Fiber Intake and Risk of Colorectal Cancer[1]

Eva Negri,[2] Silvia Franceschi, Maria Parpinel, and Carlo La Vecchia

Istituto di Ricerche Farmacologiche "Mario Negri," 20157 Milan [E. N., C. L. V.]; Servizio di Epidemiologia, Centro di Riferimento Oncologico, 33081 Aviano, Pordenone [S. F., M. P.]; and Istituto di Statistica Medica e Biometria, Università degli Studi di Milano, 20133 Milan [C. L. V.], Italy

Abstract

The relationship between various types of fiber and colorectal cancer risk was investigated using data from a case-control study conducted between January 1992 and June 1996 in Italy. The study included 1953 cases of incident, histologically confirmed colorectal cancers (1225 colon cancers and 728 rectal cancers) admitted to the major teaching and general hospitals in the study areas and 4154 controls with no history of cancer admitted to hospitals in the same catchment areas for acute nonneoplastic diseases. Dietary habits were investigated using a validated food frequency questionnaire. Odds ratios (ORs) were computed after allowance for age, sex, and other potential confounding factors, including physical activity and protein, fat, and carbohydrate intake. Fiber was analyzed both as a continuous variable and in quintiles. For most types of fiber, the OR of colon and rectal cancers was significantly below 1, and no appreciable differences emerged between the two. When the unit was set at the difference between the upper cutpoints of the fourth and first quintile, *i.e.*, the 80th and 20th percentiles, the ORs for colorectal cancer were 0.68 for total fiber (determined by the Englyst method as nonstarch polysaccharides), 0.67 for soluble noncellulose polysaccharides (NCPs), 0.71 for total insoluble fiber, 0.67 for cellulose, 0.82 for insoluble NCPs, and 0.88 for lignin. When fiber was classified according to the source, the OR was 0.75 for vegetable fiber, 0.85 for fruit fiber, and 1.09 for cereal fiber. The ORs were similar for the two sexes and the strata of age, education, physical activity, family history of colorectal cancer, and energy intake. Likewise, no appreciable differences emerged when subsites of the colon and rectum were investigated separately. This study provides additional support for a protective and independent effect of fiber on colorectal cancer, particularly for cellulose and soluble NCPs, and of fiber of vegetable or fruit origin.

Introduction

From the observation that rates of colon cancer were low in some regions of Africa where the intake of fiber was high, Burkitt (1) hypothesized that fiber might protect against colon cancer by increasing stool bulk, thus reducing transit time and hence the contact of carcinogens in fecal material with the colonic mucosa. Moreover, fiber can bind bile acids that produce carcinogenic metabolites, and fermented fiber produces volatile fatty acid that can protect against colon cancer either by a direct anticarcinogenic action or by lowering the pH in the bowel, thus preventing the conversion from primary to secondary bile acids, which seem to be carcinogenic (2).

Fiber, particularly water-soluble fiber, can also delay the absorption of starch, thus reducing the glycemic load and the consequent postprandial hyperinsulinemia, which may promote colon carcinogenesis (3).

These hypotheses are not mutually exclusive, and fiber may act in several ways to prevent colon cancer. There are animal models showing different inhibitory effects of various types of fiber on colon tumor development (4).

Several case-control studies have reported a protective effect of fiber on colon and rectal cancer (5). A combined analysis of 13 case-control studies reported relative risks of colorectal cancer of 0.79, 0.69, 0.63, and 0.53 for the four highest quintiles of intake compared to the lowest one (6). A case-control study of over 2000 colon cancer cases from California, Utah, and Minnesota (7) also showed an inverse relationship. The findings of cohort studies, however, are less consistent. The Nurses' Health Study found a weak inverse association only for fruit fiber (8), whereas in the Health Professionals Follow-Up Study, no clear relationship emerged between fiber and colon cancer risk (9). In the Iowa Women's Health Study, a nonsignificant inverse association between dietary fiber and colon cancer was reported (10).

