Short Communication

Is the Association with Fiber from Foods in Colorectal Cancer Confounded by Folate Intake?

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Abstract

The effect of multivariate adjustment including folate on the strong protective effect of fiber in foods on colorectal cancer risk in the European Prospective Investigation into Cancer and Nutrition was investigated in 1,721 cases identified in the latest follow-up. The inclusion of an additional 656 cases confirmed our previously published results, with a strong and significant reduction in colorectal cancer risk of ~9% for each uncalibrated quintile increase in fiber ($P_{\text{linear trend}}$ < 0.001) compared with an 8% reduction in our previous report, which had not been adjusted for folate. Inclusion of the other covariates (physical activity, alcohol, smoking, and red and processed meat) confirmed this significant inverse association for colon cancer and strengthened the association with left-sided colon cancer (P < 0.001). After maximum adjustment, the association between fiber and rectal cancer was not significant, as in our previous analysis. The association with fiber from different food sources was analyzed, but again, there were no significance trends after maximum adjustment. (Cancer Epidemiol Biomarkers Prev 2005;14(6):1552–6)

Introduction

In the largest prospective study on diet and cancer thus far conducted, the European Prospective Investigation into Cancer and Nutrition (EPIC), dietary fiber from foods was inversely related to incidence of large bowel cancer (1). However, it has been argued that studies in European populations are more prone to confounding by folate intake because folic acid fortification of cereals is not mandatory (2). A further contention is that the reason for the discrepancy between the results from this large European study and those from intervention and prospective studies elsewhere was that no adjustment for folate intake was made (2). Therefore, we investigated this supposition in the EPIC study, utilizing our data from a more recent follow-up of 1,721 cases for whom data on intake of folate from foods was available. In addition, we have investigated the suggestion that it is fiber from fruit, rather than total fiber, that is protective in colorectal cancer.

Materials and Methods

Outline. The total EPIC cohort consists of subcohorts recruited in 22 centers in 10 European countries: Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, United Kingdom, allowing comparisons between areas with very different rates of cancer occurrence and distribution of lifestyle and food habits. Food-related

Received 12/6/04; revised 3/15/05; accepted 4/8/05.

Grant support: ''Europe Against Cancer'' Programme of the European Commission (SANCO); Ligue contre le Cancer (France); Société 3M (France); Mutuelle Générale de l'Education Nationale; Institut National de la Santé et de la Recherche Médicale; German Cancer Aid; German Cancer Research Center; German Federal Ministry of Education and Research; Danish Cancer Society; Health Research Fund (FIS) of the Spanish Ministry of Health; ISCIII, Red de Centros RCESP, C03/09; the participating regional governments and institutions of Spain; Cancer Research UK; Medical Research Council, United Kingdom; the Stroke Association, United Kingdom; British Heart Foundation; Department of Health, United Kingdom; Food Standards Agency, United Kingdom; the Wellcome Trust, United Kingdom; Greek Ministry of Health; Greek Ministry of Education; Italian Association for Research on Cancer; Italian National Research Council; Dutch Ministry of Public Health, Welfare and Sports; Dutch Ministry of Health; Dutch Prevention Funds; LK Research Funds; Dutch Zorg Onderzoek Nederland; World Cancer Research Fund; Swedish Cancer Society; Swedish Scientific Council; Regional Government of Skane, Sweden; Norwegian Cancer Society, Norwegian Research Council and Norwegian Foundation for Health and Rehabilitation.

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questionnaires and lifestyle and personal questionnaires, as well as anthropometric measurements, were collected from all subjects at the time of enrollment in the cohort. Methods were reported in full by Riboli et al. (3).

Study Subjects. The 519,978 eligible study subjects were mostly aged 25 to 70 years and recruited from the general population residing in a given geographic area, a town or a province. Exceptions were the French cohort (based on female members of the health insurance for state school employees), the Utrecht cohort (based on women attending breast cancer screening), the Ragusa cohort (based on blood donors and their spouses), and most of the Oxford cohort (based on vegetarian volunteers and healthy eaters). Eligible subjects were invited to participate in the study by mail or by personal contact. Those who accepted gave informed consent, and diet and lifestyle questionnaires were mailed to them to be filled in. Anthropometric measurements, including height, weight, waist, hip, and sitting height, were obtained as described elsewhere (3).

