ARTICLES

Randomized Trial of Intake of Fat, Fiber, and Beta Carotene to Prevent Colorectal Adenomas

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Background: **Epidemiologic evidence of associations between the high intake of fat and low intake of dietary fiber, beta carotene, and other dietary constituents and the risk of colorectal neoplasia has been inconsistent and has not provided a sufficient basis for recommendations concerning the dietary prevention of large-bowel cancer in humans.** ***Purpose:*** **We conducted a clinical trial to assess the effects on the incidence of adenomas of reducing dietary fat to 25% of total calories and supplementing the diet with 25 g of wheat bran daily and a capsule of beta carotene (20 mg daily).** ***Methods:*** **We performed a randomized, partially double-blinded, placebo-controlled factorial trial in which half the patients were assigned to each intervention, resulting in seven intervention groups and one control group. Eligibility criteria included histologic confirmation of at least one colorectal adenoma and confidence expressed by the colonoscopist that all polyps had been removed. Dietary changes were individually initiated and monitored by dietitians and research nurses. At surveillance colonoscopy, the size and location of all polyps were recorded, and their histology was later centrally reviewed. Among 424 patients who were randomly assigned in the trial, 13 were found to be ineligible upon histologic review. Among the remaining 411, complete outcome data were collected from 390 at 24 months and from 306 at 48 months. All *P* values are from two-sided tests of statistical significance.** ***Results:*** **There was no statistically significant prevention of total new adenomas with any of the interventions. We found a statistically nonsignificant reduced risk of large adenomas (≥10 mm) with the low-fat intervention: At 24 months, the odds ratio (OR) adjusted for potential confounders = 0.4 and 95% confidence interval (CI) = 0.1-1.1; at 48 months, OR = 0.3 and 95% CI = 0.1-1.0. Less and statistically nonsignificant reductions in the risk of large adenomas were found with wheat bran: At 24 months, OR = 0.8 and 95% CI = 0.3-2.2; at 48 months, OR = 0.8 and 95% CI = 0.3-2.5. Patients on the combined intervention of low fat and added wheat bran had zero large adenomas at both 24 and 48 months, a statistically significant finding (*P* = .03).** ***Conclusions:*** **Because only small numbers of patients were studied, our finding that the combination of fat reduction and a supplement of wheat bran reduced the incidence of large adenomas in this randomized, controlled trial must be treated with caution. The results do suggest, however, that these interventions may reduce the transition from smaller to larger adenomas, a step that may critically define those adenomas most likely to progress to malignancy. [J Natl Cancer Inst 1995;87:1760-6]**

The scientific basis for the dietary prevention of large-bowel neoplasia in humans has not yet been established, despite many national and international studies during the past two decades. A review by the U.S. National Research Council (*1*) for the U.S. National Cancer Institute concluded that there was sufficient evidence that high fat consumption is linked to an increased incidence of colon cancer to warrant a reduction in both saturated and unsaturated fats in the average U.S. diet. The National Research Council considered an appropriate and practical target to be the reduction of fat intake from the then present level of approximately 40% to 30% of total calories in the diet. They also emphasized the importance of including fruits, vegetables, and whole-grain cereal products in the daily diet.

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See "Notes" section following "References" for additional information, including members of the project.

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In a review of diet and cancer, Willett and MacMahon (*2*) concluded that the weight of evidence generally supports the hypothesis that fiber protects against colon cancer and that epidemiologic studies of dietary intakes among individuals currently provide inconsistent support for the hypothesis that fat intake is related to colon cancer. A review of studies of cancer in relation to intake of some beta carotene-rich vegetables or of vitamin A by Peto et al. (*3*) found that intake of certain vegetables rich in beta carotene was associated with a reduced risk of colorectal cancer. Vitamin A prevents colon carcinogenesis in rats (*4*). In 11 of 14 case–control studies of colon cancer, a statistically significant negative relationship was found between the cancer and one index of fruit and vegetable consumption (*5*).

