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A PROSPECTIVE STUDY OF FAMILY HISTORY AND THE RISK OF COLORECTAL CANCER

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Abstract *Background.* A family history of colorectal cancer is recognized as a risk factor for the disease. However, as a result of the retrospective design of prior studies, the strength of this association is uncertain, particularly as it is influenced by characteristics of the person at risk and the affected family members.

Methods. We conducted a prospective study of 32,085 men and 87,031 women who had not previously been examined by colonoscopy or sigmoidoscopy and who provided data on first-degree relatives with colorectal cancer, diet, and other risk factors for the disease. During the follow-up period, colorectal cancer was diagnosed in 148 men and 315 women.

Results. The age-adjusted relative risk of colorectal cancer for men and women with affected first-degree relatives, as compared with those without a family history of the disease, was 1.72 (95 percent confidence interval, 1.34 to 2.19). The relative risk among study participants with two or more affected first-degree relatives was 2.75 (95 percent confidence interval, 1.34 to 5.63). For participants under the age of 45 years who had one or more affected first-degree relatives, the relative risk was 5.37 (95 percent confidence interval, 1.98 to 14.6), and the risk decreased with increasing age (P for trend, <0.001).

Conclusions. A family history of colorectal cancer is associated with an increased risk of the disease, especially among younger people. (N Engl J Med 1994;331: 1669-74.)

FAMILIAL clustering of colorectal cancer is generally believed to occur even when the cases are not part of a defined genetic syndrome. At least 12 retrospective studies have suggested that a history of colorectal cancer in a first-degree relative (a parent or sibling) elevates a person's lifetime risk of colorectal cancer 1.8-fold to 8.0-fold.[1-12] However, the strength of the association is uncertain because of the retrospective design of these analyses and their failure to control for other important risk factors.

In aggregate, prior analyses suggest that among people with a family history of colorectal cancer, those who are younger, those whose relatives received the diagnosis at a younger age, and those with two or more affected relatives are at particularly high risk. On the basis of these findings, the American Cancer Society recommends that people with one or more first-degree relatives who received a diagnosis of colorectal cancer at 55 years of age or younger should undergo screening colonoscopy every three to five years beginning at the age of 35 to 40 years.[13] In this analysis, we used data from two large prospective cohort studies to quantify the excess risk of colorectal cancer associated with a family history of the disease and to assess the influence of characteristics of the person at risk and of the affected family members on this excess risk.

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METHODS

Study Cohorts

We analyzed data from two ongoing studies: the Nurses' Health Study and the Health Professionals Follow-up Study. The Nurses' Health Study began in 1976, when 121,700 U.S. women who were registered nurses, 30 to 55 years of age, completed a mailed questionnaire on known or suspected risk factors for cancer[14] and coronary heart disease.[15] In 1980 the questionnaire was expanded to include an assessment of diet. The Health Professionals Follow-up Study began in 1986, when 51,269 U.S. men who were dentists, optometrists, osteopaths, pharmacists, podiatrists, or veterinarians, 40 to 75 years of age, completed a mailed questionnaire on known or suspected risk factors for cancer and coronary heart disease, which also included an assessment of diet.[16] Every two years since these studies began, the participants have been sent follow-up questionnaires to obtain updated information on potential risk factors and recently diagnosed cases of cancer and other diseases.

Exposure Data

The study participants provided information on their smoking history, age, height, weight, physical activity, use of aspirin, and previous examination by colonoscopy or sigmoidoscopy, as well as the indications for the procedure. A question about colorectal cancer in a father, mother, sister, or brother was included in the 1982 questionnaire for the women, and the information was updated in 1988. A question about colorectal cancer in a father or mother was

included in the 1986 questionnaire for the men. In 1990 the information on paternal or maternal colorectal cancer was updated, and a question about colorectal cancer in a sibling was included in the questionnaire for the men. No questions were asked about family size, and no attempt was made to validate reports of cancer in family members.

