Dietary fiber and whole-grain consumption in relation to colorectal cancer in the NIH-AARP Diet and Health Study[1–5]

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ABSTRACT

Background: Whether the intake of dietary fiber can protect against colorectal cancer is a long-standing question of considerable public health import, but the epidemiologic evidence has been inconsistent.

Objective: The objective was to investigate the relation between dietary fiber and whole-grain food intakes and invasive colorectal cancer in the prospective National Institutes of Health–AARP Diet and Health Study.

Design: The analytic cohort consisted of 291 988 men and 197 623 women aged 50–71 y. Diet was assessed with a self-administered food-frequency questionnaire at baseline in 1995–1996; 2974 incident colorectal cancer cases were identified during 5 y of follow-up. The Cox proportional hazards model was used to estimate the relative risks (RRs) and 95% CIs.

Results: Total dietary fiber intake was not associated with colorectal cancer. The multivariate RR for the highest compared with the lowest intake quintile ($RR_{Q5\text{-}Q1}$) was 0.99 (95% CI: 0.85, 1.15; *P* for trend = 0.96). In analyses of fiber from different food sources, only fiber from grains was associated with a lower risk of colorectal cancer (multivariate $RR_{Q5\text{-}Q1}$: 0.86; 95% CI: 0.76, 0.98; *P* for trend = 0.01). Whole-grain intake was inversely associated with colorectal cancer risk: the multivariate $RR_{Q5\text{-}Q1}$ was 0.79 (95% CI: 0.70, 0.89) for the whole cohort (*P* for trend < 0.001). The association with whole grain was stronger for rectal than for colon cancer.

Conclusions: In this large prospective cohort study, total dietary fiber intake was not associated with colorectal cancer risk, whereas whole-grain consumption was associated with a modest reduced risk. *Am J Clin Nutr* 2007;85:1353–60.

KEY WORDS Dietary fiber, whole grain, colorectal cancer, fiber sources, cohort study

INTRODUCTION

The hypothesis that generous consumption of dietary fiber reduces the risk of developing colorectal cancer was proposed >3 decades ago. In the 1960s, Burkitt (1) observed that rural Ugandans consuming a diet rich in dietary fiber had a low rate of colorectal cancer. Several plausible pathophysiologic processes, including stool bulking with subsequent dilution of colonic luminal carcinogens and production of anticarcinogenic short-chain fatty acids, have been proposed to account for the ecologic association (2).

Many epidemiologic studies have now examined this hypothesis. Earlier case-control studies tended to show a protective association of dietary fiber (3), whereas initial prospective cohort studies did not (4–10). Results of adenoma recurrence trials with fiber interventions were generally null (11–14). The inconsistency of findings concerning this association was only exacerbated by 2 recent reports from large prospective studies, which showed an inverse relation between dietary fiber intake and risk of colorectal cancer (15, 16). These results were followed by the findings of pooled prospective cohort studies, which showed either no association between dietary fiber intake and colorectal cancer or, at most, an increased risk only in persons who consumed small amounts of dietary fiber (17).

In this context of plausible biology but inconsistent epidemiologic results, we examined the relation of dietary fiber and whole-grain intakes to colorectal cancer risk in a large prospective cohort of men and women in the NIH-AARP Diet and Health Study.

SUBJECTS AND METHODS

Study population

The NIH-AARP Diet and Health Study was described previously (18). We initiated the study in 1995–1996 by mailing questionnaires to 3.5 million AARP members aged 50–71 y from 6 US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and 2 metropolitan areas (Atlanta, GA, and Detroit, MI). Of the 567 169 participants who returned

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[2] AARP, formerly known as the American Association of Retired Persons, is not an abbreviation, but is the legal name of the organization.

[3] The views expressed herein are solely those of the authors and do not necessarily reflect those of the Florida Cancer Data System under contract to the Department of Health (DOH) or the DOH. The Pennsylvania Department of Health specifically disclaims responsibility for any analyses, interpretations, or conclusions.

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questionnaires with satisfactory dietary data, we excluded individuals with duplicate questionnaires ($n = 179$), who requested to be withdrawn ($n = 1$), who moved out of the study area or died at baseline ($n = 589$), who received a diagnosis of colorectal cancer at baseline ($n = 26$), who indicated that they were proxies for the intended respondents ($n = 15\,760$), who had any self-reported prevalent cancer except nonmelanoma skin cancer at baseline ($n = 51\,207$), who had self-reported end-stage renal disease at baseline ($n = 997$), and who had cancer as a cause of death and had no cancer registry record ($n = 1660$). In addition, we excluded individuals who reported extreme intakes (>2 times the interquartile ranges of sex-specific Box-Cox log-transformed intake) of total energy ($n = 4401$), dietary fiber ($n = 1662$), and whole grains ($n = 1076$). After all exclusions, the analytic cohort consisted of 291 988 men and 197 623 women. The study was approved by the National Cancer Institute Special Studies Institutional Review Board.

