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ORIGINAL REPORT

Dietary Pattern Influences Breast Cancer Prognosis in Women Without Hot Flashes: The Women's Healthy Eating and Living Trial

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose
To determine whether a low-fat diet high in vegetables, fruit, and fiber differentially affects prognosis in breast cancer survivors with hot flashes (HF) or without HF after treatment.

Patients and Methods
A secondary analysis was conducted on 2,967 breast cancer survivors, age 18 to 70 years, who were randomly assigned between 1995 and 2000 in a multicenter, controlled trial of a dietary intervention to prevent additional breast cancer events and observed through June 1, 2006. We compared the dietary intervention group with a group who received five-a-day dietary guidelines.

Results
Independent of HF status, a substantial between-group difference among those who did and did not receive dietary guidelines was achieved and maintained at 4 years in intake of vegetable/fruit servings per day (54% higher; 10 *v* 6.5 servings/d, respectively), fiber (31% higher; 25.5 *v* 19.4 g/d, respectively), and percent energy from fat (14% lower; 26.9% *v* 31.3%, respectively). Adjusting for tumor characteristics and antiestrogen treatment, HF-negative women assigned to the intervention had 31% fewer events than HF-negative women assigned to the comparison group (hazard ratio [HR] = 0.69; 95% CI, 0.51 to 0.93; $P = .02$). The intervention did not affect prognosis in the women with baseline HFs. Furthermore, compared with HF-negative women assigned to the comparison group, HF-positive women had significantly fewer events in both the intervention (HR = 0.77; 95% CI, 0.59 to 1.00; $P = .05$) and comparison groups (HR = 0.65; 95% CI, 0.49 to 0.85; $P = .002$).

Conclusion
A diet with higher vegetable, fruit, and fiber and lower fat intakes than the five-a-day diet may reduce risk of additional events in HF-negative breast cancer survivors. This suggestive finding needs confirmation in a trial in which it is the primary hypothesis.

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INTRODUCTION

Self-report of hot flashes (HFs) after treatment for early-stage breast cancer has been associated with an approximately 25% to 30% decreased risk for additional breast cancer events, independent of the type of antiestrogen therapy.[1,2] HFs have been associated with lower estrogen levels during the menopausal transition in some,[3,4] but not all,[5] studies. Discontinuation of menopausal hormone therapy (MHT), chemotherapy-induced amenorrhea, and antiestrogen therapies such as tamoxifen or an aromatase inhibitor contribute to the development of HFs in women undergoing breast cancer therapy.[6] However, HFs are reported by women without menses, women who continue to menstruate while on chemotherapy, and women whose menses resume after temporary amenorrhea,[7] suggesting that low circulating estrogen concentrations do not fully explain HF status.

Changes in dietary pattern to either decrease energy from fat or increase fiber intake can alter the enterohepatic recirculation of estrogens, leading to lower circulating estrogen concentrations.[8,9] Binding of fiber to unconjugated estrogens in the gut impedes reabsorption of estrogen.[10,11] A 20% difference in circulating estrogen levels has been reported for postmenopausal Mexican American women in

the highest versus lowest quartile of fiber intake.[12] Pooled data from 13 dietary intervention studies with reductions in dietary fat intake (many with increases in dietary fiber intake) suggest that circulating estradiol could be decreased by 18% to 27%.[13] Conceivably, the increased risk of additional breast cancer events observed among women who do not report HFs after treatment may be reduced by lifestyle interventions that lower circulating estrogen concentrations.

The Women's Healthy Eating and Living (WHEL) Study tested whether a dietary pattern high in vegetables, fruit, and fiber and low in fat might reduce additional breast cancer events in women with early-stage breast cancer.[14] Such a dietary pattern has previously been shown to lower circulating estradiol concentrations.[15] Furthermore, women with higher circulating estradiol concentrations at baseline were less likely to report HFs and also more likely to have a secondary cancer event within a 7.3-year follow-up period.[15] The primary analyses of the WHEL Study did not demonstrate an event-free survival advantage in following the study's dietary pattern.[14] On the basis of findings of improved disease-free survival in women with HFs[1] and significantly higher circulating estradiol levels in women without HFs,[15] we performed secondary analyses to test the hypothesis that the dietary intervention had a differential impact on prognosis depending on women's baseline HF status. We hypothesized that the protective dietary effect might be limited to the subgroup of patients with potentially higher circulating estradiol levels and worse prognosis (ie, women without HFs at baseline).

