Intake of Supplemental and Total Fiber and Risk of Colorectal Adenoma Recurrence in the Wheat Bran Fiber Trial[1]

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Abstract

The Wheat Bran Fiber (WBF) trial was a double-blind Phase III clinical trial in which participants were randomized to a cereal fiber supplement of either 13.5 or 2.0 g/day. No protective effect for adenoma recurrence was observed for those randomized to the high-fiber group as compared with those in the low-fiber group. However, the high-fiber group had significantly lower adherence to the supplement as assessed by cereal box counts. The aim of this study was to determine whether reported supplemental and total fiber intake affected colorectal adenoma recurrence in the WBF trial population, regardless of treatment group assignment. A total of 1208 participants who completed the WBF trial had a colonoscopy before the date of the last cereal box count and/or at least one colonoscopy within 90 days after it and, thus, were eligible for the current analyses. Statistical analyses were done using multivariate logistic regression models that included potentially confounding variables. Compared with individuals consuming less than 1.8 g/day of supplemental fiber, the adjusted odds ratio (95% confidence interval) for adenoma recurrence for those consuming greater than 11.0 g/day was 0.94 (0.66–1.33). The odds ratio (95% confidence interval) for participants whose total fiber intake was greater than 30.3 g/day was 0.98 (0.68–1.42) compared with those whose intake was less than 17.9 g/day. The results of this study show that neither fiber intake from a wheat bran supplement nor total fiber intake affects the recurrence of colorectal adenomas, thus lending further evidence to the body of literature indicating that consumption of a high-fiber diet, especially one rich in cereal fiber, does not reduce the risk of colorectal adenoma recurrence.

Introduction

With an estimated 130,200 cases of colorectal cancer and 56,300 deaths from this disease in 2000 (1), colorectal cancer is the third most common cause of cancer mortality in the United States (2). The association between diet and colorectal cancer or adenomatous polyps has long been investigated. Specifically, dietary fiber has been the focus of numerous studies since it was first introduced as a potentially protective dietary component by Denis Burkitt in 1971 (3). He observed that diseases of the bowel, including colon cancer, were rare in Africa where a high-fiber diet was consumed (3). Many correlational and case-control epidemiological studies supported this hypothesis (4–10); however, several prospective studies have yielded equivocal results (11, 12) Recently, the results of two randomized clinical trials failed to show a protective effect of increased fiber and/or decreased fat in the diet on the risk of adenomatous polyp recurrence (13, 14). In the Polyp Prevention Trial, there was no reduction in risk of colorectal adenoma recurrence with consumption of a low-fat, high-fiber diet (14). In the WBF[3] trial, there was no difference in the rate of recurrent adenomatous polyps between those randomized to consume a high-fiber supplement as compared with those in the low-fiber group (13).

The primary analysis of the WBF trial was performed using the intention-to-treat principle (13), an analysis method that tests whether assignment to a treatment group affects the outcome without quantifying the amount of supplement consumed (15). To date, there have been no studies performed to determine whether the reported supplemental or total fiber intake consumed during a randomized clinical trial had an effect on adenoma recurrence. Participants in the high-fiber intervention arm of the WBF trial reported side effects such as nausea, diarrhea, and abdominal bloating more frequently than those in the low-fiber group (13). Therefore, it was hypothesized that participants in the high-fiber group may have compensated for the supplemental dose by eating less nonsupplemental fiber, thus driving the amount of total fiber consumed in the two treatment arms toward equality. The present study was performed to determine whether reported supplemental- and total fiber intake affected colorectal adenoma recurrence in the WBF trial population.

Materials and Methods

Study Design and Subjects. The WBF trial was a randomized, double-blind Phase III clinical trial designed to test

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[3] The abbreviations used are: WBF, Wheat Bran Fiber (trial); AFFQ, Arizona Food Frequency Questionnaire; CI, confidence interval.

Table 1 Baseline characteristics of WBF population (1304 participants) and those with complete adherence data by having had a colonoscopy prior to or within 90 days after the last count of unused cereal boxes (1208 participants)

