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LACK OF EFFECT OF A LOW-FAT, HIGH-FIBER DIET ON THE RECURRENCE OF COLORECTAL ADENOMAS

ARTHUR SCHATZKIN, M.D., DR.P.H., ELAINE LANZA, PH.D., DONALD CORLE, M.S., PETER LANCE, M.D., FRANK IBER, M.D., BETTE CAAN, DR.P.H., MOSHE SHIKE, M.D., JOEL WEISSFELD, M.D., M.P.H., RANDALL BURT, M.D., M. ROBERT COOPER, M.D., J. WALTER KIKENDALL, M.D., JACK CAHILL, M.A., AND THE POLYP PREVENTION TRIAL STUDY GROUP*

ABSTRACT

Background We tested the hypothesis that dietary intervention can inhibit the development of recurrent colorectal adenomas, which are precursors of most large-bowel cancers.

Methods We randomly assigned 2079 men and women who were 35 years of age or older and who had had one or more histologically confirmed colorectal adenomas removed within six months before randomization to one of two groups: an intervention group given intensive counseling and assigned to follow a diet that was low in fat (20 percent of total calories) and high in fiber (18 g of dietary fiber per 1000 kcal) and fruits and vegetables (3.5 servings per 1000 kcal), and a control group given a standard brochure on healthy eating and assigned to follow their usual diet. Subjects entered the study after undergoing complete colonoscopy and removal of adenomatous polyps; they remained in the study for approximately four years, undergoing colonoscopy one and four years after randomization.

Results A total of 1905 of the randomized subjects (91.6 percent) completed the study. Of the 958 subjects in the intervention group and the 947 in the control group who completed the study, 39.7 percent and 39.5 percent, respectively, had at least one recurrent adenoma; the unadjusted risk ratio was 1.00 (95 percent confidence interval, 0.90 to 1.12). Among subjects with recurrent adenomas, the mean (±SE) number of such lesions was 1.85±0.08 in the intervention group and 1.84±0.07 in the control group. The rate of recurrence of large adenomas (with a maximal diameter of at least 1 cm) and advanced adenomas (defined as lesions that had a maximal diameter of at least 1 cm or at least 25 percent villous elements or evidence of high-grade dysplasia, including carcinoma) did not differ significantly between the two groups.

Conclusions Adopting a diet that is low in fat and high in fiber, fruits, and vegetables does not influence the risk of recurrence of colorectal adenomas. (N Engl J Med 2000;342:1149-55.)

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A WEALTH of laboratory, nutritional, and epidemiologic evidence implicates dietary factors in the pathogenesis of colorectal cancer.[1] International variation in the incidence of and mortality due to large-bowel cancer,[2] rapid increases in the incidence of colorectal cancer in several countries,[3] and data on migration[4] are consistent with a role of diet in the causation of colorectal cancer. Moreover, altering the proportions of dietary fat[5] and fiber[6] influences the development of colon tumors in animals. In humans, diet affects the production of intracolonic metabolic byproducts that may influence carcinogenesis.[7-9] Observational epidemiologic studies suggest that the ingestion of red meat and dietary fat increases the risk of colorectal cancer, whereas the ingestion of vegetables, dietary fiber, and certain micronutrients lowers the risk.[10-14] These results, however, are inconsistent,[15] and the evidence that diet contributes to causing colorectal cancer is hardly conclusive.

We studied whether adults can reduce their risk of colorectal cancer by modifying their diet. Because adenomatous polyps are considered precursors of most large-bowel cancers, we chose recurrence of adenomas as the primary end point.[16]

From the National Cancer Institute, Bethesda, Md. (A.S., E.L., D.C.); the School of Medicine and Biomedical Sciences, State University of New York at Buffalo, Buffalo (P.L.); Edward Hines, Jr., Hospital, Veterans Affairs Medical Center, Hines, Ill. (F.I.); the Kaiser Foundation Research Institute, Oakland, Calif. (B.C.); Memorial Sloan-Kettering Cancer Center, New York (M.S.); the University of Pittsburgh, Pittsburgh (J.W.); the University of Utah, Salt Lake City (R.B.); Wake Forest University Baptist Medical Center, Winston-Salem, N.C. (M.R.C.); Walter Reed Army Medical Center, Washington, D.C. (J.W.K.); and Westat, Rockville, Md. (J.C.).

