 648-7160 (fax), thurstonrc@upmc.edu.

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Women's Health Initiative (WHI) and Heart and Estrogen Replacement Study (HERS) participants, 23–37% of women in their 60's and 11–20% of women in their 70's reported hot flashes.^{2, 3} Hot flashes are associated with reported sleep disruption,⁴ poorer memory performance,⁵ depressed mood,⁶ and overall poorer quality of life.⁷ Most women with menopausal symptoms, principally hot flashes, seek treatment for them.⁸

While the quality of life impact of hot flashes is substantial, hot flashes are generally considered to have few medical implications. However, recent findings have called this notion into question. For example, both the WHI and HERS found the greatest risk of myocardial infarction among women randomized to the hormone therapy (HT) arm who reported vasomotor symptoms at study baseline.^{9, 10} Several cardiovascular risk factors, particularly obesity and smoking, are also risk factors for hot flashes.^{1, 11} In Study of Women's Health Across the Nation (SWAN) Heart Study, we found hot flashes to be associated with greater aortic calcification (AC) and poorer flow mediated dilation, controlling for estradiol concentrations and traditional CVD risk factors.¹² AC and flow mediated dilation can be considered markers of subclinical cardiovascular disease (CVD), as they are associated with a subsequent increased risk of development of clinical CVD.^{13, 14}

These SWAN findings were among midlife women who were, on average, 50 years old. However, there is suggestion that the greatest cardiovascular risk with HT use may be concentrated among older women with vasomotor symptoms.^{9, 10} The aim of the current investigation was to examine among an older cohort of women whether prospectively-measured hot flashes were associated with greater AC and coronary calcification (CAC), both of which have been prospectively linked to future clinical events.^{13, 15} We evaluate this hypothesis among participants (aged 57–67) in the Healthy Women Study, a longitudinal study of cardiovascular risk in the postmenopause. We consider the history of hot flashes over the course of the study, given the extended duration over which calcification develops, with hot flash reporting at a single time point secondarily examined. Associations are examined controlling for traditional cardiovascular risk factors. Given prior evidence that associations between hot flashes and cardiovascular risk may be most apparent among HT users and women with a longer time since menopause,^{9, 10} we consider interactions by HT use and time since menopause in all models.

Materials and Methods

Subjects

The Healthy Women Study is a longitudinal study of menopause and cardiovascular risk. In 1983–1984, 541 women between the ages of 42 and 50 were recruited from Allegheny County, PA, via driver's license lists. Eligibility criteria were menstrual bleeding within the past 3 months, no surgical menopause, diastolic blood pressure (DBP) <100 mg Hg, not using anti-hypertensive, lipid-lowering, or psychotropic medications, thyroid hormone, insulin, or estrogens. 60% of eligible women enrolled. Details of the recruitment and sample characteristics are described elsewhere.¹⁶

At the baseline study visit, demographic, behavioral, and cardiovascular risk factors were measured. When a woman reported amenorrhea and/or HT with amenorrhea for 12 successive months, determined on postcards completed monthly, she was considered 1 year postmenopausal. Participants underwent a follow-up assessment at approximately 2, 5, and 8 years postmenopausal. Postmenopausal evaluations included assessment of hot flashes. In 1997, Healthy Women Study participants in the Pittsburgh area who had been postmenopausal for ≥5 years were invited to have an electron beam tomography (EBT) scan. 351 women completed this scan. The University of Pittsburgh Institutional Review Board reviewed and approved study procedures, and all participants provided written informed consent.

Of the 351 women who underwent EBT, 49 women were excluded from this analysis due to chemotherapy (n=3), missing AC data (n=9), or, hysterectomy (n=37). The hysterectomized women were excluded due to their potentially differing hot flash and cardiovascular profile.^{17–19} However, results from the primary analyses including these 37 women showed an identical pattern of results as reported herein (data not shown). An additional 20 women were excluded from risk factor-adjusted models due to missing data on one or more covariates (smoking n=2, hypertension or lipid lowering medication use n=1, alcohol use n=3, blood pressure n=1, LDL n=11, HDL n=5, triglycerides n=7, glucose n=6, HT use n=2, BMI n=5). Thus, 302 women were included in basic models and 282 women in risk factor adjusted models. Women included in analyses were younger (M= 62.1 vs. 62.2 years, p=0.01) and had lower fasting glucose (M=92.0 vs. 94.0 mg/dL, p=0.003) than women excluded.

