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Associations between Dietary Fiber and Colorectal Polyp Risk Differ by Polyp Type and Smoking Status[1,2]

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Abstract

The association of dietary fiber intake with colorectal cancer risk is established. However, the association may differ between cigarette smokers and nonsmokers. We evaluated this hypothesis in a large colonoscopy-based case-control study. Dietary fiber intakes were estimated by self-administered food frequency questionnaire. Unconditional logistic regression analysis was used to estimate ORs and 95% CIs with adjustment for potential confounders. Analysis also was stratified by cigarette smoking and sex. High dietary fiber intake was associated with reduced risk of colorectal polyps (*P*-trend = 0.003). This association was found to be stronger among cigarette smokers (*P*-trend = 0.006) than nonsmokers (*P*-trend = 0.21), although the test for multiplicative interaction was not statistically significant (*P* = 0.11). This pattern of association was more evident for high-risk adenomatous polyps (ADs), defined as advanced or multiple ADs (*P*-interaction smoking and dietary fiber intake = 0.09). Among cigarette smokers who smoked ≥23 y, a 38% reduced risk of high-risk ADs was found to be associated with high intake of dietary fiber compared with those in the lowest quartile fiber intake group (*P*-trend = 0.004). No inverse association with dietary fiber intake was observed for low-risk ADs, defined as single nonadvanced ADs. Cigarette smoking may modify the association of dietary fiber intake with the risk of colorectal polyps, especially high-risk ADs, a well-established precursor of colorectal cancer. J. Nutr. 144: 592–598, 2014.

Introduction

Colorectal adenomatous polyps (ADs)[8] are precursors of colorectal cancer (1,2). Recent evidence suggests that some hyperplastic polyps (HPPs) may develop into cancer via serrated or microsatellite unstable pathways (3). Timely removal of these polyps and reducing occurrences by lifestyle modification are critical measures for early prevention of colorectal cancer (4,5). Dietary fiber was convincingly linked to decreased risk of colorectal cancer and ADs in observational studies (6). However, randomized clinical trials failed to show protection from recurrent ADs with increased fiber intake, decreased fat intake, or both (7,8). Reasons for the inconsistent findings are unclear. We hypothesized that the inverse association of dietary fiber intake with the risk of colorectal neoplasm may be modified by cigarette smoking, an established risk factor for colorectal cancer and ADs (9,10).

Cigarette smoke contains multiple carcinogenic compounds, including polycyclic aromatic hydrocarbons, heterocyclic amines, nitrosamines, and aromatic amines (11), which can reach the colorectal mucosa through direct ingestion or the circulatory system (11,12). High dietary fiber intake can increase stool bulk, thus diluting cigarette smoke carcinogens in the colonic lumen and also reducing transit time in the colon, thereby reducing the duration of carcinogen exposure (13). Therefore, dietary fiber intake may modify colorectal neoplasm risk by offsetting the detrimental effect of cigarette smoke. We evaluated this hypothesis using data from the Tennessee Colorectal Polyp Study (TCPS).

Participants and Methods

TCPS. The TCPS is a colonoscopy-based case-control study conducted in Nashville, Tennessee. Detailed methods used in this study were described previously (5,14). Briefly, eligible participants aged 40–75 y were identified from patients scheduled for colonoscopy at an academic medical center (Vanderbilt University Medical Center) and a Veterans Affairs medical center (Tennessee Valley Health System, Nashville) between 1 February 2003 and 26 March 2010. The study was approved by the Vanderbilt University Institutional Review Board, the Veterans

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[8] Abbreviations used: AD, adenomatous polyp; HPP, hyperplastic polyp; NSAID, nonsteroidal anti-inflammatory drug; TCPS, Tennessee Colorectal Polyp Study.
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Excluded from our study were participants who had genetic colorectal cancer syndromes (e.g., hereditary nonpolyposis colorectal cancer or familial adenomatous polyposis) or previous history of inflammatory bowel disease, AD, or any cancer other than non-melanoma skin cancer. Among 12,585 eligible participants, 7621 (60.6%) provided written informed consent. Of them, 6400 (84.0%) completed a telephone interview soon after colonoscopy, and 5906 (77.5% of all responders) completed an FFQ.