The 1980 Nurses' Health Study questionnaire and the 1986 Health Professionals Follow-up Study questionnaire included semiquantitative questions about food to assess diet as well as the use of supplemental vitamins. The subjects were asked to report the average frequency of consumption of each listed food or nutrient during the previous year. The reproducibility and validity of these questionnaires have been documented elsewhere.[17-21]

Population for Analysis

We excluded women who left 10 or more questions about food items blank on the 1980 (61 item) food-frequency questionnaire, and we excluded men who left 70 or more questions about food items blank on the 1986 (131 item) food-frequency questionnaire. In addition, women and men with implausibly high or low scores for total food intake were excluded. Both women and men who reported previous cancer (other than nonmelanoma skin cancer), ulcerative colitis, or a familial polyposis syndrome were excluded. Since endoscopic examination and polypectomy can significantly alter the natural history of colorectal cancer,[22,23] we excluded participants with previous colonoscopic or sigmoidoscopic examinations or colorectal adenomas before the study period. In addition, given the relatively high prevalence of endoscopic examinations in the cohort of men, we excluded those who did not answer the questions about endoscopy. Although the women who left the endoscopy questions blank were included in the analysis, the exclusion of this group did not materially alter the relative risk of colorectal cancer associated with a family history of the disease in the cohort of women. These exclusions left 87,031 women and 32,085 men eligible for follow-up.

Identification of Cases of Colorectal Cancer

On each questionnaire we inquired whether colon or rectal cancer had been diagnosed and, if so, the date of the diagnosis. For this analysis, the follow-up rate was 96 and 94 percent of total possible person-years for the Nurses' Health Study and the Health Professionals Follow-up Study, respectively. Most of the deaths in these cohorts were reported by family members or the Postal Service in response to the follow-up questionnaires. In addition, we used the National Death Index, a highly sensitive method of identifying deaths among nonrespondents.[24] All participants who reported colorectal cancer (or the next of kin for decedents) were contacted for permission to review the relevant hospital records and confirm the diagnosis. Pathology reports were obtained for 92 and 89 percent of the cases among the women and men, respectively. Information on the histologic characteristics, stage, and anatomical location of the tumors was extracted from the reports by physicians who were unaware of the data on family history and other risk factors reported by the study participants. Although pathology reports and hospital records could not be obtained for 8 and 11 percent of cases among the women and men, respectively, we based our analysis on the total number of reported colorectal cancers, because the rate of accuracy of self-reporting was high (92 and 95 percent for the cohorts of women and men, respectively). We excluded the small number of cancers that were not adenocarcinomas, as well as carcinomas in situ. Thus, our analysis is based on the 315 cases of invasive colorectal adenocarcinoma among the women and the 148 cases among the men.

Statistical Analysis

For the primary analysis we used incidence rates, with person-years of follow-up as the denominator. For each participant, the person-years of follow-up were counted from the year when the questionnaire that contained the base-line data on family history was returned (1982 in the cohort of women and 1986 in the cohort of men) to May 31, 1990, for the women and January 31, 1992, for the men. For the participants in both cohorts who received a diagnosis of colorectal cancer or who died from another cause, the person-years of follow-up were calculated according to the most recently completed questionnaire, but the period of follow-up terminated with the diagnosis of colorectal cancer or death. If no questionnaire was returned for a follow-up interval, the most recently recorded data were used for the subsequent interval.