PATIENTS AND METHODS

Patients

Between 1995 and 2000, the WHEL Study randomly assigned women within 4 years of diagnosis of stage I ($\geq$ 1 cm), II, or IIIA breast cancer[16] to a dietary intervention or comparison group at seven clinical sites.[17] We observed 96% of participants for an average of 7.3 years (range, 6 to 11 years).[14] Institutional review boards at each clinical site approved the protocol; all participants provided written informed consent. Analyses focused on the 2,967 women (96% of all enrolled) whose baseline HF severity report in the prior 4 weeks (scored 0 [none] to 3 [severe]) was obtained using the Women's Health Initiative symptom inventory.[4] Women were classified as having any HFs (score = 1 to 3; HF positive) or no HFs (HF negative) because reporting any HFs, irrespective of severity, was associated with disease-free survival.[1] This analysis included women who were premenopausal at baseline because 30% of such women reported HFs. At baseline, participants had a mean age of 53 years; 54.2% were college graduates; 85.3% were white; 95% had had stage I or II breast cancer; 57.5% were node negative; 61.6% had had estrogen receptor (ER)–positive and progesterone receptor (PR)–positive tumors; 61.5% had received radiation therapy; 69.9% had received adjuvant chemotherapy; and 67.3% had received antiestrogen therapy.[14]

Study Groups

Details of the dietary intervention have been reported previously.[16,18] Briefly, an intensive telephone counseling intervention based on social cognitive theory promoted a daily dietary intake of five vegetable servings, an additional 16 oz of vegetable juice, three fruit servings, 30 g of fiber, and 15% to 20% of energy from fat for the intervention group.[18,19] The comparison group received printed materials (but no counseling) promoting the five-a-day guidelines[20] of daily intakes of five servings of fruit and vegetables, more than 20 g of fiber, and less than 30% of energy intake from fat.

Dietary Assessment

Dietary intake was assessed with four 24-hour telephone dietary recalls using the Nutrition Data System software (NDS-R 1994-2006; University of Minnesota, Minneapolis, MN), conducted on random days over a 3-week period, stratified for weekend and weekdays. For this analysis, we consider dietary assessment conducted at baseline (before random assignment), 1 year, and 4 years. Fasting blood samples were collected to validate self-reported intake of vegetables and fruits.[21,22]

Outcomes

Primary study end points were additional breast cancer events (local/regional recurrence or distant metastasis or new primary breast cancer) and death from any cause. Carcinoma in situ was not included as an outcome. All such additional breast cancer events reported in semiannual telephone interviews were confirmed by medical record review. Outcome ascertainment also included a search of the National Death Index.

Other Data

Reproductive history (including prior MHT use and gynecologic surgical history, eg, oophorectomy) was self-reported at baseline. At each clinic visit, height and weight were measured to calculate body mass index (BMI).[23] Women were considered postmenopausal if they were amenorrheic for more than 12 months and perimenopausal if they reported irregular menstrual cycles in the past 12 months.[24] Cancer characteristics and treatments were obtained from medical records. Depressive symptoms were measured with the eight-item Center for Epidemiologic Studies Depression Scale.[25,26] Health-related quality of life was assessed using the Medical Outcomes Study 36-Item Short Form Health Survey.[27,28]

Data Analyses

Breast cancer event rates were estimated by study group and baseline HF status. Kaplan-Meier plots of breast cancer event-free survival were generated. The breast cancer event-free interval was defined as the time from date of enrollment to the occurrence of an additional breast cancer event. Follow-up time was censored at the time of a woman's death (if not from breast cancer), at the last documented contact date, or at the study completion date (June 1, 2006). χ^2 and t tests were used to test associations of measured variables by study group and baseline HF status. We estimated between-group differences in dietary variables using a conservative imputation analysis, described previously,[21] that assumed that nonrespondents were following the comparison group dietary pattern. Tests for significant dietary differences by baseline HF status, time, and study group were examined using mixed models including group $\times$ time and group $\times$ time $\times$ HF interactions.