Variable	1304 participants	1208 participants
Age (yrs), mean ± SD	66.6 ± 8.8	66.6 ± 8.8
Body mass index (kg/m^2), mean ± SD	26.5 ± 4.3	26.5 ± 4.3
	n (%)	*n* (%)
Group		
Low-fiber	584 (44.8)	562 (46.5)
High-fiber	720 (55.2)	646 (53.5)
Gender		
Female	432 (33.1)	393 (32.5)
Male	872 (66.9)	815 (67.5)
Race		
White	1251 (95.9)	1157 (95.8)
Other	53 (4.1)	51 (4.2)
Marital Status		
Married or cohabitating	1088 (83.4)	1005 (83.2)
Single	215 (16.5)	202 (16.7)
Education		
Some or all high-school	592 (45.4)	548 (45.4)
At least 1 year college	710 (54.5)	658 (54.5)
History of colorectal cancer in one parent or sibling		
Yes	220 (16.9)	209 (17.3)
No	1084 (83.1)	999 (82.7)
History of cancer other than colorectal cancer at least 5 years prior to study entry		
Yes	85 (6.5)	72 (6.0)
No	829 (63.6)	773 (64.0)
Years on study		
≤1.0	47 (3.6)	43 (3.6)
1.1–2.0	127 (9.7)	104 (8.6)
2.1–3.0	258 (19.8)	239 (19.8)
>3.0	872 (66.9)	822 (68.1)
Polyp Characteristics		
History of adenomas prior to baseline colonoscopy		
Yes	452 (34.7)	419 (34.7)
No	701 (53.8)	654 (54.1)
Polyp Location		
Distal only	710 (54.7)	659 (54.8)
Proximal only	350 (27.0)	322 (26.8)
Proximal and distal	238 (18.3)	221 (18.4)
Number of polyps		
One	745 (57.3)	693 (57.5)
Two	290 (22.3)	261 (21.7)
Three or more	266 (20.5)	251 (20.8)
Maximum polyp size		
<0.5 cm	400 (30.7)	363 (30.1)
0.60–1.00 cm	546 (41.9)	512 (42.4)
>1.00 cm	358 (27.5)	333 (27.6)
Lifestyle Variables		
Exercise		
At least once a week	636 (55.4)	612 (55.4)
Never	512 (44.6)	492 (44.6)
Current smoker		
Yes	178 (13.7)	152 (12.6)
No	1126 (86.4)	1056 (87.4)
Ever smoker		
Yes	683 (52.4)	637 (52.7)
No	449 (34.4)	424 (35.1)
10-yr history of regular aspirin use		
Yes	368 (28.2)	345 (28.6)
No	936 (71.8)	863 (71.4)
Dietary variables, mean ± SD		
Energy (kcal/day)	1909.3 ± 666.0	1903.6 ± 663.7
Protein (g/day)	73.4 ± 26.2	73.4 ± 26.3
Carbohydrate (g/day)	233.8 ± 87.4	233.5 ± 86.6
Fat (g/day)	72.9 ± 33.3	72.5 ± 33.3
Dietary fiber (g/day)	18.7 ± 8.2	18.8 ± 8.1
Dietary calcium (mg/day)	852.7 ± 377.7	852.7 ± 379.0
Total calcium (mg/day)	975.3 ± 441.8	977.2 ± 444.2

Table 1 Continued

Variable	1304 participants	1208 participants
Alcohol (g/day)	7.5 ± 15.3	7.4 ± 14.8
Dietary folate (μg/day)	283.3 ± 120.5	284.4 ± 120.6
Total folate (μg/day)	441.4 ± 253.1	443.4 ± 249.9
Red meat (g/day)	62.5 ± 48.9	62.4 ± 49.4

whether a high-fiber wheat bran supplement (13.5 g/day) could decrease the risk of recurrent adenomatous polyps compared with a group receiving a low-fiber supplement (2.0 g/day; Ref. 13). The design of this study has been described in detail (16). Briefly, participants were recruited from three clinics in Phoenix, Arizona beginning in September 1990. A total of 1509 eligible men and women, who had had one or more colorectal adenomas removed within 3 months before recruitment, consented to enter the 6-week run-in period (13). During the run-in period, participants were given the low-fiber WBF supplement, completed several questionnaires, and had blood drawn for later analyses (13). The AFFQ, previously evaluated for reliability and validity (17), was administered at baseline and at year 1 and year 3 of the trial (16). Adherence to supplemental fiber intake was deemed adequate for 1429 participants (95% of the 1509 who entered the run-in period), who had reported consuming at least 75% of their supplement (13). The supplement for both the high- and the low-fiber groups was supplied as a cereal formulated by the Kellogg Company and was distributed as a box with an individual daily portion (13). A total of 1304 study participants completed the trial by having at least one postrandomization colonoscopy and/or a diagnosis of colorectal cancer.

Alterations in Supplement Dose. If a participant was unable to maintain the supplemental intake level required by the protocol (2.0 g/day and 13.5 g/day in the low- and high-fiber groups, respectively), he or she was permitted a dose reduction. The amount and length of time of the reduction in dose were recorded, along with the reason for the reduction. Such reasons included the taste of the supplement, dining at locations other than the home, and adverse events such as nausea, abdominal pain, diarrhea, intestinal gas, and abdominal bloating.

In addition to reduced supplement intake, two other changes were recorded. The first was a temporary stop of the supplement consumption, for which the length of time and the reasons, including vacation, illness, and hospitalization, were recorded. The second was a permanent cessation in supplement consumption before completion of the trial. Conditions resulting in permanent cessation included reports of adverse events such as gastrointestinal distress, medical conditions, or study drop-out. The date of the permanent stop in supplement use was recorded with the reason.

