Fruit, Vegetables, Dietary Fiber, and Risk of Colorectal Cancer

Paul Terry, Edward Giovannucci, Karin B. Michels, Leif Bergkvist, Holger Hansen, Lars Holmberg, Alicja Wolk

Background: **Several recent large prospective cohort studies have failed to demonstrate the presumed protective effect of fruit, vegetable, and dietary fiber consumption on colorectal cancer risk. To further explore this issue, we have examined these associations in a population that consumes relatively low amounts of fruit and vegetables and high amounts of cereals.** ***Methods:*** **We examined data obtained from a food-frequency questionnaire used in a population-based prospective mammography screening study of women in central Sweden. Women with colorectal cancer diagnosed through December 31, 1998, were identified by linkage to regional cancer registries. Cox proportional hazards models were used to estimate relative risks. All statistical tests were two-sided.** ***Results:*** **During an average 9.6 years of follow-up of 61 463 women, we observed 460 incident cases of colorectal cancer (291 colon cancers, 159 rectal cancers, and 10 cancers at both sites). In the entire study population, total fruit and vegetable consumption was inversely associated with colorectal cancer risk. Subanalyses showed that this association was due largely to fruit consumption. The association was stronger, however, and the dose–response effect was more evident among individuals who consumed the lowest amounts of fruit and vegetables. Individuals who consumed less than 1.5 servings of fruit and vegetables per day had a relative risk for developing colorectal cancer of 1.65 (95% confidence interval = 1.23 to 2.20;** P_{trend} **= .001) compared with individuals who consumed more than 2.5 servings. We observed no association between colorectal cancer risk and the consumption of cereal fiber, even at amounts substantially greater than previously examined, or of non-cereal fiber.** ***Conclusions:*** **Individuals who consume very low amounts of fruit and vegetables have the greatest risk of colorectal cancer. Relatively high consumption of cereal fiber does not appear to lower the risk of colorectal cancer.** **[J Natl Cancer Inst 2001;93:525–33]**

Colorectal cancer is a leading cause of cancer death in the United States and other developed countries *(1),* yet the etiology of this disease remains largely unknown. The rapid increase in colorectal cancer incidence in several populations previously considered to be at low risk for this disease *(2),* the 20-fold difference in incidence between high-incidence and low-incidence regions *(3),* and the changes in incidence patterns observed in migrant studies *(4,5)* suggest that environmental factors, including those related to diet *(6,7),* contribute to the etiology of colorectal cancer. Given the roles of the colon and rectum as conduits for ingested food and the many potentially anticarcinogenic substances contained in fruit *(8),* vegetables *(8),* and cereals *(9),* these food groups are among the most widely studied in relation to colorectal cancer risk.

Although the majority of more than 20 case–control studies [reviewed in *(10)*] have shown an inverse association between fruit and vegetable consumption and colorectal cancer risk, seven prospective cohort studies *(11–17)* have obtained inconsistent results. The largest and most recent of these studies *(11)* showed no association between fruit and vegetable consumption and colon or rectal cancer risk among 136 089 U.S. health professionals who were followed for 16 years (women) or 10 years (men). However, this health-conscious cohort showed higher consumption of fruit and vegetables than has been noted in the general U.S. population *(18)* and an overall high prevalence of multivitamin use. Consequently, all members of this cohort could be getting adequate amounts of these foods. A better population to study might be one with a low consumption of fruit and vegetables. Unfortunately, no similar cohort studies have

Affiliations of authors: P. Terry, Department of Medical Epidemiology, Karolinska Institutet, Stockholm, Sweden, and Division of Epidemiology, Columbia-Presbyterian Medical Center, New York, NY; E. Giovannucci, Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; K. B. Michels, Obstetrics and Gynecology Epidemiology Center, Brigham and Women's Hospital, Harvard Medical School, and Department of Epidemiology, Harvard School of Public Health, Boston; L. Bergkvist, Department of Surgery and Center for Clinical Research, Uppsala University, Central Hospital, Västerås, Sweden; H. Hansen, Department of Community Medicine, University of Connecticut Health Center, Farmington; L. Holmberg, Regional Oncologic Center, Uppsala, Sweden; A. Wolk, Department of Medical Epidemiology, Karolinska Institutet.

Correspondence to: Paul Terry, M.P.H., Department of Medical Epidemiology, Karolinska Institute, Box 281, SE-171 77 Stockholm, Sweden (e-mail: paul.terry@mep.ki.se).

See "Note" following "References."

specifically estimated colorectal cancer risk in such individuals. An inverse association among individuals with low fruit and vegetable consumption, if established, would be of considerable interest, since the implementation of targeted preventive measures within such populations would be feasible and cost-effective.