To develop parsimonious multiple regression models, we tested bivariate associations with breast cancer events and included any variables that were significant at the $P = .1$ level. We computed likelihood ratio tests using a Cox model that controlled for these variables and included baseline HF status and study group as main effects and a term for the interaction between them. To examine whether other factors modified any observed interaction between study group and HF status, further analyses included three-way interaction terms between study group, HF status, and individual variables. Finally, we conducted a sensitivity analysis of covariates that were omitted from the final Cox model.

RESULTS

Study Outcomes by Baseline HF Status and Study Group

Participants were equally allocated across random assignment arms within the HF-positive and HF-negative subgroups. Among the 2,067 HF-positive women (69.7%), 1,029 (49.8%) were randomly assigned to the intervention group, and 1,038 (50.2%) were assigned to the comparison group. Among the 900 women in the HF-negative group, 447 (50.3%) were randomly assigned to the intervention group, and 453 (49.7%) were assigned to the comparison group (χ^2

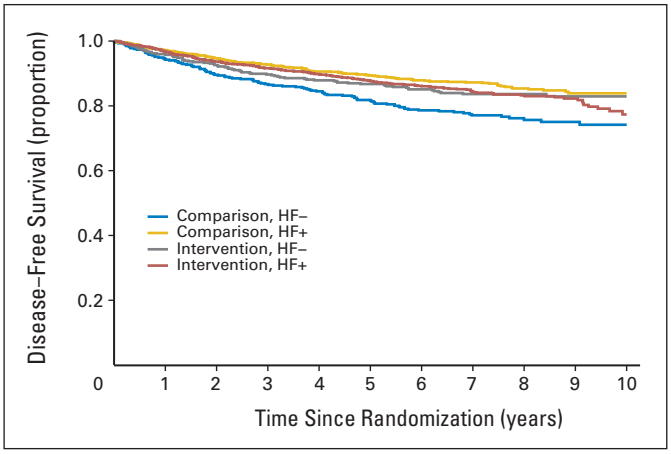

Fig 1. Kaplan-Meier curve of disease-free survival by study group and hot flash (HF) status. Comparison without HF (HF−; n = 453), unadjusted hazard ratio (HR) = 1.00; intervention HF− (n = 447), unadjusted HR = 0.67; $P = .01$. Comparison with HF (HF+; n = 1038), unadjusted HR = 0.56; $P < .001$; intervention HF+ (n = 1,029), unadjusted HR = 0.68; $P = .002$.

test of HF by group association, $P = .99$). Kaplan-Meier curves demonstrated that HF-negative women in the comparison group had significantly worse disease-free survival than the other three groups (Fig 1; likelihood ratio test for group × HF interaction, $P = .002$). Five-year disease-free survival rates by group were very similar for three of the four subgroups (88% for HF-positive women in intervention group; 89% for HF-positive women in comparison group, and 87% for HF-negative women in intervention group) but lower for the subgroup of HF-negative women in the comparison group (82%).

Within the HF-negative subgroup, women in the intervention group had a significantly lower rate of additional breast cancer events than women in the comparison group (intervention, n = 72, 16.1%; comparison, n = 107, 23.6%; log-rank test, $P < .01$) with a major between-group difference in distant recurrences (Table 1). This between-group difference was also observed in deaths from any cause (comparison = 14.1% *v* intervention = 9.4%; log-rank test, $P = .03$). Among the HF-positive women, no significant between-group difference was observed in additional breast cancer events (intervention, n = 170, 16.5%; comparison, n = 143, 13.8%; log-rank test, $P = .10$) or in all-cause mortality (comparison = 8.6% *v* intervention = 10.3%; log-rank test, $P = .20$).

