Low-Fat Dietary Pattern and Risk of Invasive Breast Cancer

The Women's Health Initiative Randomized Controlled Dietary Modification Trial

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Context The hypothesis that a low-fat dietary pattern can reduce breast cancer risk has existed for decades but has never been tested in a controlled intervention trial.

Objective To assess the effects of undertaking a low-fat dietary pattern on breast cancer incidence.

Design and Setting A randomized, controlled, primary prevention trial conducted at 40 US clinical centers from 1993 to 2005.

Participants A total of 48 835 postmenopausal women, aged 50 to 79 years, without prior breast cancer, including 18.6% of minority race/ethnicity, were enrolled.

Interventions Women were randomly assigned to the dietary modification intervention group (40% [n = 19 541]) or the comparison group (60% [n = 29 294]). The intervention was designed to promote dietary change with the goals of reducing intake of total fat to 20% of energy and increasing consumption of vegetables and fruit to at least 5 servings daily and grains to at least 6 servings daily. Comparison group participants were not asked to make dietary changes.

Main Outcome Measure Invasive breast cancer incidence.

Results Dietary fat intake was significantly lower in the dietary modification intervention group compared with the comparison group. The difference between groups in change from baseline for percentage of energy from fat varied from 10.7% at year 1 to 8.1% at year 6. Vegetable and fruit consumption was higher in the intervention group by at least 1 serving per day and a smaller, more transient difference was found for grain consumption. The number of women who developed invasive breast cancer (annualized incidence rate) over the 8.1-year average follow-up period was 655 (0.42%) in the intervention group and 1072 (0.45%) in the comparison group (hazard ratio, 0.91; 95% confidence interval, 0.83-1.01 for the comparison between the 2 groups). Secondary analyses suggest a lower hazard ratio among adherent women, provide greater evidence of risk reduction among women having a high-fat diet at baseline, and suggest a dietary effect that varies by hormone receptor characteristics of the tumor.

Conclusions Among postmenopausal women, a low-fat dietary pattern did not result in a statistically significant reduction in invasive breast cancer risk over an 8.1-year average follow-up period. However, the nonsignificant trends observed suggesting reduced risk associated with a low-fat dietary pattern indicate that longer, planned, nonintervention follow-up may yield a more definitive comparison.

Clinical Trials Registration ClinicalTrials.gov Identifier: NCT00000611

JAMA. 2006;295:629-642 www.jama.com

THE HYPOTHESIS THAT A LOW-fat dietary pattern can reduce breast cancer risk has existed for decades. Supported by early rodent experiments,[1] country-to-country comparisons linked higher dietary fat intake to breast cancer risk.[2] However, case-control and cohort studies have had mixed results. A meta-analysis[3] of 12 international case-

See also pp 643, 655, and 691.

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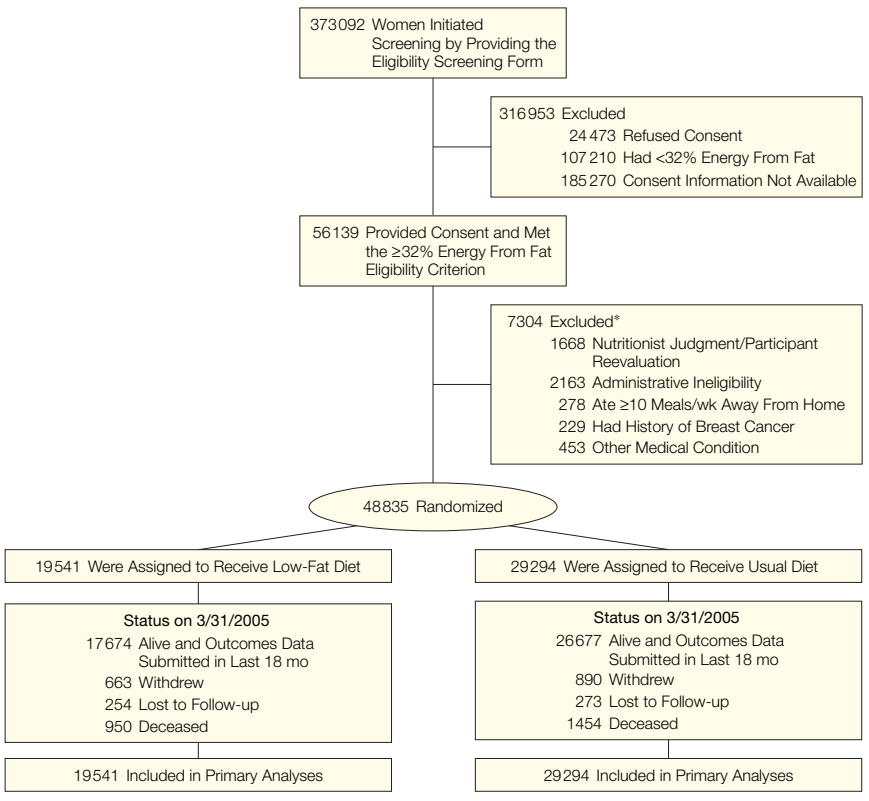
control studies reported a significant positive association between fat intake and breast cancer with relative risks of 1.00, 1.20, 1.24, 1.24, and 1.46 across total fat intake quintiles defined by one of the Canadian case-control studies. In contrast, an analysis[4] of 7 Western cohort studies found no such association with relative risks of 1.00, 1.01, 1.12, 1.07, and 1.05 across energy-adjusted fat intake quintiles. A recent meta-analysis, including both case-control and cohort studies, comparing highest and lowest fat intake categories reported a relative risk for breast cancer of 1.13 (95% confidence interval [CI], 1.03-1.25).[5] Such inconsistent results may reflect limitations of the dietary assessment methods used[6-8]; a recent study reported a significant positive association of fat intake and postmenopausal breast cancer incidence only when diet was measured with food diaries rather than a food frequency questionnaire (FFQ) used in most analytic epidemiological studies.[9]

Previous randomized controlled trials have demonstrated the feasibility of achieving a dietary fat reduction among healthy postmenopausal women in a multicenter trial setting.[10,11] Prior small-scale intervention trials have demonstrated reductions in serum estradiol levels among women undertaking a dietary pattern that is low in fat,[12-14] and observational studies have linked low dietary fat intake both with low blood estrogen levels and low breast cancer risk.[15]

Observational studies of consumption of vegetables and fruit in relation to breast cancer incidence have also yielded inconsistent results.[16,17] Some summary analyses report an association with vegetable intake[18-20] but not fruit intake,[18,19] with more evidence for association from case-control studies[19,20] than from cohort studies. Similarly, meta-analyses of case-control studies[21,22] report a marginally lower breast cancer incidence at higher whole grain consumption levels but a recent large cohort study[23] found no such association. Once again, inconsistency could be due to measurement error in dietary assessment[8,24] or to other sources of bias, including recall bias in case-control studies.

The Women's Health Initiative (WHI) began in 1992 and included a full-scale randomized controlled trial with a dietary modification intervention consisting of consumption of a reduced amount of fat (20% of energy) and of an increased amount of vegetables and fruit (≥5 servings/d) and grains (≥6 servings/d) referred to herein as the low-fat dietary pattern. Breast cancer and colorectal cancer incidence are the primary outcomes of the trial and coronary heart disease is the secondary outcome.[25,26] This dietary modification intervention trial is the first to directly assess the health benefits and risks of promoting a low-fat dietary pattern. This article reports the principal results on the incidence of breast cancer.

Figure 1. Participant Flow in the Dietary Modification Component of the Women's Health Initiative



*Categories are presented for which exclusions are known. More than 1 reason could be given for exclusion.