Cancer ascertainment

We identified incident cases of colorectal cancer that occurred during the follow-up through 31 December 2000. Cases were identified through probabilistic linkage with 8 state cancer registry databases certified by the North American Association of Central Cancer Registries as being 95% complete within 2 y of cancer occurrence. Information on the tumor site of the colorectal cancer and its histology was also obtained through linkage with state cancer registries. The case-ascertainment method used in the study was described in a previous study (19).

We followed members of the NIH-AARP study cohort annually for changes of address by matching the cohort data to the National Change of Address (NCOA) database maintained by the US Postal Service (USPS). Information on address changes also came through receipt of USPS processing of undeliverable mail, from other address-change update services, and directly from participants who reported address changes when responding to study mailings, such as questionnaires or newsletters. According to information from records of out-of-state moves in the NCOA database and other address-change databases, during the follow-up period of 1995–2000, only 5% of participants were no longer living within 1 of the 8 states included in the study, which suggests that most of the cohort remained in active follow-up for cancer-endpoint ascertainment.

We ascertained vital status through annual linkage of the cohort to the Social Security Administration Death Master File (SSA DMF) of deaths in the United States, follow-up searches of the National Death Index Plus for participants who matched to the SSA DMF, cancer registry linkage, questionnaire responses, and responses to other mailings.

Incident colorectal cancer cases [International Classification of Diseases for Oncology, 3rd ed (ICD-O) codes C180–C189, C260, C199, and C209] had to be invasive and, if multiple cancers were diagnosed in the same participant, the first malignancy had to have been diagnosed during the follow-up period. Cases diagnosed with cancer in both colon and rectum on the same day ($n = 24$) were considered to be cases for both sites. We further classified colorectal cancer by tumor site: proximal (C180–C184), distal colon (C185–C187), and rectum (C199, C209). During follow-up, we identified 2974 incident colorectal cancer cases (2049 in men and 925 in women).

Dietary assessment

At baseline, dietary intakes were assessed with a self-administered 124-item food-frequency questionnaire (FFQ), which was an early version of the Diet History Questionnaire developed at the National Cancer Institute (20). Participants were asked to report their usual frequency of intake and portion size over the past 12 mo, using 10 predefined frequency categories ranging from "never" to "≥6 times/d" for beverages, from "never" to "≥2 times/d" for solid foods and 3 categories of portion size. The food items, portion sizes, and nutrient database were constructed on the basis of Subar et al's (21) method by using the US Department of Agriculture's (USDA's) 1994–1996 Continuing Survey of Food Intake by Individuals (CSFII) (22). The nutrient database for dietary fiber was based on the Association of Official Analytic Chemist (AOAC) method (23). In addition, food groups and their serving sizes were defined by the Pyramid Servings Database corresponding to the 1994–1996 CSFII, which uses a recipe file to disaggregate food mixtures into their component ingredients and assigns them to food groups. One serving of whole grain was defined on the basis of standard portion sizes developed by the USDA, such as one slice of whole-grain bread, one cup of ready-to-eat whole-grain cereal, or 0.5 cups of cooked whole grains (24). USDA's Pyramid Servings Database enabled us to estimate whole-grain intake from all foods in the FFQ, even those with small amounts of whole grain. The sources of whole-grain intake in our FFQ were ready-to-eat cereals, high-fiber cereals, other fiber cereals, whole-grain breads or dinner rolls, cooked cereal (eg, oatmeal or grits), popcorn, pancakes, waffles, French toast or crepes, rice or other cooked grains, bagels, English muffins, tortillas, pasta, crackers, chips (potato, tortilla, or corn), cookies or brownies, sweet pastries, and pies.

The FFQ used in the study was validated by using 2 nonconsecutive 24-h dietary recalls in 1953 participants (FE Thompson, personal communication, 2006). The energy-adjusted correlation coefficients of dietary fiber intake between an FFQ and 24-h recalls were 0.72 in men and 0.66 in women.

Statistical analysis

We calculated age-standardized colorectal cancer incidence rates (per 100 000 person-years at risk). Person-years of follow-up time were calculated from the date of the baseline questionnaire until the date of colorectal cancer diagnosis, death, move out of the registry areas, or end of follow-up, whichever came first.

We estimated relative risks (RRs) and 2-sided 95% CIs with the Cox proportional hazards model (25) using the SAS PROC PHREG (26) procedure and age as the underlying time metric. To evaluated the proportional hazards assumption, we modeled cross-product interaction terms comprising time and both the fiber and whole-grain variables; no interactions were statistically significant. We used the baseline cohort distribution to determine intake quintiles for RR estimation; we used sex-specific intake quintiles in separate analyses of men and women. To evaluate the linear trend, we assigned participants the median value of their intake quintiles and entered these values as a continuous term in a regression model. We also examined the intakes of dietary fiber and whole grains in relation to colorectal cancer by anatomic site. We used a contrast test to evaluate differences in results among tumor sites (27).