Univariate Differences by Study Group Among the HF-Negative and HF-Positive Subgroups

As expected, differences were observed between the HF-positive and HF-negative subgroups. Women in the HF-negative subgroup were significantly younger, more likely to be premenopausal and node negative, and less likely to have had bilateral oophorectomy; fewer had had ER-positive/PR-positive tumors, taken MHT, or received chemotherapy or antiestrogen therapy; and they reported a better quality of life (Table 2). Random assignment achieved reasonably comparable groups for key covariates by baseline HF category (Table 2). However, history of antiestrogen therapy was marginally higher in the intervention versus comparison group within both subgroups (HF negative: 56.5% *v* 49.7%, respectively; $P = .05$; HF positive: 76.8% *v* 73.3%, respectively; $P = .0.07$). The oophorectomy rate was higher in the intervention versus comparison group, particularly in the HF-negative subgroup (HF negative: 11.7% *v* 6.4%, respectively; $P = .01$; HF positive: 16.4% *v* 13.6%, respectively; $P = .09$). Report of prior MHT use also differed by study group in the HF-negative subgroup (intervention = 42.6% *v* comparison = 33.9%; $P = .01$), as did hormone receptor status in the HF-positive subgroup ($P = .01$). BMI did not vary across HF subgroups ($P = .94$) or by intervention and comparison group for either HF-positive ($P = .47$) or HF-negative women ($P = .22$).

Dietary Change Achieved by Intervention

Regardless of baseline HF status, the intervention group changed their diets significantly; compared with baseline, at 1 year, daily vegetable servings approximately doubled, fiber consumption increased 33%, fruit servings increased 20%, and energy from fat was reduced by 20% (Table 3), whereas intakes in the comparison group remained relatively unchanged. At 4 years, the intervention group consumed approximately 65% more vegetables than the comparison group, 25% more fruit, 30% more fiber, and 13% less energy from fat.[21] Between-group differences in dietary intake were statistically significant at 1 and 4 years ($P < .001$). For each dietary component (vegetables, fruit, fiber, and energy from fat) as the dependent variable, the group × time interaction was statistically significant ($P < .001$), but the HF × group × time interaction was not statistically significant.

Table 1. Additional Breast Cancer Events Over 7.3 Years of Follow-Up by Baseline Hot Flash Status and Study Group

	Baseline Hot Flashes				No Baseline Hot Flashes			
	Comparison		Intervention		Comparison		Intervention	
Event	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Local/regional recurrence	16	1.5	27	2.6	20	4.4	15	3.3
Distant recurrence	111	10.7	119	11.6	72	15.9	42	9.4
New primary	16	1.5	24	2.3	15	3.3	15	3.4
No evidence of recurrence	895	86.2	859	83.5	346	76.4	375	83.9
Total	1,038	100	1,029	100	453	100	447	100

NOTE. Likelihood ratio test of group by hot flash status interaction, $P = .002$.

Table 2. Variables Associated With Random Assignment Group or Reported HF Status at Baseline

Variable	HF Negative at Baseline					HF Positive at Baseline					*P* (HF positive *v* HF negative)
	Comparison		Intervention			Comparison		Intervention			
	No. of Patients	%	No. of Patients	%	*P**	No. of Patients	%	No. of Patients	%	*P**	
Age, years					.35					.80	< .001
< 45	131	28.9	112	25.1		137	13.2	125	12.2		
45-54	132	29.1	132	29.5		478	46.1	491	47.7		
55-59	61	13.5	54	12.1		204	19.7	193	18.8		
≥ 60	129	28.5	149	33.3		219	21.1	220	21.4		
No. of positive lymph nodes					.58					.63	.01
0	288	63.6	269	60.2		573	55.2	578	56.2		
1-3	110	24.3	119	26.6		320	30.8	298	29		
> 3	55	12.1	59	13.2		145	14	152	14.8		
Grade					.26					.47	.04
Poor	183	40.4	167	37.4		351	33.8	364	35.4		
Moderate	170	37.5	170	38		423	40.8	422	41		
Well	54	11.9	72	16.1		184	17.7	157	15.3		
Unspecified	46	10.2	38	8.5		80	7.7	86	8.4		
Hormone receptor status					.63					.01	< .001
ER positive/PR positive	239	54.9	252	57.7		680	66.7	666	66.1		
ER positive/PR negative	54	12.4	56	12.8		105	10.3	132	13.1		
ER negative/PR positive	16	3.7	19	4.3		59	5.8	32	3.2		
ER negative/PR negative	126	29	110	25.2		175	17.2	177	17.6		
Tumor size, cm					.52					.60	.77
≤ 2	268	59.2	254	56.8		614	59.3	596	58		
> 2	185	40.8	193	43.2		422	40.7	431	42		
Chemotherapy					.99					.12	< .001
No	162	35.8	159	35.6		305	29.4	270	26.2		
Yes	290	64.2	288	64.4		732	70.6	759	73.8		
Antiestrogen therapy					.05					.07	< .001
No	225	50.3	190	43.5		274	26.7	237	23.2		
Yes	222	49.7	247	56.5		751	73.3	784	76.8		
Previous menopausal hormone therapy					.01					.75	< .001
No	297	66.1	256	57.4		507	48.9	494	48.1		
Yes	152	33.9	190	42.6		529	51.1	532	51.9		
Oophorectomy					.01					.09	<.001
No	424	93.6	393	88.3		892	86.4	857	83.6		
Yes	29	6.4	52	11.7		141	13.6	168	16.4		
Menopausal status					.21					.84	< .001
Premenopausal	128	28.3	103	23.1		51	4.9	46	4.5		
Perimenopausal	44	9.7	47	10.5		95	9.2	90	8.8		
Postmenopausal	281	62	296	66.4		891	85.9	891	86.8		
BMI, kg/m^2					.22					.47	.94
< 25	191	42	191	43		461	44	431	42		
25-29.9	152	34	129	29		309	30	327	32		
≥ 30	110	24	127	28		268	26	271	26		
Quality of life (SF-36 scale)					.31					.12	< .001
Mean	77.5		78.1			74.3		75.6			
SD	14.6		15.2			17.3		16.3			
Depression (CESD-log scale)					.31					.69	< .001
Mean	0.04		0.04			0.07		0.06			
SD	0.1		0.1			0.2		0.2			