The Australian Polyp Prevention Trial was planned because of the inconclusive epidemiologic evidence regarding dietary factors and colon cancer. Because a randomized trial with cancer as the outcome would have been too large to be feasible, the trial was done among patients under surveillance for further neoplasia following colonoscopic removal of colorectal adenomas. The preventive measures assessed in our trial were (*a*) fat reduction, (*b*) increased dietary fiber as a wheat bran supplement, and (*c*) capsules of beta carotene. At the initiation of the trial, we judged these interventions to give the optimal balance of likely efficacy with high safety. The aim of this clinical trial was to assess the effects on the incidence of adenomas of reducing dietary fat to 25% of total calories, below the 30% recommended in the U.S. National Research Council dietary guidelines for cancer prevention, and supplementing the diet with 25 g of wheat bran daily and a capsule of beta carotene (20 mg daily).

Subjects and Methods

Patient Eligibility

Fundamental eligibility criteria for patients were ages 30-74 years; confidence expressed by the colonoscopist that all polyps had been removed from the patient following colonoscopy, that the cecum had been reached, and that the quality of examination was not compromised by spasm or fecal residue in each segment of the colon; histology report of at least one adenoma (subsequently confirmed by review); and signed informed consent from the patient. Both new patients and patients seen at a surveillance colonoscopy after prior polypectomy were eligible.

Patients otherwise considered appropriate were excluded for one of the following reasons: The patient had chronic inflammatory bowel disease (such as ulcerative colitis, Crohn's disease, or serious inflammatory diverticulitis), gastrointestinal tract resection (excluding cholecystectomy), familial adenomatous polyposis, diagnosed cancer (excluding non-melanoma skin cancer) unless symptom free for 5 years (because of possible effects on diet and nutritional status), or medically supervised special diet for renal, liver, or gallbladder disease; the colonoscopist thought that it was not in the patient's best interest to have a repeat colonoscopy; or the patient was unlikely to be able to complete the trial for medical or other reasons such as place of residence or inability to comprehend English.

Patient Recruitment

Following approval by nine ethics committees in the major institutions associated with the trial, eligible patients were recruited in gastrointestinal units at collaborating centers in Brisbane, Melbourne, and Sydney. We prospectively documented 2780 colonoscopies with reported polyps from October 1985 through April 1988: At the time of colonoscopy, 1304 were potentially eligible for study entry and 1476 were ineligible (487 because of place of residence, 339 because of age, 169 as a result of cancer within 5 years, 150 because of other gastrointestinal disease, 84 already on a special diet, 76 for other medical conditions, 157 nonliterate in English, and 14 for refusal to provide information). Of the 1304 potentially eligible, 559 were definitely eligible on the basis of a histologic report of at least one adenoma and confidence expressed by the colonoscopist of a polyp-free colon; of these 559, 424 (76%) were recruited. Of the remaining 745 who were potentially eligible after colonoscopy, the reasons for nonrecruitment were various and included 282 with non-adenoma pathologic abnormalities and 136 with other bowel disease.

Study Design and Interventions

The three interventions (fat reduction, wheat bran fiber, and beta carotene) were tested in a randomized trial with a $2 \times 2 \times 2$ factorial design, resulting in the eight intervention groups presented in Table 1.

Fat was reduced through continuing professional dietary counseling to a target 25% of total energy (with at most 30%) and was compared with an unmodified diet with respect to fat. Fat reduction was achieved by not adding butter or margarine to foods at the table, by not eating visible fat on meat, by avoiding fried foods, and by use of low-fat dairy products, but not through major changes to the diet that would affect other household members. Consumption of red meat per se was not excluded in counseling.

The fiber supplement consisted of 25 g of finely milled raw wheat bran used for the manufacture of All-Bran by Kellogg, Australia, Pty. Ltd., Sydney, and contained approximately 11 g of dietary fiber. This supplement was added to the diet and compared with nil bran supplement.

Finally, all patients took a capsule daily from calendar packs, either 20 mg of beta carotene or an identical-looking placebo supplied by F. Hoffmann-La Roche Ltd., Basel, Switzerland.

Eight distinct combinations of interventions were thus available for comparison; one half of the patients were on any one of the three main interventions, one quarter were on any two of the interventions, and one eighth were on the combination of all three interventions. Patients recruited in the first 6 months of the trial and randomly assigned to receive beta carotene were given placebo capsules until government approval was obtained to use this preparation of beta carotene. Other interventions were not affected. Thus, among patients with a 24-month surveillance colonoscopy, 98% of those allocated had been on beta carotene for at least 12 months and 74.2% had been receiving it for at least 18 months.

