LACK OF EFFECT OF A HIGH-FIBER CEREAL SUPPLEMENT ON THE RECURRENCE OF COLORECTAL ADENOMAS

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ABSTRACT

Background The risks of colorectal cancer and adenoma, the precursor lesion, are believed to be influenced by dietary factors. Epidemiologic evidence that cereal fiber protects against colorectal cancer is equivocal. We conducted a randomized trial to determine whether dietary supplementation with wheat-bran fiber reduces the rate of recurrence of colorectal adenomas.

Methods We randomly assigned 1429 men and women who were 40 to 80 years of age and who had had one or more histologically confirmed colorectal adenomas removed within three months before recruitment to a supervised program of dietary supplementation with either high amounts (13.5 g per day) or low amounts (2 g per day) of wheat-bran fiber. The primary end point was the presence or absence of new adenomas at the time of follow-up colonoscopy. Subjects and physicians, including colonoscopists, were unaware of the group assignments.

Results Of the 1303 subjects who completed the study, 719 had been randomly assigned to the high-fiber group and 584 to the low-fiber group. The median times from randomization to the last follow-up colonoscopy were 34 months in the high-fiber group and 36 months in the low-fiber group. By the time of the last follow-up colonoscopy, at least one adenoma had been identified in 338 subjects in the high-fiber group (47.0 percent) and in 299 subjects in the low-fiber group (51.2 percent). The multivariate adjusted odds ratio for recurrent adenoma in the high-fiber group, as compared with the low-fiber group, was 0.88 (95 percent confidence interval, 0.70 to 1.11; P=0.28), and the relative risk of recurrence according to the number of adenomas, in the high-fiber group as compared with the low-fiber group, was 0.99 (95 percent confidence interval, 0.71 to 1.36; P=0.93).

Conclusions As used in this study, a dietary supplement of wheat-bran fiber does not protect against recurrent colorectal adenomas. (N Engl J Med 2000; 342:1156-62.)

T HE risks of colorectal cancer and adenoma, the precursor lesion, are believed to be influenced by diet.[1] Burkitt's proposal that a high-fiber diet protects against colon cancer was based on the low rates of colorectal cancer in Africa.[2] Insoluble fibers, such as wheat-bran fiber, are thought to protect against colon cancer by absorbing carcinogens in the gastrointestinal tract.[3] Indeed, wheat-bran fiber has been shown to dilute fecal concentrations of bile acids[4,5] and to bind bile acids, thereby increasing their fecal excretion.[6,7] Although an inverse correlation was observed between mortality rates from colon cancer and per capita cereal consumption,[8] the results of the few analytical epidemiologic studies of associations between the consumption of whole-grain cereal and the risk of colorectal cancer[9-15] or adenoma[16] have been equivocal. Some metabolic end-point studies,[5,17] including our own,[4] have shown that wheat-bran fiber decreases fecal mutagenicity and reduces concentrations of fecal bile acids, although no effect was found on rates of proliferation of rectal mucosal cells.[18] Two studies found that a supplement of wheat-bran fiber had no effect on the risk of recurrent colorectal adenoma.[19,20]

In 1990, we initiated a multicenter trial to determine whether wheat-bran fiber can prevent the recurrence of colorectal adenomas.

METHODS

Study Design and Subjects

Details of the design and methods of the study have been described previously.[21] Briefly, subjects were recruited between September 1990 and July 1995 from multiple centers in the Phoenix, Arizona, metropolitan area. The study protocol was approved by the institutional review boards of the 22 participating health care centers in the Phoenix area and by the human-subjects committee of the University of Arizona. All subjects provided written informed consent.

