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Dietary Intake of Fiber and Decreased Risk of Cancers of the Colon and Rectum: Evidence From the Combined Analysis of 13 Case-Control Studies

Geoffrey R. Howe, Enrique Benito, Roberto Castelleto, Jacqueline Cornée, Jacques Estève, Richard P. Gallagher, José M. Iscovich, Jiao Deng-ao, Rudolf Kaaks, Gabriel A. Kune, Susan Kune, Kristan A. L'Abbé, Hin P. Lee, Marion Lee, Anthony B. Miller, Ruth K. Peters, John D. Potter, Elio Riboli, Martha L. Slattery, Dimitrios Trichopoulos, Albert Tuyns, Anastasia Tzonou, Alice S. Whittemore, Anna H. Wu-Williams, Zheng Shu*

Background: **Colorectal cancer is a major public health problem in both North America and western Europe, and incidence and mortality rates are rapidly increasing in many previously low-risk countries. It has been hypothesized that increased intakes of fiber, vitamin C, and beta carotene could decrease the risk of colorectal cancer.** ***Purpose:*** **The objective of this study was to examine the effects of fiber, vitamin C, and beta-carotene intakes on colorectal cancer risk in a combined analysis of data from 13 case-control studies previously conducted in populations with differing colorectal cancer rates and dietary practices. The study was designed to estimate risks in the pooled data, to test the consistency of the associations across the studies, and to examine interactions of the effects of the nutrients with cancer site, sex, and age.** ***Methods:*** **Original data records for 5287 case subjects with colorectal cancer and 10470 control subjects without disease were combined. Logistic regression analysis was used to estimate relative risks and confidence intervals for intakes of fiber, vitamin C, and**

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**Correspondence to*: Geoffrey R. Howe, Ph.D., NCIC Epidemiology Unit, University of Toronto, McMurrich Bldg., 3rd Fl., 12 Queen's Park Crescent West, Toronto, ON, M5S 1A8, Canada.

K. A. L'Abbé is a recipient of a National Health Research Scholar Award (Health and Welfare, Canada). A. B. Miller is a recipient of a National Health Career Scientist Award (Health and Welfare, Canada).

G. R. Howe (Epidemiology Unit, National Cancer Institute of Canada, Faculty of Medicine), K. A. L'Abbé, A. B. Miller (Department of

beta carotene, with the effects of study, sex, and age group being adjusted by stratification. *Results:* Risk decreased as fiber intake increased; relative risks were 0.79, 0.69, 0.63, and 0.53 for the four highest quintiles of intake compared with the lowest quintile (trend, $P<.0001$). The inverse association with fiber is seen in 12 of the 13 studies and is similar in magnitude for left- and right-sided colon and rectal cancers, for men and for women, and for different age groups. In contrast, after adjustment for fiber intake, only weak inverse associations are seen for the intakes of vitamin C and beta carotene. *Conclusion:* This analysis provides substantive evidence that intake of fiber-rich foods is inversely related to risk of cancers of both the colon and rectum. *Implications:* If causality is assumed, we estimate that risk of colorectal cancer in the U.S. population could be reduced about 31% (50 000 cases annually) by an average increase in fiber intake from food sources of about 13 g/d, corresponding to an average increase of about 70%. [J Natl Cancer Inst 84:1887–1896, 1992]

Cancers of the colon and rectum are among the most common malignancies in North American and other western populations. It is estimated that 157 500 cases of these cancers and 60 500 deaths attributable to them occurred in the United States in 1991 (*1*). High rates also occur in western European and in other similar populations (e.g., Australian), and even in countries where rates are lower, colorectal cancer is still a major public health burden (*2*). Incidence and mortality rates are also rapidly increasing in many previously low-risk countries (*3*).

Several hypotheses relating dietary factors to risk of colorectal cancer have been advanced. It has been postulated that increased risk may be associated with increased intake of energy-providing nutrients, particularly fat (*3*). It has also been hypothesized that several dietary components coming primarily from fruits, vegetables, cereals, and legumes in the diet may decrease the risk of colorectal cancer (*3*). Of particular interest in this context are the postulated protective effects of fiber, beta carotene, and vitamin C (*3*).

The hypothesis that fiber decreases risk arose primarily from observations made by Burkitt in Africa (*4*). A comprehensive review of the evidence relating fiber intake to the risk of colorectal cancer has recently been published (*5*). The hypothesis is supported generally by experimental animal studies, though such studies are not totally consistent, which may be reflective of differing physiological properties of different types of fiber (*3*). The international variation in colon cancer rates has an inverse correlation with estimated per capita intake of fiber, but when such correlations are adjusted for fat intake, the only statistically significant correlation is with fiber from cereal sources and pulses (*6*).