Randomization

After giving written informed consent, eligible patients were randomly assigned to one of the eight diet intervention strategies in the factorial design. To make the groups as similar as possible with respect to factors associated with adenoma occurrence, prerandomization stratification was undertaken by age (<55 years or ≥55 years), city (Brisbane, Melbourne, or Sydney), and surveillance status (initial or follow-up colonoscopy). Separate randomized lists of groups numbered 1-8 were produced for each stratum. Each group was represented an equal number of times, and blocking was used so that each of the eight treatments was represented in some permutation for every sequence of eight patients entering the study under the stratum characteristics. This procedure ensured that strata with few patients had all treatments represented. The randomization procedure with built-in patient eligibility checks was computerized to minimize human error in allocation.

Randomization among the eight groups was apparently successful; the eight groups were reasonably similarly distributed (Table 1) with respect to age, sex, surveillance status, city (Brisbane, Sydney, or Melbourne), time to initial dietary counseling, history of smoking, body mass index, and recent intake of fat, fiber, and beta carotene. Both the time from recruitment to initial dietary counseling and the time to surveillance colonoscopy were comparable among the treatment groups. Although there were fewer adenomas at study entry in the low-fat plus added bran group, the chi-squared test for heterogeneity was not statistically significant, and this variable was included in subsequent multivariate analyses. Large adenomas (≥10 mm) were more evenly distributed; overall, they were found in 48% of patients assigned to a low-fat diet compared with 45% among those not on a low-fat diet.

Initial Dietary Assessment and Counseling

Upon recruitment, patients were asked to complete a self-administered, 4-day food diary and a comprehensive quantitative food-frequency questionnaire

Table 1. Distribution of characteristics at study entry of 395 patients with colonoscopies at 24 and/or 48 months by intervention group

Characteristic	Intervention group, No. of patients (%)							
	Normal eating* (n = 48)	Low fat* (n = 48)	Bran* (n = 50)	Beta carotene (n = 53)	Low fat–beta carotene (n = 51)	Low fat–bran* (n = 48)	Bran–beta carotene (n = 47)	Low fat–bran–beta carotene (n = 50)
Age† <55 y	19 (40)	17 (35)	20 (40)	21 (40)	22 (43)	20 (42)	19 (40)	19 (38)
New case†	37 (77)	39 (81)	41 (82)	43 (81)	41 (80)	40 (83)	40 (85)	38 (76)
City†								
Brisbane	12 (25)	13 (27)	16 (32)	15 (28)	14 (27)	15 (31)	11 (23)	16 (32)
Melbourne	19 (40)	18 (38)	17 (34)	18 (34)	20 (39)	17 (35)	20 (43)	20 (40)
Sydney	17 (35)	17 (35)	17 (34)	20 (38)	17 (33)	16 (33)	16 (34)	14 (28)
Male	29 (60)	33 (69)	31 (62)	33 (62)	36 (71)	37 (77)	31 (66)	35 (70)
Body mass index >25	25 (54)‡	21 (47)‡	30 (61)‡	30 (63)‡	26 (51)	29 (60)	20 (46)‡	27 (56)‡
Never smoked	18 (38)	14 (30)‡	18 (37)‡	17 (33)‡	15 (29)	14 (29)	19 (43)‡	10 (20)
Family history of large-bowel cancer	11 (23)	8 (17)	9 (18)	9 (17)	13 (25)	11 (23)	12 (26)	12 (24)
History of adenoma	9 (20)‡	8 (17)	7 (14)	8 (15)	8 (17)‡	8 (17)	7 (15)	11 (22)
≥2 adenomas at trial entry	12 (25)	7 (15)	9 (18)	12 (23)	16 (31)	5 (10)	10 (21)	12 (24)
Adenoma ≥10 mm at trial entry	20 (42)	24 (50)	22 (44)	29 (55)	27 (53)	20 (42)	18 (38)	23 (46)
Vitamin use	9 (19)	15 (33)‡	15 (31)‡	13 (25)	16 (31)	9 (19)	13 (29)‡	15 (31)‡

*Also took a capsule daily of a placebo for beta carotene.
†Stratification variable.
‡The percentage is higher because up to three patients in this group had missing information.

asking about food intake in the previous 12 months. The diary incorporated 2 weekdays and the weekend. Before the first face-to-face contact with the subject, the dietitian assessed usual intake from the 4-day diary using a nutrient analysis program (Nutritionist III). Initial dietary interview and counseling were done within 7 weeks of colonoscopy, with no more than 3 weeks between signed consent and interview. At the interview, the dietitian instructed the subject on any modifications required for the allocated diet plan. The group of patients not on low-fat or added bran interventions were advised to follow their normal eating pattern and for ethical reasons were provided with the current Australian guidelines for healthy eating.