Measures

Hot flashes—At each assessment, women reported whether they had hot flashes (yes/no) in the past two weeks via a standard checklist adapted from Neugarten and colleagues.²⁰ The duration of hot flash reporting over the course of the study (referred to as “hot flashes history”) was calculated as the proportion of total study visits the woman attended in which she reported hot flashes (# of visits reporting hot flashes/# visits attended with non-missing hot flashes data). In secondary analyses, the hot flash report closest to the EBT scan was chosen, typically the 8th postmenopausal assessment.

Calcification—EBT was used to assess CAC and AC using a GE-Imatron C-150 Scanner (Imatron, South San Francisco, CA), as previously described.²¹ During coronary scanning, 30–40 contiguous 3-mm thick transverse images were obtained during maximal breathholding by using electrocardiogram triggering so that each 100-ms exposure was obtained during the same phase of the cardiac cycle, 80% of the R to R interval. During a second pass, 6-mm contiguous images of the aorta (30-ms exposure) were obtained from the aortic arch to the iliac bifurcation. Agatston calcium scores²² were derived from these images based upon 3 or more contiguous pixels greater than 130 Hounsfield Units detected. Scan-to-scan score reproducibility was high (interclass correlation of 0.99).²³ CAC and AC were primarily considered as continuous variables (square root transformation for AC and log transformation for CAC). However, due to their highly skewed distributions, they were considered categorically in secondary models. AC was considered in tertiles based upon the distribution given the lack of clinical cutpoints for AC (0, N=74; >0–241, N=119; ≥242, N=109). CAC was dichotomized (0, N=162; >0, N=140). A 3-level CAC categorization was also considered (0, >0–100, >100),²⁴ with comparable findings.

Covariates—Age was that at the EBT assessment, and time since menopause was calculated as years from menopause to the EBT assessment date. Race was self-reported at baseline in response to an open-ended question, and education was assessed as the highest level of attainment, categorized as < or ≥ college. Remaining covariates were derived from the visit closest to the EBT assessment. Marital status was categorized as married or unmarried (divorced, widowed, never married). Current cigarette smoking was reported (yes/no). Alcohol use was self-reported and calculated as grams/day. Depressive symptoms were assessed via the Beck Depression Inventory.²⁵ A 24-hour food-recall interview was administered by trained nutritionists at study entry. BMI was calculated from measurements of height and weight (kg/m²). Blood pressure was measured by random zero sphygmomanometer.²⁵ Lipid-lowering and anti-hypertensive medication use was assessed by self-report. Total serum cholesterol, HDL-C, and triglyceride concentrations were determined by conventional enzymatic methods from fasting (12 hour) blood samples, with LDL-C estimated by the Friedewald equation.²⁶ Plasma fasting glucose was determined by enzymatic assay (Yellow Springs glucose analyzer). HT use was assessed at each visit. HT use at the visit concurrent with the hot flash assessment

(current HT use) was primarily considered, with the proportion of prior study visits attended in which HT use was reported considered in secondary analyses (oral or transdermal estrogen and progesterone: n=122; estrogen only: n=2, progesterone only: n=1, other: n=16).

Statistical Analysis

Relations between hot flashes and demographic, behavioral, and physiologic variables were considered using t-tests, ANOVA, and chi-square tests. Relations between hot flashes and calcification were evaluated via linear regression and secondarily in logistic regression models. Conformation to assumption of proportionality was verified for ordinal logistic models. Covariates were selected based upon their association with the outcome at $p < 0.20$. SBP and DBP were not included in the same model due to their high correlation; that with the strongest association with the outcome was included. The time difference between the last hot flash assessment and EBT scan ($M = 1.78$ years, $SD = 1.85$, range: 0–9) was considered as a covariate in all analyses. Two and three-way interactions between hot flashes history, HT use, and time since menopause in relation to calcification were considered. Tests were 2-sided, $\alpha = 0.05$.