Other authors were Laurence Freedman, Ph.D., National Cancer Institute, Bethesda, Md.; James Marshall, Ph.D., University of Arizona, Tucson; Robert E. Schoen, M.D., M.P.H., University of Pittsburgh, Pittsburgh; and Martha Slattery, Ph.D., University of Utah, Salt Lake City.

*Other members of the Polyp Prevention Trial Study Group are listed in the Appendix.

Some earlier trials tested the effects of dietary supplements, rather than an explicit dietary change, on the recurrence of adenomas.[17-22] Two pioneering studies did not find that low-fat diets (coupled with fiber supplementation) reduced the recurrence of adenomas,[23,24] but these small trials had limited statistical power. We report the results of the Polyp Prevention Trial, a large multicenter, randomized, controlled trial of the effect of a comprehensive dietary intervention — counseling of patients and assignment to a diet low in fat and high in fiber, fruits, and vegetables — on the recurrence of large-bowel adenomas.

METHODS

Study Design and Subjects

Details of the study design, eligibility criteria, randomization procedures, dietary intervention, and end-point assessment have been previously reported.[25,26] In brief, we recruited subjects who were at least 35 years old and who had had one or more histologically confirmed colorectal adenomas removed during a qualifying colonoscopy (in which the cecum was visualized, all polyps were removed, and the bowel was adequately prepared) within six months before randomization. Eligible subjects had no history of colorectal cancer, surgical resection of adenomas, bowel resection, the polyposis syndrome, or inflammatory bowel disease; weighed no more than 150 percent of the recommended level; were taking no lipid-lowering drugs; and had no medical condition or dietary restrictions or practices that would substantially limit compliance with the protocol. The institutional review boards of the National Cancer Institute and each participating center approved the study. All subjects provided written informed consent.

Staff members at eight clinical centers (listed in the Appendix) identified potential subjects through referrals by endoscopists or reviews of the records of the endoscopy service. Of 38,277 potential subjects, we enrolled 2079 (5.4 percent) in the trial. A total of 1037 were randomly assigned to adopt a diet that was low in fat and high in fiber, fruits, and vegetables (the intervention group), and 1042 were randomly assigned to follow their usual diet (the control group). The base-line characteristics of these subjects have been reported previously.[25,26]

Collection of Data

At one of two clinic visits before randomization, we measured each subject's weight and height. At the base-line visit and at subsequent annual visits at years 1, 2, 3, and 4, each subject answered a questionnaire assessing a variety of demographic, clinical, and behavioral characteristics and provided a venous blood specimen after an overnight fast.

Dietary Goals and Follow-up

For subjects in the intervention group, the dietary goals were to provide 20 percent of total calories from fat, 18 g of dietary fiber per 1000 kcal, and 3.5 servings of fruits and vegetables per 1000 kcal (range, 5 to 8 daily servings, depending on total energy intake). The intervention program included nutritional information and behavior-modification techniques. We offered each subject more than 50 hours of counseling sessions during the four-year intervention period, including 20 hours in the first year. Each subject in the intervention group was assigned to one nutritionist for counseling and another for dietary assessment. We provided subjects in the control group with general dietary guidelines from the National Dairy Council but gave them no additional nutritional or behavioral information.

We followed the subjects for approximately four years after randomization. Each year all subjects completed a four-day food record followed by a food-frequency questionnaire, the Block Health Habits and History Questionnaire,[27,28] which was modified slightly to reflect the intake of low-fat and high-fiber foods. In addition, subjects in the intervention group completed a four-day food record six months after randomization. Each year we administered unscheduled 24-hour dietary-recall questionnaires to a newly selected random sample of 10 percent of subjects.

Colonoscopy

Subjects returned to their usual endoscopist for colonoscopy one and four years after randomization. The one-year colonoscopy had to be performed at least 180 days after randomization but less than 2 years afterward. This colonoscopy served to detect and remove any lesions missed by the base-line colonoscopy. We obtained data on any unscheduled endoscopic procedure carried out in addition to the follow-up procedures at one and four years. We asked all investigators and subjects not to discuss a subject's randomization status with the endoscopists.

Assessment of Adenomas

Two central pathologists, who were unaware of the subjects' group assignment, determined the histologic features and degree of atypia (low-grade vs. high-grade) of all lesions. The endoscopists' reports provided information on the size, number, and location of all polyps.