METHODS

Study Population

The design of the WHI clinical trial, including the dietary modification component, has been previously described, as have detailed eligibility criteria and recruitment methods.[25-27] All women were postmenopausal and aged 50 to 79 years at screening (FIGURE 1 and TABLE 1). Special efforts were made to recruit minority women so that dietary intervention effects could be compared among self-reported racial/ethnic groups (18.6% of trial participants). Interested and eligible women were informed that they could be randomized to the dietary modification trial and/or the postmenopausal hormone therapy trial, which involved either estrogen alone (women without a uterus) or estrogen plus progestin (women with a uterus). After 1 year's participation in the clinical trial, women were invited to consider further randomization to calcium and vi-

tamin D supplementation or placebo. The postmenopausal hormone therapy trial components were stopped early and have been reported.[28,29]

Major exclusions for the dietary modification trial included prior breast cancer, prior colorectal cancer, other cancer except nonmelanoma skin cancer in the last 10 years, medical conditions with predicted survival of less than 3 years, adherence or retention concerns (eg, alcoholism, dementia), or a diet at baseline with fat intake of less than 32% of total energy as estimated by the FFQ created for the WHI.[30]

Eligible women were randomized to the dietary modification intervention group (40%) or to the comparison group (60%) using a permuted block algorithm with blocks of size 5, 10, or 15 and stratified by clinical center and age group (50-54 years, 55-59 years, 60-69 years, 70-79 years). The randomization rate of 40% for the intervention group and 60% for the comparison group was chosen to minimize study cost at a specified level of power. The protocol and consent forms were approved by the institutional review boards for each participating institution and all women provided written informed consent.

Low-Fat Dietary Pattern Intervention and Maintenance

Details of the dietary modification (low-fat dietary pattern) intervention have been published.[31] Briefly, the intervention was designed to promote dietary change with the goals of reducing total fat intake to 20% of total energy and increasing consumption of vegetables and fruit to at least 5 servings daily and grains to at least 6 servings daily. The intervention did not include total energy reduction or weight-loss goals. Although not a separate focus of the intervention, it was presumed that by reducing total fat to 20% of total energy the amount of saturated fat also would be reduced to about 7% of energy.

The intervention group received an intensive behavioral modification program that consisted of 18 group sessions in the first year and quarterly maintenance sessions thereafter. Each group had 8 to 15 women and was led by a specially trained and certified nutritionist.[25,26,31] Each participant was given her own total fat gram goal based on her height. The intervention emphasized self-monitoring techniques and introduced other individually tailored and targeted strategies, such as motivational interviewing. Comparison group participants received a copy of *Nutrition and Your Health: Dietary Guidelines for Americans*[32] and other health-related materials but were not asked to make dietary changes. Neither group was asked to make changes in their use of dietary supplements or in other health-related behaviors.

Follow-up and Data Collection

Dietary intake for all participants was monitored using the FFQ, which was

Table 1. Baseline Demographics of Participants in Women's Health Initiative Dietary Modification Trial*

	No. (%) of Participants		
	Intervention (n = 19 541)	Comparison (n = 29 294)	*P* Value†
Age, y			
50-59	7206 (36.9)	10 797 (36.9)	>.99
60-69	9086 (46.5)	13 626 (46.5)	
70-79	3249 (16.6)	4871 (16.6)	
Race/ethnicity			
White	15 869 (81.2)	23 890 (81.6)	.76
Black	2137 (10.9)	3129 (10.7)	
Hispanic	755 (3.9)	1099 (3.8)	
American Indian	88 (0.5)	115 (0.4)	
Asian/Pacific Islander	433 (2.2)	674 (2.3)	
Unknown	259 (1.3)	387 (1.3)	
Family history of breast cancer‡	3396 (18.3)	4929 (17.8)	.13
Gail model 5-y risk >1.7%	6812 (34.9)	10 153 (34.7)	.65
Body mass index§			
<25	5072 (26.1)	7585 (26.0)	.69
25-29	6940 (35.7)	10 446 (35.8)	
30-34	4450 (22.9)	6748 (23.1)	
≥35	2992 (15.4)	4378 (15.0)	
Postmenopausal hormone use, y			
Estrogen alone			
None	12 262 (62.8)	18 452 (63.0)	.36
<5	2711 (13.9)	3933 (13.4)	
≥5	4568 (23.4)	6909 (23.6)	
Estrogen plus progestin			
None	14 196 (72.7)	21 299 (72.7)	.92
<5	2768 (14.2)	4114 (14.0)	
≥5	2576 (13.2)	3881 (13.2)	
Mammography screening within 2 y	15 729 (83.1)	23 708 (83.6)	.12
Treated disease/condition			
Diabetes‖	866 (4.4)	1336 (4.6)	.50
Hypertension¶	7617 (42.5)	11 596 (43.2)	.15
White blood cell count, $\times 10^9$/L			
<5.1	5920 (30.3)	8921 (30.5)	.70
5.1-6.3	6752 (34.6)	10 179 (34.8)	
≥6.4	6855 (35.1)	10 166 (34.7)	

*Percentages may not sum to 100% because of rounding error.
†Based on a χ^2 test of association.
‡First-degree or second-degree female relative.
§Calculated as weight in kilograms divided by the square of height in meters.
‖Self-report of taking pills or insulin via injection.
¶Systolic blood pressure higher than 140 mm Hg, diastolic blood pressure higher than 90 mm Hg, self-report of taking pills to lower blood pressure.

Table 2. Nutrient Consumption Estimates and Body Weight at Baseline and Year 1

Factor	Nutrient Consumption Estimate, Mean (SD)*				Mean (SD) Difference in Change Between Groups		
	Baseline		Year 1				
	Intervention	Comparison	Intervention	Comparison	Year 1	Year 3	Year 6
Fat							
Percentage of energy	37.8 (5.1)	37.8 (5.0)	24.3 (7.5)	35.1 (6.9)	−10.7† (7.0)	−9.5† (7.4)	−8.1† (7.8)
Total, g	75.7 (34.1)	75.7 (33.6)	40.8 (21.4)	63.0 (31.0)	−22.4† (31.1)	−20.1† (32.0)	−18.4† (33.5)
Saturated, %	12.7 (2.5)	12.7 (2.5)	8.1 (2.8)	11.8 (2.9)	−3.7† (2.9)	−3.3† (3.1)	−2.9† (3.3)
Polyunsaturated, %	7.8 (2.0)	7.8 (2.0)	5.2 (1.8)	7.2 (2.1)	−2.0† (2.1)	−1.7† (2.2)	−1.4† (2.3)
Monounsaturated, %	14.4 (2.3)	14.4 (2.3)	8.9 (3.1)	13.3 (2.9)	−4.4† (3.0)	−3.9† (3.2)	−3.3† (3.4)
Energy, kcal	1790.2 (710.1)	1789.4 (703.0)	1500.5 (544.2)	1593.8 (644.0)	−95.8† (616.2)	−92.5† (632.1)	−119.9† (662.9)
Consumption per day							
Vegetables and fruit, servings	3.6 (1.8)	3.6 (1.8)	5.1 (2.3)	3.9 (2.0)	1.2† (1.9)	1.3† (2.0)	1.1† (2.1)
Grains, servings	4.7 (2.5)	4.8 (2.5)	5.1 (2.7)	4.2 (2.3)	0.9† (2.5)	0.7† (2.6)	0.4† (2.6)
Fiber, g	15.4 (6.4)	15.4 (6.4)	18.1 (7.5)	14.9 (6.5)	3.2† (6.1)	3.1† (6.4)	2.4† (6.6)
Folate, μg	259.2 (136.6)	259.3 (138.1)	398.5 (215.0)	346.1 (195.1)	52.3† (192.3)	62.1† (208.2)	45.6† (201.1)
Alcohol, g	4.4 (8.4)	4.4 (8.6)	4.3 (8.9)	4.3 (9.2)	0 (6.7)	0.1 (7.1)	−0.1 (7.4)
Weight, kg	76.8 (16.6)	76.7 (16.5)	74.4 (16.7)	76.3 (16.7)	−2.2† (8.4)	−1.3† (9.1)	−0.8† (9.4)

*Based on responses to the Women's Health Initiative food frequency questionnaire.
†Difference significant at $P<.001$ from a 2-sample t test.

designed specifically for the WHI trial (TABLE 2). This FFQ was administered at baseline and at 1 year following randomization and thereafter to about one third of participants each year in a rotating sample. Additionally, 4-day food records were provided by all women prior to randomization.