Demographic and Medical Information

In addition to dietary information, all patients at recruitment were asked to complete a questionnaire relating to demographic details (sex, date and place of birth, height, weight, and marital, educational, and occupational status) and medical history details (cholecystectomy, abdominal operations, use of laxatives and vitamin supplements, smoking and drinking habits, hospital status, and family history of colorectal cancer or polyps and other bowel diseases, restricted to first-degree relatives). Moreover, colonoscopists were asked to estimate the number of adenomas that had been removed before the entry colonoscopy.

Monitoring of Compliance

Compliance with low-fat and bran interventions was monitored by telephone by a dietitian in each city a week after counseling and thereafter at regular contacts every 3 months, alternating between phone calls and interviews, asking for a detailed recall of intake in the previous 24 hours and an approximate intake of food in the previous week. This information was also used for further counseling. Because of the potential for bias in reporting to the counseling dietitian, an independent assessment of dietary compliance was based on 4-day diaries, with estimated amounts, administered by a research nurse, at recruitment (prior to dietitian contact) and then every 6 months over a 2-year period for all patients. At the same time, capsule counts were done and blood was taken by the nurse to measure levels of beta carotene, retinol, and cholesterol.

Duration of the Trial and Characteristics of Patients

Patients were initially recruited for a 24-month trial. When it was subsequently decided to continue until 48 months, 78.5% of the patients consented. The low-fat and added bran interventions were continued with dietitian counseling, but monitoring was less frequent (at 36 and 48 months only). A preliminary analysis was done after all patients had colonoscopies at 24 months and indicated a possible increase in total new adenomas in patients taking beta carotene. In October 1990, the trial's steering committee decided to discontinue this intervention in all patients. The trial operated as designed with very high participation on all three interventions up to 24 months (n = 390). From 24 to 48 months, participation was lower (n = 306), and there was less frequent contact with patients. The low-fat and added bran interventions continued in all patients seen at 48 months, but beta carotene was given for only part of the second 24 months. The base-line characteristics of the 390 patients with colonoscopies at 24 months were very similar to those of the 306 patients with colonoscopies at 48 months with respect to mean age (56.3 years versus 55.9 years), mean number of adenomas at study entry (1.3 versus 1.4), percent male (66.7% versus 68.0%), percent with adenomas diagnosed for the first time at entry to the trial (80.8% versus 79.7%), percent with a history of colorectal cancer in first-degree relatives (21.5% versus 22.5%), percent who had never smoked (32.4% versus 33.6%), and percent with more than 12 years of education (29.0% versus 29.7%). The finding of an adenoma at surveillance colonoscopy performed at 24 months did not influence (not statistically significant) continuation to 48 months; of the 86 with an adenoma, 71 continued (82.6%) compared with 230 of 304 without an adenoma (75.7%).

Pathology Review, Study Power, and Outcome Measures

Surveillance colonoscopy was performed at 24 and 48 months; the colonoscopists were blinded in regard to the intervention status. As at trial entry, the location, number, and size of all polyps were recorded. Polyp size was estimated by calibration with the open biopsy forceps at the time of colonoscopy. Those polyps retrieved were sent for histologic examination and were subsequently reviewed centrally by the trial's pathologist (R. C. Newland), who was blinded as to the intervention status and who also subjectively graded dysplasia. When a

colonoscopy was indicated before the routine 2-year colonoscopy, histology was recorded on all polyps found, to be later aggregated with 24- and 48-month colonoscopy data.

Central pathologic review failed to confirm an adenoma for 13 of the 424 patients originally considered eligible and recruited to the study. Of the remaining 411, no information was available on surveillance colonoscopy at 24 months for 21 (including eight who died, nine who refused to continue after an initial period, two who were withdrawn by their doctors because of illness, one who was unable to be contacted, and one who participated but did not have a follow-up colonoscopy). Our reported results are therefore based on 390 patients (94.9% follow-up) at 24 months and 306 patients at 48 months. We aimed for 420 recruitments to detect a third reduction in adenomas from 40% to 26.7%. Our final sample size of 390 would have detected a change in new adenomas from an expected 40% down to 26.2%, with a type I error of 5% and power of 80%, using a two-tailed test.