Supplemental Fiber Intake. The intake of supplemental fiber was assessed using information from clinic visits that took place every 3 months. Participants brought unused cereal boxes to each visit; the boxes were then counted and used to calculate the percentage of boxes consumed using the following formula:

$$\frac{\text{Number of boxes given to participant at last visit} - \text{number of boxes returned at current visit}}{\text{Number of days since last visit}} \times 100$$

In addition, participants recorded their daily intake of supplemental fiber on a calendar; the correlation coefficient between the box counts and calendar reports was 0.82. To be eligible for this analysis, a participant had to have had at least one colonoscopy before the date of the last box count, and/or at least one colonoscopy within 90 days after it. Using these criteria, data were available for 1208 (92.6%) of the 1304 participants who completed the trial. The analysis period was the time between randomization and the colonoscopy that occurred before the last box count or within 90 days after the last box count.

To create an accurate accounting of the participants' supplemental fiber intake, all of the data regarding supplement reduction and cessation were added to the information from box counts. This analysis required that the data be assessed in time intervals, with each interval representing the number of days between box counts. In the case of a temporary stop in supplement consumption, a zero was entered for fiber intake during that time. For a supplement reduction, the number of boxes consumed per day was adjusted proportionally to the reduction. Permanent cessation of supplement resulted in an entry of zero fiber intake for the remainder of the study. The fiber dose for each time interval was then calculated using the following formula:

$$\frac{\text{Dose}}{\text{Interval}} = \left(\text{Days in interval}\right)\left(\frac{\%\text{ boxes consumed}}{100}\right) \cdot \left(\frac{\textit{boxes}}{\textit{day}} \times \frac{n\ \text{grams fiber}}{\text{day}}\right)$$

where n equaled 2.0 for participants in the low-fiber group and 13.5 for those in the high-fiber group. The total dose of supplemental fiber during the analysis period was the sum of the fiber intake for each interval.

Total Fiber Intake. Dietary fiber intake was assessed at baseline and at year 1 and year 3 using the AFFQ and remained equal between the two intervention groups throughout the trial. Data for baseline dietary fiber intake were available for all of the participants eligible for this analysis, whereas years 1 and 3 had incomplete data. Preliminary analyses indicated that using an average for dietary fiber intake from baseline, year 1, and year 3 did not affect the overall results. Therefore, the sum of the baseline value from the AFFQ and supplemental fiber intake per day was used to calculate total fiber intake. Data from supplemental fiber intake per day and total fiber intake per day were categorized into quartiles based on the distribution of the total population, and the lowest quartile was used as the reference category in logistic regression models.

Statistical Analysis. Recurrences and nonrecurrences of colorectal adenomas were ascertained from any colonoscopy that occurred after randomization but before or within 90 days of the last box count. Student's *t* test was used to compare baseline, year 1, and year 3 dietary fiber intake between the low-fiber and high-fiber intervention groups, and to compare supplemental and total fiber intake by each nondietary baseline variable. For baseline dietary intake, each variable was broken into quartiles based on the distribution of intake for the entire population. Trend analysis using linear regression was used to determine

Table 2 Intake of dietary fiber at baseline, supplemental fiber over the course of the trial, and total fiber (estimated by baseline dietary fiber intake plus supplemental fiber intake)

Fiber source	Mean ± SD	Median	Range	P^a
Baseline dietary fiber intake (g/day)				
Low-fiber group	18.9 ± 8.3	17.7	3.8–56.8	
High-fiber group	18.7 ± 8.0	17.6	3.4–55.0	0.70
Supplemental fiber intake (g/day)				
Low-fiber group	1.5 ± 0.4	1.7	0.0–2.1	
High-fiber group	9.6 ± 3.1	10.7	0.7–13.5	<0.001
Total fiber intake (g/day)				
Low-fiber group	20.4 ± 8.3	19.4	4.9–57.7	
High-fiber group	28.3 ± 8.8	27.5	7.0–66.3	<0.001

[a] *P* compares the fiber intake of the low-fiber group with that of the high-fiber group.

the association among the quartiles of dietary intake and supplemental and total fiber intake.

Data from both treatment groups were combined for statistical modeling. Logistic regression was used to determine which baseline variables were associated with both adenoma recurrence and supplemental or total fiber intake and, thus, would be considered potential confounders. The only variable that was significantly associated with both adenoma recurrence and supplemental fiber intake was number of years on study. The variables that were significantly related to both adenoma recurrence and total fiber intake were gender, age, and both dietary and total calcium intake. These variables were included in the multivariate logistic regression analyses for supplemental and total fiber intake. Other potential covariates that were considered were number of colonoscopies during the study period, regular aspirin use for 10 years, history of polyps before randomization, cigarette smoking, alcohol intake, fat intake, baseline polyp characteristics (number, size, and location), and family history of colorectal cancer in a parent or sibling. Energy adjustment of total fiber intake was performed using the nutrient residual method of Willett and Stampfer (18). In addition, logistic regression was used to assess whether supplemental or total fiber intake was associated with the recurrence of multiple or advanced adenomas.

Results

Baseline Characteristics. Table 1 shows a comparison of baseline characteristics of the 1304 participants who completed the trial protocol by having at least one postrandomization colonoscopy and/or a diagnosis of colorectal cancer and the 1208 participants who were eligible for the present analysis. There were no significant differences between the two populations with regard to any of the baseline characteristics.

