Low-Fat Dietary Pattern and Risk of Colorectal Cancer

The Women's Health Initiative Randomized Controlled Dietary Modification Trial

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Context Observational studies and polyp recurrence trials are not conclusive regarding the effects of a low-fat dietary pattern on risk of colorectal cancer, necessitating a primary prevention trial.

Objective To evaluate the effects of a low-fat eating pattern on risk of colorectal cancer in postmenopausal women.

Design, Setting, and Participants The Women's Health Initiative Dietary Modification Trial, a randomized controlled trial conducted in 48 835 postmenopausal women aged 50 to 79 years recruited between 1993 and 1998 from 40 clinical centers throughout the United States.

Interventions Participants were randomly assigned to the dietary modification intervention (n=19 541; 40%) or the comparison group (n=29 294; 60%).The intensive behavioral modification program aimed to motivate and support reductions in dietary fat, to increase consumption of vegetables and fruits, and to increase grain servings by using group sessions, self-monitoring techniques, and other tailored and targeted strategies. Women in the comparison group continued their usual eating pattern.

Main Outcome Measure Invasive colorectal cancer incidence.

Results A total of 480 incident cases of invasive colorectal cancer occurred during a mean follow-up of 8.1 (SD, 1.7) years. Intervention group participants significantly reduced their percentage of energy from fat by 10.7% more than did the comparison group at 1 year, and this difference between groups was mostly maintained (8.1% at year 6). Statistically significant increases in vegetable, fruit, and grain servings were also made. Despite these dietary changes, there was no evidence that the intervention reduced the risk of invasive colorectal cancer during the follow-up period. There were 201 women with invasive colorectal cancer (0.13% per year) in the intervention group and 279 (0.12% per year) in the comparison group (hazard ratio, 1.08; 95% confidence interval, 0.90-1.29). Secondary analyses suggested potential interactions with baseline aspirin use and combined estrogen-progestin use status ($P=.01$ for each). Colorectal examination rates, although not protocol defined, were comparable between the intervention and comparison groups. Similar results were seen in analyses adjusting for adherence to the intervention.

Conclusion In this study, a low-fat dietary pattern intervention did not reduce the risk of colorectal cancer in postmenopausal women during 8.1 years of follow-up.

Clinical Trials Registration ClinicalTrials.gov Identifier NCT00000611

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The Women's Health Initiative (WHI) Dietary Modification Trial is a randomized controlled trial designed in 1991-1992 to test whether a low-fat eating pattern with increased fruits, vegetables, and grains reduces the risk of breast cancer, colorectal cancer, or, secondarily, coronary heart disease in postmenopausal women. At that time, inter-

See also pp 629 and 655.

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national comparisons suggested that countries with 50% lower fat intake than the US population had approximately one third the risk of colorectal cancer.[1,2] Migration studies supported this hypothesis. Women migrating from countries with low fat consumption to countries with high fat consumption experienced the higher colorectal cancer rates of their new country.[3,4] Fairly consistent evidence existed for an effect of dietary fat, vegetables and fruits, and grains on colorectal cancer risk from within-country observational studies,[2,5-8] although the protective effect of lower fat intake was no longer clear after adjusting for energy intake.[2,9] The WHI Dietary Modification Trial is the first randomized trial to directly address the health effects of a low-fat eating pattern in predominantly healthy postmenopausal women from diverse racial/ethnic, geographic, and socioeconomic backgrounds. This article reports the principal results for colorectal cancer.

METHODS

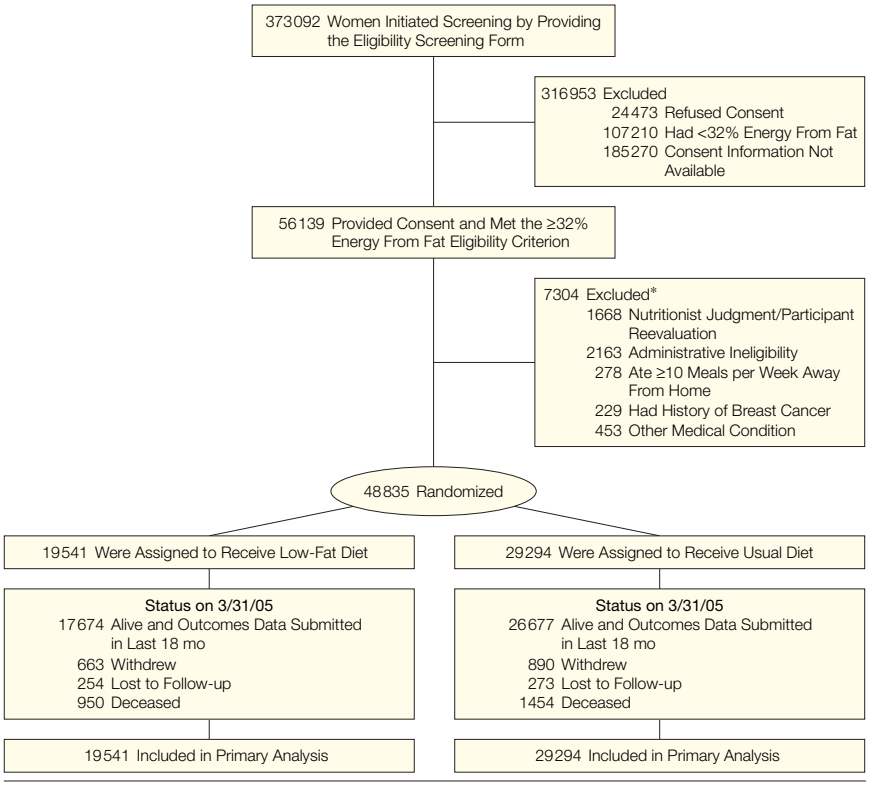
Study Population

Recruitment of postmenopausal women aged 50 to 79 years who were interested in 1 or more components of the clinical trials was conducted by 40 clinical centers throughout the United States.

Recruitment was typically by direct mail from purchased lists,[10] enhanced by advertising and other community promotion. Details of the study design and recruitment have been published previously.[10-12] Eligibility criteria for the dietary modification trial included willingness to be randomized to an intervention or comparison group and having a fat intake at baseline of 32% or more of total calories as evaluated by the WHI food frequency questionnaire.[13] Major exclusions made at screening included women with any prior colorectal cancer or breast cancer, other cancers in the last 10 years, type 1 diabetes, medical conditions with predicted survival of less than 3 years, or adherence concerns, including having meals frequently prepared away from home.

Between 1993 and 1998, 48 835 eligible women were randomly assigned to an intervention or a comparison group in the ratio of 2:3 for cost-efficiency (FIGURE 1). Randomization was based on a permuted-block algorithm with block sizes of 5, 10, or 15 and stratified by clinical center and age group (50-54, 55-59, 60-69, and 70-74 years).[14] All women provided written informed consent at baseline, as approved by institutional review boards. Of the women randomized into this trial, 16% were simultaneously randomized into 1 of the arms of the hormone therapy trial (conjugated equine estrogen trial or estrogen-plus-progestin trial)[11] and 25 210 were subsequently randomized into a trial of calcium and vitamin D supplementation.[14]

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.