To date, results have been reported from only one cohort study in which fiber intake was specifically estimated (*7*). There was a weak inverse association between fiber intake and risk of colon cancer in this study, the effect coming primarily from fiber derived from fruit. This association was not statistically significant, perhaps because of the limited number of case subjects (N = 150) in this cohort. Most case-

Preventive Medicine and Biostatistics), University of Toronto, Ontario, Canada.

E. Benito, Unitat d'Epidemiologia i Registre de Cancer de Mallorca, Palma de Mallorca, Spain.

R. Castelleto, Department of Pathology, La Plata National University, La Plata, Argentina.

J. Cornée, Institut National de la Santé et de la Recherche Médicale (INSERM), Lyon, France.

J. Estève, R. Kaaks, E. Riboli, A. Tuyns, International Agency for Research on Cancer, Lyon, France.

R. P. Gallagher, Cancer Control Agency of British Columbia, Vancouver, British Columbia, Canada.

J. M. Iscovich, Department of Epidemiology Studies, Ministry of Health, La Plata, Argentina, and Israel Center for Registration of Cancer and Allied Diseases, Ministry of Health, Jerusalem, Israel.

D. Jiao, S. Zheng, Chejiang Medical University, Hangzhou, People's Republic of China.

G. A. Kune, S. Kune, Department of Surgery, University of Melbourne, Victoria, Australia.

H. P. Lee, Department of Community, Occupational and Family Medicine, National University of Singapore.

M. Lee, Department of Epidemiology and Biostatistics, University of California, San Francisco.

R. K. Peters, A. H. Wu-Williams, Department of Preventive Medicine, School of Medicine, University of Southern California, Los Angeles.

J. D. Potter, Division of Epidemiology, School of Public Health, University of Minnesota, Minneapolis.

M. L. Slattery, Department of Family and Preventive Medicine, University of Utah, Salt Lake City.

D. Trichopoulos, Department of Epidemiology, Harvard School of Public Health, Boston, Mass.

A. Tzonou, Department of Hygiene and Epidemiology, University of Athens, Greece.

A. S. Whittemore, Department of Health Research and Policy, Division of Epidemiology, Stanford University, Stanford, Calif.

Space limitations preclude the inclusion as authors of the following individuals who contributed substantially to this analysis and to the original studies: Drs. A. Bernedo, A. Calzona, N. Chopita, and A. Jmelnitzsky, Unit of Gastroenterology, San Martin Hospital, La Plata, Argentina; Drs. F. X. Bosch and J. Kaldor and N. Munoz, International Agency for Research on Cancer, Lyon, France; Drs. K. Chen, C. Ling, J. Y. Xu, X. Wang, and L. Zhou, Chejiang Medical University, Hangzhou, People's Republic of China; S. W. Duffy, Biostatistics Unit, Medical Research Council, Cambridge, England; L. Gourley, Gleneagles Hospital, Singapore; Drs. B. E. Henderson, T. M. Mack, and M. C. Pike, Department of Preventive Medicine, University of Southern California, Los Angeles; Dr. M. Jain, Epidemiology Unit, National Cancer Institute of Canada, Faculty of Medicine, University of Toronto, Ontario, Canada; Drs. D. Jung and R. S. Paffenbarger, Department of Health Research and Policy, Division of Epidemiology, Stanford University, Stanford, Calif.; Dr. O. Manousos, Department of Hygiene and Epidemiology, University of Athens, Greece; Dr. A. J. McMichael, Department of Community Medicine, Royal Adelaide Hospital, Adelaide, Australia; M. Mulet, Unitat d'Epidemiologia i Registre de Cancer de Mallorca, Palma de Mallorca, Spain; A. Obrador, Gastroenterology Unit, Hospital Son Dureta, Palma de Mallorca, Spain; A. Sorenson and Dr. D. West, Department of Family and Preventive Medicine, University of Utah, Salt Lake City; A. Stigglebout, The Netherlands Cancer Institute, Amsterdam; Dr. C. Z. Teh, Cancer Control Agency of British Columbia, Vancouver, Canada; L. F. Watson, Department of Surgery, University of Melbourne, Victoria, Australia.

control studies have found inverse associations with the consumption of fruits and vegetables, though attribution of this effect to any specific dietary component has not been established (*8,9*).

Identification of a specific dietary factor which affords protection against the risk of colorectal cancer would be important for two reasons. First, it directly impinges upon any recommended use of dietary supplements, as opposed to the increased consumption of foods rich in certain nutrients. Second, dietary modification that involves the increased consumption of foods such as fruits and vegetables may be easier to achieve than, for example, reducing total energy intake or reducing the proportion of total energy intake that comes from fat.

This article presents the results from the combined analysis of 13 case-control studies of diet and colorectal cancer with respect to the intakes of fiber, beta carotene, and vitamin C. These studies have been conducted previously in various populations with differing colorectal cancer rates and dietary practices. The individual data records for 5287 case subjects and 10 470 control subjects have been pooled for a common analysis. This approach thus differs from the usual meta-analysis in which estimates of risk are pooled from published summary results. Using the individual data records has the advantage of eliminating artifactual differences due to different procedures for coding and analyzing data that may have been used in the respective original study analyses.