TABLE 1
Characteristics of study participants by quintile of dietary fiber and whole-grain intakes

	Dietary fiber			Whole grain		
	Quintile 1	Quintile 3	Quintile 5	Quintile 1	Quintile 3	Quintile 5
Incidence rate[1]	175	137	121	173	144	115
Dietary fiber (g · 1000 kcal^{-1} · d^{-1})[2]	6.6	10.3	15.9	7.9	10.1	13.1
Whole grain (servings · 1000 kcal^{-1} · d^{-1})[2]	0.3	0.6	0.9	0.2	0.6	1.3
Age (y)[3]	61 ± 5	62 ± 5	63 ± 5	62 ± 5	62 ± 5	63 ± 5
Sex (%)						
Men	69	60	49	63	58	60
Women	31	40	51	37	42	40
Physical activity (%)						
Never or rarely	27	17	12	24	16	15
1–3 times/mo	17	14	10	16	14	12
1–2 times/wk	22	23	18	21	22	20
3–4 times/wk	20	28	32	22	28	30
≥5 times/wk	13	18	28	16	19	23
Smoking (%)						
Never	27	37	42	29	37	39
Past, ≤20 cigarettes/d	23	29	31	24	28	30
Past, >20 cigarettes/d	24	21	19	23	21	21
Current, ≤20 cigarettes/d	13	7	4	12	7	5
Current, >20 cigarettes/d	10	3	1	8	3	2
Menopausal hormone therapy in women						
Never	52	46	44	53	46	43
Past	9	9	9	8	9	9
Current	39	45	46	39	45	48
Dietary calcium (mg · 1000 kcal^{-1} · d^{-1})[3]	394 ± 218	427 ± 169	477 ± 163	380 ± 327	437 ± 177	469 ± 171
Dietary folate (μg · 1000 kcal^{-1} · d^{-1})[3]	170 ± 45	230 ± 46	303 ± 69	198 ± 63	234 ± 61	264 ± 73
Red meat (g · 1000 kcal^{-1} · d^{-1})[3]	45 ± 24	36 ± 19	21 ± 16	41 ± 24	35 ± 20	27 ± 18
Energy (kcal/d)[3]	2062 ± 931	1829 ± 759	1577 ± 625	1969 ± 968	1852 ± 757	1640 ± 634

[1] Age-adjusted colorectal cancer incidence rate per 100 000 person-years.
[2] Median intake.
[3] All values are $\bar{x}$ ± SD. P for trend < 0.001.

We used a nutrient-density model, in which daily dietary fiber intake was expressed as g/1000 kcal of total energy. We tested known colorectal cancer risk factors as potential confounders by comparing risk estimates of dietary fiber intake to those obtained in models with each risk factor. In multivariate models, we adjusted for physical activity (never or rarely, 1–3 times/mo, and 1–2, 3–4, or ≥5 times/wk), smoking (never, ≤20 cigarettes/d in the past, >20 cigarettes/d in the past, ≤20 cigarettes/d currently, and >20 cigarettes/d currently), menopausal hormone therapy in women (never, past, and current), and intakes of red meat (quintiles), dietary calcium (quintiles), dietary folate (quintiles), and total energy (continuous). The nutrient-density models included a variable for total energy intake. For each covariate, we created a specific indicator value that reflected missing data. When we further adjusted for race-ethnicity, education, body mass index, alcohol consumption, family history of colorectal cancer, screening for colorectal cancer, and nonsteroidal antiinflammatory drug use, the results were similar to those from the parsimonious model. We also examined interactions between dietary fiber intake and each of the covariates included in multivariate models. Finally, we used the residual method (28) to repeat analyses of energy-adjusted dietary fiber intake; results were similar to those generated with the nutrient-density method.

To evaluate whether intake of dietary fiber and whole grains was log-linearly associated with risk of colorectal cancer, we compared nonparametric regression curves derived from restricted cubic splines to the linear model (29).

RESULTS

The 10th and 90th percentiles for dietary fiber intake (g/1000 kcal per day) were 6.6 and 15.9 in the whole cohort, 6.4 and 15.2 in men, and 7.0 and 16.8 in women. (Comparable values based on the residual method were 11.8 and 28.2 g/d in the whole cohort, 12.5 and 29.5 g/d in men, and 10.9 and 25.8 g/d in women.) The 10th and 90th percentile values for whole grains (servings/1000 kcal per day) were 0.2 and 1.3 in the whole cohort, 0.2 and 1.3 in men, and 0.2 and 1.3 in women. The correlations between intakes of dietary fiber and whole grains were 0.60 in the whole cohort, 0.59 in men, and 0.60 in women. Participants who reported high intakes of both dietary fiber and whole grains were more likely to be physically active, have never smoked, consume more calcium and folate, and consume less red meat and total energy than participants with low intakes of dietary fiber and whole grains (**Table 1**).

