Vasomotor Symptoms, Adoption of a Low-Fat Dietary Pattern, and Risk of Invasive Breast Cancer: A Secondary Analysis of the Women's Health Initiative Randomized Controlled Dietary Modification Trial

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ABSTRACT

Purpose

To assess whether the effect of a low-fat dietary pattern on breast cancer incidence varied by report of baseline vasomotor symptoms.

Methods

Postmenopausal women age 50 to 79 years enrolled onto the Women's Health Initiative (WHI) Dietary Modification trial from 1993 to 1998 were randomly assigned to a low-fat dietary intervention ($n = 19,541$) or comparison ($n = 29,294$). Presence of vasomotor symptoms at baseline was ascertained from a 34-item self-report symptom inventory. Women were queried semi-annually for a new diagnosis of breast cancer. Each case report was verified by medical record and pathology report review by centrally trained WHI physician adjudicators.

Results

Among participants who reported hot flashes (HFs) at baseline ($n = 3,375$), those assigned to the low-fat diet had a breast cancer rate of 0.27 compared with their counterparts in the control group who had a rate of 0.41 (hazard ratio [HR] = 0.65; 95% CI, 0.42 to 1.01). Among women reporting no HFs ($n = 45,160$), the breast cancer rate was 0.42 in those assigned to the low-fat diet compared with 0.46 in the control group (HR = 0.93; 95% CI, 0.84 to 1.03; P for interaction = .12 by HF status). Furthermore, the dietary benefits observed seemed to be specific to estrogen receptor (ER) –positive/progesterone receptor (PR) –positive tumors (ER positive/PR positive v other, P for risk = .03). Although women with and without HFs differed with regard to breast cancer risk factors, the effect of the diet intervention on breast cancer incidence by HF status was consistent across risk factor strata.

Conclusion

The results of this trial, which are hypothesis generating, suggest that HFs may identify a subgroup of postmenopausal women whose risk of invasive breast cancer might be reduced with the adoption of a low-fat eating pattern.

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INTRODUCTION

The presence of hot flashes (HFs) after initiation of the estrogen antagonist tamoxifen or an aromatase inhibitor has recently been reported to be associated with reduced recurrence of breast cancer compared with reporting no vasomotor symptoms.^{1,2} Studies of the *CYP2D6* gene, which regulates the conversion of tamoxifen to one of its key metabolites, endoxifen,³ suggest the hypothesis that HFs may be an independent predictor of tamoxifen efficiency and an indirect measure of genetic variation of *CYP2D6* activity.

After these aforementioned reports, researchers from the Women's Healthy Eating and Living (WHEL) study recently reported an interaction between the presence or absence of HFs and the effectiveness of the WHEL low-fat, plant-based dietary intervention in reducing breast cancer recurrence.⁴ Notably, among WHEL trial participants who did not report hot flashes (HF negative) at study entry (which averaged 2 years after diagnosis), those assigned to the dietary intervention had a significantly reduced risk of additional breast cancer events compared with those assigned to the comparison group (hazard ratio [HR] = 0.69; 95% CI, 0.51 to 0.93); whereas, among the WHEL participants who did

report HFs at baseline (HF positive), there was no difference in breast cancer recurrence between the diet and control groups. Recognizing that most breast carcinomas have estrogen receptors (ERs) and progesterone receptors (PRs), that estrogen plays an important role in malignant transformations, and that reducing dietary fat has been shown to reduce endogenous estrogen levels,⁵⁻⁷ the authors suggested that one mechanism for the protective effect of the WHEL dietary intervention in the HF-negative women may have arisen because HF-negative women may have had higher estrogen levels at baseline⁷ and, thus, might have benefited more from estrogen reductions associated with the intervention diet compared with HF-positive women (who tended to have lower baseline estrogen levels).⁴ This hypothesis was supported by the WHEL study finding that circulating estrogen concentrations were associated with both HFs and study outcomes.⁷

Noting that the Women's Health Initiative (WHI) Dietary Modification (DM) trial⁸ also demonstrated reductions in serum estradiol levels among women assigned to the low-fat dietary pattern intervention, we sought to determine whether the presence or absence of HFs at baseline predicted the responsiveness to the potentially estrogen-modulating effects of a low-fat dietary pattern in the WHI DM trial.