Diet and Lifestyle Questionnaires. Following the results of several methodologic studies conducted in the early 1990s, diet was measured by country-specific questionnaires designed to capture local dietary habits and to provide high compliance. Seven countries adopted an extensive self-administered dietary questionnaire, which provided data on up to 300- to 350-food items per country. In Spain and Sicily, a dietary questionnaire, very similar in content to the above but administered by direct interview, was used. A food frequency questionnaire and a 7-day record were adopted in the United Kingdom. The food frequency questionnaire was used in this analysis. The lifestyle questionnaires included questions on education, occupation, leisure and job-related physical activity, history of previous illness and disorders or surgical operations, and lifetime history of consumption of tobacco and alcoholic beverages.

End Points. The follow-up was based on population cancer registries in seven of the participating countries: Denmark, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom. A combination of methods, including health insurance records, cancer and pathology registries, and active follow-up through study subjects and their next-of-kin, was used in three countries—France, Germany, and Greece. Mortality data are also collected from either the cancer registry or mortality registries at the regional or national level. By April 2004, for all centers using cancer registry data, reports to the IARC represented complete follow-up until December 2000 (Asturias, Murcia, Bilthoven, and Cambridge), 2001 (Italy, Granada, Navarra, San Sebastian, Oxford, Norway, and Malmo), 2002 (Umea, Denmark, and France), or 2003 (Utrecht). In Turin, the follow-up was completed until December 1999. For the three countries using individually based follow-up, the end of the follow-up was considered to be the last known contact, or date of diagnosis, or death.

The 10th Revision of the International Statistical Classification of Diseases, Injuries, and Causes of Death was used. Mortality data were coded following the rules of ICD-10, and cancer incidence data following ICD-0-2. Cancer of the rectum included tumors occurring at the rectosigmoid junction (C19) and rectum (C20). Anal canal tumors were excluded. Right colon tumors included the cecum, appendix, ascending colon, hepatic flexure, transverse colon, and splenic flexure (C18.0-18.5). Left colon tumors included the descending and sigmoid colon (C18.6-18.7). All colorectal incident cases (ICD-0-2 C18, C19, and C20) with dietary data were included, but prevalent cases were excluded.

Statistical Methods. Detailed descriptions of the statistical methods used are described in the original publication (1). For this analysis, sex-specific cohort-wide quintiles of total dietary fiber and fiber from different sources were used. Data from individuals in the top and bottom 1% of the ratio of energy intake to estimated energy requirement (calculated from age, sex, and body weight) and from the top 1% of sex-specific fiber intakes were excluded from the analysis to reduce the impact of implausible extreme values. Results are reported using Cox regression, stratified by center to control for different methods of fiber analysis used in European food

Table 1. Baseline characteristics by quintile of fiber intake in EPIC participants

Quintile of dietary fiber	Men					Women					P
	Q_1	Q_2	Q_3	Q_4	Q_5	Q_1	Q_2	Q_3	Q_4	Q_5	
Dietary fiber (mean g/d)	18.2	21.0	23.2	25.6	30.1	15.9	17.8	19.4	21.3	24.3	
Colorectal cancer cases	198	167	156	136	107	238	231	197	199	197	
Age (y)	52.0	52.5	52.4	52.1	51.2	50.8	51.2	51.4	51.3	51.2	<0.001
Weight (kg)	81.1	81.3	81.2	81.3	81.4	66.9	67.4	67.4	67.6	68.1	0.01
Height (m)	1.74	1.75	1.75	1.75	1.76	1.62	1.62	1.63	1.63	1.63	<0.001
Body mass index (kg/m^2)	26.8	26.7	26.5	26.4	26.4	25.6	25.6	25.5	25.5	25.6	<0.001
Physical activity (%)											<0.001*
Inactive	33.1	28.9	26.4	22.6	17.2	31.0	28.3	26.4	25.0	23.7	
Moderately inactive	27.9	32.1	33.0	32.3	30.3	22.6	24.1	24.9	25.4	26.9	
Moderately active	18.4	19.4	19.9	21.6	23.9	23.8	25.7	26.6	28.7	32.2	
Active	17.7	16.8	17.6	19.8	24.2	7.7	7.1	7.0	7.0	7.3	
Unknown	2.9	2.7	3.2	3.7	4.4	14.9	14.8	15.1	13.9	9.9	
Smoking status (%)											<0.001*
Never	29.7	31.5	32.8	33.9	35.3	48.1	53.7	55.8	58.3	61.2	
Former	34.8	38.2	37.8	36.9	35.2	21.7	23.3	23.4	23.0	21.9	
Smoker	33.6	28.8	27.9	27.8	28.1	28.2	20.8	18.5	16.2	14.2	
Unknown	1.9	1.5	1.5	1.5	1.4	2.0	2.2	2.3	2.5	2.7	
Energy from fat (kcal/d)	694	791	862	938	1,060	561	637	690	748	833	<0.001
Energy from nonfat (kcal/d)	1,195	1,397	1,547	1,712	1,975	930	1,109	1,233	1,359	1,565	<0.001
Red and processed meat (g/d)	123.3	111.8	104.4	95.9	79.7	83.4	76.1	70.6	64.6	53.6	<0.001
Folate (μg/d)	243.8	282.2	308.9	336.5	389.6	209.6	247.1	271.2	297.3	350.8	<0.001
Alcohol (g/d)	33.5	25.6	20.3	15.3	7.8	11.8	9.3	7.8	6.2	3.8	<0.001