We used relative risk as a measure of association, defined as the incidence of colorectal cancer among the study participants with a family history of colorectal cancer, divided by the corresponding rate among the participants who had no family history of the disease. Age-adjusted relative risks were calculated after stratification according to five-year age categories. We used proportional-hazards models to adjust for multiple risk factors simultaneously.[25] We conducted additional stratified analyses to evaluate the influence of characteristics of the study participants and affected family members on the risk associated with a family history of colorectal cancer. Tests for the homogeneity of risk estimates across strata were based on a weighted sum of the squared deviations of the stratum-specific log-odds ratios from their weighted mean.[26]

To obtain stable estimates of the cumulative incidence of colorectal cancer among people with a family history of the disease, we used both estimates of relative risk from our analysis and incidence rates for the general population from the Surveillance, Epidemiology, and End Results (SEER) program. Although the SEER data base does not include family history, we assumed that the prevalence of a family history of colorectal cancer among people with colorectal cancer in the SEER data base was similar to the prevalence of a family history among people with colorectal cancer in our cohorts. In addition, we assumed that the multivariate age-specific relative risks associated with a family history were stable for each five-year age category. Incidence rates within each five-year age category among study participants without a family history were calculated according to the following formula:

$$\text{incidence rate}_{\text{no family history}} = \text{incidence rate}_{\text{SEER}} \div (P_{\text{no family history}} + [P_{\text{family history}} \times \text{relative risk}_{\text{family history}}]),$$

where P denotes prevalence. We calculated incidence rates among people with a family history of colorectal cancer by multiplying the multivariate age-specific relative risk associated with a family history by the incidence rate of colorectal cancer among people in the corresponding five-year age category who had no family history of the disease. In the determination of cumulative incidence rates, the study participants who were alive and free of colorectal cancer at the start of the five-year interval were considered to be at risk for the disease.

The proportion of all cases of colorectal cancer in each cohort that were attributable to a family history of colorectal cancer was calculated as the proportion of cases among those with a family history that were attributable to a family history ([relative risk − 1] ÷ relative risk) multiplied by the prevalence of a family history among the people with colorectal cancer.[26]

Results

A history of colorectal cancer in a first-degree relative was reported by 3007 (9.4 percent) of the 32,085 men in the Health Professionals Follow-up Study and by 8727 (10.0 percent) of the 87,031 women in the Nurses' Health Study who were eligible for analysis. During the study period, colorectal cancer was diagnosed in 148 of the men and 315 of the women. Of these 463 participants with colorectal cancer, 17 percent had previously reported a family history of colorectal cancer. Base-line characteristics of the study participants according to the presence or absence of a family history of colorectal cancer are shown in Table 1. Within each cohort, the patterns of dietary intake, body-mass index, level of physical activity, and smok-

Table 1. Characteristics of the Study Participants According to the Presence or Absence of a Family History of Colorectal Cancer.*

Characteristic	Men (N = 32,085)		Women (N = 87,031)	
	No family history (N = 29,078)	Family history (N = 3007)	No family history (N = 78,304)	Family history (N = 8727)
Age (yr)	51.3	53.7	48.9	51.3
Body-mass index†	25.5	25.5	23.7	23.7
Total energy intake (kcal/day)	1967	1981	1638	1660
Alcohol intake (g/day)	12.4	12.1	6.9	7.0
Dietary intake				
Folate (μg/day)‡	457	463	364	365
Methionine (g/day)	2.1	2.1	1.9	1.9
Animal fat (g/day)	39.9	39.1	52.4	52.0
Dietary fiber (g/day)	21.9	22.5	16.8	16.9
Red meat (g/day)	75.5	75.3	209	210
Calcium (mg/day)‡	939	939	731	731
Vitamin D (IU/day)‡	392	393	290	291
Regular aspirin use (% of participants)§	28.3	25.6	23.5	25.4
Screening endoscopy (% of participants)	20.2	34.1	4.5	12.8
Physical activity (met/day)¶	19.7	19.7	24.8	25.0
History of smoking (% of participants)	48.0	47.5	56.2	55.3

*Values for men and women are means directly standardized according to the age distribution of the respective cohort in its entirety. Dietary values represent the mean energy-adjusted intake for men and women.

†The weight in kilograms divided by the square of the height in meters.

‡Includes the use of supplements.

§Two or more days per week.