METHODS

The WHI DM intervention was a low-fat dietary pattern (20% of energy from fat) that recommended increased intake of fruits and vegetables (five servings per day) and grains (six servings per day). Detailed accounts of the intervention and methodology of the WHI DM trial have been published.⁸ Briefly, participating women were postmenopausal and 50 to 79 years old at recruitment during 1993 to 1998. Interested and eligible women could be randomly assigned to the DM trial and/or the companion trials of postmenopausal hormone therapy (HT) and had the opportunity for further random assignment onto a trial of calcium and vitamin D supplementation after 1 year of DM trial participation. DM intervention and maintenance activities continued throughout the follow-up period that averaged 8.1 years, which concluded as planned on March 31, 2005. Major DM trial exclusions included any prior breast or colorectal cancer, other cancer except nonmelanoma skin cancer within the last 10 years, medical conditions yielding predicted survival of less than 3 years, adherence or retention concerns, and a baseline diet estimated to have less than 32% of energy from fat, as assessed by the WHI food frequency questionnaire.

The 40% of women assigned to a low-fat dietary pattern received an intensive behavioral modification program to assist them in achieving the previously mentioned dietary intervention goals. Details of the intervention program and diet measurements have been previously described.⁸ The WHI dietary intervention did produce dietary differences between intervention and control groups in the overall trial. The percentage of energy from fat was lower in the intervention group (*v* the comparison group) by 10.7% at 1 year, 9.5% at 3 years, and 8.1% at 6 years. Consumption of vegetables and fruit was also higher in the intervention group by 1.2, 1.3, and 1.1 servings at 1, 3, and 6 years from random assignment, respectively.

Presence of HFs and night sweats at baseline was obtained from a 34-item self-report symptom inventory, which asked individually about HF and night sweat occurrence/severity in the prior 4 weeks (scored from 0 = none to 3 = severe). Women were asked how bothersome the symptom was. Mild symptoms were considered ones that did not interfere with usual activities, moderate symptoms were ones that interfered somewhat with usual activities, and severe symptoms were ones that were so bothersome that usual activities could not be performed. We classified women as having moderate or severe HFs (score = 2 or 3) as HF positive because others have reported that subjective reporting of HFs is associated with a 31% to 33% false-positive rate.⁹ Those who reported mild or no HFs were considered HF negative. We did the same for night sweats; women who reported moderate

or severe night sweats were considered to have night sweats (positive), and those who reported mild or no sweats were considered to have no night sweats (negative).

Outcome

Details of clinical outcome definitions, documentation, and classification have been published.⁸ In brief, women underwent mammography screening at baseline and every 2 years thereafter. They were queried twice each year to determine whether they had been hospitalized for or diagnosed with breast cancer. Self-report of breast cancer was verified by medical record and pathology report review by centrally trained WHI physician adjudicators at each participating clinical center. Coding of histology, extent of disease, and ER and PR status (positive or negative per local pathology report) was performed at the clinical coordinating center using the National Cancer Institute's Surveillance, Epidemiology, and End Results coding system.

Tumors were classified with respect to hormone receptor status in the following three ways: ER positive or ER negative; PR positive or PR negative; and ER positive/PR positive or all others. The first two classifications have been commonly used in previous studies of dietary risk factors for breast cancer,¹⁰⁻¹³ and the third classification separates out the most common tumor subtype from all other subtypes.

Statistical Analyses

The statistical design and analysis methods for the main trial have been described previously.⁸ Disease incidence comparisons between the intervention and comparison groups are based on the intent-to-treat principle using Cox proportional hazards models. HR estimates and nominal 95% CIs from Cox regression¹⁴ models, stratified by DM and age, are presented. To investigate potential confounding and to confirm that there was no bias, we also fit multivariable adjusted models (adjusted for age, race, alcohol, smoking, body mass index, physical activity, parity, age at first birth, years since menopause, baseline mammogram, family history of breast cancer, Gail risk, duration of hormone replacement therapy use reported at baseline, recent hormone replacement therapy use reported at baseline, calcium intake, and vitamin D intake, and stratified by age and HT trial assignment). Two-way interactions between DM and selected baseline characteristics (ie, HFs, night sweats, and vasomotor symptoms) were examined one at a time by the inclusion of product terms between the DM randomization assignment and baseline characteristic in the Cox regression analysis. Additionally, three-way interactions were examined between DM, baseline HF status, and other baseline factors (eg, age, race/ethnicity, body mass index, baseline diet, and change in diet [year 1 – baseline]) to see if the benefits associated with DM and HFs varied by any of these characteristics. The HR estimates also were compared across tumor characteristics using competing risk partial likelihood methods. We define statistical significance as $P = .05$. All statistical tests were two sided.

