Dietary fiber intake and risk of colorectal cancer and incident and recurrent adenoma in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial[1,2]

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ABSTRACT

Background: Dietary fiber has been associated with a reduced risk of colorectal cancer. However, it remains unclear at which stage in the carcinogenic pathway fiber may act or which food sources of dietary fiber may be most beneficial against colorectal cancer development.

Objective: The objective was to prospectively evaluate the association between dietary fiber intake and the risk of incident and recurrent colorectal adenoma and incident colorectal cancer.

Design: Study participants were identified from the intervention arm of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Participants received flexible sigmoidoscopy at baseline and 3 or 5 y after. Dietary fiber intake was measured by using a self-reported dietary questionnaire. The colorectal cancer, incident adenoma, and recurrent adenoma analyses were based on 57,774, 16,980, and 1667 participants, respectively. Unconditional logistic regression was used to assess the risk of incident and recurrent adenoma, and Cox proportional hazards models were used to assess the risk of colorectal cancer across categories of dietary fiber intake, with adjustment for potential confounders.

Results: Elevated total dietary fiber intake was associated with a significantly reduced risk of incident distal colorectal adenoma ($OR_{\text{highest vs. lowest tertile of intake}}$: 0.76; 95% CI: 0.63, 0.91; *P*-trend = 0.003) but not recurrent adenoma (*P*-trend = 0.67). Although the association was not statistically significant for colorectal cancer overall (HR: 0.85; 95% CI: 0.70, 1.03; *P*-trend = 0.10), a reduced risk of distal colon cancer was observed with increased total fiber intake (HR: 0.62; 95% CI: 0.41, 0.94; *P*-trend = 0.03). Protective associations were most notable for fiber originating from cereals or fruit.

Conclusions: This large, prospective study within a population-based screening trial suggests that individuals consuming the highest intakes of dietary fiber have reduced risks of incident colorectal adenoma and distal colon cancer and that this effect of dietary fiber, particularly from cereals and fruit, may begin early in colorectal carcinogenesis. This trial was registered at clinicaltrials.gov as NCT01696981. *Am J Clin Nutr* 2015;102:881–90.

Keywords: cancer risk, colorectal adenoma, colorectal cancer, dietary fiber, epidemiology

INTRODUCTION

Dietary fiber was first hypothesized as being of potential etiological importance for colorectal cancer in the early 1970s by Burkitt, who observed lower rates of colorectal cancer among Africans who consumed a diet high in fiber (1). Several biologically plausible mechanisms have been postulated to explain the link between fiber and prevention of colorectal cancer. Increased fiber intake may lead to a dilution of fecal carcinogens, reduced transit time, and bacterial fermentation of fiber to short-chain fatty acids with anticarcinogenic properties (2, 3). Numerous prospective studies have evaluated the association between fiber and colorectal cancer (4–9), and a meta-analysis showed a reduced risk of colorectal cancer with dietary fiber intake (10). In 2011, the World Cancer Research Fund and American Institute of Cancer Research continuous update report on colorectal cancer concluded that there was now "convincing" evidence that increased fiber intake was protective against the risk of colorectal cancer (11).

Nevertheless, questions still remain about which food sources of dietary fiber may be most beneficial against colorectal cancer development and at which stages along the adenoma-carcinoma pathway fiber may act (10). A Cochrane systematic review of 5 randomized controlled trials found no evidence that dietary fiber was associated with reduced colorectal adenoma recurrence 2–4 y later (12); however, the time period for evaluation may have been too short. Alternatively, fiber may only prevent disease progression to colorectal cancer and not early lesions such as adenoma. A previous publication from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial identified that individuals with the highest quartile of fiber intake had a 27% reduced risk of prevalent adenoma (13). A recent meta-analysis reported that total fiber

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intake was associated with a reduced risk of adenoma; however, the reduction in risk was greater and only significant for retrospective case-control studies and not significant for prospective studies (14). Given the potential for recall and selection bias in case-control studies and the limited number of prospective studies to date (15–18), there is a clear need for additional prospective studies of incident adenoma and fiber intake. Individuals with high fiber intakes may be more likely to engage in other healthy behaviors, including attending regular colorectal screening, which could lead to earlier detection of adenoma (19). In addition, because adenoma is detected only through endoscopy, many studies, even if prospective, do not have information on previous screenings and therefore many of the adenomas detected may have been present for years before diagnosis and are likely prevalent cases as opposed to incident cases.

We sought to further examine the temporal association between various food sources of dietary fiber intake and the risk of incident and recurrent colorectal adenoma and incident colorectal cancer in the intervention arm of a large prospective colorectal cancer screening trial. Unlike many previous observational cohorts in which opportunities for screening may be variable and thus potentially prone to detection bias, in the screening arm of this trial individuals had equitable opportunities for colorectal screening and neoplasm detection.

METHODS

Study population

Study participants were identified from the intervention arm of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, described previously (20). Briefly, 154,952 individuals were recruited via 10 centers in the United States (Birmingham, Alabama; Boulder, Colorado; Detroit, Michigan; Hawaii; Los Angeles, California; Minneapolis, Minnesota; Pittsburgh, Pennsylvania; Salt Lake City, Utah; St Louis, Missouri; Wisconsin; Washington, DC) between 1993 and 2001. Individuals were eligible for randomization if they were aged 55–74 y; had no history of prostate, lung, colorectal, or ovarian cancer; had not undergone cancer treatment; were not currently participating in another cancer screening or prevention trial; and had not taken finasteride in the previous 6 mo. From 1995 onward, individuals were ineligible if they had undergone a colonoscopy, sigmoidoscopy, barium enema, or multiple prostate-specific antigen tests in the previous 3 y. Participants were given a food-frequency questionnaire (FFQ) and a baseline risk factor questionnaire, which collected information on personal and family medical history, tobacco smoking habits, medication use, and anthropometric data. All participants provided written informed consent, and the study was approved by the Institutional Review Boards at the National Cancer Institute and 10 recruitment centers.