In analysis of outcomes for each patient, three measures were considered: the presence of at least one adenoma of any size and two indicators of advanced neoplasia—the presence of adenomas 10 mm or larger and the presence of adenomas with moderate or severe dysplasia (grouped because of small numbers).

Statistical Methods

Analyses were based on intention to treat, i.e., on the initial randomization. They included all patients with outcome information irrespective of whether they remained in the trial or the extent of their compliance. Only patients with a colonoscopy at 48 months were included in the 48-month results. If they also had a 24-month colonoscopy, the 24- and 48-month results were combined. In five patients in whom only the 48-month colonoscopy was performed, this was interpreted as a measure of outcome over a 48-month period. Patients with a colonoscopy at 24 months but not at 48 months were excluded from the 48-month results.

Crude relative risks (RRs) of adenomas for the three main intervention factors were calculated with the SAS procedure FREQ according to the method of Kleinbaum et al. (*6*).

Logistic regression was used to estimate the effect of the three dietary interventions simultaneously and to allow for the effect of potential confounders. Models for the proportions of patients with each outcome measure were fitted using EGRET (*7*). Estimates of effect are quoted as odds ratios with 95% confidence intervals (CIs) for the true values based on maximum likelihood estimates of standard error. No potential confounders substantially altered the estimated effects of any of the dietary factors. Nonetheless, potential confounders with statistically significant effects were included in the final model. Interaction effects, apart from those between the three dietary factors, were considered only if based on sound a priori reasons for their potential existence and were restricted to second-order effects. For the outcome of any new adenoma at 24 months among all patients, the potential confounders considered were variables at entry to the trial (age, case status, city, sex, country of birth, marital status, years of education, body mass index, smoking status, family history of large-bowel cancer, clinician's best estimate of adenomas prior to study, adenomas at entry colonoscopy, use of laxatives, and use of vitamins); average alcohol intake during the trial; and, among women, use of oral contraceptive agents, history of pregnancy, menopausal status, and parity at entry to the study.

The final logistic model used to examine influences on the outcome of any new adenoma at 24 months included the three interventions, the number of adenomas at trial entry, the number of adenomas before the study, and family history of large-bowel cancer among first-degree relatives. This model was applied in subsequent analyses of neoplastic outcomes at 24 and 48 months. All *P* values presented are for two-sided tests.

Results

An initial univariate screen of potential nondietary confounders of risk for new adenomas at 24 months identified the following three variables for inclusion in subsequent multivariate analytic models: 1) a history of adenomas before entry into the trial (RR and 95% CIs of 2 or more compared with nil = 2.1 [95% CI = 1.3-3.3]); 2) the number of adenomas at study entry (RR of 3 or more compared with 1 = 2.5 [95% CI =1.6-3.9]); and 3) a history of large-bowel cancer in first-degree relatives compared with no history (RR = 1.4 [95% CI = 0.9-2.1]).

Table 2 gives the numbers of patients and percentages with various neoplastic outcomes at surveillance colonoscopy. In this unadjusted analysis, there was no evidence that any intervention protected against the primary end point of adenoma of any size, and there was a statistically nonsignificant increase among those randomly assigned to receive beta carotene compared with those randomly assigned to receive placebo (50 patients versus 36 patients after 24 months). Fitting a multivariate model that included the three interventions, family history of large-bowel cancer in first-degree relatives, number of adenomas at study entry, and number of adenomas before study entry did not substantially alter the estimated effect of the interventions on adenomas of any size (Table 3). This model did not include interaction terms.

Further analysis of large adenomas (≥10 mm) and of adenomas with moderate or severe dysplasia, which have increased malignant potential (*8*), found that patients on reduced fat had a reduction in large adenomas (five versus 13 at 24 months); those on added bran had a statistically nonsignificant lower rate of large adenomas (seven versus 11 at 24 months); and those on beta carotene had more large adenomas (10 versus eight), but fewer moderate or severe dysplasias (nine versus 11), although none of the differences was statistically significant. Upon logistic regression analysis with the same model as above (Table 3), the odds ratios of large adenomas referent to nil plus small adenomas were reduced with the low-fat intervention—0.4 at 24 months (P = .06) and 0.3 at 48 months (P = .05). Wheat bran was moderately protective against the risk of dysplasia (statistically nonsignificant).