We defined an adenoma as recurrent if it was found during any endoscopic procedure after the one-year colonoscopy or, for subjects who missed the one-year colonoscopy, during any endoscopic procedure performed at least two years after randomization. Adenomas found during the one-year colonoscopy were not considered recurrent. An end-points committee of gastroenterologists who were unaware of the subjects' group assignment evaluated complicated cases, including those involving lost tissue specimens or failure to reach the cecum. The few colorectal cancers diagnosed after the one-year colonoscopy were counted as recurrent lesions.

Statistical Analysis

We used the intention-to-treat principle to compare the intervention and control groups, defining groups according to the initial random assignment rather than according to actual or reported compliance with the protocol.[29] The primary end point was the recurrence of adenomas during the interval from the one-year to the four-year colonoscopy. Secondary end points were the number, size, location, and histologic features of the adenomas that were found. We calculated risk ratios and 95 percent confidence intervals in order to compare end-point events in the two groups.[30] We used logistic regression to adjust the effect of intervention for base-line prognostic factors. We used logistic-regression models to determine whether there was an interaction between dietary intervention and various covariates, and where appropriate, we performed covariate stratum-specific analyses.

RESULTS

Characteristics of the Subjects

The base-line demographic, clinical, nutritional, and behavioral characteristics were similar in the 958 subjects in the intervention group and the 947 subjects in the control group who completed the study (Table 1). Of these 1905 subjects, 1768 (92.8 percent) underwent a colonoscopy during year 1; the procedure was performed in 93.8 percent of the subjects in the intervention group and 91.8 percent of the subjects in the control group (Table 2). The median observation period (3.05 years) and the mean number of colonoscopic examinations after randomization (2.31) were the same in both groups (Table 2).

Subjects in the intervention group reduced their

TABLE 1. BASE-LINE CHARACTERISTICS OF THE SUBJECTS WHO COMPLETED THE STUDY.*

CHARACTERISTIC	INTERVENTION GROUP (N=958)	CONTROL GROUP (N=947)
Age (yr)	61.0±0.3	61.1±0.3
Male sex (%)	65.8	63.2
Minority race or ethnic group (%)	11.7	9.2
More than high school education (%)	65.3	65.2
Married (%)	78.2	80.8
Current smoker (%)	13.4	13.2
Alcohol intake (g/day)	7.4±0.4	8.0±0.5
Body-mass index	27.6±0.1	27.5±0.1
Vigorous or moderate activity or both (hr/wk)	12.6±0.5	11.6±0.4
Current aspirin use (%)	23.3	22.0
Use of calcium supplements (%)	15.4	14.1
Use of vitamin E supplements (%)	18.8	15.1
Plasma total cholesterol (mg/dl)†	202.6±1.8	200.2±1.7
Serum total carotenoids (μg/dl)‡	92.9±2.0	92.4±2.0
Serum α-tocopherol (μg/dl)§	1442±39	1335±27
Family history of colorectal cancer (%)	24.3	26.0
Adenoma ≥1 cm in maximal diameter (%)	27.2	31.5
≥2 Adenomas (%)	35.0	33.8
≥1 Villous or tubulovillous adenomas (%)¶	19.2	21.0
Advanced adenoma (%)‖	36.0	39.1
History of adenomas within previous 5 yr (%)	19.6	16.9

*Plus–minus values are means ±SE. Body-mass index is calculated as the weight in kilograms divided by the square of the height in meters.

†To convert values for cholesterol to millimoles per liter, multiply by 0.02586. A total of 414 subjects in the intervention group and 412 subjects in the control group were assessed after an overnight fast.

‡To convert values for carotenoids to millimoles per liter, multiply by 0.0185. A total of 415 subjects in the intervention group and 411 subjects in the control group were assessed after an overnight fast.

§A total of 418 subjects in the intervention group and 415 subjects in the control group were assessed after an overnight fast.

¶Information is based on the histologic analysis conducted by the central pathologists.

‖Advanced adenoma was defined as one that had a maximal diameter of at least 1 cm or at least 25 percent villous elements or evidence of high-grade dysplasia (including carcinoma).

TABLE 2. FOLLOW-UP COLONOSCOPY AMONG THE SUBJECTS WHO UNDERWENT RANDOMIZATION.

