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Fruits, Vegetables, and Colon Cancer Risk in a Pooled Analysis of 14 Cohort Studies

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Background Fruit and vegetable intakes have been associated with a reduced risk of colon cancer; however, in more recent studies associations have been less consistent. Statistical power to examine associations by colon site has been limited in previous studies.

Methods Fruit and vegetable intakes in relation to colon cancer risk were examined in the Pooling Project of Prospective Studies of Diet and Cancer. Relative risks (RRs) and 95% confidence intervals (CIs) were estimated separately in 14 studies using Cox proportional hazards model and then pooled using a random-effects model. Intakes of total fruits and vegetables, total fruits, and total vegetables were categorized according to quintiles and absolute cutpoints. Analyses were conducted for colon cancer overall and for proximal and distal colon cancer separately. All statistical tests were two-sided.

Results Among 756 217 men and women followed for up to 6 to 20 years, depending on the study, 5838 were diagnosed with colon cancer. The pooled multivariable RRs (95% CIs) of colon cancer for the highest versus lowest quintiles of intake were 0.91 (0.82 to 1.01, P_{trend} = .19) for total fruits and vegetables, 0.93 (0.85 to 1.02, P_{trend} = .28) for total fruits, and 0.94 (0.86 to 1.02, P_{trend} = .17) for total vegetables. Similar results were observed when intakes were categorized by identical absolute cut points across studies (pooled multivariable RR = 0.90, 95% CI = 0.77 to 1.05 for 800 or more versus <200 g/day of total fruits and vegetables, P_{trend} = .06). The age-standardized incidence rates of colon cancer for these two intake categories were 54 and 61 per 100 000 person-years, respectively. When analyzed by colon site, the pooled multivariable RRs (95% CIs) comparing total fruit and vegetable intakes of 800 or more versus less than 200 g/day were 0.74 (0.57 to 0.95, P_{trend} = .02) for distal colon cancers and 1.02 (0.82 to 1.27, P_{trend} = .57) for proximal colon cancers. Similar site-specific associations were observed for total fruits and total vegetables.

Conclusion Fruit and vegetable intakes were not strongly associated with colon cancer risk overall but may be associated with a lower risk of distal colon cancer.

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CONTEXT AND CAVEATS

Prior knowledge

Fruit and vegetable intakes have been associated with a reduced risk of colon cancer; however, in more recent studies, associations have been less consistent.

Study design

Pooled analysis of 14 prospective studies.

Contribution

Increasing fruit and vegetable intakes were not associated with colon cancer risk overall, although the lowest intakes were associated with an elevation in risk. When examined by colon site, the inverse association for fruits and vegetables was limited to cancers of the distal colon, although the risk estimates for distal and proximal colon cancer were not statistically significantly different. Results for each fruit and vegetable group were generally consistent between men and women.

Implications

Diets plentiful in fruits and vegetables remain important given these findings and the benefits that have been observed for other health outcomes.

Limitations

The study was survey based, and there may have been inaccuracies in reported fruit and vegetable intake. Further, only data on diet at the beginning of each study were available for each study so it was not possible to evaluate associations between fruit and vegetable intakes during childhood, adolescence, or early adulthood and colon cancer risk.

The risk of colon cancer in relation to fruit and vegetable consumption has been reported in more than 50 epidemiologic studies (1). In 1997, an international panel reviewed 21 case–control and four cohort studies and concluded that there was convincing evidence that vegetable consumption reduces the risk of colon and rectal cancers (2). The panel also stated that the data available for fruit consumption were limited and inconsistent. In a subsequent evaluation of 27 case–control and 13 cohort studies published through early 2003, a different panel concluded that higher vegetable intake probably reduces the risk of colorectal cancer and that higher fruit intake possibly reduces risk (3). The conclusion for vegetables was more conservative in the latter evaluation because the reported associations for vegetable consumption and colorectal cancer risk were weaker in the cohort studies than in the case–control studies, suggesting that the inverse associations in the case–control studies may have resulted from recall and/or selection biases. Similarly, a meta-analysis published in 2003 (4) reported modest inverse associations between both fruit and vegetable intakes and colorectal cancer in case–control and cohort studies combined; however, the relative risks were essentially null when restricted to the cohort studies. Heterogeneity between the results from the cohort studies was observed for fruit intake, which may have been due to the observed differences in associations between men and women (4). Also, associations for vegetable intake differed according to cancer site (colon or rectal), although there was no statistically significant heterogeneity between studies for vegetable intakes in this meta-analysis. Inconsistencies in previous studies may also reflect differences in the specific fruits and vegetables consumed or differences in the prevalence of colon cancer risk factors that may modify associations of diet and cancer. Because analyses of specific food items and of modification of associations by other factors are not routinely reported, meta-analyses of the published literature are unable to analyze these potential sources of heterogeneity. Recent evidence also indicates that proximal and distal colon cancers may have distinct etiologies (5–7). Previous cohort studies may have been insufficiently powered to examine associations according to colon site.