Intervention

The intervention was designed to promote dietary change with the goals of reducing total fat to 20% of energy intake, increasing vegetables and fruits to at least 5 servings daily and grains to at least 6 servings daily.[15,16] We refer to this as a low-fat eating pattern. The intervention did not include total energy reduction or weight loss goals. Although not a separate focus of the intervention, it was anticipated that by reducing fat to 20% of energy intake, saturated fat would also be reduced (7% energy intake). The intervention was an intensive behavioral modification program, using 18 group sessions in the first year and quarterly sessions thereafter, led by specially trained and certified nutritionists.[15] Each participant was given her own dietary fat-gram goal according to her height. The intervention emphasized self-monitoring techniques and introduced other tailored and targeted strategies, such as motivational interviewing,[17] to lower fat intake throughout the intervention period. Comparison group participants received a copy of the US Department of Health and Human Services' *Di-*

Table 1. Baseline Participant Characteristics Pertinent to Colorectal Cancer Risk

Characteristics	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)	
Education			
Up to high school diploma/GED	4267 (21.0)	6466 (22.3)	.65
School after high school	7711 (39.7)	11 597 (39.8)	
College degree or higher	7445 (38.3)	11 042 (37.9)	
First-degree relatives with colorectal cancer			
0	14 968 (86.2)	22 458 (86.3)	.63
≥1	2400 (13.8)	3552 (13.7)	
History of polyp removal			
No	15 726 (91.5)	23 567 (91.6)	.90
Yes	1453 (8.5)	2168 (8.4)	
Colonoscopy history at baseline			
None	8834 (50.7)	13 176 (50.5)	.21
<5 y ago	5338 (30.7)	7872 (30.2)	
≥5 y ago	3240 (18.6)	5021 (19.3)	
Alcohol use at baseline			
Never drinker	1888 (9.7)	2875 (9.9)	.89
Past drinker	3553 (18.3)	5347 (18.4)	
<1 drink/d	12 058 (62.2)	18 116 (62.2)	
≥1 drink/d	1881 (9.7)	2769 (9.5)	
Aspirin dosage at baseline (minimum duration, 14 d), mg/d			
None	15 956 (81.7)	23 658 (80.8)	.03
<325	807 (4.1)	1319 (4.5)	
≥325	2777 (14.2)	4317 (14.7)	
Aspirin use duration at baseline (minimum dosage, 75 mg/d), y			
Nonuser	15 956 (81.7)	23 658 (80.8)	.01
<1	700 (3.6)	1119 (3.8)	
1-8	1981 (10.1)	3110 (10.7)	
≥8	903 (4.6)	1407 (4.8)	
Randomized to WHI E+P or estrogen-alone studies			
No	16 359 (83.7)	24 426 (83.4)	.05
Estrogen-alone active group	615 (3.2)	1039 (3.6)	
Estrogen-alone placebo group	670 (3.4)	1068 (3.7)	
E+P active group	972 (5.0)	1457 (5.0)	
E+P placebo group	925 (4.7)	1304 (4.5)	
Randomized to WHI CaD study			
No	9896 (50.6)	13 729 (46.9)	<.001
CaD active group	4878 (25.0)	7738 (26.4)	
CaD placebo group	4767 (24.4)	7827 (26.7)	

(continued)

etary Guidelines for Americans[18] and other health-related materials but were not asked to make dietary changes.

Evaluation Procedures

Dietary intake was monitored using the WHI food frequency questionnaire at 1 year[13] and in a rotating one-third subsample every year thereafter. Reported values after year 1 are based on the 3-year intervals in which all participants were assessed. At baseline, all women completed a 4-day food record after receiving instruction in keeping food records. Nutrition staff at each clinical center checked each record for completeness. The records of women who developed colorectal cancer were analyzed in a case-case design to contrast intervention and comparison cases according to baseline dietary intake.

Fasting blood specimens were obtained at baseline, at the first annual follow-up, and in a 5.8% subsample (n=2816) at years 3 and 6 and were centrally stored at –70°C. Biomarkers of dietary change (plasma total cholesterol, plasma triglycerides, serum γ-tocopherol and serum total carotenoids [α- and β-carotene, β-cryptoxanthin, zeaxanthin, and lutein]) were measured in baseline and year 3 specimens from the 5.8% subsample after excluding participants experiencing a trial end point during the previous year.

Women completed a medical update questionnaire every 6 months, and medical records were sought for all women reporting colorectal cancer. Locally trained, blinded physician adjudicators reviewed medical records and pathology reports from the self-reported colorectal cancer cases (available for 97%). Colorectal cancer was confirmed by blinded central adjudicators and coded using the 1992 Surveillance, Epidemiology, and End Results system.[19] In all clinical centers, study personnel involved in delivery of the dietary intervention were not part of outcomes ascertainment or adjudication.

The medical update also monitored the frequencies of bowel examinations and incident intestinal polyps or adenomas. Frequency of bowel exami-

Table 1. Baseline Participant Characteristics Pertinent to Colorectal Cancer Risk (cont)

Characteristics	No. (%) of Participants* Intervention (n = 19 541)	Comparison (n = 29 294)	*P* Value†
	Mean (SD)	Mean (SD)	
Food frequency questionnaire			
Total energy, kcal/d	1790.2 (710.1)	1789.4 (703.0)	.90
Daily energy from fat, %	37.8 (5.1)	37.8 (5.0)	.84
Daily energy from saturated fat, %	12.7 (2.5)	12.7 (2.5)	.54
Dietary fiber, g/d	15.4 (6.4)	15.4 (6.4)	.63
Red meat, medium servings/d	0.9 (0.6)	0.9 (0.6)	.65
Combined fruits/vegetables, medium servings/d	3.6 (1.8)	3.6 (1.8)	.52
Grains, medium servings/d	4.7 (2.5)	4.8 (2.5)	.33
Total calcium intake from food frequency questionnaire and dietary supplements, mg/d	1123.7 (686.8)‡	1117.5 (662.9)	.33
Total dietary folate equivalent from food frequency questionnaire and dietary supplements, µg/d	541.6 (421.1)‡	541.2 (423.4)	.93
Total carotenoids (alpha carotene, beta carotene, beta cryptoxanthin, lutein, and zeaxanthin), µg/mL per d	0.68 (0.42)§	0.67 (0.42)‖	.40

Abbreviations: CaD, calcium and vitamin D; E+P, estrogen plus progestin; GED, general equivalency diploma; WHI, Women's Health Initiative.
*Percentages may not sum to 100% because of rounding error.
†Test of association from χ^2 test (categorical variables) or *t* test (continuous variables), excluding categories of missing values.
‡n = 19 469.
§n = 1068.
‖n = 1662.

nations was not dictated by the WHI protocol. Decisions regarding screening and diagnostic workups for colorectal cancer were made by the women's personal physicians.

