Effect of Postdiagnosis Weight Change on Hot Flash Status Among Early-Stage Breast Cancer Survivors

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ABSTRACT

Purpose

Hot flashes (HF) affect a large proportion of breast cancer (BC) survivors and can negatively affect their quality of life. Treatments other than estrogen replacement to alleviate HF are needed. Body weight is related to hot flashes, but little is known about the effect of weight change on HF.

Patients and Methods

We used data from 3,088 women previously treated for early-stage BC who were enrolled onto the Women's Healthy Eating and Living study to examine the association between weight change after a breast cancer diagnosis and the odds of reporting HF.

Results

Overall, 36.1% of participants reported moderate to severe HF at study entry. At 2 years postdiagnosis, 69.2% of women remained within 10%, 4.8% lost at least 10%, and 26.0% gained at least 10% of their prediagnosis weight. Those who gained at least 10% of their prediagnosis weight had a greater risk of reporting HF than women who remained weight stable in that same period (odds ratio [OR], 1.33; 95% CI, 1.11 to 1.60; $P = .003$). Weight loss of at least 10% of prediagnosis weight was associated with a nonsignificant reduced risk (OR, 0.72; 95% CI, 0.47 to 1.08; $P = .118$) of reporting HF. However, the trend of weight change (weight loss and weight gain) on HF was significant both when examined categorically ($P = .03$) and continuously ($P < .001$).

Conclusion

Prevention of weight gain after a BC diagnosis—a modifiable behavior—may offer a viable intervention for relief of HF. Effects of intentional weight loss in BC survivors requires further study.

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INTRODUCTION

Hot flashes (HF) occur frequently among breast cancer survivors, largely resulting from the use of antiestrogen therapies. Approximately 65% of breast cancer survivors report having HF and more than two thirds of those survivors report that the intensity of the HF was severe or bothersome.¹ HF can negatively affect a women's quality of life^{1,2} by disrupting sleep,³ interfering with work and leisure activities, and exacerbating anxiety and depression.⁴ In women who are naturally menopausal, risk factors for HF include increased adiposity, smoking, being African American, Hispanic ethnicity, less education, previous history of premenstrual symptoms, previous history of depressive and anxiety symptoms, and lower endogenous hormone levels.⁵⁻⁷ However, less is known about the etiology of HF in women who have survived breast cancer.

The mechanisms responsible for HF in breast cancer survivors are likely multifactorial. In part, the mechanisms are similar to those proposed for women going through the menopause transition, such as alterations in hypothalamic thermoregulation⁸ or endothelial function.⁹ However, some mechanisms may be unique to breast cancer survivors, such as accelerated estrogen withdrawal associated with adjuvant hormonal therapy and an accelerated aging process caused by chemotherapy-induced ovarian failure.¹

In observational studies, greater adiposity (indicated by high body mass index [BMI] or body fat) has been associated with more reports of frequent or severe HF compared with women with a lower BMI or lower levels of body fat.^{7,10-15} Two studies have reported that weight gain¹⁶ or fat gain¹⁷ is also related to more reports of HF, and one randomized weight loss intervention trial reported that, at the end of the trial, women in the intervention group

had fewer and less bothersome incidents of HF than women in the control group.¹⁸ Because breast cancer survivors tend to gain weight after a breast cancer diagnosis and treatment,¹⁹⁻²³ prevention of weight gain may be a viable strategy to alleviate HF associated with breast cancer treatments. We evaluated this question among women participating in the Women's Healthy Eating and Lifestyle (WHEL) study to examine whether gaining or losing weight after a breast cancer diagnosis was associated with the risk of HF.

PATIENTS AND METHODS

The WHEL study population has been previously described.²⁴ Briefly, 3,088 breast cancer survivors who enrolled onto a dietary intervention trial between 1995 and 2000 were followed until completion of the trial, which ended in 2006. Participants were enrolled an average of 2 years postdiagnosis; were diagnosed with stage I, II, or III invasive breast cancer (defined by American Joint Committee on Cancer VI classification); and had completed active treatment. Participants were 18 to 70 years old and had no evidence of disease within the 12 months before study enrollment. At baseline (median, 23.0 months postdiagnosis), the mean age of patients was 53 years; 54.2% were college graduates; 85.3% were non-Hispanic white; 85% had had stage I or II breast cancer; 57.5% were node-negative; 61.6% had estrogen receptor-positive and progesterone receptor-positive tumors; 61.5% had received radiation therapy; 69.9% had received adjuvant chemotherapy; and 67.3% had received antiestrogen therapy.²⁴ Women included in this study were followed semiannually and had a median follow-up of 7.3 years from the time of enrollment.

