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Association of Low-Fat Dietary Pattern With Breast Cancer Overall Survival

A Secondary Analysis of the Women's Health Initiative Randomized Clinical Trial

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IMPORTANCE In a randomized clinical trial, a low-fat eating pattern was associated with lower risk of death after breast cancer. However, the extent to which results were driven by dietary influence on survival after breast cancer diagnosis was unknown.

OBJECTIVE To determine the association of a low-fat dietary pattern with breast cancer overall survival (breast cancer followed by death from any cause measured from cancer diagnosis).

DESIGN, SETTING, AND PARTICIPANTS This is a secondary analysis of the Women's Health Initiative randomized clinical trial that was conducted at 40 US clinical centers enrolling participants from 1993 through 1998. Participants were 48 835 postmenopausal women with no previous breast cancer and dietary fat intake of greater than 32% by food frequency questionnaire.

INTERVENTIONS Participants were randomized to a dietary intervention group (40%; n = 19 541) with goals to reduce fat intake to 20% of energy and increase fruit, vegetable, and grain intake or a usual-diet comparison group (60%; n = 29 294). Dietary group participants with incident breast cancers continued to participate in subsequent dietary intervention activities.

MAIN OUTCOMES AND MEASURES Breast cancer overall survival for incident breast cancers diagnosed during the 8.5-year (median) dietary intervention, examined in post hoc analyses after 11.5 years (median) postdiagnosis follow-up.

RESULTS Of 1764 women diagnosed with breast cancer during the dietary intervention period, mean (SD) age at screening was 62.7 (6.7) years and age at diagnosis was 67.6 (6.9) years. With 516 total deaths, breast cancer overall survival was significantly greater for women in the dietary intervention group than in the usual-diet comparison group (10-year survival of 82% and 78%, respectively; hazard ratio [HR], 0.78; 95% CI, 0.65-0.94; *P* = .01). In the dietary group there were fewer deaths from breast cancer (68 vs 120; HR, 0.86; 95% CI, 0.64-1.17), other cancers (36 vs 65; HR, 0.76; 95% CI, 0.50-1.17), and cardiovascular disease (27 vs 64; HR, 0.62; 95% CI, 0.39-0.99).

CONCLUSIONS AND RELEVANCE In women who received a diagnosis of breast cancer during the dietary intervention period, those in the dietary group had increased overall survival. The increase is due, in part, to better survival from several causes of death.

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Supplemental content

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In the Women's Health Initiative (WHI) Dietary Modification (DM) trial, 48 835 postmenopausal women were randomly assigned to a dietary intervention or a usual-diet comparison group to assess low-fat dietary pattern effects on the primary prevention of breast cancer. Baseline characteristics of women in the randomization groups were closely comparable for breast cancer risk factors, as was screening mammography frequency throughout.[1]

Nutrient intake changes associated with the low-fat eating plan after 1 year included a statistically significant reduction in percent energy from fat (mean [SD], 24.3% [7.5%] vs 35.1% [6.9%], respectively) and an increase in fruit and/or vegetable and grain consumption vs the comparison group (all $P < .001$). Although not an intervention target, body weight was 2.2 kg lower in the dietary group as well ($P < .001$).[1,2] At 4.5 years (median) after entry, statistically significant dietary changes and weight differences in the entire dietary group were sustained when compared with the usual-diet comparison group.[3]

At the end of the 8.5 years' (median) dietary intervention, of 1764 incident breast cancers, there were 8% fewer in the dietary intervention group, a difference that was not statistically significant ($P = .09$).[1] Most breast cancer characteristics were balanced between randomization groups. However, there were fewer poor-prognosis, estrogen receptor–positive, progesterone receptor–negative cancers in the dietary group ($P = .04$).[3] Subsequent median cumulative follow-up through 16.1 years found deaths after breast cancer, measured from randomization, to be significantly reduced in the dietary intervention group (HR, 0.82; 95% CI, 0.70-0.96; $P = .01$).[3] These findings suggested that following a low-fat dietary pattern may reduce breast cancers associated with greater mortality. However, as prior analyses of mortality were measured from randomization, it is unclear to what extent the results were driven by dietary influence on postdiagnosis survival.

The observed favorable effect on deaths after breast cancer[3] could have resulted from prediagnosis dietary influences on cancer characteristics.[1,3] Alternatively, or in addition,[4] as dietary group participants with incident breast cancer continued to participate in subsequent intervention activities, the dietary intervention exposure after diagnosis could have affected processes influencing not only breast cancer recurrences but also other clinical outcomes.[5] To address this issue of postdiagnosis dietary intervention influences, we provide findings for breast cancer overall survival measured from breast cancer diagnosis.

Key Points

Question Is implementation of a low-fat eating pattern associated with breast cancer outcome?

Finding In this secondary analysis of the Women's Health Initiative randomized clinical trial that included 1764 postmenopausal women who received a diagnosis of breast cancer during the dietary intervention period, those randomized to a low-fat dietary pattern had increased breast cancer overall survival.

Meaning A dietary change may be able to influence breast cancer outcome.

Methods

Study details have been published.[6] Institutional review board approval was obtained at each center and all participants provided written informed consent. Body weight, height, and waist circumference were measured at baseline, the former 2 measured annually,[2] while physical activity was self-reported at baseline and every 3 years. Mammography screening was performed every 2 years, or annually for participants in the WHI hormone therapy trials.