¶Measured in metabolic equivalents (met).

ing history were similar in the groups of participants with and without a family history. In both cohorts, participants with a family history of colorectal cancer underwent screening endoscopy during the study period more frequently than those without a family history.

Participants in the Health Professionals Follow-up Study and the Nurses' Health Study who reported a history of colorectal cancer in one or more first-degree relatives had similarly increased risks of colorectal cancer. For men with a family history, the age-adjusted relative risk was 1.64 (95 percent confidence interval, 1.04 to 2.58), and for women with a family history, the age-adjusted relative risk was 1.77 (95 percent confidence interval, 1.32 to 2.37) (Table 2). Furthermore, the relative risk associated with a family history of colorectal cancer was not materially altered by multivariate adjustment for known or suspected environmental risk factors for the disease.

In both cohorts, the relative risk of colorectal cancer associated with a family history of the disease was higher for the younger participants (Table 3). Among the women, for whom there were substantially more person-years of follow-up, the relative risk associated with a family history was highest for those younger than 50 years of age, and the risk decreased progressively for older women. This trend in the association between relative risk and age among the women was significant (P = 0.005). When the cohorts of men and women were combined, the results were similar. For participants younger than 45 years of age, the relative risk of colorectal cancer was 5.37 (95 percent confidence interval, 1.98 to 14.6), and the risk decreased monotonically for older people. For participants 65 years of age or older, the relative risk associated with a family history approached 1. These results remained essentially unchanged after other risk factors for colorectal cancer had been controlled for. For men and women combined, the linear trend of a decreasing relative risk in association with increasing age was significant (P<0.001).

Our estimates of age-specific relative risk and incidence rates from the SEER program were used to estimate the cumulative incidence of colorectal cancer among people with a family history of the disease and those without a family history (Fig. 1). Partly on the basis of data on the age-specific cumulative incidence of colorectal cancer, the National Cancer Institute, American Cancer Society, American College of Physicians, American Gastroenterological Association, and World Health Organization all recommend screening sigmoidoscopy beginning at the age of 50 years for Americans with an average risk of the disease.[13] For people with a family history of colorectal cancer, we found a similar cumulative incidence of the disease at approximately 35 to 40 years of age.

We also examined the association between the risk of colorectal cancer and the type and number of affected first-degree relatives. The type of affected rela-

Table 2. Risk of Colorectal Cancer among Study Participants According to the Presence or Absence of a Family History of the Disease.*

Participants	No. of Cases	Person-Years of Follow-up	Age-Adjusted RR (95% CI)	Multivariate RR (95% CI)
Men				
No family history	127	161,716	1.0	1.0
Family history	21	14,377	1.64 (1.04–2.58)	1.60 (1.01–2.55)
Women				
No family history	263	607,577	1.0	1.0
Family history	52	56,359	1.77 (1.32–2.37)	1.76 (1.31–2.38)
Total				
No family history	390	769,293	1.0	1.0
Family history	73	70,736	1.72 (1.34–2.19)	1.72 (1.33–2.20)

*The multivariate relative risks (RR) and 95 percent confidence intervals (CI) are adjusted for age in five-year increments, screening endoscopy, smoking history (no history or <10, 10 to 19, 20 to 29, 30 to 39, or ≥40 pack-years), alcohol consumption (abstinence, history of greatly reduced consumption, or <15, 15 to 30, or >30 g per day), regular aspirin use (two or more days per week), body-mass index (in quintiles), physical activity (in quintiles), total energy intake (in quintiles), and the following energy-adjusted nutrients (in quintiles): folate, dietary fiber, methionine, red meat, animal fat, vitamin D, and calcium. For the analysis of men and women combined, the multivariate relative risks and 95 percent confidence intervals are adjusted for sex as well as for all the covariates listed above.

tive (mother, father, or sibling) did not have a significant influence on the relative risk (P = 0.75 for the test of the homogeneity of odds ratios).