A total of 77,445 individuals were randomly assigned to the screening arm of the trial. Participants in the intervention arm underwent a flexible sigmoidoscopy at baseline and at one follow-up visit, either 3 y (T3) or 5 y (T5) after baseline, whereas individuals in the control arm received usual medical care. Individuals with abnormalities detected at screening were referred for follow-up to their usual health care providers. Medical records from follow-up procedures were reviewed by trained personnel for relevant outcomes. Additional colorectal cancer diagnoses were ascertained through annual questionnaires and linkage to the National Death Index and confirmed via medical record review. This study was limited to individuals randomly assigned to the intervention arm, who completed a baseline questionnaire and had no personal history of cancer (excluding nonmelanoma skin cancer) (n = 72,139). Additional exclusions and analytic criteria for each of the 3 outcomes evaluated are described below.

Colorectal cancer

For analysis of incident colorectal cancer, individuals who did not complete the FFQ or had an inadequate FFQ (defined as ≥8 FFQ items missing) or reported extreme energy intakes (<1st percentile or >99th percentile of intake) were excluded (n = 13,495). Individuals reporting a history of colitis, Crohn disease, polyposis syndromes, or Gardner disease at baseline or who received a diagnosis of cancer before completion of the FFQ were excluded from analysis (n = 869). Individuals were followed up from the time of FFQ completion to the date of colorectal cancer diagnosis, death, loss to follow-up, 13 y of follow-up, or 31 December 2009, whichever came first. After exclusions, 57,774 individuals remained for analysis, of whom 733 developed colorectal cancer over a median 12.1 y of follow-up.

Incident colorectal adenoma

For this analysis, only individuals who received an adequate sigmoidoscopy (defined as insertion ≥50 cm with ≥90% of mucosa visible) at baseline with no polyps detected and no abnormal or suspicious findings, received an adequate sigmoidoscopy at T3/T5, and had no personal history of colorectal cancer history by T3/T5 were considered for analysis (n = 22,500). Persons without evidence of polyps on both the T0 and T3/T5 screening examinations were considered controls, and persons with a histologically confirmed adenoma in the distal colon or rectum detected on the T3/T5, but not on the T0 screen, were considered to have incident adenoma. Persons were excluded if they had an inadequate or missing FFQ (n = 2729); reported a personal history of colitis, Crohn disease, polyposis, or Gardner syndrome (n = 211); reported a previous diagnosis of colorectal polyps (n = 1000) or cancer (n = 634); or developed cancer during the trial period (n = 944). After exclusions, 16,980 individuals were left for analysis, of whom 1004 had an incident adenoma detected at either T3 or T5. The remaining 15,976 individuals without evidence of polyps were considered controls.

Recurrent colorectal adenoma

A subset of individuals randomly assigned to the screening arm of the trial (n = 5013) completed a telephone-administered questionnaire regarding all colonoscopies performed over the 10-y period after the baseline sigmoidoscopy. The current analysis was restricted to individuals who had an adenoma diagnosed at baseline and at least one follow-up endoscopy within the 10-y period after baseline (n = 1905). Individuals who received a diagnosis of adenoma at any follow-up endoscopy were defined as recurrent adenoma cases, and all others were defined as controls. Again, individuals with an inadequate or missing FFQ (n = 147); who reported a personal history of colitis, Crohn disease, polyposis, or Gardner syndrome (n = 13); who had cancer (n = 76); or who had an unknown case status (n = 2) were excluded from analysis. After exclusions, 1667 individuals remained for analysis, of whom 738 had a recurrent colorectal adenoma during the time period. The remaining 929 were analyzed as controls.

Exposure assessment

As described previously (13), dietary intake of fiber was measured by using a self-administered 137-item FFQ administered at baseline, which inquired about usual dietary intake (but not supplemental fiber intake) over the preceding year. The FFQ was modeled based on 3 validated FFQs, the National Cancer Institute's Diet History Questionnaire, the Block FFQ, and the Willett FFQ, which were found to have moderate to high correlation coefficients (between 0.56 and 0.82) (21). Nutrient and food group values were estimated by using the My Pyramid food group servings database from the USDA (22). Specific fiber food groups (e.g., grain and cereal, fruit, vegetables, and legumes) were created based on the pyramid food groups by calculating the fiber content of each food item belonging to the group and multiplying it by the reported amount consumed.

Statistical analysis

Dietary fiber was energy adjusted by using the nutrient-density method (23). Energy-adjusted dietary fiber was categorized into tertiles of intake per 1000 kcal/d, based on the distribution of intake in the colorectal cancer cohort. Chi-square tests (categorical variables) and ANOVA (continuous variables) were used to assess the association between baseline characteristics and outcomes. Cox proportional hazards models were used to estimate the HR and corresponding 95% CIs for the risk of colorectal cancer associated with fiber intake. The risk of incident and recurrent adenoma was estimated by using unconditional logistic regression to calculate the ORs and 95% CIs. Tests for trend were assessed by assigning each individual in a particular tertile of fiber intake the median value for that tertile, before inclusion in the statistical model. A 2-tailed P value <0.05 was considered significant, and analyses were conducted by using Stata/SE statistical software (version 11.0).

Base models were developed for each outcome, which included age, sex, ethnicity, study center, total energy intake (kcal/d), screening during the trial, adenoma at baseline or follow-up screens (for colorectal cancer), trial year (T3 or T5) of screening (for incident adenoma), surveillance period, and number of surveillance endoscopies (for recurrent adenoma) as covariates.

To further control for other possible confounders in the analysis, full models were developed for each outcome (i.e., incident adenoma, recurrent adenoma, and colorectal cancer). For the full models, additional confounders were added to the base model if they led to a change of $\geq$10% in the β coefficient for total dietary fiber (24). Additional factors tested included education, exercise, smoking status, family history of colorectal cancer, use of nonsteroidal anti-inflammatory drugs, menopausal hormone therapy use (HRT), BMI, and intakes of calcium, total folate (prefortified diet and supplements), red meat, processed meat, and alcohol.

The association between fiber intake and risk of incident adenoma, recurrent adenoma, and colorectal cancer was also assessed with fiber as a continuous variable [per 5 g/1000 kcal increase, for approximate comparability with the 10 g/d used in prior meta-analyses (10)] using the respective fully adjusted models.

Stratified analyses were conducted by age, sex, and additional confounders included in the respective fully adjusted models. Interactions were tested by using likelihood-ratio tests. Additional analyses by neoplasm location and disease severity were conducted.