The major goal of the low-fat dietary program was to implement a change in eating behaviors to reduce fat intake to 20% of total energy. Increases in consumption of vegetable, fruit, and grains were also targeted.[7] Caloric intake reduction and weight loss were not intervention targets. The dietary intervention sessions were led by specially trained and certified nutritionists, and included 18 group sessions in year 1, an individual session between 12 and 16 weeks to ensure nutritional balance of each participant's new dietary pattern, and quarterly maintenance group sessions throughout the dietary intervention period.[7] The objective and content of each session are provided in appendix 1 of the WHI design article.[7] Each dietary group participant was given her own fat gram goal and was asked to monitor her food intake. Usual-diet comparison group participants received written diet-related education materials. Participants provided a 4-day food record at baseline. During the dietary intervention period, dietary intake was assessed using food frequency questionnaires, after 1 year in all and every 3 years thereafter on a 33% rotating subsample. Although dietary change fell short of design goals, intentional dietary changes lasted substantially throughout the trial dietary intervention period, and into the extension period.[8]

Women who received a diagnosis of breast cancer continued participation in dietary group activities. Thus, women who received a diagnosis of breast cancer shortly after entry would have more contact with the dietary intervention program, including contact with study nutritionists, after their breast cancer diagnosis than women who received a diagnosis of breast cancer later during the trial. All contact with study nutritionists ended on March 31, 2005, at the end of the 8.5-year (median) dietary intervention period.

Outcome information was collected every 6 months during the dietary intervention period and annually thereafter. Reported breast cancers were initially verified by medical record review by trained physician adjudicators at the local Clinical Centers. Final adjudication and coding was performed centrally.[9] As previously reported, breast cancer therapy was directed by the participant's own physicians. Among the subset (n = 1403) with Medicare treatment information, radiation therapy (338 [64%] vs 571 [65%]) and adjuvant chemotherapy (130 [25%] vs 236 [27%]) did not differ between randomization groups.[3] Endocrine adjuvant therapy, based on self-report (n = 673), was similar in the 2 groups (171 [71%]

vs 277 [68%] users, respectively; 26 [10 vs 16] responded "don't know"). In addition, physical activity did not significantly differ between groups.[3]

In the present report, we examined, as the primary analyses, dietary modification influence on breast cancer overall survival (breast cancer followed by death from any cause) for the 1764 breast cancer cases diagnosed during the dietary intervention period and followed through September 2013. Note that breast cancer overall survival, defined in the same way, is a commonly accepted end point in adjuvant breast cancer trials.[10]

At the protocol-specified end date (March 31, 2005), after 8.5 years' (median) follow-up, dietary intervention ended. Postintervention follow-up (for 2005-2010, beyond 2010) required written consent, obtained from 83% and 86% of surviving participants willing to be contacted, respectively. Periodic National Death Index queries provided reliable information on survival independent of reconsent status. Cause of death was determined at the WHI Clinical Coordinating Center by medical record or death certificate review. All adjudicators were blind to randomization assignment.

Statistical Analysis

Annualized rates of breast cancer overall survival by randomization group for women who received a diagnosis during the dietary intervention period were assessed by dividing the event number by the corresponding person-time in each period. Cumulative incidence curves were generated and hazard ratios (HRs), 95% CI, and *P* values computed from Cox regression models stratified by age at diagnosis, randomization status in the WHI hormone trials, and study period for the survival analyses (intervention or postintervention; time dependent). Analyses of dietary modification influence on breast cancer overall survival included the 1764 breast cancer cases diagnosed during the dietary intervention period with outcome measured from diagnosis. An exploratory analysis examined dietary modification influence on deaths after breast cancer (breast cancer followed by deaths from breast cancer) for the same 1764 breast cancer cases. The present analyses were not protocol defined, and comparison of randomization groups, among incident cancer cases, may not be free from confounding.

All statistical tests were 2 sided. The level of significance was .05 or less. Additional analyses examined time trends of dietary modification association with breast cancer overall survival for deaths during the dietary intervention period and postintervention. An exploratory analysis examined time trends of dietary modification association with breast cancer-specific survival (breast cancer followed by death attributed to the cancer) for deaths during the dietary intervention period. Because dietary effects in 17 subgroups were investigated, 1 statistically significant interaction was expected by chance alone.

Results

The characteristics of women who received a diagnosis of invasive breast cancer during the dietary intervention period by randomization group are outlined in the **Table**. No significant differences were found for demographic variables, breast cancer risk factors, or characteristics associated with risk of death (self-rated health, body mass index [BMI], smoking, physical functioning, alcohol consumption, treated diabetes, and comorbidities) in the 2 randomization groups. Participant flow for analyses of breast cancer overall survival for cases diagnosed during the dietary intervention period is outlined in **Figure 1**.

Breast cancer overall survival of the 1764 breast cancer cases diagnosed during the dietary intervention (671 in intervention and 1093 in comparison groups, respectively), with 11.5 years (median) post–breast cancer diagnosis follow-up with 516 deaths, was significantly greater for women in the dietary group (10-year survival of 82% and 78%, respectively; HR, 0.78; 95% CI, 0.65-0.94; *P* = .01) (**Figure 2**). Findings are similar in analyses stratified on stage (regional/distant vs local) (HR, 0.76; 95% CI, 0.63-0.92; *P* = .006), progesterone receptor status (HR, 0.80; 95% CI, 0.66-0.97; *P* = .03), estrogen receptor plus progesterone receptor status (HR, 0.78; 95% CI, 0.64-0.95; *P* = .01), and after adjustment for baseline weight and most proximate weight preceding diagnosis (HR, 0.78; 95% CI, 0.64-0.94; *P* = .009). Findings for dietary intervention association with breast cancer–specific survival (breast cancer followed by death from breast cancer) are provided in eFigure 1 in the Supplement.