Abbreviations: HF, hot flash; ER, estrogen receptor; PR, progesterone receptor; BMI, body mass index; SF-36, Medical Outcomes Study 36-Item Short Form Health Survey; SD, standard deviation; CESD, Center for Epidemiologic Studies Depression Scale.

*P values are for comparison within random assignment arm based on χ^2 tests for categorical variables or t tests for continuous variables.

Predictors of Additional Breast Cancer Events

As expected, larger tumor size, positive nodes, higher grade/proliferation markers, and being premenopausal were significantly associated with worse breast cancer event-free survival in the final multiple regression model. After controlling for these variables in the Cox model, HF-negative intervention women were 31% less likely to have an additional breast cancer event than HF-negative comparison women (hazard ratio [HR] = 0.69; 95% CI, 0.51 to 0.93; $P = .02$; Table 4). Both the intervention (HR = 0.77; 95% CI, 0.59 to 1.00; $P = .05$) and

Table 3. Mean Dietary Intake Over Time by Random Assignment Group and HF Status

Dietary Intake by Random Assignment Group	Baseline				1 Year*				4 Years*			
	HF Negative†		HF Positive‡		HF Negative†		HF Positive‡		HF Negative†		HF Positive‡	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Total vegetable servings per day												
Intervention	3.7	0.08	3.9	0.06	7.8	0.15	7.8	0.10	6.2	0.14	6.5	0.10
Comparison	3.8	0.09	3.8	0.06	3.9	0.09	3.8	0.06	3.6	0.08	3.7	0.06
Total fruit servings per day												
Intervention	3.4	0.10	3.5	0.07	4.0	0.09	4.3	0.06	3.5	0.10	3.7	0.06
Comparison	3.3	0.10	3.5	0.06	3.3	0.09	3.4	0.06	2.8	0.09	2.8	0.06
Fiber, g/d												
Intervention	20.8	0.37	21.2	0.26	29.2	0.47	29.2	0.26	24.5	0.40	25.7	0.31
Comparison	21.2	0.40	21.2	0.25	21.4	0.40	21.2	0.26	19.3	0.30	19.4	0.20
Fat, % energy												
Intervention	28.4	0.34	28.6	0.22	22.9	0.33	22.5	0.22	27.5	0.40	26.6	0.22
Comparison	28.9	0.34	28.6	0.22	28.5	0.33	28.3	0.22	31.2	0.40	31.4	0.20

NOTE. No significant three-way interactions between HF status, group, and time were observed (ie, the differences in intake by study group did not differ by HF status or duration of follow-up).
Abbreviation: HF, hot flash.
*Differences between intervention and comparison group at this time period, $P < .001$ mixed models.
†HF negative indicates no HFs reported at baseline.
‡HF positive indicates HFs reported at baseline.

comparison groups (HR = 0.65; 95% CI, 0.49 to 0.85; $P = .002$) in the HF-positive subgroup had a significantly better prognosis than the HF-negative comparison group (HF × group interaction, $P = .005$).