RESULTS

Cohort characteristics

Of the 57,774 individuals in the cohort who had an adequate FFQ, the median dietary intake of fiber was 23.3 g/d, and the median energy intake was 1911.5 kcal/d. Individuals in the highest tertile of energy-adjusted fiber intake were more likely to be older, be female, have lower BMIs, be physically active, be an HRT user, and be a college graduate and less likely to be of non-Hispanic white ethnicity, be a current smoker, have regularly used nonsteroidal anti-inflammatory drugs, or have an adenoma detected on the T0 or T3/T5 screen (**Table 1**). Individuals with higher fiber intakes also had greater supplemental calcium and total folate intakes but lower alcohol and red and processed meat intakes.

Within the incident colorectal adenoma subset, adenoma cases were more likely to be male, to be of non-Hispanic white ethnicity, to be current smokers, and to have higher intakes of total energy, alcohol, and red and processed meats and a higher BMI but less likely to have higher total calcium intakes or to undertake regular physical activity than noncases (**Table 2**). Within the recurrent colorectal adenoma subset, adenoma cases were more likely to be male, to be current smokers, and to have higher intakes of alcohol and processed meat but less likely to be non-Hispanic white or to have high total calcium intakes than noncases (Table 2).

Incident left-sided colorectal adenoma

In minimally adjusted models, an inverse dose-response association was observed between incident colorectal adenoma risk and total fiber intake ($OR_{tertile\ 3\ vs.\ tertile\ 1}$: 0.65; 95% CI: 0.54, 0.77; P-trend $<$ 0.001) and fiber originating from cereal, vegetables, and fruit (**Table 3**). After further adjustment for smoking status, alcohol intake, and total folate intake, the reduction in risk of incident colorectal adenoma remained for individuals in the highest compared with the lowest tertile of total fiber intake ($OR_{tertile\ 3\ vs.\ tertile\ 1}$: 0.76; 95% CI: 0.63, 0.91; P-trend = 0.003) and for individuals in the highest tertile of fiber from cereal ($OR_{tertile\ 3\ vs.\ tertile\ 1}$: 0.78; 95% CI: 0.66, 0.92) but not fiber from vegetables or fruit. For total fiber, an inverse association was observed for both distal colon and rectal adenoma. This protective effect for total fiber was also evident for advanced adenoma ($OR_{tertile\ 3\ vs.\ tertile\ 1}$: 0.64; 95% CI: 0.44, 0.92; P-trend = 0.02) (**Supplemental Table 1**). When the association between fiber intake and risk of incident adenoma was analyzed with fiber as a continuous variable, the results were similar, with associations for total fiber ($OR_{per\ 5\ g/1000\ kcal\ increment}$: 0.87; 95% CI: 0.78, 0.97) and cereal fiber ($OR_{per\ 5\ g/1000\ kcal\ increment}$: 0.81; 95% CI: 0.67, 0.97) but not for other sources of fiber intake (data not shown).

No significant interactions with most demographic or lifestyle characteristics were found; however, we did observe that the protective effect of fiber was stronger for select groups. The association between cereal fiber and risk of incident adenoma was stronger for males ($OR_{tertile\ 3\ v\ tertile\ 1}$: 0.69; 95% CI: 0.56, 0.85) than for females ($OR_{tertile\ 3\ vs.\ tertile\ 1}$: 1.03; 95% CI: 0.77, 1.38; $P_{-interaction}$ = 0.001), and the association with total fiber was stronger for individuals with a higher alcohol intake ($OR_{tertile\ 3\ vs.\ tertile\ 1}$: 0.63; 95% CI: 0.49, 0.81) than for those with a low intake ($OR_{tertile\ 3\ vs.\ tertile\ 1}$: 0.94; 95% CI: 0.71, 1.24; P-interaction = 0.05) (**Supplemental Table 2**).

TABLE 1
Characteristics of participants in the colorectal cancer data set by tertiles of fiber intake[1]

	Tertiles of total fiber intake			
Characteristic	<9.9 g/1000 kcal	≥9.9 to <12.8 g/1000 kcal	≥12.8 g/1000 kcal	*P* value
Age at baseline, y	61.6 ± 5.1[2]	62.7 ± 5.3	63.7 ± 5.4	<0.001
Male sex, *n* (%)	12,685 (65.9)	9609 (49.9)	7511 (39.0)	<0.001
Ethnicity, *n* (%)				<0.001
Non-Hispanic white	17,545 (91.1)	17,780 (92.3)	17,151 (89.1)	
Non-Hispanic black	790 (4.1)	602 (3.1)	821 (4.3)	
Asian	494 (2.6)	518 (2.7)	823 (4.3)	
Other	429 (2.2)	358 (1.9)	463 (2.4)	
Education, *n* (%)				
College graduate or postgraduate	6091 (31.7)	7126 (37.0)	7604 (39.5)	<0.001
BMI, kg/m^2	28.0 ± 4.8	27.4 ± 4.8	26.6 ± 4.7	<0.001
Physical activity ≥4 h/wk, *n* (%)	3429 (17.8)	4246 (22.1)	5823 (30.2)	<0.001
Smoking status, *n* (%)				<0.001
Never	6052 (31.4)	8544 (44.4)	10,062 (52.3)	
Former	3275 (17.0)	1494 (7.8)	904 (4.7)	
Current	8993 (46.7)	8414 (43.7)	7643 (39.7)	
Pipe or cigar smoker only	935 (4.9)	800 (4.2)	645 (3.4)	
Alcohol intake, g/1000 kcal	8.1 ± 12.2	4.2 ± 6.9	2.5 ± 4.8	<0.001
Family history of colorectal cancer, *n* (%)	1919 (10.0)	2006 (10.5)	2062 (10.8)	0.14
Adenoma at T0 screen, *n* (%)	1989 (10.3)	1622 (8.4)	1316 (6.8)	<0.001
Adenoma at T3/T5 screen, *n* (%)	2995 (15.5)	2410 (12.5)	1990 (10.3)	<0.001
Ever regular NSAID use, *n* (%)	11,946 (62.0)	11,950 (62.1)	11,643 (60.5)	0.004
Total energy intake, kcal/d	2303.3 (891.7)	2028.3 (746.1)	1816.1 (662.6)	<0.001
Dietary calcium intake, mg/1000 kcal	445.4 (182.0)	473.8 (157.1)	497.1 (152.0)	<0.001
Supplemental calcium intake, mg/1000 kcal	111.5 (204.2)	167.1 (252.4)	229.4 (306.7)	<0.001
Total folate intake, mg/1000 kcal	248.6 (175.4)	317.7 (192.9)	407.6 (236.7)	<0.001
Red meat intake, g/1000 kcal	34.9 (20.9)	28.8 (16.6)	20.8 (14.0)	<0.001
Processed meat intake, g/1000 kcal	11.3 (9.7)	8.01 (7.1)	5.1 (5.6)	<0.001
Hormone replacement therapy, *n* (%)[3]	3308 (50.3)	5082 (52.67)	6019 (51.2)	<0.001

[1]*n* = 19,258 participants. NSAID, nonsteroidal anti-inflammatory drug; T0, baseline; T3/T5, year 3 or 5.
[2]Mean ± SD (all such values).
[3]In females only.

