Baseline Dietary Fiber Intake and Colorectal Adenoma Recurrence in the Wheat Bran Fiber Randomized Trial

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Background: The Wheat Bran Fiber (WBF) trial was a double-blind, high-fiber versus low-fiber phase III intervention trial in which participants were randomly assigned to receive a cereal fiber supplement of either 2.0 g/day or 13.5 g/day to assess whether a high-fiber supplement could decrease risk of recurrent colorectal adenomas. Although no effect of the supplement on polyp recurrence was observed, participants consumed a baseline average of 17.5 grams of fiber per day, which may have been sufficient to protect against adenoma recurrence. Therefore, we examined whether baseline fiber intake affected colorectal adenoma recurrence or modified the effect of treatment group in the WBF trial participants. Methods: Quartiles of baseline fiber intake were calculated on the basis of the distribution in the study population. Odds ratios (ORs) for adenoma recurrence were calculated using the lowest quartile of fiber intake as the reference. The effect of fiber from specific food sources on adenoma recurrence was also assessed. All statistical tests were two-sided. Results: Adjusted ORs (95% confidence intervals) for adenoma recurrence were 0.79 (0.56 to 1.12), 0.76 (0.54 to 1.08), and 0.83 (0.57 to 1.19) for the second, third, and fourth quartiles, respectively. Fiber from the three primary food sources (fruits; breads, cereals and crackers; and vegetables) had no appreciable effect on adenoma recurrence. Baseline fiber intake also had little effect on adenoma recurrence when the population was stratified by treatment group. In addition, there was no interaction between treatment group and quartile of baseline fiber intake. Conclusions: No association was found between amount of fiber consumed at baseline and adenoma recurrence in the WBF trial participants. The baseline fiber intake, whether considered as a whole or from specific sources, did not modify the effect of treatment group. [J Natl Cancer Inst 2002;94:1620–5]

Colorectal cancer is the third most common cause of cancer mortality among men and women in the United States (1) with a projected 148,300 cases and 56,600 deaths from this disease in 2002 (1). Evidence that the etiology of colorectal cancer is in part related to environmental factors includes the rapid increase in incidence rates occurring in countries with previously low rates (2) and migrant data showing that, in populations moving from low-risk to high-risk areas for colorectal cancer, incidence rates of the migrant population rapidly reach those of the adopted country (3,4). The observation that there is likely an environmental influence on the development of colorectal cancer led to the investigation of many modifiable risk factors for this disease, including diet and physical activity. It has been estimated that adoption of a healthy diet could prevent 50%–75% of colorectal cancers (5).

Dietary fiber has been investigated as a potentially protective dietary component since Burkitt (6) observed that diseases of the bowel, including colon cancer, were rare in Africa where a high-fiber diet was consumed. Although many case–control studies supported this hypothesis (7–13), the results of two randomized clinical trials failed to show a protective effect of increased dietary fiber and/or decreased fat in the diet on the risk of adenomatous polyp recurrence (14,15). The results of the Wheat Bran Fiber (WBF) trial showed no difference in the rate of recurrence of adenomatous polyps between those consuming a supplement of 13.5 grams of fiber per day and those consuming 2.0 grams of fiber per day (14).

Participants in the WBF trial consumed greater mean quantities of dietary fiber at baseline compared with the general population of the United States [17.5 grams versus 14.8 grams (16), respectively]. Therefore, it has been suggested that these participants had baseline fiber intakes that were providing adequate protection from colorectal adenoma recurrence and thus no effect would be observed from the addition of a high-fiber supplement (14). Alternatively, it is possible that total fiber intake as a whole may not be a protective factor in colorectal neoplasia and that a specific component or source of fiber may be more important. Recently, a protective effect of higher levels of fruit and vegetable consumption on colorectal cancer risk in 61,463 women was shown in the Swedish Mammography Screening Cohort (SMSC) (17). Further analyses indicated that when individuals in the lowest quartile of intake were further stratified, a stronger dose–response relationship with fruit and vegetable intake was observed (17). Although cereal fiber was not associated with colorectal cancer risk in the SMSC, women in this study consumed considerably more fiber from cereal than did participants in the WBF trial (17).