Using the Women's Health Initiative symptom inventory,²⁵ women were asked at baseline, year 1, and year 4 about the occurrence and severity of HF during the previous 4 weeks: not occurring (score, 0), mild but not interfering with usual activities (score, 1), moderate and interfering somewhat with usual activities (score, 2), or severe such that usual activities could not be performed (score, 3). Women were categorized as having no or mild HF (score, 0 or 1) or moderate to severe HF (score, 2 or 3). Weight and height were measured in clinic by trained technicians at the baseline (median, 23 months after diagnosis; range, 2 months to 4 years after diagnosis), year 1, and year 4 visits. Self-reported weight (1 year before breast cancer diagnosis [Prediagnosis]) was retrospectively collected at baseline and used as a reference level for comparison with weights measured at the baseline, year 1, and year 4 clinic visits.

Other Data

Additional data collected included demographic characteristics, self-reported menopausal status, and adjuvant hormonal therapy. For tamoxifen use, women were categorized at each time point as current- or ever-users versus never-users. At enrollment, women were considered postmenopausal if they were amenorrheic for more than 12 months and perimenopausal if they reported irregular menstrual cycles during the last 12 months.²⁶ Clinical characteristics and original treatments of patients' breast cancer were obtained from medical records. Depression was assessed by the 8-item short version of the Center for Epidemiologic Studies Depression screen (Cronbach's $\alpha = .73$), which has been validated in cancer patients.^{27,28} The sum of the items yield a total score that can be converted to a logarithmic scale. A value of $\geq .06$ in the logarithmic scale suggests clinical levels of depressive symptoms and the possibility of a diagnosable mood disorder.²⁹ Health-related quality of life was assessed using the Medical Outcomes Study 36-Item Short Form Health Survey.^{30,31} Physical activity was assessed using a 9-item physical activity measure adapted from the Women's Health Initiative.³²

The institutional review boards of all the participating institutions approved procedures for this study, and written informed consent was obtained from all study participants before enrollment.

Data Analyses

Baseline measures were summarized by HF status as means and standard deviations (SD) or medians and interquartile ranges (IQR) for continuous

measures, or as frequency counts and percentages for categorical measures. Distributions were compared by HF status using *t* tests, Wilcoxon rank-sum tests, or χ^2 tests, as appropriate. Weight change from prediagnosis to each time point (baseline [median, 23 months postdiagnosis], 1 year after baseline, and 4 years after baseline) was categorized as follows: $\leq 10\%$, within 10%, and $\geq 10\%$.¹⁶ Weight change was summarized by HF status at each of the three aforementioned time points.

A multivariate logistic regression model was fit to compute the odds of moderate or severe HF versus no or mild HF at baseline for prediagnosis to baseline weight change both as categorical and continuous variables, adjusted for prediagnosis BMI. Baseline measures that differed by baseline HF status ($P < .10$) were included as covariates in the model. These measures included age at diagnosis, race/ethnicity, college education, smoking status, menopausal status, tamoxifen treatment, chemotherapy use, depression score, and physical activity level. This model was also used to compute the odds of moderate or severe HF versus no or mild HF at year 1 and year 4 for prediagnosis to year 1 and prediagnosis to year 4 weight change, adjusted for prediagnosis BMI. Covariates were updated using year 1 and year 4 values, as appropriate. As HF symptoms can be an adverse effect of tamoxifen use,³³ likelihood ratio tests were used to examine the interaction between weight change and tamoxifen use on HF status. All analyses were conducted with R, version 2.9.2 (Vienna University of Economics and Business, Vienna, Austria).

RESULTS

At baseline, 36.1% of the 2,938 patients reported moderate or severe HF. Women were more likely to report moderate or severe HF if they had not graduated from college, were former or current smokers, or were postmenopausal (Table 1). Additionally, African American and Hispanic women reported HF more often than women of other races or ethnicities. Women who had received tamoxifen or chemotherapy were more likely to report HF than women who did not receive those treatments. Depressive symptoms were associated with those women reporting more severe HF, and physical activity levels were low among those who reported more severe HF symptoms.