Results from a meta-analysis of 13 case–control studies *(19)* have suggested that increased dietary fiber intake is associated with decreased risk of colorectal cancer, although prospective cohort studies *(12,15,20–24)* do not support such an association. Nonetheless, evidence from animal studies and some clinical trials continues to suggest that cereals *(9,16,25–29),* especially wheat bran, contain substances, such as fiber, phytic acid, various phenolic compounds, lignins, and flavonoids, that might lower the risk for colorectal cancers *(9).* Cereal fiber might also bind carcinogens and modify glycemic index *(9).* The consumption of foods with a high glycemic index has been hypothesized to lead to colorectal cancer through the tumor-promoting effect of elevated levels of insulin, glucose, or triglycerides *(30).* Nevertheless, two large prospective cohort studies *(20,21)* or two recent clinical trials of recurrent colorectal adenomas *(31,32)* found no association between colorectal cancer risk and cereal fiber consumption. However, these findings have been criticized on the following grounds: Negative results from the large prospective study of U.S. nurses *(20)* have led some researchers to speculate that cereal fiber intake in this cohort was too low to observe an association; in contrast, in the clinical trials, the short-term study of recurrent adenomas *(33)* may have little relevance to the evolution of adenomas to colorectal cancer.

We prospectively analyzed data from a population-based cohort of 61 463 Swedish women with a relatively low consumption of fruit and vegetables and a high intake of cereal fiber, especially wheat fiber *(34).* In addition to conducting traditional analyses of exposure quartiles, we also examined the risk of colorectal cancer among individuals who consumed the highest and the lowest amounts of fruit, vegetables, and cereal fiber.

Subjects and Methods

The Swedish Mammography Screening Cohort

From 1987 through 1990, a population-based mammography screening program was introduced in two counties in central Sweden. In Västmanland County, all of the women born during the period from 1917 through 1948 (n = 41 786) received a mailed invitation to be screened by mammography from March 1987 through March 1989 and a six-page questionnaire; 31 735 women (76%) returned completed questionnaires. In Uppsala County, all women born during the period from 1914 through 1948 (n = 48 517) were invited to participate in the mammography screening program and received the same questionnaire during the period from January 1988 through December 1990; 34 916 women (72%) returned completed questionnaires. Hence, completed questionnaires, which included items about age, weight (kg), height (cm), educational level, and diet, were obtained from 66 651 (73.8%) women in the source population before the mammography was performed.

For the present analyses, we excluded the following women: women who were younger than 40 years and older than 74 years (n = 165); women whose questionnaires had missing (n = 707) or incorrect (n = 415) identification numbers, were not properly dated (n = 608), or lacked the date that the woman moved out of the study area (n = 79); and women whose dates of death were verified through the Swedish Death Registry (n = 16). We excluded an additional 793 women because their answers on the dietary portion of the questionnaire suggested that they had extreme energy intakes (3 standard deviations below or above the mean value for natural logarithm-transformed calories, with the use of cut points of 417 and 3729 kcal) or had carelessly completed the dietary questionnaire. By linkage to the Swedish Cancer Registry, we identified and excluded all women with a previous cancer diagnosis other than nonmelanoma skin cancer (n = 2405). Thus, the study cohort comprised 61 463 women at the start of follow-up.

Dietary Assessment

Diet was assessed with the use of a self-administered food-frequency questionnaire (FFQ) that included 67 food items commonly eaten in Sweden. Participants were asked how often, on average, per day during the past 6 months they had consumed these foods, using eight predefined frequency categories that ranged from "never/seldom" to "four or more times per day." For bread products only, there were open-ended questions about the number of slices of crisp bread, whole-grain bread, and other bread consumed per day. For each food item, these frequencies were converted to frequency per day. In the FFQ, we asked how often such vegetables as cabbage, tomatoes, lettuce, spinach, potatoes, and carrots and beets were consumed. We did not obtain information on the consumption of cucumbers and onions, which made up only 5.0% and 3.5%, respectively, of the total vegetables consumed in Sweden in 1987 and were the only other commonly eaten vegetables in Sweden at baseline assessment *(35).* Specific fruit items included in the FFQ were citrus fruit, fruit juice, bananas, apples, and pears. We did not obtain information on the consumption of peaches, plums, grapes, and berries, each of which constituted a small percentage of the total fruit consumed but, when combined, constituted 13.1% of the total *(35).* The average 4.0 servings of total fruit and vegetables consumed in Sweden according to a national survey from 1989 *(36)* was the same as the average 4.0 servings of fruit and vegetables in our data; thus, our study population was representative of the general population. Total fruit and vegetable consumption in our data ranged from 0 to 8 servings/day. In terms of weight, the average serving sizes for fruit and vegetables were 95–110 g for fruit, 55 g for carrots and beets, 70 g for cabbage, 55 g for tomatoes, 30 g for spinach and lettuce, 115 g for potatoes, and 160 g for juice. We did not have information on supplement use in our data.