Table 4. Final Multiple Regression Model* of Predictors of Additional Breast Cancer Events

Factor	Hazard Ratio	95% CI	*P*
Menopausal status at baseline			
Postmenopausal	1.00		
Perimenopausal	1.10	0.80 to 1.52	.55
Premenopausal	1.75	1.33 to 2.29	< .001
Tumor size, cm			
≤ 2	1.00		
> 2	1.71	1.40 to 2.07	< .001
No. of positive lymph nodes			
0	1.00		
1-3	1.53	1.22 to 1.90	< .001
> 3	3.24	2.58 to 4.09	< .001
Tumor grade (differentiation)			
Well	1.00		
Moderate	1.49	1.05 to 2.12	.03
Poor	1.74	1.21 to 2.49	.003
Unspecified	1.62	1.05 to 2.51	.03
Hormone receptor status			
ER positive/PR positive	1.00		
ER positive/PR negative	1.22	0.93 to 1.61	.15
ER negative/PR positive	1.47	0.98 to 2.20	.07
ER negative/PR negative	1.01	0.76 to 1.33	.96
Antiestrogen therapy			
No	1.00		
Yes	0.84	0.66 to 1.06	.14
HF × group interaction†			
HF negative,‡ comparison group	1.00		
HF negative,‡ intervention group	0.69	0.51 to 0.93	.02
HF positive,§ comparison group	0.65	0.49 to 0.85	.002
HF positive,§ intervention group	0.77	0.59 to 1.00	.05

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HF, hot flash.
*Adjusted for all variables listed and for clinical site and quality of life.
†Likelihood ratio test from group × HF status interaction, $P = .005$.
‡HF negative indicates no hot flashes reported at baseline.
§HF positive indicates hot flashes reported at baseline.

Sensitivity Analyses

Additional stratified multiple regression analyses were conducted to test the robustness of this association (Table 5). The trends reported earlier were also observed for the following subgroups: postmenopausal women, antiestrogen users, nonusers of MHT, women with ER-positive/PR-positive tumors, and nonoophorectomized women. However, although the dietary intervention effect was observed in postmenopausal women (HR = 0.53, $P = .003$), no such effect of the intervention was observed for premenopausal women in the HF-negative subgroup (HR = 1.16; 95% CI, 0.68 to 1.97; $P = .60$). The protective trends for the intervention diet were in the same direction but not statistically significant for perimenopausal women, all subgroups of ER/PR status, nonusers of antiestrogen therapy, and users of prior MHT.

Furthermore, additional separate Cox models were run that included covariates omitted by the modeling criteria, excluded women who were premenopausal or ≤ 45 years old, and excluded 205 women who had stopped taking antiestrogen therapy before enrollment. None of these models yielded different results. When previously omitted covariates (eg, stage, tumor type, history of chemotherapy or radiation therapy, oophorectomy, race, smoking status, age, prior MHT use, and BMI) were included, the HRs changed less than 10% for study group, HF status, and group × HF interaction terms. Additional analyses tested three-way interaction terms in the Cox models, considering HF × study group with hormone receptor status, menopausal status, and use of antiestrogen therapy, none of which were statistically significant (all likelihood ratio tests for interactions, $P > .3$). When we reran the Cox model excluding women who were premenopausal or ≤ 45 years old at baseline, the HR for HF-negative women in the intervention group was 0.49 (95% CI, 0.32 to 0.75; $P = .001$; reference = HF-negative women in comparison group), indicating a strong diet effect among HF-negative peri-/postmenopausal women. Exclusion of the 205 women who had stopped antiestrogen therapy before entering the study also did not alter the results.