The age- and sex-adjusted analyses showed a statistically significant inverse relation between dietary fiber and colorectal cancer, with a reduction in risk of ≈25% in those in the highest, compared with those in the lowest, intake quintile (RR: 0.73; 95% CI: 0.65, 0.82; **Table 2**). Further adjustment for physical

TABLE 2
Relative risks (and 95% CIs) of colorectal cancer by quintile of dietary fiber intake

	Quintile					
	1	2	3	4	5	*P* for trend
Colorectal cancer						
Median intake (g · 1000 kcal^{-1} · d^{-1})	6.6	8.6	10.3	12.3	15.9	
Cases/person-years	704/423 602	617/425 196	585/425 675	531/426 553	537/427 501	
Age-and sex-adjusted	1.00	0.84 (0.76, 0.94)	0.80 (0.71, 0.89)	0.72 (0.64, 0.81)	0.73 (0.65, 0.82)	< 0.001
Multivariate[1]	1.00	0.92 (0.82, 1.03)	0.93 (0.82, 1.06)	0.90 (0.78, 1.04)	0.99 (0.85, 1.15)	0.96
By sex[2]						
Men						
Cases/person-years	470/251 397	425/252 152	413/251 938	353/252 355	388/252 626	
Age-adjusted	1.00	0.86 (0.76, 0.99)	0.82 (0.72, 0.94)	0.69 (0.60, 0.79)	0.74 (0.65, 0.85)	< 0.001
Multivariate[1]	1.00	0.94 (0.82, 1.09)	0.98 (0.84, 1.14)	0.89 (0.75, 1.05)	1.06 (0.88, 1.28)	0.55
Women						
Cases/person-years	205/172 759	192/173 683	168/173 795	164/173 696	196/174 126	
Age-adjusted	1.00	0.88 (0.72, 1.07)	0.75 (0.61, 0.92)	0.72 (0.59, 0.89)	0.85 (0.70, 1.04)	0.07
Multivariate[1]	1.00	0.94 (0.76, 1.16)	0.86 (0.68, 1.08)	0.88 (0.69, 1.13)	1.10 (0.84, 1.43)	0.45
By tumor site						
Colon cancer						
Cases/person-years	498/423 602	436/425 196	425/425 675	381/426 553	400/427 501	
Age-and sex-adjusted	1.00	0.84 (0.74, 0.96)	0.81 (0.71, 0.93)	0.72 (0.63, 0.83)	0.76 (0.67, 0.87)	< 0.001
Multivariate[1]	1.00	0.90 (0.79, 1.03)	0.93 (0.80, 1.08)	0.87 (0.74, 1.02)	0.96 (0.80, 1.15)	0.77
Proximal colon cancer						
Cases/person-years	265/423 602	211/425 196	243/425 675	198/426 553	222/427 501	
Age-and sex-adjusted	1.00	0.75 (0.63, 0.90)	0.85 (0.71, 1.01)	0.68 (0.56, 0.82)	0.75 (0.63, 0.90)	0.003
Multivariate[1]	1.00	0.82 (0.68, 1.00)	0.99 (0.81, 1.21)	0.82 (0.65, 1.03)	0.93 (0.72, 1.18)	0.68
Distal colon cancer						
Cases/person-years	216/423 602	208/425 196	160/425 675	169/426 553	161/427 501	
Age- and sex-adjusted	1.00	0.94 (0.78, 1.14)	0.73 (0.59, 0.89)	0.77 (0.63, 0.94)	0.75 (0.61, 0.92)	0.002
Multivariate[1]	1.00	0.98 (0.80, 1.20)	0.80 (0.63, 1.01)	0.90 (0.70, 1.15)	0.97 (0.73, 1.28)	0.80
Rectal cancer						
Cases/person-years	207/423 602	186/425 196	166/425 675	153/426 553	146/427 501	
Age-and sex-adjusted	1.00	0.87 (0.72, 1.07)	0.78 (0.64, 0.96)	0.72 (0.58, 0.89)	0.70 (0.56, 0.86)	< 0.001
Multivariate[1]	1.00	0.99 (0.80, 1.23)	1.00 (0.79, 1.26)	1.03 (0.79, 1.33)	1.13 (0.84, 1.51)	0.39

[1] Adjusted for sex, physical activity (never or rarely; <3 times/mo; 1–2, 3–4, or ≥5 times/wk; or missing), smoking (never, ≤20 cigarettes/d in the past, >20 cigarettes/d in the past, ≤20 cigarettes/d currently, >20 cigarettes/d, or missing), menopausal hormone therapy use in women (never, past, current, or missing), and intakes of red meat (quintiles), dietary calcium (quintiles), dietary folate (quintiles), and total energy (continuous).