Furthermore, various types of fiber differ in the extent to which they increase stool bulk (and thus affect transit time) and in fermentation. They also delay starch digestion to different degrees. Thus, it is important to analyze the effect of fiber separately by type and origin (*i.e.*, fiber from vegetables, fruit, or cereals). Previous case-control studies that looked separately at the source or type of fiber were often based on limited numbers and yielded inconsistent results (11–14). In a study conducted in Hawaii on about 1200 cases, the protective effect of fiber was limited to fiber from vegetables, whereas no clear relationship emerged for fiber from fruit and cereals (15).

We investigated the issue using data from a large case-control study on colorectal cancer conducted in Italy (16). In 1988–1992, mortality from colorectal cancer in Italy was 19.8/100,000 males and 13.0/100,000 females; incidence ranged between 20/100,000 in southern Italy and 50/100,000 in northern Italy for males, and between 16/100,000 and 30/100,000 for

Received 1/7/98; revised 5/26/98; accepted 6/5/98.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

[1] This work was conducted within the framework of the Consiglio Nazionale delle Ricerche (Italian National Research Council) Applied Project "Clinical Applications of Oncological Research" (Contracts 96.00759.PF39 and 96.00701.PF39) and with the contribution of the Italian Association for Cancer Research.

[2] To whom requests for reprints should be addressed, at Istituto di Ricerche Farmacologiche "Mario Negri," Via Eritrea 62, 20157 Milan, Italy. Fax: 39-2-33200231.

Table 1 Distribution of 1225 cases of colon cancer, 728 cases of rectal cancer, and 4154 controls according to selected covariates, Italy, 1992–1996

Variable	Colon cancers		Rectal cancers		Controls	
	No.	%	No.	%	No.	%
Sex						
Males	688	56	437	60	2073	50
Females	537	44	291	40	2081	50
Age group (yr)						
<50	169	14	93	13	1079	26
50–64	583	48	339	47	1928	46
65–74	473	39	296	41	1147	28
Education (yr)[a]						
<7	621	51	422	58	2276	55
7–11	331	27	181	25	1156	28
≥12	267	22	122	17	693	17
Physical activity (at work)[a,b]						
Low	444	36	231	32	1378	33
Medium	451	37	258	35	1476	36
High	330	27	239	33	1299	31
Family history of colorectal cancer[c]						
No	1091	89	675	93	4008	96
Yes	134	11	53	7	146	4
Energy intake[d]						
I (lowest)	374	31	228	31	1385	33
II	428	35	241	33	1384	33
III (highest)	423	35	259	36	1385	33

[a] The sum does not add up to the total because of some missing values.
[b] Self-assessed score of physical activity.
[c] Family history in first-degree relatives.
[d] Sex-specific tertiles of controls. Upper cutpoints were 2397 and 3026 kcal for men and 1860 and 2411 kcal for women.

females (17). Specific attention was paid to the separate effect of various types of fiber.

Subjects and Methods

The data were derived from a case-control study of colorectal cancer conducted between January 1992 and June 1996 in six areas of Italy: (*a*) greater Milan, the provinces of Pordenone and Gorizia, the urban area of Genoa, and the province of Forlì in northern Italy (16); (*b*) the province of Latina in central Italy; and (*c*) the urban area of Naples in southern Italy. The same structured questionnaire and coding manual were used by centrally trained interviewers in all study centers. Data were checked centrally for consistency and reliability. On average, less than 4% of cases and controls approached for an interview refused to participate.

Cases were incident (*i.e.*, diagnosed within 1 year before the interview; mean, 2.5 months) histologically confirmed patients with colorectal cancer, were less than 75 years of age, and were admitted to the major teaching and general hospitals in the area under surveillance. Overall, 1225 subjects with cancer of the colon (International Classification of Diseases 9, 153.0–153.9) and 728 subjects with cancer of the rectum (International Classification of Diseases 9, 154.0–154.1), ages 23–74 years (median age, 62 years), were included. Controls were patients with no history of cancer from the same catchment areas as the cases who were admitted to the same hospitals for acute non-neoplastic conditions unrelated to digestive tract diseases and not associated with long-term modifications of diet. A total of 4154 controls, ages 20–74 years (median age, 58 years), were interviewed. Of these, 23% were admitted for traumas (mostly fractures and sprains), 28% were admitted for other orthopedic disorders, 20% were admitted for acute surgical conditions, 19% were admitted for eye diseases, and 10% were admitted for miscellaneous other illnesses, such as ear, nose, and throat; skin; and dental conditions.