We identified men and women who were 40 to 80 years of age from whom one or more colorectal adenomas, measuring at least 3 mm in diameter at colonoscopy, had been removed within the three months before recruitment. To be eligible, subjects had to have an adequate nutritional status and normal renal and liver function and to have a Southwest Oncology Group performance status of 0, 1, or 2.[22] We excluded persons who had had invasive cancer within the previous five years; those with a history of colon resection; those who had two or more first-degree relatives with

colorectal cancer, severe metabolic disorders, or other severe illnesses; and those with an intake of more than 30 g of dietary fiber per day on the basis of their responses to the Arizona Food-Frequency Questionnaire.[23]

Subjects who successfully completed a six-week run-in period by consuming at least 75 percent of the amount of a low-fiber supplement supplied (2 g per day) were randomly assigned to receive a high-fiber supplement (13.5 g per day) or a low-fiber supplement (2 g per day) of wheat-bran cereal. With the exception of the cereal-fiber intervention, no other dietary changes were required. The treatment assignments were not revealed to the subjects, their physicians, or members of the study staff. The fiber supplements were provided by Kellogg (Battle Creek, Mich.) and were available in several forms: unsweetened loop-shaped cereal and sweetened and unsweetened shredded cereal. Analysis of the fiber content per serving showed the following: high-fiber loops, 13 g; low-fiber loops, 2 g; high-fiber unsweetened shredded cereal, 13 g; low-fiber unsweetened shredded cereal, 4 g; high-fiber sweetened shredded cereal, 10 g; and low-fiber sweetened shredded cereal, 3 g. Cereal boxes were color coded into six groups to help maintain the study blinding. Midway through the study, high-fiber wheat-bran–fiber bars (containing 10 g of fiber) and low-fiber fiber bars (4 g of fiber) were developed by Kellogg. Subjects who had completed two years of the study were allowed to elect to consume up to 25 percent of their daily fiber supplement in the form of a fiber bar.

Compliance with the protocol was evaluated primarily by counts of returned cereal boxes and fiber bars at each visit and secondarily through a specialized intake calendar. Each index was used to generate an overall compliance score; subjects who consumed more than 75 percent of the cereal supplement were classified as complying with the protocol. On the basis of these data, members of the clinic research staff initiated individualized measures, as necessary, to increase compliance.

Colonoscopy

The study protocol specified that follow-up colonoscopy be performed twice after the initial qualifying colonoscopy. The first colonoscopy was to take place one year after randomization (to identify and remove adenomas missed at the qualifying colonoscopy), and the second two years thereafter. However, the national recommendations regarding the frequency of colonoscopic surveillance of patients with a history of colorectal adenomas changed during the study from one and three years after the initial resection to three years after resection.[24-26] Thus, there was a decrease in the rate of colonoscopy at one year among subjects enrolled in the latter part of the trial.

Data Collection

Results of endoscopy and pathological analysis were collected for each colonoscopy reported during the study. Using standardized guidelines, we abstracted data on the completeness of the examination and on the location, size, and histologic features of any resected adenomas.

Complete blood counts and blood chemical analyses were performed during screening and during the run-in phase of the study and annually thereafter. Diet was assessed according to the same schedule with use of the Arizona Food-Frequency Questionnaire, which has been evaluated with respect to reliability and validity in this population.[27] Information on adverse events was obtained every three months at the time the dietary supplement was dispensed.

Statistical Analysis

The original trial design and approach to analysis were described in detail by Emerson et al.[28] The target sample size of 1400 subjects was based on a three-year rate of recurrence of adenomas of 40 percent and on an estimate that 10 to 15 percent of adenomas would be missed during the colonoscopy at base line. Given a predicted dropout rate of 25 percent over a period of three years, we estimated that 950 subjects would complete the intervention. Given this sample size, the study had a statistical power of 0.82 to detect a 25 percent reduction in the recurrence of adenomas and a power of 0.94 to detect a 30 percent reduction.

An interim analysis conducted in the latter part of the study suggested a difference between groups in the proportion of subjects who stopped taking the assigned supplement: 12.7 percent stopped in the low-fiber group, and 23.3 percent stopped in the high-fiber group. Therefore, for the remainder of the accrual period, the original 1:1 schedule of randomization was changed to 4:1, with four subjects assigned to the high-fiber group for every one assigned to the low-fiber group.