Study participants were contacted every 6 months for outcome ascertainment. Height, weight, waist circumference, and blood pressure were measured using standardized procedures at annual clinic visits. A fasting serum sample was collected at baseline and at 1 year after randomization. A 4.6% subsample (n=2245) with an overrepresentation of minority women provided an additional 4-day food record at 1 year after randomization and 24-hour dietary recalls at 3 and 6 years after randomization. This 4.6% subsample combined with additional women who were participating in both the dietary modification trial and the hormone therapy trial yields a 5.8% subsample (n=2816) of women who provided fasting serum samples at 1, 3, and 6 years after randomization. The serum samples were centrally stored and analyzed for diet-related biomarkers.[27] Changes in levels of α-carotene, β-carotene, total carotenoids, α-tocopherol, γ-tocopherol, β-cryptoxanthin, lycopene, lutein plus zeaxanthin, retinol, glucose, insulin, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides from baseline to year 3 were compared for the intervention group with the comparison group (TABLE 3). These measures provide an objective assessment of some aspects of the dietary changes reported by the participating women. Further independent 1% subsamples of women provided a 24-hour dietary recall annually.

To examine whether a low-fat dietary pattern could influence breast cancer risk through changes in circulating hormones, serum hormone concentrations at baseline and 1 year after randomization were compared between random samples from 150 women in the intervention group and 150 women in the comparison group who were not enrolled in the WHI hormone therapy trials and who were not taking postmenopausal hormones at baseline (TABLE 4). Analyte determinations were performed at Esoterix Laboratory Services (Calabasas Hills, Calif). Baseline and follow-up samples were included in the same batches along with split duplicates. Intrabatch coefficients of variation were 7.6% for estradiol, 7.3% for estrone, 8.9% for testosterone, and 5.7% for sex hormone–binding globulin.

Outcome Ascertainment

Women were expected under the study protocol to undergo mammography screening at baseline and every 2 years thereafter. Clinical centers made arrangements with a mammography facility or instructed women to undergo mammography screening through their usual sources of care.

Details of clinical outcome definitions, documentation, and classification have been published.[33] In brief, women were queried twice each year to determine whether they had been hospitalized or diagnosed with any of the clinical outcomes on a prespecified list, including 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. Central adjudication and coding of histology, extent of disease, and estrogen receptor and progesterone receptor status (positive or negative per local pathology report) were performed at the clinical coordinating center using the National Cancer Institute's Surveillance, Epidemiology, and End Results coding system.

Statistical Design and Analysis

Trial design assumptions included a linear dependence of breast cancer risk on the lifetime dietary percentage of energy from fat: a 50% lower breast cancer incidence among women with a diet consisting of 20% of energy from fat compared with women with a diet consisting of 40% of energy from fat. These assumptions also specify that the risk reduction for women undertaking a low-fat dietary pattern would be achieved linearly over a 10-year intervention period.[25] Adherence assumptions, motivated by preceding feasibility studies,[10,11] included a 13% lower energy from fat consumption in the intervention group compared with the comparison group at 1 year after randomization, decreasing to an 11% difference by 9 years after randomization. These assumptions led to a projected 14% lower breast cancer incidence in the intervention group compared with the comparison group and to a study power of 86% for a test at the .05 level of significance at a sample size of 48 000 over a planned 9-year follow-up period.

Blood analyte concentrations were analyzed by examining mean changes from baseline for log-transformed concentrations. Logarithmic transformation was used to obtain distributions that are approximately normal and differences in changes between intervention and comparison groups were assessed using *t* tests. Back-transformed (geometric) means and associated 95% CIs are presented herein.

Event rate comparisons between the intervention group and the comparison group are based on the intent-to-treat principle using time-to-event methods.[34] A (2-sided) weighted log-rank test for cancer incidence and mortality was specified in the protocol with weights increasing linearly from zero at randomization to a maximum value of 1 at 10 years after randomization, and constant thereafter, to enhance trial power under design assumptions. Both weighted and unweighted log-rank tests are presented herein to assess the null hypothesis for breast cancer and for other major trial outcomes and to assess the simultaneous null hypothesis for breast cancer and for colorectal cancer.

The time to an event for a particular outcome was defined as the number of days after randomization to the first diagnosis of the designated event (eg, invasive breast cancer). Follow-up time was censored at the time of a woman's

Table 3. Blood Biomarkers for Baseline and Year 3*

Biomarker	Geometric Mean (95% CI)		Relative Change (95% CI)†
	Intervention	Comparison	
Total carotenoids, μg/mL			
Baseline	0.78 (0.76-0.81)	0.77 (0.75-0.79)	1.05 (1.00-1.10)
Year 3	0.75 (0.72-0.78)	0.72 (0.69-0.74)	
α-Carotene, μg/10 mL			
Baseline	0.59 (0.56-0.63)	0.59 (0.56-0.62)	1.10 (1.03-1.18)
Year 3	0.53 (0.50-0.57)	0.49 (0.47-0.51)	
β-Carotene, μg/mL			
Baseline	0.22 (0.21-0.23)	0.22 (0.21-0.23)	1.09 (1.01-1.17)
Year 3	0.21 (0.20-0.23)	0.19 (0.18-0.20)	
α-Tocopherol, μg/mL			
Baseline	14.77 (14.39-15.16)	15.19 (14.85-15.53)	1.01 (0.97-1.04)
Year 3	16.77 (16.28-17.29)	16.81 (16.41-17.22)	
γ-Tocopherol, μg/mL			
Baseline	1.76 (1.66-1.86)	1.71 (1.64-1.79)	0.85 (0.79-0.91)
Year 3	1.11 (1.04-1.19)	1.29 (1.23-1.36)	
β-Cryptoxanthin, μg/10 mL			
Baseline	0.69 (0.66-0.73)	0.67 (0.64-0.69)	1.07 (1.01-1.14)
Year 3	0.80 (0.75-0.84)	0.73 (0.69-0.76)	
Lycopene, μg/mL			
Baseline	0.37 (0.36-0.38)	0.36 (0.35-0.37)	1.00 (0.94-1.05)
Year 3	0.33 (0.31-0.34)	0.33 (0.32-0.34)	
Lutein plus zeaxanthin, μg/mL			
Baseline	0.19 (0.19-0.20)	0.19 (0.18-0.19)	1.03 (0.99-1.06)
Year 3	0.19 (0.18-0.19)	0.17 (0.17-0.18)	
Retinol, μg/mL			
Baseline	0.59 (0.58-0.60)	0.60 (0.59-0.61)	1.02 (1.00-1.04)
Year 3	0.59 (0.58-0.60)	0.59 (0.58-0.60)	
Glucose, mg/dL			
Baseline	97.90 (96.42-99.41)	97.70 (96.63-98.77)	0.99 (0.97-1.00)
Year 3	96.47 (95.02-97.94)	97.06 (95.88-98.26)	
Insulin, μIU/mL			
Baseline	9.95 (9.60-10.31)	10.22 (9.92-10.54)	0.98 (0.93-1.02)
Year 3	10.53 (10.12-10.97)	11.24 (10.88-11.61)	
Cholesterol, mg/dL			
Total			
Baseline	220.90 (218.38-223.48)	220.90 (218.76-223.11)	0.98 (0.97-1.00)
Year 3	211.20 (208.51-213.87)	213.60 (211.44-215.78)	
Low-density lipoprotein			
Baseline	128.40 (125.91-131.04)	129.40 (127.32-131.47)	0.97 (0.95-1.00)
Year 3	118.70 (116.18-121.33)	122.20 (120.13-124.39)	
High-density lipoprotein			
Baseline	58.05 (56.95-59.17)	56.44 (55.59-57.30)	0.99 (0.98-1.01)
Year 3	57.65 (56.47-58.86)	56.20 (55.29-57.13)	
Triglycerides, mg/dL			
Baseline	138.60 (133.98-143.29)	141.10 (137.35-144.95)	1.00 (0.97-1.04)
Year 3	142.30 (137.17-147.53)	144.60 (140.76-148.50)	

