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Weight gain is associated with increased risk of hot flashes in breast cancer survivors on aromatase inhibitors

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Abstract

Hot flashes in breast cancer survivors (BCS) receiving adjuvant aromatase inhibitor (AI) therapy are common, but risk factors for these symptoms are ill-defined. This study tested if body size is associated with hot flashes in BCS on AI therapy. A cross-sectional study of postmenopausal BCS receiving adjuvant AI therapy was performed. The primary outcome was occurrence of patient-reported hot flashes. The primary exposures of interest were current body size and weight change since breast cancer diagnosis. Three hundred participants were enrolled at a mean age of 61 years (range 33–86) after an average AI exposure of 23 months (range 1 month–9 years). Fifty-nine percent reported hot flashes, 32% reported moderate to severe hot flashes, and 25% reported significant worsening of hot flashes since starting AI therapy. Sixty-one percent experienced

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weight maintenance (±10 lb), while 27% had weight gain (gained 10 lb or more), and 11% had weight loss (lost 10 lb or more). In multivariable analysis, weight gain was independently associated with hot flash occurrence (OR 2.1, 95% CI 1.1–4.4) and hot flash severity (OR 2.6, 95% CI 1.3–5.0) after adjusting for confounding. Current body size was not associated with hot flash occurrence, severity or change with AI therapy. In an outpatient BCS population on AI therapy, weight gain is a risk factor for hot flash occurrence. Women who gained at least 10 lb since breast cancer diagnosis were two times more likely to have hot flashes than women who maintained or lost weight. These results support the thermoregulatory model of hot flashes and argue against a protective effect of body fat in this population.

Keywords

Hot flash; Body size; Weight; Aromatase inhibitor; Breast cancer

Introduction

Hot flashes are a common and debilitating symptom in breast cancer survivors (BCS) [1–4]. About two-thirds of postmenopausal BCS being treated for symptoms exhibit hot flashes [1, 2], and six times as many BCS experience hot flashes as compared to age-matched controls [5]. Women with hot flashes report worse quality of life, including greater fatigue, poorer sleep quality, and worse physical health, than those without them [1, 6, 7].

Aromatase inhibitors (AI), which block the final step in estrogen synthesis, are used as adjuvant endocrine therapy in postmenopausal BCS with hormone receptor-positive tumors. Estrogen withdrawal has been strongly associated with vasomotor symptoms such as hot flashes. Thus, AI therapy may render postmenopausal women even more vulnerable to experiencing hot flashes. Much is known about vasomotor symptoms in BCS treated with tamoxifen [8], but such data are more limited for AIs. In the clinical trial setting, the overall prevalence of hot flashes in BCS is high, and risk is significantly higher on letrozole (47%) than on placebo (41%) [9]. Compared to the selective estrogen receptor modulator tamoxifen, patients receiving anastrozole had less frequent hot flashes (35%) than those receiving tamoxifen (40%) or both in combination (41%) [10]. Further, treatment-emergent symptoms such as hot flashes have recently been associated with AI effect and outcomes [11].

Despite the above studies, the prevalence and risk factors for hot flashes in postmenopausal BCS on AIs in the ambulatory setting are largely unknown. In the general menopausal population, risk factors for hot flashes include increased body size, smoking, race, depressive and anxiety symptoms, and endogenous hormone levels [12–17]. Importantly, several of these risk factors are modifiable and, if validated in BCS, represent potential treatment options. Unfortunately, existing information about hot flashes in healthy women can be difficult to transfer to breast cancer survivors, as the severity and frequency of bother caused by hot flashes are significantly different in naturally menopausal women as compared to women with breast cancer [7]. Only by defining the prevalence and risk factors for hot flashes in ambulatory BCS on AI therapy can we improve the communication about diagnosing and treating hot flashes in this population.

The objectives of the study were: (1) to describe the characteristics (frequency, severity, and perceived change) of self-reported hot flashes in postmenopausal women with early stage breast cancer receiving aromatase inhibitors; (2) to identify the demographic and clinical factors that are associated with hot flashes. Specifically, we hypothesized that increased body size would be associated with hot flashes in BCS on AI treatment.