Nutrient calculations were based on the mean values of age-specific portion sizes (40–52, 53–65, and 66–74 years) of scaled-weighed foods that were recorded for a total of 5922 days by 213 women who were randomly selected from the study population. Nutrient composition values obtained from Swedish National Food Administration data *(37)* were used for these calculations. The intake of dietary fiber and other nutrients was computed by multiplying the frequency of consumption of each unit of food by the nutrient content of the specified portions. The main food sources for cereal fiber were whole-grain bread, crisp bread, oats, muesli as well as other breakfast cereal, pasta, and rice. Values for the fiber content of foods were derived from published measurements that were made with the use of a combination of enzymatic and gravimetric procedures *(38).*

The validity of nutrient estimates based on the self-reported food-consumption frequencies was evaluated for 129 of the 213 women who weighed and recorded what they consumed during four 7-day periods at 3- to 4-month intervals. The validity estimates for fruit and vegetable intake were measured as a Pearson correlation coefficient (r) between the food questionnaire and food records (r for individual items varied from .3 to .6). The validity estimate for total dietary fiber intake was $r = .54$.

Identification of Colon and Rectal Cancer Cases and Follow-up of the Cohort

We identified incident cases of colon and rectal cancers that occurred in our study cohort through December 31, 1998, by matching with two types of independent sources: 1) the computerized regional cancer registries that recorded all diagnoses of colon and rectal cancers in the two counties and 2) a list of all pathology reports from the two pathology departments covering the study area. This method of case ascertainment and diagnosis is even more rigorous than the method employed by the national Swedish Cancer Registry, in which 98% of all colorectal cancers occurring in Sweden were correctly identified and accounted for *(39).*

We identified 460 colorectal cancers in total. Colon cancers were defined as those occurring above the peritoneal delineation of the abdominal cavity (n = 291), and rectal cancers were defined as those occurring below this delineation (n = 159); 10 women were diagnosed with both colon and rectal cancers. For subanalyses by colon cancer site, proximal colon cancers were defined as those occurring from the cecum through the splenic flexure (n = 118), and distal colon cancers were defined as those occurring from the descending colon through the sigmoid colon (n = 101); locations of 72 colon cancers were not specified. Dates of deaths in the cohort were ascertained through the Swedish Death

Registry. The date that a study subject moved out of the study area was obtained by matching the cohort to the computerized and continuously updated Swedish Population Registry. This study was approved by the Ethics Committee at Uppsala University Hospital, Västerås, Sweden, and by the Regional Ethics Committee of the Karolinska Institute, Stockholm, Sweden.

Statistical Analysis

Energy adjustment of nutrients was performed with the use of the residuals methodology recommended by Willett and Stampfer *(40)*. In the first step of the method, each nutrient is regressed on total energy (both variables in continuous form). Calorie-adjusted nutrients (residuals from this procedure were standardized to the mean caloric intake of 1350 kcal/day) then were used with total energy scores in the models. Cox proportional hazards models were used to estimate relative risks (RRs) with 95% confidence intervals (CIs). Follow-up was censored at the date of death, the date of migration out of the study area, or at the end of the follow-up period (December 31, 1998). For fruit and vegetable consumption, all multivariate risk-factor models were adjusted for age (in 5-year age groups), consumption of red meat and dairy products (in quartiles), and total energy (as a continuous variable). For dietary fiber consumption, all multivariate risk-factor models were adjusted for age (in 5-year age groups), body mass index, educational level (three categories), intake of energy (as a continuous variable), and quartiles of alcohol, red meat, total fat, folic acid, vitamin D, vitamin C, and calcium. For the trend tests, median values for each exposure category of a categorized variable were placed together in the model *(41)*. Variables were also analyzed in continuous form when the results from our categorized analyses were compatible with the assumption that the effects are linear.

Results

During an average 9.6 years of follow-up of our cohort of 61 463 women (corresponding to 588 270 person-years), we observed 460 incident cases of colorectal cancer (291 colon cancers, 159 rectal cancers, and 10 cancers at both sites). The average age at diagnosis was 67 years for colon cancer patients and 68 years for rectal cancer patients.

Fruit and Vegetables

Median intakes of total fruit and vegetables varied widely in the cohort, ranging from 2.0 servings/day in the lowest quartile to 6.1 servings/day in the highest (Table 1). Fruit and vegetable consumption was positively correlated with consumption of dairy products ($r = .11$) and, as expected, with total dietary fiber ($r = .48$). No appreciable difference was observed in median age, body mass index, or consumption of meat and alcohol among women in the various quartiles of fruit and vegetable consumption.

Consumption of fruit and vegetables was inversely associated with risk of colorectal cancer (Table 2). Total consumption of fruit and vegetables combined was inversely associated with colon cancer and rectal cancer, but the association was stronger for the consumption of fruit, especially in relation to rectal cancer. For colon cancer and, consequently, for total colorectal cancer, the reduction in risk appeared to be fairly small in all quartiles relative to the lowest quartile (Table 2).

We further explored the association between fruit and vegetable consumption and colorectal cancer risk among individuals in the lowest quartile by using the remainder of the cohort (i.e., quartiles 2, 3, and 4) as the referent category (Table 3). A linear inverse association between total colorectal, colon, and rectal cancers and total fruit and vegetable consumption was observed when the lowest quartile of consumption was further divided into subtertiles ($P_{trend} = .03$). With the use of a continuous variable to describe fruit and vegetable consumption, the RR for an increase of one serving per day in this restricted analysis was 0.77 (95% CI = 0.60 to 0.97; $P = .03$). We further examined fruit and vegetable consumption after categorization of the entire cohort into deciles. Individuals in the highest decile of consumption compared with those in the lowest decile showed a statistically significant 40% decreased risk ($P = .04$) of colorectal cancer (data not shown).