Because of previously reported interactions between fat and fiber and the risk of colorectal cancer (*9*), the outcomes (Table 4) of large adenomas at 24 and 48 months were analyzed separately, using Fisher's exact test for a 4 × 2 contingency table and logistic regression. Fisher's exact test was used to test for differences between the four intervention groups (ignoring beta carotene); the differences were found to be statistically significant for both the 24-month and the 48-month data (P = .032 and P = .030, respectively). Logistic regression analysis (with the same multivariate model used in Table 3) was used to investigate the effect of the low-fat and bran interventions and showed the main effect of the low-fat intervention and the interaction between the low-fat and bran interventions to be statistically significant at the 5% level at both 24 months and 48 months. Likelihood ratio tests were used; the main effects of the low-fat and bran interventions were evaluated in the absence of interactions. The zero frequencies in Table 4 for large adenomas for the patients given low-fat and added bran interventions made it difficult to estimate odds ratios for this group.

Discussion

The smaller numbers of the secondary end points of large adenomas and dysplasia have resulted in greater uncertainty with regard to the estimates. Nevertheless, the estimates of the risk of large adenomas (≥10 mm) were compatible with a reduc-

Table 2. Patients with neoplastic outcomes at 24 months and at 48 months, by intervention group*

	Intervention group					
	Low fat		Bran		Beta carotene	
	Yes	No	Yes	No	Yes†	No
			24 months (n = 390)			
Total patients	195	195	193	197	198	192
No. (%) with adenoma of any size	43 (22.1)	43 (22.1)	45 (23.3)	41 (20.8)	50 (25.3)	36 (18.7)
Unadjusted odds ratio (95% confidence interval)	1.0 (0.6-1.6)		1.2 (0.7-1.9)		1.5 (0.9-2.4)	
No. (%) with adenoma ≥10 mm	5 (2.6)	13 (6.7)	7 (3.6)	11 (5.6)	10 (5.1)	8 (4.2)
Unadjusted odds ratio (95% confidence interval)	0.4 (0.1-1.1)		0.6 (0.2-1.7)		1.2 (0.5-3.2)	
No. (%) with moderate or severe dysplasia	11 (5.6)	9 (4.6)	7 (3.6)	13 (6.6)	9 (4.5)	11 (5.7)
Unadjusted odds ratio (95% confidence interval)	1.2 (0.5-3.1)		0.5 (0.2-1.4)		0.8 (0.3-1.9)	
			48 months (n = 306)‡			
Total patients	151	155	150	156	156	150
No. (%) with adenoma of any size	46 (30.5)	49 (31.6)	49 (32.7)	46 (29.5)	54 (34.6)	41 (27.3)
Unadjusted odds ratio (95% confidence interval)	0.9 (0.6-1.5)		1.2 (0.8-2.0)		1.5 (0.9-2.5)	
No. (%) with adenoma ≥10 mm	4 (2.6)	13 (8.4)	7 (4.7)	10 (6.4)	12 (7.7)	5 (3.3)
Unadjusted odds ratio (95% confidence interval)	0.4 (0.09-0.9)		0.7 (0.3-1.9)		2.4 (0.8-7.0)	
No. (%) with moderate or severe dysplasia	8 (5.3)	8 (5.2)	6 (4.0)	10 (6.4)	6 (3.8)	10 (6.7)
Unadjusted odds ratio (95% confidence interval)	1.0 (0.4-2.8)		0.6 (0.2-1.7)		0.6 (0.2-1.6)	

*The null outcome in all analyses is the absence of the specified outcome. Odds ratios below 1.0 indicate the desired effect of the intervention, i.e., a reduction in the risk of the specified neoplastic outcome.
†Time on beta carotene varied; *see* "Subjects and Methods" section.
‡Excludes 24-month results in patients who were not seen at 48 months.