Outcome assessment. Patient colonoscopy results were recorded using standardized data-entry forms. Information regarding number, locations, and sizes of polyps was collected. Polyps were classified as AD only (including villous, tubulovillous, tubular, sessile serrated, and traditional serrated on the basis of histologic review), HPP only, or synchronous HPP/AD (both). Nearly 9% of ADs were classified as either sessile or traditional serrated AD and were categorized as ADs for analysis. A polyp was considered an advanced AD if it met 1 of the following 3 criteria: *1*) size ≥1.0 cm; *2*) ≥25% villous component; or *3*) contained high-grade dysplasia. High-risk ADs were defined as advanced or multiple ADs, whereas nonadvanced single ADs were defined as low-risk ADs. Controls were eligible participants who received a complete colonoscopy reaching the cecum and had a normal exam with no polyps or cancer. For statistical analysis, cases were assigned as patients with HPPs only, ADs only, or synchronous HPP/ADs. The current analyses included 566 cases with only HPPs, 1315 cases with only ADs, and 394 cases with synchronous HPP/ADs. The latter 2 case groups were combined into a single AD group for some analyses. Controls included 3184 polyp-free patients.

Exposure assessment. After colonoscopy, a standardized telephone interview was conducted by trained interviewers to obtain information regarding medication use, demographics, medical history, and selected lifestyle factors, including detailed information about cigarette smoking (15). Briefly, regular cigarette smoking (ever smoker) was defined as smoking at least 1 cigarette/d for at least 3 mo continuously. Former smokers were regular smokers who had stopped smoking at least 1 y before colonoscopy. Never smokers were those who had never smoked regularly. Among those who had ever smoked cigarettes regularly, participants were also classified as above or below the median of control duration (years) or intensity (cigarettes per day). Regular alcohol

TABLE 1 Selected demographic characteristics and major known risk factors for colorectal cancer by study groups, the Tennessee Colorectal Polyp Study, 2003–2010[1]

		Polyp cases			
Characteristic	Controls	AD only	HPP only	Both	*P*
Sample size, *n*	3184	1315	566	394	
Study site, %					<0.001
Vanderbilt University	76.7	70.6	63.6	57.4	
Veterans Affairs	23.3	29.4	36.4	42.6	
Mean age, *y*	57.5	59.2	57.5	58.8	<0.001
Sex (females), %	45.6	30.6	33.2	23.4	<0.001
Indications for colonoscopy, screening, %					0.02
Screening	57.7	59.8	56.7	54.8	
Family history	13.2	11.3	12.9	13.2	
Diagnostic	21.1	20.9	20.1	18.5	
Other	8.0	8.1	10.3	13.5	
Educational attainment, %					<0.001
High school or less	21.7	28.7	29.7	37.1	
Some college	27.6	25.2	29.4	34.5	
College graduate	22.4	22.6	20.8	15.2	
Graduate or professional education	28.3	23.5	20.1	13.2	
Race (white), %	89.9	87.2	90.1	91.4	0.04
Family history of colorectal cancer in a first-degree relative,[2] %	9.1	9.8	8.5	11.3	0.55[3]
Ever regular cigarette smoking,[2] %	45.0	51.2	67.4	73.2	<0.001[3]
Ever regular alcohol consumption,[2] %	39.5	43	45.6	44.2	0.003[3]
BMI,[4] *kg/m²*	27.4 ± 1.0	27.74 ± 1.0	27.74 ± 1.0	27.84 ± 1.1	0.37[3]
Regularly exercised in the past 10 y,[2] %	58.8	54.6	52.9	47.5	<0.001[3]
Ever used NSAIDs regularly in the past 10 y,[2] %	51.5	45.7	52.2	49.2	0.009[3]
Ever used a multivitamin in the past 12 mo,[2] %	55.9	47.3	50.5	47.4	<0.001[3]
Postmenopausal,[2,5] %	73.8	73.3	78.2	86.3	0.02[3]
Ever used hormone replacement therapy,[2,5] %	62.0	59.2	61.5	57.4	0.49[3]
Daily dietary intake[4]					
Red meat, *g/d*	44.3 ± 1.0	50.9 ± 1.0	54.3 ± 1.0	60.7 ± 1.0	<0.001[3,6]
Total energy, *kcal/d*	1860 ± 1.0	1910 ± 1.0	1940 ± 1.0	1920 ± 1.0	0.22[3]
Dietary calcium, *mg/d*	843 ± 1.0	834 ± 1.0	812 ± 1.0	801 ± 1.0	<0.001[3,6]
Dietary folate equivalents, *μg/d*	558 ± 1.0	552 ± 1.0	546 ± 1.0	520 ± 1.0	<0.001[3,6]
Dietary fiber, *g/d*	17.3 ± 1.0	17.0 ± 1.0	17.0 ± 1.0	15.7 ± 1.0	<0.001[3,6]