Table 5. Multiple Regression* HRs for Additional Breast Cancer Events Stratified by Key Tumor or Treatment Variables

Variable and Group†	HR	95% CI	*P*
All			
HF negative, comparison group	1.0		
HF negative, intervention group	0.69	0.51 to 0.93	.02
HF positive, comparison group	0.65	0.49 to 0.85	.002
HF positive, intervention group	0.77	0.59 to 1.00	.05
Received antiestrogen			
HF negative, comparison group	1.0		
HF negative, intervention group	0.54	0.34 to 0.84	.007
HF positive, comparison group	0.57	0.40 to 0.82	.002
HF positive, intervention group	0.65	0.46 to 0.92	.01
Did not receive antiestrogen			
HF negative, comparison group	1.0		
HF negative, intervention group	0.79	0.52 to 1.21	.28
HF positive, comparison group	0.67	0.43 to 1.03	.07
HF positive, intervention group	0.83	0.55 to 1.27	.4
Received prior menopausal hormone therapy			
HF negative, comparison group	1.0		
HF negative, intervention group	0.77	0.44 to 1.34	.36
HF positive, comparison group	0.80	0.51 to 1.25	.32
HF positive, intervention group	0.91	0.59 to 1.42	.68
Did not receive prior menopausal hormone therapy			
HF negative, comparison group	1.0		
HF negative, intervention group	0.70	0.48 to 1.01	.06
HF positive, comparison group	0.60	0.42 to 0.86	.005
HF positive, intervention group	0.73	0.52 to 1.02	.07
ER positive/PR positive			
HF negative, comparison group	1.0		
HF negative, intervention group	0.65	0.42 to 1.00	.05
HF positive, comparison group	0.60	0.42 to 0.87	.007
HF positive, intervention group	0.65	0.45 to 0.93	.02
ER positive/PR negative			
HF negative, comparison group	1.0		
HF negative, intervention group	0.48	0.20 to 1.13	.09
HF positive, comparison group	0.51	0.24 to 1.12	.09
HF positive, intervention group	0.66	0.33 to 1.30	.23
ER negative/PR positive			
HF negative, comparison group	1.0		
HF negative, intervention group	0.81	0.16 to 4.01	.80
HF positive, comparison group	0.56	0.14 to 2.23	.42
HF positive, intervention group	1.00	0.23 to 4.25	1.0
ER negative/PR negative			
HF negative, comparison group	1.0		
HF negative, intervention group	0.82	0.47 to 1.44	.48
HF positive, comparison group	0.66	0,38 to 1.15	.14
HF positive, intervention group	0.95	0.56 to 1.60	.84
Premenopausal			
HF negative, comparison group	1.0		
HF negative, intervention group	1.16	0.68 to 1.97	.60
HF positive, comparison group	0.53	0.22 to 1.25	.15
HF positive, intervention group	0.70	0.31 to 1.57	.39
Perimenopausal			
HF negative, comparison group	1.0		
HF negative, intervention group	0.52	0.17 to 1.62	.26
HF positive, comparison group	0.65	0.26 to 1.59	.34
HF positive, intervention group	0.60	0.25 to 1.47	.26
Postmenopausal			
HF negative, comparison group	1.0		
HF negative, intervention group	0.53	0.35 to 0.81	.003
HF positive, comparison group	0.61	0.45 to 0.84	.003
HF positive, intervention group	0.72	0.53 to 0.98	.04
Had bilateral oophorectomy			
HF negative, comparison group	1.00		
HF negative, intervention group	2.49	0.48 to 13.01	.28
HF positive, comparison group	3.50	0.79 to 15.47	.10
HF positive, intervention group	2.23	0.50 to 9.95	.29
Did not have bilateral oophorectomy			
HF negative, comparison group	1.00		
HF negative, intervention group	0.64	0.46 to 0.88	.006
HF positive, comparison group	0.59	0.44 to 0.78	.0002
HF positive, intervention group	0.75	0.57 to 0.99	.04

Abbreviations: HR, hazard ratio; HF, hot flash; ER, estrogen receptor; PR, progesterone receptor.

*Adjusted for all variables listed as well as tumor size, grade, number of lymph nodes, clinical site and quality of life. (Note: tumor grade was omitted from the ER−/PR+ model, and menopause status was omitted from the "had bilateral oophorectomy" model due to small cell counts).

[b]HF− = no hot flashes reported at baseline.

[c]HF+ = hot flashes reported at baseline.