Abbreviation: CI, confidence interval.
SI conversion factors: To convert glucose to mmol/L, multiply by 0.0555; low-density, high-density, and total cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113.
*Values based on a 5.8% subsample (n = 2816).
†Calculated as the ratio of year 3 to baseline geometric means and is the ratio of changes in the intervention group to the comparison group.

last documented follow-up contact or death. Quantitative comparisons of event rates between the intervention group and the comparison group are presented as hazard ratios (HRs) and nominal 95% CIs from Cox regression[34] and are stratified by age and randomization status in the hormone therapy trials. Annualized event rates also were calculated for absolute disease rate comparisons. Cumulative hazard rates were estimated by the Kaplan-Meier method (FIGURE 2).

The HR estimates among women who were adherent to dietary goals are of particular interest. Because of the limited reliability of individual dietary assessment, we chose to define adherence in terms of participation in trial activities. A comparison group participant was considered nonadherent and her follow-up time was censored the first time she missed an annual visit. An intervention group participant was considered nonadherent at the earliest missed annual visit, when she failed to participate in 9 or more of the first-year intervention sessions, or when she failed to participate in 2 or more of the 4 maintenance sessions in subsequent years.

To produce a fair comparison between randomization groups, each participant who continued to be adherent was included in the HR estimation procedure that used the inverse of the participant's estimated adherence probability as a weighting factor. This method[35] yields valid HR estimates among participants meeting adherence criteria provided that censoring probabilities can be accurately estimated (FIGURE 3 and TABLE 5). To control for factors that may relate to adherence, time to nonadherence (censoring) was modeled separately for the intervention group and the comparison group using Cox models,[34] which included age, ethnicity, education, income, body mass index, alcohol consumption, multivitamin use, randomization into the hormone therapy trial, Gail risk score, percentage of energy from fat, vegetable, fruit, and grain consumption, physical activity, and several psychosocial variables (social support, optimism, life events, hostility, and negative emotions).

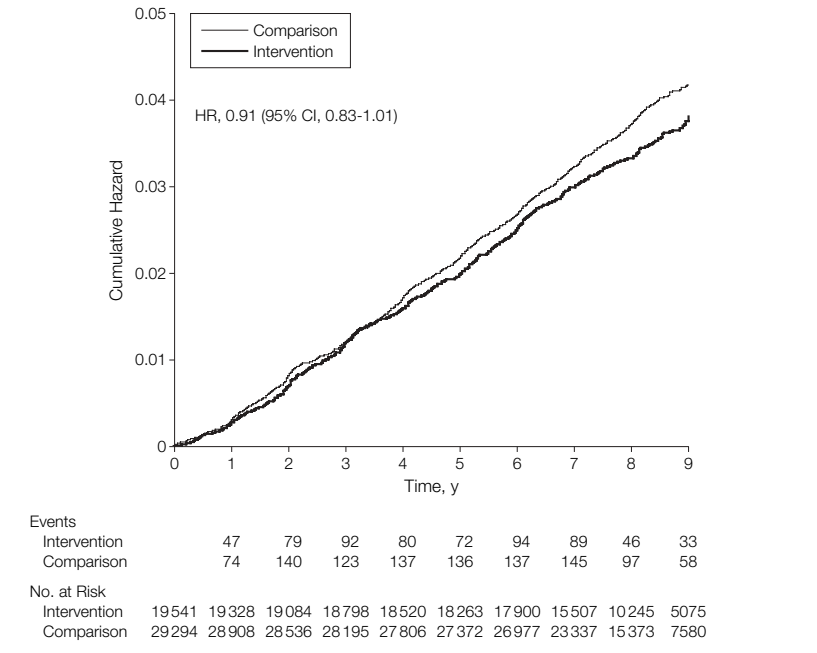
The HRs were estimated in subsets of the study population defined by baseline dietary factors and by including product terms between randomization assignment and indicator variables for the subsets of interest in the Cox models. Interactions between the HRs and the baseline dietary factors were examined by testing equality of the product term coefficients (TABLE 6). These analyses also are related to adherence because women in the intervention group who had a comparatively high-fat diet

Table 4. Blood Hormone Concentrations for Baseline and Year 1*

Biomarker	Geometric Mean (95% CI)		Relative Change (95% CI)†
	Intervention	Comparison	
Estradiol, pg/mL			
Baseline	7.6 (6.6-8.8)	6.4 (5.6-7.4)	0.85 (0.72-1.00)
Year 1	6.7 (5.9-7.7)	6.6 (5.9-7.4)	
Estrone, pg/mL			
Baseline	24.5 (21.9-27.5)	23.5 (21.2-26.1)	0.98 (0.87-1.11)
Year 1	23.7 (21.3-26.5)	23.8 (21.5-26.3)	
Testosterone, pg/mL			
Baseline	201.8 (185.0-220.2)	192.0 (176.3-209.1)	0.99 (0.94-1.05)
Year 1	199.4 (182.5-217.8)	192.4 (177.6-208.4)	
Sex hormone–binding globulin, nmol/L			
Baseline	67.0 (60.8-73.7)	66.2 (61.3-71.5)	1.09 (1.03-1.16)
Year 1	72.3 (66.4-78.8)	65.3 (60.3-70.8)	

Abbreviation: CI, confidence interval.
*Values based on a subsample of 150 women in the intervention group and 150 women in the comparison group. Women taking postmenopausal hormone therapy or randomized in the hormone therapy trials were excluded from the sample for hormone analysis.
†Change is calculated as the ratio of year 1 to baseline geometric means and is the ratio of changes in the intervention group to the comparison group.

Figure 2. Kaplan-Meier Estimates of the Cumulative Hazard for Invasive Breast Cancer



CI indicates confidence interval; HR, hazard ratio.

or low consumption of vegetables, fruit, or grains at baseline needed to make larger dietary changes to achieve specified dietary goals.

We used 4-day food records rather than FFQs to characterize participants' baseline diets in terms of total fat, total energy, and percentage of energy from fat because the 32% of energy from fat trial eligibility criterion in conjunction with the random measurement error yields distorted baseline FFQ estimates of these quantities. This is the same phenomenon as the regression to the mean problem. In this study, baseline FFQs overestimate the percentage of energy from fat by about 3%. To avoid a costly analysis of 4-day food records for all trial participants, the HR estimates were based on the 4-day food records of women who developed breast cancer. The resulting case-only HR estimates[36] are nearly identical to those that would arise from Cox regression on the entire cohort in the circumstances (rare disease and high follow-up rates) of this trial. Technically, the logarithm of HR estimates in these analyses are obtained by logistic regression of randomization assignment on indicator variables for the baseline 4-day food record dietary categories, with a constant term of log (2/3) that acknowledges the 2 to 3 randomization ratio between the intervention group and the comparison group.