To more fully understand the role of fiber intake at baseline, as well as fiber from specific sources on risk of adenomatous polyp recurrence, we investigated this association in the WBF trial population. The current report presents data on the effect of baseline fiber intake from all sources on adenoma recurrence among participants in the WBF trial, as well as the association between dietary fiber obtained from different food sources and the recurrence of adenomatous polyps.

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SUBJECTS AND METHODS
Study Design and Subjects
The WBF trial was a randomized, double-blind phase III clinical trial designed to test whether consuming a high-fiber wheat bran supplement (13.5 g/day) for 3 years could decrease the risk of recurrent adenomatous polyps compared with consuming a low-fiber supplement (2.0 g/day) (14). The design of this study has been described in detail (18). 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 prior to recruitment consented to enter the 6-week run-in period (14). During the run-in period, participants were given the low-fiber wheat bran supplement, completed several questionnaires, and had blood drawn for later analyses (14). The Arizona Food Frequency Questionnaire (AFFQ) was administered at baseline, at year 1, and at year 3 of the trial (18). The run-in period was deemed successful for 1429 participants (95% of the 1509 who entered the run-in period), who had reported consuming at least 75% of their supplement (14). The supplement for both the high- and low-fiber groups was supplied as a cereal formulated by the Kellogg Company (14). A total of 1304 study participants completed the trial by having at least one post-randomization colonoscopy and/or a diagnosis of colorectal cancer. For each colonoscopy completed during the trial, the endoscopy results were obtained; if a polyp was removed, a pathology report was obtained, and information about the number, size, and location of any resected polyps was recorded (14). The study was approved by the University of Arizona Human Subjects Committee and local hospital committees, and written informed consent was obtained from each subject.

The Arizona Food Frequency Questionnaire
The AFFQ has been described in detail elsewhere (19) and has been evaluated for reliability and validity (20). Briefly, the AFFQ was modified from the food frequency section of the National Cancer Institute’s Health Habits and History Questionnaire (21). To capture specific information regarding dietary fiber intake, detailed items regarding fiber consumption were added to the questionnaire (19). In addition, the questionnaire was modified to include food items that are frequently consumed in the Southwest (19). The AFFQ is a semiquantitative, scan- nable instrument with 113 items. Study participants were asked to report their usual intake of foods for the prior 12-month period (19). Specifically, participants indicated their frequency of consumption of most foods using a scale of seven categories ranging from >6 times/day to rarely/never. For beverages and frequently consumed foods, the scale ranges from >6 times/day to rarely/never (19). Portion size for each food item was reported as small, medium, or large (19). In addition, there were open-ended items designed to capture information about cereals, fruits, and vegetables that were not specifically listed on the questionnaire (20). Nutrient composition of foods that were added to the questionnaire were derived from the United States Department of Agriculture’s (USDA’s) Continuing Survey of Food Intake of Individuals (1986) and the USDA National Food Consumption Survey (1987–1988) (22). Dietary fiber intake from several sources was collected using the AFFQ. Following the calculation of fiber intake from each food consumed by the participants, dietary fiber intake was categorized into eight groups based on the original fiber source: beans, nuts, and seeds; cakes, cookies, and pastries; salty snacks; breads, cereals, and crackers; fruits; juices; vegetables; and mixed dishes, such as casseroles.

Statistical Analysis
Quartiles of baseline dietary fiber intake were created based on the distribution of intake for the entire population. Trend analysis with simple linear regression was used to determine the association among the quartiles of baseline dietary fiber intake and continuous variables; for categorical variables, Pearson’s chi-square tests were used. Mean baseline intake of dietary fiber from the eight fiber sources was calculated for the total study population.