NOTE: Values are means adjusted for center (all variables) and age at enrollment (all variables except age). Quintiles of fiber are based on the food frequency questionnaires, and means were estimated from 24-hour recall data. Means of other dietary variables are based on food frequency questionnaires and adjusted for energy intake.

*P values for trend and association were the same for men and women. All values are significant due to large size of the cohort.

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Table 2. Multivariate hazard ratios and 95% confidence intervals of colorectal cancer by quintile of dietary fiber using different variables for adjustment

Fiber (g/d)	Study-wide quintiles* 1 Range	1 Mean	2 Range	2 Mean	3 Range	3 Mean	4 Range	4 Mean	5 Range	5 Mean	P_{trend}	HR (95% CI) for one quintile of increase
Men	<16.0	18.2	16-20	21.0	20.1-24	23.2	24.1-29.4	25.6	>29.4	30.1		
Women	<15.5	15.9	15.5-19	17.8	19.1-22.4	19.4	22.5-26.7	21.3	>26.7	24.3		
Colorectum												
Base (n =1,065)†		1	0.94 (0.78-1.13)		0.77 (0.63-0.95)		0.76 (0.61-0.95)		0.75 (0.59-0.96)		0.005	0.92 (0.87-0.97)
Base (n = 1,721)‡		1	0.90 (0.78-1.04)		0.77 (0.66-0.90)		0.73 (0.62-0.86)		0.70 (0.58-0.85)		<0.001	0.91 (0.87-0.95)
Base + folate (n = 1,721)§		1	0.89 (0.77-1.03)		0.76 (0.64-0.89)		0.71 (0.60-0.85)		0.68 (0.55-0.84)		<0.01	0.90 (0.86-0.95)
Maximally adjusted (n = 1,721)∥		1	0.93 (0.80-1.08)		0.82 (0.69-0.97)		0.79 (0.66-0.96)		0.79 (0.63-0.99)		0.01	0.93 (0.89-0.99)
Colon												
Base (n = 706)†		1	0.95 (0.75-1.19)		0.75 (0.58-0.96)		0.71 (0.55-0.94)		0.72 (0.54-0.97)		0.006	0.91 (0.85-0.97)
Base (n = 1,118)‡		1	0.88 (0.74-1.05)		0.71 (0.58-0.86)		0.68 (0.55-0.84)		0.74 (0.58-0.93)		<0.001	0.91 (0.86-0.96)
Base + folate (n = 1,118)§		1	0.87 (0.73-1.04)		0.70 (0.57-0.85)		0.66 (0.53-0.83)		0.71 (0.55-0.92)		<0.001	0.90 (0.85-0.96)
Maximally adjusted (n = 1,118)∥		1	0.89 (0.74-1.07)		0.72 (0.59-0.89)		0.70 (0.55-0.88)		0.77 (0.58-1.02)		0.01	0.92 (0.86-0.98)
Colon left												
Base (n = 286)†		1	0.66 (0.46-0.93)		0.55 (0.37-0.80)		0.51 (0.34-0.77)		0.65 (0.43-0.99)		0.006	0.89 (0.80-0.99)
Base (n = 496)‡		1	0.68 (0.53-0.89)		0.60 (0.45-0.80)		0.49 (0.36-0.67)		0.65 (0.46-0.91)		0.001	0.87 (0.80-0.95)
Base + folate (n = 496)§		1	0.67 (0.51-0.88)		0.58 (0.43-0.77)		0.47 (0.33-0.65)		0.60 (0.42-0.86)		<0.001	0.86 (0.78-0.93)
Maximally adjusted (n = 496)∥		1	0.66 (0.50-0.86)		0.56 (0.42-0.76)		0.45 (0.32-0.64)		0.58 (0.39-0.86)		<0.001	0.85 (0.77-0.93)
Colon right												
Base (n = 287)†		1	1.21 (0.84-1.71)		0.93 (0.63-1.37)		0.89 (0.59-1.35)		0.73 (0.46-1.19)		0.09	0.91 (0.82-1.05)
Base (n = 476)‡		1	1.19 (0.90-1.58)		0.94 (0.68-1.28)		0.95 (0.68-1.34)		0.88 (0.59-1.29)		0.09	0.95 (0.87-1.04)
Base + folate (n = 452)§		1	1.18 (0.88-1.57)		0.92 (0.66-1.27)		0.93 (0.65-1.32)		0.85 (0.54-1.28)		0.21	0.94 (0.85-1.03)
Maximally adjusted (n = 452)∥		1	1.22 (0.91-1.64)		0.97 (0.69-1.35)		1.00 (0.69-1.45)		0.93 (0.59-1.47)		0.47	0.96 (0.87-1.07)
Rectum												
Base (n = 359)†		1	0.92 (0.66-1.27)		0.83 (0.59-1.18)		0.85 (0.59-1.24)		0.80 (0.53-1.22)		0.22	0.95 (0.85-1.05)
Base (n = 603)‡		1	0.94 (0.73-1.19)		0.88 (0.68-1.15)		0.84 (0.63-1.10)		0.62 (0.44-0.87)		0.01	0.91 (0.84-0.98)
Base + folate (n = 603)§		1	0.92 (0.72-1.18)		0.87 (0.67-1.14)		0.81 (0.60-1.10)		0.60 (0.41-0.87)		0.01	0.90 (0.83-0.98)
Maximally adjusted (n = 603)∥		1	1.02 (0.79-1.31)		1.01 (0.77-1.34)		1.01 (0.74-1.38)		0.81 (0.55-1.21)		0.50	0.97 (0.89-1.06)