Recurrent colorectal adenoma

In contrast with incident adenoma, no significant associations were found between dietary fiber intake and recurrent adenoma risk with or without adjustment for potential confounders, except for an inverse association between cereal/grain fiber intakes and risk of recurrent rectal adenoma ($OR_{tertile\ 3\ vs.\ tertile\ 1}$: 0.44; 95% CI: 0.21, 0.94; **Table 4**). No differences were observed by adenoma location (Table 4) or advanced compared with nonadvanced adenoma (data not shown). When the association between fiber intake and risk of recurrent adenoma was analyzed with fiber as a continuous variable, the results were similar, with no association for total fiber ($OR_{per\ 5\ g/1000\ kcal\ increment}$: 1.03; 95% CI: 0.81, 1.30) or fiber from each food source (data not shown).

Incident colorectal cancer

In the minimally adjusted models, a significantly reduced risk of colorectal cancer was observed for individuals with higher total fiber intakes ($HR_{tertile\ 3\ vs.\ tertile\ 1}$: 0.79; 95% CI: 0.65, 0.95), but this association became attenuated after further adjustment for smoking status and processed meat intake ($HR_{tertile\ 3\ vs.\ tertile\ 1}$: 0.85; 95% CI: 0.70, 1.03) (**Table 5**). When different fiber groups were examined, fruit fiber intake was associated with a reduced risk of colorectal cancer, even after further adjustment ($HR_{tertile\ 3\ vs.\ tertile\ 1}$: 0.81; 95% CI: 0.67, 0.99); however, associations with other fiber groups were largely null. The association for total dietary fiber was strongest and statistically significant for distal colon cancer (adjusted $HR_{tertile\ 3\ vs.\ tertile\ 1}$: 0.62; 95% CI: 0.41, 0.94) (Table 5). No significant differences were observed by cancer stage (data not shown). When the association between fiber intake and risk of colorectal cancer was analyzed with fiber as a continuous variable, the results were largely similar, with a borderline association for total fiber ($HR_{per\ 5\ g/1000\ kcal\ increment}$: 0.90; 95% CI: 0.80, 1.01) and no association for fiber from cereals, vegetables, or legumes (data not shown). However, the association for fruit fiber was no longer statistically significant ($HR_{per\ 5\ g/1000\ kcal\ increment}$: 0.78; 95% CI: 0.60, 1.02).

The associations between fiber intakes and colorectal cancer risk did not vary significantly by age, sex, BMI, or folate intake; however, the protective association with total fiber was stronger for those with intakes of processed meats above median ($HR_{tertile\ 3\ vs.\ tertile\ 1}$: 0.69; 95% CI: 0.52, 0.93) than for those with intakes below the median ($HR_{tertile\ 3\ vs.\ tertile\ 1}$: 0.92; 95% CI: 0.69, 1.23; P-$_{interaction}$ = 0.04) (**Supplemental Table 3**).

DISCUSSION

Overall, the results of this large prospective cohort of screened individuals showed an inverse association between intakes of dietary fiber, particularly cereal and fruit fiber, and risk of incident

TABLE 2
Characteristics of participants in the incident adenoma and recurrent adenoma data set by case status

	Incident adenoma			Recurrent adenoma		
Characteristic	Cases (*n* = 1004)	Noncases (*n* = 15,976)	*P* value	Cases (*n* = 738)	Noncases (*n* = 929)	*P* value
Total fiber intake, g/1000 kcal	11.2 ± 3.5[1]	12.0 ± 3.6	<0.001	11.1 ± 3.4	11.2 ± 3.5	0.50
Age at diagnosis or endoscopy, y	66.6 ± 5.0	66.7 ± 4.9	0.62	66.9 ± 5.3	68.2 ± 5.4	<0.001
Male sex, *n* (%)	665 (66.2)	8756 (54.8)	<0.001	535 (72.5)	570 (61.4)	<0.001
Ethnicity, *n* (%)			0.02			0.001
Non-Hispanic white	910 (90.6)	14,181 (88.8)		689 (93.4)	887 (95.5)	
Non-Hispanic black	36 (3.6)	461 (2.9)		14 (1.9)	27 (2.9)	
Asian	42 (4.2)	957 (6.0)		15 (2.0)	4 (0.4)	
Other	16 (1.6)	377 (2.4)		20 (2.7)	11 (1.2)	
Education						
College graduate or postgraduate, *n* (%)	389 (38.9)	6266 (39.3)	0.89	282 (38.4)	325 (35.0)	0.51
BMI, kg/m^2	27.7 ± 4.7	27.1 ± 4.6	<0.001	27.8 ± 4.2	27.5 ± 4.5	0.15
Physical activity ≥4 h/wk, *n* (%)	229 (22.8)	4167 (26.1)	<0.001	168 (22.8)	212 (22.8)	0.38
Hormone replacement therapy use, *n* (%)[2]			0.09			0.97
Never	130 (38.4)	2291 (31.7)		81 (39.9)	145 (40.4)	
Former	46 (13.6)	1072 (14.9)		27 (13.3)	52 (14.5)	
Current	161 (47.5)	3816 (52.9)		94 (46.3)	160 (44.6)	
Smoking status, *n* (%)			<0.001			0.001
Never	392 (39.0)	7854 (49.2)		205 (27.8)	309 (33.3)	
Former	469 (46.7)	6521 (40.8)		386 (52.3)	459 (49.5)	
Current	100 (10.0)	810 (5.1)		96 (13.0)	131 (14.1)	
Pipe or cigar smoker only	43 (4.3)	786 (4.9)		51 (6.9)	29 (3.1)	
Alcohol intake, g/d	14.8 ± 29.8	10.2 ± 21.9	<0.001	17.2 ± 29.5	14.8 ± 29.7	0.11
Family history of colorectal cancer, *n* (%)	93 (9.3)	1367 (8.6)	0.71	99 (13.5)	123 (13.4)	0.73
Ever regular NSAID[3] use, *n* (%)	600 (59.8)	9602 (60.1)	0.59	412 (55.8)	552 (59.4)	0.14
Total energy intake, kcal/d	2182.8 ± 824.8	2077.6 ± 796.6	<0.001	2169.0 ± 813.0	2098.5 ± 795.8	0.08
Dietary calcium intake, mg/1000 kcal	452.5 ± 156.8	473.4 ± 164.4	<0.001	443.8 ± 148.3	468.5 ± 175.1	0.002
Supplemental calcium intake, mg/d	223.9 ± 332.2	277.1 ± 375.8	<0.001	165.9 ± 297.8	216.9 ± 327.0	0.001
Dietary folate intake, μg/1000 kcal	179.7 ± 62.0	190.5 ± 64.9	<0.001	177.6 ± 58.9	181.8 ± 67.8	0.19
Supplemental folic acid intake, μg/d	211.6 ± 304.9	240.1 ± 307.5	0.004	172.3 ± 265.4	203.4 ± 274.1	0.02
Red meat intake, g/1000 kcal	30.3 ± 18.7	27.9 ± 18.4	<0.001	31.0 ± 17.7	29.4 ± 18.2	0.07
Processed meat intake, g/1000 kcal	6.8 ± 7.1	5.8 ± 6.5	<0.001	7.1 ± 7.1	6.5 ± 6.7	0.05