To better understand fruit and vegetable consumption in relation to colon cancer risk, we analyzed intakes of total and specific fruits and vegetables in a pooled analysis of 14 North American and European prospective cohort studies (8–20). All but three of these studies (11,16,18) have previously published results on fruit and vegetable intake and colorectal cancer risk. In our analysis, we have included an extended follow-up period for most of the studies. Because colon and rectal cancers may have different etiologies (21,22), we restricted our analysis to colon cancer. Using the primary data from each study, we standardized definitions of fruit and vegetable intakes and covariate categories across studies and analyzed the risks of colon cancer overall and of proximal and distal colon cancer separately. We also examined whether associations were modified by colon cancer risk factors.

Methods

Study Population

The Pooling Project of Prospective Studies of Diet and Cancer (Pooling Project) is an international consortium of cohort studies and has been described previously (23). Each of the 14 studies included in these analyses met the following predefined criteria: publication of a diet and cancer association, diagnosis of at least 50 incident colorectal cancer cases, assessment of usual diet, and conduct of a validation study of the dietary assessment method or a closely related instrument. The exclusion criteria used by each study were first applied to the data from that study, after which we excluded participants with a prior cancer diagnosis (except nonmelanoma skin cancer) at baseline or who reported energy intakes beyond three standard deviations from the study-specific $\log_e$-transformed mean energy intake. Studies that enrolled both men and women were separated into sex-specific cohorts. Each of the studies included was reviewed and approved by the institutional review board of the institution at which the study was conducted.

Colon Cancer Ascertainment

Incident colon cancer case were identified by self-report with subsequent medical record review, linkage with a cancer registry, or both (23). Mortality registries served as an additional source of incident cases in some studies. Estimated ascertainment of cancer diagnoses was high in each study and exceeded 90% in most studies. (23). Only colon cancers (International Classification of Diseases, Ninth Revision [ICD-9] codes 153.0–153.4, 153.6–153.9) were analyzed for the present report. Proximal colon cancers included tumors from the cecum to the splenic flexure (ICD-9 codes 153.0, 153.1, 153.4, 153.6, 153.7); distal colon cancers included tumors in the descending (153.2) and sigmoid (153.3) colon.

Dietary Assessment

A self-administered food-frequency questionnaire was used at baseline in each of the 14 studies to assess usual consumption of specific food items (23). In most studies, the time frame for the diet assessment was the past year (23). Food intake data were converted to units of grams per day. We examined three main food groups: total fruits and vegetables (fruits, vegetables, and juices), total fruits (fruits and fruit juices), and total vegetables (vegetables and vegetable juices). Food group intakes were calculated by summing the intakes of specific foods included in that group. Potatoes and mature beans were not classified as vegetables because of their high starch and protein content (24), respectively, compared with other vegetables. The validity of total fruit and total vegetable intake estimates was evaluated only in the Netherlands Cohort Study (Spearman correlation coefficient = .60 for total fruits and 0.38 for total vegetables) (25), the Cancer Prevention Study II Nutrition Cohort (Pearson correlation coefficient = .62 for total fruits and 0.52 for total vegetables) (26), and the Health Professionals Follow-up Study (deattenuated Pearson correlation coefficient = .71 for total fruits and 0.19 for total vegetables) (27). Therefore, we were unable to correct our analyses for measurement error in dietary assessment.

We also examined fruits and vegetables grouped according to botanical taxonomy to evaluate potentially rich sources of particular bioactive compounds. The botanical classifications analyzed were Compositae, Cruciferae, Cucurbitaceae, Leguminosae, Rosaceae, Rutaceae, Solanaceae, and Umbelliferae (28). Also, green leafy vegetables (e.g. lettuce, spinach) and individual fruits and vegetables for which intake was assessed in at least half of the studies were examined. The individual foods analyzed were apples, pears, apple sauce, bananas, cantaloupe, grapefruit, oranges, peaches, fruit juices, broccoli, brussels sprouts, cabbage, carrots, lettuce, peas, lima beans, string beans, spinach, tomatoes, yams, mature beans, and potatoes.