We counted all adenomas, whether detected during the first colonoscopy (at year 1) or subsequent colonoscopic examinations. Subjects in whom an adenoma was found during the one-year colonoscopy were not withdrawn from the study. Two separate analyses were performed. The first included all subjects who underwent colonoscopy one or more times after randomization, with recurrence defined as the identification of one or more adenomas after randomization. The second set of analyses included only subjects who underwent colonoscopy at one year and one or more times thereafter. Recurrence was defined for these analyses as the identification of any adenoma after the one-year colonoscopy. Differences between the high-fiber group and the low-fiber group in the rates of colonoscopy at one year and during follow-up were analyzed with the use of chi-square tests, and the difference between the groups in the length of time from randomization to the last colonoscopy was assessed with a log-rank test. Differences in characteristics and in the incidence of adverse events among patients with recurrent adenomas in the two groups were tested with chi-square tests.

Multivariate adjustment to test for an effect of wheat-bran fiber was initially performed with the use of logistic regression (presence vs. absence of an adenoma). We used generalized estimating equations with a Poisson link function to model the number of recurrent adenomas at each colonoscopy, adjusting for the timing of colonoscopy and assuming an exchangeable correlation structure among the repeated procedures.[29] Generalized estimating equations were used to estimate the adjusted relative risk of the recurrence of adenomas for the high-fiber group as compared with the low-fiber group, whereas logistic regression was used to estimate the adjusted odds ratio (as an estimate of the adjusted relative risk). Initial models fitted to test the effect of group assignment were adjusted only for the randomization period. Subsequent statistical modeling also adjusted for sex and the number of adenomas at the base-line colonoscopy (both of which are strong predictors of the risk of recurrence) and factors that were found to be significantly different between groups at base line. The significance of the treatment effect was assessed with the Wald statistic.

RESULTS

Enrollment and Randomization

We identified 4705 potentially eligible subjects. Of these, 2088 declined to participate, 1006 were found to be ineligible, and 102 dropped out before the run-in phase. The remaining 1509 subjects entered the six-week run-in phase, which consisted of the daily intake of a supplement low in wheat-bran fiber (2 g per day). Of the 3699 eligible subjects, 1429 (38.6 percent) successfully completed the run-in period and underwent randomization, 627 to the low-fiber group and 802 to the high-fiber group.

Base-Line Characteristics of the Subjects

Table 1 shows the base-line characteristics of all 1429 randomized subjects and of the 1303 subjects (91.2 percent) who completed the study by undergoing at least one colonoscopy after randomization.

TABLE 1. BASE-LINE CHARACTERISTICS OF THE SUBJECTS.*

CHARACTERISTIC	ALL RANDOMIZED SUBJECTS (N=1429)		SUBJECTS WHO COMPLETED THE STUDY (N=1303)	
	LOW-FIBER GROUP (N=627)	HIGH-FIBER GROUP (N=802)	LOW-FIBER GROUP (N=584)	HIGH-FIBER GROUP (N=719)
Age — yr	66.0±8.8	66.8±9.0	66.0±8.8	66.4±8.8
Male sex — no. (%)	409 (65.2)	538 (67.1)	385 (65.9)	486 (67.6)
Dietary intake				
Energy — kcal/day	1875±636	1941±709	1874±629	1939±692
Total fat — g/day	71.0±32.0	75.1±35.1	70.7±31.4	74.7±34.6
Dietary fiber — g/day	18.8±8.3	18.5±8.2	18.9±8.3	18.6±8.1
Calcium — mg/day	852±371	858±385	849±368	856±385
Alcohol — g/day	6.1±10.9	8.1±17.9	6.4±11.1	8.4±18.0
10-year history of regular aspirin use — no. (%)	165 (26.3)	230 (28.7)	154 (26.4)	213 (29.6)
Current smoker — no. (%)	67 (10.7)	136 (17.0)	57 (9.8)	121 (16.8)
History of adenomas before base-line colonoscopy — no./total no. (%)	210/544 (38.6)	272/722 (37.7)	199/504 (39.5)	253/648 (39.0)
History of colorectal cancer in 1 parent or sibling — no. (%)	99 (15.8)	141 (17.6)	91 (15.6)	129 (17.9)
Adenomas				
Size of largest adenoma — mm	9.7±7.1	10.1±7.6	9.5±6.8	10.1±7.7
No. of adenomas	1.8±1.5	1.8±1.2	1.8±1.5	1.8±1.2
Location in proximal colon alone — no./total no. (%)	165/624 (26.4)	220/799 (27.5)	155/581 (26.7)	195/716 (27.2)
Villous histologic findings — no./total no. (%)†	95/625 (15.2)	119/801 (14.9)	91/582 (15.6)	107/718 (14.9)