[1]Mean ± SD (all such values).
[2]In females only.
[3]NSAID, nonsteroidal anti-inflammatory drug.

adenoma. Importantly, the reduction was also evident for advanced adenoma, which may be more likely to progress to colorectal cancer (25). No associations were observed between dietary fiber and recurrent adenoma risk, apart from a reduced risk of rectal adenoma among individuals with higher cereal fiber intakes. A modest inverse association was found between total fiber and colorectal cancer risk, which was statistically significant for distal colon cancer.

To our knowledge, this was the first study to assess the association between dietary fiber and incident adenoma risk in a population-based screening trial. Unlike most previous studies, individuals in this adenoma study were systematically screened at baseline, had no evidence of distal polyps on the baseline screen, and received a second screen 3 or 5 y later as part of the trial. Thus, although not all individuals returned for their second screen within the trial (26), there was a lower likelihood of self-selection of screening causing bias in our study compared with other cohort studies, in which factors such as family history and medical care coverage may play a greater role in case-control selection.

The inverse association between dietary fiber and incident adenoma risk observed in our study is consistent with findings from case-control studies of prevalent adenoma (13, 14). Our findings were somewhat stronger than those of other prospective studies (15, 16) of incident adenoma; however, this may have been because everyone in our study was screened uniformly, unlike in other prospective studies in which individuals were screened at different time points depending on symptoms, the physician's perceived risk of the patient developing colorectal cancer, access to screening, or personal desire to be screened. Unlike retrospective case-control studies, which have the potential for recall bias, this prospective study provides further evidence of a temporal association between dietary fiber and colorectal adenoma and suggests that the protective effect against colorectal cancer may arise early in the adenoma-carcinoma sequence. The results support population-wide recommendations regarding fiber intakes (11, 27).

The lack of an association between dietary fiber and recurrent adenoma risk in the current study is consistent with that in previous randomized controlled trials (12); however, the lack of association does not necessarily negate the findings for incident adenoma or cancer. The nature of a recurrent adenoma cohort, in which all individuals must have an initial adenoma, may make associations harder to detect because the individuals may have an increased susceptibility to adenoma development due to genetic or lifestyle

TABLE 3
Incident colorectal adenoma risk of dietary fiber intake

		Any incident distal colon or rectal adenoma			Distal colon adenoma[1]		Rectal adenoma[1]	
Tertile[2]	Noncases (n = 15,976)	Cases (n = 1004)	Base model[3] OR (95% CI)	Adjusted[4] OR (95% CI)	Cases (n = 770)	Adjusted[4] OR (95% CI)	Cases (n = 262)	Adjusted[4] OR (95% CI)
Total fiber								
<9.9 (8.4) g/1000 kcal	4793	394	1.00	1.00	298	1.00	106	1.00
≥9.9 to <12.8 (11.3) g/1000 kcal	5496	340	0.81 (0.69, 0.94)	0.88 (0.75, 1.04)	266	0.91 (0.76, 1.09)	87	0.80 (0.59, 1.09)
≥12.8 (15.0) g/1000 kcal	5687	270	0.65 (0.54, 0.77)	0.76 (0.63, 0.91)	206	0.75 (0.61, 0.92)	69	0.68 (0.48, 0.96)
P-trend			<0.001	0.003		0.006		0.03
Cereal/grain fiber								
<3.0 (2.4) g/1000 kcal	4898	382	1.00	1.00	296	1.00	94	1.00
≥3.0 to <4.3 (3.6) g/1000 kcal	5380	317	0.75 (0.64, 0.87)	0.80 (0.68, 0.94)	240	0.77 (0.65, 0.92)	85	0.86 (0.64, 1.17)
≥4.3 (5.4) g/1000 kcal	5698	305	0.70 (0.59, 0.81)	0.78 (0.66, 0.92)	234	0.76 (0.63, 0.91)	83	0.86 (0.63, 1.18)
P-trend			<0.001	0.006		0.007		0.39
Vegetable fiber								
<3.6 (2.9) g/1000 kcal	5086	353	1.00	1.00	272	1.00	91	1.00
≥3.6 to <5.1 (4.3) g/1000 kcal	5375	372	1.05 (0.90, 1.23)	1.10 (0.94, 1.28)	286	1.09 (0.91, 1.30)	97	1.10 (0.82, 1.47)
≥5.1 (6.4) g/1000 kcal	5515	279	0.83 (0.70, 0.98)	0.90 (0.76, 1.08)	212	0.88 (0.72, 1.07)	74	0.91 (0.65, 1.27)
P-trend			0.02	0.22		0.18		0.54
Fruit fiber								
<1.5 (1.0) g/1000 kcal	4873	409	1.00	1.00	319	1.00	105	1.00
≥1.5 to <2.8 (2.2) g/1000 kcal	5487	306	0.73 (0.62, 0.85)	0.80 (0.68, 0.94)	228	0.76 (0.63, 0.91)	85	0.84 (0.62, 1.13)
≥2.8 (3.9) g/1000 kcal	5616	289	0.72 (0.61, 0.85)	0.85 (0.71, 1.01)	223	0.82 (0.67, 1.00)	72	0.78 (0.55, 1.10)
P-trend			<0.001	0.09		0.07		0.17
Legume fiber								
<1.0 (0.7) g/1000 kcal	5057	329	1.00	1.00	245	1.00	90	1.00
≥1.0 to <1.5 (1.2) g/1000 kcal	5392	344	0.98 (0.84, 1.15)	1.02 (0.87, 1.19)	259	1.03 (0.86, 1.24)	96	1.03 (0.77, 1.38)
≥1.5 (2.1) g/1000 kcal	5527	331	0.88 (0.75, 1.03)	0.93 (0.79, 1.10)	266	1.01 (0.84, 1.22)	76	0.77 (0.56, 1.06)
P-trend			0.09	0.35		0.94		0.09