Definitions of Outcomes and Subgroups

The primary study outcome was invasive colorectal cancer incidence; subclassifications of colorectal cancer were secondary outcomes. These include groupings within the intestinal tract of distinct etiology[20]; namely, invasive cancer of the proximal colon (cecum, ascending colon, hepatic flexure of colon, transverse colon, splenic flexure), of the distal colon (descending colon, sigmoid colon),[21-23] and of the rectum, including rectosigmoid junction.[24] Results are also presented for total cancer incidence, total cancer mortality, total mortality, and a global index to provide a context for the colorectal cancer results. Throughout the trial, a global index end point was monitored. This consisted of the first to occur of invasive breast cancer, colorectal cancer, coronary heart disease, or death from other causes. The intervention effects on breast cancer and cardiovascular disease are reported separately.[25,26]

Potential interactions were explored in subgroups of participants identified prior to analysis. These were baseline health characteristics known to influence colorectal cancer risk and baseline dietary patterns. Two post hoc interactions were also examined with composite variables of baseline hormone therapy use and assignment to the active treatment group in the hormone therapy trial.

Statistical Analysis

The protocol-designated analysis to evaluate the efficacy of the low-fat eating pattern intervention was a weighted log-rank test, with weights defined by time since randomization as 0 at randomization rising linearly to 1 at 10 years of follow-up, and constant (at 1) thereafter. Design assumptions included a linear dependence of colorectal cancer risk on percentage of energy from fat, with 80% lower colorectal cancer incidence for a 20%- compared with a 40%-energy-from-fat diet (from observational studies[2,5,9]). Information from the Women's Health Trial[27] suggested that women in the intervention group would consume a 13% lower percentage of energy from fat in the intervention compared with the comparison group at 1 year, which was projected to decrease linearly to an 11% difference by 10 years. With a sample size of 48 000 women, the study had 90% power to detect a 20% relative reduction in colorectal cancer incidence over a mean 9 years of follow-up.[11]

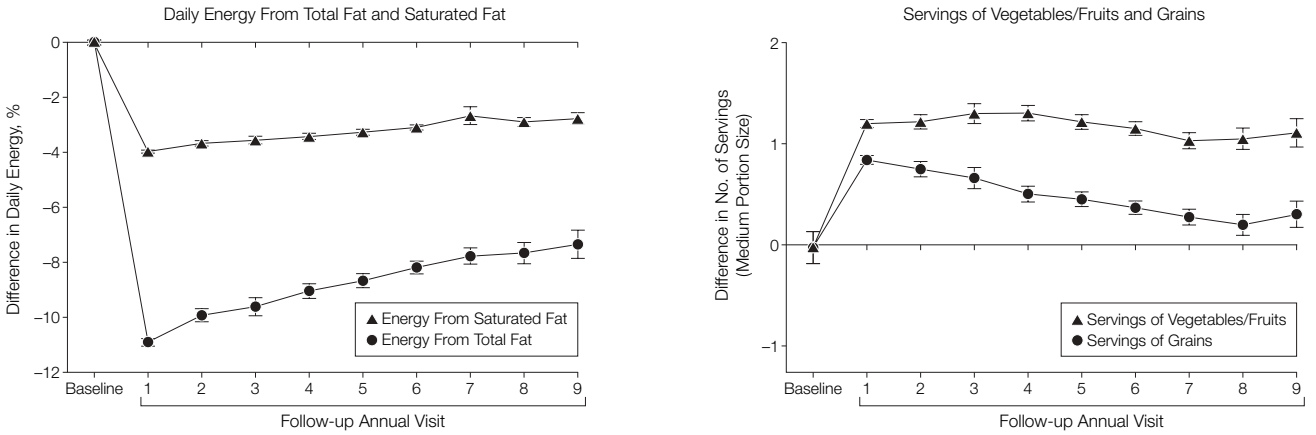
Intervention effects on incidence rates were assessed using time-to-event methods based on the intention-to-treat principle. Women without the diagnosis were censored for that event at the time of their last follow-up contact. Comparisons of rates of colorectal cancer (intervention effects) are presented as hazard ratios (HRs) and nominal 95% confidence intervals (95% CIs) from Cox regression models, stratified by age, prior colorectal cancer, and randomization status in the hormone therapy trial. Although history of colorectal cancer was an exclusion criterion, after randomization, 16 women were found to have reported prior colorectal cancer. Consistent with the intention-to-treat principle, these women were included as a separate stratum in the Cox models, but these women reported no further diagnoses of colorectal cancer. Adjustment for participation in the calcium and vitamin D trial was based on the randomization date as a time-dependent covariate. Cumulative disease rates over time were estimated using the Kaplan-Meier method. Annualized incidence rates were calculated as the ratio of number of events to total person-years of follow-up. Since colon cancer has a long preclinical phase,[28] perhaps as long as 10 years, analyses exploring variation in intervention effect by period of follow-up were conducted by classifying events into early (0-24 months), middle (25-60 months), and late (≥61 months) follow-up. A test for trend with time was used to assess departure from nonproportional effects.

Tests for interactions were performed as likelihood ratio tests in ex-

panded Cox models. Continuous variables were tested on the original linear scale but are described with relevant categories. Subgroups using baseline dietary factors obtained from 4-day food records were analyzed using a case-only approach,[29,30] essentially equivalent to a test that would arise from a "full-cohort" analysis of interaction. Because about 23 interactions were tested, at least 1 significant test would be expected to occur by chance at the .05 level of significance.

We examined the extent to which the intervention was associated with change

Figure 2. Differences in Mean Dietary Intake Between Intervention and Comparison Groups for Each Year of Follow-up



Differences were calculated by subtracting comparison group data from intervention group data. Error bars indicate 95% confidence intervals.