[1] AD, adenomatous polyp; HPP, hyperplastic polyp; NSAID, nonsteroidal anti-inflammatory drug.
[2] Frequencies are standardized to the age (5-y categories) and sex distribution of the control population.
[3] *P* values were derived from models adjusted for age (5-y categories) and sex.
[4] Least-square mean ± SE of log-transformed data from ANOVA models adjusted for age (5-y categories) and sex.
[5] Among women only.
[6] Additionally adjusted for total energy intake.

drinking was defined as consumption of ≥5 drinks/wk for 12 mo continuously. Regular nonsteroidal anti-inflammatory drug (NSAID) users were defined as those who used NSAIDs at least 3 times each week for at least 12 mo continuously (16).

Dietary factors and energy intake amounts for each participant were derived from a self-administered, semiquantitative 108-item FFQ that was developed and validated (17) for a similar southern U.S. population. The FFQ was developed using the NHANES III database to capture diet information in the study population (18). The FFQ also contained 5 items to survey eating habits and 13 items to capture vitamin and supplement use. Usual dietary intake of fiber was estimated by using data from NHANES III and USDA food-composition tables. Usual dietary intake of nutrients (19), including dietary fiber, dietary fat, dietary calcium, dietary folate equivalents, total energy, and red meat, were calculated as described previously (20,21). Dietary intakes were log-transformed and adjusted for total energy intake using the residual method (22,23), in which intakes of dietary factors of interest are regressed on total-energy intake in a linear regression model. Residuals from this model were used in the multivariate analysis. The current analysis includes 5459 participants who completed both the telephone interview and the FFQ and reported a daily energy intake ≥600 kcal.

Statistical analyses. General linear models and Mantel-Haenszel χ^2 tests were used to compare the distribution of demographic characteristics and known risk factors for colorectal polyps between case and control groups with additional adjustment for age and sex when appropriate. Unconditional logistic regression models were used to estimate ORs and their 95% CIs for the association between dietary fiber intake and polyp risk. Factors were included in models as potential confounders if they were statistically significantly associated with fiber intake among controls (data not shown) and with case-control status (**Table 1**). Confounding variables selected for adjustment included age (5-y categories), sex, study site (academic medical center, Veterans Affairs medical center), educational attainment (high school or less, some college, college graduate, graduate or professional education), regular exercise (yes or no), use of a multivitamin (yes or no), and daily dietary intakes of energy, calcium, and dietary folate equivalents. When not stratified by cigarette smoking, additional adjustments were made for cigarette smoking status. Adjustment for other factors (**Table 2**) made no appreciable differences in the models. Percentile cut points for dietary intake and medium cut points for smoking duration and intensity were based on the distributions in control participants.

P values for trend tests were derived by entering categorical variables as continuous variables in the models (24). Likelihood ratio tests for multiplicative interaction were used to compare the models with and without interaction terms. In tests for interaction, the median fiber intake was assigned within each category and treated as a continuous measure in the model. To evaluate heterogeneity among AD types, we made case-only analyses and pairwise case comparisons by unconditional logistic regression models. *P* values of ≤ 0.05 (2-sided probability) were considered statistically significant. All analyses were conducted using SAS statistical software (version 9.3; SAS Institute).