Prediagnosis BMI was unrelated to HF status, but BMI taken at study baseline after diagnosis was associated with reporting HF (Table 2). Women who were overweight or obese at baseline entry onto the study were more likely to report moderate to severe HF than women with normal or below-normal weight at baseline. Overall, average weight change from one year prediagnosis to baseline was a gain of 6.9 lbs. This change was greater for those who reported moderate to severe HF (mean, 9.0 lbs; SD, 16.2 lbs) than for those who reported no or mild HF (mean, 5.8 lbs; SD, 16.7 lbs; $P < .001$). The majority of women (69.2%) remained within 10% of their prediagnosis weight, whereas 4.8% of women lost at least 10% and 26.0% of women gained at least 10% of their prediagnosis weight. Of the women who gained at least 10% of their prediagnosis weight, the average weight gain was 26.5 lbs (SD, 12.3 lbs). Of the women who lost at least 10% of their prediagnosis weight, average weight loss was 27.9 lbs (SD, 18.8 lbs). The average weight change for those who remained at a stable weight was a gain of 1.93 lbs (SD, 7.8 lbs).

Although the proportion of women experiencing moderate or severe HF declined over time since diagnosis, weight gain from diagnosis to baseline, year 1, or year 4, all of which represented postdiagnosis weight gain up until that point, was consistently associated with moderate to severe HF at all three time points (Fig 1). Adjusted for prediagnosis BMI, the odds ratios (OR) of moderate to severe HF for women who gained weight compared with women whose weight remained stable were 1.54 at baseline (95% CI, 1.30 to 1.82; $P < .001$),

Table 1. Baseline Characteristics by Hot Flash Symptom Status

Characteristic	Hot Flash Symptoms				Overall	P
	None/Mild		Moderate/Severe			
	No. of Patients	%	No. of Patients	%		
Overall	1,876	64	1,062	36	2,938	—
Age at diagnosis, years						.091
Mean	50.6		51.2		50.8	
SD	9.5		7.6		8.8	
Age at random assignment, years						.137
Mean	52.6		53.1		52.8	
SD	9.6		7.7		9.0	
Years since diagnosis						.155
Mean	2.0		1.9		1.9	
SD	1.1		1.1		1.1	
Race/ethnicity						
White, non-Hispanic	1,609	64	900	36	2,509	.012
Black, non-Hispanic	58	54	49	46	107	
Hispanic	92	58	66	42	158	
Asian	68	76	22	24	90	
Other	49	66	25	34	74	
College graduate						
No	816	61	533	40	1,349	< .001
Yes	1,060	67	529	33	1,589	
Smoking status						
Current/former smoker	836	62	519	39	1,355	.027
Never smoker	1,040	66	543	34	1,583	
Menopausal status						
Postmenopausal	1,371	59	961	41	2,332	< .001
Perimenopausal	200	73	74	27	274	
Premenopausal	302	92	26	8	328	
Years since menopause						< .001
Median	6		4		6	
IQR	2-15		2-13		2-14	
Tamoxifen use						
No	755	76	243	24	998	< .001
Yes	1,121	58	819	42	1,940	
Chemotherapy						
No	591	67	295	33	886	.037
Yes	1,283	62	767	37	2,050	
Radiation						
No	724	64	405	40	1,129	.827
Yes	1,149	64	656	36	1,805	
Depression*						
No	1,613	66	826	34	2,439	< .001
Yes	262	53	234	47	496	
Physical activity (METs per week)						.009
Median	660		560		615	
IQR	225-1,311		150-1,250		215-1,290	
Alcohol intake, g/d						.801
Median	0.2		0.2		0.2	
SD	0-6.9		0-7.1		0-6.9	
Abbreviations: IQR, interquartile range; METs, metabolic equivalents; SD, standard deviation.						
*Depressive symptoms assessed with the Center for Epidemiologic Studies Depression short scale; a score of 0.06 or higher on the log-transformed scale used to denote depression.						

Abbreviations: IQR, interquartile range; METs, metabolic equivalents; SD, standard deviation.

*Depressive symptoms assessed with the Center for Epidemiologic Studies Depression short scale; a score of 0.06 or higher on the log-transformed scale used to denote depression.