Cause of death is available for 510 of 516 breast cancer cases. Breast cancer was the most common cause (188 deaths [37%]), followed by other cancer (101 deaths [20%]) and cardiovascular disease (91 deaths [18%]).[3] There were fewer deaths from breast cancer in the dietary group (68 vs 120 deaths; HR, 0.86; 95% CI, 0.64-1.17), with fewer other-cancer deaths (36 vs 65 deaths; HR, 0.76; 95% CI, 0.50-1.17), fewer cardiovascular disease deaths (27 vs 64 deaths; HR, 0.62; 95% CI, 0.39-0.99), and fewer other-cause deaths (42 vs 88 deaths; HR, 0.82; 95% CI, 0.56-1.20), with no evidence of differential association of diet with cause of death (*P* = .70).

Dietary modification association with breast cancer overall survival was examined in 17 subgroups (**Figure 3** and **Figure 4**). The only statistically significant test of interaction was for BMI, in which a greater DM association was seen with higher BMIs. Almost all subgroup HRs were less than 1, suggestive of generally favorable influence of dietary intervention on breast cancer overall survival.

Women continued dietary group activities after breast cancer diagnosis,[3] and the cumulative distribution of the duration of dietary intervention before and after breast cancer diagnosis is shown in eFigure 2 in the Supplement. Women with breast cancer participated in the dietary intervention for a median of 4.5 (interquartile range, 2.4-6.3) years before breast cancer diagnosis and a median of 4.0 (interquartile range, 2.3-6.0) years after diagnosis (eFigure 2 in the Supplement).

During the dietary intervention period, dietary benefit on breast cancer overall survival was observed (HR, 0.67; 95% CI, 0.46-0.97) and benefit increased as time from breast cancer diagnosis increased, reflecting longer exposure to the dietary intervention. Time-varying HRs, by tertiles of time from diagnosis to death, were 0.98, 0.70, and 0.40, respectively

Table. Participant Characteristics of Invasive Breast Cancer Cases in Dietary Modification (DM) Trial

Characteristic	No. (%)[a] Intervention (N = 671)	Comparison (N = 1093)	*P* Value[b]
Age group at screening (10 y intervals), y			
50-59	233 (34.7)	367 (33.6)	.79
60-69	314 (46.8)	530 (48.5)	
70-79	124 (18.5)	196 (17.9)	
Race/ethnicity			
White	573 (85.4)	954 (87.3)	.84
Black	56 (8.3)	75 (6.9)	
Hispanic	17 (2.5)	27 (2.5)	
American Indian	2 (0.3)	2 (0.2)	
Asian/Pacific islander	14 (2.1)	24 (2.2)	
Unknown	9 (1.3)	11 (1.0)	
Education			
High school/GED or less	135 (20.3)	196 (18.1)	.33
School after high school	260 (39.0)	411 (37.9)	
College degree or higher	271 (40.7)	477 (44.0)	
Marital status			
Never married	33 (4.9)	62 (5.7)	.70
Divorced/separated	100 (15.0)	178 (16.3)	
Widowed	93 (13.9)	157 (14.4)	
Presently married/living as married	442 (66.2)	693 (63.6)	
Self-reported health			
Excellent	114 (17.1)	190 (17.5)	.84
Very good	291 (43.6)	451 (41.5)	
Good	212 (31.8)	364 (33.5)	
Fair/poor	50 (7.5)	83 (7.6)	
Time since menopause, y			
<10	230 (36.7)	365 (35.9)	.31
10 to <20	236 (37.7)	358 (35.2)	
≥20	160 (25.6)	294 (28.9)	
BMI at baseline			
<25	161 (24.1)	267 (24.6)	.80
25 to <30	239 (35.7)	376 (34.6)	
30 to <35	162 (24.2)	282 (25.9)	
≥35	107 (16.0)	162 (14.9)	
Smoking			
Never	327 (49.5)	526 (48.8)	.96
Past	292 (44.2)	480 (44.6)	
Current	42 (6.4)	71 (6.6)	
Alcohol consumption			
Nondrinker	164 (24.7)	300 (27.7)	.35
≤1 Drink/d	421 (63.4)	665 (61.5)	
>1 Drink/d	79 (11.9)	117 (10.8)	
Treated diabetes (pills or shots)	22 (3.3)	47 (4.3)	.28
Age at menarche, y			
<12	160 (24.0)	244 (22.3)	.28
12 to <14	361 (54.1)	633 (58.0)	
≥14	146 (21.9)	215 (19.7)	

(continued)

Table. Participant Characteristics of Invasive Breast Cancer Cases in Dietary Modification (DM) Trial (continued)