*Plus–minus values are means ±SD.

†This category included tubulovillous and villous adenomas.

TABLE 2. SELF-REPORTED COMPLIANCE WITH THE PROTOCOL AMONG THE 1303 SUBJECTS WHO COMPLETED THE STUDY.*

GROUP	TOTAL NO. OF SUBJECTS	YEAR 1		YEAR 2		YEAR 3	
		COUNT OF BOXES AND BARS	CALENDAR RECORD	COUNT OF BOXES AND BARS	CALENDAR RECORD	COUNT OF BOXES AND BARS	CALENDAR RECORD
		number of subjects/total number (percent)					
Low-fiber	584	548/584 (93.8)	536/584 (91.8)	472/544 (86.8)	459/543 (84.5)	425/508 (83.7)	399/504 (79.2)†
High-fiber	719	626/719 (87.1)	597/719 (83.0)	468/601 (77.9)†	442/598 (73.9)†	409/552 (74.1)†	376/544 (69.1)†

*Compliance was defined as consumption of more than 75 percent of the assigned dietary supplements. Numbers of subjects do not total 1303 because of dropouts, deaths, or missing data. Compliance was assessed by a count of the boxes of cereal and fiber bars returned at each planned clinic visit and by an assessment of required calendar notations made by subjects concerning the number of cereal boxes or fiber bars consumed each day.

†P<0.05 for the comparison with the low-fiber group.

Of these 1303 subjects, 138 underwent only the one-year colonoscopy. The results for all randomized subjects who underwent colonoscopy after randomization were included in an intention-to-treat analysis.

Compliance

We assessed compliance with the dietary-supplement regimen by two methods: a count of cereal boxes returned to the study sites and a calendar record of consumption kept by each subject. With the exception of the first year of the study, there was a significant difference in compliance between the two groups (Table 2): the proportion of subjects who consumed more than 75 percent of the cereal supplement was lower in the high-fiber group than in the low-fiber group (P<0.05). Counts of returned boxes indicated that compliance declined with each year of the study, so that by the third year, 84 percent of the low-fiber group and 74 percent of the high-fiber group were consuming more than 75 percent of the

supplement. On the basis of responses to the Arizona Food-Frequency Questionnaire, which includes intake of fiber from the wheat-bran–fiber supplement and other sources, the mean total intake of fiber was 27.5 g per day in the high-fiber group and 18.1 g per day in the low-fiber group.

Recurrence of Adenomas

As noted in the Methods section, we changed the randomization scheme during the latter part of the study. As a result, 276 of the 1303 subjects underwent randomization according to a 4:1 ratio (high fiber to low fiber) (Table 3). We did not detect significant differences between the high-fiber and low-fiber groups in the number of colonoscopic procedures performed among subjects who underwent randomization ac-

TABLE 3. NUMBER OF COLONOSCOPIC EXAMINATIONS AFTER RANDOMIZATION, ACCORDING TO TREATMENT GROUP AND RANDOMIZATION SCHEME.*

VARIABLE	LOW-FIBER GROUP (N=523)	HIGH-FIBER GROUP (N=504)
1:1 Randomization scheme (n=1027)		
Mean no. of colonoscopies	2.17±0.83	2.15±0.90
1 Colonoscopy — no. (%)	101 (19.3)	113 (22.4)
≥2 Colonoscopies — no. (%)	422 (80.7)	391 (77.6)
	LOW-FIBER GROUP (N=61)	**HIGH-FIBER GROUP (N=215)**
4:1 Randomization scheme (n=276)		
Mean no. of colonoscopies	1.64±0.61†	1.66±0.58†
1 Colonoscopy — no. (%)	26 (42.6)	86 (40.0)
≥2 Colonoscopies — no. (%)	35 (57.4)	129 (60.0)

*Plus–minus values are means ±SD.