Table 2. Weight Change From Prediagnosis to Baseline by Hot Flash Symptom Status

Characteristic	Hot Flash Symptoms				Overall (N = 2,938)	P
	None/Mild (n = 1,876)		Moderate/ Severe (n = 1,062)			
	No. of Patients	%	No. of Patients	%		
Pre-Dx BMI						.368
Mean	26.0		26.2		26.1	
SD	5.7		5.7		5.7	
Pre-Dx BMI						
< 18.5	21	54	18	46	39	.197
18.5-24.9	983	65	524	35	1,507	
25-29.9	508	62	316	38	824	
≥ 30	364	64	204	36	568	
Baseline BMI						.002
Mean	27.0		27.7		27.3	
SD	6.1		6.0		6.1	
Baseline BMI						< .001
< 18.5	21	70	9	30	30	
18.5-24.9	841	68	395	32	1,236	
25-29.9	548	60	359	40	907	
≥ 30	466	61	299	39	765	
Weight change as a percentage of pre-Dx weight, pre-Dx to BL						< .001
Mean	4.1%		6.1%		4.8%	
SD	10		10		10	
Within 10%	1,345	66	668	34	2,033	
Loss ≥ 10%	101	72	39	28	140	
Gain ≥ 10%	430	56	335	44	765	

Abbreviations: BL, baseline; BMI, body mass index; Dx, diagnosis; SD, standard deviation.

1.45 at year 1 (95% CI, 1.30 to 1.82; $P < .001$), and 1.32 at year 4 (95% CI, 1.05 to 1.66; $P = .016$).

In adjusted models, women who gained 10% or more of their prediagnosis weight between prediagnosis and baseline entry had a higher OR of experiencing moderate or severe HF than women who remained within 10% of their prediagnosis weight in that same time period (OR, 1.33; 95% CI, 1.11 to 1.60; $P = .003$; Table 3). Weight loss decreased the OR of reporting moderate or severe HF but results did not reach statistical significance (OR, 0.72; 95% CI, 0.47 to 1.08; $P = .118$). However, there was a significant trend in reports of moderate to severe HF for the weight loss (median, −12.73%), weight stable (median, 1.67%), and weight gain categories (median, 15.40%; P for trend = .039). In adjusted models in which percent weight change was used as a continuous variable in lieu of a categorical variable, the OR for a 5% increase in weight from prediagnosis to baseline was 1.07 (95% CI, 1.03 to 1.12; P for linear trend = < .001).

No significant interaction was observed with tamoxifen use at baseline (likelihood ratio test, $\chi^2 P = .627$). Further, sensitivity analyses showed that tamoxifen use did not modify the relationship of weight change and the likelihood of moderate to severe HF symptoms. OR from models excluding women on tamoxifen were 0.72 for women with weight loss and 1.34 for women with weight gain.

Fig 1. Distribution of participants reporting moderate/severe hot flash symptoms at baseline, year 1, and year 4 follow-up visits, by change from prediagnosis (Pre-Dx) weight. Change in weight presented as the percentage change from the Pre-Dx weight at each study visit. *P* values are from unadjusted χ^2 comparison of distribution.

Results were similar when we examined how weight change from prediagnosis to year 1 and prediagnosis to year 4 affected HF experienced in year 1 and year 4, respectively. After adjusting for covariates, women who gained weight were more likely to report moderate to severe HF at year 1 (OR, 1.24; 95% CI, 1.00 to 1.52; $P = .048$) and at year 4 (OR, 1.13; 95% CI, 0.89 to 1.43; $P = .329$) than women who remained within 10% of their prediagnosis weight. Similarly, weight loss seemed to protect against HF, though not reaching statistical significance (data not shown). As would be expected, because the report of HF at all three time points are highly correlated, adjusting for the presence of HF at baseline attenuated the association between weight gain and HF at year 1 (OR, 1.12; 95% CI, 0.88 to 1.42; $P = .348$) and weight gain and HF at year 4 (OR, 1.05; 95% CI, 0.81 to 1.35; $P = .717$). Consistent with the results for weight change from predi-

agnosis to baseline, no interactions were seen with tamoxifen use at year 1 ($P = .826$) or year 4 ($P = .737$).

Finally, we repeated all analyses examining weight change as absolute change (within 10 lbs, ≥ 10 lbs weight loss, and ≥ 10 lbs weight gain) from prediagnosis to baseline and to each follow-up period. Results for weight gain consistently demonstrated an increased likelihood of moderate to severe HF symptoms at each time point, whereas the reduced likelihood of such symptoms with weight loss was greatly attenuated. For example, the adjusted OR of moderate to severe HF symptoms at baseline were 1.34 for women with weight gain of at least 10 lbs from prediagnosis (95% CI, 1.13 to 1.60; $P = .001$) and 0.90 for women with weight loss of at least 10 lbs (95% CI, 0.67 to 1.19; $P = .449$) when compared with women with stable weight.