Fiber Intake. An analysis was conducted to compare the differences between the low- and high-fiber groups for fiber intake from supplemental, dietary, and total fiber sources (Table 2). Dietary fiber intake decreased from baseline to years 1 and 3 by 2.7 and 2.4 g/day, respectively (data not shown). However, there were no differences in baseline dietary fiber intake between the two treatment groups (18.9 ± 8.3 and 18.7 ± 8.0 g/day), nor were there significant differences between the groups for dietary fiber intake throughout the trial. For supplemental fiber intake throughout the course of the trial, the low-fiber group consumed an average of 1.5 g/day, whereas the high-fiber group consumed a mean of 9.6 g/day, ($P < 0.001$). Similar to supplemental fiber, total fiber intake between the two groups was significantly different ($P < 0.001$). Fig. 1*A* shows that the reported supplemental fiber intake was generally lower in the low-fiber group compared with the high-fiber group. However, there was a small number of participants in the high-fiber group who took in much less supplemental fiber than would have been expected had there been full adherence to the protocol. Fig. 1*B* shows the total fiber intake for the low-and high-fiber groups. As shown, there was considerable overlap in total fiber intake between the two treatment groups.

Supplemental and Total Fiber Intake. Table 3 shows the results for the supplemental and total fiber intake by baseline characteristics for both treatment groups. Supplemental fiber intake was significantly higher among subjects who were on the study longer (*P* for trend, <0.001) and who were smokers ($P < 0.05$). Total fiber intake was significantly higher for men ($P < 0.001$), nonwhite subjects (Asian, African-American, Hispanic, Native American, and Pacific Islander; $P < 0.05$), participants who exercised at least once a week ($P < 0.01$), those who were not current smokers ($P < 0.001$), used aspirin regularly ($P < 0.05$), or were older (*P* for trend, <0.001). Furthermore, each dietary variable presented in Table 3 exhibited a significant trend for increasing intake associated with increasing total fiber intake, with the exception of alcohol.

Fiber Intake and Adenoma Recurrence. Table 4 shows the crude and adjusted odds ratios for adenoma recurrence by category of supplemental and total fiber intake. The ranges of supplemental fiber intake for the first, second, third, and fourth quartiles were 0.0–1.7, 1.8–3.4, 3.5–11.0, and 11.1–13.5 g/day, respectively. For total fiber intake, the ranges were 4.9–17.8, 17.9–23.7, 23.8–30.3, and 30.4–66.3 g/day for the first through fourth quartiles. The adjusted odds ratios for adenoma recurrence by increasing quartile of supplemental fiber intake were 1.06 (95% CI, 0.75–1.50), 1.13 (95% CI, 0.80–1.59), and 0.94 (95% CI, 0.66–1.33; *P* for trend, 0.82). For increasing quartiles of total fiber intake, the odds ratios were 0.87 (95% CI, 0.62–1.23), 0.80 (0.56–1.14), and 0.98 (0.68–1.42; *P* for trend, 0.82). No appreciable differences in the overall results were shown when energy-adjusted nutrients were used, nor did the inclusion of variables for regular aspirin use for 10 years, number of years on study, cigarette smoking, alcohol intake, total fat intake, or size and location of baseline polyps (data not shown). Furthermore, when comparing participants whose dietary fiber intake had either decreased or increased by 2 g/day with those whose intake remained stable throughout the trial, there was no effect of fiber intake on recurrence (data not shown). Finally, there was no effect of supplemental or total fiber on the recurrence of multiple or advanced adenomas (data not shown).

Discussion

To our knowledge, the present study is the first to use data from a chemoprevention trial to quantitate actual fiber intake, based on adherence records, and evaluate whether actual fiber intake was associated with colorectal adenoma recurrence. Despite a large variation in actual fiber intake, no association was found between reported intake of either supplemental or total fiber and adenoma recurrence in the WBF trial. Adjustment for potential confounding variables such as history of prior adenomas, age, number of colonoscopies, gender, and baseline polyp characteristics did not alter the results. The findings of this analysis concur with those of the primary analysis of this study population (13), as well as with reports of a null-fiber effect from other studies (11, 12, 14, 19, 20). These data, therefore, provide further evidence indicating that fiber supplementation