Among the men who reported two or more affected first-degree relatives, there were no cases of colorectal cancer (Table 4). This finding may reflect the small number of men who had two or more affected relatives and had not undergone screening endoscopy before the start of the study (543 person-years of follow-up for a total of 176,093 person-years for the entire cohort). Among the women with two or more affected first-degree relatives, the age-adjusted relative risk of colorectal cancer was 3.79 (95 percent confidence interval, 1.88 to 7.62); the linear trend toward an increase in relative risk with the increasing number of affected relatives was significant (P<0.001). Even when the cohorts of men and women were combined, the relative risk for people with two or more affected relatives was 2.75 (95 percent confidence interval, 1.34 to 5.63; P for trend, <0.001).

In both cohorts, a family history of colorectal cancer was associated with an excess risk of colon cancer but not of rectal cancer (Table 5). Among men and women combined, the age-adjusted relative risk of colon cancer was 1.99 (95 percent confidence interval, 1.51 to 2.61) and the age-adjusted relative risk of rectal cancer was 0.86 (95 percent confidence interval, 0.44 to 1.70). Adjustment for various known or suspected environmental risk factors for colorectal cancer did not materially change these results, and the risk estimates for colon and rectal cancer differed significantly (P = 0.02). The site of disease within the colon had no significant association with the relative risk.

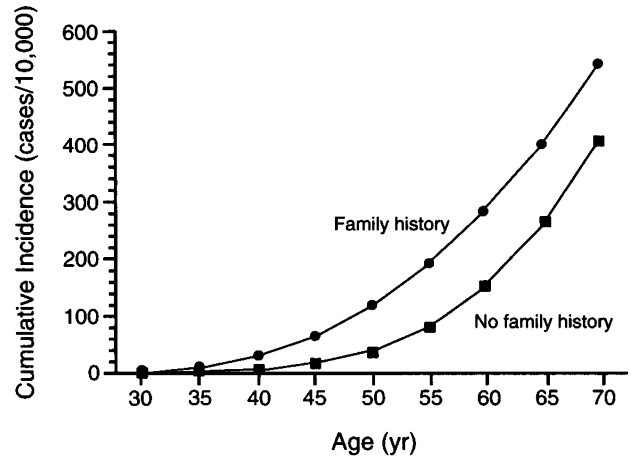

Figure 1. Cumulative Incidence of Colorectal Cancer According to Age and the Presence or Absence of a Family History of the Disease.

We investigated the possibility that the excess risk associated with a family history of colorectal cancer was the result of a detection bias caused by closer surveillance of people with a family history of the disease. When we excluded from the analysis men and women whose cancers may have been detected incidentally or only by screening (Dukes' stages A and B), the multivariate relative risk of colorectal cancer associated with a family history did not decrease (relative risk, 2.00; 95 percent confidence interval, 1.32 to 3.03). Moreover, when we restricted our analysis to fatal colorectal cancers among the study participants, the relative risk was 1.72 (95 percent confidence interval, 1.03 to 2.89).

Table 3. Age-Specific Relative Risk of Colorectal Cancer among Study Participants with a Family History of Colorectal Cancer.*