Our results did not change when we examined fruit and vegetable consumption and adjusted either for age alone or for age and body mass index (quartiles), educational level (less than high school, high school, and university), and quartiles of total fat, dietary fiber, or alcohol. The relationships between fruit and vegetable consumption and colon and rectal cancer risk were similar across different strata of alcohol consumption and body mass index.

Cereal Fiber

The median intake of cereal fiber (±standard deviation) was 9.3 g/day (±3.6 g/day) for the entire cohort. The median intake in the highest quartile was 13.6 g/day (±2.7 g/day), an amount that was comparable to the 13.5 g/day tested in a recent clinical trial to assess the effect of dietary supplementation with cereal fiber *(31)* (Table 4). There was a greater than twofold difference in average cereal fiber intake between study subjects in the lowest versus the highest intake quartiles. Cereal fiber intake

Table 1. Baseline characteristics of the study cohort according to total fruit and vegetable consumption

Characteristic	Quartiles of total fruit and vegetable consumption			
	1 (n = 15 544)	2 (n = 15 056)	3 (n = 15 308)	4 (n = 15 555)
Person-years	147 394	145 007	149 877	145 992
Fruit and vegetables,* servings/day ± standard deviation	2.0 ± 3.9	3.1 ± 3.9	4.3 ± 3.9	6.1 ± 3.9
Age at baseline,* y	54	52	52	52
Body mass index,* kg/m^2	24.3	24.1	24.1	24.2
Dietary intake*,†				
Energy, kcal/day	1360	1267	1331	1443
Dairy products, servings/wk	17.0	18.4	19.1	20.7
Red meat, servings/wk	4.1	4.6	4.6	4.6
Alcohol, drinks/wk	1.7	2.3	2.4	2.3

*Median value.

†Nutrients adjusted to 1350 kcal, which is the rounded value corresponding to the mean energy intake in the study group. Values presented are age standardized.

Table 2. Multivariate-adjusted relative risks for fruit and vegetable categories*

	Servings per day	Colorectal cancer (n = 460)†		Colon cancer (n = 291)†		Proximal colon cancer (n = 118)†		Distal colon cancer (n = 101)†		Rectal cancer (n = 159)†	
		RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Total fruit and vegetable consumption											
Quartile 1	<2.5	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent
Quartile 2	2.5–3.5	0.74	0.58 to 0.96	0.68	0.49 to 0.95	0.77	0.47 to 1.26	0.68	0.37 to 1.23	0.82	0.55 to 1.24
Quartile 3	3.5–5.0	0.77	0.60 to 1.00	0.84	0.62 to 1.15	0.64	0.38 to 1.09	1.12	0.67 to 1.88	0.66	0.42 to 1.02
Quartile 4	>5.0	0.73	0.56 to 0.96	0.81	0.59 to 1.13	0.91	0.55 to 1.51	0.87	0.49 to 1.54	0.60	0.38 to 0.96
P trend‡		.03		.36		.48		.96		.02	
Vegetable consumption											
Quartile 1	<1.0	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent
Quartile 2	1.0–1.5	0.87	0.67 to 1.12	0.88	0.64 to 1.21	0.71	0.43 to 1.17	1.28	0.76 to 2.17	0.84	0.54 to 1.30
Quartile 3	1.5–2.0	0.92	0.72 to 1.19	0.82	0.59 to 1.14	0.73	0.44 to 1.20	0.70	0.38 to 1.29	1.05	0.69 to 1.58
Quartile 4	>2.0	0.84	0.65 to 1.09	0.90	0.66 to 1.24	0.72	0.44 to 1.20	1.13	0.66 to 1.94	0.71	0.45 to 1.12
P trend‡		.25		.43		.19		.85		.29	
Fruit consumption											
Quartile 1	<1.0	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent
Quartile 2	1.0–1.5	0.68	0.53 to 0.87	0.54	0.39 to 0.76	0.77	0.47 to 1.28	0.54	0.30 to 0.98	0.95	0.63 to 1.43
Quartile 3	1.5–2.0	0.74	0.58 to 0.96	0.74	0.54 to 1.02	0.89	0.54 to 1.48	0.86	0.51 to 1.46	0.79	0.51 to 1.22
Quartile 4	>2.0	0.68	0.52 to 0.89	0.76	0.55 to 1.06	0.97	0.57 to 1.64	0.91	0.53 to 1.55	0.54	0.33 to 0.89
P trend‡		.009		.23		.99		.95		.01	

*Multivariate models included age (in 5-year age groups), consumption of red meat and dairy products (in quartiles), and total calories (as continuous variables). RR = relative risk; CI = confidence interval.

†72 cases of colon cancer were of unspecified location; 10 women were diagnosed with both colon and rectal cancers.

‡All *P* values are from two-sided tests of trend.