[1]Includes 52 patients who had adenomas in both the descending/sigmoid colon and rectum.

[2]Values in parentheses in this column are median intakes.

[3]The ORs and 95% CIs were calculated by using unconditional logistic regression. The base models adjusted for age at the year 3 or 5 screen (y), study center (10 centers), sex, ethnicity (non-Hispanic white, non-Hispanic black, Asian, other), total energy intake (kcal/d), and energy by using the nutrient-density method [fiber (g/1000 kcal)].

[4]The fully adjusted model was additionally adjusted for smoking status (never, former, current, or pipe or cigar smoker only), alcohol intake (<0.5, 0.5 to <5, or ≥5 g/1000 kcal), and total folate intake from diet (prefortification) and supplements (μg/d). Other confounders tested but that did not change the β coefficient by ≥10% included education (<high school, completed high school, some college, or college graduate or postgraduate), family history of colorectal cancer (yes, no, or unknown), BMI (in kg/m^2; ≤25, 25 to <30, ≥30, or unknown), regular nonsteroidal anti-inflammatory drug use (yes, no, or unknown), hormone replacement therapy use (current, former, never, or unknown), exercise per week (<1 h, 1–3 h, ≥4 h, or unknown), dietary calcium intake (g/1000 kcal/d), supplemental calcium intake (mg/d), processed meat intake (g/1000 kcal/d), and red meat intake (g/1000 kcal/d).

influences. This is highlighted by the lower mean ± SD fiber intake among noncases in the recurrent adenoma data set (11.2 ± 3.5 g/1000 kcal) compared with the incident adenoma data set (12.0 ± 3.6 g/1000 kcal), which may have prevented a benefit of high fiber intakes from being observed.

The previous evidence regarding an association between dietary fiber and colorectal cancer risk was deemed to be "convincing" in the World Cancer Research Fund/American Institute for Cancer Research continuous update report (12). Whereas the current study did not find a statistically significant association with risk of overall colorectal cancer, the magnitude of the association is in line with a systematic review conducted for the World Cancer Research Fund and American Institute of Cancer Research report ($HR_{\text{per 10-g/d increase}}$: 0.90; 95% CI: 0.86, 0.94) (28). Therefore, the lack of statistical significance in the current study could be attributable to insufficient statistical power, despite the large sample size. Also, despite the lack of an association with risk of colorectal cancer overall, dietary fiber was associated with a reduced risk of distal colon cancer.

Interestingly, a stronger protective association was also observed between total fiber intakes and risk of colorectal cancer among individuals with higher processed meat intakes. Whereas the results of this subgroup analysis should be interpreted cautiously, it is biologically plausible. Fiber could reduce exposure of the colorectal passage to carcinogenic *N*-nitroso compounds produced on processed meat consumption (29). Given the elevated risk of colorectal cancer for those consuming high intakes of processed meat (30), this novel finding suggests that fiber may reduce some of that excess risk and therefore warrants further investigation.

The findings of stronger reductions in colorectal neoplasm risk associated with cereal and fruit fiber, but not for vegetable or legume fiber, are largely consistent with the literature (10, 14). Possible biological reasons for the observed differences in risk may stem from the type of fiber, with cereals being particularly high in insoluble fiber, which binds carcinogens and reduces transit time to a greater extent (31). Alternatively, the beneficial effects of cereal fiber could be attributable to higher intakes of fiber-rich whole grains rather than to intakes of cereal fiber per se, particularly