Table 3. Neoplasia at 24 months and at 48 months—odds ratios and 95% confidence intervals for effects of the three interventions*

Outcome	Odds ratio (95% confidence interval)		
	Low fat	Bran	Beta carotene
		24 months (n = 381)†	
Adenoma of any size	0.9 (0.6-1.6)	1.5 (0.9-2.4)	1.4 (0.8-2.3)
Adenoma ≥10 mm	0.4 (0.1-1.1)	0.8 (0.3-2.2)	1.5 (0.5-4.2)
Adenoma with moderate or severe dysplasia	1.4 (0.5-3.8)	0.6 (0.2-1.6)	0.8 (0.3-2.2)
		48 months‡ (n = 299)†	
Adenoma of any size	0.9 (0.5-1.5)	1.5 (0.9-2.5)	1.3 (0.8-2.2)
Adenoma ≥10 mm	0.3 (0.1-1.0)§	0.8 (0.3-2.5)	3.0 (0.9-10.2)
Adenoma with moderate or severe dysplasia	1.2 (0.4-3.6)	0.7 (0.2-2.0)	0.6 (0.2-1.8)

*Adjusted for the number of adenomas at entry colonoscopy, number of adenomas before study entry, and history of large-bowel cancer in first-degree relatives; the null outcome in all analyses is the absence of the specified outcome. Odds ratios below 1.0 indicate the desired effect of the intervention, i.e., a reduction in the risk of the specified neoplastic outcome.
†Number of patients for each model is based on patients with data for all covariates in model.
‡Excludes 24-month results in patients who were not seen at 48 months.
§$P = .05$.

tion in risk with combined low-fat and wheat bran interventions. But we found no protective effect on the primary outcome, the incidence of total (predominantly small) adenomas after 24 months, by counseling reduction in fat intake to below levels advocated for the prevention of large-bowel cancer (*1*). Large adenomas were chosen for separate examination because they have a greater malignant potential than small adenomas (*10*). The bran supplement had no effect on the incidence of total adenomas, but our data suggest that bran may interact with low fat to reduce the incidence of large adenomas. The effects of the combination of low-fat and high-fiber intake on inhibiting the development of larger adenomas (none was observed in this dietary group in our study) are consistent with the suppressive effects of fat and fiber on cell proliferation seen in the same patients in our kinetic study (*11*). They are also consistent with the hypothesis of Hill et al. (*12,13*) that growth from small to large adenomas is associated with the fecal bile concentration whose main determinants are fat and (inversely) cereal fiber in-

Table 4. Frequency of patients with adenomas ≥10 mm in diameter at 24 and 48 months, stratified by wheat bran fiber and low-fat interventions

Intervention		Adenomas ≥10 mm			
		24 mo		48 mo*	
Wheat bran fiber	Low-fat	No	Yes	No	Yes
No	No	93	6	74	6
	Yes	93	5	72	4
Yes	No	89	7	68	7
	Yes	97	0	75	0

*Excludes 24-month results in patients who were not seen at 48 months.

take. Moreover, these effects are in accord with observational research (*9,14*). While our intention-to-treat analysis has not examined actual intake during the trial, our results are consistent with the hypothesis (*15*) that, specifically, fat from red meat increases the risk of colon cancer, since the avoidance of such fat was a strategy used to reduce fat intake. A randomized trial in Toronto of a low-fat–high-fiber diet (*16*) found no reduction in the risk of new total neoplastic polyps after 2 years, which is similar to our findings for total adenomas; however, no analysis of large polyps was reported. Future trials should focus on the interaction of fat and fiber, particularly in relation to large adenomas that have more accumulated genetic abnormalities (*17*).

The association between intervention and occurrence rates of adenomas at 24 months appears reasonably free from bias, given randomization, high follow-up, and blind assessment of outcome. The play of chance remains an issue, given the lower event rate than predicted with consequent lower power and wide CIs. Together with less than perfect compliance, the implication is that null results cannot be confidently interpreted as no effect. Outcomes at 24 and 48 months were generally similar, despite some theoretical, possible loss of control over unknown confounders at the later time as a result of nonrandom withdrawal from the trial.

The incidence of histologically confirmed adenomas at follow-up in this study was lower than generally reported in the literature and lower than anticipated. We think that the lower rates of new adenomas may be explained by more thorough clearing of polyps from the colon at study entry because of the advances in colonoscopic technology made during the 1980s. The U.S. National Polyp Study (*18*), which began in 1980, found similar rates from 12 to 36 months among patients cleared of polyps at 0 and 12 months. In patients in our trial in whom new adenomas were detected, an average of 1.7 adenomas was found at the 24-month colonoscopy, and an average of 1.3 was found at the 48-month colonoscopy.