The possibility of differential intervention effects across other subsets of the study population also was explored by including product terms between the randomization assignment and indicator variables for the subsets in the Cox models and by testing the equality of the product term coefficients. Because 17 interactions with baseline characteristics are reported, about 1 significant test at the α level of .05 can be expected based on chance alone. Baseline factors were restricted to established breast cancer risk factors, postmenopausal hormone therapy use or randomization assignment in the hormone therapy trial, and a small number of other factors that plausibly relate to intervention efficacy. The HR estimates also were compared across tumor characteristics using competing risk partial likelihood methods and Cox models.[37] Characteristics considered included hormone receptor status, grade, and measures to determine the extent of disease (TABLE 7). SAS version 9.1.3 (SAS Institute Inc, Cary, NC) was used for these analyses.

Data and Safety Monitoring

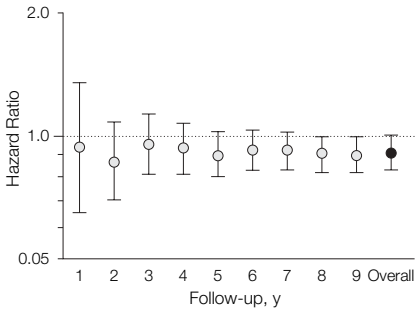
Statistical monitoring boundaries were based on the O'Brien-Fleming group sequential procedures[38] with additional Bonferroni correction for the 2 primary outcomes. Monitoring guidelines[39] adopted by the external data and safety monitoring board involved breast cancer, colorectal cancer, coronary heart disease, and deaths from other causes, as well as a global index defined as the time to the earliest of any of these 4 outcomes. This study proceeded to its planned termination.

RESULTS

Recruitment and Baseline Characteristics

Between 1993 and 1998, a total of 48 835 women (102% of goal) were randomized into the dietary modification trial: 19 541 women to the intervention group and 29 294 women to the comparison group (Figure 1). Most women were recruited to the study by population-based direct mailing campaigns and by media awareness programs.[27] Baseline participant characteristics have been described.[26] Briefly, participants were on average 62.3 years old, 18.6% were of minority race/ethnicity, and the average body mass index was 29.1. Risk factors for breast cancer were closely comparable in the 2 study groups including age, prior hormone therapy use, family history, education, ethnicity, and Gail 5-year risk estimate (Table 1). Tamoxifen and raloxifene use was nonexistent at baseline and remained low and balanced throughout follow-up (eg, tamoxifen use was approximately 1.5% and raloxifene use was approximately 2.9% in either group at year 6). Participants were at moderate risk for breast cancer based on a mean (SD) Gail 5-year risk estimate of 1.7% (0.9%).

Figure 3. Hazard Ratio Estimates for Invasive Breast Cancer Based on Cumulative Data Through Each Follow-up Year



Error bars indicate 95% confidence intervals.

Table 5. Risk of Invasive Breast Cancer and Other Major Clinical Outcomes

	No. of Cases (Annualized %)			*P* Value	
	Intervention	Comparison	HR (95% CI)*	Unweighted*	Weighted†
Breast cancer					
Incidence	655 (0.42)	1072 (0.45)	0.91 (0.83-1.01)	.07	.09
Mortality	27 (0.02)	53 (0.02)	0.77 (0.48-1.22)	.26	.27
Total cancer					
Incidence	1946 (1.23)	3040 (1.28)	0.96 (0.91-1.02)	.15	.10
Mortality	436 (0.28)	690 (0.29)	0.95 (0.84-1.07)	.41	.22
Total mortality	950 (0.60)	1454 (0.61)	0.98 (0.91-1.07)	.70	.29
Global index‡	2051 (1.30)	3207 (1.35)	0.96 (0.91-1.02)	.16	.16

Abbreviations: CI, confidence interval; HR, hazard ratio.
*Proportional hazards model stratified by prevalent condition (when appropriate), age, and randomization group.
†Weighted log-rank test stratified by prevalent condition (when appropriate), age, and randomization group. Weights increase linearly from zero at randomization to a maximum of 1 at 10 years.
‡Defined for a participant as the time to the earliest invasive breast cancer, colorectal cancer, coronary heart disease, or mortality from any other cause.

Dietary Intervention Effects on Nutrients and Other Factors

Table 2 provides information at baseline and at 1 year after randomization for the nutrients targeted in the intervention group as well as for other dietary variables, body weight, and factors that may be affected by participation in intervention group. These baseline variables are nearly equal between the intervention group and the comparison group. Also, differences from baseline in these factors at 1, 3, and 6 years after randomization are compared between the intervention group and the comparison group. Based on data from women who provided FFQs, the average reductions in percentage of energy from fat for the intervention group compared with the comparison group was 10.7 at year 1 and decreased to 8.1 at year 6. Compared with the comparison group, the consumption of vegetable and fruit servings in the intervention group was more than 1 serving per day greater, while the difference for the consumption of grain servings was significant but appeared to decline as the study progressed.

A small reduction in energy consumption was reported in the intervention group compared with the comparison group. Women in the intervention group experienced a modest weight loss early in the trial and maintained a greater weight change from baseline throughout follow-up than women in the comparison group.

Dietary differences were similar to those reported in Table 2 when assessment was based on a 4-day food record or 24-hour dietary recall. For example, based on 4-day food record assessments, the percentage of energy from fat was 11.3% lower and intake of fat was 26.3 g lower in the intervention group compared with the comparison group at year 1. At year 3, using 24-hour recall assessments, the percentage of energy from fat was 8.2% (19.4 g) lower in the intervention group compared with the comparison group and at year 6 was 7.5% (24 g) lower, respectively, in the intervention group.

The changes from baseline to year 3 for blood markers between the intervention group and the comparison group appear in Table 3 and are based on values from the 5.8% subsample. Most blood concentration changes were