The objectives of the present study were (*a*) to examine dietary hypotheses in the complete data set to identify the risk model that best described the pooled data and (*b*) to test the consistency of any observed associations across the various studies. The amalgamation of data for the large number of case subjects and control subjects also enables examination of interaction effects. It has been postulated that dietary effects on colorectal cancer may operate differentially for men and women, by site of cancer and by age, and that there may be interactions among various nutrients (*10*).

Methods

Studies and Data

The studies included in the present analysis are summarized in Table 1. Details of case subjects and control subject selection and of the diet histories employed in the individual studies have been reported in the references given in Table 1 (*9,11-36*). All investigators of case-control studies of diet and colon or colorectal cancer of which we were aware were invited to participate in the analysis on the basis of two criteria: The study must have been completed by 1989, and it must have contained individual estimates of the consumption of the majority of the dietary factors of interest based on reasonably complete diet histories. Subsequently, we became aware of another case-control study in Sweden (*37*), but it was too late to include this study in the combined analysis. Apart from the Swedish study, another case-control study in New York State (*38*), and an earlier study in Utah (*39*), the studies included in this analysis represent, to the best of our knowledge, a complete set of such analyses.

Data on the nutrient intakes for each study subject were calculated within each particular study with nutrient values relevant to the population being studied. Nutrient intakes from supplemental sources, such as from the use of vitamin supplements, were not included in the present analysis, since such data were available only for a small number of studies. Therefore, the nutrient data in this article refer only to nutrients derived from food sources. Individual data records for each study subject were provided to the Epidemiology Unit of the National Cancer Institute of Canada and were converted to a common format with a standardized coding procedure.

Two approximations had to be used in order to make the data for all studies directly comparable. First, several of the studies had data available only on crude fiber intake, whereas others had data only on dietary fiber. In the Utah study (*35,36*), although estimates of dietary fiber were available, the crude fiber measure was used in the present analysis, since the method for estimating dietary fiber in the Utah study was different than other more commonly used methods. Dietary and crude fiber intakes are very highly correlated on an individual basis. For example, the correlation coefficient between crude and dietary fiber based on the control subjects in the Canadian study is .94. Therefore, in order to make the measure of fiber intake more directly comparable across studies, we multiplied the crude fiber estimates by a factor of 3.8, the mean ratio of dietary and crude fiber in the control data from the Canadian study. This approximation is unlikely to introduce any substantial differences in inferences concerning dietary fiber.

The second approximation was to multiply the estimated total energy intake from the Singapore study by a factor of 1.25. In this study, it was decided a priori not to study simple carbohydrates; therefore, foods relating

Table 1. Case-control studies included in analysis

Study	Location	Years data collected	Type of control*	No. of subjects			Ref. No.
				Case patients	Control subjects	Total	
Argentina	La Plata	1985-1987	P	110	220	330	(*11,12*)
Australia I	Adelaide	1979-1981	P	220	438	658	(*13,14*)
Australia II	Melbourne	1980-1981	P	715	727	1442	(*9,15-20*)
Belgium	Liège and Oost-Vlaanderen	1978-1983	P	818	2848	3666	(*21*)
Canada	Calgary and Toronto	1976-1978	H and P	542	1077	1619	(*22*)
China	Hangzhou and Ningbo	1981-1986	P	432	1296	1728	(*23*)
France	Marseille	1979-1984	H	399	399	798	(*24,25*)
Greece	Athens	1979-1980	H	100	100	200	(*26,27*)
North American Chinese	Los Angeles, San Francisco, and Vancouver	1981-1986	P	473	1192	1665	(*23*)
Singapore	Singapore	1985-1987	H	203	426	629	(*28*)
Spain	Majorca	1984-1988	H and P	286	498	784	(*29,30*)
United States I	Los Angeles	1984-1988	P	746	746	1492	(*31-34*)
United States II†	Utah	1979-1983	P	243	503	746	(*35,36*)
All combined				5287	10 470	15 757	

*P = population; H = hospital.

†The present analysis includes some additional study subjects who were not available for the original analysis of these data (*31,32*).

primarily to simple carbohydrate intake were not included in the dietary questionnaire. As a result, the estimates of energy intake in the Singapore data represent, on average, about 80% of the total energy intake (*28*). However, analyses excluding the Singapore data gave essentially the same results as those reported here, so this approximation appears unlikely to have introduced any substantial error.