Participants	No. of Cases	Person-Years of Follow-up	Age-Adjusted RR (95% CI)	Multivariate RR (95% CI)
Men				
No family history	127	161,716	1.0	1.0
Family history				
40–49 yr	2	4,370	3.35 (0.79–14.2)	2.02 (0.36–11.4)
50–59 yr	8	4,692	3.98 (1.87–8.47)	3.58 (1.56–8.20)
60–69 yr	8	3,980	1.11 (0.51–2.42)	1.12 (0.51–2.64)
≥70 yr	3	1,335	1.08 (0.38–3.03)	1.00 (0.35–2.80)
Women				
No family history	263	607,577	1.0	1.0
Family history				
30–44 yr	4	9,496	4.34 (1.37–13.8)	4.66 (1.24–17.4)
45–49 yr	7	10,126	4.48 (2.15–9.34)	4.15 (1.83–9.44)
50–54 yr	11	11,899	2.22 (1.14–4.32)	2.22 (1.12–4.41)
55–59 yr	14	13,699	1.40 (0.78–2.51)	1.44 (0.80–2.60)
≥60 yr	16	11,139	1.35 (0.82–2.22)	1.29 (0.78–2.15)
Total				
No family history	390	769,293	1.0	1.0
Family history				
30–44 yr	5	11,356	5.37 (1.98–17.4)	4.63 (1.43–15.0)
45–49 yr	8	12,636	3.85 (1.93–7.68)	3.47 (1.62–7.44)
50–54 yr	15	14,208	2.54 (1.45–4.46)	2.53 (1.41–4.54)
55–59 yr	18	16,082	1.66 (1.00–2.78)	1.69 (1.01–2.85)
60–64 yr	17	11,433	1.35 (0.81–2.25)	1.35 (0.81–2.26)
65–69 yr	6	3,686	1.09 (0.52–2.28)	1.15 (0.55–2.42)
≥70 yr	4	1,335	1.00 (0.36–2.79)	0.91 (0.32–2.62)

*The multivariate relative risks (RR) and 95 percent confidence intervals (CI) are adjusted as described in Table 2. Tests for trends were performed with age used as a continuous variable in the multivariate model. P = 0.10 (χ = −1.64) for the men, P = 0.005 (χ = −2.81) for the women, and P<0.001 (χ = −3.33) for the men and women combined.

Discussion

This prospective analysis found a consistent increase in the risk of colorectal cancer among men and women with a family history of the disease. The increase in risk, which was about 1.7-fold, was virtually identical in cohorts from two independently conducted studies, and the risk increased significantly if there was a history of two or more affected relatives. The effect of family history was greatest for people who were 44 years of age or younger; a family history of the disease was not associated with a significant elevation in risk among people 60 years or older, although we

Table 4. Relative Risk of Colorectal Cancer According to the Number of Affected Relatives.*

No. of Affected Relatives	No. of Cases	Person-Years of Follow-up	Age-Adjusted RR (95% CI)	Multivariate RR (95% CI)
Men				
1	21	13,834	1.72 (1.09–2.71)	1.68 (1.06–2.69)
≥2	0	543	0	0
Women				
1	45	53,534	1.63 (1.20–2.23)	1.63 (1.18–2.24)
≥2	7	2,825	3.79 (1.88–7.62)	3.93 (1.84–8.38)†
Total				
1	66	67,368	1.65 (1.28–2.13)	1.64 (1.26–2.14)
≥2	7	3,368	2.75 (1.34–5.63)	2.83 (1.33–6.02)†

*The multivariate relative risks (RR) and 95 percent confidence intervals (CI) are adjusted as described in Table 2.

†$P<0.001$ for a trend according to the number of affected relatives (0, 1, or 2 or more).

had limited power to determine risk estimates for people over the age of 75. Within the combined cohorts, 7 percent of all cases of colorectal cancer were attributable to a family history in a first-degree relative, and 23 percent of colorectal cancers diagnosed in cohort members under the age of 45 years were attributable to a family history of the disease.

The prospective nature of this study substantially reduces the possibility of a recall bias, a potential source of distortion that is inherent in retrospective studies of family history and the risk of cancer. Data on family history were obtained only from the study participants; we did not ask relatives to verify these reports, and we did not determine family size. Since the participants were all health care professionals, the accuracy of the reports is likely to be high. Moreover, because the data on family history were collected before the diagnosis of any cases of colorectal cancer, any errors in recall would have attenuated rather than exaggerated a true association. Familial clusters that may have occurred simply because of large families would also have attenuated our results.