RESULTS

Approximately 7% of the women (3,375 of 48,835 women) enrolled onto the DM trial reported moderate or severe HFs at baseline. There were no differences in the proportion of women reporting HFs by intervention assignment. Women who reported moderate or severe HFs were younger and more likely to be African American, obese, less physically active, current smokers, and non-alcohol drinkers than those who did not report HFs (Table 1). They were also more likely to report pregnancy before age 20 years, to be within 5 years of menopause onset, and to be a recent quitter of hormones. HFs are highly related to the presence of night sweats. Sixty-four percent of women who reported HFs also reported night sweats, whereas only 2.9% of women who did not have HFs reported night sweats. Although vaginal dryness (18.0% HF positive *v* 6.2% HF negative) and breast tenderness (10.0% HF positive *v* 2.0% HF negative) were also more prevalent among women who had HFs than women who did not, the differences

Table 1. Baseline Demographics and Clinical Characteristics in Dietary Modification Trial by Moderate or Severe Hot Flashes at Baseline (N = 48,835)*

Demographics and Clinical Characteristics	Hot Flash Negative (n = 45,160)		Hot Flash Positive (n = 3,375)		P*
	No. of Women	%	No. of Women	%	
Age group at screening, years					< .001
50-59	15,967	35.4	1,946	57.7	
60-69	21,395	47.4	1,183	35.1	
70-79	7,798	17.3	246	7.3	
Race					< .001
White	37,491	83.0	2,093	62.0	
Black	4,277	9.5	929	27.5	
Hispanic	1,555	3.4	245	7.3	
American Indian	179	0.4	23	0.7	
Asian/Pacific Islander	1,063	2.4	36	1.1	
Unknown	595	1.3	49	1.5	
Alcohol use status					< .001
Nondrinker	18,604	41.3	1,684	50.0	
≤ 1 drink a day	21,986	48.8	1,465	43.5	
> 1 drink a day	4,421	9.8	218	6.5	
Smoking status					< .001
Never smoked	23,216	51.9	1,578	47.3	
Past smoker	18,581	41.6	1,422	42.7	
Current smoker	2,901	6.5	334	10.0	
Body mass index, kg/m ² (collapsed categories)					< .001
< 25	11,997	26.7	589	17.5	
25 to < 30	16,130	35.9	1,145	34.1	
≥ 30	16,826	37.4	1,624	48.4	
Quartiles of physical activity, METs					< .001
< 1.5	9,975	24.6	898	29.8	
≥ 1.5 to < 6.25	9,692	23.9	773	25.6	
≥ 6.25 to < 14.75	10,531	26.0	737	24.4	
≥ 14.75	10,331	25.5	610	20.2	
Parity, No. of pregnancies					.005
Never pregnant/never had term pregnancy	4,974	11.1	341	10.2	
1	3,783	8.4	332	9.9	
2	10,870	24.2	843	25.1	
≥ 3	25,351	56.4	1,842	54.9	
Age at first birth, years					< .001
Never pregnant/no term pregnancy	4,974	12.0	341	11.5	
< 20	6,105	14.8	770	26.0	
20-29	27,068	65.5	1,680	56.7	
≥ 30	3,204	7.7	173	5.8	
Time since menopause, years					< .001
< 5	5,950	14.2	808	25.4	
5-10	8,119	19.4	718	22.6	
10-15	8,734	20.9	560	17.6	
> 15	19,048	45.5	1,098	34.5	
Mammogram within the last 2 years	36,651	83.7	2,577	79.9	< .001
Family history of breast cancer (female)	7,705	18.0	569	17.9	.93
Quartiles of Gail risk					< .001
< 1.12	10,327	22.9	1,574	46.6	
1.12 to < 1.46	11,569	25.6	756	22.4	
1.46 to < 1.92	11,328	25.1	500	14.8	
≥ 1.92	11,936	26.4	545	16.1	
HRT status					< .001
Never used	18,562	41.1	1,459	43.3	
Past user	6,212	13.8	741	22.0	
Current user	20,342	45.1	1,172	34.8	
Time since quitting HRT, years					< .001
Never used	18,562	41.1	1,459	43.3	
Current user	20,342	45.1	1,172	34.8	
1	1,178	2.6	207	6.1	
2	569	1.3	97	2.9	
3-5	1,062	2.4	167	5.0	
> 5	3,403	7.5	270	8.0	