Table 2. Percentage Changes From Baseline to Year 3 for Dietary Factors and Selected Biomarkers Related to Colorectal Cancer Risk*

Risk Factors	Baseline, Mean (SD)		Year 3, Mean (SD)		Change at Year 3, %		
	Intervention	Comparison	Intervention	Comparison	Intervention, Mean (SD)	Comparison, Mean (SD)	Difference, Mean (95% Confidence Interval)
Dietary Factors							
Total energy, kcal/d	1790.2 (710.1)	1789.4 (703.0)	1495.9 (546.1)	1581.9 (647.5)	−10.0 (33.6)	−6.0 (35.1)	−4.1 (−5.6 to −2.5)†
Fiber, g/d	15.4 (6.4)	15.4 (6.4)	17.9 (7.7)	14.8 (6.5)	25.8 (60.7)	1.9 (44.4)	23.8 (21.6 to 26.1)†
Daily energy from fat, %	37.8 (5.1)	37.8 (5.0)	26.7 (7.9)	36.2 (7.1)	−28.6 (20.7)	−3.2 (18.5)	−25.4 (−26.3 to −24.5)†
Daily energy from saturated fat, %	12.7 (2.5)	12.7 (2.5)	8.8 (3.0)	12.1 (3.0)	−28.9 (24.8)	−2.4 (23.1)	−26.4 (−27.5 to −25.4)†
Servings/d							
Red meat	0.9 (0.6)	0.9 (0.6)	0.6 (0.4)	0.8 (0.6)	−9.7 (128.4)	10.5 (114.1)	−20.2 (−25.5 to −14.8)†
Fish	0.3 (0.3)	0.3 (0.2)	0.3 (0.2)	0.3 (0.2)	39.3 (175.8)	43.2 (218.8)	−3.9 (−13.1 to 5.2)
Poultry	0.4 (0.3)	0.4 (0.3)	0.4 (0.3)	0.4 (0.3)	25.6 (151.9)	23.3 (166.4)	2.3 (−4.9 to 9.5)
Vegetables and fruits	3.6 (1.8)	3.6 (1.8)	5.2 (2.5)	3.9 (2.0)	67.7 (134.1)	20.3 (89.2)	47.4 (42.5 to 52.2)†
Fruit	1.6 (1.0)	1.6 (1.1)	2.6 (1.5)	1.8 (1.2)	156.6 (542.9)	57.5 (295.7)	99.1 (80.8 to 117.5)†
Vegetables	2.0 (1.1)	2.0 (1.1)	2.6 (1.5)	2.1 (1.2)	60.1 (168.3)	22.7 (120.9)	37.4 (31.1 to 43.7)†
Grains	4.7 (2.5)	4.8 (2.5)	4.6 (2.5)	4.0 (2.2)	15.5 (80.6)	−2.0 (123.5)	17.6 (12.7 to 22.4)†
Vitamin E, mg/d	9.1 (5.7)	9.1 (5.5)	7.3 (5.4)	8.1 (5.0)	−9.1 (72.0)	2.0 (63.8)	−11.2 (−14.2 to −8.2)†
Dietary folate equivalent, μg/d	541.6 (421.1)	541.2 (423.4)	872.4 (480.8)	815.2 (492.7)	133.5 (210.0)	116.7 (192.4)	16.9 (7.8 to 25.9)†
Biomarkers							
Total cholesterol, mg/dL‡	224.0 (36.5)	224.2 (39.2)	214.1 (35.3)	216.6 (35.9)	−3.6 (14.0)	−2.1 (13.6)	−1.5 (−2.9 to −0.1)§
Triglycerides, mg/dL‡	155.8 (85.7)	158.5 (87.2)	161.2 (106.6)	159.6 (76.3)	8.9 (41.4)	8.3 (40.6)	0.6 (−3.5 to 4.6)
Total carotenoids, μg/mL‡	0.7 (0.4)	0.7 (0.4)	0.7 (0.4)	0.6 (0.4)	6.7 (49.5)	1.1 (47.2)	5.7 (0.8 to 10.5)§
γ-Tocopherol, μg/mL‡	2.2 (1.4)	2.2 (1.4)	1.6 (1.4)	1.7 (1.3)	−21.7 (52.8)	−5.2 (102.2)	−16.5 (−24.4 to −8.7)†
Weight, kg	76.8 (16.6)	76.7 (16.5)	75.7 (17.1)	76.7 (16.8)	−0.7 (11.0)	1.2 (11.5)	−1.8 (−2.1 to −1.6)†

SI conversions: To convert total cholesterol to mmol/L, multiply by 0.0259; to convert triglycerides to mmol/L, multiply by 0.0113.
*Dietary data were estimated using a food frequency questionnaire.
†Difference is significant at $P<.001$ by 2-sample t test using log-transformed values.
‡Measured in a 5.8% subsample (n = 2816). Means (SDs) are weighted by race/ethnicity using the racial/ethnic distribution of participants randomized to the entire trial. Tests of differences between the randomization groups were performed on the weighted means (SDs).
§Difference is significant at $P<.05$ by 2-sample t test using log-transformed values.

in other hypothesized dietary risk factors for colorectal cancer, including biomarkers. Differential changes at 3 years were expressed as a percentage of initial mean.

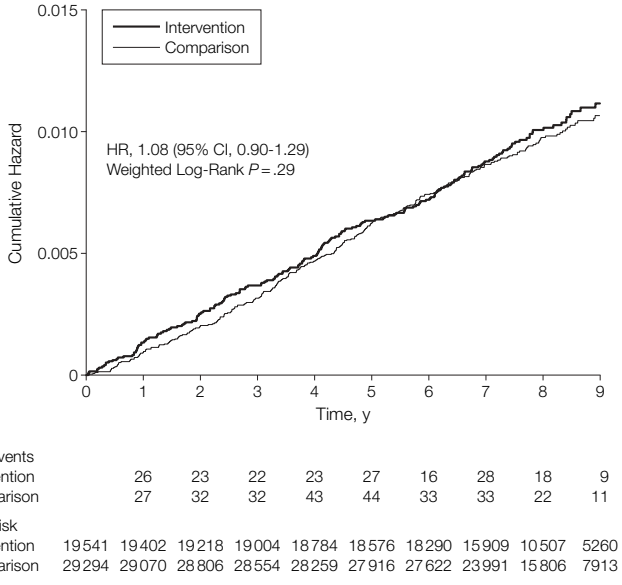
Analyses were carried out using SAS statistical software, version 9.1 (SAS Institute Inc, Cary, NC). $P<.05$ was considered statistically significant for all analyses.

Table 3. Annualized Incidence Rate of Outcomes in Intervention vs Comparison Groups

Outcomes	Intervention, No. (%) (n = 19 541)*	Comparison, No. (%) (n = 29 294)*	Hazard Ratio (95% CI)†
Invasive colorectal cancer‡	201 (0.13)	279 (0.12)	1.08 (0.90-1.29)
Colon cancer	153 (0.10)	218 (0.09)	1.05 (0.85-1.30)
Proximal colon (C18.0, C18.2-C18.5)§	106 (0.07)	127 (0.05)	1.25 (0.96-1.61)
Distal colon (C18.6, C18.7)§	41 (0.03)	76 (0.03)	0.86 (0.56-1.19)
Rectal cancer	50 (0.03)	67 (0.03)	1.11 (0.77-1.61)
Rectosigmoid junction (C19.9)§	17 (0.01)	21 (0.01)	1.18 (0.62-2.23)
Rectum (C20.9)§	33 (0.02)	47 (0.02)	1.06 (0.68-1.65)
Other (overlapping lesions/unknown/missing)	8 (0.01)	12 (0.01)	ND
Colorectal cancer mortality‖	47 (0.03)	56 (0.02)	1.26 (0.85-1.85)
Incidence of polyps/adenomas¶	3402 (2.16)	5567 (2.35)	0.91 (0.87-0.95)
Total cancer incidence	1946 (1.24)	3040 (1.28)	0.97 (0.89-1.05)
Total cancer mortality	436 (0.28)	690 (0.29)	0.96 (0.90-1.01)
Global index#	2051 (1.30)	3207 (1.35)	0.95 (0.90-1.01)
Total mortality	950 (0.60)	1454 (0.61)	0.97 (0.89-1.05)