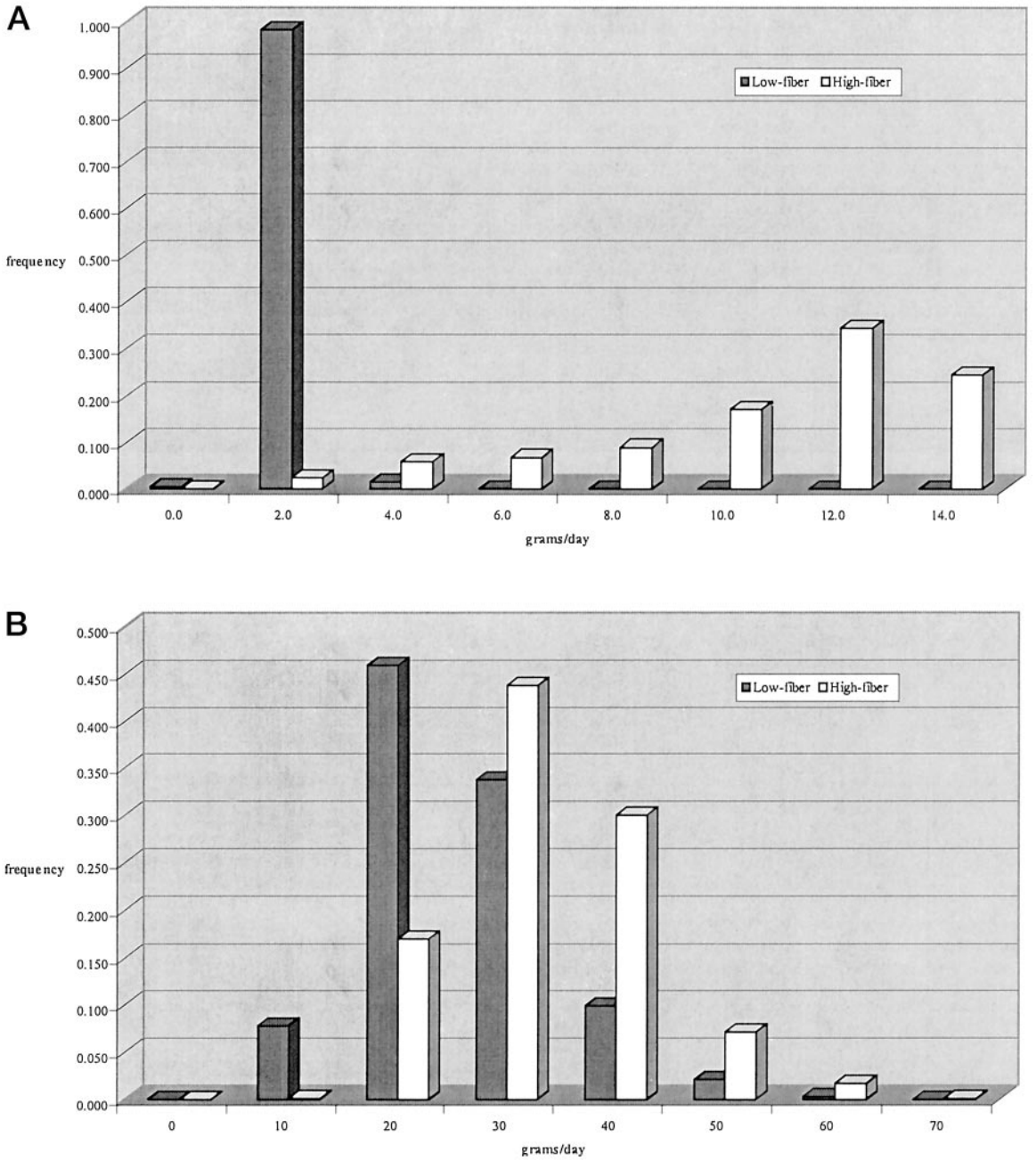

Fig. 1. Frequency histograms of supplemental and total fiber intake (*grams/day*). *A*, supplemental fiber; *B*, total fiber.

with a wheat bran supplement does not protect against colorectal adenoma recurrence.

The Food and Drug Administration and the NIH recommend that the intention-to-treat principle be used for the primary evaluation of a therapeutic agent (21). This technique requires that data from all randomized participants be used in determining the effectiveness of the treatment without assessing adherence to the treatment protocol (22). Another analysis option is examination of the amount of agent consumed by participants to determine whether there is an effect. The intention-to-treat principle is the more conservative approach to analysis; in the presence of nonadherence the results from the analysis will dilute the effect of the intervention agent (23). Therefore, investigators are now examining data by using the both the intention-to-treat approach and a secondary method that accounts for amount and/or duration of treatment (23). The primary analysis of the WBF trial was performed using the intention-to-treat paradigm, and no effect of supplemental wheat bran fiber was observed (13). It was hypothesized that the lack of effect in the primary analysis may have been partially explained by significantly lower adherence in the high-fiber group as compared with the low-fiber group in the 2nd and 3rd years of the trial (13), resulting in an overlap of total fiber intake between two treatment arms.

Table 3 Mean supplemental fiber intake and total fiber intake during the WBF trial, by baseline characteristics ($n = 1208$)