Methods

Study design and patient population

We conducted a cross-sectional survey of breast cancer patients receiving care at the Rowan Breast Cancer Center of the Abramson Cancer Center of the University of Pennsylvania (Philadelphia, PA) between April and October 2007. Potential participants included all postmenopausal women with a history of histologically confirmed stage I to III, hormone receptor-positive breast cancer who were currently taking a third-generation aromatase inhibitor (anastrozole, letrozole, or exemestane), completed chemotherapy or radiotherapy at least 1 month prior to enrollment, and had the ability to understand and provide informed consent in English. Research assistants obtained permission from the treating oncologist, screened medical records and approached potential study subjects for enrollment at their regular follow-up appointments. After informed consent was obtained, each participant was given a self-administered survey. The study was approved by the Institutional Review Board of the University of Pennsylvania and the Scientific Review and Monitoring Committee of the Abramson Cancer Center.

Outcome measurement

Participants reported the average number of hot flashes daily for the past 7 days. For the primary outcome of hot flash occurrence, we dichotomized this measure into hot flashes (yes, no). We also assessed hot flash severity and perceived change in hot flashes since start of AI therapy as secondary outcomes. Participants were asked to rate their hot flashes over the last 7 days on a 5-point likert scale (None, mild, moderate, severe, very severe). The rating is modified from the hot flash daily diary used in many clinical trials of hot flashes [18]. Based on work by Sloan et al. one day's recall of hot flashes can reflect the week's worth of hot flash data. Finally, in order to capture patient-perceived changes in hot flashes related to AI exposure, subjects were asked to compare their hot flashes since start of AI therapy to hot flashes prior to AI therapy on a 7-point likert Patient Global Impression of Change scale (much improved, moderately improved, little improved, not changed, little worse, moderately worse, much worse). Perceived change in hot flashes since AI exposure was grouped as significant improvement (moderately/much improved), little or no change (no change/little improved/little worse), and significant worsening (moderately/much worse).

Covariates were collected, including age, race, ethnicity, education level, and employment status. Demographic, clinical, and treatment characteristics were assessed by either self-report (i.e. timing of the last menstrual period [LMP], height and weight at breast cancer diagnosis, smoking and alcohol use, and co-morbidities including prior arthritis) or medical record abstraction (i.e. stage, chemotherapy, tamoxifen use, aromatase inhibitor use). Body mass index (BMI) were calculated with self-reported current height and weight using the formula BMI = kg/m^2. Weight change since breast cancer diagnosis was categorized as ±10 lb, gaining more than 10 lb, or losing more than 10 lb. Anxiety and depression were measured by subject rating whether they have experienced these moods in the previous 24 h.

Statistical analysis

Data analysis was performed using STATA 9.0 (STATA Corporation, College Station, TX). Summary statistics were performed for all variables. Demographic, clinical, and treatment characteristics were compared by hot flash occurrence, frequency and severity status using Student's *t*-test or Chi-square test, as appropriate. Multivariable logistic regression models were constructed to examine the independent associations of body size and change in body size with our outcomes of interest while controlling for confounding. Covariates with *P*-

values <0.20 in bivariable analyses were carried forward to the multivariable model. Statistical tests were two-sided with $P < 0.05$ indicating significance.

Results

Of 484 consecutive patients screened, 50 (10%) were ineligible due to discontinuation of AI therapy prior to screening, 45 (9%) had metastatic disease, 64 (13%) did not keep their scheduled appointment, and 25 (5%) declined enrollment, resulting in 300 subjects. Characteristics of the study population are listed in Table 1. Among participants, the mean age (range) was 61 (33–86). The majority of subjects (84%) were Caucasian, and a substantial proportion (13%) was non-Hispanic black. In the analysis, we combined the race categories to Caucasians and Others. Mean BMI (range) was 27.2 (17.6–48.7). One hundred and seventy-three (58%) patients were taking anastrozole, 69 (23%) were taking letrozole, and 58 (19%) were taking exemestane.

Hot flashes over the past week were reported by 59% of subjects (Table 1). Figure 1 depicts the distribution of hot flash frequency, severity and change with AI exposure. One-third of subjects who experienced hot flashes reported moderate to very severe symptoms. Mean daily hot flash frequency (range) was 3.6 (1–25). Twenty-five percent of subjects reported significant worsening of hot flashes since starting AI therapy.

In univariate analysis, hot flash occurrence was significantly associated with weight gain since breast cancer diagnosis, but not associated with current body size, depressive and anxiety symptoms, or race (Table 2). Younger age, shorter time since menopause, smoking, prior chemotherapy, and prior tamoxifen therapy were also associated with higher risk of hot flashes. Subjects with weight gain were more likely to report greater hot flashes severity (48%) compared to subjects who maintained weight (25%) and subjects who lost weight (23%) ($P = 0.001$). Perceived change in hot flashes since starting AI therapy was not associated with weight change or BMI.