Results

Distributions of characteristics for the study groups are presented in Table 1. A higher percentage of controls than cases were enrolled at Vanderbilt Medical Center than the Veterans Affairs Medical Center. Female cases with non-AD or synchronous HPP/ADs were more likely to be postmenopausal, whereas AD-only cases were similar to controls. Case-control distributions of race, BMI, hormone replacement therapy (in females only), family history of colorectal cancer, and indications for colonoscopy were, in general, comparable, although some comparisons were significant because of large sample size. Compared with controls, polyp cases were more likely to be male, regular smokers, and regular alcohol consumers, have lower educational attainment, and were less likely to use NSAIDs regularly. Polyp cases had significantly higher daily intake of total energy and red meat but significantly lower daily intake of dietary folate, dietary calcium, dietary fiber, and multivitamins. There was no significant difference in total energy intake. Exclusion of participants recruited after colonoscopy (n = 894) did not appreciably change the association (data not shown).

The association between fiber intake and polyp risk varied by type of polyp case (Table 2; *P*-heterogeneity = 0.03). High fiber intake was associated with statistically significant reduced risks of both any polyp (OR = 0.80; 95% CI: 0.67, 0.97; *P*-trend = 0.003) and synchronous HPPs and ADs (OR = 0.53; 95% CI: 0.36, 0.78; *P*-trend = 0.001) compared with lowest fiber intake. Fiber intake was marginally associated with risk of AD only (*P*-trend = 0.06). However, no apparent association was observed for HPPs only (*P*-trend = 0.30).

Polyp risk varied by cigarette smoking status (**Table 3**). Statistically significant inverse associations were observed between the risk of any polyp and dietary fiber intake for ever smokers (OR = 0.75; 95% CI: 0.58, 0.97 for highest vs. lowest intake; *P*-trend = 0.006) but not for never smokers (*P*-trend = 0.21). The effect modification by smoking status was of borderline significance (*P*-interaction = 0.11). A similar association pattern was found for both males and females when analyzed separately, although none of the tests of effect modification by smoking status was statistically significant. We also did not observe any effect modification by sex for the association of dietary fiber intake and colorectal polyp risk (data not shown).

TABLE 2 Associations between dietary fiber intake quartiles and risk of colorectal polyps, the Tennessee Colorectal Polyp Study, 2003–2010[1]

		Polyp type								
		Any polyp		AD only		Non-AD only		Both types		
Dietary fiber intake quartile[2]	Controls, *n*	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	*P*-heterogeneity
Q1 (11.6 g/d)	796	712	1.00 (reference)	389	1.00 (reference)	172	1.00 (reference)	151	1.00 (reference)	0.03
Q2 (16.1 g/d)	796	647	1.02 (0.87, 1.19)	363	1.02 (0.85, 1.22)	175	1.18 (0.92, 1.51)	109	0.88 (0.66, 1.18)	
Q3 (19.7 g/d)	796	471	0.80 (0.68, 0.95)	285	0.85 (0.69, 1.04)	105	0.79 (0.59, 1.05)	81	0.71 (0.51, 0.99)	
Q4 (24.8 g/d)	796	445	0.80 (0.67, 0.97)	278	0.85 (0.68, 1.06)	114	0.96 (0.70, 1.31)	53	0.53 (0.36, 0.78)	
P-trend			0.003		0.06		0.30		0.001	

[1] ORs adjusted for age, sex, study sites, educational attainment, smoking status, regular exercise, use of a multivitamin, dietary calcium intake, dietary folate equivalents intake, and total energy intake. AD, adenomatous polyp; Q, quartile.
[2] Median intakes in parentheses.

TABLE 3 Association of dietary fiber intake with all polyp risk stratified by smoking status, the Tennessee Colorectal Polyp Study, 2003–2010[1]