The questionnaire included information on sociodemographic characteristics such as education and occupation, lifetime smoking and alcohol-drinking habits, physical activity, anthropometric measures at various ages, a problem-oriented personal medical history, and family history of cancer.

An interviewer-administered food frequency questionnaire was developed to assess the usual diet during the 2 years preceding diagnosis (for cases) or hospital admission (for controls) and the intake of total energy as well as that of macronutrients and micronutrients. The questionnaire included 78 foods, groups of foods, or dishes divided into 6 sections: (*a*) bread, cereals, and first courses; (*b*) second courses (meat and other main dishes); (*c*) side dishes (*i.e.*, vegetables); (*d*) fruits; (*e*) sweets, desserts, and soft drinks; and (*f*) milk, hot beverages, and sweeteners. An additional section concerned alcoholic beverages.

For a few seasonal vegetables and fruits, consumption in season and the corresponding duration were elicited. At the end of each section, one or two open questions were used to report foods that were not included in the questionnaire but eaten at least once per week. For 40 food items, the portion was defined in "natural" units (*e.g.*, one teaspoon of sugar, one egg), and for the remaining items, it was defined as small, average, or large with the help of pictures. Dietary supplements were not considered, given their low level of consumption by this population.

To compute energy and nutrient intake, Italian food composition databases were used for about 80% of the food items and integrated with other sources when needed (18). The reproducibility and validity of the food frequency questionnaire were satisfactory (19, 20).

Table 2 ORs[a] of colon cancer and rectal cancer according to the intake of various types of fiber, Italy, 1992–1996