Statistical Analysis

All statistical analyses were conducted using the Statistical Analysis System (SAS) software (Cary, NC). We used a two-stage method to estimate pooled relative risks (RRs). First, study- and sex-specific RRs and 95% confidence intervals (CIs) were estimated with the Cox proportional hazards model (29) using SAS PROC PHREG (30). Person-years of follow-up were calculated from the date of the baseline questionnaire until the date of colorectal cancer diagnosis, death, or end of follow-up. The cases occurring and person-time experienced during follow-up in the Nurses' Health Study were considered to be two different cohorts (1980–1986, Nurses' Health Study [a]; 1986–2000, Nurses' Health Study [b]) so that the more detailed dietary assessment conducted in 1986 could be utilized. According to the underlying theory of survival analysis, blocks of person-time in different time periods are asymptotically uncorrelated, regardless of the extent to which they are derived from the same people (31). The Canadian National Breast Screening Study and Netherlands Cohort Study were analyzed as case–cohort studies (32). To adjust for age and calendar time, analyses were stratified on age at baseline (in years) and the year the baseline questionnaire was returned. We also conducted multivariable analyses adjusted for other colon cancer risk factors including body mass index, height, education, physical activity, family history of colorectal cancer, postmenopausal hormone use, oral contraceptive use, use of nonsteroidal anti-inflammatory drugs, multivitamin use, smoking habits, red meat intake, total milk intake, alcohol, and total energy (see fourth footnote to Table 2 for categories). In additional multivariable analyses, we simultaneously adjusted total fruits for total vegetables and adjusted for quintiles of intakes of dietary fiber, dietary folate, and vitamin C.

After estimating the study-specific relative risks, pooled relative risks were calculated by combining the study-specific $\log_e$ relative risks, weighted by the inverse of their variance, using a random-effects model (33). The presence of heterogeneity between studies was tested for using the Q statistic, which follows an approximate chi-square distribution (33,34). To verify the assumption of proportional hazards, we fitted models that included an interaction term between age and fruit and vegetable intake. The study-specific parameter estimates for the interaction terms were pooled using the random-effects model, and we tested the statistical significance of the pooled interaction term. We observed no evidence of violation of the proportional hazards assumption. All statistical tests were two-sided, and a P value of .05 was considered to be statistically significant.

Fruit and vegetable intakes were categorized according to study-specific quantiles and by identical absolute cut points across studies. Study-specific quantiles were chosen to maximize the contrast between the highest and lowest levels of intake and to ensure a sufficient number of participants in each category. The categories based on absolute cut points represented multiples of fruit/vegetable servings, about 100 g per serving on average (24), and were chosen to ensure that the referent category within each study was not so small as to lead to unstable relative risk estimates. To calculate the P value for the test for trend across categories of intake, participants were assigned the median value of their category, and this variable was entered as a continuous term in the regression model, the coefficient for which was evaluated by the Wald test.

To assess the presence of heterogeneity by sex, age at diagnosis, and follow-up period and to evaluate whether associations were modified by colon cancer risk factors, including smoking (never, past, current), alcohol consumption (non-drinker, <1 drink/day, ≥1 drink/day), body mass index (<25 kg/m^2, ≥25 kg/m^2), red meat intake (tertiles) and postmenopausal hormone use among women (never, past, current), we used a mixed-effects meta-regression model (35). A two-sided Wald test statistic was used to test the null hypothesis that there was no modification of the fruit/vegetable–colon cancer association by levels of the potential effect modifiers. To test for differences in associations by colon site (proximal versus distal), we used the contrast test, testing the null hypothesis that there was no difference in the pooled estimates across colon sites. This test statistic has an approximate chi-square distribution.

Results

Among 242 362 men and 513 855 women, a total of 5838 developed colon cancer (1890 men, 3948 women) during a maximum follow-up that ranged from 6 to 20 years across the 14 studies (Table 1). Of the 5838 colon cancers, 3063 occurred in the proximal colon and 2313 occurred in the distal colon (colon site information was missing for 462 subjects). Total fruit and vegetable intake was lowest in

Table 1. Characteristics of the cohort studies included in the pooled analysis of fruit and vegetable intake and risk of colon cancer