Logistic regression was used to determine which baseline variables were associated with both adenoma recurrence and baseline dietary fiber intake and thus should be considered confounders. The variables that were independently associated with both adenoma recurrence and baseline dietary fiber intake were age, sex, and baseline calcium intake. These variables were included in the multivariable logistic regression analyses for the association between baseline dietary fiber intake and adenoma recurrence. In addition, other potential covariates were tested in a model with age, sex, and baseline calcium intake, including number of colonoscopies during the study period, history of polyps prior to the baseline colonoscopy, baseline polyp characteristics (number, size, and location), family history of colorectal cancer (i.e., in a parent or sibling), regular aspirin use in the previous 10 years, and cigarette smoking. The variables that were associated with adenomatous polyp recurrence using a likelihood ratio test were included in the final model. The \( P_{\text{trend}} \) was calculated using the categorical variable for the baseline fiber quartiles in maximum likelihood regression models. The crude and adjusted logistic regression analyses were repeated to assess whether baseline fiber intake from specific food sources was associated with adenoma recurrence and whether baseline fiber intake, as a whole or from specific sources, affected the number, severity, or location of recurrent polyps. All statistical tests were two-sided and were considered to be statistically significant if \( P < 0.05 \) and/or if the 95% confidence interval (CI) did not include 1.0.

RESULTS
Baseline Characteristics and Baseline Fiber Intake
Table 1 presents baseline characteristics by quartile of baseline dietary fiber intake. Baseline dietary fiber intake increased statistically significantly with increasing age. The mean ages for the lowest and highest quartiles of intake were 64.6 and 68.0 years, respectively (\( P_{\text{trend}} < 0.001 \)). Participants who were male, exercised at least once a week, and were nonsmokers consumed statistically significantly greater amounts of fiber at baseline than women (\( P = 0.03 \)), nonexercisers (\( P = 0.002 \)), or smokers (\( P < 0.001 \)), respectively.

The mean dietary fiber intake from each fiber source for the total study population is shown in Table 2. Fruits were the major source of dietary fiber in this population (5.7 g/day), followed by breads, cereals, and crackers (4.3 g/day), and vegetables (3.7 g/day). Fiber from these three sources made up 73% of the total dietary fiber intake.

Baseline Dietary Fiber Intake and Adenoma Recurrence
Table 3 shows the crude and adjusted odds ratios (ORs) for adenoma recurrence by quartile of baseline dietary fiber intake,
with the lowest category of intake as the reference group. Compared with the lowest quartile of baseline fiber intake, the adjusted ORs (95% CI) for adenoma recurrence were 0.79 (0.56 to 1.12), 0.76 (0.54 to 1.08), and 0.83 (0.57 to 1.19) for the second, third, and fourth (highest) quartiles, respectively ($P_{\text{trend}} = .31$).

Table 4 shows the effect of baseline dietary fiber intake from the three leading sources of fiber on adenoma recurrence, with the lowest category of intake for each food source as the reference group. No association was observed between fiber intake from fruit ($P_{\text{trend}} = .62$), from breads, cereals, and crackers ($P_{\text{trend}} = .31$), or from vegetables ($P_{\text{trend}} = .21$) and adenoma recurrence.

We performed several analyses to explore whether baseline fiber had an effect on adenoma recurrence within each treatment group. First, we assessed the effect of baseline fiber on adenoma recurrence stratified by treatment group. In the low-fiber group,
with the lowest quartile of baseline fiber intake as the reference, the adjusted ORs (95% CI) for adenoma recurrence for increasing quartiles of baseline fiber intake were 1.03 (0.61 to 1.74), 0.88 (0.51 to 1.50), and 1.17 (0.68 to 2.03) \( (P_{\text{trend}} = 0.70) \). For the high-fiber group, the ORs were 0.66 (0.42 to 1.04), 0.66 (0.41 to 1.06), and 0.59 (0.35 to 0.97) \( (P_{\text{trend}} = 0.05) \). Second, to explore whether there may have been modification of the effect of treatment by baseline fiber intake, we tested an interaction term for treatment group and quartile of baseline fiber intake in crude and multivariable models. The interaction term was not statistically significant in either model \( (P = .11 \) and \( P = .41 \), respectively). Third, a stratified analysis was performed in which the treatment groups were compared within each quartile of baseline fiber intake. There was no statistically significant effect of treatment within any strata of baseline fiber intake, and no trend was observed by quartile (data not shown).