VARIABLE	INTERVENTION GROUP	CONTROL GROUP
No. randomized	1037	1042
No adenoma at base line — no. (%)	3 (0.3)	1 (0.1)
Lost to follow-up — no. (%)	76 (7.3)	94 (9.0)
Withdrew*	34 (44.7)	48 (51.1)
Died before follow-up colonoscopy	42 (55.3)	46 (48.9)
Follow-up colonoscopy — no. (%)†	958 (92.4)	947 (90.9)
Colonoscopy at year 1‡	899 (93.8)	869 (91.8)
Colonoscopy at year 4	638 (71.0)	550 (63.3)
Colonoscopy at year 4 and unscheduled colonoscopy	150 (16.7)	169 (19.4)
Unscheduled colonoscopy only	111 (12.3)	150 (17.3)
No colonoscopy at year 1	59 (6.2)	78 (8.2)
Colonoscopy only at year 4	19 (32.2)	30 (38.5)
Colonoscopy at year 4 and unscheduled colonoscopy	26 (44.1)	23 (29.5)
Unscheduled colonoscopy only	14 (23.7)	25 (32.1)
Median follow-up — yr	3.05	3.05
No. of procedures — mean ±SE	2.31±0.02	2.31±0.03

*The reasons for withdrawal were as follows: no colonoscopy at year 4 in 29 subjects in the intervention group and 43 subjects in the control group; refusal to participate in the case of 5 and 4 subjects, respectively; and illness in 1 subject in the control group.

†Among subjects in the intervention group who underwent follow-up colonoscopy, in 38 the cecum was not visualized; in 22 the bowel was poorly prepared, which might have caused small polyps to be overlooked; and in 53 one or more tissue specimens were lost during the procedure and therefore were not analyzed, no slides were available for pathological review, or data on histologic findings were unknown. The respective numbers in the control group were 40, 25, and 44. Five subjects (three in the intervention group and two in the control group) underwent sigmoidoscopy as the follow-up procedure.

‡P=0.10 for the difference between groups.

fat intake from a mean (±SE) of 35.6±0.2 percent of calories at the beginning of the trial to 23.8±0.2 percent at four years, according to data obtained from the food-frequency questionnaire (Table 3). The values from four-day food records from a random sample of 20 percent of subjects were 32.2 percent at base line and 20.6 percent at four years. Fat intake in the control group declined from 36.0±0.2 percent of calories at base line to 33.9±0.2 percent at four years. The values from four-day food records in this group were 32.5 percent and 31.1 percent, respectively. The absolute difference between the intervention and control groups in the change in dietary fat as a proportion of total calories over the four-year period was 9.7 percent (95 percent confidence interval, 9.0 to 10.3 percent).

Subjects in the intervention group raised their fiber intake by nearly 75 percent; subjects in the control group had a slight increase (Table 3). By the end of the study, the difference between the two groups in the change in fiber consumption was 6.9 g of dietary fiber per 1000 kcal (95 percent confidence interval, 6.4 to 7.3). As compared with subjects in the control group, those in the intervention group who consumed 2000 kcal per day increased their fiber intake by nearly 14 g on average. Data from the four-day food records were similar to those from the food-frequency questionnaires.

The number of servings of fruits and vegetables per 1000 kcal increased by about two thirds in the intervention group; subjects in the control group raised their fruit and vegetable intake only slightly (Table 3). The difference between the two groups in the change in fruit and vegetable intake was 1.13 servings per 1000 kcal (95 percent confidence interval, 1.04 to 1.21). As compared with subjects in the control group, subjects in the intervention group who consumed 2000 kcal per day increased their fruit and vegetable intake by approximately 2.25 servings. Data from the