Table 6. Breast Cancer Risk by Baseline Dietary Factors

Baseline Quartiles	Year 1, Mean (SD)*		Mean (SD) Difference Between Groups	No. (%) of Breast Cancer Cases		HR (95% CI)†	Interaction *P* Value‡
	Intervention	Comparison		Intervention (n = 655)	Comparison (n = 1072)		
Fat							
Percentage of energy, kcal							
<27.9	18.8 (6.2)	28.6 (6.2)	9.7 (6.2)	144 (22)	222 (21)	0.97 (0.79-1.20)	.04
27.9-<32.3	21.0 (7.0)	31.4 (6.0)	10.4 (6.5)	186 (28)	259 (24)	1.08 (0.89-1.30)	
32.3-<36.8	21.7 (6.7)	33.5 (6.5)	11.7 (6.6)	160 (24)	283 (26)	0.85 (0.70-1.03)	
≥36.8	23.6 (7.9)	35.8 (6.3)	12.2 (7.0)	151 (23)	291 (27)	0.78 (0.64-0.95)	
Total intake, g							
<46.2	29.5 (12.8)	45.5 (16.5)	16.1 (15.1)	128 (20)	221 (21)	0.87 (0.70-1.08)	.42
46.2-<59.8	32.9 (12.5)	57.8 (19.9)	24.9 (17.1)	176 (27)	261 (24)	1.01 (0.84-1.22)	
59.8-<76.0	35.0 (14.9)	61.9 (20.4)	27.0 (18.5)	194 (30)	300 (28)	0.97 (0.81-1.16)	
≥76.0	38.9 (17.0)	73.9 (26.6)	35.0 (23.3)	143 (22)	273 (25)	0.79 (0.64-0.96)	
Energy intake, kcal							
<1391.8	1225 (301.5)	1314 (339.1)	89.1 (324.2)	139 (21)	226 (21)	0.92 (0.75-1.14)	.89
1391.8-<1663.6	1376 (314.1)	1541 (353.4)	164.7 (338.2)	164 (25)	290 (27)	0.85 (0.70-1.03)	
1663.6-<1958.7	1470 (298.5)	1690 (386.4)	219.3 (353.0)	179 (27)	271 (25)	0.99 (0.82-1.20)	
≥1958.7	1608 (397.3)	1927 (468.3)	318.5 (440.7)	159 (24)	268 (25)	0.89 (0.73-1.08)	
Vegetables and fruit, servings/d							
<2.3	3.7 (2.1)	2.4 (1.4)	−1.3 (1.7)	155 (24)	259 (24)	0.90 (0.73-1.09)	.07
2.3-<3.3	4.6 (2.0)	3.3 (1.4)	−1.3 (1.7)	158 (24)	268 (25)	0.88 (0.72-1.07)	
3.3-<4.6	5.3 (2.1)	4.1 (1.6)	−1.2 (1.8)	144 (22)	264 (25)	0.82 (0.67-1.00)	
≥4.6	6.5 (2.2)	5.5 (2.0)	−1.0 (2.1)	197 (30)	276 (26)	1.08 (0.90-1.29)	
Grains, servings/d							
<3	3.7 (2.1)	2.8 (1.5)	−0.9 (1.7)	160 (24)	258 (24)	0.94 (0.77-1.15)	.98
3-<4.3	4.6 (2.1)	3.7 (1.7)	−0.8 (1.9)	171 (26)	242 (23)	1.02 (0.84-1.25)	
4.3-<5.9	5.4 (2.4)	4.5 (2.0)	−0.9 (2.1)	178 (27)	311 (29)	0.85 (0.70-1.02)	
≥5.9	6.7 (3.1)	5.9 (2.7)	−0.8 (2.9)	145 (22)	256 (24)	0.88 (0.71-1.07)	

Abbreviations: CI, confidence interval; HR, hazard ratio.
*Baseline classification and year 1 data for percentage of energy from fat, total fat intake, and total energy based on 4-day food records from the 4.6% subsample. Consumption of vegetables and fruit and grains based on food frequency questionnaires from the entire trial cohort.
†Based on case-only analysis for percentage of energy from fat, total fat intake, and total energy and standard Cox regression for vegetables and fruit and grains. An unweighted proportional hazards model stratified by age and randomization group was used.
‡Test of interaction between the randomization assignment and the variable of interest.

minor. There was a greater reduction in levels of γ-tocopherol in the intervention group compared with the comparison group and small positive differences in levels of α-carotene, β-carotene, and β-cryptoxanthin. Low-density lipoprotein cholesterol level was modestly decreased in the intervention group compared with the comparison group, but changes in levels of high-density lipoprotein cholesterol, triglycerides, insulin, and glucose did not differ significantly between the 2 groups. Corresponding biomarker changes were similar at the other time points considered (year 1 and year 6) and differences between the intervention group and the comparison group were somewhat larger at year 1 than at the later time points.

Changes from baseline to year 1 in blood hormone metabolites based on the subsample of 150 women in the intervention group and 150 women in the comparison group appear in Table 4. A greater reduction in estradiol and a greater increase in sex hormone–binding globulin occurred for women in the intervention group compared with women in the comparison group.

Clinical Outcomes

The average follow-up time was 8.1 years in both the intervention group and the comparison group. Over the course of the trial, 4.7% of the women in the intervention group withdrew from participation or were lost to follow-up compared with 4.0% women in the comparison group (Figure 1). Frequencies of mammography screening were 87% at baseline, 92% at year 2, 91% at year 4, 89% at year 6, and 88% at year 8 in the intervention group. There were nearly identical frequencies of mammography screening in the comparison group: 87% at baseline, 92% at year 2, 92% at year 4, 90% at year 6, and 88% at year 8. Overall, 655 (3.35%) women in the intervention group and 1072 (3.66%) women in the comparison

Table 7. Risk of Breast Cancer by Tumor Characteristics

Tumor Characteristic	No. of Cases (Annualized %)*		HR (95% CI)	*P* Value	
	Intervention	Comparison		Unweighted†	Competing Risks Analysis‡
Estrogen receptor status					
Positive	486 (0.31)	817 (0.34)	0.89 (0.80-1.00)	.04	>.99
Negative	94 (0.06)	159 (0.07)	0.89 (0.69-1.14)	.36	
Progesterone receptor status					
Positive	407 (0.26)	634 (0.27)	0.96 (0.85-1.09)	.54	.04
Negative	162 (0.10)	319 (0.13)	0.76 (0.63-0.92)	.004	
Ratio of estrogen to progesterone receptors§					
Estrogen+/progesterone+	399 (0.25)	616 (0.26)	0.97 (0.86-1.10)	.64	.04
Estrogen+/progesterone–	77 (0.05)	179 (0.08)	0.64 (0.49-0.84)	.001	
Estrogen–/progesterone+	8 (0.01)	18 (0.01)	0.67 (0.29-1.54)	.34	
Estrogen–/progesterone–	82 (0.05)	138 (0.06)	0.89 (0.68-1.17)	.41	
Differential grade					
Good	164 (0.10)	283 (0.12)	0.87 (0.72-1.05)	.15	.63
Moderate	235 (0.15)	404 (0.17)	0.87 (0.74-1.02)	.09	
Poor	176 (0.11)	271 (0.11)	0.97 (0.80-1.18)	.77	
SEER stage					
In situ‖	178 (0.11)	263 (0.11)	1.01 (0.83-1.22)	.93	.79
Localized	475 (0.30)	789 (0.33)	0.90 (0.80-1.01)	.07	
Regional	148 (0.09)	243 (0.10)	0.91 (0.74-1.12)	.39	
Distant	8 (0.01)	12 (0.01)	1.00 (0.41-2.44)	.99	
No. of positive lymph nodes					
None	437 (0.28)	723 (0.30)	0.90 (0.80-1.02)	.10	.91
1-3	104 (0.07)	164 (0.07)	0.95 (0.74-1.22)	.69	
>3	38 (0.02)	67 (0.03)	0.85 (0.57-1.27)	.44	
Tumor size, cm					
<0.5	70 (0.04)	132 (0.06)	0.80 (0.60-1.07)	.13	.20
0.5-1	156 (0.10)	279 (0.12)	0.84 (0.69-1.02)	.07	
>1-2	249 (0.16)	373 (0.16)	1.00 (0.85-1.17)	.99	
>2-5	97 (0.06)	190 (0.08)	0.76 (0.60-0.98)	.03	
>5	18 (0.01)	20 (0.01)	1.35 (0.71-2.56)	.35	

Abbreviations: CI, confidence interval; HR, hazard ratio; SEER, Surveillance, Epidemiology, and End Results program of the National Cancer Institute.
*Numbers for some characteristics are less than the total number of invasive breast cancers because of missing tumor characteristic data.
†From an unweighted proportional hazards model stratified by age and randomization group; tests whether HRs equal unity.
‡Analysis of the partial likelihoods; tests whether HRs are equal between tumor types.
§The numbers of cases do not total due to missing data for receptor status.
‖In situ breast tumors included in this portion of table only.

group developed invasive breast cancer during follow-up. The comparison group incidence rate is slightly in excess of design assumptions. The estimated HR for invasive breast cancer is 0.91 (95% CI, 0.83-1.01). The corresponding log-rank significance level is .07. The protocol-specified weighted log-rank test significance level was .07. The cumulative hazard curves separate in favor of the intervention group after about 4 years (Figure 2). As an alternate view of these same data, the HRs for the cumulative data through each of years 1 to 9 after randomization appear in Figure 3.