	Never smoker (N = 2602)[2]			Ever smoker (N = 2852)[2]			
		Any polyp			Any polyp		
Dietary fiber intake quartile	Controls, *n*	*n*	OR (95% CI)	Controls, *n*	*n*	OR (95% CI)	*P*-interaction
All participants[3]							0.11
Q1	389	206	1.00 (reference)	407	506	1.00 (reference)	
Q2	438	246	1.14 (0.89, 1.45)	358	400	0.97 (0.79, 1.19)	
Q3	448	195	0.90 (0.69, 1.17)	346	276	0.75 (0.59, 0.94)	
Q4	477	203	0.90 (0.68, 1.19)	319	240	0.75 (0.58, 0.97)	
P-trend			0.21			0.006	
Males[4]							0.15
Q1	207	133	1.00 (reference)	284	389	1.00 (reference)	
Q2	196	137	1.10 (0.79, 1.51)	243	319	1.04 (0.82, 1.32)	
Q3	192	103	0.88 (0.62, 1.26)	217	206	0.80 (0.61, 1.05)	
Q4	193	120	1.06 (0.72, 1.56)	199	183	0.83 (0.61, 1.14)	
P-trend			0.96			0.10	
Females[4]							0.22
Q1	182	73	1.00 (reference)	123	117	1.00 (reference)	
Q2	242	109	1.16 (0.80, 1.68)	115	81	0.79 (0.53, 1.18)	
Q3	256	92	0.92 (0.62, 1.37)	129	70	0.62 (0.41, 0.95)	
Q4	284	83	0.74 (0.48, 1.13)	120	57	0.55 (0.35, 0.90)	
P-trend			0.07			0.008	

[1] Q, quartile.
[2] Counts may not sum to the total because of missing data.
[3] Adjusted for age, sex, study sites, educational attainment, regular exercise, use of a multivitamin, dietary calcium intake, dietary folate equivalents intake, and total energy intake.
[4] Adjusted for the variables listed in footnote 3 except sex.

Table 4 shows adjusted associations of dietary fiber intake with colorectal adenoma risk stratified by smoking status. Overall, stronger inverse associations were observed among ever smokers than among never smokers. Furthermore, in stratified analyses, the inverse association with high fiber intake was limited to high-risk adenomas (OR = 0.65; 95% CI: 0.45, 0.94 for highest vs. lowest intake; *P*-trend = 0.003; *P*-interaction = 0.09) among smokers. No statistically significant association was observed for either high-risk adenomas among never smokers (*P*-trend = 0.15) or low-risk adenomas regardless of smoking status.

Table 5 shows adjusted associations among cigarette smokers of dietary fiber intake with colorectal AD risk stratified by smoking duration and intensity. Overall, stronger inverse associations were observed only among those who smoked longer than 23 y. Furthermore, in stratified analyses, the inverse association with high fiber intake was limited to high-risk ADs (OR = 0.52; 95% CI: 0.32, 0.85 for highest vs. lowest intake; *P*-trend = 0.003). No statistically significant association was observed for smokers who smoked <23 y or low-risk ADs regardless of smoking duration. There was no significant interaction between fiber intake and cigarette smoking intensity and risk of any adenomatous type. There was no significant interaction between sex, smoking intensity or duration, fiber intake, and polyp risk (data not shown).

Discussion

In this study, we found that increased consumption of dietary fiber is significantly inversely associated with risk of colorectal polyps, especially high-risk colorectal ADs among those smokers who smoked longer than 23 y, but not among those who smoked for a shorter duration or for low-risk colorectal ADs. Our results imply that dietary fiber may play a protective role against cigarette carcinogens in the risk of high-risk colorectal ADs, a well-established precursor of colorectal cancer.

Case-control studies demonstrated an inverse relation between dietary fiber intake and risk of colorectal cancer, but prospective cohort studies and randomized trials were equivocal. One pooled analysis found a significant 16% reduction in colorectal cancer risk among individuals in the highest quintile of dietary fiber intake compared with those in the lowest (25). However, this association disappeared after adjusting for other dietary factors. A recent meta-analysis of prospective studies showed that high intake of dietary fiber, particularly cereal fiber and whole grains, was associated with reduced risk of colorectal cancer (26). A recent study from European Prospective Investigation into Cancer and Nutrition did not report a significant interaction between smoking status and fiber intake and colorectal cancer risk (27). However, most other studies did not evaluate possible interactions between dietary fiber intake and cigarette smoking in colorectal tumor risk. Studies regarding the association between dietary fiber intake and colorectal tumor risk have not been entirely consistent, and these inconsistencies may be explained in part by the possible interaction of dietary fiber and cigarette smoking in colorectal tumor risk, as suggested in this study. The possibility that dietary fiber consumption may provide a protective effect against risk of colorectal cancer among cigarette smokers is biologically plausible. Dietary fiber, especially insoluble fiber, may decrease the risk of colorectal cancer by increasing stool bulk, diluting fecal carcinogens, and decreasing transit time, thus reducing the contact between cigarette-smoke carcinogens and the lining of the colorectum (28).