(continued on following page)

Table 1. Baseline Demographics and Clinical Characteristics in Dietary Modification Trial by Moderate or Severe Hot Flashes at Baseline (N = 48,835)* (continued)

Demographics and Clinical Characteristics	Hot Flash Negative (n = 45,160)		Hot Flash Positive (n = 3,375)		P*
	No. of Women	%	No. of Women	%	
HT trial					< .001
E active	1,412	3.1	229	6.8	
E placebo	1,484	3.3	241	7.1	
E + P active	2,145	4.7	266	7.9	
E + P placebo	1,994	4.4	220	6.5	
NR (no uterus)	16,586	36.7	1,117	33.1	
NR (uterus)	21,539	47.7	1,302	38.6	
Moderate/severe night sweats at baseline	1,288	2.9	2,160	64.5	< .001
Moderate/severe breast tenderness at baseline	1,303	2.9	337	10.0	< .001
Moderate/severe vaginal dryness at baseline	2,775	6.2	610	18.2	< .001

NOTE. Three hundred participants had missing hot flash and night sweat information; missing information is not displayed.

Abbreviations: MET, metabolic equivalent; HRT, hormone replacement therapy; HT, hormone therapy; E, estrogen; P, progesterone; NR, not randomly assigned.

*P value based on χ^2 test of association.

in the two HF groups were not as large as seen for night sweats (Table 1).

As shown in Table 2, among women assigned to the low-fat dietary intervention, women who were HF positive at baseline had a 35% risk reduction in breast cancer incidence (HR = 0.65; 95% CI, 0.42 to 1.01) compared with a 7% reduction in the women who were HF negative (HR = 0.93; 95% CI, 0.84 to 1.03), although the interaction was not statistically significant (P for interaction = .12). Similar trends, but with less marked differences between groups, were seen for women who had night sweats (HR = 0.74; 95% CI, 0.50 to 1.10) compared with women who reported no night sweats (HR = 0.93; 95% CI, 0.84 to 1.02; Table 2).

Although women who reported HFs differed from women who did not report HFs on a number of breast cancer prognostic factors reported in Table 1, the effect of the intervention on breast cancer incidence by vasomotor status was consistent across strata of these baseline prognostic factors (eg, HT history, obesity, race, baseline diet, and breast cancer risk profile; Table 3). Within strata, breast cancer risk was consistently lower in HF-positive women assigned to the low-fat dietary intervention versus the control group, whereas the diet intervention was minimally effective in HF-negative women. Of note,

when only the subsample of women not currently on HT were considered, HRs for the effect of the diet on breast cancer incidence by HF status were not altered substantially from those reported for the total sample.

Among women who reported vasomotor symptoms (HFs and night sweats combined), there was a nonsignificant 34% reduction in breast cancer incidence of tumors that were ER positive/PR positive if women were assigned to the DM intervention versus the control group (HR = 0.66; 95% CI, 0.42 to 1.05), whereas among women who did not report vasomotor symptoms, no intervention benefit was seen for ER-positive/PR-positive tumors (HR = 1.01; 95% CI, 0.89 to 1.15; P for interaction = .09). Additionally, the effect seen for the interaction of diet intervention and vasomotor symptom status for ER-positive/PR-positive tumors differed significantly from the other receptor types combined (P for risk = .05; Table 4). When examining the interactions stratifying women by report of the presence or absence of HFs only (Table 5), findings were similar but somewhat stronger. Among women who were HF positive, there was a 44% reduction in risk of ER-positive/PR-positive breast cancer (HR = 0.56; 95% CI, 0.42 to 1.03) if assigned to the diet intervention group versus control group, whereas among HF-negative women,