Statistical Analysis

Data were stratified into the 130 possible combinations of study (13 categories), sex (two categories), and age group (five categories: 0-44, 45-54, 55-64, 65-74, and ≥75 years). The stratification on 10-year age groups was necessitated by the fact that this level of categorization was the finest that was available for one large study. However, finer stratification on age for the other studies gave essentially identical results to those reported here. Unconditional logistic regression techniques (*40*) were used to estimate relative risks, confidence intervals, and *P* values. Indicator terms for each of the strata were included in the regression models where appropriate to account for the effects of study, sex, and age group. Because of the large number of subjects in each stratum, this approach yields essentially unbiased estimates (*40*), as was confirmed by comparison with analyses based on conditional logistic regression.

Two types of models were used to examine the effects of the dietary factors. In the first, variables were divided into quintiles based on their distribution among all study subjects. Appendix 1 shows the 10 percentile points corresponding to the medians and bounds for the quintiles. For example, the bounds for the third quintile are given by the 40th and 60th percentiles, and the median for this quintile is the 50th percentile point. In the second approach, each dietary factor was represented by a continuous variable. Relative risks were expressed in scaled units corresponding to the difference in the mean of the highest and lowest quintile of intake on the basis of the control data from the three North American studies of Whites (i.e., Canada, United States I, and United States II). This approach thus provides relative risk estimates corresponding approximately to risks between the highest and lowest quintile of subjects on a typical diet consumed by North American Whites.

It should be noted that this approach can lead to units that are considerably greater than the usual variations seen in some studies. However, the use of this approach does make relative risk estimates directly comparable across studies, even if the estimate within a particular study is based on a much narrower distribution of intake than would be indicated by the unit. It should also be noted that dietary histories generally overestimate intake by about 25% (*41*), so the true differences between quintiles in North American populations is likely to be about 80% of that which would be indicated by the units used. In practice, both approaches to modeling led to very similar inferences.

Values more than three times the standard deviation away from the mean on the log scale, computed separately by study and by dietary factor (fiber, beta carotene, vitamin C, and total energy), were excluded from those analyses that included the particular variable in order to remove possible outliers. This requirement eliminated only a very small number of records. Models (except where indicated) included total energy intake as a continuous variable (*42*). Models in which the energy intake effect was represented by its components (fat, protein, and carbohydrate) gave essentially identical results to those presented, as did models in which total energy was replaced by total fat or saturated fat. The detailed analysis of the associations observed in the dataset with those nutrients contributing to total energy intake will be reported at a later date. All *P* values quoted are two-sided.

Results

Inverse associations with risk of colorectal cancer were observed for the intakes of fiber, vitamin C, and beta carotene. However, these latter associations were substantially modified by the effect of total energy intake, and for the vitamin C and beta-carotene associations, by the effect of fiber. Table 2 shows the relative risk estimates for fiber, vitamin C, and beta carotene obtained from models adjusted only for age, sex, and study with data from the 10 studies that had values for all three variables. The effect of adjusting these estimates for total energy intake and for the two remaining dietary factors is also shown in Table 2. The inverse associations seen for fiber, vitamin C, and beta carotene are substantially strengthened by adjustment for total energy intake. However, whereas the estimate for fiber intake is essentially unaffected by adjustment for vitamin C and/or beta carotene, the effects of vitamin C and beta carotene are considerably diminished by adjustment for fiber intake.

Table 3 shows the estimated relative risks and 95% confidence intervals for the four highest quintiles of intake of fiber, vitamin C, and beta carotene compared with the

Table 2. Effect of adjustment on relative risk estimates for fiber, vitamin C, and beta carotene: restricted to studies with data for fiber, vitamin C, and beta carotene*

Dietary factor	Adjusted for†	Relative risk	95% confidence interval
Fiber, 27 g/d		0.78	0.68-0.88
	Total energy	0.50	0.42-0.58
	Total energy and beta carotene	0.53	0.44-0.64
	Total energy and vitamin C	0.56	0.47-0.67
	Total energy, beta carotene, and vitamin C	0.58	0.47-0.70
Vitamin C, 220 mg/d		0.79	0.70-0.89
	Total energy	0.65	0.57-0.74
	Total energy and fiber	0.82	0.71-0.95
	Total energy and beta carotene	0.72	0.62-0.82
	Total energy, fiber, and beta carotene	0.83	0.72-0.96
Beta carotene, 12000 IU/d		0.81	0.72-0.91
	Total energy	0.69	0.61-0.79
	Total energy and fiber	0.91	0.78-1.05
	Total energy and vitamin C	0.79	0.69-0.91
	Total energy, fiber, and vitamin C	0.94	0.81-1.09

*Number of cases = 4326; number of controls = 8946.
†Also adjusted for study, age group, and sex.