Abbreviations: CI, confidence interval; ND, analysis not done because the events were not part of the major subdivisions of invasive colorectal cancer.
*Mean follow-up time for both groups was 8.1 (SD, 1.7) years.
†Cox regression models stratified according to age group, prior colorectal cancer, and hormone therapy study participation; calcium and vitamin D study participation was adjusted as a time-dependent variable.
‡Earliest event from all possible subsites.
§C18 indicates cecum; C18.2, ascending colon, right colon; C18.3, hepatic flexure of colon; C18.4, transverse colon; C18.5, splenic flexure of colon; C18.6, descending colon, left colon; C18.7, sigmoid colon; C19.9, rectosigmoid junction; C20.9, rectum, not otherwise specified.
‖All colorectal cancer–related mortality, with or without prior reporting of colorectal cancer.
¶Self-reported outcomes only.
#Global index is defined as the first of invasive breast cancer, any colorectal cancer, coronary heart disease, or death due to other causes.

Figure 3. Kaplan-Meier Estimated Cumulative Hazards for Invasive Colorectal Cancer (N=48 835)



HR indicates hazard ratio; CI, confidence interval.

RESULTS

A total of 19 541 women (40%) were assigned to the intervention group and 29 294 (60%) were assigned to the comparison group. The last intervention session was held in August 2004, and end points were accrued to the study through March 2005. Mean length of follow-up was 8.1 (SD, 1.7) years (maximum, 11.2 years).

Baseline Characteristics

Colorectal cancer risk characteristics were very similar in the 2 study groups, including age, self-reported race/ethnicity, education, family history of colorectal cancer, prior colorectal cancer screening, alcohol use, and mean intake of energy, fat, fiber, red meat, vegetables and fruits, grains, calcium, and folate (TABLE 1). There were small imbalances in 3 characteristics: reported use of aspirin at baseline with respect to both frequency ($P=.03$) and duration ($P=.01$), proportion of women randomized to the various groups in the hormone therapy trials ($P=.05$), and proportion of women subsequently joining the randomized trial of calcium and vitamin D supplementation ($P<.001$).

Dietary Behavior Change

By the end of the first year, the difference in percentage of energy from fat between the comparison group and the interventions groups was 10.7% (FIGURE 2). During the entire intervention period, the differential reduction in percentage of energy from fat was about 70% of the design goals of the trial. Relatively few women met the dietary target of 20% energy from fat (31.4% at year 1 and 14.4% at year 6). Reductions in saturated fat consumption and increases in fruit and vegetable servings and servings of grain (Figure 2) were statistically significant by 1 year. The intervention was also associated with statistically significant increases in dietary intake of folate and in plasma total carotenoids and reductions in reported red meat consumption, total vitamin E intake, weight, serum cholesterol, and plasma γ-tocopherol (TABLE 2).

Colorectal Cancer Risk and Other Clinical Outcomes

As of March 31, 2005, there were 201 cases of invasive colorectal cancer (0.13% per year) in the intervention group and 279 (0.12% per year) in the comparison group, similar to national statistics for women in this age range (0.12%).[19] The WHI low-fat eating pattern intervention did not reduce the risk of invasive colorectal cancers (HR, 1.08; 95% CI, 0.90-1.29) (TABLE 3). Adjustment for the small imbalance in aspirin use did not alter these results (HR, 1.08; 95% CI, 0.90-1.29). The cumulative hazards for colorectal cancer in the 2 groups were very similar over follow-up time (weighted $P=.29$) (FIGURE 3). There was no evidence of a time trend for invasive colorectal cancer in secondary analyses ($P=.60$ for trend), with HRs in the early, middle, and late periods of 1.24 (95% CI, 0.85-1.81), 0.91 (95% CI, 0.68-1.22), and 1.19 (95% CI, 0.89-1.60), respectively.

There was no evidence of reduced risk for any category of colorectal cancer outcome associated with the intervention. The estimated intervention effects in proximal and distal colon cancer were somewhat different (HRs, 1.25 vs 0.86; $P=.07$ from likelihood ratio test), but there was no other evidence of differential effect by colorectal cancer subsite. None of the HRs for total cancer incidence, total cancer mortality, global index, or total mortality were statistically significant. The annualized incidence rates of colon polyps or adenomas (self-report) were lower in the intervention group than in the comparison group (2.16% vs 2.35%, respectively; HR, 0.91; 95% CI, 0.87-0.95). No differences were seen between groups for tumor characteristics (TABLE 4).

Colorectal clinical examination rates were similar between the intervention groups (FIGURE 4). There were small differences in the percentage of women with no colonoscopy or sigmoidoscopy during follow-up (45.7% for intervention vs 44.1% for comparison; $P=.04$). Overall, 10.6% in the intervention group and 9.9% in the comparison group had neither colon nor rectal screenings during follow-up ($P=.30$).

Subgroup Analyses

Among the 23 subgroups examined, only the interactions with aspirin use and the composite variable of combined hormone use (personal use at baseline or randomization to active estrogen plus progestin) were significant at the .01 level (FIGURE 5). Although the risk of colon cancer increased with age, there was no interaction of intervention with age at baseline ($P=.18$). Intervention HRs were not significantly different among the 4 different racial/ethnic groups with sufficient numbers of events ($P=.78$). The estimated intervention effect was lower in baseline high-dose aspirin users compared with that in nonusers ($P=.01$); however, the higher incidence observed (0.19%) in this subgroup of comparison women is an anomaly, suggesting that other factors may be relevant. No interaction was seen with duration of aspirin use, statin use, or nonaspirin nonsteroidal anti-

Table 4. Annualized Incidence Rate of Invasive Colorectal Cancer by Tumor Characteristics in Intervention vs Comparison Groups