Characteristic	No. (%)[a] Intervention (N = 671)	Comparison (N = 1093)	*P* Value[b]
Age at first birth, y			
Never/no term pregnancy	79 (13.0)	148 (14.7)	.81
<20	84 (13.9)	135 (13.4)	
20 to <30	387 (63.9)	627 (62.5)	
≥30	56 (9.2)	94 (9.4)	
No. of term pregnancies			
0	79 (11.9)	148 (13.6)	.34
1	62 (9.4)	90 (8.3)	
2	165 (24.9)	275 (25.3)	
3	180 (27.1)	256 (23.6)	
≥4	177 (26.7)	317 (29.2)	
No. first-degree female relatives with breast cancer			
0	512 (80.5)	814 (79.2)	.52
≥1	124 (19.5)	214 (20.8)	
Bilateral oophorectomy	112 (16.9)	182 (17.0)	.97
Unopposed estrogen use status			
Never	440 (65.6)	689 (63.1)	.26
Past	69 (10.3)	140 (12.8)	
Current	162 (24.1)	263 (24.1)	
Estrogen + progesterone use status			
Never	455 (67.8)	702 (64.2)	.28
Past	50 (7.5)	97 (8.9)	
Current	166 (24.7)	294 (26.9)	
History of stroke prior to diagnosis	7 (1.0)	16 (1.5)	.45
History of coronary heart disease prior to diagnosis	10 (1.5)	30 (2.7)	.09
Baseline characteristics of invasive breast cancer cases in DM trial, mean (SD)			
Age at screening, y	62.7 (6.7)	62.8 (6.7)	.71
Age at breast cancer diagnosis, y	67.5 (6.9)	67.6 (6.9)	.66
Time to invasive breast cancer, y	4.5 (2.5)	4.5 (2.5)	.87

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared.

[a] Data are given as number (percentage) unless otherwise indicated.

[b] *P* values are based on χ^2 tests (categorical variables) or *t* tests (continuous variables).

(*P* = .02 for trend) (left panel of eFigure 3 in the Supplement). Postintervention, after nutritionist contacts ended, the HR was nonsignificant (HR, 0.83; 95% CI, 0.66-1.03) and significant temporal trends were not observed (*P* = .50 for trend). Additional analyses used time from randomization as the basic time metric for overall survival during the intervention period. While dietary benefit remained (HR, 0.66; 95% CI, 0.45-0.96) (right panel of eFigure 3 in the Supplement), benefit did not increase as time from randomization increased (*P* = .42 for trend), suggesting that longer exposure has the most influence after breast cancer diagnosis (left panel vs right panel of eFigure 3 in the Supplement).

The observed association of the low-fat eating pattern with breast cancer incidence and subsequent overall survival is summarized in eFigure 4 in the Supplement, where the more general hypothesis of whether the dietary intervention has no effect on either invasive breast cancer incidence or breast cancer overall survival was assessed jointly in the entire randomized cohort with a statistically valid omnibus test.[11,12] The observed reduction of breast cancer during the intervention period, followed by improved survival, was not attributable to chance (*P* = .006).

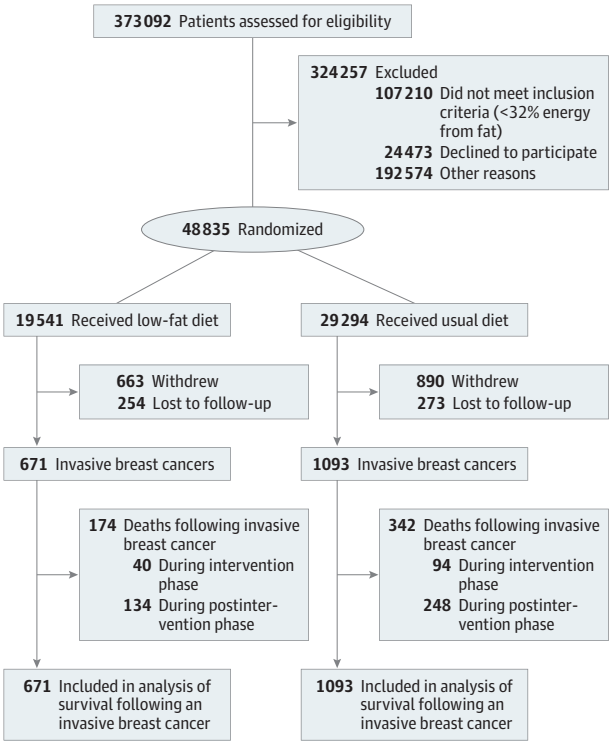
Discussion

Among the 1764 women who received a diagnosis of breast cancer during the dietary intervention period, breast cancer overall survival from diagnosis was significantly higher in the dietary group. Also contributing to the favorable dietary association with breast cancer overall survival was lower mortality from other causes.

The focus on breast cancer cases diagnosed during the dietary intervention period was based on earlier temporal trend study findings,[3,8] which suggested that it was unlikely that outcome of breast cancers diagnosed postintervention, when there was no contact with the dietary modification program, would differ between randomization groups. In

the present analyses, a temporal trend for greater improvement in breast cancer overall survival is seen as dietary intervention duration increases. Postintervention, attenuation of dietary association with breast cancer overall survival is seen as time from the last nutritionist contact increases. These findings suggest that sustained dietary intervention is needed to maintain effect. Dietary intervention after breast cancer diagnoses had more favorable influence on breast cancer overall survival, with potential implications for adjuvant breast cancer management.