Table 3. Relative risks by quintiles of intake: combined analysis for all studies

Dietary factor	n* Case patients	n* Control subjects	n* Total	Relative risk (95% confidence interval) for quintile 1	2	3	4	5	P, trend
Fiber†	5225	10349	15574	1.00	0.79 (0.71-0.89)	0.69 (0.61-0.78)	0.63 (0.55-0.71)	0.53 (0.47-0.61)	<.0001
Vitamin C‡	4970	9866	14836	1.00	0.98 (0.87-1.11)	0.93 (0.81-1.06)	0.90 (0.79-1.04)	0.85 (0.72-0.99)	.02
Beta carotene‡	4564	9408	13972	1.00	1.05 (0.92-1.18)	0.97 (0.85-1.11)	0.90 (0.78-1.04)	0.88 (0.75-1.04)	.03

*Number of subjects included in analysis.
†Adjusted for total energy intake, study, age group, and sex.
‡Adjusted for total energy and fiber intakes and study, age group, and sex.

lowest quintile based on the combined data from all studies. Table 4 shows the corresponding data from the combined analysis of those studies that had data for all three dietary factors. The results shown in Tables 3 and 4 are essentially identical.

There is a monotonic decreasing dose–response relationship seen for the intake of fiber, which essentially could not have arisen by chance ($P<10^{-10}$). Those in the highest quintile of intake (median, 31.2 g/d) have about half the risk of those in the lowest quintile (median, 10.1 g/d). Although vitamin C and beta carotene demonstrate inverse relationships that achieve conventional levels of statistical significance (i.e., $P<.05$), the effect is much weaker than that seen for fiber and, as discussed subsequently, could be accounted for by measurement error.

The strong inverse association seen with fiber intake in Tables 3 and 4 was essentially unaffected by adjustment for height, weight, body-mass index [weight/height^2], or education. There was also no evidence of any confounding by the latter factors for beta carotene or vitamin C.

Possible interaction effects of fiber with total energy intake, beta carotene, and vitamin C were examined by estimating the relative risk per 27 g of fiber intake per day by tertile of intake of the other nutrients. The relative risks for fiber intake by tertile of total energy intake were 0.48, 0.45, and 0.56 from lowest to highest tertile of total energy intake, respectively (P interaction = .72). For tertiles of beta-carotene intake, the relative risks for fiber intake were 0.44, 0.66, and 0.54 (P interaction = .54). For tertiles of vitamin C intake, relative risks for fiber were 0.37, 0.54, and 0.53 (P interaction = .66). Thus, there appears to be little evidence of any systematic variation in the relative risks for fiber intake within tertiles of the other nutrients. Examination of the relative risks for beta carotene and vitamin C by tertiles of the other nutrients in the same way also provided little evidence of any interaction effects; all P values for their interaction were .09 or more.

The consistency of the fiber effect across the studies is examined in Table 5. In these models, fiber intake is treated as a continuous variable, with the relative risk shown being that for 27 g of fiber per day corresponding approximately to that between the highest and lowest quintile of intake for subjects on a typical diet consumed by North American Whites. The statistical significance of the effect of fiber is, however, independent of the unit chosen to scale the relative risk. It should be noted that the data in Table 5 can be used to estimate a pooled relative risk for any particular subset of studies. This estimation can be made by exponentiating the mean of the log of the relative risk weighted inversely by its variance obtained from the confidence interval expressed on the log scale, since a standard model is used for all studies in this table.

Twelve of the 13 studies provide estimates of relative risk for fiber intake that are less than 1.0, and for eight, the decrease in risk is statistically significant as indicated by the 95% confidence intervals. A global test of heterogeneity was computed for the fiber effect across the studies; the test yielded a P value of less than .001. This statistic tests the

Table 4. Relative risks by quintiles of intake: combined analysis for all studies with data for fiber, vitamin C, and beta carotene

Dietary factor	n* Case patients	n* Control subjects	n* Total	Relative risk (95% confidence interval) for quintile 1	2	3	4	5	P, trend
Fiber†	4326	8946	13272	1.00	0.77 (0.68-0.87)	0.66 (0.58-0.75)	0.58 (0.50-0.66)	0.51 (0.44-0.60)	<.0001
Vitamin C‡	4326	8946	13272	1.00	0.99 (0.87-1.12)	0.93 (0.81-1.06)	0.90 (0.77-1.04)	0.88 (0.75-1.04)	.06
Beta carotene‡	4326	8946	13272	1.00	1.05 (0.92-1.19)	0.99 (0.86-1.13)	0.91 (0.79-1.06)	0.89 (0.75-1.05)	.07

*Number of subjects included in analysis.
†Adjusted for total energy intake, study, age group, and sex.
‡Adjusted for total energy and fiber intakes and study, age group, and sex.