[2] Quintiles were defined within each sex. The median intakes of dietary fiber for quintiles 1 to 5 were, respectively, 6, 8, 10, 12, and 15 g · 1000 kcal^{-1} · d^{-1} in men and 7, 9, 11, 13, and 17 g · 1000 kcal^{-1} · d^{-1} in women.

activity, smoking, and menopausal hormone therapy use in women somewhat attenuated these results, but the inverse trend remained statistically significant (RR for the highest compared with the lowest quintile: 0.81; 95% CI: 0.72, 0.92; *P* for trend ≤0.001). With additional adjustment for red meat, dietary calcium, and dietary folate, the association between fiber and colorectal cancer became null (RR for the highest compared with the lowest quintile: 0.99; 95% CI: 0.85, 1.15; *P* for trend = 0.96). There was no significant interaction between sex and dietary fiber intake (*P* for interaction = 0.86). The associations between dietary fiber intake and risk of colorectal cancer were null in separate analyses of men and women. In addition, the association between dietary fiber intake and risk of colorectal cancer was linear, with no threshold effect evident in the spline analysis (*P* value for linearity = 0.65). None of the interactions between dietary fiber and each covariate in the multivariate model, including a variable for colorectal cancer screening, was statistically significant. We also examined the association by each anatomic colorectal cancer sites and found no significant relations.

Results of the analyses of fiber from different food sources (grains, fruit, vegetables, and beans) in relation to colorectal cancer are shown in **Table 3**. The age- and sex-adjusted models for fiber from grains, fruit, vegetables, and beans showed inverse relations. After adjustment for other colorectal cancer risk factors, these inverse relations essentially disappeared for fiber from fruit, vegetables, and beans but remained statistically significant for fiber from grains (multivariate RR for the highest compared with the lowest quintile: 0.86; 95% CI: 0.76, 0.98; *P* for trend = 0.01). None of the interactions between sex and fiber from each source were significant.

Whole-grain intake was inversely related to colorectal cancer in both age- and sex-adjusted analyses and in the multivariate analyses, with a statistically significant 20% reduction in risk for those in the highest quintile compared with the lowest quintile (**Table 4**). No significant interaction between whole-grain intake and sex was observed (*P* for interaction by sex = 0.52). When we further adjusted for fiber intake from grains in a multivariate model, the results for whole-grain intake were not materially changed (multivariate RR for the highest quintile compared with the lowest quintile: 0.80; 95% CI: 0.67, 0.94; *P* for trend = <0.001). In nonparametric regression analysis, the association between whole-grain intake and risk of colorectal cancer was not

TABLE 3
Relative risks (and 95% CIs) of colorectal cancer by source of dietary fiber intake

	Quintile					
	1	2	3	4	5	*P* for trend
Fiber from grains						
Median intake (g · 1000 kcal^{-1} · d^{-1})	1.7	2.5	3.2	4.0	5.7	
Cases/person-years	652/424 227	660/425 715	583/425 996	569/426 245	510/426 344	
Age-and sex-adjusted	1.00	0.98 (0.88, 1.09)	0.85 (0.76, 0.95)	0.81 (0.73, 0.91)	0.71 (0.63, 0.79)	< 0.001
Multivariate[1]	1.00	1.03 (0.92, 1.15)	0.94 (0.83, 1.05)	0.94 (0.83, 1.06)	0.86 (0.76, 0.98)	0.01
Fiber from fruit						
Median intake	0.5	1.2	2.0	2.9	4.8	
Cases/person-years	678/424 344	613/424 958	563/425 460	527/426 776	593/426 989	
Age-and sex-adjusted	1.00	0.86 (0.77, 0.96)	0.78 (0.70, 0.87)	0.73 (0.65, 0.81)	0.83 (0.74, 0.92)	0.001
Multivariate[1]	1.00	0.95 (0.85, 1.06)	0.91 (0.81, 1.03)	0.90 (0.80, 1.02)	1.08 (0.95, 1.23)	0.14
Fiber from vegetables						
Median intake	1.7	2.5	3.2	4.2	6.0	
Cases/person-years	689/423 597	599/425 480	586/425 853	550/426 468	550/427 128	
Age-and sex-adjusted	1.00	0.88 (0.79, 0.98)	0.87 (0.78, 0.97)	0.83 (0.74, 0.93)	0.87 (0.77, 0.97)	< 0.001
Multivariate[1]	1.00	0.91 (0.81, 1.02)	0.93 (0.83, 1.04)	0.92 (0.81, 1.03)	1.01 (0.89, 1.15)	0.70
Fiber from beans						
Median intake	0.2	0.5	0.8	1.3	2.3	
Cases/person-years	623/425 769	620/425 786	561/425 569	595/425 666	575/425 737	
Age-and sex-adjusted	1.00	0.98 (0.87, 1.09)	0.87 (0.78, 0.98)	0.91 (0.81, 1.02)	0.89 (0.79, 0.99)	0.04
Multivariate[1]	1.00	0.98 (0.88, 1.09)	0.88 (0.78, 0.99)	0.92 (0.83, 1.04)	0.93 (0.83, 1.04)	0.25

[1] Adjusted for sex, physical activity (never or rarely; <3 times/mo; 1–2, 3–4, or ≥5 times/wk; or missing), smoking (never, ≤20 cigarettes/d in the past, >20 cigarettes/d in the past, ≤20 cigarettes/d currently, >20 cigarettes/d, or missing), menopausal hormone therapy use in women (never, past, current, or missing), and intakes of red meat (quintiles), dietary calcium (quintiles), dietary folate (quintiles), and total energy (continuous).

linear; the multivariate RR was flattened out in the higher intake range (*P* for nonlinearity ≤0.001; **Figure 1**).