Type of fiber	Q of intake in controls[b]				Continuous [OR (CI)]	
	Q_2	Q_3	Q_4	Q_5	P_{80}–P_{20} [c]unit	5-g unit
Total (Englyst) fiber[d,e]	(15.68)	(19.63)	(23.15)	(27.86)		
Colon	0.83	0.71	0.61	0.50[f]	0.69 (0.59–0.81)	0.86 (0.81–0.92)
Rectum	0.84	0.57	0.56	0.53[f]	0.67 (0.55–0.81)	0.85 (0.78–0.92)
Colon and rectum	0.83	0.65	0.58	0.51[f]	0.68 (0.60–0.78)	0.85 (0.81–0.90)
Soluble NCP[d]	(7.75)	(9.76)	(11.54)	(13.89)		
Colon	0.93	0.80	0.63	0.56[f]	0.68 (0.58–0.80)	0.73 (0.64–0.84)
Rectum	0.91	0.58	0.66	0.55[f]	0.64 (0.52–0.79)	0.69 (0.58–0.83)
Colon and rectum	0.92	0.71	0.63	0.55[f]	0.67 (0.58–0.77)	0.72 (0.64–0.81)
Total insoluble fiber[d]	(7.83)	(9.81)	(11.58)	(13.93)		
Colon	0.78	0.68	0.60	0.49[f]	0.71 (0.62–0.82)	0.76 (0.67–0.85)
Rectum	0.82	0.62	0.53	0.57[f]	0.71 (0.59–0.85)	0.76 (0.65–0.87)
Colon and rectum	0.80	0.65	0.56	0.52[f]	0.71 (0.63–0.80)	0.76 (0.69–0.84)
Cellulose[d]	(4.13)[d]	(5.35)	(6.38)	(7.78)		
Colon	0.83	0.69	0.60	0.49[f]	0.68 (0.59–0.78)	0.59 (0.49–0.72)
Rectum	0.83	0.56	0.56	0.50[f]	0.65 (0.55–0.87)	0.55 (0.44–0.71)
Colon and rectum	0.83	0.63	0.58	0.49[f]	0.67 (0.60–0.76)	0.58 (0.48–0.68)
Insoluble NCP[d]	(3.56)	(4.42)	(5.16)	(6.22)		
Colon	0.87	0.69	0.67	0.62[f]	0.80 (0.69–0.92)	0.62 (0.47–0.83)
Rectum	0.89	0.61	0.61	0.68[f]	0.85 (0.71–1.01)	0.74 (0.53–1.03)
Colon and rectum	0.88	0.65	0.64	0.64[f]	0.82 (0.73–0.92)	0.69 (0.55–0.85)
Lignin[d]	(1.49)	(1.85)	(2.20)	(2.68)		
Colon	1.00	0.95	0.90	0.85	0.84 (0.71–1.00)	0.49 (0.24–0.98)
Rectum	0.79	0.74	0.69	0.82	0.95 (0.77–1.17)	0.81 (0.34–1.92)
Colon and rectum	0.91	0.85	0.81	0.83	0.88 (0.77–1.02)	0.59 (0.32–1.07)
Vegetable fiber[d,g]	(4.72)	(6.10)	(7.52)	(9.51)		
Colon	0.93	0.77	0.65	0.56[f]	0.72 (0.63–0.82)	0.71 (0.62–0.81)
Rectum	0.73	0.73	0.57	0.61[f]	0.80 (0.69–0.94)	0.79 (0.68–0.93)
Colon and rectum	0.85	0.75	0.62	0.58[f]	0.75 (0.68–0.84)	0.74 (0.67–0.83)
Fruit fiber[d,g]	(5.43)	(7.93)	(10.25)	(13.38)		
Colon	0.76	0.87	0.72	0.76[h]	0.88 (0.78–0.99)	0.92 (0.85–0.99)
Rectum	0.77	0.73	0.71	0.62[f]	0.87 (0.79–0.96)	0.87 (0.79–0.96)
Colon and rectum	0.76	0.80	0.71	0.70[f]	0.85 (0.77–0.94)	0.90 (0.85–0.96)
Grain fiber[d,g]	(3.30)	(4.26)	(5.19)	(6.54)		
Colon	1.15	1.11	1.38	1.32[h]	1.05 (0.91–1.21)	1.08 (0.87–1.33)
Rectum	1.19	1.13	1.19	1.34	1.29 (1.01–1.66)	1.25 (1.01–1.66)
Colon and rectum	1.14	1.10	1.29	1.29[h]	1.09 (0.97–1.22)	1.14 (0.95–1.36)

[a] Estimates from multiple logistic regression models including terms for center, sex, age, education, physical activity, and intake of various energy components, *i.e.*, proteins, fats, carbohydrates, and alcohol.
[b] Q, quintile. The reference category is the first (lowest) quintile. Quintiles are computed on the distribution of controls.
[c] The unit is the difference between the 80th and 20th percentiles of the distribution of controls, *i.e.*, between the upper cutpoint of the fourth and first quintiles. Consequently, the OR refers to a difference in intake between the 80th and 20th percentiles in the control distribution.
[d] The upper cutpoint of the quintile (in grams) is given in parentheses.
[e] Nonstarch polysaccharides.
[f] $P < 0.01$ (significance of the test for trend).
[g] Vegetable, fruit, and grain fibers were entered simultaneously in one model.
[h] $P < 0.05$ (significance of the test for trend).

Dietary fiber intake was derived using the Englyst procedure (21, 22), which measures fiber as nonstarch polysaccharides. A value was obtained for total fiber and for soluble and insoluble fiber. A modification of the method allows cellulose to be measured separately from insoluble NCPs.[3] Values for lignin, a minor component of the human diet, were provided separately. We did not include resistant starch in the computation of total fiber because the amount depends on how each food is processed and consumed (23), and related food composition tables were not available. Fiber intake was also divided according to the food from which it originated (*i.e.*, vegetable, fruit, or cereal).

[3] The abbreviations used are: NCP, noncellulose polysaccharide; OR, odds ratio; CI, confidence interval.