DISCUSSION

Although the WHEL Study found no overall benefit to early-stage breast cancer survivors who were assigned to adopt the dietary intervention pattern that was high in vegetables, fruit, and fiber and low in fat compared with survivors who were assigned to the five-a-day group, this dietary intervention was associated with reduced risk of second breast cancer events among women who reported no HFs at baseline. These women had a 31% lower event rate than HF-negative women in the comparison group over 7.3 years of follow-up; among HF-negative postmenopausal women, the intervention effect was even stronger, with a 47% reduction in risk compared with HF-negative women assigned to the comparison group. Compared with HF-negative women in the comparison group, women with baseline HFs had a lower risk of additional breast cancer events, regardless of whether they were randomly assigned to the dietary intervention group or to the comparison group.

The poorer prognosis among HF-negative women and the protective effect of the WHEL intervention diet in this subgroup may be related to circulating estrogen concentrations. In our study, circulating estrogen concentrations were significantly associated both with HFs and with study outcomes.[15] Furthermore, early work suggests that this dietary pattern may lower bioavailable estradiol, at least in the short term.[29] Such an effect is expected from the between-group differences in both dietary fiber and energy from fat that were achieved and maintained in the study. Measurement of changes in circulating estrogen concentrations over the duration of the study will enable us to address this issue more fully in the future.

Although lower circulating estrogen concentrations may be at least partially responsible for the favorable impact of the intervention in the HF-negative group, other studies have reported that fewer

women taking the aromatase inhibitor anastrozole had HFs than those taking tamoxifen, despite having lower circulating levels of estradiol;[30] consistent with our findings, women without HFs had a poorer prognosis.[2] Polymorphisms of genes involved in estrogen synthesis and metabolism are also linked to HFs,[31,32] and polymorphism phenotypes of CYP2D6 have been hypothesized to metabolize tamoxifen differentially to its active form (eg, endoxifen), thus leading to differential success of antiestrogen therapy and also differential occurrence of HFs. We are currently measuring polymorphisms of CYP2D6 and endoxifen levels to test this hypothesis further. However, in the WHEL Study, baseline HFs were associated with more favorable disease outcomes, regardless of whether the woman was on antiestrogen therapy (ie, tamoxifen). Thus, the explanations of the etiology of HFs, their apparent relationship to breast cancer outcome, and the interaction with dietary intake are likely to be much more complex than that provided by simple estrogen concentrations.[33–38]

It is possible that the observed protective effect of the dietary intervention among HF-negative women was an artifact resulting from the intervention group having a higher proportion of women who had either used antiestrogens or had an oophorectomy or were postmenopausal or perimenopausal (86% in the intervention group *v* 78% in the comparison group, $P = .003$). Imbalances in antiestrogen use and bilateral oophorectomy between study groups were observed in both the HF-negative and HF-positive subgroups but were statistically significant only in the HF-negative subgroup and could, by themselves, have resulted in a small reduction in breast cancer–related events. Similar imbalances between intervention and comparison groups were observed in the entire WHEL sample but did not result in any overall difference in event rates.[14] Notably, in the present analyses, the selective protective effect of the WHEL dietary intervention in the HF-negative subgroup persisted when we controlled for these imbalances in the multiple regression Cox model and when the study population was limited to the following groups: women who received antiestrogen therapy; women who did not receive antiestrogen therapy; women who did not have bilateral oophorectomy; and postmenopausal women. Nonetheless, because we did not stratify on these important variables in our original random assignment scheme, our findings need to be interpreted with caution.

In this secondary analysis of the WHEL Study, a diet high in vegetables, fruit, and fiber with reduced fat seemed to remove the excess risk of additional breast cancer events after treatment for early-stage breast cancer in women without HFs, previously reported for both the WHEL comparison group[1] and in the Arimidex, Tamoxifen Alone or in Combination study.[2] This dietary effect was robustly observed across a series of sensitivity analyses. It was not modified by hormone receptor status or use of antiestrogen therapy and was not observed in participants who reported HFs. These results suggest that a major change in dietary pattern may be beneficial for some breast cancer survivors, although these findings need to be confirmed in a trial that has as its primary objective the determination of the differential effect of the diet in breast cancer survivors with and without HFs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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