Some studies observed increased colorectal cancer risk associated with cigarette smoking predominantly in males but

TABLE 4 Association of dietary fiber intakes with high- and low-risk adenomatous polyps stratified by smoking status, the Tennessee Colorectal Polyp Study, 2003–2010[1]

	Never smoker			Ever smoker			
	Controls, *n*	Cases		Controls	Cases		
Dietary fiber intake quartile	(*n* = 1752)	*n*[2]	OR (95% CI)	(*n* = 1430)	*n*[2]	OR (95% CI)	*P*-interaction
Any adenomatous polyp							0.45
Q1	389	170	1.00 (reference)	407	370	1.00 (reference)	
Q2	438	195	1.08 (0.84, 1.40)	358	277	0.92 (0.73, 1.15)	
Q3	448	163	0.89 (0.68, 1.18)	346	203	0.75 (0.58, 0.96)	
Q4	477	149	0.78 (0.57, 1.05)	319	181	0.76 (0.57, 1.00)	
P-trend			0.05			0.02	
High-risk adenomatous polyp							0.09
Q1	389	63	1.00 (reference)	407	185	1.00 (reference)	
Q2	438	84	1.25 (0.87, 1.82)	358	145	0.96 (0.73, 1.27)	
Q3	448	64	0.89 (0.59, 1.35)	346	84	0.63 (0.45, 0.87)	
Q4	477	63	0.79 (0.51, 1.24)	319	79	0.65 (0.45, 0.94)	
P-trend			0.15			0.003	
Low-risk adenomatous polyp							0.55
Q1	389	94	1.00 (reference)	407	136	1.00 (reference)	
Q2	438	86	0.90 (0.64, 1.25)	358	106	0.94 (0.69, 1.27)	
Q3	448	86	0.93 (0.65, 1.32)	346	86	0.81 (0.58, 1.14)	
Q4	477	78	0.85 (0.57, 1.25)	319	87	0.93 (0.64, 1.34)	
P-trend			0.47			0.49	

[1] All polyp groups adjusted for age, sex, study sites, educational attainment, regular exercise, use of a multivitamin, dietary calcium intake, dietary folate equivalents intake, and total energy intake. Q, quartile.
[2] Counts may not sum to the total because of missing data.

not females (29–35). A pooled analysis of 2 clinical trials suggested that there might be sex differences in response to fiber (36). Three prospective cohort studies found different associations with fiber intake between men and women (37–39). Some analyses indicated that men may experience more benefits from dietary fiber than women (36). We did not find significant sex differences (interactions) in the associations of fiber with colorectal polyp by cigarette-smoking status in our current

TABLE 5 Association of dietary fiber intake by duration of cigarette smoking or number of cigarettes smoked per day among regular cigarette smokers, the Tennessee Colorectal Polyp Study, 2003–2010[1]