Statistical Analysis. ORs and the corresponding 95% CIs were obtained by means of multiple logistic regression models (24). The various types of fiber were entered in the models both as quintiles of the distribution of controls and continuously. In the latter case, two different measurement units were used: (*a*) the difference between the 80th and 20th percentiles of the control distribution, *i.e.*, between the upper cutpoints of the fourth and first quintiles; and (*b*) 5 g. Several models were fitted to the data, all of which were adjusted for age, sex, and center. Additional models included terms for education, physical activity, alcohol and energy intake, or fat, protein, and carbohydrate intakes instead of energy. The inverse association between fiber intake and colorectal cancer emerged only after adjustment for energy intake, whereas models allowing for total energy or for its components (fat, protein, and carbohydrates) yielded similar results. The latter model was chosen for presentation.

Table 3 ORs[a] and 95% CIs of colorectal cancer according to the intake of various types of fiber in men and women, Italy, 1992–1996

Type of fiber	OR (95% CI)	
	Men	Women
Total (Englyst) fiber	0.66 (0.54–0.79)	0.67 (0.55–0.82)
Soluble NCP[b]	0.64 (0.52–0.77)	0.66 (0.54–0.82)
Total insoluble fiber	0.69 (0.59–0.82)	0.69 (0.58–0.84)
Cellulose	0.65 (0.55–0.76)	0.66 (0.55–0.79)
Insoluble NCP[b]	0.81 (0.69–0.94)	0.81 (0.67–0.97)
Lignin	0.84 (0.70–1.02)	0.90 (0.72–1.12)
Vegetable fiber	0.69 (0.60–0.80)	0.78 (0.66–0.93)
Fruit fiber	0.87 (0.75–1.00)	0.82 (0.70–0.96)
Grain fiber	1.05 (0.90–1.23)	1.15 (0.96–1.38)

[a] Estimates from multiple logistic regression models including terms for center, age, education, physical activity, and intake of proteins, fats, carbohydrates, and alcohol. Vegetable, fruit, and grain fibers were entered simultaneously in one model. The unit for intake is the difference between the 80th and 20th percentiles of the distribution of controls, *i.e.*, between the upper cutpoints of the fourth and first quintiles.
[b] Nonstarch polysaccharides.

Table 4 ORs[a] and 95% CIs of colorectal cancer, according to total fiber intake, in strata of selected covariates, Italy, 1992–1996

Stratum	OR (95% CI)
Age (yr)	
<50	0.74 (0.56–1.00)
50–64	0.61 (0.50–0.73)
≥65	0.75 (0.59–0.95)
Education (yr)	
<7	0.64 (0.54–0.77)
≥7	0.72 (0.60–0.88)
Physical activity (at work)	
Low	0.64 (0.52–0.80)
Medium	0.70 (0.57–0.87)
High	0.66 (0.50–0.87)
Family history of colorectal cancer	
No	0.66 (0.58–0.76)
Yes	0.77 (0.43–1.38)
Energy intake[b]	
I (lowest)	0.58 (0.43–0.78)
II	0.59 (0.46–0.77)
III (highest)	0.76 (0.63–0.92)

[a] Estimates from multiple logistic regression models including terms for center, sex, age, education, physical activity, and intake of proteins, fats, carbohydrates, and alcohol. The unit for fiber intake is the difference between the 80th and 20th percentiles of the distribution of controls, *i.e.*, between the upper cutpoints of the fourth and first quintiles.
[b] Sex-specific tertiles of controls.

Results

Table 1 shows the distribution of cases and controls according to sex, age, education, physical activity, family history of colorectal caner, and tertiles of energy intake. Colon and rectal cancer cases were older than controls and more frequently reported a family history of intestinal cancer and a higher energy intake. Colon but not rectal cancer cases were more educated than controls and reported a lower level of physical activity.