Figure 1. Participant Flow for Women Who Received a Breast Cancer Diagnosis During the Dietary Intervention Period for Analyses of Breast Cancer Overall Survival

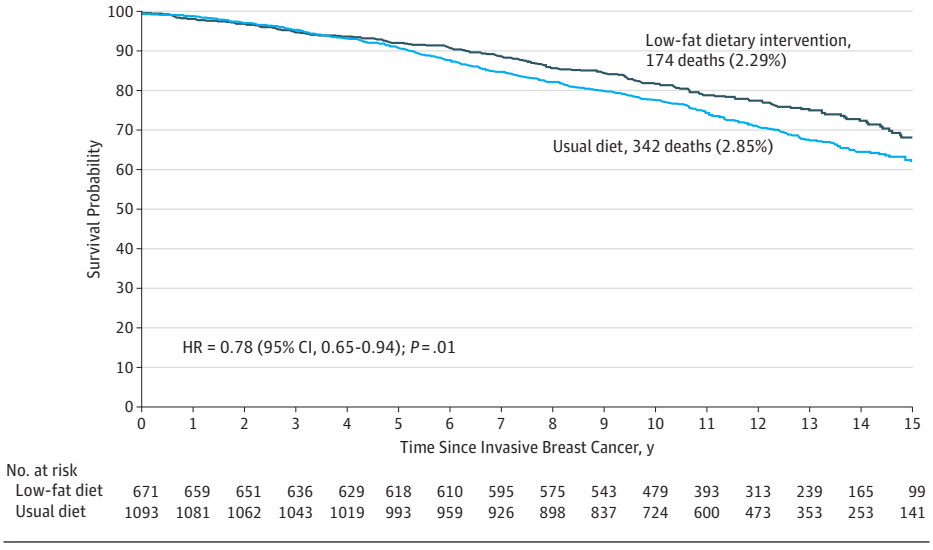


Clinical findings support a need for long-term intervention for continued breast cancer effect. Full-scale, randomized adjuvant breast cancer trials demonstrate superiority for 10 or more years of endocrine therapy over 5 years' use in reducing breast cancer recurrence.[13-15] Thus, a dietary program with impact on factors influencing breast cancer growth, including estrogens,[1,16] metabolic syndrome components, and inflammation mediators,[17-19] also could require continuous exposure for continued benefit.

Observational studies of dietary fat association with breast cancer survival, largely based on prediagnosis measures of intake, have mixed results,[20-23] which could reflect observational study limitations such as intake measurement error and limited dietary differences across the study population. In addition, as lifestyle change can occur following breast cancer diagnosis,[24,25] the multiyear, sustained differences in dietary intake seen in the dietary intervention group in this randomized clinical trial represent another difference from observational studies, which are often based on a single dietary intake assessment.

Because of possible selection bias consequent to breast cancer diagnosis, the present breast cancer overall survival analyses do not compare randomized groups. Specifically, women at trial entry could have been simultaneously at elevated (or reduced) risk for both breast cancer incidence and for death from any cause, possibly confounding the survival comparison. However, baseline characteristics regarding general health were balanced between arms, so control for known mortality risk factors such as smoking, obesity, and self-rated health did not materially affect HR estimates. For example, after adjustment, risk estimates for overall breast cancer survival edged slightly toward greater benefit (HR, 0.77; 95% CI, 0.64-0.93). Frailty assessment by random-effects methods[26] was used to address the possibility of

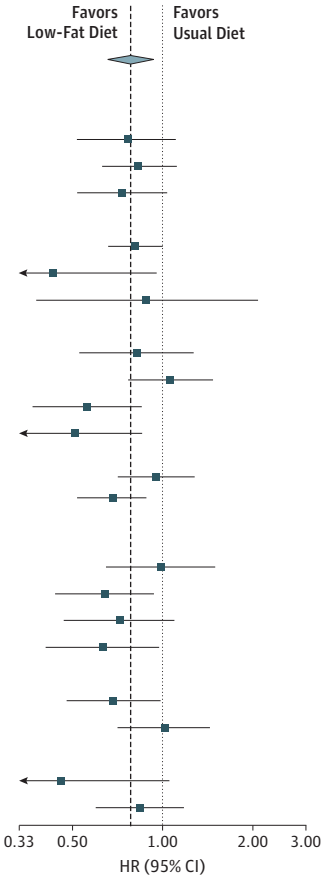
Figure 2. Dietary Modification Association With Breast Cancer Overall Survival



Kaplan-Meier estimates for breast cancer overall survival (survival from diagnosis with death from any cause) among the 1764 breast cancer cases diagnosed during the dietary intervention period, measured from cancer diagnosis and observed through September 2013. Summary statistics are from a Cox model stratified by age at diagnosis, randomization status in the hormone therapy trials, and study period (intervention period, postintervention period extension 1, or postintervention period extension 2; time dependent). The *P* value corresponds to a 2-sided score (log-rank) test. Percentages are annualized. HR indicates hazard ratio.

Figure 3. Forest Plot of Hazard Ratios, Dietary Intervention vs Comparison, for Association of Participant Characteristics With Breast Cancer Overall Survival