Results

Participants were predominantly white, well-educated, and had a favorable cardiovascular risk profile because of the eligibility criteria imposed at the beginning of the Healthy Women Study (Table 1). At the time of the EBT evaluation, most women were in their sixties and many were using HT. Women reporting hot flashes at any study visit had less education, were less likely to use HT, and had higher aortic calcification scores than women reporting no hot flashes. Findings were similar when hot flashes history was considered as a continuous variable, with the exception of a positive correlation with depressive symptoms ($r = 0.12$, $p = 0.03$).

Significant associations between the history of hot flashes and AC were observed in basic models, with findings attenuated with adjustment for cardiovascular risk factors (Table 2). However, a significant interaction with current HT use (visit closest to the EBT scan) was observed ($p = 0.04$), with significant associations between hot flashes history and AC observed among HT users. Findings were consistent considering AC as a tertiled variable (e.g., hot flashes history, $OR = 4.32$, 95%CI 1.10–16.99, $p = 0.04$; HT users, covariate-adjusted models). No significant associations were observed for CAC (continuous CAC: $b = 0.27$, $SE = 0.33$, $p = 0.41$; categorical CAC: $OR = 0.89$, 95%CI 0.48–1.66, $p = 0.72$; full sample, minimally adjusted models).

A threshold in the association between the hot flash history and AC was apparent. HT users reporting hot flashes at $\geq 50\%$ study visits had significantly higher AC scores relative to those women reporting hot flashes at 0 to $< 50\%$ of visits ($b = 2.12$, $SE = 0.80$, $p = 0.009$, minimally adjusted models; $b = 1.90$, $SE = 0.80$, $p = 0.02$, risk factor adjusted models). When AC was considered categorically, among HT users, women reporting hot flashes at $\geq 50\%$ of visits had over 3-folds odds of increased AC relative to women reporting hot flashes at none or $< 50\%$ of visits ($OR = 3.07$, 95%CI 1.26–7.48, $p = 0.01$, risk factor adjusted models). Figure 1 depicts the raw aortic calcification score by history of hot flash reporting for illustrative purposes.

Several additional analyses were considered. To control for the potential impact of prior HT use, we considered the history of HT use over the study as an additional covariate in risk factor-adjusted models stratified by current HT use. Findings persisted (e.g., risk factor adjusted models, HT users, hot flashes history: $b = 2.61$, $SE = 1.23$, $p = 0.04$). Notably, there was a high stability of HT use over the study, with current HT users at the time closest to the EBT visit using HT for the majority of study visits ($M = 78.5\%$ of study visits using HT, $SD = 26.5\%$) in contrast to non-users ($M = 11.1\%$ of study visits using HT, $SD = 21.8\%$). In addition, to examine how current HT users may have differed from non-users, of all study covariates, HT users had

lower LDL (HT users: M=123.1 mg/dl, HT non-user: M=134.3 mg/dl, $t=2.72$, $p=0.007$) and higher triglycerides (HT users: M=118, HT non-user: M=99, $t=-3.20$, $p=0.002$) at the time closest to the EBT visit compared to non-users. Current HT users also had a lower proportion of visits reporting hot flashes (HT users: M=0.19, HT non-user: M=0.38, $t=4.84$, $p<0.0001$), an association that was not eliminated when also controlling for prior HT use ($b=-0.16$, $SE=0.07$, $p=0.03$). Further, given prior research indicating potential effect modification of years postmenopausal in relations between hot flashes and CVD risk,⁹ we also considered all 2- and 3- way interactions with number of years postmenopausal, HT use, and hot flashes history. No significant interactions were observed. Finally, associations between hot flashes at the single visit closest to the EBT assessment and calcification were examined; none of the models were significant.

Discussion

The present investigation indicated that a longer history of reporting hot flashes was associated with greater AC among postmenopausal women using HT. Associations persisted controlling for traditional cardiovascular risk factors. These findings further add to the growing literature drawing links between hot flashes and cardiovascular risk.

The present findings are largely consistent with our prior work showing significantly increased AC among middle-aged women reporting hot flashes.¹² This investigation extends these findings to an older sample of women. Moreover, this investigation considered the history of hot flashes over the course of this longitudinal study as opposed to earlier work examining hot flashes at a single time point. Further, unlike our prior work,¹² yet consistent with findings from the WHI⁹ and HERS¹⁰ showing elevated cardiovascular risk with HT most clearly among women with hot flashes, associations between hot flashes and AC observed only among women reporting HT use.