DISCUSSION

In this population of breast cancer survivors, 66% of whom reported using tamoxifen at baseline, both BMI at baseline and weight gain after breast cancer diagnosis were associated with a greater risk of moderate to severe HF at time of study entry and for up to 6 years after breast cancer diagnosis. Weight loss of at least 10% of prediagnosis weight after breast cancer diagnosis and treatment was associated with a nonsignificant reduction in reports of HF. There was a significant linear trend for the effect of weight change on reports of HF at baseline whether weight loss was examined categorically or continuously.

Our results for weight gain are in agreement with the two previous studies published on weight change and HF status. Su et al¹⁶ found that among breast cancer survivors who were prescribed aromatase inhibitors, a two-fold increase was observed in reports of HF in women who gained 10 or more pounds between diagnosis and study enrollment. Our report of an approximately 30% increased odds ratio of HF is of a smaller magnitude, but differences in treatments (the WHEL study women used tamoxifen primarily) and the fact that Su et al analyzed any reports of HF compared with our analysis which examined only moderate and severe HF could be responsible for the different effect sizes observed. In the Study of Women's Health Across the Nation, Thurston et al¹⁷ found that body fat gains of greater than 1% over 4 years were associated with a 23% increased risk of reporting HF, an increase in magnitude similar to ours.

Our result for postdiagnosis body weight is also consistent with the recent literature among the general population. Others have demonstrated that women reporting more frequent or more severe HF averaged a higher level of body fat^{12,13} or BMI.¹⁰ Our results for the association of BMI and weight gain with HF lend support to the thermoregulation theory that body fat acts as insulation and vasomotor symptoms provide a regulatory mechanism allowing heat to dissipate.⁸ However, in breast cancer survivors, it is likely that other mechanisms also contribute to the presence of HF. In the WHEL study, we previously observed that women who were taking tamoxifen and reported HF were less likely to have a recurrence.³⁴ We proposed, as have others,³⁵ that the experience of HF while on treatment with tamoxifen is an indicator of a CYP2D6 genotype (extensive metabolizers) that allows successful metabolism of tamoxifen to its more potent antiestrogen metabolites endoxifen and 4-hydroxy tamoxifen. Given that we observed HF in women who were not treated with tamoxifen, and that weight gain increased the risk of HF in both tamoxifen and nontamoxifen users, we believe weight gain is an

Table 3. OR of Moderate/Severe Hot Flash Symptoms Versus None/Mild Symptoms by Prediagnosis to Baseline Weight Change

Weight Change As Percentage of Prediagnosis Weight	OR	95% CI	<i>P</i>
Model 1*			
Loss $\geq 10\%$	0.72	0.49 to 1.05	.100
Within 10%	Referent		—
Gain $\geq 10\%$	1.54	1.30 to 1.82	< .001
<i>P</i> for trend			.124
Model 2†			
Loss $\geq 10\%$	0.72	0.47 to 1.08	.118
Within 10%	Referent		—
Gain $\geq 10\%$	1.33	1.11 to 1.60	.003
<i>P</i> for trend			.039

NOTE. Test for interaction between weight change category and baseline tamoxifen use on odds of moderate/severe hot flashes: $P = .627$.

Abbreviations: BMI, body mass index; OR, odds ratio.

*Model 1 is adjusted for prediagnosis BMI only.

†Model 2 is adjusted for prediagnosis BMI, age at diagnosis, race/ethnicity, college education, smoking status, menopausal status, chemotherapy, tamoxifen treatment, depression, and physical activity level.

independent and important predictor of HF status regardless of CYP2D6 genotype.

Our results for weight loss, though not quite reaching statistical significance, are of a similar magnitude to the increased risk associated with weight gain in this study and the *P* for trend test demonstrated a significant linear relationship.