In a multivariable model adjusting for age, smoking, race, prior tamoxifen and prior chemotherapy, current height and weight, subjects who reported gaining more than 10 lb since breast cancer diagnosis had a two-fold increase in odds of experiencing hot flashes ($P = 0.038$) (Table 3a) when compared to subjects who maintained their weight. Younger age and current smoking were also associated with increased odds of hot flash occurrence.

Weight gain remained independently associated with hot flash severity (OR 2.6 [1.3–5.0]) in a model adjusting for age, smoking, race, current height and weight, depressive and anxiety symptoms (Table 3b). Younger age and depressive symptoms were two additional risk factors for hot flash severity. Because of collinearity with age, time since menopause was not incorporated into both models.

Discussion

In an outpatient BCS population on AI therapy, hot flashes were reported by the majority of patients. While current body mass index was not associated with the hot flash outcomes, weight gain was a significant risk factor for hot flash occurrence and severity even after adjusting for known confounders. Our data also confirmed that BCS share several of the same risk factors for hot flashes as the general menopausal population, namely younger age, closer timing to menopause, smoking and depressive symptoms. These results further support the notion that hot flashes of cancer survivors and healthy women share significant similarities and potential pathogenesis [19].

Approximately 60% of our ambulatory BCS reported currently experiencing hot flashes while on AI therapy. While higher than reported by clinical trial data in BCS [9], this prevalence is similar to smaller observational studies of BCS [1, 2] and the general menopausal population [20]. Data on whether AI therapy is associated with higher risk of hot flashes is conflicting [9, 21]. Nonetheless, this high prevalence indicates that hot flashes are a common problem for the growing population of BCS on AI therapy.

Our interest in the relationship between body size and hot flashes stems from limited understanding of the physiology of hot flashes and options for treatment in the BCS population. Contrary to our hypothesis, the data did not show any relationship between current BMI and hot flashes. Further, there was no protective effect from lower BMI. The traditional thin hypothesis that decreased adiposity would be associated with decreased peripheral estrone production and hence greater vasomotor symptoms have largely been refuted in recent years [17, 20, 22]. Other studies have hypothesized that higher adiposity would provide greater insulation, prevent heat loss and increase the experience of hot flashes.

The association of hot flashes with significant weight gain is consistent with the current thermoregulatory model of vasomotor symptoms. Weight gain has been frequently reported in BCS, especially those who have undergone chemotherapy or menopause [23], To our knowledge, there are no studies on whether weight loss will improve hot flash symptoms in either BCS or general menopausal women. Our cross-sectional data suggest a decreased risk of hot flashes in women who lost more than 10 lb, but this did not reach statistical significance and cannot show causation. However, weight management is a modifiable risk factor that can be incorporated into the care of BCS. Because weight gain in this population has also been associated with worse cancer prognosis, higher incidence of comorbidities such as cardiovascular disease, and quality of life [23], our data give additional impetus for both future intervention studies on weight loss in BCS and clinical counseling of these patients.

Several limitations should be considered. Anthropomorphic measurements and hot flash outcomes were self-reported. In large cohorts such as the Nurses' Health Study, recalled weight and height have been highly correlated with measured values; mean difference between recalled and actual weight was small (−1.4 kg) [24]. To account for this potential measurement error, we designated a wider interval (±10 lb) as no weight change in order to minimize misclassification. For hot flash outcomes, our questionnaire was modified from the hot flash daily diary and relied on self-report [18]. Though hot flashes may be measured "objectively" through skin conductance, there is limited correlation between subjective and objective measures of hot flashes [21] to support skin conductance as the "gold standard" over self-report. We did not obtain more precise measures of body fat and lean mass through techniques such as bioelectrical impedance analysis [25]. Such techniques can be incorporated into future studies. Finally, hormone levels were not available for this cohort to examine the association between estrogen levels on AIs and hot flashes, but this was not our primary aim.

Despite these limitations, we believe this is the first large study reporting the prevalence and risk factors for hot flashes in the ambulatory setting among women on AIs. Contrary to data in clinical trial, hot flashes are common in this population. Furthermore, the risk of hot flashes doubled with significant weight gain, a result that supports the thermoregulatory model of hot flashes and argues against a protective effect of body fat in this population.