TABLE 3. REPORTED DAILY DIETARY AND SUPPLEMENT INTAKES, BIOMARKERS, AND WEIGHT.*

VARIABLE	INTERVENTION GROUP		CONTROL GROUP		ABSOLUTE DIFFERENCE IN CHANGE BETWEEN GROUPS (95% CI)†
	AT RANDOMIZATION (N=958)	AT YEAR 4 (N=903)	AT RANDOMIZATION (N=947)	AT YEAR 4 (N=883)	
Fat (% of calories)	35.6±0.2	23.8±0.2	36.0±0.2	33.9±0.2	−9.7 (−10.3 to −9.0)
Fiber (g/1000 kcal)	10.0±0.1	17.4±0.2	9.5±0.1	10.0±0.1	6.9 (6.4 to 7.3)
Fruits and vegetables (servings/1000 kcal)	2.05±0.03	3.41±0.04	2.00±0.03	2.23±0.03	1.13 (1.04 to 1.21)
Calories (kcal/day)	1972±19	1870±16	1981±20	1910±18	−25 (−72 to 22)
Red and processed meat (g/day)	93.2±1.7	74.5±1.4	97.9±1.8	94.9±1.7	−15.8 (−20.2 to −11.5)
Ratio of red meat to chicken and fish	2.6±0.1	1.8±0.1	2.6±0.1	2.9±0.1	−1.0 (−1.3 to 0.7)
Whole grains (g/day)	83.4±2.0	115.3±2.3	76.8±1.9	72.6±1.9	35.9 (30.3 to 41.6)
Legumes (g/day)	14.2±0.6	48.5±1.6	13.7±0.6	16.2±0.7	31.9 (28.9 to 35.0)
Cruciferous vegetables (g/day)	28.9±0.9	44.4±1.5	26.5±1.0	27.7±1.0	14.2 (10.8 to 17.5)
Calcium from food and supplements (mg/day)	1032±20	1193±23	1002±20	1096±23	77.2 (16.1 to 138.3)
Folate from food and supplements (μg/day)	435.0±8.8	593.9±12.7	423.9±9.0	487.5±12.5	95.4 (62.0 to 128.9)
Multivitamin use (%)	36.6	42.2	36.4	41.7	−0.3 (−4.8 to 4.2)
No. of subjects	958	921	947	912	
Plasma total cholesterol (mg/dl)‡	5.30±0.01	5.27±0.01	5.29±0.01	5.27±0.01	−0.01 (−0.03 to 0.01)
No. of subjects	414	372	412	364	
Serum total carotenoids (mg/dl)§	4.46±0.02	4.50±0.02	4.45±0.02	4.42±0.02	0.06 (0.01 to 0.11)
No. of subjects	415	369	411	361	
Weight (lb)¶	179.9±1.1	178.5±1.1	178.3±1.1	179.3±1.1	−2.5 (−3.6 to −1.4)
No. of subjects	958	919	947	907	

*Plus–minus values are means ±SE. CI denotes confidence interval. To convert values for cholesterol to millimoles per liter, multiply by 0.02586; to convert values for carotenoids to millimoles per liter, multiply by 0.0185. Cholesterol and carotenoids were measured after an overnight fast.

†Differences were calculated only for subjects who had values at randomization and at year 4.

‡Log-transformed values are shown. The log-transformed values of −0.02 mg per deciliter in the intervention group and −0.01 mg per deciliter in the control group for the difference within groups from randomization to year 4 reflect respective decreases in absolute cholesterol concentrations of approximately 2 percent and 1 percent; the absolute difference in the change between groups is about −1 percent (95 percent confidence interval, −3 percent to 1 percent).

§Log-transformed values are shown. The log-transformed values of 0.04 mg per deciliter in the intervention group and −0.01 mg per deciliter in the control group for the difference within groups from randomization to year 4 reflect an increase of approximately 5 percent in absolute carotenoid concentrations in the intervention group and a decrease of 1 percent in the control group; the absolute difference in the change between groups is about 6 percent (95 percent confidence interval, 1 percent to 11 percent).

¶To convert values for weight to kilograms, divide by 2.2.

four-day food records showed a difference in the change between groups of 1.8 servings per 1000 kcal.

Changes in the intake of fat, fiber, and fruits and vegetables generally occurred within the first year and were subsequently maintained. Data from the food-frequency questionnaire showed that during the first year subjects in the intervention group obtained 24.6 percent of calories from fat, consumed 17.7 g of dietary fiber per 1000 kcal, and ate 3.3 servings of fruits and vegetables per 1000 kcal. These changes were similar for men and women. As compared with subjects in the control group, subjects in the intervention group also significantly altered their intake of other nutrients and foods, including red and processed meat, whole grains, legumes, calcium, and folate (Table 3). Data from the 24-hour dietary recall were similar to those from the four-day food records.

Over the four-year period of observation, the subjects in the intervention group had a significant increase in serum carotenoid concentrations and decrease in weight (Table 3), as compared with changes measured in subjects in the control group. The small reductions in plasma total cholesterol concentrations did not differ significantly between the two groups. The differences in the changes in total cholesterol, total carotenoids, and weight (calculated as the change in the control group over time minus the change in the intervention group over time) were somewhat greater after one year than after four years.