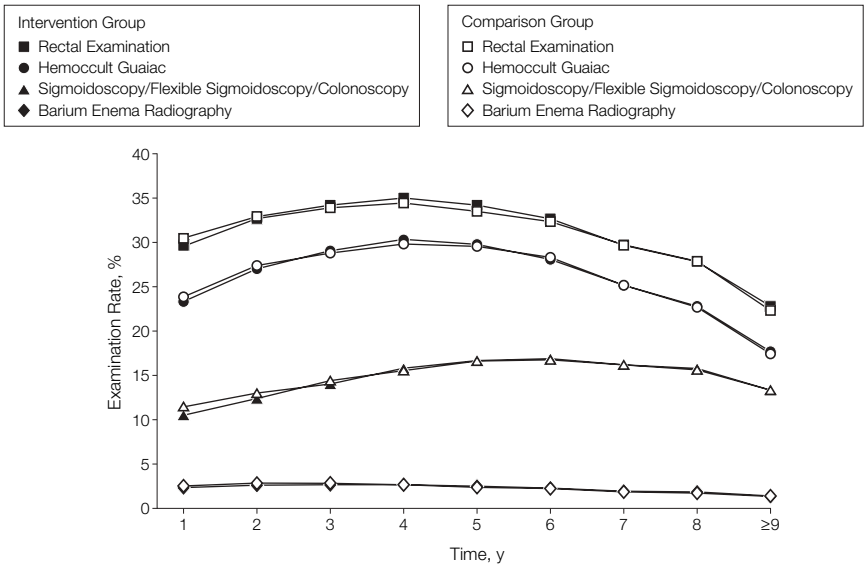
Variables	No. (%) Intervention (n = 19 541)	No. (%) Comparison (n = 29 294)	Hazard Ratio (95% CI)*
Histology			
8140/8210/8220/8261/8263 Adenocarcinoma†	171 (0.11)	226 (0.09)	1.13 (0.93-1.38)
8480/8481 Mucinous†	22 (0.01)	41 (0.02)	0.80 (0.48-1.34)
Other (8010/8020/8490/missing data)†	8 (0.01)	12 (0.01)	ND
SEER stage			
Localized	93 (0.06)	119 (0.05)	1.17 (0.89-1.53)
Regional	77 (0.05)	113 (0.05)	1.02 (0.76-1.36)
Distant	25 (0.02)	35 (0.01)	1.08 (0.64-1.80)
Missing data	6 (<.01)	12 (0.01)	ND
Tumor grade			
Well differentiated	19 (0.01)	23 (0.01)	1.25 (0.68-2.29)
Moderately differentiated	117 (0.07)	173 (0.07)	1.01 (0.80-1.28)
Poorly differentiated/anaplastic	46 (0.03)	58 (0.02)	1.19 (0.81-1.76)
Missing data	19 (0.01)	25 (0.01)	ND
Tumor size, cm			
<3	35 (0.02)	41 (0.02)	1.26 (0.80-1.98)
3-3.9	26 (0.02)	48 (0.02)	0.81 (0.50-1.30)
4-5.9	47 (0.03)	58 (0.02)	1.22 (0.83-1.80)
≥6	30 (0.02)	54 (0.02)	0.82 (0.52-1.28)
Missing data	63 (0.04)	78 (0.03)	ND
Lymph node involvement			
No	121 (0.08)	157 (0.07)	1.15 (0.91-1.46)
Yes	65 (0.04)	94 (0.04)	1.04 (0.76-1.43)
Missing	15 (0.01)	28 (0.01)	ND
No. of positive lymph nodes			
0	109 (0.07)	148 (0.06)	1.10 (0.86-1.41)
1-2	32 (0.02)	44 (0.02)	1.10 (0.70-1.74)
≥3	27 (0.02)	45 (0.02)	0.90 (0.56-1.46)
Unknown/missing data	33 (0.02)	42 (0.02)	ND

Abbreviations: CI, confidence interval; ND, analysis not done because the events were not part of the major histological groupings or were related to missing codes for stage, grade, etc; SEER, Surveillance, Epidemiology, and End Results.

*Cox regression models stratified according to age group, prior colorectal cancer, and hormone therapy study participation; calcium and vitamin D study participation was adjusted as a time-dependent variable. None of the carcinoma characteristics had significant interactions with intervention effect by χ^2 test on the case frequencies ($P>.05$).

†Histology code details[19]: 8140, adenocarcinoma, not otherwise specified ; 8210, adenocarcinoma in adenomatous polyp; 8220, adenocarcinoma in adenomatous polyposis coli; 8261, adenocarcinoma in villous adenoma; 8263, adenocarcinoma in tubulovillous adenoma; 8480, colloid (mucinous); 8481, mucin-secreting; 8010, carcinoma; 8020 carcinoma, undifferentiated, not otherwise specified; 8490, signet-ring cell.

Figure 4. Bowel Examinations by Dietary Intervention vs Comparison Group and Follow-up Year



inflammatory drug use at baseline, or with aspirin use during follow-up, examined as a time-dependent covariate.

Using data from the baseline 4-day food record of cases, no interactions with intervention effect were found with energy intake, percentage of energy from fat, percentage of energy from saturated fat, or dietary fiber. Similarly, using baseline food frequency questionnaire data, there were no interactions with servings of vegetables and fruits (FIGURE 6), of red meat, or of grains or folate intake. The interaction test with baseline alcohol consumption was not significant ($P = .09$) and did not appreciably change when folate intake was considered.

Further Analyses

To explore the effect of nonadherence to trial activities, a Cox regression model was fit censoring follow-up for a participant when she first became nonadherent (did not attend the annual clinic visit or, for intervention women, completed 50% or fewer intervention sessions in a given year). Inverse censoring probability weights, derived from Cox regression models of 18 baseline variables (demographic, dietary, psychosocial, family history of colorectal cancer, physical activity, body mass index, alcohol consumption, multivitamin use, and randomization into the hormone therapy trial) for intervention and comparison groups separately, were used to adjust for the imbalance created by the adherence censoring.[25]

Adherence rates from these models were 85%, 75%, and 66% at years 3, 6, and 9, respectively, among comparison women and 61%, 37%, and 25% among intervention women. The difference between adherent intervention vs adherent comparison women in percentage of energy from fat (from the food frequency questionnaire) was 12.1%, 11.4%, 10.4%, and 9.5% at years 1, 3, 6, and 9. The HR for colorectal cancer from the inverse probability–weighted analysis was 1.09 (95% CI, 0.88-1.36). Exploratory analyses using other adherence measures did not appreciably change the interpretation.

COMMENT

An intervention aimed toward a low-fat eating pattern did not reduce colorectal cancer risk in postmenopausal women. Despite a significant change in fat intake and increases in vegetable, fruit, and grain consumption, the intervention hazard ratio is in the direction of an increased risk. There were no substantial differences in tumor characteristics or in rates of bowel screening between groups. Although self-reported incidence of colorectal polyps or adenomas was lower in the intervention group, no evidence of a trend toward lower colorectal cancer risk with time in the intervention group was observed over the mean 8.1-year study period.