Table 2 presents the ORs according to the intake of various types of fiber, both in quintiles and continuously. There was a significant inverse association of total fiber intake and that of its components with the risk of both colon and rectal cancer; the ORs were very similar for the two cancers. The OR of colon and rectal cancers combined for a difference in intake of the magnitude of the difference between the 80th and 20th percentiles of the control distribution was 0.68 for total fiber, 0.67 for soluble NCPs, 0.71 for total insoluble fiber, 0.67 for cellulose, and 0.82 for insoluble NCPs. The OR was also below unity for lignin, although not significantly (OR = 0.88).

Regarding the food source of the fiber, vegetable and fruit fiber were protective; the corresponding OR for the two cancers combined was 0.75 for vegetables and 0.85 for fruit fiber. Conversely, grain fiber was not associated with the risk of colorectal cancer, and, if anything, the OR tended to be above 1. The results were consistent when the unit was set at 5 g for all fibers. However, the ORs reflect the different absolute intake of the various types of fiber, because these were highly correlated. Consequently, a 5-g increase in the intake of lignin implies a much greater increase in the intake of total fiber.

Table 3 presents the OR of colorectal cancer for the various types of fiber separately for men and women. The OR of total fiber was 0.66 in men and 0.67 in women, and for all types of fiber considered, the ORs were very similar in both sexes.

In Table 4, the association between total fiber intake and the risk of colorectal cancer is analyzed in the strata of selected covariates. No apparent differences emerged in the strata of age or any of the other covariates considered, with the OR ranging from 0.58–0.77 in the various strata. Likewise, no material difference emerged when the ORs were computed separately for various subsites of the colon and rectum; the OR was 0.69 for the right colon, 0.75 for the transverse and descending colon, 0.68 for the sigmoid colon, 0.60 for the rectosigmoid junction, and 0.69 for the rectum (Table 5).

Discussion

This case-control study, one of the largest to date on fiber and colorectal cancer, shows an inverse relationship between the risk of colorectal cancer and the intake of various types of fiber. The association was strong for fiber of vegetable origin, and in fact, no association was observed for cereal fiber. No differences emerged in the strength of the association between colon and rectum or various subsites, sex and strata of age or other selected covariates.

The use of hospital controls has been widely debated (24), and several strengths and weaknesses have been highlighted. Dietary habits of hospital controls may differ from those of the general population, but we took great care to exclude from the control group all diagnoses that might have involved any long-term modification of diet. On the other hand, the similar interview setting for cases and controls and the almost-complete participation are reassuring, as are the satisfactory reproducibility and validity of the food frequency questionnaire (19, 20). With reference to confounding, further allowance for other factors, including tobacco smoking and body mass index, did not materially modify any of the associations.

Furthermore, the results of our study are in line with those of most case-control studies (5, 6, 25). They are of specific interest, because they come from a Southern European population, for which little was known; moreover, they include detailed information on various types of fiber.

In this study, the protection conferred by cellulose and soluble NCPs seemed slightly stronger than that conferred by insoluble NCPs and lignin. However, plant foods contain the various types of fiber together, and in this study, the intakes of various types of fiber were highly correlated. This makes it difficult to distinguish between their effects. Vegetables and fruit, however, contain proportionally more cellulose and sol-

Table 5 Number of cases, OR,[a] and 95% CI of cancer in various subsites of the colon and rectum according to the total fiber intake,[b] Italy, 1992–1996

Site	No. of cases[c]	OR	95% CI
Right colon	185	0.69	0.49–0.98
Transverse and descending colon	188	0.75	0.53–1.06
Sigmoid colon	442	0.68	0.53–0.87
Rectosigmoid junction	159	0.60	0.40–0.89
Rectum	569	0.69	0.55–0.86

[a] Estimates from multiple logistic regression models including terms for center, sex, age, education, physical activity, and intake of proteins, fats, carbohydrates, and alcohol. The unit for fiber intake is the difference between the 80th and 20th percentiles of the distribution in controls.
[b] Nonstarch polysaccharides.
[c] For 456 cases of colon cancer, there were multiple subsites or the subsite was not specified.