Recurrence of Adenomas

Adenomatous polyps recurred in 754 of the 1905 subjects who completed the study (39.6 percent). At least one recurrent adenoma was found in 39.7 per-

TABLE 4. RISK OF RECURRENCE OF ADENOMAS AMONG THE SUBJECTS WHO COMPLETED THE STUDY.

VARIABLE	INTERVENTION GROUP (N=958)	CONTROL GROUP (N=947)	RISK RATIO (95% CI)*	P VALUE
	no. of subjects (%)			
No. of adenomas				
⩾1†	380 (39.7)	374 (39.5)	1.00 (0.90–1.12)	0.98
1	219 (22.9)	217 (22.9)	1.00 (0.85–1.18)	1.00
2	88 (9.2)	82 (8.7)	1.06 (0.80–1.41)	0.75
⩾3	73 (7.6)	75 (7.9)	0.96 (0.71–1.31)	0.87
Location of adenomas‡				
Proximal	203 (21.2)	173 (18.3)	1.16 (0.97–1.39)	0.12
Distal	100 (10.4)	124 (13.1)	0.80 (0.62–1.02)	0.08
Proximal and distal	69 (7.2)	72 (7.6)	0.95 (0.69–1.30)	0.81
Unknown	8 (0.8)	5 (0.5)	1.58 (0.52–4.82)	0.59
Largest adenoma ⩾1 cm	47 (4.9)	53 (5.6)	0.88 (0.60–1.28)	0.57
Advanced adenoma§	60 (6.3)	66 (7.0)	0.90 (0.64–1.26)	0.60

*CI denotes confidence interval.

†The absolute difference between groups was 0.2 percent (95 percent confidence interval, −4.2 percent to 4.6 percent). The mean (±SE) number of recurrent adenomas among those with a recurrence was 1.85±0.08 in the intervention group and 1.84±0.07 in the control group. The distributions of adenomas according to size were not significantly different in the two groups (P=0.77).

‡Proximal is defined as the portion of the large bowel from the cecum up to, but not including, the splenic flexure. Distal is defined as the portion of the large bowel from the splenic flexure up to and including the rectum. The distributions of adenomas according to location were not significantly different in the two groups (P=0.17).

§An advanced adenoma was one that had a maximal diameter of at least 1 cm or at least 25 percent villous elements or evidence of high-grade dysplasia (including carcinoma).

cent of subjects in the intervention group and 39.5 percent of subjects in the control group; the unadjusted risk ratio was 1.00 (95 percent confidence interval, 0.90 to 1.12; P=0.98) (Table 4). Of these recurrent adenomas, the mean number was 1.85±0.08 in the intervention group and 1.84±0.07 in the control group (P=0.93). Among the 638 subjects in the intervention group and 550 subjects in the control group who underwent colonoscopy only at year 1 and year 4 after randomization, 36.7 percent and 35.8 percent, respectively, had one or more recurrent adenomas; the unadjusted risk ratio was 1.02 (95 percent confidence interval, 0.88 to 1.19; P=0.81).

The intervention and control groups did not differ significantly with respect to the number with recurrent large adenomas (with a maximal diameter of at least 1 cm) or advanced adenomas (defined as those that had a maximal diameter of at least 1 cm or at least 25 percent villous elements or evidence of high-grade dysplasia, including carcinoma); this was true when the analysis included all those who completed the study (Table 4) as well as when it included those who underwent only the scheduled colonoscopies at year 1 and year 4 after randomization (data not shown). In both groups, approximately 27 percent of subjects had at least one recurrent adenoma proximal to the splenic flexure (Table 4). Sixty-three percent of recurrent adenomas were proximal to the splenic flexure, whereas 58 percent of base-line adenomas were distal to that site (data not shown).

Colorectal cancer was diagnosed in 14 subjects after randomization (10 in the intervention group and 4 in the control group); the unadjusted risk ratio was 2.5 (95 percent confidence interval, 0.8 to 7.9; P=0.19). Of these 14 subjects, 6 (4 in the intervention group and 2 in the control group) were given a diagnosis after the one-year colonoscopy; the unadjusted risk ratio was 2.0 (95 percent confidence interval, 0.4 to 10.8; P=0.69).

To adjust for an imbalance in influential base-line variables between the groups, we used logistic-regression models that included as covariates the random group assignment and the base-line characteristics listed in Table 1. Adjustment for these factors had no effect on the risk of recurrence.