Su et al¹⁶ also demonstrated a nonsignificant reduction in HF associated with women experiencing large weight loss compared with women who kept their weight within a more stable range. Several factors may contribute to the lack of a statistically significant finding. Weight gain after a breast cancer diagnosis occurs with moderate frequency,^{20,23} probably in response to treatment and accompanying metabolic changes.³⁶ In contrast, weight loss is seen less frequently and thus we may have inadequate power to observe a stronger relationship between weight loss and fewer HF reports. Additionally, weight change after breast cancer is characterized by gains in adipose tissue in the absence of gains in lean tissue or even in the presence of losses of lean tissue.³⁶ Thus, even for women who have stable weight or some weight loss, gains or stability in adipose tissue composition may still contribute to women experiencing significant HF. Without measurements of adiposity, we were unable to test this hypothesis in the WHL data set. However, we note that in a study of overweight women without breast cancer,³⁷ intentional weight loss in a randomized trial was significantly related to a decreased risk of bothersome hot flashes.

The strengths of our study include being the only study of breast cancer survivors with longitudinal data on both weight change and HF status postdiagnosis at several points in time, including up to 6 years postdiagnosis. In addition, weight at all time periods (except prediagnosis weight) was measured in clinic. However, self-reported weight correlates well with measured weight in breast cancer survivors.²⁰ Although we report on subjec-

tive and not objective HF, a woman's perception of the bother related to her HF is a valid indicator of symptoms.³⁸

In conclusion, breast cancer survivors who gained 10% or more of their prediagnosis weight after a breast cancer diagnosis more frequently experienced moderate to severe HF than women who remained within 10% of their prediagnosis weight, and this effect persisted for several years after the breast cancer diagnosis. In addition, there was a suggestion that weight loss was associated with a reduction of HF.

Further research needs to focus on whether intentional weight loss in breast cancer survivors can positively affect the occurrence of HF. For now, prevention of weight (and fat) gain after a breast cancer diagnosis, a modifiable behavior that may have other prognostic benefits, may be a viable intervention for relief of hot flashes.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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REFERENCES

- Carpenter JS, Andrykowski MA, Cordova M, et al: Hot flashes in postmenopausal women treated for breast carcinoma: Prevalence, severity, correlates, management, and relation to quality of life. *Cancer* 82:1682-1691, 1998
- Avis NE, Ory M, Matthews KA, et al: Health-related quality of life in a multiethnic sample of middle-aged women: Study of Women's Health Across the Nation (SWAN). *Med Care* 41:1262-1276, 2003
- Kravitz HM, Ganz PA, Bromberger J, et al: Sleep difficulty in women at midlife: A community survey of sleep and the menopausal transition. *Menopause* 10:19-28, 2003
- Freeman EW, Sammel MD, Liu L, et al: Hormones and menopausal status as predictors of depression in women in transition to menopause. *Arch Gen Psychiatry* 61:62-70, 2004
- Greendale GA, Gold EB: Lifestyle factors: Are they related to vasomotor symptoms and do they modify the effectiveness or side effects of hormone therapy? *Am J Med* 118:148-154, 2005 (suppl 12B)
- Sabia S, Fournier A, Mesrine S, et al: Risk factors for onset of menopausal symptoms: Results from a large cohort study. *Maturitas* 60:108-121, 2008
- 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* 96:1226-1235, 2006
- Freedman RR, Krell W: Reduced thermoregulatory null zone in postmenopausal women with hot flashes. *Am J Obstet Gynecol* 181:66-70, 1999
- 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* 118:1234-1240, 2008
- Freeman EW, Sammel MD, Grisso JA, et al: Hot flashes in the late reproductive years: Risk factors for African American and Caucasian women. *J Womens Health Genet Based Med* 10:67-76, 2001
- Gold EB, Block G, Crawford S, et al: Lifestyle and demographic factors in relation to vasomotor symptoms: Baseline results from the Study of Women's Health Across the Nation. *Am J Epidemiol* 159:1189-1199, 2004
- Thurston RC, Sowers MR, Sutton-Tyrrell K, et al: Abdominal adiposity and hot flashes among midlife women. *Menopause* 15:429-434, 2008
- Thurston RC, Sowers MR, Chang Y, et al: Adiposity and reporting of vasomotor symptoms among midlife women: The study of women's health across the nation. *Am J Epidemiol* 167:78-85, 2008
- Whiteman MK, Staropoli CA, Langenberg PW, et al: Smoking, body mass, and hot flashes in midlife women. *Obstet Gynecol* 101:264-272, 2003
- Wilbur J, Miller AM, Montgomery A, et al: Sociodemographic characteristics, biological factors, and symptom reporting in midlife women. *Menopause* 5:43-51, 1998
- Su H, Sammel MD, Springer E, et al: Weight gain is associated with increased risk of hot flashes in breast cancer survivors on aromatase inhibitors. *Breast Cancer Res Treat* 124:205-211, 2010
- Thurston RC, Sowers MR, Sternfeld B, et al: Gains in body fat and vasomotor symptom reporting over the menopausal transition: The study of women's health across the nation. *Am J Epidemiol* 170:766-774, 2009
- Huang AJ, Subak LL, Wing R, et al: An intensive behavioral weight loss intervention and hot flashes in women. *Arch Intern Med* 170:1161-1167, 2010
- Caan BJ, Emond JA, Natarajan L, et al: Post-diagnosis weight gain and breast cancer recurrence in women with early stage breast cancer. *Breast Cancer Res Treat* 99:47-57, 2006
- Caan BJ, Kwan ML, Hartzell G, et al: Pre-diagnosis body mass index, post-diagnosis weight change, and prognosis among women with early stage breast cancer. *Cancer Causes Control* 19:1319-1328, 2008
- Patterson RE, Cadmus LA, Emond JA, et al: Physical activity, diet, adiposity and female breast cancer prognosis: A review of the epidemiologic literature. *Maturitas* 66:5-15, 2010
- Rock CL, Flatt SW, Newman V, et al: Factors associated with weight gain in women after diagnosis of