Several characteristics of recurrent polyps were also considered in relation to baseline fiber intake. The number, severity, or location of recurrent polyps was not associated with intake of either baseline fiber as a whole or fiber from specific food sources (data not shown).

**DISCUSSION**

Participants in the WBF trial reported a wide range of fiber intake at baseline, with the median for the lowest quartile at 10.1 g/day and the median for the highest quartile at 27.7 g/day. This variability provided an opportunity to determine whether usual levels of dietary fiber consumption affected colorectal adenoma recurrence. In addition, the effect of fiber from the three leading sources of dietary fiber in this population (fruits; breads, cereals, and crackers; and vegetables) was assessed. The present study showed that baseline dietary fiber intake was not associated with recurrence of adenomatous polyps. Furthermore, no association was observed between baseline intake of fiber from the three most common sources of dietary fiber and adenoma recurrence.

Because the two treatment groups were exposed to different levels of supplemental fiber during the WBF trial, we conducted secondary analyses to assess whether there was a differential effect of baseline fiber intake within each treatment group. In these exploratory analyses, no association was observed between baseline fiber intake and adenoma recurrence for the low-fiber group. However, among those in the high-fiber group, there was a statistically significant trend for decreased risk of adenoma recurrence in the higher quartiles of baseline fiber intake. While these results are intriguing, they must be interpreted with caution because they resulted from secondary analyses; furthermore, additional exploratory analyses were not consistent with this finding.

The median baseline fiber intake of participants who completed the WBF trial was 17.5 g/day, higher than the U.S. national medians of 14.7 g/day for men and 11.2 g/day for women \( (16) \). Therefore, it has been suggested that in the WBF trial, supplemental fiber might be protective only in persons with lower baseline fiber intakes in the WBF trial \( (14) \). The wide range of baseline fiber intake among WBF trial participants allowed comparison of those with low baseline fiber intakes to those with higher intakes; however, no trend was observed for increasing baseline fiber consumption and risk of colorectal adenomas. Furthermore, baseline fiber intake did not modify the effect of treatment on adenoma recurrence.

The results of the present study support those of most prospective studies and clinical trials of fiber intake and risk of adenomatous polyps, where no association is generally reported \( (14,15,23–25) \). Exceptions include the work of Platz and colleagues \( (14,15,23–25) \). Inclusion of the Health Professionals Follow-up Study (HPFS) \( (26) \) and the European Cancer Prevention (ECP) Organisation Intervention Study \( (27) \). In the HPFS, a protective effect of fruit fiber for distal colorectal adenoma was found, but no effect was observed for cereal fiber \( (26) \). In the ECP, participants were randomly assigned to receive a fiber supplement of 3.5 g/day or a placebo. The participants in the fiber intervention arm of the ECP had an increased risk of adenoma recurrence \( (27) \). Bonithon-Kopp and colleagues \( (27) \) assessed whether the treatment effect of the fiber was influenced by baseline fiber intake and found no relationship. The ECP participants received 3.5 g/day of ispaghula husk, a soluble fiber, whereas participants in the WBF trial received 13.5 g/day of an insoluble fiber supplement. As a result of their differing chemical properties, soluble and