For all but one of the covariates listed in Table 1, we found on logistic-regression analysis that there was no statistically significant (P<0.01) interaction with group assignment. We observed a significant interaction (P=0.005 before adjustment for multiple comparisons) between the randomization group and sex. We therefore examined the recurrence of adenomas among men and women separately. Among men, the recurrence rate was lower in the intervention group than in the control group (41.9 percent vs. 46.7 percent); the unadjusted risk ratio was 0.89 (95 percent confidence interval, 0.79 to 1.02; P=0.11). Among women, the rate of recurrence was higher in the intervention group than in the control group (35.4 percent vs. 27.2 percent); the unadjusted risk ratio was

1.30 (95 percent confidence interval, 1.04 to 1.63; P=0.03). With respect to both large and advanced recurrent lesions, the differences between groups were not significant for either men or women; the interaction between the randomization group and sex was not significant for either end point. There were also no significant ($P<0.05$) differences between the groups in the number of either deaths or hospitalizations (for all causes and for specific diagnoses).

DISCUSSION

We found that the rate of recurrent adenomas was not changed by dietary intervention. Our results are compatible with, at most, an absolute reduction related to the intervention of about 4 percent in the incidence of recurrent adenomas (Table 4). We also found no effect of the dietary intervention on the incidence of large or advanced recurrent lesions.

Two previous trials also found that dietary changes had no effect on the overall risk of recurrence of colorectal adenomas. The Toronto Polyp Prevention Trial reported no significant difference in recurrence after two years between subjects in the intervention group and those in the control group (a total of 201 subjects) who reported ingesting 25 and 33 percent of calories from fat and 35 and 16 g of fiber per day, respectively.[23] In the Australian Polyp Prevention Project, which included 424 subjects, none of the interventions (a reduction in dietary fat, use of a wheat-bran–fiber supplement, and supplementation with beta carotene) resulted in a statistically significant reduction in the risk of recurrence after 48 months of observation.[24] The Australian trial did report a marginally significant reduction in the recurrence of large adenomas (⩾1 cm in diameter) among subjects eating a low-fat diet, but in that study large recurrent adenomas developed in only 17 subjects, as compared with 100 in our study.

The straightforward interpretation of our finding is that a diet that is low in fat, and high in fiber, fruits, and vegetables does not reduce the risk of recurrent adenomas or, by inference, colorectal cancer. Alternative explanations, however, merit consideration.

Most recurrent adenomas were small; only about 5 percent of subjects had a recurrent lesion 1 cm or more in diameter (Table 4). Adopting a diet that was low in fat and high in fiber, fruits, and vegetables might affect only the growth of small adenomas into large adenomas or the transformation of large adenomas into invasive carcinomas.[31]

The dietary-assessment data indicated that the intervention and control groups differed substantially in the consumption of fat, fiber, and fruits and vegetables. The findings regarding carotenoid concentrations and weight were consistent with such differences. (The changes in blood lipid concentrations were minimal but compatible with the results of other studies of dietary intervention as well as with predictions based on the equation of Keys et al.[32]) These data, however, do not preclude the possibility that in the light of the dietary expectations fostered by the trial, subjects in the intervention group systematically underreported their intake of fat or overreported their consumption of fiber or fruits and vegetables. Another possibility is that the dietary intervention was inadequate; a reduction in fat intake to no more than 15 percent of calories or a greater intake of fiber or fruits and vegetables might be required to reduce the risk of recurrent adenomas. Moreover, we may not have chosen the optimal set of dietary targets. The 20 percent reduction in the consumption of red and processed meat among subjects in the intervention group may have been too small to affect the risk of recurrence of adenomas. The same may be true for reductions in the consumption of meat cooked at high temperatures (which contains high concentrations of heterocyclic amines)[33] or sugar.[11]

The mean age of the subjects at base line was 61 years. If nutritional factors influence critical events in colorectal neoplasia at the molecular, cellular, or tissue level only earlier in life, then a change in diet later in adult life may be ineffective. A relatively short period of dietary intervention (four years) might also fail to reduce the risk of recurrent adenomas. A longer period of intervention as well as follow-up might allow the development of enough adenomas to reveal the protective effect of the intervention, if there were one. In a recent clinical trial of calcium supplementation to prevent colorectal adenoma,[22] however, the average age of the subjects, the duration of the intervention, and the length of follow-up were similar to those in our study, but that study did find a lower recurrence rate among subjects in the intervention group.