TABLE 4
Recurrent colorectal adenoma risk of dietary fiber intake

Tertile[2]	Noncases ($n = 929$)	Any adenoma: Cases ($n = 738$)	Any adenoma: Base model[3] OR (95% CI)	Any adenoma: Adjusted[4] OR (95% CI)	Proximal colon adenoma[1]: Cases ($n = 460$)	Proximal colon adenoma[1]: Adjusted[4] OR (95% CI)	Distal colon adenoma[1]: Cases ($n = 257$)	Distal colon adenoma[1]: Adjusted[4] OR (95% CI)	Rectal adenoma[1]: Cases ($n = 78$)	Rectal adenoma[1]: Adjusted[4] OR (95% CI)
Total fiber										
<9.9 (8.4) g/1000 kcal	355	293	1.00	1.00	173	1.00	105	1.00	29	1.00
≥9.9 to <12.8 (11.3) g/1000 kcal	314	242	1.05 (0.83, 1.34)	1.01 (0.75, 1.35)	171	1.19 (0.85, 1.67)	82	0.99 (0.65, 1.50)	23	0.60 (0.29, 1.23)
≥12.8 (15.0) g/1000 kcal	260	203	1.16 (0.89, 1.50)	1.08 (0.75, 1.55)	116	1.01 (0.66, 1.55)	70	0.99 (0.59, 1.66)	26	0.88 (0.39, 1.99)
P-trend			0.28	0.67		0.97		0.96		0.86
Cereal/grain fiber										
<3.0 (2.4) g/1000 kcal	324	257	1.00	1.00	155	1.00	91	1.00	33	1.00
≥3.0 to <4.3 (3.6) g/1000 kcal	326	254	1.06 (0.83, 1.34)	1.06 (0.80, 1.40)	159	1.07 (0.77, 1.49)	90	1.02 (0.68, 1.53)	25	0.72 (0.39, 1.36)
≥4.3 (5.4) g/1000 kcal	279	227	1.20 (0.93, 1.54)	1.21 (0.88, 1.67)	146	1.31 (0.90, 1.90)	76	1.02 (0.63, 1.63)	20	0.44 (0.21, 0.94)
P-trend			0.15	0.23		0.15		0.95		0.03
Vegetable fiber										
<3.6 (2.9) g/1000 kcal	323	266	1.00	1.00	156	1.00	98	1.00	31	1.00
≥3.6 to <5.1 (4.3) g/1000 kcal	332	252	0.94 (0.74, 1.19)	0.94 (0.71, 1.24)	167	1.03 (0.74, 1.42)	87	0.87 (0.58, 1.29)	19	0.59 (0.30, 1.15)
≥5.1 (6.4) g/1000 kcal	274	220	1.08 (0.84, 1.39)	1.06 (0.78, 1.46)	137	1.12 (0.77, 1.62)	72	1.12 (0.71, 1.77)	28	0.93 (0.47, 1.84)
P-trend			0.53	0.68		0.55		0.62		0.88
Fruit fiber										
<1.5 (1.0) g/1000 kcal	348	285	1.00	1.00	166	1.00	94	1.00	24	1.00
≥1.5 to <2.8 (2.2) g/1000 kcal	297	268	1.35 (1.06, 1.71)	1.18 (0.88, 1.57)	173	1.28 (0.91, 1.79)	100	1.39 (0.92, 2.11)	30	1.72 (0.85, 3.49)
≥2.8 (3.9) g/1000 kcal	284	185	1.09 (0.83, 1.43)	0.98 (0.70, 1.37)	121	1.07 (0.72, 1.58)	63	0.94 (0.58, 1.54)	24	1.30 (0.57, 2.95)
P-trend			0.58	0.83		0.82		0.70		0.71
Legume fiber										
<1.0 (0.7) g/1000 kcal	336	239	1.00	1.00	142	1.00	91	1.00	28	1.00
≥1.0 to <1.5 (1.2) g/1000 kcal	312	275	1.24 (0.97, 1.57)	1.26 (0.96, 1.66)	179	1.30 (0.94, 1.80)	91	1.09 (0.74, 1.61)	26	0.92 (0.48, 1.74)
≥1.5 (2.1) g/1000 kcal	281	224	1.09 (0.85, 1.40)	1.08 (0.80, 1.45)	139	1.17 (0.82, 1.65)	75	1.05 (0.68, 1.60)	24	0.98 (0.51, 1.90)
P-trend			0.64	0.75		0.48		0.86		0.98

[1]May have concurrent recurrent adenomas elsewhere.

[2]Values in parentheses in this column are median intakes.

[3]The ORs and 95% CIs were calculated by using unconditional logistic regression. The base models adjusted for age at the year 3 or 5 screen (y), study center (10 centers), sex, ethnicity (non-Hispanic white, non-Hispanic black, Asian, or other), total energy intake (kcal/d), and energy by using the nutrient-density method [fiber (g/1000 kcal)].

[4]The fully adjusted model additionally adjusted for education (<high school, completed high school, some college, college graduate or postgraduate), smoking status (never, former, current, or pipe or cigar smoker only), alcohol intake (<0.5, 0.5 to <5, or ≥5 g/1000 kcal), supplemental calcium intake (mg/d), dietary calcium intake (g/1000 kcal/d), processed meat intake (g/1000 kcal/d), total folate intake from diet (prefortification) and supplements (μg/d), hormone replacement therapy use (current, former, never, or unknown), surveillance period (y), and number of surveillance endoscopies. Other confounders tested but that did not change the β coefficient by ≥10% included family history of colorectal cancer (yes, no, unknown), BMI (in kg/m^2; ≤25, 25 to <30, ≥30, or unknown), regular nonsteroidal anti-inflammatory drug use (yes, no, or unknown), exercise per week (<1 h, 1–3 h, ≥4 h, or unknown), and red meat intake (g/1000 kcal/d).