Table 2. Risk of Invasive Breast Cancer by DM Intervention Versus Comparison Group and by Hot Flash Status Subgroup

DM Group (intervention v comparison)	Intervention Group		Comparison Group		Unadjusted Analysis*			Multivariable Adjusted Analysis†		
	No. of Women	%	No. of Women	%	HR	95% CI	P	HR	95% CI	P
All women	655	0.42	1,072	0.45	0.91	0.83 to 1.01	.07	0.91	0.83 to 1.01	.07
No hot flashes at baseline	621	0.42	996	0.46	0.93	0.84 to 1.03	.13‡	0.93	0.84 to 1.03	.12‡
Hot flashes at baseline	28	0.27	69	0.41	0.66	0.42 to 1.02		0.65	0.42 to 1.01	
No night sweats at baseline	611	0.42	988	0.45	0.93	0.84 to 1.02	.27‡	0.93	0.84 to 1.02	.27‡
Night sweats at baseline	36	0.33	75	0.44	0.73	0.49 to 1.09		0.74	0.50 to 1.10	

Abbreviations: DM, dietary modification; HR, hazard ratio.

*Stratified by age and hormone therapy trial assignment.

†Adjusted for age, race, alcohol, smoking, body mass index, physical activity, parity, age at first birth, years since menopause, baseline mammogram, family history of breast cancer, Gail risk, duration of hormone replacement therapy use reported at baseline, recent hormone replacement therapy use reported at baseline, calcium intake, and vitamin D intake, and stratified by age and hormone therapy trial assignment.

‡P value for interaction.

Table 3. Multivariable Adjusted Risk of Invasive Breast Cancer As a Result of DM Intervention by Subgroups (three-way interactions)

Select WHI Participants and DM Participants (intervention v comparison)	Intervention Group		Comparison Group		Multivariable Adjusted Analysis*		
	No. of Women	%†	No. of Women	%	HR‡	95% CI	P§
Women not in HT trial							.88
No hot flashes at baseline	537	0.43	869	0.47	0.92	0.83 to 1.03	
Hot flashes at baseline	21	0.27	48	0.40	0.66	0.40 to 1.11	
Women in HT trial							.90
No hot flashes at baseline	84	0.37	127	0.38	0.99	0.75 to 1.30	
Hot flashes at baseline	7	0.26	21	0.41	0.66	0.28 to 1.55	
Women not currently on HT (no current use or placebo)							
No hot flashes at baseline	275	0.40	404	0.39	1.02	0.86 to 1.19	
Hot flashes at baseline	14	0.25	30	0.33	0.73	0.39 to 1.37	
Women currently on HT (current use or placebo)							
No hot flashes at baseline	346	0.45	592	0.51	0.87	0.76 to 1.00	
Hot flashes at baseline	14	0.30	39	0.49	0.59	0.32 to 1.08	
Normal/overweight women							> .99
No hot flashes at baseline	376	0.41	595	0.43	0.94	0.83 to 1.07	
Hot flashes at baseline	11	0.21	29	0.32	0.66	0.33 to 1.32	
Obese women							
No hot flashes at baseline	243	0.45	395	0.49	0.91	0.77 to 1.07	
Hot flashes at baseline	17	0.33	40	0.51	0.64	0.36 to 1.13	
White women							.42
No hot flashes at baseline	536	0.44	886	0.48	0.91	0.82 to 1.01	
Hot flashes at baseline	20	0.30	47	0.44	0.67	0.40 to 1.13	
Black women							
No hot flashes at baseline	48	0.34	58	0.29	1.23	0.84 to 1.79	
Hot flashes at baseline	5	0.18	15	0.32	0.55	0.20 to 1.51	
Low Gail risk (< 1.25)							.61
No hot flashes at baseline	150	0.32	229	0.33	0.98	0.80 to 1.20	
Hot flashes at baseline	14	0.24	29	0.31	0.78	0.41 to 1.48	
Medium Gail risk (1.25 to < 1.75)							
No hot flashes at baseline	197	0.39	325	0.43	0.92	0.77 to 1.10	
Hot flashes at baseline	5	0.20	20	0.47	0.41	0.15 to 1.10	
High Gail risk (≥ 1.75)							
No hot flashes at baseline	274	0.55	442	0.60	0.91	0.78 to 1.06	
Hot flashes at baseline	9	0.44	20	0.58	0.70	0.32 to 1.53	
Energy from fat, first tertile (< 34.75%)							.63
No hot flashes at baseline	218	0.44	334	0.46	0.94	0.79 to 1.12	
Hot flashes at baseline	8	0.29	16	0.33	0.84	0.36 to 1.95	
Energy from fat, second tertile (34.75% to < 39.39%)							
No hot flashes at baseline	206	0.42	331	0.44	0.94	0.79 to 1.12	
Hot flashes at baseline	7	0.20	22	0.39	0.46	0.20 to 1.08	
Energy from fat, third tertile (≥ 39.39%)							
No hot flashes at baseline	195	0.42	326	0.46	0.91	0.76 to 1.09	
Hot flashes at baseline	13	0.31	28	0.43	0.69	0.36 to 1.34	
Age 50-59 years							.83
No hot flashes at baseline	212	0.39	323	0.40	0.98	0.82 to 1.16	
Hot flashes at baseline	15	0.25	35	0.35	0.72	0.39 to 1.32	
Age 60-69 years							
No hot flashes at baseline	289	0.43	487	0.48	0.88	0.77 to 1.02	
Hot flashes at baseline	11	0.31	27	0.47	0.62	0.31 to 1.25	
Age 70-79 years							
No hot flashes at baseline	120	0.50	186	0.51	0.98	0.78 to 1.24	
Hot flashes at baseline	2	0.29	7	0.59	0.42	0.09 to 2.04	