Table 5. Relative risks for intake of 27 g of fiber per day by individual study*

Study	Relative risk†	95% confidence interval
Argentina	0.07	0.02-0.26
Australia I	1.57	0.86-2.90
Australia II	0.21	0.13-0.35
Belgium	0.43	0.28-0.65
Canada	0.61	0.43-0.87
China	0.68	0.46-1.00
France	0.52	0.24-1.15
Greece	0.47	0.13-1.66
North American Chinese	0.41	0.27-0.63
Singapore	0.36	0.10-1.34
Spain	0.34	0.15-0.75
United States I	0.74	0.51-1.07
United States II	0.35	0.19-0.63
All studies combined	0.51	0.44-0.59

*Fiber intake is treated as a continuous variable, with the relative risks shown being that for 27 g of fiber per day corresponding approximately to that between the highest and lowest quintile of intake for subjects on a typical North American diet consumed by Whites.

†Adjusted for total energy intake, age group, and sex.

Table 6. Relative risks for intake of vitamin C and beta carotene by individual study*

	Vitamin C†		Beta carotene‡	
Study	Relative risk	95% confidence interval	Relative risk	95% confidence interval
Argentina	1.19	0.18-7.72	1.31	0.40-4.26
Australia I	—	—	0.83	0.51-1.36
Australia II	0.57	0.43-0.75	0.84	0.59-1.21
Belgium	1.52	0.85-2.73	1.69	0.94-3.06
Canada	0.79	0.60-1.05	0.74	0.44-1.23
China	1.25	0.59-2.63	1.15	0.70-1.87
France	0.19	0.08-0.46	—	—
Greece	0.27	0.03-2.58	0.26	0.04-1.17
North American Chinese	0.60	0.33-1.07	0.36	0.22-0.60
Singapore	1.39	0.77-2.51	1.99	0.58-6.83
Spain	0.54	0.23-1.27	0.81	0.34-2.05
United States I	1.15	0.80-1.66	1.03	0.80-1.32
United States II	0.66	0.28-1.54	—	—
All studies combined	0.79	0.68-1.91	0.93	0.81-1.07

*— = not available.

†Relative risk per 220 mg/d, adjusted for total energy and fiber intakes, age group, and sex.

‡Relative risk per 12000 IU/d, adjusted for total energy and fiber intakes, age group, and sex.

hypothesis that the variation in individual estimates for the studies shown in Table 5 could have arisen by chance. Thus, the individual point estimates of the fiber effect show considerable heterogeneity, which is unlikely to be due to chance.

Table 6 shows individual study results for vitamin C and beta carotene. For vitamin C, five of the 12 studies have relative risks greater than 1.0, though none are statistically significant. Of the seven studies in which the relative risk is less than 1.0, two had results that were statistically significant. Again, there is significant heterogeneity of effect across the studies ($P<.001$).

Of the 11 studies with data for beta carotene, five have relative risks greater than 1.0, with only one of the other six studies having a statistically significant relative risk less than unity. There is significant heterogeneity ($P<.001$), with a combined point estimate close to 1.0.

Table 7 shows estimates of relative risk per 27 g fiber per day estimated separately for cases of left- and right-sided

Table 7. Relative risks for intake of 27 g of fiber per day by cancer site, sex, and age group

	No.			
Subjects	Case patients	Control subjects	Total	Relative risk* (95% confidence interval)
Right-side colon cancer cases and all controls*	1586	6220	7806	0.52 (0.42-0.65)
Left-side colon cancer cases and all controls*	733	6220	6953	0.45 (0.33-0.61)
Rectal cancer cases and all controls*	1265	5874	7139	0.43 (0.34-0.56)
All females†	2433	4893	7326	0.60 (0.48-0.75)
All males†	2792	5456	8248	0.44 (0.37-0.53)
All subjects, age <50 y*	515	1842	2357	0.66 (0.43-0.99)
All subjects, age ≥50 y*	4710	8507	13217	0.49 (0.42-0.57)
Females, age <50 y†	266	940	1206	0.73 (0.41-1.31)
Females, age ≥50 y†	2167	3953	6120	0.58 (0.46-0.74)
Males, age <50 y†	249	902	1151	0.55 (0.31-1.00)
Males, age ≥50 y†	2543	4554	7097	0.43 (0.35-0.53)

*Adjusted for total energy intake, study, age group, and sex.

†Adjusted for total energy intake, study, and age group.

colon cancer and for rectal cancer, for females and males, and by two age groups (<50 and ≥50 years). The latter categorization was chosen because of the postulated possible differential effect of dietary factors before and after the menopause in women (*10*). Similar results are obtained with cut points of 55 and 60 years of age. The estimates are very consistent for all subgroups shown in Table 7, and the large number of study subjects makes it unlikely that there are any true underlying strong differential effects for fiber intake by cancer site, sex, or age group.