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval.
*The ranges are based on the food frequency questionnaires, and the means are estimated from 24-hour recall data from participants in the calibration study.
†From published results (1).
‡Base: Cox regression using age, sex, energy from nonfat sources (continuous variable), energy from fat sources (continuous variable), height, and weight (tertiles defined for each sex and center), and stratified for center (same adjustment as in ref. 1).
§Base + folate: Same covariates as base and folate.
∥Maximally adjusted: Same covariates as base + folate and physical activity (five categories), alcohol consumption (g/d), smoking status (never, former, current smoker, missing), educational level, and intake of red and processed meat.

tables and other center effects, such as follow-up procedures and questionnaire design. Age was used as the primary time variable in all Cox regression models. Age at colorectal cancer incidence or at censoring date was used as time variable of end of the study. The analysis focused on dietary fiber, with some other dietary and lifestyle variables included as covariates. Analyses were run using variables both as categorical and as continuous scored from 1 to 5 according to the interquintile interval in which an observation lay. Trend tests were computed using these quintile-based scores. Categorical relative risks were calculated from the hazard ratio. Estimated energy intake was divided into energy from fat and energy from nonfat sources as described elsewhere (1). Models were run first using the same model as previously published with age, sex, energy from nonfat sources and fat energy (continuous variable), height, and weight (tertiles defined for each sex and center; base model). Analyses were then run including folate from food as a continuous variable in the model (base model plus folate). Third, risks were adjusted in addition for physical activity (five categories of leisure and occupational activities), smoking status (four categories), alcohol consumption (grams per day), and red and processed meat (grams per day; maximally adjusted model).

Results

There were 2,279,075 person-years in 6.2 average years of follow-up (3-8.4 years) since 1992, and 1,826 colorectal cancer cases; 1,178 tumors were located in the colon and 648 were rectal tumors; 523 colon cancers were located on the right side, and 476 on the left side of the colon. The analyses presented here are based on 1,721 cases because folate intake in participants from Greece and Heidelberg was not available in the central data set.