Abbreviations: DM, Dietary Modification; WHI, Women's Health Initiative; HR, hazard ratio; HT, hormone therapy.

*Adjusted for age, race, alcohol, smoking, body mass index, physical activity, parity, age at first birth, years since menopause, baseline mammogram, family history of breast cancer, Gail risk, duration of HRT use reported at baseline, recent HRT use reported at baseline, calcium intake, and vitamin D intake, and stratified by age and HT trial assignment.

†Annualized rate.

‡HR from Cox proportional hazards models stratified by age and HT random assignment status.

§P value corresponds to the three-way interaction between DM, hot flash status at baseline, and subgroup characteristic.

Table 4. Risk of Invasive Breast Cancer Types As a Result of DM Intervention by Baseline Vasomotor Symptoms

DM (intervention v comparison)	No Vasomotor Symptoms						Vasomotor Symptoms						P for Interaction*	P for Risk†
	Intervention Group		Comparison Group		Risk		Intervention Group		Comparison Group		Risk			
	No. of Women	%	No. of Women	%	HR	95% CI	No. of Women	%	No. of Women	%	HR	95% CI		
Receptor status														
ER and PR positive	370	0.26	546	0.26	1.01	0.89 to 1.15	26	0.18	61	0.26	0.66	0.42 to 1.05	.09	.05
Other	156	0.11	308	0.15	0.76	0.62 to 0.92	11	0.08	27	0.12	0.66	0.32 to 1.33	.71	
ER positive	450	0.32	737	0.35	0.91	0.81 to 1.02	32	0.22	71	0.30	0.72	0.47 to 1.09	.28	.99
ER negative	85	0.06	141	0.07	0.90	0.69 to 1.18	9	0.06	18	0.08	0.76	0.34 to 1.70	.70	
PR positive	377	0.27	563	0.27	1.00	0.88 to 1.14	27	0.19	62	0.27	0.68	0.43 to 1.07	.11	.10
PR negative	152	0.11	292	0.14	0.78	0.64 to 0.94	10	0.07	27	0.12	0.60	0.29 to 1.23	.49	
Tumor size, cm														
≤ 1.0	210	0.15	381	0.18	0.82	0.69 to 0.97	12	0.08	28	0.12	0.69	0.35 to 1.35	.61	.37
> 1.0	333	0.24	518	0.25	0.96	0.84 to 1.10	28	0.19	59	0.25	0.75	0.48 to 1.18	.30	
Differential grade														
Good	152	0.11	257	0.12	0.89	0.72 to 1.08	12	0.08	24	0.10	0.79	0.39 to 1.59	.76	.90
Moderate	216	0.15	360	0.17	0.89	0.75 to 1.06	16	0.11	40	0.17	0.63	0.35 to 1.13	.26	
Poor	160	0.11	241	0.11	0.99	0.81 to 1.21	14	0.10	29	0.12	0.75	0.40 to 1.43	.42	
No. of positive lymph nodes														
None	404	0.29	651	0.31	0.92	0.82 to 1.05	30	0.21	67	0.29	0.71	0.46 to 1.09	.24	.78
≥ 1	129	0.09	207	0.10	0.93	0.75 to 1.16	13	0.09	22	0.09	0.95	0.47 to 1.88	.97	
SEER stage														.80
In situ	170	0.12	243	0.11	1.03	0.85 to 1.26	7	0.05	17	0.07	0.67	0.28 to 1.62	.35	
Local	440	0.31	713	0.34	0.92	0.82 to 1.04	30	0.21	71	0.30	0.66	0.43 to 1.02	.15	
Regional/distant	141	0.10	227	0.11	0.93	0.75 to 1.15	14	0.10	25	0.11	0.90	0.47 to 1.74	.93	