Could the results be partly due to base-line differences, despite the randomization? Although there were base-line differences among the eight groups in the prevalence of two or more adenomas and of large adenomas (Table 1), the differences were small when patients on the low-fat intervention were compared with those not on low fat. The latter had a 22% prevalence of two or more adenomas at study entry compared with 20% in patients assigned to the low-fat intervention (23% in those assigned to low fat plus bran). Large adenomas at study entry had a prevalence (48%) in the low-fat group (44% in those also on bran) similar to that in the non-low-fat group (44%). Hence, base-line differences are unlikely to account for the possible reduction in risk with low fat or with low fat plus added bran.

During the trial, measures based on capsule counts and short-term recall indicated that compliance was good to excellent in all arms of the trial. (Median compliance of individuals averaged 95% or greater for each.) This result will be reported on in detail elsewhere. In summary, a sustained, average 10-fold rise in serum beta carotene confirms the high uptake of this intervention. In the bran intervention group, the diet diary data suggest that the median increase over base line was about 7 g dietary fiber per day. Changes in the low-fat intervention group are more difficult to interpret; diet diary data showed an apparent median 19-g-per-day decrease in intake across the first 2 years. Given the parallel fall in reported energy intake, however, the absence of substantial weight loss in this group suggests that this figure exaggerates the true decline. Nevertheless, despite the imprecision of measures of compliance, we found lower rates of large adenomas and of moderate or severe dysplasia among those estimated to be good compliers with the low-fat and bran interventions. This finding further supports the intention-to-treat data that suggest protective effects of low fat and added bran intake.

Historically, the approach to fat reduction has been to change categories of food, a strategy potentially disruptive to household menus. We chose to avoid this where possible, including reduction in the intake of visible fat, such as fat on beef and pork, and the avoidance of fatty cuts such as lamb chops. There was also increased use of low-fat dairy products as well as a reduction in butter or margarine added to foods at the table. Patients were not counseled to exclude red meat from the diet. While we have no quantitative support for the superiority of this approach, the outcome data support its possible utility.

Wheat bran supplements supplying 11 g per day of dietary fiber have been shown to inhibit rectal adenomas in patients with familial adenomatous polyposis (*19*) and to suppress rectal epithelial proliferation characteristics in cancer patients (*20*). The amount of wheat fiber was similar in our study. We used fine-particle-size raw bran because preliminary tests showed its greater palatability and ease of incorporation into the diet by mixing with such foods as cereals and sauces compared with coarse bran. We found that breath hydrogen was increased from 2 to 4 hours after consumption of this fine-particle-size bran, which is evidence of at least partial colonic fermentation (*21*). Wheat bran is poorly soluble, and its metabolism to short-chain fatty acids, including butyrate, is sustained throughout the length of the colon, including the high-risk rectosigmoid region (*22*).

Our finding of a lack of protective effect with beta carotene is consistent with results from two recent trials (*23,24*). In the study from Finland (*23*), the formulation and dose of beta carotene were identical to those used in our trial, and the incidence of colorectal cancer was reported to be 9.0 per 10 000 person-years in the treated group compared with 8.6 in the

group given placebo. In the study from the United States (*24*), no protective effect against new colorectal adenomas was found with 25 mg beta carotene given daily. Nevertheless, the possible reduction in moderate and severe dysplasia in our trial is consistent with a study of rectal labeling index in an unselected subset of 54 consecutive participants at one of our study centers (*11*), where the zone of proliferation was contracted toward the crypt base in patients on beta carotene. Our patients taking beta carotene had a statistically significantly lower proportion of positive nuclei in the upper rectal crypt compartments than those taking placebo, which suggests that beta carotene modifies preneoplastic mucosal proliferation rather than adenoma growth. Among persons with esophageal dysplasia in China, there was a statistically significant increase in reversion to nondysplastic cytology with a multivitamin, multimineral supplement (*25*).

Our trial supports current guidelines for cancer prevention (*1*), particularly with regard to reducing fat intake and at the same time eating more fiber-rich foods (specifically, wheat bran). The possible joint effects of eating less fat and more wheat fiber need further testing with much larger numbers of subjects than were available to us. This may be feasible in the analysis of ongoing trials in Europe (*26*) and North America (*27*) or in the design of new trials. The intermediate end points that best predict carcinoma also need to be clarified.

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Notes

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