Baseline characteristics by quintile of fiber intake are shown in Table 1. Age was positively associated with fiber intake in women and inversely in men. Body mass index was inversely related with fiber intake in men only. Physical activity was positively related with fiber intake, whereas smoking, alcohol, and red meat intakes were inversely related to fiber intake. Trends for folate by quintile of dietary fiber were significant because of a significant correlation between the two (Spearman partial correlation coefficient adjusted for age, energy intake, and center, r = 0.35 men, r = 0.28 women). Partial correlation coefficients between fiber from vegetables and folate intake were also positive (0.55 men, 0.61 women), as were fiber from fruits (0.25 men, 0.27 women) and from legumes (0.21 men, 0.34 women). The partial correlation

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coefficients between cereal fiber and folate were heterogeneous (0.09 men; −0.21 women overall EPIC; negative or close to zero in France, Italy, and Spain; and of similar value to the correlation with fiber from fruits and legumes in the remaining countries).

Table 2 shows hazard ratios for 1,721 cases adjusted as in the previously published report. The inclusion of an additional 656 cases confirmed our previously published results, with a strong and significant reduction in colorectal cancer risk of ~9% for each quintile increase of fiber ($P_{\text{linear trend}} < 0.001$) compared with an 8% reduction in our previous report (1). As before, the reduction in risk was apparent at the third quintile of fiber intake of approximately >20 g of fiber per day compared with <16 g/d. Adjustment for folate, in addition (base model plus folate), did not materially alter the results for colon cancer but the inverse association with left-sided colon cancer was slightly strengthened. Results for right-sided colon cancer were not significant, as before. Adjustment for folate did not materially affect results for rectal cancer. Results were not changed when use of educational levels (five categories) or multivitamins (yes/no) was also included; for example, the hazard ratio for colon cancer for the highest versus lowest quintile of fiber was 0.74 (confidence interval, 0.56-0.98). Results were consistent across countries ($P_{\text{heterogeneity}} = 0.72$; Fig. 1).

In the maximally adjusted model, inclusion of the other covariates (physical activity, alcohol, smoking, and red and processed meat) with folate strengthened the results for left-sided colon cancer ($P < 0.001$). After maximum adjustment, the association between fiber and rectal cancer was not significant, as in our previous analysis.

Table 3 shows hazard ratios for colorectal cancer by different types of fiber. With more cases, the hazard ratios remained essentially the same for all types of fiber as before (1), although the trends became significant for fiber from cereals ($P = 0.01$) and from fruit ($P = 0.04$). Adjustment for folate (base model plus folate) did not materially affect categorical results, although the trend for fiber from fruit became nonsignificant. In the maximally adjusted model, the hazard ratios and the trend for fiber from cereals also became nonsignificant. In the maximally adjusted model, hazard ratios for fruit fiber were statistically significant for the 2nd, 3rd, and 5th quintile of intake compared with the 1st quintile, but the trend for fiber from fruits was not significant.

Discussion

Our original publication was the largest prospective study published to date on fiber in food in colorectal cancer prevention (1). The size of the study allowed analysis by subsite and, furthermore, the detailed dietary analysis of heterogeneous populations allowed some correction for measurement error in dietary intake, a problem that has increasingly caused concern in nutritional epidemiology in relation to cancer (4, 5). These results have, however, been questioned because no adjustment was made for dietary folate (2). The present report in which an even larger number of cases was included confirms our original results of a strong protective association between fiber intake in food and risk of colon cancer. Furthermore, hazard ratios were somewhat strengthened for left-sided colon cancer. Contrary to the suggestion that results for colorectal cancer would be confounded by folate intake in this European population, adjustment for folate did not modify our findings.

A recent editorial (6) on the finding of a null association of fruits and vegetables with cancer risk in two cohort studies raises the problem of multivariate modeling in the presence of measurement error and weak associations. Although prospective epidemiologic evidence to date does not provide strong support for a protective association between fruit and vegetable intake and cancer, ''... it is important to be alert to the possibility that findings emerging from new, large cohort studies could shift the preponderance of the evidence, as may be occurring with the dietary fiber-colorectal cancer association'' (6). In our report, we showed that the protective association of fiber with colon cancer is observed in both less and more adjusted models. As stated in the editorial, efforts should be made to study diet and cancer in populations with a wide range of dietary intake, because it is the ratio of interindividual variation to intraindividual measurement error that determines the magnitude of relative risk distortion. Such was the approach behind the EPIC study (7).