The mechanisms underlying the associations between hot flashes and AC are not fully clear, in part due to an incomplete understanding of hot flashes. Hot flashes are thought to represent primarily a thermoregulatory event.²⁷ However, many investigations show key cardiovascular risk factors to be associated with hot flashes, including smoking,¹ obesity,¹ and potentially a more adverse lipid and blood pressure profile.¹¹ In this investigation, traditional CVD risk factors were unrelated to hot flashes history, potentially due to the restricted range in these variables among these healthy women. Accordingly, findings persisted controlling for CVD risk factors. Women with hot flashes also tend to have lower endogenous estrogen concentrations,²⁸ which have been linked to cardiovascular risk.²⁹ Reproductive hormones were not assessed here among women using HT, and therefore we could not determine their role in the associations between hot flashes and AC among the women in whom associations were observed. Notably, in prior work, endogenous hormone concentrations have not accounted for associations between hot flashes and AC.¹² Further, research has indicated a link between the potent endothelial-dependent vasodilator calcitonin gene-related peptide and hot flashes.³⁰ Thus, multiple mechanisms, as yet fully identified, may be responsible for the observed links between hot flashes and cardiovascular risk.

Relations between hot flashes and AC were observed in HT users only. Given the documented differences between women who elect to take HT versus those who do not (e.g., the healthy user bias),³¹ these interactions cannot definitively be attributed to HT. Although differences between HT users and nonusers may be fully eliminated with covariate adjustment, it is notable that the effect-modifying role of HT use persisted controlling for demographic and CVD risk factors linked to HT use. Findings of interactions by HT use are consistent with the findings from the WHI and HERS indicating that it was the women with vasomotor symptoms and randomized to HT who had the greatest CVD risk.^{9, 10} The reasons for the interaction by HT

use observed here and in other studies is not well understood. However, the inter-relations between HT, hot flashes, and cardiovascular function are important to consider. First, hot flashes are often a reason women take HT. Thus, HT use may indicate women who have had severe or bothersome hot flashes. Moreover, in randomized trials, HT use has been associated with small but significantly increased risk of cardiovascular events, particularly among older women,^{9, 32, 33} potentially presenting a cardiovascular challenge to women with some level of vulnerability. Thus, the relations between hot flashes, HT use, and cardiovascular risk are complex and interactive. These findings indicate that efforts to better understand relations between hot flashes and cardiovascular risk should consider a potential modifying role of HT use.

It is notable that associations were observed for the duration of hot flashes over time, rather than for hot flashes at a single time point. These findings may be understandable given the time period over which calcification develops. AC is a measure of calcified plaques in the aorta, a marker of calcified atheroma and total plaque burden, as well as arteriosclerotic remodeling of the arteries, developing over an extended period.²⁴ Further, significant associations with hot flashes were observed for AC and not CAC. Although it is possible that these differences arise from variations in the physiology underlying relations between hot flashes and calcification in the aorta versus coronary arteries, CAC scores were low in this sample, with 54% of women with no CAC, in contrast to 25% of women with no AC. This more limited range for CAC, consistent with previous findings among women,^{12, 13} may have impacted the ability to detect associations for CAC.

Several limitations deserve mention. Participants were primarily Caucasian, well-educated, and healthy, limiting the generalizability of results. However, results are largely consistent with findings in more ethnically diverse samples.¹² As noted above, reproductive hormones deserve further investigation as a potential mechanism linking hot flashes to AC. Moreover, this study was an observational study, and any causal relations cannot be inferred. Accordingly, although the effect modification by HT is consistent with findings from randomized trials,^{9, 10} it is unclear here whether effects are attributable to HT versus some other aspect of HT users. Further, women excluded were slightly older and had a higher fasting glucose than included women, which may have impacted findings, such as a more limited range in the calcification measures observed here. Finally, hot flashes were assessed at each study visit via questionnaire about the presence/absence of hot flashes in the past two weeks. These self-report instruments are vulnerable to recall and reporting biases. Although useful for identifying women with versus without hot flashes, further investigation with more detailed prospective measures of frequency, severity, and bothersomeness is warranted.