uble NCPs and less insoluble NCPs than do cereals. This study found that only fiber from vegetables and, to a lesser extent, fiber from fruit (but not that from cereals) protected against colorectal cancer. This lends support to the hyperinsulinemia hypothesis, because vegetables and fruit are richer in soluble fiber, which is the most effective type in delaying starch absorption (26), and a clinical history of diabetes mellitus was related to colorectal cancer risk in this dataset (27). The risk of colorectal cancer in our study was directly associated with the intake of bread or pasta (16). In the Italian population, the cereals consumed are mostly refined grains; hence, the ratio between starch and fiber intake from cereals may be much higher than that in other populations. Thus, the (possible) promotional action of starch may totally overwhelm the protective action of fiber. In a large study from California, Utah, and Minnesota, high intakes of refined grains were associated with an increased risk of colon cancer, whereas the opposite was true for whole-grain intake (7).

Finally, our data do not suggest that the effect of fiber is different in the two sexes (28), because the association of all types of fiber with colorectal cancer was similar for both sexes.

Acknowledgments

We thank Judy Baggott, M. Paola Bonifacino, and the G. A. Pfeiffer Memorial Library staff for editorial assistance.

References

1. Burkitt, D. P. Epidemiology of cancer of the colon and rectum. Cancer (Phila.), *28:* 3–13, 1971.

2. Nagengast, F. M., Grubben, M. J. A. L., and van Munster, I. P. Role of bile acids in colorectal carcinogenesis. Eur. J. Cancer, *31A:* 1067–1070, 1995.

3. Giovannucci, E. Insulin and colon cancer. Cancer Causes Control, *6:* 164–179, 1995.

4. Reddy, B. S. Dietary fat, calories, and fiber in colon cancer. Prev. Med., *22:* 738–749, 1993.

5. Potter, J. D. Nutrition and colorectal cancer. Cancer Causes Control, *7:* 127–146, 1996.

6. Howe, G. R., Benito, E., Castelleto, R., Cornée, J., Estève, J., Gallagher, R. P., Iscovich, J. M., Deng-ao, J., Kaaks, R., Kune, G. A., Kune, S., L'Abbé, K. A., Lee, H. P., Lee, M., Miller, A. B., Peters, R. K., Potter, J. D., Riboli, E., Slattery, M. L., Trichopoulos, D., Tuyns, A., Tzonou, A., Whittemore, A. S., Wu-Williams, A. H., and Shu, Z. Dietary intake of fiber and decreased risk of cancers of the colon and rectum: evidence from the combined analysis of 13 case-control studies. J. Natl. Cancer Inst., *84:* 1887–1896, 1992.

7. Slattery, M. L., Potter, J. D., Coates, A., Ma, K-N., Berry, T. D., Duncan, D. M., and Caan, B. J. Plant foods and colon cancer: an assessment of specific foods and their related nutrients (United States). Cancer Causes Control, *8:* 575–590, 1997.

8. Willett, W. C., Stampfer, M. J., Colditz, G. A., Rosner, B. A., and Speizer, F. E. Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. N. Engl. J. Med., *323:* 1664–1672, 1990.

9. Giovannucci, E., Rimm, E. B., Stampfer, M. J., Colditz, G. A., Ascherio, A., and Willett, W. C. Intake of fat, meat, and fiber in relation to risk of colon cancer in men. Cancer Res., *54:* 2390–2397, 1994.

10. Steinmetz, K. A., Kushi, L. H., Bostick, R. M., Folsom, A. R., and Potter, J. D. Vegetables, fruit, and colon cancer in the Iowa Women's Health Study. Am. J. Epidemiol., *139:* 1–15, 1994.

11. Slattery, M. L., Sorenson, A. W., Mahoney, A. W., French, T. K., Kritchevsky, D., and Street, J. C. Diet and colon cancer: assessment of risk by fiber type and food source. J. Natl. Cancer Inst., *80:* 1474–1480, 1988.

12. Freudenheim, J. L., Graham, S., Horvath, P. J., Marshall, J. R., Haughey, B. P., and Wilkinson, G. Risks associated with source of fiber and fiber components in cancer of the colon and rectum. Cancer Res., *50:* 3295–3300, 1990.