	Cigarette smoking duration					Cigarette smoking intensity				
	<23 y		≥23 y			<20 cigarettes/d		≥20 cigarettes/d		
Dietary fiber intake quartiles	Controls/ cases, *n/n*	OR (95% CI)	Controls/ cases, *n/n*	OR (95% CI)	*P*-interaction	Controls/ cases, *n/n*	OR (95% CI)	Controls/ cases, *n/n*	OR (95% CI)	*P*-interaction
Any adenomatous polyps					0.22					0.05
Q1	165/62	1.00 (reference)	242/287	1.00 (reference)		158/121	1.00 (reference)	248/248	1.00 (reference)	
Q2	176/94	1.10 (0.75, 1.63)	182/182	0.90 (0.67, 1.20)		141/84	0.80 (0.54, 1.17)	216/193	0.99 (0.75, 1.31)	
Q3	194/66	0.75 (0.49, 1.16)	152/136	0.85 (0.62, 1.17)		138/92	0.91 (0.61, 1.36)	208/111	0.65 (0.47, 0.90)	
Q4	176/81	1.09 (0.69, 1.71)	143/99	0.67 (0.46, 0.97)		138/78	0.72 (0.46, 1.13)	179/103	0.77 (0.53, 1.11)	
P-trend		0.84		0.04			0.26		0.03	
High-risk adenomatous polyp					0.21					0.25
Q1	165/41	1.00 (reference)	242/144	1.00 (reference)		158/55	1.00 (reference)	248/129	1.00 (reference)	
Q2	176/46	1.15 (0.69, 1.91)	182/98	0.92 (0.65, 1.30)		141/49	1.00 (0.62, 1.63)	216/96	0.94 (0.67, 1.34)	
Q3	194/30	0.73 (0.41, 1.30)	152/54	0.65 (0.42, 0.99)		138/37	0.88 (0.51, 1.50)	208/47	0.51 (0.33, 0.78)	
Q4	176/37	1.03 (0.56, 1.90)	143/41	0.52 (0.32, 0.85)		138/31	0.67 (0.36, 1.24)	179/48	0.63 (0.39, 1.00)	
P-trend		0.68		0.004			0.20		0.005	
Low-risk adenomatous polyp					0.54					0.15
Q1	165/33	1.00 (reference)	242/103	1.00 (reference)		158/53	1.00 (reference)	248/83	1.00 (reference)	
Q2	176/43	1.20 (0.70, 2.03)	182/63	0.87 (0.59, 1.29)		141/26	0.55 (0.31, 0.95)	216/80	1.24 (0.58, 1.82)	
Q3	194/32	0.89 (0.50, 1.58)	152/54	0.88 (0.58, 1.36)		138/43	0.88 (0.53, 1.47)	208/43	0.77 (0.49, 1.21)	
Q4	176/39	1.29 (0.70, 2.36)	143/48	0.85 (0.52, 1.38)		138/41	0.71 (0.40, 1.26)	179/46	1.07 (0.65, 1.75)	
P-trend		0.67		0.51			0.49		0.66	

[1] Counts may not sum to the total because of missing data. All polyp groups adjusted for age, sex, study site, educational attainment, regular exercise, use of a multivitamin, dietary calcium intake, dietary folate equivalents, and total energy intake. Q, quartile.

study. Rather, we found the association of fiber with colorectal high-risk AD significantly differed by smoking status. Therefore, previous findings of sex difference in the association of colorectal cancer with fiber might be driven by sex differences in smoking: males are more likely to smoke and smoke more heavily than females.

As with any case-control study, the possibility of selection and recall biases may be a concern in this study. Colonoscopy was used to classify case-control status in our study, minimizing misclassification error from incomplete examination of the entire colon. However, because this is a colonoscopy-based (screening) population, our findings might not be fully generalizable to nonscreening populations. The vast majority of study participants (n = 6406) were recruited before colonoscopy and, thus, before polyp diagnosis, which reduces possible selection bias. Exclusion of participants recruited after colonoscopy did not appreciably change the associations. Because it was difficult to conduct the lengthy interview in the clinics, all interviews were done by phone soon after colonoscopy. We cannot fully exclude the possibility of recall bias. Although measurement error for dietary intake is also a concern, dietary measurement errors are likely to be random, which typically attenuates risk estimates. The observed association could also be a result of other dietary constituents that are closely correlated with dietary fiber. However, in previous analyses, we only found a significant independent association with polyp risk for dietary calcium intake and dietary fiber intake in the TCPS (5). In this study, results regarding dietary fiber intake were essentially unchanged with adjustment of multivitamin intake, total folate intake, red-meat intake, alcohol consumption, and dietary calcium intake. Furthermore, no interaction between dietary calcium intake and cigarette smoking was found in relation to polyp risk.

In conclusion, our results suggest that cigarette smoking may modify the association of dietary fiber intake with the risk of colorectal polyps, especially high-risk ADs. Additional studies are needed to further examine this interaction.

Acknowledgments

W.Z. designed and directed the study with M.J.S. and R.M.N.; Z.F. and M.J.S. analyzed the data; Z.F., W.Z., and M.J.S. drafted the manuscript; and R.M.N. and W.E.S. provided support for the clinical operation. All authors reviewed and approved the final manuscript.

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