This investigation had multiple strengths. Participants were a well-characterized sample followed since the beginning of the postmenopause, enabling quantification of the history of hot flash reporting measured prospectively over the course of the study. Our study included detailed calcification measures as well as multiple CVD risk factors, allowing the evaluation of AC and CAC aside from the potentially confounding impact of cardiovascular risk factors. Finally, this investigation allowed for the examination of associations between hot flashes and cardiovascular risk using a measure of subclinical CVD, allowing detection of risk before manifesting clinical events.

Conclusion

A longer prospectively-assessed history of hot flash reporting among current HT users was associated with greater AC in this sample of postmenopausal women. These findings persisted controlling for cardiovascular risk factors. These findings contribute to emerging research linking hot flashes and cardiovascular risk, and suggest the importance of continuing the

investigation of these relations and potential underlying mechanisms. If findings are replicated, this body of work would raise the possibility that hot flashes, in addition to their quality of life impact, may have potential medical implications among some women.

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Figure 1.
Association between reported hot flashes and AC among women using HT, Healthy Women Study

Table 1

Sample characteristics by history of hot flashes, Healthy Women Study

	Study history of hot flash reporting	
	None (N=163)	Any (N=139)
Age, M (SD)	62.2 (1.2)	62.0 (1.7)
Race, n (%)		
White	150 (92.0)	131 (94.2)
Nonwhite	13 (8.0)	8 (5.8)
Education, n (%) *		
< College	65 (39.9)	82 (59.0)
≥ College	98 (60.1)	57 (41.0)
Marital status, n (%)		
Married	104 (64.6)	93 (68.4)
Unmarried	57 (35.4)	43 (31.6)
Smoker, n (%)		
No	142 (87.7)	118 (85.5)
Yes	20 (12.4)	20 (14.5)
Alcohol use (grams/day) M (SD)	4.6 (6.5)	5.4 (9.9)
Dietary intake, Kcal/day, M (SD)	2006.7 (1824.4)	2127.6 (1566.4)
BMI, M (SD)	27.6 (6.3)	27.0 (4.4)
SBP, mmHg, M (SD)	122.3 (18.8)	123.7 (18.3)
DBP, mmHg, M (SD)	71.2 (8.9)	71.7 (9.8)
LDL, mg/dl, M (SD)	130.9 (38.2)	126.9 (32.9)
HDL, mg/dl, M (SD)	62.5 (17.1)	60.0 (17.1)
Triglycerides, mg/dl, M (SD)	117.6 (74.1)	127.2 (70.6)
Fasting glucose, mg/dL, M(SD)	92.7 (15.6)	91.1 (13.2)
Beck Depression Score, M (SD)	4.5 (4.1)	5.4 (4.8)
Hypertensive medication use, n (%)	17 (10.4)	15 (10.9)
Lipid lowering medication use, n (%)	11 (6.8)	12 (8.7)
HT use, n (%) *	91 (55.8)	50 (36.5)
Number of study visits attended	3.9 (1.1)	3.9 (0.9)
Coronary calcium score	33.2 (79.3)	67.7 (68.7)
Aortic calcium score *	359.3 (770.0)	537.7 (873.6)

* differed between groups, $p < 0.05$

Table 2
Association between history of hot flash reporting and AC, full sample and stratified by HT use, Healthy Women Study

AC [‡]					
Full sample			HT users		Non-HT users
Model 1	Model 2		Model 1	Model 2	Model 1
b (SE)	b (SE)		b (SE)	b (SE)	b (SE)
(N=302)	(N=282)	(N=141)	(N=133)	(N=159)	(N=149)
Duration of hot flash reporting history [‡]	1.79 (0.66)**	0.57 (0.68)	3.65 (1.18)**	2.87 (1.21)*	0.59 (0.86)
					-0.59 (0.86)

[‡] Cubic root transformed

[‡] As indexed by the number of study visits reporting hot flashes/number of visits attended

Model 1: Age, time difference between HF and AC measurements

Model 2: Age, race, smoking, SBP, LDL, HDL, triglycerides, fasting glucose, BMI, education, alcohol use, anti-hypertensive medication use, lipid lowering medication use, years since menopause, time difference between measurements, and for the full sample models, HT use.

** p<0.01,

* p<0.0