Abbreviations: DM, Dietary Modification; HR, hazard ratio; ER, estrogen receptor; PR, progesterone receptor; SEER, Surveillance, Epidemiology, and End Results.

*Test of interaction between DM and baseline vasomotor symptoms.

†Analysis of the partial likelihoods; tests whether HRs are equal between tumor types.

ER-positive/PR-positive tumors were not reduced in the intervention group versus control group (HR = 1.01; 95% CI, 0.88 to 1.15; *P* for interaction = .07). There was no observable difference in benefit observed for the diet by HF group in tumors that were not ER positive/PR positive (*P* for interaction = .96), again suggesting that the interaction between HFs and the effect of DM on breast cancer incidence varied by tumor subtype (*P* for risk = .03).

DISCUSSION

These data suggest that women who are experiencing HFs or vasomotor symptoms may be more likely to reduce their risk of breast

cancer by adopting a low-fat eating pattern; however, such dietary benefit may be less successful in women who are not experiencing these symptoms. Although our overall finding of a 35% reduction of breast cancer risk among HF-positive women who were assigned to a low-fat dietary pattern versus control was in the same direction and not statistically significantly different from the 7% breast cancer risk reduction in the intervention group versus control group among HF-negative women, the findings are intriguing and warrant further investigation.

These analyses were prompted by the report in the WHEL study that the effect of a low-fat dietary pattern on risk of new breast cancer events varied by HF status at baseline; however, we were not able to

Table 5. Risk of Invasive Breast Cancer Types As a Result of DM Intervention by Baseline Hot Flash Status

Breast Cancer Type	No Hot Flashes at Baseline						Hot Flashes at Baseline						P for Interaction*	P for Risk†
	Intervention Group		Comparison Group		Risk		Intervention Group		Comparison Group		Risk			
	No. of Women	%	No. of Women	%	HR	95% CI	No. of Women	%	No. of Women	%	HR	95% CI		
ER positive/PR positive	383	0.26	568	0.26	1.01	0.88 to 1.15	14	0.14	42	0.25	0.56	0.30 to 1.03	.07	.03
Other	158	.11	315	.14	0.75	0.62 to 0.90	9	0.09	19	0.11	0.76	0.34 to 0.70	.96	

Abbreviations: DM, Dietary Modification; HR, hazard ratio; ER, estrogen receptor; PR, progesterone receptor.

*Test of interaction between DM and baseline hot flash symptoms.

†Analysis of the partial likelihoods; tests whether HRs are equal between tumor types.

replicate those findings. In the WHEL study, the HF-negative women seemed to benefit from adopting a low-fat, plant-based diet, and the diet did not seem to influence breast cancer recurrence in HF-positive women, whereas in the WHI study, the greatest benefit of a low-fat diet on breast cancer risk seems to be in HF-positive women. Notable differences between the WHEL cohort of breast cancer survivors and the WHI cohort of women who were initially free of breast cancer include age, current HT use, and tamoxifen use, which are all factors that clearly influence the prevalence and perhaps etiology of HFs. In addition, primary outcomes differ between the two trials (eg, breast cancer recurrence in WHEL v incidence in WHI). Furthermore, in WHEL women who are HF positive, dietary effects may be diluted as a result of the higher efficacy of tamoxifen observed in this group compared with WHEL women who are HF negative. However, it is of interest that in both trials, vasomotor status seems to identify women who may benefit the most from adopting a low-fat diet.