Source	Low-Fat Diet, No. (%)	Usual Diet, No. (%)	HR (95% CI)	P Value
All-cause mortality	174 (2.29)	342 (2.85)	0.78 (0.65-0.94)	.01
Participant characteristics				
Age at cancer diagnosis, y				.86
50 to <65	45 (1.43)	88 (1.90)	0.76 (0.52-1.10)	
65 to <75	74 (2.21)	149 (2.62)	0.83 (0.63-1.11)	
≥75	55 (4.88)	105 (6.20)	0.73 (0.52-1.03)	
Race/ethnicity				.29
White	152 (2.33)	293 (2.78)	0.81 (0.66-1.00)	
Black	11 (1.85)	28 (3.69)	0.43 (0.20-0.95)	
Other	11 (2.25)	21 (3.04)	0.88 (0.38-2.07)	
BMI				.03
<25	37 (2.02)	69 (2.26)	0.82 (0.53-1.26)	
25 to <30	70 (2.60)	108 (2.57)	1.06 (0.77-1.46)	
30 to <35	39 (2.11)	100 (3.31)	0.56 (0.37-0.85)	
≥35	28 (2.29)	62 (3.72)	0.51 (0.31-0.85)	
Waist circumference ≥88 cm				.09
No	81 (2.12)	135 (2.28)	0.95 (0.71-1.27)	
Yes	93 (2.47)	207 (3.41)	0.68 (0.52-0.88)	
Percent energy from fat (quartiles)				.23
<27.9	42 (2.52)	66 (2.64)	0.98 (0.65-1.49)	
27.9 to <32.3	50 (2.33)	96 (3.37)	0.64 (0.44-0.93)	
32.3 to <36.8	41 (2.14)	86 (2.68)	0.72 (0.47-1.09)	
≥36.8	34 (1.98)	90 (2.71)	0.63 (0.41-0.97)	
Estrogen plus progestin use				.13
No	52 (2.27)	93 (3.12)	0.68 (0.48-0.98)	
Yes	54 (2.12)	102 (2.19)	1.01 (0.71-1.43)	
Estrogen-alone use				.18
No	9 (1.29)	30 (3.05)	0.46 (0.21-1.05)	
Yes	59 (2.84)	117 (3.46)	0.84 (0.60-1.17)	



Subgroup analysis by participant characteristics (ascertained at baseline except for age at cancer diagnosis) among breast cancer cases diagnosed during the dietary intervention period. Annualized percentages are shown for all subgroups. *P* values correspond to a test of the interaction between randomization group and subgroup. Analysis for percent energy from fat based on findings in subgroup with 4-day food records. Percentages are annualized. The diamond summarizes the overall influence of dietary intervention on breast cancer overall survival. BMI indicates body mass index, calculated as weight in kilograms divided by height in meters squared; HR, hazard ratio.

shared unobserved risk factors that may influence breast cancer incidence and total mortality, and act multiplicatively on the 2 hazard rates. Frailty models produced risk estimates for survival after breast cancer that also edged slightly toward greater benefit.

The WHI low-fat dietary intervention reduced fat intake and body weight and increased intake of other nutrients that potentially influence breast cancer.[27] Nevertheless, dietary fat reduction was the largest absolute dietary change and adjustment for weight change during the intervention did not attenuate the dietary effect on breast cancer overall survival. As the contribution of the individual components of dietary intake to the breast cancer outcome cannot be fully separated, the WHI-DM trial evaluated all consequences of the low-fat eating pattern.

The Women's Intervention Nutrition Study (WINS) evaluated a similar low-fat dietary pattern in a different clinical situation, in 2437 women with early-stage breast cancer, and also reported findings that sustained intervention is needed to maintain a beneficial effect. The WINS dietary program resulted in a statistically significant, 24% reduction in breast cancer recurrence risk during the intervention period (HR, 0.76; 95% CI, 0.60-0.98),[28] which was attenuated during postintervention follow-up.[29] Another randomized adjuvant study of similar design with 2361 patients with breast cancer did not find an influence on breast cancer recurrence for an intervention focused on increased vegetable, fruit, and fiber intake; however, little sustained reduction in fat intake was reported with the intervention.[30,31]

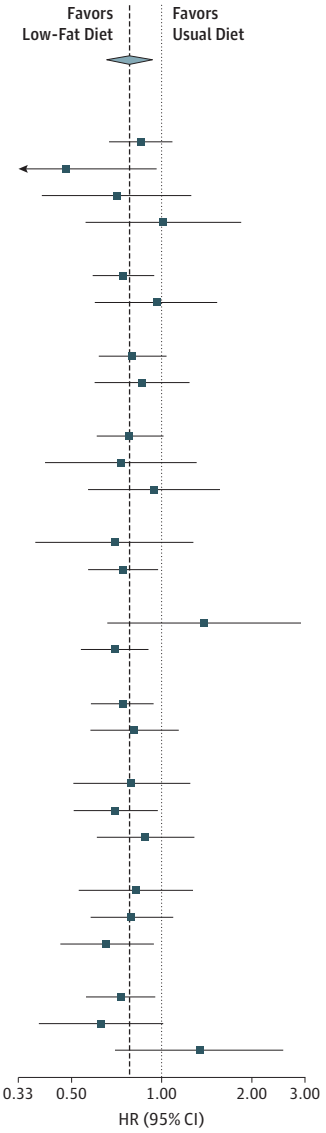
The American Cancer Society (ACS)[32] and the American Institute for Cancer Research (AICR)[33] have provided guidelines for cancer prevention that, similar to the WHI intervention, both endorse increase in vegetable, fruit, and grain intake. However, ACS and AICR recommendations also include smaller portion size for maintenance or weight loss, which was an unintended consequence of the presently reported dietary intervention, while neither endorses limiting total fat intake. The ACS also has a guideline for breast cancer survivors that emphasizes weight loss or maintenance with no strong advice for individual nutrient components.[34]

Limitations

Study strengths include the randomized design, a large population of 48 835 postmenopausal women with racial/ethnic diversity (18.6% minority) approximating that of the US population at the time of recruitment (18.2%)[35] but somewhat lacking in recruitment of Hispanics, follow-up of all 1764 breast cancer cases diagnosed during the dietary