Discussion

The present analysis has provided strong evidence of monotonically decreasing risk with increasing intake of fiber, an association that, in essence, could not be due to chance. Twelve of the 13 studies display inverse associations with dietary fiber, although there is considerable statistical heterogeneity in the individual point estimates. Such heterogeneity could have arisen from a number of sources. Differential measurement errors due to the use of different dietary instruments could have occurred among the studies, leading to differential attenuation of the measured relative risks. The composition of total fiber in the different populations studied could have been different in terms of the physiological properties of those components. Confounding by or interaction with specific foods, the consumption of which varies in the different study areas, could also have contributed to the heterogeneity. Despite this heterogeneity, the studies are very consistent in their finding of an inverse association, all (with the exception of Australia I) showing a decrease in risk of at least 26% per 27 g of fiber per day. The probability of twelve of 13 studies finding an inverse association by chance is only about .003. A very similar inverse association with dietary fiber is seen for both left- and right-sided colon cancers, for cancer of the rectum, for both females and males, and for those under 50 years of age and those 50 years of age or older.

Although inverse associations are seen for two other markers of fruit and vegetable intake, namely vitamin C and beta carotene, the effects are much weaker and much less consistent across studies. The latter associations could be the consequence of measurement error. The strong positive association between fiber intake and both vitamin C and beta-carotene intakes and the strong inverse association seen with fiber intake mean that measurement error in dietary fiber intake would lead to incomplete adjustment for the confounding effect of fiber. This could explain the weak inverse associations seen with vitamin C and beta carotene. However, the possibility of real residual, though weak, inverse associations with vitamin C and beta carotene cannot be completely excluded.

Before the implications of these findings can be considered, it is first necessary to assess potential biases that may occur in case-control studies. These biases may be classified as selection, information, and confounding (*43*).

Selection bias would occur if participation rates for case subjects and control subjects were differentially affected by dietary practices. Although one cannot exclude the possibility of this bias, the fact that inverse associations were seen in 12 of the 13 studies (Table 5) argues against the existence of any strong selection bias. This bias would have to operate in a similar manner in all studies to produce such consistent results, and this seems inherently unlikely.

Information bias would occur if case subjects recalled their diet differently from control subjects and, in particular, underestimated their intake of dietary fiber. Again, the consistency of the fiber effect across studies argues against this possibility. It should be noted that adjustment for total energy intake effectively would account for any general under- or over-reporting of food intake by case subjects as compared with control subjects.

There are no obvious contenders for confounding variables of the observed fiber effect, except possibly for dietary factors that are highly correlated with fiber in the foods that provide such intake and for which no measures were available in the present analysis. This possibility cannot be excluded, but the specificity of the relationship with fiber as opposed to vitamin C and beta carotene might argue against such confounding. Interestingly, a recent qualitative assessment of data from case-control studies also concluded that fiber appears to be more consistently related to reduced risk than either vitamin C or beta carotene (*9*).

Although potential biases cannot be excluded, the consistency and specificity of the relationship observed with fiber in the present analysis suggest that such biases have not substantially contributed to the inverse association with fiber.

There are several potential mechanisms by which fiber could modify the carcinogenic process in the colon and rectum (*44,45*). These mechanisms include the physicochemical capacity of fiber to bind bile acids, which are plausibly involved as promoting or trophic agents, (*46,47*) and the physiologic and mechanical effects of fiber on stool bulk (a diluting effect) (*46-48*) or on transit time (a duration of exposure effect) (*46-48*). While stool bulk does appear to be related to colon cancer, transit time is less obviously a risk factor. A third effect of fiber on carcinogenesis is via the capacity of fiber to act as a substrate for bacterial fermentation. Fermentation results in an increase in bacterial mass (thus increasing stool bulk) and the production of short-chain (volatile) fatty acids (*48,49*). These acids can have two plausible effects—one direct and one indirect. Short-chain fatty acids, particularly butyrate, have been shown to have anticarcinogenic effects in vitro and may be a preferred colonic epithelial cell fuel (*48,49*). The indirect effect is via the lowering of gut pH, resulting in a lower rate of conversion of primary to secondary bile acids via pH-dependent bacterial enzymes (*46*). There are, however, some animal experimental data to show that while high fiber diets indeed decrease pH, this decrease is associated with an increased rate of cell proliferation and cancer (*50*).

If the inverse association with fiber intake is simply reflective of some other closely associated dietary factor, one potential candidate would be the trace anticarcinogens found in a number of plant foods that are the source of the

bulk of dietary fiber intake. Such anticarcinogens are found widely in vegetables, fruits, legumes, nuts, and grains and include not only vitamins with antioxidant properties, such as ascorbate and carotenoids, but also non-nutrient substances with established anticarcinogenic properties (*45,51*). These substances include phenolic compounds, sulfur-containing compounds, and flavones. It is not inconceivable, given their ubiquity in plant foods, that fiber may be a good marker of this more molecular anticarcinogenic capacity (*52*).

It must be emphasized that the fiber intake measured in the present studies refers to that derived from foods and not from fiber supplements. Therefore, recommendations to increase the consumption of fiber should be couched in terms of increasing the consumption of foods rich in fiber such as vegetables, fruits, cereal products, and pulses. This also safeguards against the possibility that the actual anticarcinogenic effect is due to some dietary component other than fiber, but which is highly associated with fiber intake.