†P<0.05 for the comparison with the corresponding group in the 1:1 randomization scheme.

cording to either the initial 1:1 scheme or the 4:1 subsequent scheme; however, subjects who underwent randomization during the later period underwent significantly fewer colonoscopic examinations during year 1 than those who underwent randomization during the initial period. This difference clearly resulted from the change in clinical screening practice.

Table 4 shows the rates of recurrent adenomas among the 1303 subjects who completed the study. The median observation period was 34 months in the high-fiber group and 36 months in the low-fiber group (P=0.006). By the time of the last follow-up colonoscopy, the percentage of subjects with one or more recurrent adenomas was 51.2 percent in the low-fiber group and 47.0 percent in the high-fiber group (P=0.13). After adjustment for the randomization scheme used, the odds ratio for the presence of at least one recurrent adenoma in the high-fiber group, as compared with the low-fiber group, was 0.88 (95 percent confidence interval, 0.70 to 1.11; P=0.28).

When the analysis was restricted to the 889 subjects who underwent both a one-year colonoscopy and another examination two years later, the recurrence rates in the high-fiber and low-fiber groups were not significantly different. With the use of generalized estimating equations, the relative risk in the high-fiber group, as compared with the low-fiber group, was 0.99 (95 percent confidence interval, 0.71 to 1.36; P=0.93) for all 1303 subjects and 1.08 (95 percent confidence interval, 0.71 to 1.64; P=0.73) for the 889 subjects who underwent colonoscopy during year 1. Additional adjustments for sex, the number of colonoscopic examinations, the number of adenomas found at the base-line colonoscopy, and base-line variables that differed significantly between treatment groups did not change the results. Separate analyses revealed no significant differences in the rates of re-

TABLE 4. RISK OF RECURRENT ADENOMAS.*

FOLLOW-UP PERIOD	NO. ANALYZED	HIGH-FIBER GROUP	LOW-FIBER GROUP	ADJUSTED ODDS RATIO (95% CI)†	HIGH-FIBER GROUP	LOW-FIBER GROUP	ADJUSTED RELATIVE RISK (95% CI)‡
		no. with ≥1 recurrent adenomas/total no. (%)			mean no. of recurrent adenomas		
After randomization	1303	338/719 (47.0)	299/584 (51.2)	0.88 (0.70–1.11)	0.61	0.57	0.99 (0.71–1.36)
After colonoscopy at 1 year	889	168/468 (35.9)	153/421 (36.3)	1.04 (0.79–1.38)	0.60	0.53	1.08 (0.71–1.64)

*CI denotes confidence interval.

†The odds ratio for the presence of at least one recurrent adenoma in the high-fiber group as compared with the low-fiber group, adjusted for the randomization scheme, is shown.

‡The relative risk of recurrent adenomas in the high-fiber group as compared with the low-fiber group, adjusted for the randomization scheme and timing of colonoscopies with the use of generalized estimating equations (Poisson link function), is shown.

TABLE 5. CHARACTERISTICS OF ADENOMAS IDENTIFIED AFTER RANDOMIZATION AMONG SUBJECTS WITH RECURRENT ADENOMAS.