It has been postulated that in the case of tamoxifen, individual expression of the *CYP2D6* gene (and perhaps other genes as well) exists, where the extensive metabolizer phenotype is able to enhance the conversion of tamoxifen to the more active metabolite, endoxifen, resulting in greater treatment efficacy and manifested by the presence of vasomotor symptoms.

Conceivably, a similar biologic mechanism exists for diet, so that the effect of adopting a low-fat diet hypothesized to influence estrogen metabolism varies in part as a result of differential individual expression of specific genes, and vasomotor symptoms may be a predictor of an enhanced ability to respond to these dietary interventions. Polymorphisms of genes involved in estrogen synthesis and metabolism have previously been linked to HFs.^{15,16} Additionally, it is known that certain dietary components of the low-fat dietary pattern, specifically flavones, which are components of select fruits and vegetables and soy foods, modulate the CYP450 system, including the induction or inhibition of these enzymes by various mechanisms, including the stimulation of gene expression via specific receptors and/or CYP protein or mRNA stabilization.¹⁷

Our results demonstrating that effects were strongest for women who developed ER-positive/PR-positive tumors, a tumor subtype responsive to an estrogenic microenvironment, support the hypothesis that HFs may be a marker for women who are most likely to be able to modulate their estrogenic microenvironment through diet. We previously reported that the WHI low-fat intervention diet resulted in a slight reduction in circulating estrogens,⁸ and preliminary data in a limited WHI subsample suggest that women who had HFs had larger decreases in circulating estradiol levels between baseline and year 1 (-0.63 pg/mL) in response to the intervention diet compared with estradiol changes in women without vasomotor symptoms (-0.11 pg/mL). These differences may in part account for our observed effects. We also examined whether those who reported HFs had larger decreases in weight in response to the intervention compared with those who did not have vasomotor symptoms, another factor that may account for observed effects, but we found no differences in weight changes.

That results vary by hormone receptor subtype also supports substantial previous evidence suggesting that breast cancer is a heterogeneous disease and risk factors, especially those relating to the potential modulation of the estrogenic environment such as diet,

adiposity, parity, age at first birth, and age at menarche, may vary by breast cancer subtype.^{8,12,18-21}

Several limitations that may impact study results should be noted. First, the present study is a secondary analysis of the original trial, and thus, random assignment was not intentionally performed within the vasomotor symptom subgroup. However, although women with HFs differ from women without HFs, the random assignment procedure is likely to have balanced breast cancer risk factors between the diet intervention group and control group within the HF subgroup, and as noted, the effect of the intervention on breast cancer incidence by vasomotor symptom status did not vary across strata of these baseline factors.

Second, this study may have had limited power to detect strong interaction effects. Only 7% of the women reported moderate to severe HFs at baseline. This low prevalence of more severe HFs is not surprising given that the mean age of women in the WHI DM trial was 61.3 years, HFs are most frequent in late perimenopause²² and within 5 years after the final menstrual period,^{23,24} and 51% of the women were on HT at baseline.

There are also several factors that warrant these results to be interpreted with caution. The interaction by HF group did not reach the traditional $P < .05$ level, and thus, the results could have occurred by chance alone. The HRs in the HF-positive and HF-negative groups for diet intervention versus control on breast cancer incidence were both less than 1.0, and the benefits observed for diet were for the HF-positive group, not the HF-negative group as was initially observed in the WHEL study.

In summary, our findings, which are at this point only hypothesis generating, suggest that HFs, a symptom that is easily determined in a clinical setting, may be a useful indicator of which women will most likely reduce their risk of breast cancer if they adopt a low-fat dietary intervention. Furthermore, breast cancer is a heterogeneous disease with different etiologic risk factors, and the utility of HFs as a predictor of response to a low-fat dietary intervention may be most beneficial for the prevention of ER-positive/PR-positive tumors, the most common tumor subtype. Clearly, further research in this area is needed, and these findings will need to be replicated in primary prevention settings before any clinical application can be considered.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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