Bias is an unlikely explanation for our results. Subjects in the intervention and control groups who completed the study did not differ appreciably with respect to base-line characteristics, and the main results did not change after adjustment for multiple covariates in logistic-regression analysis. Although we could not disguise the group assignments from the subjects or guarantee that the endoscopists were unaware of these assignments, we have no reason to suspect that endoscopists tended to search more diligently for — and therefore find more — adenomas among subjects in the intervention group than in the control group. A series of imputations based on the age and sex of subjects who did not undergo follow-up colonoscopy made no appreciable difference in estimates of recurrence.[34]

The higher rate of recurrent adenomas among women in the intervention group than among those in the control group and the interaction between sex and group was not affected by a multivariate adjustment for age and the number of adenomas at base line (both of which were predictive of the risk of recurrence) and other covariates listed in Table 1. Never-

theless, we conclude that this interaction resulted from chance observations arising from repeated testing. In the Toronto trial, the rate of recurrence was lower among women in the intervention group but higher among men in that group, as compared with the risk in the control subjects, though these differences were not statistically significant.[23]

In summary, our study provided no evidence that a diet low in fat and high in fiber, fruits, and vegetables reduces the risk of recurrent colorectal adenomas. Nevertheless, we cannot definitively conclude that a change in diet is ineffective in reducing the risk of colorectal cancer. Nor should we overlook the abundant data indicating that a diet low in saturated fats and rich in fruits, vegetables, and whole grains has a favorable influence on the risk of chronic disease and mortality.[35-37]

APPENDIX

Other members of the Polyp Prevention Trial Study Group were as follows: *National Cancer Institute* — R. Ballard-Barbash, C. Clifford, J. Tangrea; *State University of New York at Buffalo* — D. Hayes, N.J. Petrelli, M. Beddome, K. Kroldart, S. Rauth, L. Wodarski; *Edward Hines, Jr., Hospital, Veterans Affairs Medical Center* — P. Murphy, E.C. Boté, L. Brandt-Whittington, N. Haroon, N. Kazi, M.A. Moore, S.B. Orloff, W.J. Ottosen, M. Patel, R.L. Rothschild, M. Ryan, J.M. Sullivan, A. Verma; *Kaiser Foundation Research Institute* — J.V. Selby, G. Friedman, M. Lawson, G. Taff, D. Snow, M. Belfay, M. Schoenberger, K. Sampel, T. Giboney, M. Randel; *Memorial Sloan-Kettering Cancer Center* — S. Winawer, A. Bloch, J. Mayer, R. Morse, L. Latkany, D. D'Amato, A. Schaffer, L. Cohen; *University of Pittsburgh* — R.R. Schade, L. Kuller, B. Gahagan, A. Caggiula, T. Coyne, C. Lucas, S. Pappert, G. Landis, L. Dyjak, R. Robinson, L. Search, D. Hanson; *University of Utah* — N. Viscofsky, J. Benson, J. Neilson, R. O'Donnel, M. Briley, K. McDivitt, K. Heinrich; W. Samowitz; *Wake Forest University Baptist Medical Center* — E. Paskett, S. Quandt, C. DeGraffinreid, K. Bradham, L. Kent, M. Self, D. Boyles, D. West, L. Martin, N. Taylor, E. Dickenson, P. Kuhn, J. Harmon, I. Richardson, H. Lee, E. Marceau; *Walter Reed Army Medical Center* — D.J. Mateski, R.K.H. Wong, C. Cheney, E. Rueda-Pedraza, V. Jones-Miskovsky, A. Greaser, E. Stoute, S. Hancock, S. Chandler, M. Burman, E. Crutchfield, C. Slivka, L. Johnson; *Data and Nutrition Coordinating Center (Westat)* — M. Hasson, C. Daston, B. Brewer, C. Sharbaugh, B. O'Brien, N. Odaka, K. Umbel, J. Pinsky, H. Price, P. Clark; *Central Pathologists* — K. Lewin (University of California, Los Angeles), H. Appelman (University of Michigan); *Laboratories* — P.S. Bachorik, K. Lovejoy (Johns Hopkins University), A. Sowell (Centers for Disease Control and Prevention); *Data and Safety Monitoring Committee* — E.R. Greenberg (Norris Cotton Cancer Center and Dartmouth Medical School), E. Feldman (Augusta, Ga.), C. Garza (Cornell University), R. Summers (University of Iowa); S. Weiand (University of Minnesota), D. DeMets (University of Wisconsin).

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