Figure 4. Forest Plot of Hazard Ratios, Dietary Intervention vs Comparison, for Association of Invasive Breast Cancer Characteristics With Breast Cancer Overall Survival

Source	Low-Fat Diet, No. (%)	Usual Diet, No. (%)	HR (95% CI)	*P* Value
All-cause mortality	174 (2.29)	342 (2.85)	0.78 (0.65-0.94)	.01
Invasive breast cancer characteristics				
Histologic type				.38
Ductal	114 (2.31)	209 (2.64)	0.85 (0.67-1.08)	
Lobular	14 (1.84)	37 (3.59)	0.48 (0.23-0.96)	
Ductal and lobular	22 (2.41)	52 (3.25)	0.71 (0.40-1.25)	
Other	22 (2.21)	39 (2.66)	1.01 (0.56-1.84)	
ER status				.33
Positive	119 (1.97)	243 (2.57)	0.74 (0.59-0.94)	
Negative	34 (3.32)	66 (3.91)	0.96 (0.60-1.53)	
PR status				.77
Positive	104 (2.06)	187 (2.49)	0.80 (0.62-1.03)	
Negative	47 (2.42)	117 (3.41)	0.86 (0.60-1.23)	
ER/PR status				.76
ER positive/PR positive	100 (2.02)	181 (2.48)	0.78 (0.61-1.01)	
ER positive/PR negative	19 (1.88)	57 (2.87)	0.73 (0.41-1.30)	
ER negative/PR negative	28 (3.08)	58 (4.03)	0.94 (0.57-1.56)	
HER2 overexpression				.86
Yes	23 (2.42)	40 (2.88)	0.70 (0.38-1.28)	
No	85 (2.02)	176 (2.70)	0.74 (0.57-0.97)	
Triple-negative tumor				.08
Yes	15 (3.82)	23 (3.03)	1.38 (0.66-2.90)	
No	92 (1.98)	187 (2.66)	0.70 (0.54-0.90)	
Stage				.68
Local	107 (1.83)	219 (2.35)	0.74 (0.58-0.94)	
Regional or distant	59 (3.52)	114 (4.42)	0.81 (0.58-1.13)	
Grade				.63
Well differentiated	34 (1.68)	69 (2.13)	0.79 (0.51-1.24)	
Moderately differentiated	59 (2.15)	134 (2.90)	0.70 (0.51-0.97)	
Poorly differentiated	57 (2.92)	91 (3.15)	0.88 (0.61-1.28)	
Tumor size, cm				.41
<1	37 (1.83)	67 (1.87)	0.82 (0.53-1.27)	
1 to <2	66 (1.97)	122 (2.65)	0.79 (0.58-1.09)	
≥2	49 (2.99)	116 (4.16)	0.65 (0.46-0.94)	
Positive lymph nodes				.25
0	90 (1.69)	182 (2.15)	0.73 (0.56-0.95)	
1-3	26 (2.09)	61 (3.49)	0.63 (0.39-1.01)	
≥4	21 (6.52)	37 (5.66)	1.34 (0.70-2.54)	



Subgroup analysis by tumor characteristics among breast cancer cases diagnosed during the dietary intervention period. Annualized percentages are shown for all subgroups. *P* values correspond to a test of the interaction between randomization group and subgroup. Percentages are annualized. The diamond summarizes the overall influence of dietary intervention on breast cancer overall survival. ER indicates estrogen receptor; HR, hazard ratio; PR, progesterone receptor.

intervention period, dietary program adherence supported by body weight and biomarker differences, protocol-specified serial screening mammography, medical record confirmation of breast cancers, and long follow-up enhanced by serial National Death Index queries. Study limitations include those associated with post hoc analyses; the modest absolute increases in vegetable, fruit, and grain intake; the need for confirmatory trials; and incomplete breast cancer therapy information.

Conclusions

In summary, in women who received a diagnosis of breast cancer during the dietary intervention period, those in the dietary group had increased breast cancer overall survival compared with those in the usual-diet comparison group. This increase is likely due, in part, to better survival from several causes of death.

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REFERENCES

1. Prentice RL, Caan B, Chlebowski RT, et al. Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA*. 2006;295(6):629-642.

2. Howard BV, Manson JE, Stefanick ML, et al. Low-fat dietary pattern and weight change over 7 years: the Women's Health Initiative Dietary Modification Trial. *JAMA*. 2006;295(1):39-49.

3. Chlebowski RT, Aragaki AK, Anderson GL, et al. Low-fat dietary pattern and breast cancer mortality in the Women's Health Initiative randomized controlled trial. *J Clin Oncol*. 2017;35(25):2919-2926.

4. Cespedes Feliciano EM, Prentice RL, Aragaki AK, et al. Methodological considerations for disentangling a risk factor's influence on disease incidence versus postdiagnosis survival: the example of obesity and breast and colorectal cancer mortality in the Women's Health Initiative. *Int J Cancer*. 2017;141(11):2281-2290.

5. Prentice RL, Aragaki AK, Van Horn L, et al. Low-fat dietary pattern and cardiovascular disease: results from the Women's Health Initiative randomized controlled trial. *Am J Clin Nutr*. 2017;106(1):35-43.

6. Anderson GL, Manson J, Wallace R, et al. Implementation of the Women's Health Initiative study design. *Ann Epidemiol*. 2003;13(9)(suppl):S5-S17.

7. Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials*. 1998;19(1):61-109.