A simultaneous test of the null hypothesis for the primary outcomes of breast cancer and colorectal cancer had a significance level of .14 using either weighted or unweighted log-rank tests.

More than half (51.6%) of the participants also enrolled in the calcium and vitamin D trial, mainly at 1 year after enrollment in the dietary modification trial. The enrollment rate was slightly lower among women in the intervention group (49.4%) than among women in the comparison group (53.1%). However, the HR estimate remained at 0.91 (95% CI, 0.83-1.01) following control for calcium and vitamin D trial enrollment and randomization assignment as time-dependent covariates.

The incidence rates, HRs, and weighted and unweighted log-rank tests for breast cancer mortality, total cancer (exclusive of nonmelanoma skin cancer) incidence and mortality, total mortality, and the global index appear in Table 5. For each outcome, the event rates are slightly lower in the intervention group compared with the comparison group but the differences are not significant at the .05 level.

HRs for Adherent Women

The HR for invasive breast cancer for the intervention group compared with the comparison group was estimated among women who participated actively in the dietary modification trial. Under these criteria, the comparison group adherence rates (estimated from a Cox regression model) were 87% at year 3, 75% at year 6, and 65% at year 9, while the corresponding intervention group adherence rates were 57%, 31%, and 19%. The inverse adherence probability-weighted HR estimate under these adherence criteria is 0.85 (95% CI, 0.71-1.02). The weighting procedure aims to produce valid HR estimates even when adherence rates differ between the 2 groups. The difference in the percentage of energy from fat on the FFQ between adherent women in the intervention group and adherent women in the comparison group was 12.1% at year 1, 11.8% at year 3, 11.1% at year 6, and 10.1% at year 9. The use of more stringent adherence criteria for the intervention group (eg, ≥10 first-year intervention sessions, ≥3 maintenance sessions annually) leads to even smaller HR estimates and to 95% CIs that exclude 1. However, these estimates may be sensitive to adherence model inadequacies.

HRs in Relation to Baseline Dietary Factors

The numbers of invasive breast cancers and the HRs across quartiles of baseline dietary factors appear in Table 6. The HR estimates for fat, energy, and percentage of energy from fat are based on case-only analyses of 4-day food records at baseline and quartiles are defined by food records from the 4.6% subsample of the trial cohort, whereas the HR estimates for consumption of vegetables and fruit and grains are based on FFQs from the entire cohort. A significant ($P = .04$) trend in HR with baseline percentage of energy from fat is observed. Women with higher baseline percentages of energy from fat show greater evidence for a reduction in breast cancer risk. There is also a suggestive trend ($P = .07$) with baseline consumption of vegetables and fruit. The means and SDs for baseline dietary factors at year 1 appear in Table 6. The limited variation in the comparison group means at year 1 across these baseline categories, in conjunction with intervention group vs comparison group differences, suggests that the HR variation for the percentage of energy from fat may primarily reflect study adherence differences. For example, the year 1 trend from a 12.2% difference in the highest percentage of energy from fat quartile to a 9.7% difference in the lowest quartile is significant ($P = .001$).

Breast Tumor Characteristics

The grade, size, lymph node status, and stage of breast cancers occurring in the intervention group were similar to those seen in the comparison group (Table 7). The HR estimate was lower for tumors negative for the progesterone receptor than for tumors positive for the progesterone receptor ($P = .04$) but did not depend on estrogen receptor status. When tumors were classified by both estrogen and progesterone receptor status, there was an indication ($P = .04$) of HR variation with stronger evidence for a reduction in the occurrence of tumors that are positive for the estrogen receptor and negative for the progesterone receptor.

Subgroup Analyses

Invasive breast cancer HR estimates for the subgroups defined by baseline demographic, medical history, and health behavioral factors appear in TABLE 8. Two of 17 interactions were significant at the .05 level (hypertension and white blood cell count) and another was significant at the .10 level (estrogen plus progestin use).

COMMENT

The WHI Dietary Modification Trial is the first large-scale randomized trial to test whether adopting a low-fat dietary pattern in the middle to later decades of life reduces the risk for breast cancer. The relatively intensive dietary intervention implemented in the WHI resulted in a significant and sustained reduction in fat intake and an increase in vegetable and fruit intake. After approximately 8 years of follow-up, breast cancer incidence was 9% lower for women in the dietary intervention group compared with women in the comparison group (HR, 0.91; 95% CI, 0.83-1.01). Because incidence rates did not differ

Table 8. Breast Cancer Risk Based on Baseline Demographics, Medical History, and Health Behavior Variables

	No. of Participants (Annualized %)			
	Intervention (n = 655)	Comparison (n = 1072)	HR (95% CI)	*P* Value for Interaction*
Age, y				
50-59	227 (0.37)	359 (0.39)	0.95 (0.81-1.13)	.79
60-69	304 (0.42)	519 (0.48)	0.87 (0.76-1.01)	
70-79	124 (0.49)	194 (0.51)	0.96 (0.76-1.20)	
Race/ethnicity				
White	560 (0.43)	936 (0.48)	0.90 (0.81-1.00)	.87
Black	55 (0.32)	73 (0.29)	1.09 (0.77-1.55)	
Hispanic	17 (0.29)	26 (0.31)	0.94 (0.51-1.74)	
American Indian	2 (0.28)	2 (0.22)	1.24 (0.17-8.82)	
Asian/Pacific Islander	12 (0.36)	24 (0.45)	0.79 (0.39-1.57)	
Unknown	9 (0.46)	11 (0.36)	1.26 (0.52-3.04)	
Family history of breast cancer				
Yes	140 (0.51)	247 (0.62)	0.81 (0.66-1.00)	.19
No	488 (0.40)	771 (0.42)	0.95 (0.85-1.07)	
Gail model 5-y risk, %				
<1.25	175 (0.31)	276 (0.33)	0.95 (0.78-1.15)	.47
1.25-1.74	196 (0.39)	330 (0.43)	0.90 (0.75-1.07)	
≥1.75	284 (0.55)	466 (0.60)	0.90 (0.78-1.05)	
Mammography screening within 2 y				
Yes	533 (0.42)	905 (0.47)	0.89 (0.80-0.99)	.16
No	104 (0.41)	140 (0.38)	1.08 (0.84-1.39)	
Hypertension†				
Yes	262 (0.44)	464 (0.51)	0.85 (0.73-0.99)	.05
No	349 (0.43)	498 (0.41)	1.04 (0.91-1.19)	
Diabetes‡				
Yes	23 (0.35)	46 (0.45)	0.75 (0.46-1.24)	.43
No	632 (0.42)	1026 (0.45)	0.92 (0.83-1.02)	
White blood cell count, $\times 10^9$/L				
<5.1	195 (0.40)	285 (0.39)	1.03 (0.85-1.23)	.04
5.1-6.3	242 (0.44)	368 (0.44)	0.99 (0.84-1.16)	
≥6.4	218 (0.40)	419 (0.52)	0.77 (0.66-0.91)	
Postmenopausal hormone use, y				
Estrogen alone				
None	431 (0.44)	676 (0.45)	0.96 (0.85-1.08)	.33
<5	82 (0.37)	153 (0.47)	0.77 (0.59-1.01)	
≥5	142 (0.39)	243 (0.44)	0.89 (0.72-1.09)	
Estrogen plus progestin, y				
None	447 (0.39)	683 (0.40)	0.98 (0.87-1.11)	.10
<5	87 (0.38)	175 (0.51)	0.73 (0.57-0.95)	
≥5	121 (0.59)	214 (0.68)	0.85 (0.68-1.06)	
Randomized to estrogen alone				
Active	10 (0.20)	23 (0.28)	0.73 (0.35-1.53)	.35
Placebo	18 (0.34)	25 (0.29)	1.15 (0.63-2.10)	
Randomized to estrogen plus progestin				
Active	36 (0.46)	64 (0.54)	0.85 (0.56-1.28)	.48
Placebo	29 (0.39)	38 (0.36)	1.07 (0.66-1.73)	
Baseline postmenopausal hormone use				
Estrogen alone or randomized to estrogen alone				
Yes	162 (0.37)	275 (0.42)	0.89 (0.73-1.08)	.84
No	88 (0.34)	146 (0.37)	0.92 (0.71-1.20)	
Estrogen plus progestin or randomized to estrogen plus progestin				
Yes	188 (0.53)	345 (0.64)	0.83 (0.69-0.99)	.06
No	217 (0.41)	306 (0.39)	1.04 (0.88-1.24)	
Body mass index§				
<24.9	151 (0.38)	251 (0.42)	0.89 (0.73-1.09)	.88
24.9-<28.2	156 (0.40)	260 (0.43)	0.92 (0.76-1.13)	
28.2-<32.5	175 (0.44)	278 (0.48)	0.92 (0.76-1.12)	
≥32.5	171 (0.44)	277 (0.48)	0.92 (0.76-1.12)	
Waist >88 cm				
Yes	312 (0.42)	547 (0.49)	0.86 (0.75-0.99)	.24
No	341 (0.41)	524 (0.42)	0.97 (0.84-1.11)	
Physical activity, METs				
<1.5	146 (0.43)	235 (0.46)	0.94 (0.76-1.15)	.12
1.5-<6.3	134 (0.40)	242 (0.49)	0.80 (0.65-0.99)	
6.3-<14.8	145 (0.41)	264 (0.49)	0.85 (0.69-1.04)	
≥14.8	158 (0.45)	201 (0.39)	1.17 (0.95-1.44)	