Although calibration was previously shown to considerably strengthen associations with fiber and colorectal cancer, in this report, which specifically addresses the issue of confounding factors, results were essentially the same as previously published; therefore, we have not calibrated our results. We have presented more detailed results of our previous findings on the effect of other suggested confounders, which were reported before. In our previous report, there was no effect of

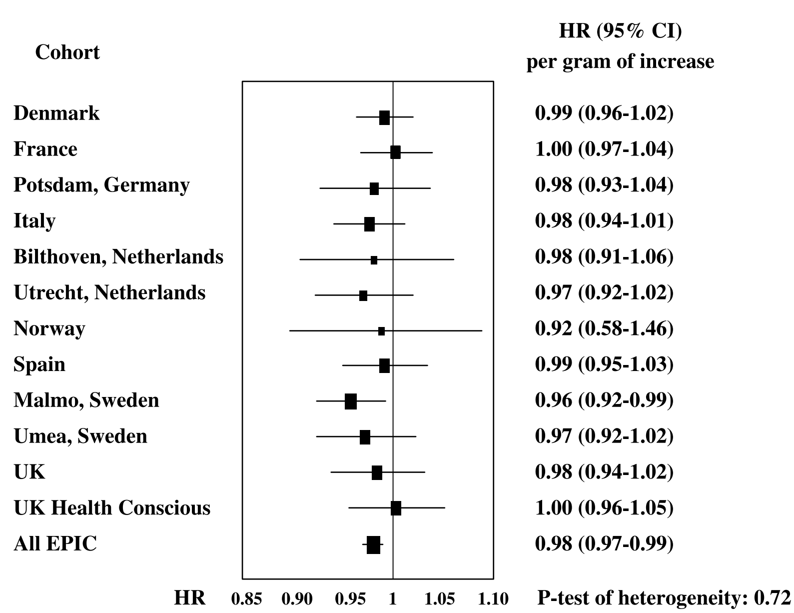

Figure 1. Multivariate hazard ratio (*HR*) and 95% confidence intervals (*95% CI*) of colorectal cancer for dietary fiber in EPIC cohorts. Cox regression using age, sex, energy from nonfat sources (continuous variable), energy from fat sources (continuous variable), height and weight (tertiles defined for each sex and center), folate, physical activity (five categories), alcohol consumption (g/d), smoking status (never, former, current smoker, missing), and intake of red meat and processed meat.

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Table 3. Multivariate hazard ratios of colorectal cancer and 95% confidence intervals for quintiles of fiber intake by source of fiber