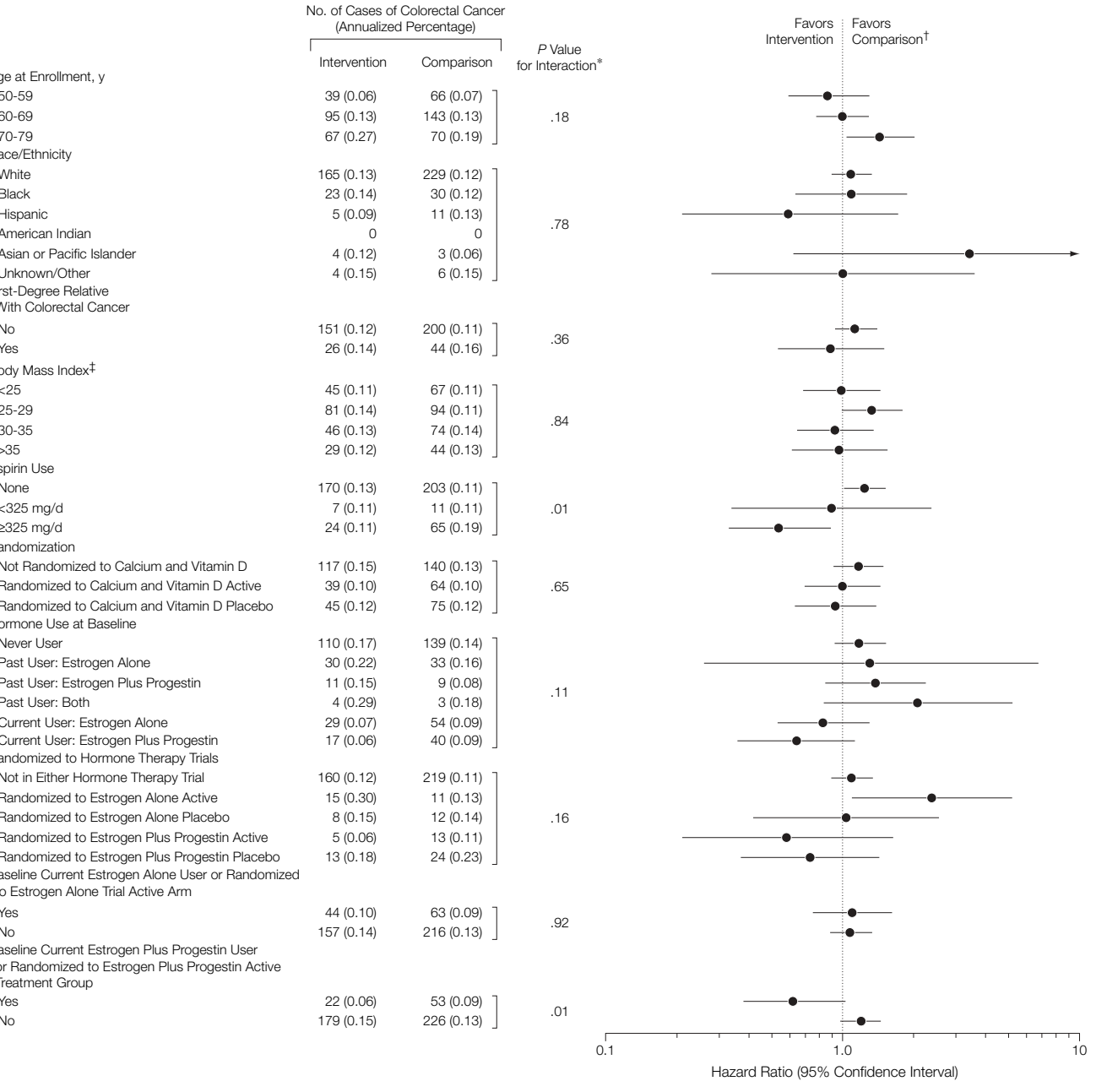
These findings are consistent with the findings from the Polyp Prevention Trial,[31] a secondary prevention trial of polyp recurrence, which had a similar goal for fat, fruit, and vegetable intake but also included a goal of 18 g/1000 kcal of dietary fiber.[32] The Polyp Prevention Trial observed no effect on polyp recurrence in the 2079 participants followed up for 4 years.[32] A small trial in Toronto, Ontario, of high fiber and low fat showed no effect on recurrence of neoplastic polyps, but, within an intensive counseling subgroup, concentrations of fecal bile acids appeared to be reduced.[33] A small factorial trial in Australia of a low-fat intervention, β-carotene supplementation, or wheat bran supplementation found no reduction in recurrence rates of adenomas but suggested that the combination of low fat and wheat bran reduced the transition from smaller to larger adenomas.[34]

Since the WHI Dietary Modification Trial was designed, the hypothesized relationship between dietary fat and risk of colorectal cancer has been questioned.[35] More recently, higher red meat consumption has been associated with increased colorectal cancer risk,[23,36-39] particularly in the distal colon.[23] The putative mechanism may be related to heme, the iron carrier of red meat, rather than to its fat content.[23] In the WHI, the dietary intervention reduced red meat consumption (Table 2), with no apparent overall benefit on colorectal cancer risk but, perhaps, some shift in risk in distal vs proximal colon cancers.

Mixed support exists for an influence of vegetables and fruits on colorectal cancer risk.[37,40-42] Some of the antioxidants they contain have not proved efficacious in reducing colorectal adenomas or preventing incident colorectal can-

cer in randomized trials.[43-45] Regular consumption of alcohol has been associated with elevated risk of colorectal cancer in some prospective studies, particularly among persons with low folate status.[46] This pattern was not found in the comparison group of this study. Observations in East Africa by Burkitt[47] led to the hypothesis that very high fiber reduces colorectal cancer risk. This has mixed support from observational studies[48-50] and polyp and adenoma recurrence trials.[31,33,34,51,52] A European trial found an adverse effect of soluble fiber on colorectal adenoma recurrence,[51]

Figure 5. Invasive Colorectal Cancer Hazard Ratios and Annualized Incidence by Baseline Demographic and Medical History Characteristics



Error bars indicate 95% confidence intervals.
*Interaction test from likelihood ratio test (factors on the continuous scale were tested as continuous variables when possible.
†Cox regression models stratified according to age group, hormone therapy study participation, and prevalence condition; calcium and vitamin D study participation was adjusted as a time-dependent variable.
‡Body mass index was calculated as weight in kilograms divided by the square of height in meters.