Variable	n^a	Supplemental fiber intake (g/day) Mean ± SD	Total fiber intake (g/day) Mean ± SD
Age at randomization (yr)			
40.3–61.1	302	5.7 ± 4.6	23.1 ± 9.1
61.2–68.1	302	6.3 ± 4.7	24.2 ± 9.7
68.2–73.1	302	5.8 ± 4.7	25.1 ± 9.4
73.2–81.1	302	5.7 ± 4.6	26.2 ± 9.2[b]
Gender			
Female	393	5.6 ± 4.6	23.4 ± 9.3
Male	815	6.0 ± 4.7	25.3 ± 9.4[c]
Race			
White, non-Hispanic	1157	5.9 ± 4.6	24.5 ± 9.3
Other	51	6.0 ± 4.8	27.2 ± 11.0[d]
Marital status			
Married or cohabitating	1005	5.9 ± 4.6	24.8 ± 9.4
Single	202	5.6 ± 4.6	24.0 ± 9.5
Education			
Some or all high school	548	5.7 ± 4.6	24.3 ± 9.8
At least 1 year of college	658	6.0 ± 4.7	24.9 ± 9.1
History of colorectal cancer in one parent or sibling			
Yes	209	6.0 ± 4.6	25.2 ± 9.4
No	999	5.8 ± 4.6	24.5 ± 9.4
History of cancer other than colorectal cancer at least 5 years prior to study entry			
Yes	72	6.3 ± 4.8	24.0 ± 7.9
No	773	5.9 ± 4.6	25.0 ± 9.5
Years on Study			
≤1.0	43	2.7 ± 2.5	20.9 ± 9.0
1.1–2.0	104	3.4 ± 3.2	22.9 ± 8.9
2.1–3.0	239	6.0 ± 4.5	24.7 ± 9.8
>3.0	822	6.3 ± 4.8[b]	25.1 ± 9.3[b]
Body mass index (kg/m^2)			
8.2–23.8	304	5.9 ± 4.7	25.0 ± 9.5
23.9–26.1	301	6.1 ± 4.7	24.5 ± 9.2
26.2–28.8	302	5.9 ± 4.6	24.2 ± 9.0
28.9–48.1	301	5.6 ± 4.6	24.8 ± 9.9
Polyp Characteristics			
History of adenomas prior to baseline colonoscopy			
Yes	419	5.9 ± 4.6	25.3 ± 9.5
No	654	6.0 ± 4.7	24.6 ± 9.5
Poly Location			
Distal only	659	5.9 ± 4.7	24.4 ± 9.2
Proximal only	322	5.8 ± 4.6	25.4 ± 10.4
At least one proximal polyp	221	5.9 ± 4.6	24.2 ± 8.7
Number of Polyps			
One	693	5.8 ± 4.6	24.7 ± 9.4
Two	261	6.1 ± 4.8	25.1 ± 9.6
Three or more	251	5.7 ± 4.6	24.0 ± 9.1
Maximum polyp size			
<0.5 cm	363	6.0 ± 4.7	25.2 ± 10.2
0.60–1.00 cm	512	5.8 ± 4.6	24.7 ± 9.1
>1.00 cm	333	5.9 ± 4.6	24.1 ± 8.9
Lifestyle variables			
Exercise			
At least once a week	612	6.2 ± 4.7	25.7 ± 9.2
Never	492	5.7 ± 4.6	23.9 ± 9.7[e]
Current smoker			
Yes	152	6.8 ± 4.5	22.2 ± 9.3
No	1056	5.7 ± 4.6[c]	25.0 ± 9.4[c]
Ever smoker			
Yes	637	5.8 ± 4.7	24.7 ± 9.3
No	424	5.7 ± 4.6	25.4 ± 9.4
10-yr history of regular aspirin use			
Yes	345	6.1 ± 4.7	25.6 ± 9.5
No	863	5.8 ± 4.6	24.3 ± 9.3[d]
Dietary Variables			
Energy (kcal/day)			
327.9–1437.7	302	5.7 ± 4.7	18.6 ± 7.2
1438.2–1819.6	302	5.8 ± 4.6	23.1 ± 7.6
1820.8–2260.5	302	5.9 ± 4.6	25.7 ± 7.7