13. Benito, E., Stiggelbout, A., Bosch, F. X., Obrador, A., Kaldor, J., Mulet, M., and Munoz, N. Nutritional factors in colorectal cancer risk: a case-control study in Majorca. Int. J. Cancer, *49:* 161–167, 1991.

14. Meyer, F., and White, E. Alcohol and nutrients in relation to colon cancer in middle-aged adults. Am. J. Epidemiol., *138:* 225–236, 1993.

15. Le Marchand, L., Hankin, J. H., Wilkens, L. R., Kolonel, L. N., Englyst, H. N., and Lyu, L-C. Dietary fiber and colorectal cancer risk. Epidemiology, *8:* 658–665, 1997.

16. Franceschi, S., Favero, A., La Vecchia, C., Negri, E., Conti, E., Montella, M., Giacosa, A., Nanni, O., and Decarli, A. Food groups and risk of colorectal cancer in Italy. Int. J. Cancer, *72:* 56–61, 1997.

17. Levi, F., Lucchini, F., Boyle, P., Negri, E., and La Vecchia, C. Cancer incidence and mortality in Europe, 1988–92. J. Epidemiol. Biostat., in press, 1998.

18. Salvini, S., Gnagnarella, P., Parpinel, M. T., Boyle, P., Decarli, A., Ferraroni, M., Giacosa, A., La Vecchia, C., Negri, E., and Franceschi, S. The food composition database for an Italian food frequency questionnaire. J. Food Compos. Anal., *9:* 57–71, 1996.

19. Franceschi, S., Barbone, F., Negri, E., Decarli, A., Ferraroni, M., Filiberti, E., Giacosa, A., Gnagnarella, P., Nanni, O., Salvini, S., and La Vecchia, C. Reproducibility of an Italian food frequency questionnaire for cancer studies. Results for specific nutrients. Ann. Epidemiol., *5:* 69–75, 1995.

20. Decarli, A., Franceschi, S., Ferraroni, M., Gnagnarella, P., Parpinel, M. T., La Vecchia, C., Negri, E., Salvini, S., Falcini, F., and Giacosa, A. Validation of a food frequency questionnaire to assess dietary intakes in cancer studies in Italy: results for specific nutrients. Ann. Epidemiol., *6:* 110–118, 1996.

21. Englyst, H. N., and Cummings, J. H. Improved method for measurement of dietary fiber as non-starch polysaccharides in plant foods. J. Assoc. Off. Anal. Chem., *71:* 808–814, 1988.

22. Englyst, H. N., Quigley, M. E., Hudson, G. J., and Cummings, J. H. Determination of dietary fibre as non-starch polysaccharides by gas liquid chromatography. Analyst, *117:* 1707–1714, 1992.

23. Cummings, J. H., and Englyst, H. N. Gastrointestinal effects of food carbohydrate. Am. J. Clin. Nutr., *61* (Suppl.)*:* 938S–945S, 1995.

24. Breslow, N., and Day, N. E. Statistical methods in cancer research: the analysis of case-control studies. IARC Sci. Publ., *32:* 192–247, 1980.

25. Hill, M. J. Cereals, cereal fibre and colorectal cancer risk: a review of the epidemiological literature. Eur. J. Cancer Prev., *6:* 219–225, 1997.

26. Riccardi, G., and Rivellese, A. A. Effects of dietary fiber and carbohydrate on glucose and lipoprotein metabolism in diabetic patients. Diabetes Care, *14:* 1115–1125, 1991.

27. La Vecchia, C., Negri, E., Decarli, A., and Franceschi, S. Diabetes mellitus and colorectal cancer risk. Cancer Epidemiol. Biomark. Prev., *6:* 1007–1010, 1997.

28. McMichael, A. J., and Potter, J. D. Do intrinsic sex differences in lower alimentary tract physiology influence the sex-specific risks of bowel cancer and other biliary and intestinal diseases? Am. J. Epidemiol., *118:* 620–627, 1983.