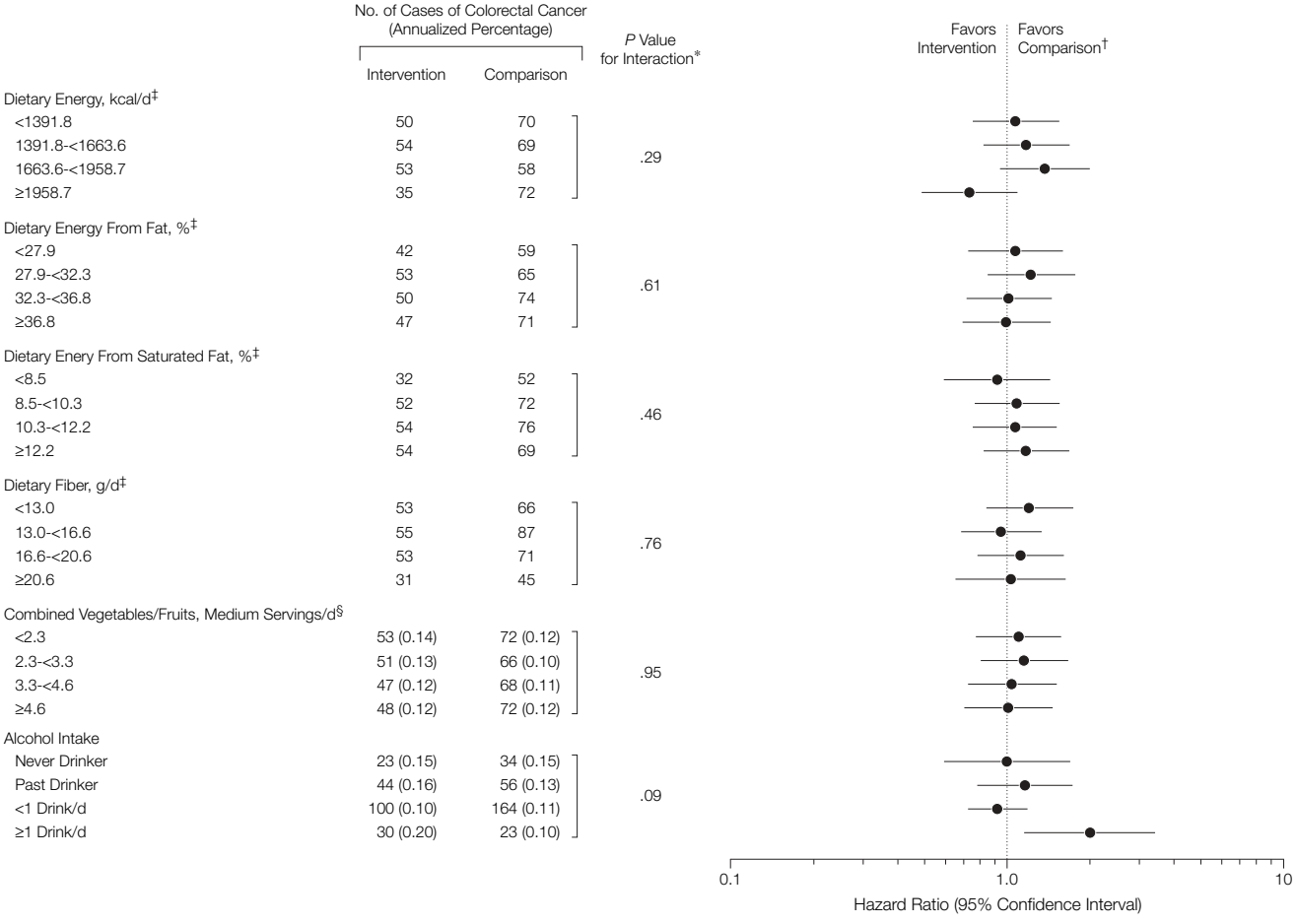
while an Arizona trial found no effect of wheat bran supplement on colorectal adenoma recurrence.[52] Our study is consistent with lack of association in that women in the intervention group modestly increased their fiber (Table 2) with no apparent benefit over 8.1 years of follow-up.

The observed interactions between the intervention and baseline aspirin use, and between intervention and use of combined hormone therapy, are consistent with synergistic effects of a low-fat dietary pattern and these potentially protective agents. However, given the large number of interactions tested, these findings could also have occurred by chance.

While the trial was ongoing, national dietary recommendations moved from recommending less than 30% of energy from fat intake through 1997 to 25% to 35% of energy from fat in 2002.[53] From National Health and Nutrition Examination Survey (NHANES) data, in 1977, women reported consuming 40.5% of their energy from fat, while in 1987, the average was only 35.9%,[54] and in 2000, the average was 33% (NHANES 1999-2000). Organizations including the National Cancer Institute, American Cancer Society, and Institute for Cancer Prevention have recommended both lower fat intake and increased vegetable and fruit use.[55,56]

One explanation for a lack of intervention effect on colorectal cancer could be that the intervention did not achieve a large enough difference between the intervention and comparison groups. Although the changes achieved were substantial, and likely as large as could be achieved in a trial of free-living individuals, they fell short of the original design assumptions based on the Women's Health Trial studies.[27] Using food frequency data, the WHI intervention on average achieved only about

Figure 6. Invasive Colorectal Cancer Hazard Ratios and Annualized Incidence by Baseline Dietary Factors



Error bars indicate 95% confidence intervals.
*Interaction test from likelihood ratio test (factors on the continuous scale were tested as continuous variables when possible.
†Cox regression models stratified according to age group, hormone therapy study participation, and prevalence condition; calcium and vitamin D study participation was adjusted as a time-dependent variable.
‡Case-only analysis using 4-day food record data; no annualized rates available.
§Data are from food frequency questionnaire.

70% of the designed reduction in fat. If design assumptions are revised to take into account this departure from goal, the predicted HR would have been 0.86, an effect size excluded by these results. The power to detect this effect size under the observed comparison group incidence rate and the achieved adherence is approximately 40%.

Whether greater adherence, intervention of longer duration, or initiation of change at an earlier age would influence colorectal cancer risk remain unanswered questions. The self-reported first occurrence of polyps or adenomas was lower in dietary intervention women, suggesting that longer follow-up (currently planned) may reveal delayed benefit in favor of the intervention. Yet no time trends regarding colorectal cancer risk over 8 years of follow-up have been seen. To the extent that the WHI Dietary Modification Trial intervention addressed the recommendations from national organizations, the current results suggest that changing dietary patterns to meet these recommendations in mid to late life will have limited or no benefit in preventing colorectal cancers in postmenopausal women.

The strengths of this study are its randomized design, long-term follow-up, large numbers of participants, diversity of race/ethnicity and socioeconomic status, and high retention rate. The limitations of this study include not attaining intervention goals as designed for reducing fat intake or achieving large separation from the comparison group in increased fruit, vegetable, or grain intake. Thus the potential intervention effect of the WHI low-fat dietary pattern may be underestimated. Furthermore, there was no study-specified colonoscopy, nor was there systematic screening for adenomatous polyps; hence, the incidence of both colorectal cancer and polyps or adenomas would be underestimated.

In conclusion, there is no evidence that a low-fat dietary pattern intervention reduces colorectal cancer risk over an average of 8.1 years of follow-up. Evidence from this study, along with that from polyp prevention trials, strongly suggests that lowering dietary fat intake and increasing fruit, vegetable, and fiber intake in mid to late life cannot be expected to reduce the risk of colorectal cancer in this length of time.

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