When we examined the whole-grain association by anatomic tumor sites, we found that the inverse association was strongest for rectal cancer, with a 35% reduction in risk among those in the highest compared with the lowest quintile of whole-grain intake [multivariate RR: 0.64; 95% CI: 0.51, 0.81; *P* for difference by tumor site (colon compared with rectum) for the highest quintile = 0.03].

DISCUSSION

The dietary fiber–colorectal cancer hypothesis has long held an attraction for both medical researchers and the general public. The ecologic observations in Africa of lower digestive diseases among men who consumed a high-fiber diet were intriguing. Biologic explanations for a link between fiber and large-bowel cancer are plentiful and plausible, although animal experiments have been inconclusive (2). Results of trials of adenoma recurrence have been largely null (11–14, 30), but the interpretation of results concerning neoplastic precursor lesions in these studies of relatively short-duration is problematic, and an etiologic role for dietary fiber in colorectal carcinogenesis cannot be ruled out (14).

A major obstacle to acceptance of fiber's anticolorectal cancer benefits has been inconsistent observational epidemiologic evidence. Findings from case-control studies were generally supportive (3), but these studies are subject to recall bias. The hypothesis was thrown into serious question by results from a number of cohort studies (4–10); however, 2 recent prospective investigations with colorectal cancer (15) and prevalent colorectal adenoma endpoints (16) gave new life to the hypothesis. However, the essentially null results from the Pooling Project of Prospective Studies of Diet and Cancer (at least with respect to protection from high fiber intake (17), and now from this study, leave the question unresolved.

Could the fiber–colorectal cancer hypothesis be true in the face of such murky observational epidemiologic evidence? Three methodologic issues need to be considered: range of intake, confounding by other nutritional factors, and measurement error.

Some investigators have argued that the amount of fiber consumed by participants in the earlier null prospective studies was too low for an association with colorectal cancer to be observed, whereas, in the European Prospective Investigation into Cancer and Nutrition (EPIC), which showed an inverse association (15), participants in the upper intake category consumed more fiber than in previous cohorts. For example, the median amounts of dietary fiber consumed by the Nurses' Health Study participants in the first and fifth quintiles of intake were 12 and 24 g/d, respectively, whereas comparable intakes in women in the EPIC cohort were <15.9 and >26.7 g/d. This explanation, however, is undermined by the results from the Pooling Project, which found no association between high fiber intakes and colorectal cancer, even though the median intakes for the first and fifth quintiles of intake (9–20 and 23–41 g/d for men across studies; 8–17 and 20–35 g/d for women across studies) were comparable with those in the EPIC study. In our study, the median intakes for the first and fifth quintiles were 13 and 30 g/d in men and 11 and 26 g/d in women, again comparable with the ranges of intake in the EPIC study. This finding further suggests that the intake range does not account for the inconsistency in the prospective data.

Michels et al (10) argued that failure to control for confounding, especially by folate, could have accounted for the protective

TABLE 4
Relative risks (and 95% CIs) of colorectal cancer by quintiles of whole-grain intake

	Quintile					
	1	2	3	4	5	*P* for trend
Colorectal cancer						
Median intake (g · 1000 kcal^{-1} · d^{-1})	0.2	0.4	0.6	0.8	1.3	
Cases/person-years	717/424 327	614/425 549	611/426 196	523/426 211	509/426 243	
Age-and sex-adjusted	1.00	0.87 (0.78, 0.96)	0.85 (0.76, 0.94)	0.71 (0.63, 0.79)	0.67 (0.60, 0.75)	< 0.001
Multivariate[1]	1.00	0.92 (0.82, 1.02)	0.93 (0.83, 1.04)	0.81 (0.72, 0.91)	0.79 (0.70, 0.89)	< 0.001
By sex[2]						
Men						
Cases/person-years	482/251 436	460/251 974	407/252 250	357/252 240	343/252 567	
Age-adjusted	1.00	0.95 (0.83, 1.07)	0.82 (0.72, 0.94)	0.71 (0.62, 0.81)	0.66 (0.58, 0.76)	
Multivariate[1]	1.00	1.01 (0.88, 1.15)	0.91 (0.79, 1.04)	0.81 (0.70, 0.93)	0.79 (0.68, 0.91)	
Women						
Cases/person-years	212/173 138	179/173 602	199/173 795	170/173 848	165/173 676	
Age-adjusted	1.00	0.84 (0.69, 1.03)	0.92 (0.76, 1.11)	0.76 (0.62, 0.93)	0.72 (0.59, 0.89)	
Multivariate[1]	1.00	0.91 (0.75, 1.11)	1.04 (0.85, 1.26)	0.89 (0.72, 1.10)	0.87 (0.70, 1.07)	
By tumor site						
Colon cancer						
Cases/person-years	500/424 327	422/425 549	449/426 196	378/426 211	391/426 243	
Age- and sex-adjusted	1.00	0.85 (0.75, 0.97)	0.89 (0.78, 1.01)	0.73 (0.64, 0.84)	0.74 (0.64, 0.84)	<0.001
Multivariate[1]	1.00	0.91 (0.79, 1.03)	0.98 (0.86, 1.12)	0.83 (0.73, 0.96)	0.86 (0.75, 0.99)	0.03
Proximal colon cancer						
Cases/person-years	266/424 327	211/425 549	247/426 196	208/426 211	207/426 243	
Age- and sex-adjusted	1.00	0.79 (0.66, 0.95)	0.91 (0.76, 1.08)	0.74 (0.62, 0.89)	0.72 (0.60, 0.86)	<0.001
Multivariate[1]	1.00	0.84 (0.70, 1.01)	1.00 (0.84, 1.19)	0.85 (0.70, 1.02)	0.84 (0.69, 1.01)	0.10
Distal colon cancer						
Cases/person-years	217/424 327	192/425 549	190/426 196	152/426 211	163/426 243	
Age- and sex-adjusted	1.00	0.90 (0.74, 1.09)	0.88 (0.72, 1.07)	0.69 (0.56, 0.85)	0.72 (0.59, 0.88)	<0.001
Multivariate[1]	1.00	0.96 (0.79, 1.17)	0.98 (0.80, 1.19)	0.79 (0.64, 0.98)	0.85 (0.69, 1.06)	0.05
Rectal cancer						
Cases/person-years	221/424 327	197/425 549	166/426 196	150/426 211	124/426 243	
Age- and sex-adjusted	1.00	0.90 (0.75, 1.10)	0.75 (0.61, 0.92)	0.66 (0.54, 0.82)	0.54 (0.43, 0.67)	<0.001
Multivariate[1]	1.00	0.95 (0.78, 1.16)	0.82 (0.67, 1.01)	0.76 (0.61, 0.94)	0.64 (0.51, 0.81)	<0.001