CHARACTERISTIC	LOW-FIBER GROUP (N=299)	HIGH-FIBER GROUP (N=338)	P VALUE*
	no. of subjects (%)		
Size of largest adenoma			0.71
<1 cm	205 (68.6)	227 (67.2)	
≥1 cm	94 (31.4)	111 (32.8)	
No. of adenomas			0.03
1	145 (48.5)	144 (42.6)	
2	66 (22.1)	61 (18.0)	
≥3	88 (29.4)	133 (39.3)	
Location of adenoma			0.004
Distal colon and rectum	87 (29.1)	77 (22.8)	
Proximal colon	144 (48.2)	140 (41.4)	
Both	60 (20.1)	110 (32.5)	
Not specified	8 (2.7)	11 (3.3)	
Histologic findings			0.51
Tubular adenoma	197 (65.9)	224 (66.3)	
Tubulovillous or villous adenoma	25 (8.4)	28 (8.3)	
Both	10 (3.3)	19 (5.6)	
Not specified	67 (22.4)	67 (19.8)	

*The chi-square test was used.

TABLE 6. INCIDENCE OF DEATH AND OTHER ADVERSE EVENTS AFTER RANDOMIZATION.*

VARIABLE	LOW-FIBER GROUP (N=584)	HIGH-FIBER GROUP (N=719)
	no. of subjects (%)	
Death	10 (1.7)	13 (1.8)
Disease*		
All cancers	38 (6.5)	51 (7.1)
Cardiovascular disease	11 (1.9)	6 (0.8)
Stroke	5 (0.9)	6 (0.8)
Gastrointestinal effects*		
Nausea	21 (3.6)	44 (6.1)†
Abdominal pain	69 (11.8)	136 (18.9)†
Diarrhea	65 (11.1)	145 (20.2)†
Constipation	78 (13.4)	91 (12.7)
Intestinal gas	135 (23.1)	243 (33.8)†
Abdominal bloating	59 (10.1)	121 (16.8)†

*Some subjects had more than one adverse event.

†P<0.01 for the comparison with the low-fiber group.

currence between women in the low-fiber group and women in the high-fiber group (40.7 percent vs. 40.8 percent, P=0.99). Among the men, there were fewer recurrent adenomas in the high-fiber group than in the low-fiber group (50.0 percent vs. 56.6 percent); this difference was of borderline statistical significance (P=0.05). There was no evidence of an effect of supplementation with wheat-bran fiber among male subjects who underwent colonoscopy during the first year.

When we assessed the characteristics of the recurrent adenomas (Table 5), there was no significant difference between the two groups regarding the size of the adenomas (P=0.71) or their histologic appearance (P=0.51). However, there was a significantly higher proportion of subjects with three or more recurrent adenomas in the high-fiber group than in the low-fiber group (P=0.03). When subjects were classified according to the sites of the recurrent adenomas (proximal colon or distal colon and rectum or both), the high-fiber and low-fiber groups were significantly different (P=0.004); this result was largely due to the higher number of subjects in the high-fiber group who had recurrent adenomas in both the proximal colon and distal colon and rectum.

Adverse Events

During the course of the study, nine cases of colorectal cancer were reported, two in the low-fiber group and seven in the high-fiber group (P=0.20). As shown in Table 6, among the 1303 subjects who completed the study, there were 23 deaths: 10 in the low-fiber group and 13 in the high-fiber group. There were no significant differences between groups in the occurrence of extracolonic cancer (P=0.58), cardiovascular disease (P=0.37), or stroke (P=0.69). The number of subjects who reported gastrointestinal effects was significantly higher in the high-fiber group than in the low-fiber group for all effects except constipation (Table 6). Most of these adverse effects were mild.

DISCUSSION

In this double-blind trial, we found that a dietary supplement of wheat-bran fiber had no statistically significant protective effect against recurrent colorectal adenomas. This finding was unchanged whether the analysis was based on all colonoscopic procedures performed after randomization or only those performed after one year in the study. This method of analysis has been used in other intervention studies of recurrent colorectal adenoma.[30] Moreover, the high-dose supplement of wheat-bran fiber had no effect on the number of recurrent adenomas in subjects who had a recurrence. Our results are consistent with those of the Toronto Polyp Prevention Trial[19] and the Australian Polyp Prevention Project.[20] Although our secondary analyses suggested an effect of the high-fiber supplement among men, this result probably represents a chance finding; in the Toronto Polyp Prevention Trial the effect of a low-fat, high-fiber diet was greater among women than men.[19] Furthermore, contrary to the findings of the Australian trial, we did not see any evidence that the high-fiber supplement we used reduced the rate of recurrence of large adenomas. We observed no protective effect of the high-fiber supplement on the number, location, or histologic fea-

tures of the recurrent adenomas. The combination of these observations argues against the idea that dietary supplementation with wheat-bran fiber can protect against recurrent colorectal adenomas. As reported in this issue of the *Journal,* Schatzkin et al. found that a low-fat, high-fiber diet also failed to lower the risk of recurrence of colorectal adenomas.[31]