breast cancer: Women's Healthy Eating and Living Study Group. *J Am Diet Assoc* 99:1212-1221, 1999

23. Saquib N, Flatt SW, Natarajan L, et al: Weight gain and recovery of pre-cancer weight after breast cancer treatments: Evidence from the women's healthy eating and living (WHEL) study. *Breast Cancer Res Treat* 105:177-186, 2007

24. Pierce JP, Natarajan L, Caan BJ, et al: Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: The Women's Healthy Eating and Living (WHEL) randomized trial. *JAMA* 298:289-298, 2007

25. Matthews KA, Wing RR, Kuller LH, et al: Influence of the perimenopause on cardiovascular risk factors and symptoms of middle-aged healthy women. *Arch Intern Med* 154:2349-2355, 1994

26. World Health Organization: Research on the Menopause in the 1990s: Report of WHO Scientific Group. Geneva, Switzerland, World Health Organization, 1996, pp 1-79

27. Bardwell WA, Natarajan L, Dimsdale JE, et al: Objective cancer-related variables are not associated with depressive symptoms in women treated

for early-stage breast cancer. *J Clin Oncol* 24:2420-2427, 2006

28. Wassertheil-Smoller S, Shumaker S, Ockene J, et al: Depression and cardiovascular sequelae in postmenopausal women: The Women's Health Initiative (WHI). *Arch Intern Med* 164:289-298, 2004

29. Tuunainen A, Langer RD, Klauber MR, et al: Short version of the CES-D (Burnam screen) for depression in reference to the structured psychiatric interview. *Psychiatry Res* 103:261-270, 2001

30. Bardwell WA, Major JM, Rock CL, et al: Health-related quality of life in women previously treated for early-stage breast cancer. *Psychooncology* 13:595-604, 2004

31. Ware JE Jr, Sherbourne CD: The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. *Med Care* 30:473-483, 1992

32. Hong S, Bardwell WA, Natarajan L, et al: Correlates of physical activity level in breast cancer survivors participating in the Women's Healthy Eating and Living (WHEL) Study. *Breast Cancer Res Treat* 101:225-232, 2007

33. Howell A, Cuzick J, Baum M, et al: Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 365:60-62, 2005

34. Mortimer JE, Flatt SW, Parker BA, et al: Tamoxifen, hot flashes and recurrence in breast cancer. *Breast Cancer Res Treat* 108:421-426, 2008

35. Goetz MP, Kamal A, Ames MM: Tamoxifen pharmacogenomics: The role of CYP2D6 as a predictor of drug response. *Clin Pharmacol Ther* 83:160-166, 2008

36. Demark-Wahnefried W, Peterson BL, Winer EP, et al: Changes in weight, body composition, and factors influencing energy balance among premenopausal breast cancer patients receiving adjuvant chemotherapy. *J Clin Oncol* 19:2381-2389, 2001

37. Huang AJ, Sawaya GF, Vittinghoff E, et al: Hot flashes, coronary heart disease, and hormone therapy in postmenopausal women. *Menopause* 16:639-643, 2009

38. Miller HG, Li RM: Measuring hot flashes: Summary of a National Institutes of Health workshop. *Mayo Clin Proc* 79:777-781, 2004