[1] Adjusted for sex, physical activity (never or rarely; <3 times/mo; 1–2, 3–4, or ≥5 times/wk; or missing), smoking (never, ≤20 cigarettes/d in the past, >20 cigarettes/d in the past, ≤20 cigarettes/d currently, >20 cigarettes/d, or missing), menopausal hormone therapy use in women (never, past, current, or missing), and intakes of red meat (quintiles), dietary calcium (quintiles), dietary folate (quintiles), and total energy (continuous).

[2] Quintiles were defined within each sex. The median intakes of whole grain for quintiles 1 to 5 were, respectively, 0.2, 0.4, 0.6, 0.8, and 1.3 servings · 1000 kcal^{-1} · d^{-1} in men and 0.2, 0.4, 0.6, 0.8, and 1.3 servings · 1000 kcal^{-1} · d^{-1} in women.

associations observed in the EPIC study (15). Control for folate, however, had little effect on the inverse relation in the EPIC study, and control for other factors attenuated but did not eliminate the association (31). Similarly, in the Prostate, Lung, Colorectal and Ovarian Cancer screening trial, the inverse association between fiber intake and colorectal adenoma was attenuated after control for folate and other nutritional factors, but a statistically significant 27% reduction in risk for those in the highest quintile remained (16). In contrast, both the Pooling Project (17) and this study found that modest inverse associations in age-adjusted analyses essentially disappeared after control for nutritional covariates. The interrelations between exposure and covariates may well differ among studies, and confounding does not account for—one way or the other—the observed fiber–colorectal cancer findings.

Dietary measurement error has increasingly concerned investigators working in the field of the nutritional epidemiology of cancer. It is well accepted that the FFQ, the main instrument used in this study and in most other epidemiologic studies, measures intake with considerable error. Researchers have differed on whether this error would cause substantial distortion of observed findings (32, 33). Recent biomarker-based studies of dietary assessment instruments suggest that, at least for some nutritional factors, errors associated with the FFQ are substantial and could lead to severe attenuation of RRs in epidemiologic studies (34). Two recent studies, in which dietary fat was measured by dietary records and an FFQ, have shown direct, statistically significant associations between energy-adjusted fat measured by a food record and breast cancer but no such association for intake derived from an FFQ (35, 36).

The issue of measurement error issue has not been resolved and could bear on the inconsistent epidemiologic findings concerning the association between fiber intake and colorectal cancer. It is certainly plausible that a weak signal, in the context of a true but rather modest protective effect, could lead to a situation in which small inverse associations are observed in some studies but not in others. At the present time there is no unbiased recovery biomarker of fiber intake that can be used in calibration studies to evaluate the measurement error of the FFQ with respect to fiber intake, as has been done for energy and dietary protein (37). In studies similar to the recent investigations of dietary fat and breast cancer (35, 36), it would be helpful to analyze data from a