Table 3. Multivariate-adjusted relative risks for lowest subtertiles of fruit and vegetable categories*

Total fruit and vegetable consumption	Servings per day	Colorectal cancer (n = 460)†		Colon cancer (n = 291)†		Proximal colon cancer (n = 118)†		Distal colon cancer (n = 101)†		Rectal cancer (n = 159)†	
		RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Quartiles 2–4	>2.5	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent
Subtertile 1	2.0–2.5	1.05	0.74 to 1.48	1.02	0.66 to 1.58	0.63	0.27 to 1.45	1.36	0.72 to 2.58	1.00	0.55 to 1.82
Subtertile 2	1.5–2.0	1.23	0.90 to 1.69	1.24	0.84 to 1.84	1.56	0.90 to 2.70	0.36	0.11 to 1.15	1.29	0.76 to 2.20
Subtertile 3	<1.5	1.65	1.23 to 2.20	1.67	1.17 to 2.39	1.64	0.95 to 2.81	1.59	0.86 to 2.93	1.65	1.00 to 2.71
P trend‡		.001		.007		.04		.60		.05	

*Multivariate models included age (in 5-year age groups), consumption of red meat and dairy products (in quartiles), and total calories (as continuous variables). RR = relative risk; CI = confidence interval.

†72 cases of colon cancer were of unspecified location.

‡All *P* values are from two-sided tests of trend.

was positively correlated with intakes of dietary folic acid ($r = .13$) and was inversely correlated with intakes of dietary fat ($r = -.36$), calcium ($r = -.16$), vitamin C ($r = -.13$), alcohol ($r = -.16$), and red meat ($r = -.22$).

Cereal fiber intake was not associated with colorectal cancer risk (Table 5). In age-adjusted and multivariate models, no trend in risk was observed over quartiles of energy-adjusted or unadjusted fiber intake. The RR of colorectal cancer associated with an increased total dietary fiber intake of 10 g/day was 1.08 (95% CI = 0.84 to 1.40; $P = .53$), when total fiber was analyzed as a continuous variable. Even higher levels of cereal fiber consumption showed no associations with colorectal cancer risk (RR for the highest [median, 16.0 g/day] versus the lowest decile [median, 4.3 g/day] of cereal fiber was 1.02 [95% CI = 0.69 to 1.51; $P_{trend} = .63$]). When specific cancer sites were analyzed separately, no association was observed for either colon cancer (total, proximal, or distal) or rectal cancer. Cereal fiber consumption was not related to the risk of colorectal cancer among the subgroups of our study population defined by categories of age, body mass index, and intakes of total fat, energy, alcohol, calcium, or folic acid. In additional analyses, we observed no association between colorectal cancer and the consumption of foods high in whole grains or the total intake of sugar.

In contrast to our negative findings for cereal fiber consumption, we found that consumption of fiber from fruit showed an inverse association with colorectal cancer risk in a model adjusted only for age (Table 6). However, this association disappeared with multivariate adjustment. Neither intake of total dietary fiber nor intake of fiber from vegetables was associated with risk.

Early stages of cancer (before diagnosis) could make an affected individual less inclined to consume certain foods that might aggravate unpleasant symptoms. To eliminate the possibility that undiagnosed preclinical colorectal cancer could influence our results, we reanalyzed the data after excluding cases of colorectal cancer that occurred within the first 3 years of follow-up. Exclusion of such cases did not alter the results for fruit and vegetable consumption or for fiber consumed from any source.

Table 4. Baseline characteristics of the study cohort according to total dietary fiber intake

Characteristic	Quartiles of energy-adjusted cereal fiber intake			
	1 (n = 15 336)	2 (n = 15 366)	3 (n = 15 366)	4 (n = 15 365)
Person-years	146 602	146 978	147 280	147 410
Cereal fiber,* g/day ± standard deviation	5.7 ± 1.4	8.3 ± 0.6	10.4 ± 0.7	13.6 ± 2.7
Age at baseline,* y	48	52	54	55
Body mass index,* kg/m^2	23.8	24.2	24.4	24.2
Dietary intake*,†				
Energy, kcal/day	1357	1248	1250	1351
Fat, g/day	50.9	46.8	44.5	34.8
Vitamin C, mg/day	47.6	57.9	66.2	79.0
Folic acid, μg/day	162	182	195	215
Calcium, mg/day	767	753	739	696
Vitamin D, μg/day	3.5	3.4	3.3	3.1
Alcohol, g/wk	2.5	2.4	2.1	1.6
Red meat, servings/wk	5.5	4.6	4.6	4.1

*Median value.

†Nutrients adjusted to the rounded mean energy intake in the cohort of 1350 kcal. Values presented are age standardized.