Table 3 Continued

Variable	n^a	Supplemental fiber intake (g/day) Mean ± SD	Total fiber intake (g/day) Mean ± SD
2260.5–6287.8	302	6.1 ± 4.7	31.2 ± 10.1[b]
Protein (g/day)			
14.2–54.3	302	5.9 ± 4.6	18.9 ± 7.7
54.4–70.0	302	5.8 ± 4.7	23.0 ± 7.4
70.1–87.9	302	5.7 ± 4.5	25.8 ± 8.5
88.0–253.2	302	6.2 ± 4.7	31.0 ± 9.6[b]
Carbohydrate (g/day)			
45.7–173.7	302	5.8 ± 4.6	17.2 ± 6.3
173.8–223.8	302	5.9 ± 4.7	22.4 ± 6.6
224.2–278.5	302	5.9 ± 4.6	26.1 ± 6.9
278.6–729.7	302	6.0 ± 4.7	32.9 ± 9.5[b]
Fat (g/day)			
6.7–49.2	302	5.9 ± 4.7	21.8 ± 8.9
49.3–67.5	302	5.9 ± 4.6	23.4 ± 8.4
67.6–89.9	302	5.7 ± 4.6	25.6 ± 9.3
90.0–321.1	302	6.1 ± 4.6	27.9 ± 9.8[b]
Dietary Calcium (mg/day)			
125.8–595.9	302	6.0 ± 4.6	19.7 ± 7.6
596.0–815.6	302	5.8 ± 4.8	24.3 ± 8.8
815.7–1042.0	302	5.7 ± 4.6	24.9 ± 8.5
1042.1–3364.3	302	6.0 ± 4.6	29.7 ± 9.9[b]
Total calcium (mg/day)			
125.8–666.3	302	5.9 ± 4.6	20.2 ± 7.7
667.0–928.7	302	5.8 ± 4.7	24.2 ± 9.1
929.2–1162.6	302	5.5 ± 4.5	25.4 ± 8.1
1162.7–3364.3	302	6.2 ± 4.7	28.8 ± 10.4[b]
Alcohol (g/day)			
0.00–0.00	444	5.7 ± 4.7	25.6 ± 10.4
0.43–1.6	164	5.3 ± 4.5	23.5 ± 9.6
1.7–10.3	298	6.2 ± 4.6	24.6 ± 8.2
10.4–268.7	302	6.1 ± 4.6	24.0 ± 8.8
Dietary folate (μg/day)			
38.6–201.5	302	5.6 ± 4.5	17.8 ± 7.0
201.9–265.0	302	6.2 ± 4.7	23.1 ± 7.0
265.1–346.3	302	5.6 ± 4.6	25.7 ± 7.5
346.9–818.4	302	6.1 ± 4.7	32.1 ± 9.6[b]
Total folate (μg/day)			
38.6–242.7	302	5.8 ± 4.6	19.1 ± 7.2
243.0–370.6	302	5.6 ± 4.6	25.6 ± 7.8
370.9–633.3	302	6.4 ± 4.7	26.1 ± 9.7
635.2–1697.9	302	5.8 ± 4.6	27.8 ± 10.3[b]
Red meat (g/day)			
0.00–26.4	302	6.0 ± 4.7	24.5 ± 9.5
26.5–50.0	302	5.9 ± 4.6	23.7 ± 9.4
50.1–84.1	302	5.4 ± 4.6	24.6 ± 9.4
84.3–370.1	302	6.3 ± 4.7	25.8 ± 9.3[f]

[a] Numbers for each category may not add up to 1208 because of missing data for some observations.
[b] P for trend, <0.001.
[c] $P < 0.001$.
[d] $P < 0.05$.
[e] $P < 0.01$.
[f] P for trend, <0.05.

By design, there were marked differences in supplemental fiber intake between the low- and high-fiber groups. The low-fiber group was uncontaminated by participants increasing the amount of supplemental fiber; however, some participants in the high-fiber group did not consume all of their assigned fiber dose. The inability to consume the full high-fiber dose may have been related to reports of side effects resulting from the addition of 13.5 grams of fiber per day to the diet. These side effects included nausea, abdominal pain, diarrhea, intestinal gas, and abdominal bloating and were reported significantly more often in the high-fiber group compared with the low-fiber group (13). Despite a greater number of reported side effects, mean supplemental and total fiber intake remained significantly greater in the high-fiber group, indicating that most participants were able to follow the study protocol. However, there was some overlap between the two groups with regard to total fiber intake. The overlap in total fiber intake provided an intriguing area of investigation, with the possibility that no effect was observed between the two groups because there was no difference in total fiber intake between the low- and high-fiber treatment groups. However, the results of this analysis indicated that total fiber intake was not associated with adenoma recur-

Table 4 Crude and adjusted odds ratios for adenoma recurrence by supplemental and total fiber intake

	Recurrence	No recurrence	Odds ratio (95% CI)	Adjusted odds ratio[a] (95% CI)	*P* for trend
Supplemental fiber intake (g/day)					
1 (0.0–1.7)	141 (46.7%)	161 (53.3%)	1.00	1.00	
2 (1.8–3.4)	146 (48.3%)	156 (51.7%)	1.07 (0.78–1.47)	1.06 (0.75–1.50)	
3 (3.5–11.0)	148 (49.0%)	154 (51.0%)	1.10 (0.80–1.51)	1.13 (0.80–1.59)	
4 (11.1–13.5)	140 (46.4%)	162 (53.6%)	0.99 (0.72–1.36)	0.94 (0.66–1.33)	0.82
Total fiber intake (g/day)					
1 (4.9–17.8)	147 (48.7%)	155 (51.3%)	1.00	1.00	
2 (17.9–23.7)	142 (47.0%)	160 (53.0%)	0.94 (0.68–1.29)	0.87 (0.62–1.23)	
3 (23.8–30.3)	136 (45.0%)	166 (55.0%)	0.86 (0.63–1.19)	0.80 (0.56–1.14)	
4 (30.4–66.3)	150 (49.7%)	152 (50.3%)	1.04 (0.76–1.43)	0.98 (0.68–1.42)	0.82

[a] Odds ratio for supplemental and total fiber intake adjusted for history of polyps prior to baseline colonoscopy, age at randomization, gender, number of colonscopies, total calcium intake at baseline, and number of baseline adenomas.

rence in this population, even after adjustment for potential confounders.

One consideration that must be addressed in the present analysis is whether the selected sample of participants retains the characteristics of the original study population (23). For the current analysis, ~93% of the participants had sufficient adherence data for inclusion. These 1208 participants in the present analysis are representative of the 1304 participants who completed the WBF trial, as evidenced by the absence of significant differences in the baseline characteristics between the two populations.