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Median baseline dietary fiber intake, g/day</th>
<th>No. of participants with recurrence of adenomas</th>
<th>No. of participants with no recurrence of adenomas</th>
<th>OR (95% CI)</th>
<th>Adjusted OR (95% CI)†</th>
<th>( P_{\text{trend}})‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.1</td>
<td>175</td>
<td>151</td>
<td>1.00 (referent)</td>
<td>1.00 (referent)</td>
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<td>2</td>
<td>15.3</td>
<td>158</td>
<td>168</td>
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<td>0.79 (0.56 to 1.12)</td>
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</tr>
<tr>
<td>3</td>
<td>20.0</td>
<td>149</td>
<td>177</td>
<td>0.73 (0.53 to 0.99)</td>
<td>0.76 (0.54 to 1.08)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>27.7</td>
<td>156</td>
<td>170</td>
<td>0.79 (0.58 to 1.08)</td>
<td>0.83 (0.57 to 1.19)</td>
<td>0.31</td>
</tr>
</tbody>
</table>

*Each quartile contained 326 participants.

† OR adjusted for history of polyps prior to baseline colonoscopy, age at randomization, sex, number of colonoscopies, aspirin use, total calcium intake at baseline, and number of baseline adenomas. The referent group is the lowest category of baseline fiber intake.

‡ \( P_{\text{trend}} \) calculated using the categorical variable for the baseline fiber quartiles in maximum likelihood regression models.
insoluble fibers are metabolized via different mechanisms and thus have varying effects on the gastrointestinal tract, preventing a direct comparison of the ECP and WBF trial.

Like most studies of fiber and colorectal adenoma recurrence, prospective studies of dietary fiber and risk of colorectal cancer have found either weak or no associations (23,28–32). However, Thun et al. (33) found a significant inverse association for colorectal cancer mortality with increased consumption of vegetables, citrus, and high-fiber grains in men and women from the Cancer Prevention Study II. Because cancer mortality was the study endpoint, it is difficult to compare these results to those of the WBF trial. The results are in agreement with the recent clinical trial, these variables were expected to be equally distributed between the two treatment groups. Although there were differences in alcohol and tobacco consumption between the two treatment groups (14), these factors did not substantially alter any associations (data not shown).

Another consideration with regard to the results is the statistical power of the secondary analyses. The WBF trial was carefully designed to assess the effect of a cereal fiber supplement on adenoma recurrence. However, it was also important to evaluate the potential effect of baseline fiber consumption. Because the trial was not designed specifically to evaluate the effect of baseline fiber intake, there may not have been sufficient power to observe a statistically significant association between baseline fiber intake and adenoma recurrence.

This report sought to determine whether intake of baseline fiber from all sources, as well as from the three leading sources of dietary fiber, affected the recurrence of colorectal adenomas in the WBF trial. The results are in agreement with the recent reports of clinical trials and observational studies showing that dietary intervention with fiber does not prevent the recurrence of adenomatous polyps (14,15,27). Foods high in fiber may confer protection against heart disease (34) and diabetes (35) and therefore should still be considered a potentially beneficial component of a healthy diet.

REFERENCES


NOTES

Supported in part by Public Health Service grants CA41108 and CA23074 from the National Cancer Institute (NCI), National Institutes of Health, Department of Health and Human Services, and by the Kellogg Company. Supported by R-25 predoctoral cancer prevention fellowship CA78447 (to E. T. Jacobs) and Career Development Award K01CA7906910 (to M. E. Martinez) from the NCI. This manuscript was submitted in partial fulfillment of Dr. Jacobs’ doctoral dissertation requirements.

We thank Barbara van Leeuwen for her dedication to the WBF trial and Michael McBurney of the Kellogg Company for his support of this project. In addition, we express our gratitude to the nurses who assisted with the trial, including Liane Fales, R.N., M.P.H., Kristi Koonce, R.N., Dianne Parish, R.N., Karen Moore, R.N., Jo Avey R.N., and Evelyn Anthony, R.N.

Manuscript received March 12, 2002; revised August 6, 2002; accepted August 26, 2002.