Table 5. Relative risks of colorectal cancer according to cereal fiber intake*

	Quartile of energy-adjusted cereal fiber intake				
	1†	2	3	4	P_{trend}‡
Median cereal fiber intake, g/day ± standard deviation	5.7 ± 1.4	8.3 ± 0.6	10.4 ± 0.7	13.6 ± 2.7	
All colorectal cancers					
No. of cases	104	87	144	125	
Age-adjusted RR (95% CI)	1.0	0.79 (0.60 to 1.05)	1.16 (0.90 to 1.50)	0.89 (0.68 to 1.15)	.99
Multivariate RR (95% CI)	1.0	0.80 (0.60 to 1.07)	1.20 (0.93 to 1.56)	0.91 (0.69 to 1.20)	.82
Colon cancer					
No. of cases	68	65	84	74	
Age-adjusted RR (95% CI)	1.0	0.90 (0.64 to 1.27)	1.04 (0.75 to 1.43)	0.80 (0.57 to 1.11)	.29
Multivariate RR (95% CI)	1.0	0.93 (0.66 to 1.32)	1.10 (0.79 to 1.52)	0.84 (0.59 to 1.20)	.52
Proximal colon cancer					
No. of cases	28	28	31	31	
Age-adjusted RR (95% CI)	1.0	0.94 (0.56 to 1.59)	0.90 (0.54 to 1.50)	0.76 (0.45 to 1.27)	.28
Multivariate RR (95% CI)	1.0	1.01 (0.59 to 1.72)	0.98 (0.58 to 1.66)	0.77 (0.45 to 1.32)	.34
Distal colon cancer					
No. of cases	22	24	31	24	
Age-adjusted RR (95% CI)	1.0	1.04 (0.59 to 1.86)	1.22 (0.70 to 2.10)	0.84 (0.47 to 1.51)	.68
Multivariate RR (95% CI)	1.0	1.09 (0.61 to 1.95)	1.31 (0.75 to 2.30)	0.86 (0.47 to 1.60)	.81
Rectal cancer					
No. of cases	34	20	54	51	
Age-adjusted RR (95% CI)	1.0	0.56 (0.32 to 0.97)	1.35 (0.88 to 2.07)	1.13 (0.73 to 1.75)	.11
Multivariate RR (95% CI)	1.0	0.54 (0.31 to 0.95)	1.32 (0.85 to 2.05)	1.10 (0.69 to 1.76)	.15

*Includes subjects with cancers of the colon, the rectum, and both. Multivariate models included age (in 5-year age groups), body mass index, educational level (three categories), intake of energy (as a continuous variable), and quartiles of alcohol, red meat, total fat, folic acid, vitamin D, vitamin C, and calcium. RR = relative risk; CI = confidence interval.

†Referent category.

‡All *P* values are from two-sided tests of trend.

Discussion

In this cohort of Swedish women, total fruit and vegetable consumption was inversely associated with colorectal cancer risk. This association was driven mainly by fruit consumption and was strongest for the risk of rectal cancer. In contrast, risk reduction for colon cancer appeared to be relatively small in all quartiles of fruit and vegetable consumption except the lowest. Thus, for total colorectal cancer risk, the inverse association was stronger and the dose–response effect was more evident among individuals who consumed very low amounts of fruit and vegetables.

Four previous cohort studies have examined total fruit and vegetable consumption as an independent risk factor for colon and rectal cancers combined *(11,14)* or for colon cancer alone *(15,17).* In a combined analysis of data from the Nurses' Health Study and the Health Professionals' Follow-up Study *(11),* no association was observed between the risk for these cancers and consumption of fruit or vegetables. The high prevalence of multivitamin use among these health professionals (40%–42% ever-

Table 6. Relative risks of colorectal cancer according to total dietary fiber intake and fruit and vegetable fiber*

Types of fiber	Quartile of energy-adjusted total dietary fiber intake				P_{trend}‡
	1†	2	3	4	
Total dietary fiber					
Median fiber intake, g/day	12.3	15.6	18.1	21.8	
No. of cases of colorectal cancer	101	111	128	120	
Age-adjusted RR (95% CI)	1.0	0.93 (0.71 to 1.22)	0.99 (0.76 to 1.29)	0.90 (0.69 to 1.17)	.54
Multivariate RR (95% CI)	1.0	0.96 (0.73 to 1.28)	1.05 (0.79 to 1.40)	0.96 (0.70 to 1.33)	.98
Fruit fiber					
Median fiber intake, g/day	0.8	2.0	3.1	5.2	
No. of cases of colorectal cancer	133	111	111	105	
Age-adjusted RR (95% CI)	1.0	0.83 (0.65 to 1.07)	0.80 (0.62 to 1.03)	0.76 (0.59 to 0.98)	.04
Multivariate RR (95% CI)	1.0	0.92 (0.70 to 1.20)	0.97 (0.72 to 1.31)	0.97 (0.69 to 1.38)	.93
Vegetable fiber					
Median fiber intake, g/day	0.6	1.0	1.5	2.5	
No. of cases of colorectal cancer	117	97	117	129	
Age-adjusted RR (95% CI)	1.0	0.83 (0.64 to 1.09)	0.95 (0.73 to 1.23)	0.95 (0.74 to 1.22)	.94
Multivariate RR (95% CI)	1.0	0.89 (0.68 to 1.18)	1.08 (0.81 to 1.44)	1.17 (0.85 to 1.61)	.22

*Multivariate models included age (in 5-year age groups), body mass index, educational level (three categories), intake of energy (as a continuous variable), and quartiles of alcohol, red meat, total fat, folic acid, vitamin D, vitamin C, and calcium. RR = relative risk; CI = confidence interval.