8. Thomson CA, Van Horn L, Caan BJ, et al. Cancer incidence and mortality during the intervention and postintervention periods of the Women's Health Initiative dietary modification trial. *Cancer Epidemiol Biomarkers Prev*. 2014;23(12):2924-2935.

9. National Cancer Institute. Surveillance, Epidemiology and End Results program. https://seer.cancer.gov/. Accessed December 16, 2015.

10. Perez EA, Romond EH, Suman VJ, et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. *J Clin Oncol*. 2014;32(33):3744-3752.

11. Prentice RL, Williams BJ, Peterson AV. On the regression analysis of multivariate failure time data. *Biometrika*. 1981;68(2):373-379.

12. Boher J, Cook RJ. Implications of model misspecification in robust tests for recurrent events. *Lifetime Data Anal*. 2006;12(1):69-95.

13. Davies C, Pan H, Godwin J, et al; Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet*. 2013;381(9869):805-816.

14. Gray RG, Rea D, Handley K, et al; aTTom Collaborative Group. aTTom: long-term effects continuing adjuvant tamoxifen to 10 years versus stopping at five years in 6953 women with early breast cancer. *J Clin Oncol*. 2013;31(18 suppl):5.

15. Goss PE, Ingle JN, Pritchard KI, et al. Extending aromatase inhibitor adjuvant therapy to 10 years. *N Engl J Med*. 2016;375(3):209-219.

16. Rose DP, Connolly JM, Chlebowski RT, Buzzard IM, Wynder EL. The effects of a low-fat dietary intervention and tamoxifen adjuvant therapy on the serum estrogen and sex hormone-binding globulin concentrations of postmenopausal breast cancer patients. *Breast Cancer Res Treat*. 1993;27(3):253-262.

17. Lohmann AE, Goodwin PJ, Chlebowski RT, Pan K, Stambolic V, Dowling RJ. Association of obesity-related metabolic disruptions with cancer risk and outcome. *J Clin Oncol*. 2016;34(35):4249-4255.

18. Makarem N, Chandran U, Bandera EV, Parekh N. Dietary fat in breast cancer survival. *Annu Rev Nutr*. 2013;33:319-348.

19. Vitale M, Masulli M, Rivellese AA, et al. Influence of dietary fat and carbohydrates proportions on plasma lipids, glucose control and low-grade inflammation in patients with type 2 diabetes: the TOSCA.IT Study. *Eur J Nutr*. 2016;55(4):1645-1651.

20. Chlebowski RT. Nutrition and physical activity influence on breast cancer incidence and outcome. *Breast*. 2013;22(suppl 2):S30-S37.

21. Kroenke CH, Kwan ML, Sweeney C, Castillo A, Caan BJ. High- and low-fat dairy intake, recurrence, and mortality after breast cancer diagnosis. *J Natl Cancer Inst*. 2013;105(9):616-623.

22. Boeke CE, Eliassen AH, Chen WY, et al. Dietary fat intake in relation to lethal breast cancer in two large prospective cohort studies. *Breast Cancer Res Treat*. 2014;146(2):383-392.

23. Brennan SF, Woodside JV, Lunny PM, Cardwell CR, Cantwell MM. Dietary fat and breast cancer mortality: a systematic review and meta-analysis. *Crit Rev Food Sci Nutr*. 2017;57(10):1999-2008.

24. Irwin ML, McTiernan A, Manson JE, et al. Physical activity and survival in postmenopausal women with breast cancer: results from the Women's Health Initiative. *Cancer Prev Res (Phila)*. 2011;4(4):522-529.

25. Steinhilper L, Geyer S, Sperlich S. Health behavior change among breast cancer patients. *Int J Public Health*. 2013;58(4):603-613.

26. Aalen OO. Heterogeneity in survival analysis. *Stat Med*. 1998;7(11):1121-1137.

27. Thomson CA, Thompson PA. Dietary patterns, risk and prognosis of breast cancer. *Future Oncol*. 2009;5(8):1257-1269.

28. Chlebowski RT, Blackburn GL, Thomson CA, et al. Dietary fat reduction and breast cancer outcome: interim efficacy results from the Women's Intervention Nutrition Study. *J Natl Cancer Inst*. 2006;98(24):1767-1776.

29. Chlebowski RT, Blackburn G, Hoy KM, Thomson CA, Giuliano AE, McAndrew P. Survival analyses from the Women's Intervention Nutrition Study (WINS) evaluating dietary fat reduction and breast cancer therapy outcome. *J Clin Oncol*. 2008; 26(15 suppl):522.

30. 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*. 2007;298 (3):289-298.

31. Ligibel JA, Chlebowski RT. Lifestyle issues in breast cancer survivors. In: Harris JR, Lippman ME, Morrow M, Osborne CK, eds. *Diseases of the Breast*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2014:676-681.

32. Kushi LH, Doyle C, McCullough M, et al; American Cancer Society 2010 Nutrition and Physical Activity Guidelines Advisory Committee. American Cancer Society Guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. *CA Cancer J Clin*. 2012; 62(1):30-67.

33. World Cancer Research Fund/American Institute for Cancer Research. *Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective*. Washington, DC: AICR; 2007.

34. Rock CL, Doyle C, Demark-Wahnefried W, et al. Nutrition and physical activity guidelines for cancer survivors. *CA Cancer J Clin*. 2012;62(4):243-274.

35. Byerly ER, Edwin R, Deardorff K. *National and State Population Estimates: 1990 to 1994, US Bureau of the Census, Current Population Reports*. Washington, DC: US Government Printing Office; 1995:25-1127.