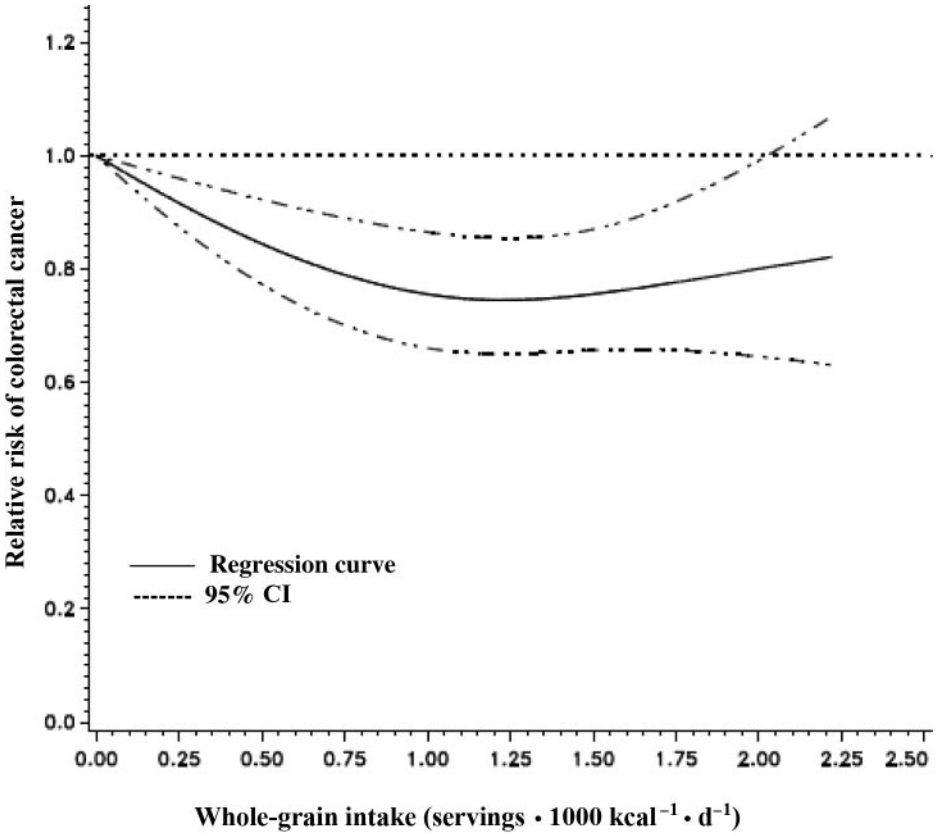

FIGURE 1. Nonparametric regression curve for the association between whole-grain intake and risk of colorectal cancer. Intakes were adjusted for sex, physical activity (never or rarely; <3/mo; 1–2, 3–4, or ≥5 times/wk; or missing), smoking (never, ≤20 cigarettes/d in the past, >20 cigarettes/d in the past, ≤20 cigarettes/d currently, >20 cigarettes/d currently, or missing), menopausal hormone therapy use in women (never, past, current, or missing), and intakes of red meat (quintiles), dietary calcium (quintiles), and total energy (continuous).

prospective study in which fiber intake data were obtained from both an FFQ and a food record or recall. Such studies may give us valuable information on whether or not fiber assessments based on FFQs are too inaccurate to provide true associations. What we have begun to see for energy-laden nutritional factors, such as dietary fat (35, 36), may or may not hold true for relatively energy-poor nutrients such as dietary fiber.

Although our dietary fiber results were essentially null, we did observe an inverse association for whole-grain intake. This inverse association was statistically significant in the cohort as a whole and among men; among women, the association was somewhat weaker and nonsignificant. Although there is some evidence that dietary assessment error is greater in women than in men, at least for some nutritional factors (34), whether this accounts for the weaker protective association for whole-grain foods among the women in the present study is unclear.

When we further adjusted for intake of fiber from grains in a multivariate model, the risk estimates for whole grains were largely unaffected. This suggests that whole-grain components other than fiber—eg, vitamins (including B vitamins), minerals, phenols, and phytoestrogens (38)–affect colorectal carcinogenesis. Some caution, however, should be exercised in inferring such a specific biologic conclusion from the results of regression analyses involving several variables measured with error, such as dietary fiber, whole grains, and energy (32, 34).

Larsson et al (39), in a prospective cohort study in Sweden, also found that whole grains were inversely related to colon cancer (multivariate RR for ≥4.5 servings/d compared with <1.5 servings/d: 0.67; 95% CI: 0.47, 0.96), although there was some attenuation of the whole-grain association with incorporation of dietary fiber in the multivariate models (multivariate RR: 0.75; 95% CI: 0.49, 1.15); these results are consistent with both fiber and nonfiber effects. The Cancer Prevention Study II Nutrition Cohort Study (7) and the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (ATBC), however, reported null associations for whole grains and colorectal cancer (8). A meta-analysis of whole grain and colorectal cancer and polyps in case-control studies reported a pooled odds ratio of 0.79 (95% CI: 0.69, 0.89) (40).

Whole grains have been shown to reduce the risk of other chronic diseases, including coronary heart disease (41, 42) and diabetes (43). Although the limited epidemiologic evidence to date for colorectal cancer is inconsistent, the hypothesis that whole grains are protective warrants further investigation.

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