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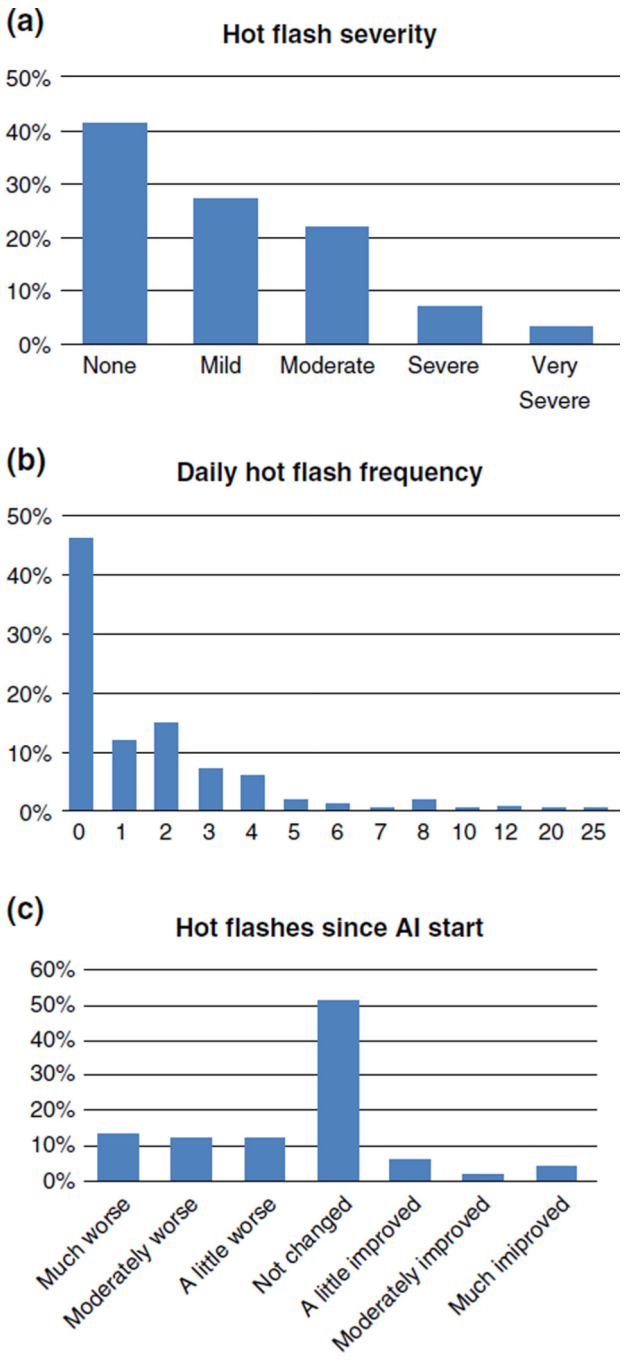

Fig. 1.

Distributions of hot flash severity (**a**), daily hot flash frequency (**b**), and change in hot flashes since starting AI therapy (**c**). **a** Hot flash severity. **b** Hot flash frequency. **c** Change in hot flash since AI therapy

Table 1

Participant characteristics (n = 300)

	Subjects (%) (n = 300)
Age	61 (33–86)
≤55	73 (24)
56–65	131 (44)
≥66	96 (32)
Race	
Caucasian	253 (84)
Other	47 (16)
Current smoking	20 (6.7)
Current alcohol	84 (28)
Years since menopause	
<5 years	51 (18)
5–10 years	95 (33)
>10 years	144 (49)
Cancer treatment	
Cancer stage	
I	100 (37)
II	142 (52)
III	32 (12)
Prior chemotherapy	179 (62)
Prior tamoxifen	136 (47)
Type of AI	
Anastrazole	173 (58)
Letrozole	69 (23)
Exemestane	58 (19)
Duration of AI exposure	
<1 year	126 (43)
1–3 years	79 (27)
>3 years	86 (30)
Body size	
BMI	
Normal/underweight (<18.5–25)	110 (37)
Overweight (25–30)	93 (31)
Obese (≥30)	95 (32)
Weight change since breast cancer diagnosis	
±10 lb	182 (61)
Gained > 10 lb	81 (27)
Lost > 10 lb	34 (12)
Mood and vasomotor symptoms	
Depressive symptoms in last 24 h	113 (38)

	Subjects (%) (*n* = 300)
Anxiety symptoms in last 24 h	151 (51)
Hot flash occurrence	
No	123 (41)
Yes	177 (59)
Hot flash severity	
Mild	81 (27)
Moderate, severe, very severe	96 (32)
Perceived change in hot flashes since AI therapy	
Significant worsening	74 (25)
Little or no change	202 (69)
Significant improvement	19 (6)