†Referent category.

‡All *P* values are from two-sided tests of trend.

use in women and 70% in men compared with only 23% in Swedish women in a representative sample of the adult population in 1989 [Messerer M, Johansson SE, Wolk A: unpublished data]) might have limited the number of individuals who obtained anticarcinogenic substances, such as antioxidant vitamins and folic acid, only from fruit and vegetables. Indeed, among health professionals who consumed one serving of fruit and vegetables or less per day, there was a suggestion that the women had an increased cancer risk compared with the men, probably because the majority of men took multivitamins. Nonsupplement users in this cohort showed no clear association between cancer risk and fruit and vegetable consumption, even among individuals with low consumption. However, the total number of individuals with cancer in that subanalysis was reduced to 207 women and 109 men, which may have limited its statistical power. Other cofactors in the population may also modify the effect of fruit and vegetable consumption, such as the folic acid supplementation of breakfast cereals in the United States, which does not occur in Sweden.

The Iowa Women's Health Study *(15)* also reported no association between diet (with the exception of garlic consumption) and colon cancer risk. However, the risk of colon cancer decreased noticeably above the lowest quartile of fruit consumption (approximately 2 servings/day) without further reduction as fruit consumption increased, a pattern similar to that which we have observed in our cohort of Swedish women. Similar patterns of risk were observed in the Leisure World Study of an elderly cohort in California *(17)* and in The Netherlands Cohort Study on Diet and Cancer *(14):* Women who consumed more fruit and vegetables than defined by the lowest consumption categories (i.e., >5.9 servings/day in the Leisure World cohort and >325 g/day in The Netherlands cohort) had a decreased risk of colorectal cancer. In both cohorts, however, further reduction in risk with increasing fruit and vegetable consumption above the lowest category was minimal.

Three other prospective cohort studies *(12,13,16)* have also examined whether the consumption of fruit and vegetables is associated with colorectal cancer risk, although none directly examined combined fruit and vegetable consumption. An inverse association was observed among those in the American Cancer Society cohort who consumed large amounts of vegetables, citrus fruit, and high-fiber grains *(16).* In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort of male smokers in Finland *(12),* neither fruit nor vegetable consumption showed any association with colorectal cancer risk. In the Adventists' Health Study *(13),* "green vegetables" and "salad" showed nonlinear inverse associations with colorectal cancer risk. As with most previous studies, however, associations in the lower range of consumption of these categories of vegetables were not examined closely.

In light of our findings, it is interesting to note that results of clinical trials of antioxidant supplements conducted in well-nourished populations have not shown reductions in the risk of any cancer *(42–44),* whereas reductions in overall cancer rates were observed in a trial conducted in a nutritionally deficient population *(45).* The former trials *(42–44)* did not, however, stratify their findings on baseline nutritional status. Such an analysis might have shown an inverse association between antioxidants and cancer risk among individuals with low baseline nutritional status.

Dietary fiber intake was not associated with the risk of total colorectal cancer or cancer at any specific site in our cohort. This lack of an association was most notable for cereal fiber consumption, which is considerably higher in our Swedish cohort than it is in the U.S. cohorts *(20).* Cereal fiber is thought to lower the risk of colorectal cancer, either by altering the site of resistant starch fermentation from the proximal to the distal colon *(25)* or by changing the absorption and metabolism of carcinogens in food *(26).* We found that the median intake of cereal fiber in the highest quartile was 13.6 g/day, which is approximately three times greater than that consumed in the highest baseline quintile in the Nurses' Health Study, which found no association between cereal fiber consumption and colon cancer risk *(20).* Even when the Nurses' Health Study reassessed the

diets of its participants with a more comprehensive FFQ *(46),* the median cereal fiber intake in their highest consumption quintile (8.0 g/day) was still considerably lower than the median intake in our highest quintile (14.2 g/day). It is important to note that our cohort differs from the nurses and male health professionals with respect to the composition of the fiber (from cereal, fruit, and vegetables) consumed. The total amount of fiber consumed by our cohort and the nurses and male health professionals was, however, similar in terms of total grams of fiber consumed per day because of the higher intake of fiber from fruit and vegetables by the nurses and health professionals.

We observed no decrease in colorectal cancer risk, even among subjects in the highest decile of cereal fiber consumption, in which the median intake was 16.0 g/day. This amount exceeds the 13.5 g/day of cereal fiber supplementation tested in the recently reported clinical trial of cereal fiber *(31),* which found no reduction in risk compared with 2.0 g/day of cereal fiber supplementation. In addition, our average follow-up time of 9.6 years is considerably longer than the 4-year follow-up of that trial, which examined only recurrent adenomas and, therefore, could not determine the effect of fiber on the progression of adenomas to colorectal cancer *(33).* In total, these results suggest that high consumption of cereal fiber does not affect colorectal cancer risk.