TABLE 5
Colorectal cancer risk of intakes of dietary fiber

		Colorectal cancer			Proximal colon		Distal colon		Rectal cancer	
Tertile[1]	Person-years[2]	Cases (n = 733)	Base model[3] HR (95% CI)	Adjusted[4] HR (95% CI)	Cases (n = 415)	Adjusted[4] HR (95% CI)	Cases (n = 155)	Adjusted[4] HR (95% CI)	Cases (n = 152)	Adjusted[4] HR (95% CI)
Total fiber										
<9.9 (8.4) g/1000 kcal	211,601	262	1.00	1.00	135	1.00	65	1.00	59	1.00
≥9.9 to <12.8 (11.2) g/1000 kcal	215,671	246	0.91 (0.76, 1.08)	0.94 (0.79, 1.13)	143	1.02 (0.80, 1.30)	45	0.66 (0.45, 0.98)	54	1.10 (0.75, 1.61)
≥12.8 (14.9) g/1000 kcal	217,035	225	0.79 (0.65, 0.95)	0.85 (0.70, 1.03)	137	0.95 (0.73, 1.23)	45	0.62 (0.41, 0.94)	39	0.85 (0.54, 1.33)
P-trend			0.01	0.10		0.66		0.03		0.47
Cereal/grain fiber										
<3.0 (2.3) g/1000 kcal	211,182	245	1.00	1.00	129	1.00	58	1.00	55	1.00
≥3.0 to <4.3 (3.5) g/1000 kcal	215,658	232	0.93 (0.78, 1.12)	0.96 (0.80, 1.15)	122	0.93 (0.73, 1.20)	53	0.90 (0.62, 1.32)	55	1.12 (0.77, 1.64)
≥4.3 (5.4) g/1000 kcal	217,446	256	0.99 (0.83, 1.18)	1.04 (0.87, 1.25)	164	1.22 (0.96, 1.54)	44	0.72 (0.48, 1.08)	42	0.91 (0.60, 1.37)
P-trend			0.98	0.60		0.06		0.11		0.60
Vegetable fiber										
<3.6 (2.8) g/1000 kcal	212,781	258	1.00	1.00	136	1.00	62	1.00	58	1.00
≥3.6 to <5.1 (4.3) g/1000 kcal	216,670	228	0.86 (0.72, 1.03)	0.88 (0.74, 1.06)	132	0.94 (0.74, 1.20)	44	0.70 (0.47, 1.03)	47	0.88 (0.60, 1.30)
≥5.1 (6.4) g/1000 kcal	214,856	247	0.93 (0.77, 1.11)	0.97 (0.81, 1.17)	147	1.07 (0.84, 1.37)	49	0.76 (0.52, 1.13)	47	0.93 (0.62, 1.40)
P-trend			0.50	0.86		0.53		0.21		0.75
Fruit fiber										
<1.5 (1.0) g/1000 kcal	211,824	258	1.00	1.00	136	1.00	51	1.00	66	1.00
≥1.5 to <2.8 (2.1) g/1000 kcal	216,210	260	0.95 (0.80, 1.13)	0.99 (0.83, 1.18)	150	1.02 (0.80, 1.30)	56	1.05 (0.71, 1.56)	49	0.88 (0.60, 1.30)
≥2.8 (3.8) g/1000 kcal	216,273	215	0.76 (0.63, 0.93)	0.81 (0.67, 0.99)	129	0.85 (0.65, 1.11)	48	0.90 (0.58, 1.39)	37	0.73 (0.47, 1.13)
P-trend			0.01	0.03		0.18		0.58		0.16
Legume fiber										
<1.0 (0.7) g/1000 kcal	214,823	235	1.00	1.00	133	1.00	52	1.00	49	1.00
≥1.0 to <1.5 (1.2) g/1000 kcal	215,768	271	1.11 (0.94, 1.33)	1.13 (0.95, 1.35)	164	1.20 (0.95, 1.51)	50	0.94 (0.64, 1.39)	54	1.11 (0.75, 1.63)
≥1.5 (2.1) g/1000 kcal	213,715	227	0.90 (0.75, 1.09)	0.93 (0.77, 1.12)	118	0.87 (0.67, 1.12)	53	0.94 (0.64, 1.40)	49	0.96 (0.64, 1.44)
P-trend			0.17	0.29		0.16		0.80		0.77

[1]Values in parentheses in this column are median intakes.

[2]Total person-years = 644,307.

[3]The HRs and 95% CIs were calculated by using a Cox proportional hazards model. The base models adjusted for age at randomization (60–64, 65–69, ≥70 y); sex; center; race (non-Hispanic white, non-Hispanic black, Asian, or other); calories (kcal); year of follow-up screening; adenoma at year 0, 3, or 5 (yes, no); and adequate screening at year 0, 3, or 5 (yes, no).

[4]The HRs and 95% CIs were calculated by using Cox proportional hazards model. The adjusted models adjusted for all variables in the base model plus smoking history (current, former, never, pipe or cigar smoker only, unknown) and processed meat intakes per 1000 kcal (continuous). Other confounders tested but that did not change the β coefficient by ≥10% included education (<11 y, 12 y or completed high school, some college, or college graduate or postgraduate), BMI (in kg/m^2; <25, 25 to <30, >30, or unknown), nonsteroidal anti-inflammatory drug use (yes, no), exercise (<1 h, 1–3 h, ≥4 h, or unknown), hormone replacement therapy use (never, former, current, unknown, or male), family history of colorectal cancer (yes, no, or possibly), alcohol (<0.5, ≥ 0.5 to <5, or ≥5g), total calcium intake per 1000 kcal, total folate intake per 1000 kcal, and red meat intake per 1000 kcal (all continuous).

because the previous systematic review suggested a stronger protective effect of whole grains than of cereal fiber for colorectal cancer risk (10). Whole-grain consumption was, unfortunately, not ascertained in our questionnaire, but it would warrant inclusion in future questionnaires. Nevertheless, the consistent reductions in risk associated with cereal fiber suggest that there are health benefits of high-fiber, whole-grain cereal products. Similarly, the reductions associated with fruit fiber may relate to the type of fiber or to other components of fruit or a synergistic interaction between fiber and other components.

Our study had many strengths and limitations. In addition to the minimization of detection or selection bias for the adenoma outcomes, the prospective study design prevented the possibility of recall bias. The study also had robust data on many potential confounders, including smoking, BMI, physical activity, and other dietary factors, which allowed for multivariate adjustment, although residual confounding was possible. The use of the same source population for each of the outcomes allowed a more direct comparison of the association with incident adenoma and cancer. However, because flexible sigmoidoscopy—which only assesses the distal (left-sided) colon and rectum—was used for screening, proximal adenoma could not be evaluated, and the results observed for distal or rectal adenoma may not be generalizable to proximal adenoma. Dietary assessment is also complex and FFQs are not a perfect measure of habitual dietary intakes; therefore, intakes of some foods, including fruit and vegetables, may have been underestimated because of difficulty in the accurate recall of usual intakes (32). Whereas the misreporting and misclassification was likely equal between groups, it may still have reduced the ability to detect associations and resulted in residual confounding. Residual confounding from the use of the FFQ is likely to have affected both the assessment of fiber intake and the adjustments made for other potential dietary confounders. Despite excellent response rates of >80%, FFQ nonresponders differed from FFQ responders based on age, sex, education, BMI, and smoking status. In general, FFQ responders were older, more likely to be female, more educated, and less likely to smoke. Thus, although our study had some limitations, it adds crucial knowledge to the relation between fiber intake and the development of colorectal adenoma and cancer.

In conclusion, in this large prospective study, in which all individuals underwent the same colorectal screening protocol, we found evidence that high fiber intakes, particularly from cereals or grains and fruit, are associated with a reduced risk of incident colorectal adenoma and cancer. This study provides more evidence that dietary fiber may act early in the adenoma-carcinoma sequence and reduce both the risk of adenoma and cancer.

The authors' responsibilities were as follows—ATK and HGC: analyzed the data; HGC, W-YH, CMK, MMC, and SIB: designed the research; ATK, HGC, W-YH, CMK, and SIB: wrote the manuscript; ATK: had primary responsibility for the final content; and all authors: read and approved the final manuscript. None of the authors had a potential conflict of interest.

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