Numbers do not add to 300 for all variables due to missing data

Table 2

Univariate associations with hot flash occurrence and significant worsening of hot flashes since AI therapy

	Hot flashes occurrence (%) (*n* = 177)	***P*-value**	**Hot flash severity (%) (*n* = 96)**	***P*-value**	**Significant worsening of hot flashes (%) (*n* = 74)**	***P*-value**
Age		<0.001		<0.001		0.09
≤55	58 (33)		39 (53)		22 (30)	
56–65	73 (41)		34 (26)		33 (46)	
≥66	46 (26)		23 (24)		19 (26)	
Race		0.87		0.24		0.33
Caucasian	148 (84)		76 (79)		60 (81)	
Other	29 (16)		20 (21)		14 (19)	
Current Smoking	18 (10)	0.006	12 (12)	0.02	8 (11)	0.28
Current Alcohol	46 (26)	0.48	69 (72)	1.00	52 (70)	0.75
Years since menopause		<0.001		<0.001		0.003
>5 years	41 (24)		27 (29)		16 (22)	
5–10 years	66 (38)		38 (40		29 (40)	
>10 years	65 (38)		29 (31)		27 (38)	
Cancer stage		0.27		0.88		0.18
I	55 (34)		30 (35)		28 (42)	
II	92 (56)		47 (54)		27 (40)	
III	17 (10)		10 (11)		12 (18)	
Prior chemotherapy	116 (67)	0.02	61 (65)	0.44	39 (53)	0.007
Prior tamoxifen	90 (53)	0.03	49 (53)	0.21	35 (49)	0.32
Duration of AI exposure		0.96		0.33		0.91
< 1 year	48 (28)		39 (41)		18 (25)	
1–3 years	74 (43)		31 (33)		30 (42)	
>3 years	51 (29)		25 (26)		24 (33)	
AI type		0.71		0.67		0.52
Anastrazole	103 (58)		54 (56)		38 (51)	
Letrozole	38 (21)		17 (17)		20 (27)	
Exemestane	36 (20)		25 (26)		16 (22)	

	Hot flashes occurrence (%) (*n* = 177)	*P*-value	Hot flash severity (%) (*n* = 96)	*P*-value	Significant worsening of hot flashes (%) (*n* = 74)	*P*-value
BMI		1.0		0.79		0.09
Underweight (<18.5)	2 (1)		1 (1)		0 (0)	
Normal (18.5–25)	65 (36)		34 (35)		23 (31)	
Overweight (25–30)	54 (31)		27 (28)		22 (30)	
Obese (≥30)	56 (32)		34 (35)		29 (39)	
Weight change since breast cancer diagnosis		<0.001		0.001		0.31
±10 lb	99 (57)		39 (41)		42 (58)	
Gained >10 lb	62 (35)		47 (50)		24 (33)	
Lost >10 lb	14 (8)		8 (9)		6 (8)	
Depression	67 (38)	0.95	46 (48)	0.01	43 (59)	<0.001
Anxiety	90 (51)	0.85	57 (60)	0.03	43 (59)	0.23

Table 3

Multivariable models for hot flashes occurrence (a) and severity (b)

Risk factor	Hot flash occurrence OR (95% CI)	*P*-value
(a) *Hot flash occurence*		
Weight change since breast cancer diagnosis		
±10 lb (reference)	1	
Gained >10 lb	2.15 (1.04–4.42)	0.038
Lost >10 lb	0.57 (0.24–1.38)	0.21
Age	0.93 (0.90–0.97)	<0.001
Current smoking		
No (reference)	1	
Yes	5.15 (1.08–24.43)	0.039
Race		
Caucasian (reference)	1	
Other	1.20 (0.50–2.87)	0.68
Prior chemotherapy		
No (reference)	1	
Yes	1.09 (0.58–2.05)	0.78
Prior tamoxifen		
No (reference)	1	
Yes	1.04 (0.58–1.86)	0.12
b. *Hot flash severity*		
Weight change since breast cancer diagnosis		
±10 lb (reference)	1	
Gained > 10 lb	2.57 (1.31–5.03)	0.006
Lost > 10 lb	0.65 (0.23–1.79)	0.40
Age	0.93 (0.90–0.96)	<0.001
Current smoking		
No (reference)	1	
Yes	2.55 (0.88–7.46)	0.09
Race		
Caucasian (reference)	1	
Other	2.07 (0.87–4.94)	0.10
Depression	1.98 (1.02–3.82)	0.04
Anxiety	1.09 (0.58–2.08)	0.78

Final models also adjusted for current height, weight