Abbreviations: CI, confidence interval; HR, hazard ratio; METs, metabolic equivalent units.
*Unweighted proportional hazards model stratified by age and randomization group.
†Systolic blood pressure higher than 140 mm Hg, diastolic blood pressure higher than 90 mm Hg, or self-report of taking pills to lower blood pressure.
‡Self-report of taking pills or insulin via injection.
§Calculated as weight in kilograms divided by the square of height in meters.

between the intervention group and the comparison group at the conventional .05 level of significance, chance provides an explanation for the modestly lower breast cancer incidence rates in the intervention group.

However, interpretation of these results needs to take into account the following. There were departures from the design assumptions that likely reduced study power. In addition, there was a significant interaction between the HR for the intervention group compared with the comparison group for baseline dietary fat consumption. Women in the intervention group with a higher baseline percentage of energy from fat provided stronger evidence for breast cancer reduction than women in the comparison group. Also, the HR varied among breast cancer subtypes defined by tumor hormone receptor characteristics. Such variation would not be expected if the intervention had no effect on breast cancer risk.

As noted above, there were certain departures from the original study design. Although accrual goals were met, recruitment took longer than anticipated and therefore the average follow-up at the planned trial completion date was 8.1 years, rather than the original target of 9 years. In addition, the difference in the percentage of energy from fat between the women in the intervention group and women in the comparison group was only about 70% of the design goal. Relatively few women met the dietary target of 20% of energy from fat: 31.4% at year 1 and 14.4% at year 6. Also, the differences in the consumption of vegetables and fruit and grains between the intervention and comparison groups were modest. If the WHI design assumptions are revised to take into account these departures, projections are that breast cancer incidence in the intervention group would be 8% to 9% lower than in the comparison group the trial would be somewhat underpowered (projected power of approximately 60%) to detect a statistically significant difference,[40] which is consistent with the observed results. This perspective is further supported by our analyses demonstrating that the magnitude of the breast cancer HR was consistent with original design assumptions in the subset of adherent women.

The argument for some intervention effect on breast cancer risk is strengthened also by the HR variation (Table 7) according to the progesterone receptor status of the tumor and according to the combined estrogen and progesterone receptor status. These variations were detected even though the tumor classification was based on local receptor laboratory results without standardization across clinical centers. Dependence of dietary pattern associations on breast tumor hormone receptor status also has been described in a preliminary report[41] from the Women's Intervention Nutrition Study and in the Nurses' Health Study cohort.[42] The HR variations across tumor characteristics are perhaps not surprising because breast cancer is increasingly recognized as a heterogeneous diagnosis in which medical interventions[43-45] are effective primarily in subgroups defined by specific biological properties.[46,47] Of interest also in relation to the finding of estradiol reduction among women in the intervention group (Table 4) are clinical trial results demonstrating the effectiveness of aromatase inhibitors, such as anastrazole in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial,[48] for breast cancer treatment.

Trial results may suggest that factors other than estrogen[48] contribute to any effect of a low-fat dietary pattern on breast cancer risk. Potential mechanisms include influence on insulin levels,[49] insulin-like growth factors,[50] and markers of inflammation. The last is consistent with the suggestion that women having higher baseline white blood cell counts show greater evidence of intervention benefit (Table 8).

There are a number of limitations to the WHI dietary modification trial, including the reliance on self-report methods to assess differences in dietary consumption between the intervention and comparison groups. However, relative changes between randomization groups in serum levels of γ-tocopherol are consistent with intervention participant reports of decreases in consumption of added fats and oils[51] and those of the carotenoids with FFQ differences in consumption of vegetables and fruit. Also, the available data are somewhat limited for the purpose of separating any breast cancer effect resulting from dietary fat reduction from that due to increases in the consumption of vegetables and fruit and/or grains. Similarly, there is limited potential to separate out the influence of any lifestyle changes or other nontargeted dietary changes that may result from adopting a low-fat dietary pattern. Additional biomarker data are being assembled to facilitate analyses of this kind.

In light of our findings, additional research on diet and breast cancer prevention could focus on those women most likely to benefit from a low-fat dietary pattern, such as those with diets habitually high in fat. The potential differential effect of a low-fat dietary pattern by tumor subtype should continue to further characterize these subtypes and encourage the exploration of underlying mechanisms. Observational studies examining associations between diet and breast cancer should consider the use of consumption estimates that are calibrated with appropriate biomarkers.

In conclusion, among postmenopausal women, a low-fat dietary pattern did not result in a statistically significant reduction in the risk of invasive breast cancer over an 8.1-year average follow-up period. However, nonsignificant trends were observed suggesting a reduced risk with a low-fat dietary pattern and incidence rate differences between groups are in agreement with design assumptions on acknowledging the dietary differences achieved. Because the health implications of a low-fat dietary pattern may take years to be fully realized, longer, planned, nonintervention follow-up may yield a more definitive comparison.

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Financial Disclosures: Dr Assaf is an employee of Pfizer. Dr Black has received research grants from Pfizer and AstraZeneca; served on the speaker's bureau for Pfizer, Novartis, Sanofi-Aventis, Bristol-Myers Squibb, Searle, Pharmacia, and Boehringer; and served as a consultant to or on an advisory board for Myogen, Merck Sharp & Dohme, Novartis, Mylan-Bertek, Pfizer, Bristol-Myers Squibb, and Sanofi-Aventis. No other authors reported disclosures.

Funding/Support: The Women's Health Initiative program was funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health, Department of Health and Human Services.

Role of the Sponsor: The funding organization had representation on the steering committee, which governed the design and conduct of the study, the interpretation of the data, and the preparation and approval of manuscripts. The National Heart, Lung, and Blood Institute Program Office reviewed the manuscript prior to publication.

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Acknowledgment: We acknowledge the dedicated efforts of the dietary modification trial participants and that of project staff, particularly nutritionists involved in delivering the dietary modification intervention and Aaron Aragaki, MS, of the clinical coordinating center of the Fred Hutchinson Cancer Research Center, who contributed much to the analytical aspects of this article.

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