If it were to be assumed that the association seen in the present data represents causality, it is of interest to estimate the approximate percentage of colorectal cancers that might be prevented by modification of fiber intake. Using the case data from the two U.S. studies and the Canadian study, we estimated that, if the U.S. and Canadian populations increased their fiber intakes from food sources so that all had an intake of at least 39 g/d (the mean of the highest quintile), the corresponding reduction in risk would be about 31%, or about 50 000 cases per year in the United States. (For details of this calculation, *see* Appendix 2.) Such a dietary change would represent an increase of about 16 g of fiber per day, or 70% for the average individual on a typical diet consumed by North American Whites. Given the fact that dietary histories generally overestimate intakes by about 25%, this change would mean a true increase of about 13 g dietary fiber per day. It must be emphasized that increases in fiber consumption should preferably come from increases in the consumption of a wide variety of fiber-rich foods; such an increase does appear to be feasible in terms of substitution of fruits, vegetables, cereals, and legumes for other sources of energy such as fat. Further definition of the specific role of fiber in terms of its sources and physicochemical properties should come from future epidemiologic and metabolic studies.

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Appendix

Appendix 1. Ten Percentile Points for Dietary Factors

Appendix Table 1 shows the 10 percentile points corresponding to the medians and bounds for the quintiles. For example, the bounds for the third quintile are given by the 40th and 60th percentiles, and the median for this quintile is the 50th percentile point.

Appendix 2: Estimation of Fractional Reduction in Population Risk From Modification of Fiber Intake

Let the total number of cases of colorectal cancer (N) occurring in a defined population during a defined time period be classified by level of "exposure" to fiber intake and by level of potential confounders (age, sex, and total energy intake), so that the number of cases occurring at the j'th level of exposure and the i'th level of covariates is a_{ij}, i.e.,

$$N = \Sigma_i \Sigma_j a_{ij}.$$

If there is a change in fiber intake in the population so that the number of cases occurring at the j'th exposure level and i'th covariate level is b_{ij}, then the fractional reduction in the total number of cases due to modification of fiber intake (P) will be

$$P = (N - \Sigma_i \Sigma_j b_{ij})/N \quad [1]$$

or

$$P = 1 - (1/N) \Sigma_i \Sigma_j b_{ij}. \quad [2]$$

If RR_{ij} is the decreased risk for an individual after dietary modification relative to the risk before modification, then

$$RR_{ij} = b_{ij}/a_{ij}. \quad [3]$$

Substituting equation 3 in 2 gives

$$P = 1 - (1/N) \Sigma_i \Sigma_j a_{ij} RR_{ij}. \quad [4]$$

If the relative risk is assumed constant across strata of covariates, which is approximately the case in the present analysis, then

$$P = 1 - \Sigma_j f_j RR_j, \quad [5]$$

where $f_j = (\Sigma_i a_{ij})/N$, i.e., the total fraction of cases exposed at the j'th level. Equation 5 will hold if the cases observed in a case-control or cohort study are regarded as a random sample of the cases arising in the defined population; i.e., the sampling fraction of cases is constant across level of exposure and level of covariates. If an individual case is regarded as defining one level of exposure, then equation 5 may be written as

$$P = 1 - (1/N) \Sigma_j RR_j, \quad [6]$$

where N is the total number of cases, the summation runs over all individual cases, and RR_j is the risk for an individual following the postulated dietary modification

Appendix Table 1. Ten percentile points for dietary factors

	Percentile points								
Dietary factor	10	20	30	40	50	60	70	80	90
Fiber, g/d	10.1	12.5	14.7	16.7	18.6	20.8	23.2	26.2	31.2
Vitamin C, mg/d	45	65	82	96	113	130	151	177	220
Beta carotene, IU/d	2095	3004	3738	4387	5102	5960	7097	8810	12140

relative to the risk under the existing scenario. The relative risk is then estimated in the usual way by

$$RR_j = \exp\{\beta(x_{1j} - x_{2j})\}, \quad [7]$$

where x_{1j} is the current fiber intake for the j'th case and x_{2j} is the postulated new fiber intake, and β has a value of 0.025 per gram of fiber per day estimated from the logistic regression model in which fiber is treated as a continuous variable and which includes terms for study, age, sex, and total energy intake. For the present analysis, the "target" level of fiber intake was defined as the age- and sex-standardized mean intake of fiber in the highest quintile based on the data for control subjects in the three North American studies of Whites. This target had a value of 39 g of fiber per day, as compared with the age- and sex-standardized mean for all controls in those three studies which had a value of 22.5 g of fiber per day. These mean values were similar among each of the three individual studies. Individuals currently consuming more than 39 g of fiber per day were assumed not to make any change. Using these values in combination with equations 6 and 7 and the combined case series from the three North American studies of Whites led to the quoted estimate of 31%.