Another consideration is the potential effect of confounding variables. Because the WBF trial was a randomized clinical trial, the distribution of potentially confounding factors is expected to be equal between the two treatment arms. As previously reported (13), the proportion of smokers and the amount of alcohol and fat intake was larger in the high-fiber group than in the low-fiber group, although none of these variables had a significant effect on recurrence. In addition, potentially confounding variables were included in the models for recurrence.

The evaluation of supplemental fiber intake for this analysis relied on the participants returning the proper number of empty cereal boxes. There was a high correlation between box counts done by trial personnel and data from calendars completed daily by the participants. Furthermore, as discussed above, there were more reports of side effects among those in the high-fiber group. Therefore, it is reasonable to believe that the data regarding supplemental fiber intake are reliable.

The median level of intake for total fiber was 14.5 g/day for the lowest and 35.8 g/day for the highest quartile. This difference of ~20 g of fiber per day did not confer a benefit in regard to adenoma recurrence for the participants in the highest quartile of intake in the WBF trial. The results are in agreement with the results of Platz *et al.* (11) who found no effect of total fiber intake on distal colorectal adenomas and in whose study the difference between the median intake for highest and lowest quartiles was 20.7 g/day. In a randomized trial of a low-fat, high-fiber diet and polyp recurrence, the men in the intervention group achieved a fiber intake that was 16.4 g/day higher than the nonintervention group; among the women, the difference was 12.6 g/day (19). No differences in polyp recurrence were observed between the intervention groups (19). The National Cancer Institute recommends a fiber intake of 20–35 grams of fiber per day (24), whereas the American Dietetic Association recommends 25–35 grams per day after age 20 (25). The population in this study consumed an average of 28 grams (high-fiber group) and 20 grams of fiber (low-fiber group) from all sources throughout the course of the trial. This represents an increase in fiber intake from baseline of ~10 g/day for those in the high-fiber group and 1.5 g/day for the low-fiber group. Both groups were, on average, within the recommended range of intake during the course of the trial. It is possible that the treatment group did not reach the level of fiber intake necessary for protection, despite having maintained intake within the recommended levels. However, at least two reports have compared male subjects who consumed over 30 g of total fiber per day with those who consumed less fiber and did not show a benefit for total fiber intake on the risk of colon cancer (26) or on distal colorectal adenoma (11), although the latter report indicated that fruit fiber was protective. Furthermore, male participants in the Toronto Polyp Prevention Trial randomized to a low-fat, high-fiber diet were able to achieve average intakes of at least 35 g of total fiber per day, but no significant difference was observed in recurrence of neoplastic polyps between the intervention and the control groups (19). Therefore, it seems unlikely that the treatment group in the present analysis would have benefited from increased fiber supplementation. Furthermore, given the side effects related to the ingestion of supplemental fiber (13), it may not be plausible to recommend a level of total fiber intake greater than 35 g/day.

In addition to the amount of fiber necessary for protection against colorectal cancer, the type of fiber with the best protective properties remains in question because of the complexity of this nutrient. Many fiber-rich foods, such as cereals, fruits, and vegetables, contain different fiber components in different concentrations. For example, cereals and grains have high levels of cellulose and hemicellulose, whereas apples and citrus fruit are high in pectin (27). It is possible that the consumption of a diet rich in many types of dietary fiber, rather than a supplement of one type of fiber, is necessary for protection against colorectal carcinogenesis.

Another consideration is the optimal stage in carcinogenesis during which fiber may be most beneficial. Many mechanisms have been proposed to describe its protective effects at different points in the carcinogenesis pathway. Dietary fiber reduces fecal transit time through the large bowel, thereby decreasing the amount of time that the mucosal cells of the colon are exposed to carcinogens in fecal matter and reducing the exposure of mucosal cells to the carcinogens (3). Fiber also binds bile acids and decreases the concentration of these compounds in the feces (28, 29), thus preventing conversion to secondary bile acids, which are thought to promote carcinogenesis by increasing cellular proliferation (30) and which have been shown to act as tumor promoters in a rat model (31). Therefore, dietary fiber may be important in both early as well as later stages of carcinogenesis, and supplementation for a

period of 3 years in persons who have already developed adenomas may be insufficient to confer protection (13). Consumption of a high-fiber diet throughout life may be necessary to prevent adenoma development and recurrence.

This analysis used the approach of determining whether reported fiber intake from all sources affected adenoma recurrence, by taking into account adherence to the fiber supplement, reduction in fiber dose, and temporary or permanent cessation of supplement use. The results of this study show that neither fiber intake from a wheat bran supplement nor total fiber intake affects the recurrence of colorectal adenomas, thus lending further evidence to the body of literature that indicates that the consumption of a high-fiber diet does not reduce the risk of colorectal adenoma recurrence (12–14, 19). Foods high in fiber may confer protection against heart disease (32) and diabetes (33) and, therefore, should still be considered an integral component of a healthy diet.

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