Source of fiber	Study-wide quintiles*										*P* trend
	1		2		3		4		5		
	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	
Fiber from fruits (g/d)											
Men	<1.4	2.7	1.4-2.3	3.1	2.4-3.5	3.8	3.5-5.2	4.3	>5.2	5.3	
Women	<2.1	2.8	2.1-3.2	3.4	3.3-4.5	3.9	4.6-6.6	4.4	>6.6	5.4	
Base (*n* = 1,065)†	1		0.69 (0.57-0.85)		0.76 (0.63-0.92)		0.82 (0.66-0.99)		0.78 (0.64-0.97)		0.17
Base (*n* = 1,721)‡	1		0.73 (0.62-0.85)		0.74 (0.63-0.87)		0.84 (0.71-0.98)		0.74 (0.62-0.87)		0.04
Base + folate (*n* = 1,721)§	1		0.73 (0.62-0.86)		0.74 (0.63-0.87)		0.84 (0.72-0.99)		0.75 (0.63-0.89)		0.07
Maximally adjusted (*n* = 1,721)‖	1		0.75 (0.64-0.89)		0.78 (0.67-0.92)		0.90 (0.76-1.06)		0.81 (0.68-0.97)		0.42
Fiber from cereals (g/d)											
Men	<4.6	6.6	4.6-7.4	8.1	7.5-10.1	9.5	10.2-13.5	10.5	>13.5	13.1	
Women	<3.9	4.9	3.9-5.8	5.9	5.9-7.7	6.8	7.8-10.6	7.5	>10.6	9.2	
Base (*n* = 1,065)†	1		0.89 (0.74-1.08)		0.85 (0.69-1.03)		0.88 (0.71-1.08)		0.78 (0.62-0.98)		0.06
Base (*n* = 1,721)‡	1		1.01 (0.87-1.18)		0.88 (0.74-1.04)		0.90 (0.75-1.07)		0.81 (0.66-0.99)		0.02
Base + folate (*n* = 1,721)§	1		0.99 (0.84-1.16)		0.88 (0.74-1.05)		0.90 (0.75-1.07)		0.82 (0.67-1.00)		0.03
Maximally adjusted (*n* = 1,721)‖	1		1.02 (0.87-1.20)		0.94 (0.79-1.11)		0.98 (0.82-1.17)		0.93 (0.76-1.15)		0.44
Fiber from vegetables (g/d)											
Men	<1.4	2.7	1.4-2.3	3.1	2.4-3.4	3.8	3.5-5.2	4.3	>5.2	5.3	
Women	<2.1	2.8	2.1-3.2	3.4	3.3-4.6	3.9	4.6-6.6	4.4	>6.6	5.4	
Base (*n* = 1,065)†	1		0.94 (0.77-1.15)		0.95 (0.77-1.16)		1.00 (0.81-1.24)		0.88 (0.70-1.11)		0.52
Base (*n* = 1,721)‡	1		0.98 (0.83-1.16)		0.96 (0.80-1.13)		0.94 (0.79-1.12)		0.92 (0.76-1.10)		0.60
Base + folate (*n* = 1,721)§	1		0.99 (0.84-1.17)		0.97 (0.82-1.15)		0.96 (0.80-1.16)		0.96 (0.77-1.18)		0.63
Maximally adjusted (*n* = 1,721)‖	1		0.99 (0.84-1.17)		0.97 (0.82-1.16)		0.96 (0.80-1.16)		0.94 (0.76-1.16)		0.52
Fiber from legumes (g/d)											
Men	0	NC	0-0.1	NC	0.1-0.4	0.5	0.5-1.3	0.9	>1.3	1.9	
Women	0	NC	0-0.1	NC	0.1-0.5	0.4	0.6-1.3	0.7	>1.3	1.0	
Base (*n* = 1,065)†	1		1.02 (0.83-1.26)		1.10 (0.91-1.34)		1.18 (0.97-1.43)		1.04 (0.84-1.30)		0.31
Base (*n* = 1,721)‡	1		0.98 (0.83-1.16)		0.96 (0.82-1.12)		1.04 (0.89-1.23)		0.94 (0.79-1.12)		0.77
Base + folate (*n* = 1,721)§	1		0.98 (0.83-1.16)		0.96 (0.82-1.13)		1.05 (0.89-1.24)		0.95 (0.80-1.14)		0.90
Maximally adjusted (*n* = 1,719)‖	1		1.00 (0.84-1.18)		0.97 (0.83-1.14)		1.08 (0.91-1.27)		0.98 (0.82-1.17)		0.86

Abbreviation: NC, not computed.

*The ranges are based on the food frequency questionnaires, and the means are estimated from 24-hour recall data from participants in the calibration study. Mean fiber from legumes from 24-hour recall was not computed for the 1st and 2nd quintile because of many zero or extreme values.

†From published results (1).

‡Base: Cox regression using age, sex, energy from nonfat sources (continuous variable), energy from fat sources (continuous variable), height and weight (tertiles defined for each sex and center), and stratified for center (same adjustment as in ref. 1).

§Base + folate: Same covariates as base and folate.

‖Maximally adjusted: Same covariates as base + folate and physical activity (five categories), alcohol consumption (g/d), smoking status (never, former, current smoker, missing), educational level, and intake of meat and processed meat.

adjustment for physical activity, alcohol, smoking status, and red and processed meat in colon cancer (1), whereas in the current analysis this adjustment has minor effects. Further investigation of the use of multivitamin tablets in this European population did not modify our conclusions either. Our former results for rectal cancer were weaker than for colon cancer results and in this report, when fully adjusted, were substantially weakened.

In our first report, we were unable to attribute the effects of fiber to any particular food source. It has been suggested that fiber from fruit is more strongly associated with protection from colorectal cancer than fiber from all sources (2). However, in this EPIC population, trends with fiber intake from fruits were not significant. The effect of fiber from cereals was statistically significant but the significance was lost in the maximally adjusted model. Any mechanism whereby fruit fiber should protect against colorectal cancer is not established but is unlikely to be folate because adjustment for folate had little effect on our results.

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Sheila A. Bingham, Teresa Norat, Aurelie Moskal, et al.

Cancer Epidemiol Biomarkers Prev 2005;14:1552-1556.

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