Although we observed an inverse association between colorectal cancer risk and fruit fiber consumption in age-adjusted models, that association disappeared after multivariate adjustment of the data for a wide range of other dietary factors. Although the most recent analysis of dietary fiber in the Nurses' Health Study cohort *(20)* also showed no statistically significant association of colorectal cancer risk and intake of fiber from fruit or vegetables, a report on the health professionals cohort *(47)* did show an inverse association between intake of fruit fiber and risk of adenomas. Our nutrient composition database did not allow us to directly assess the risk of colorectal cancer associated with intake of soluble or insoluble fiber. However, because fiber from fruit and vegetables is largely soluble and cereal fiber is largely insoluble, fiber from these different food sources can be used as crude measures of these two fiber types. Nonetheless, we found no evidence that associations with fiber intake from any source varied as a function of age, body mass index, or various dietary factors.

The strengths of our study include the large sample size and population-based character of our cohort, the diagnosis of colorectal cancer at specific subsites, the completeness of follow-up in the Swedish Cancer Registry system, and the availability of a large number of patients with colorectal cancers. These features allowed us to examine associations within subgroups of our population with reasonable statistical power. In addition, the prospective assessment of diet in our study eliminates the potential for differential recall bias, which is of particular concern because preconceptions about the healthy effects of fruit, vegetables, and whole grains are common among the public. It is also unlikely that undiagnosed early stages of colon or rectal cancer have altered the diets of our participants, because we observed the same associations when we restricted our analyses to individuals whose cancers occurred after the first 3 years of follow-up.

Our study has four potential limitations. First, we could not adjust our RR estimates for the potentially confounding effect of physical activity because that information was not collected at baseline. However, we found that energy intake, which is a rough indicator of physical activity *(48),* was not associated with colorectal cancer risk in our cohort and that our results did not change when we adjusted for the effects of energy intake or body mass index. Because it has been suggested that physical activity is positively correlated with dietary fiber intake *(20),* confounding from physical activity is predicted to drive risk estimates toward an inverse association, which we did not observe. Adjustment for physical activity also did not alter cancer risk estimates associated with fruit and vegetable consumption in the Nurses' Health Study and Health Professionals' Follow-up Study data *(11)* or in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort *(12).*

Second, we did not reassess dietary information during the follow-up period. Instead, we assumed that the relative ranking of subjects with respect to consumption of fruit, vegetables, and dietary fiber was maintained during the follow-up period. The validity of this assumption is supported by Goldbohm et al. *(49),* who observed a high consistency of within-subject dietary patterns related to fruit, vegetables, and grains that has been demonstrated through five successive annual assessments using an FFQ.

Third, we did not adjust our estimates for measurement error. However, the methods for this adjustment may not be appropriate for our study because the two instruments that were used to self-report diet, the 7-day diet records and the FFQ, are likely to generate similar reporting errors *(50).* It is, therefore, doubtful that adjustment for measurement error would improve the validity of our estimates.

Fourth, our 67-item FFQ may not allow an accurate estimation of energy intake. Therefore, the adjustments that we made for total caloric intake may not fully account for between-person variation in energy intake or physical activity; as a result, some residual effects due to these factors (i.e., confounding) may exist. Although we have no reason to suspect that such confounding would bias our findings only in the lower range of fruit and vegetable consumption, this possibility cannot be ruled out, especially since estimates of energy intake and fruit and vegetable consumption may be associated with measurement error that is not very well understood. For example, misclassification of energy intake and physical activity can differ in different categories of self-reported fruit and vegetable consumption, producing bias toward or away from an estimate of no effect in the lower, middle, or upper ranges of fruit and vegetable consumption. Greater misclassification among individuals in the middle and upper ranges of fruit and vegetable consumption compared with those in the lower range of consumption could, to some degree, account for the stronger inverse associations that we observed among individuals in the lower range. However, because nondifferential misclassification can attenuate any association that might exist toward no effect *(41),* we cannot rule out the possibility that the inverse association between fruit and vegetable consumption and risk of colorectal cancers that we observed among individuals with low fruit and vegetable consumption would be even stronger in the absence of such measurement error.

On the basis of our results, we conclude that recommendations to increase fruit and vegetable consumption to decrease colorectal cancer risk may be most beneficial for those individuals who consume less than 2 servings/day of fruit and veg-

etables. However, it is also likely that the frequency of fruit and vegetables consumption that is adequate to decrease cancer risk, taking into account other health consequences, probably varies with individual factors and, perhaps, with other cofactors in the population, such as multivitamin use and whether foods are fortified with folic acid and other micronutrients. Nevertheless, our data suggest that even moderate increases in fruit and vegetable consumption among persons with very low intake may confer benefits to this group.

Our data do not support the hypothesis that high consumption of cereal fiber decreases the risk of colon or rectal cancer, even though we examined a much broader range of cereal fiber intake than had been examined in previous cohort studies. The vast temporal and geographic differences in occurrence of colorectal cancer, however, suggest that some other environmental factors are indeed important.

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NOTE

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