We observed a relatively high rate of recurrent adenomas in the proximal colon in both the low-fiber group and the high-fiber group (48.2 percent and 41.4 percent, as compared with respective rates of 26.4 percent and 27.5 percent at base line). When rates of recurrent adenomas in the proximal colon are added to the rates of recurrence occurring in both the proximal colon and the distal colon or rectum, 68.2 percent of the subjects in the low-fiber group and 74.0 percent of those in the high-fiber group had recurrences in the proximal colon. The high rates of recurrent adenomas in the proximal colon strongly suggest that colonoscopy, rather than sigmoidoscopy, is the preferred method of surveillance, especially in patients with a history of adenoma in the proximal colon.

In large, randomized clinical trials, randomization is expected to result in a relatively equal distribution of subjects with respect to risk factors of interest. In our trial, there was a balanced distribution with respect to base-line age and sex, but imbalances in terms of exposure to tobacco, alcohol consumption, and total intake of fat. Nevertheless, the multivariate logistic-regression analysis, after adjustment for randomization period, sex, smoking status, alcohol consumption, and energy intake, did not show a significant effect of supplementation with wheat-bran fiber on the recurrence of colorectal adenomas. Thus, our results do not appear to be related to an imbalance in the base-line characteristics of the subjects or to the change in the randomization scheme from a 1:1 ratio to a 4:1 ratio in favor of the high-fiber group.

Our experience underscores the difficulty of performing large-scale nutritional intervention trials, in terms of both recruitment and compliance with the protocol. Of 3699 eligible subjects, 1303 (35.2 percent) successfully completed the trial. In addition, by the third year of the study, only 74 percent of the subjects in the high-fiber group, as compared with 84 percent of those in the low-fiber group, consumed more than 75 percent of their supplemental cereal on a daily basis (a level we defined as indicative of compliance). Despite these difficulties, the mean intake of total fiber was 27.5 g per day in the high-fiber group and 18.1 g per day in the low-fiber group. It can be argued that this level of intake over a period of three years is inadequate to prevent recurrent adenomas; however, our compliance data indicate that higher daily consumption of wheat-bran fiber for longer periods is not practical in adults older than 65 years of age.

The lack of effect of three years of supplementa-

tion with wheat-bran fiber may reflect inadequate follow-up: three years may be too short. It could be argued that the total amount of dietary and cereal fiber consumed by the subjects in the high-fiber group was insufficient to protect against recurrent adenomas. It is also possible that a high-fiber diet may be beneficial only in persons with lower base-line intakes of total fiber than those in our study. Alternatively, the use of wheat-bran–fiber supplements may only protect against the progression of large adenomas to carcinomas. However, both the Nurses' Health Study[15] and the Health Professionals' Follow-up Study[16] failed to find that cereal fiber prevents colon cancer. Since cereal fiber has potentially healthful effects in the prevention of coronary heart disease,[32,33] public health recommendations[34,35] that emphasize increased consumption of complex carbohydrates, whole-grain foods, and cereal products may nevertheless be appropriate.

APPENDIX

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CORRECTION

Lack of Effect of a High-Fiber Cereal Supplement on the Recurrence of Colorectal Adenomas

Lack of Effect of a High-Fiber Cereal Supplement on the Recurrence of Colorectal Adenomas . On page 1161, four additional names should have appeared in the Appendix: Andrew Collins, M.D., George Walker, M.D., Joan Mitrius, M.D., and Salem Ganem, M.D.