Other forms of bias are unlikely to explain the observed relations. To minimize the possibility of a selection bias, we excluded people who had undergone either polypectomy or endoscopy before the start of our analysis. Such people were more likely to report a family history of colorectal cancer (14.5 percent), and those with a family history had a markedly attenuated excess risk of disease, which is consistent with the presumed effect of endoscopy on the natural history of colorectal neoplasia (data not shown).

Differential follow-up is unlikely to have had a material influence, since follow-up was nearly complete for both fatal and nonfatal end points. A detection bias also appears unlikely, since the association between relative risk and family history persisted when the analysis was restricted to either advanced or fatal cases of colorectal cancer. Finally, since new cases of cancer may develop in relatives during follow-up in a prospective study, we used updated information on family history to minimize misclassification.

Previous studies that have addressed the relation between family history and the risk of colorectal cancer used retrospective data. The relative risk associated with a family history of the disease has varied considerably, although estimates in the three largest case–control studies ranged from 1.8 to 2.1.[4,9,10] In these three studies, investigators reported an increased risk of colorectal cancer among people with two or more affected relatives[4,10] and an increased risk among people with a family history who were younger than 50 years of age,[4,9] findings consistent with ours. In support of other recent observations, our analysis refutes the tenet that the familial predisposition to colon cancer is associated predominantly with tumors that have a proximal site of origin.[4,9,10,27] Although we observed an increased risk of colon cancer but not of rectal cancer, we were unable to detect a difference in risk according to the specific site of the tumor within the colon.

Previous analyses have been unable to distinguish between genetic and common environmental contributions to familial clustering of colorectal cancer. However, kindred studies suggest that familial clustering of common (i.e., apparently sporadic) colorectal cancer probably occurs as a result of a partially penetrant inherited susceptibility.[28] In the present analysis, the excess risk associated with a family history did not change materially after adjustment for other known or suspected risk factors for colorectal cancer, which is consistent with the existence of an important genetic contribution.

In conclusion, for the majority of people with a family history of colorectal cancer, particularly those who are 60 years or older, the excess risk of colorectal cancer is not large. Nevertheless, the increased risk among younger people with a family history supports the recommendation of the American Cancer Society that people with a family history of colorectal cancer undergo earlier screening.

Table 5. Risk of Colorectal Cancer among Study Participants According to the Specific Site of the Disease.*

Participants	No. of Cases	Age-Adjusted RR (95% CI)	Multivariate RR (95% CI)
Men			
Rectum	32	0.67 (0.16–2.77)	0.65 (0.15–2.72)
Colon	99	1.90 (1.12–3.21)	1.89 (1.10–3.24)
Proximal	39	2.14 (1.97–4.74)	1.94 (0.85–4.44)
Distal	57	1.84 (0.92–3.71)	1.99 (0.97–4.10)
Women			
Rectum	72	0.96 (0.44–2.07)	0.98 (0.44–2.14)
Colon	238	2.03 (1.48–2.79)	2.01 (1.44–2.80)
Proximal	110	1.37 (0.80–2.36)	1.34 (0.77–2.32)
Distal	128	2.69 (1.81–3.99)	2.72 (1.79–4.14)
Total			
Rectum	104	0.86 (0.44–1.70)	0.86 (0.43–1.70)†
Colon	337	1.99 (1.51–2.61)	1.99 (1.50–2.63)
Proximal	149	1.56 (1.00–2.44)	1.54 (0.98–2.43)
Distal	185	2.40 (1.71–3.39)	2.42 (1.69–3.46)

*The multivariate relative risks (RR) and 95 percent confidence intervals (CI) are adjusted as described in Table 2. In some cases, the specific site of the cancer was unknown. For three of the men with colon cancer, the specific site was not recorded. Proximal colon denotes the segment from the cecum to the splenic flexure, and distal colon the segment from the splenic flexure to the rectosigmoid junction.

†$P = 0.02$ for the comparison with the multivariate risk ratio for colon cancer.

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