Study	Follow-up years	Baseline cohort size*	No. of colon cancer diagnoses†	Baseline age range, y	Total fruits		Total vegetables	
					No. of questions	Median intake (10%–90%), g/day	No. of questions	Median intake (10%–90%), g/day
Men								
Adventist Health Study	1976–1982	12896	52	25–90	7	310 (104–604)	6	151 (63–251)
Alpha-Tocopherol Beta-Carotene Cancer Prevention Study	1984–1999	26987	187	50–69	26	122 (28–299)	38	94 (36–197)
Cancer Prevention Study II Nutrition Cohort	1992–1999	66071	467	50–74	7	182 (44–394)	10	177 (76–351)
Health Professionals Follow-up Study	1986–2000	47766	456	40–75	15	300 (97–621)	28	293 (141–550)
Netherlands Cohort Study	1986–1993	58279	393	55–69	12	153 (45–331)	25	156 (83–276)
New York State Cohort	1980–1987	30363	335	50–93	8	258 (69–492)	23	185 (75–340)
Women								
Adventist Health Study	1976–1982	18403	67	25–90	7	355 (133–654)	6	162 (74–269)
Breast Cancer Detection Demonstration Project Follow-up Study	1987–1999	41987	349	40–93	5	173 (33–389)	10	135 (51–288)
Canadian National Breast Screening Study	1980–2000	49613	431	40–59	6	314 (110–577)	15	221 (101–438)
Cancer Prevention Study II Nutrition Cohort	1992–1999	74046	349	50–74	7	195 (52–396)	10	147 (61–302)
Iowa Women's Health Study	1986–2001	34588	799	55–69	15	338 (130–625)	31	195 (91–383)
Netherlands Cohort Study	1986–1993	62573	353	55–69	12	206 (82–388)	25	164 (88–293)
New York State Cohort	1980–1987	22550	223	50–93	8	289 (86–539)	23	188 (72–364)
New York University Women's Health Study	1985–1998	13258	96	34–65	11	290 (94–595)	17	200 (75–424)
Nurses' Health Study (a)	1980–1986	88651	162	34–59	6	272 (73–560)	13	150 (68–292)
Nurses' Health Study (b)	1986–2000	68502‡	429	40–65	21	329 (115–643)	33	259 (129–470)
Prospective Study on Hormones, Diet and Breast Cancer	1987–2001	9027	43	34–70	6	330 (174–541)	23	190 (94–348)
Swedish Mammography Cohort	1987–2003	60775	484	40–74	4	166 (46–373)	5	77 (29–158)
Women's Health Study	1993–2003	38384	163	45–89	15	266 (86–539)	28	236 (111–452)

* Cohort sizes after applying study-specific exclusion criteria and then excluding participants with $\log_e$-transformed energy intake values beyond three standard deviations from the study-specific mean and previous cancer diagnoses (other than nonmelanoma skin cancer); the Canadian National Breast Screening Study and the Netherlands Cohort Study are analyzed as case–cohort studies so their baseline cohort sizes do not reflect the above exclusions; total cohort size = 756217.

† Total number of participants who developed colon cancer was 5838.

‡ Nurses' Health Study (b) is not included in the total cohort size because they are included in Nurses' Health Study (a).

the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (median = 226 g/day) and highest in Health Professionals Follow-up Study (median = 611 g/day).

In models that were adjusted for age, colon cancer risk was lower by 8%–13% for the highest versus the lowest quintile of total fruit and vegetable, total fruit, and total vegetable intakes for men and women combined (Table 2). In the corresponding multivariable analyses, relative risks were attenuated and no longer statistically significant. The pooled multivariable RRs (95% CIs) for the highest compared with the lowest quintiles were 0.91 (0.82 to 1.01) for total fruits and vegetables, 0.93 (0.85 to 1.02) for total fruits, and 0.94 (0.86 to 1.02) for total vegetables. For these comparisons, a statistically significant lower risk of colon cancer was observed for total fruits and vegetables only in the Netherlands Cohort Study women and the Nurses' Health Study (b) (Fig. 1) and for total fruits in the Nurses' Health Study (b) (data not shown). However, there was no statistically significant heterogeneity between studies for any food group (Table 2). The magnitude of the pooled multivariable relative risks for quintile 5 was similar across the three food groups. Also, for each food group, the pooled multivariable relative risks for quintiles 2 through 5 did not differ greatly.

The results for total fruits not including fruit juices (results not shown) were similar to the results for total fruits. Relative risks for total fruits and total vegetables did not change greatly when both were included simultaneously in the same model (results not shown). Further adjustment for dietary fiber, dietary folate, or total vitamin C intake did not appreciably change the relative risks for any of the three food groups (results not shown).

The pooled relative risks for the European studies were similar to those for the North American studies (results not shown). In addition, the pooled relative risks were not modified by sex (Table 2) or age at diagnosis. For men and women diagnosed before the age of 65 years (n = 2056 cases), the pooled multivariable RRs (95% CIs) comparing the highest with the lowest quintile of intake were 0.90 (0.77 to 1.05) for total fruits and vegetables, 0.92 (0.79 to 1.07) for total fruits and 0.93 (0.80 to 1.09) for total vegetables, whereas for men and women diagnosed at the age of 65 years or

Table 2. Pooled relative risks (95% confidence intervals) of colon cancer for quintiles of fruit and vegetable intake

	Quintile of intake (g/day)					*P* value, test for trend*	*P* value, test for between-studies heterogeneity, quintile 5†	*P* value, test for between-studies heterogeneity due to sex,* quintile 5
	1	2	3	4	5			
Total fruits and vegetables‡								
Number of cases								
Women	822	765	767	821	769			
Men	363	374	394	372	387			
Age-adjusted								
Total	1.00	0.92 (0.85 to 1.00)	0.91 (0.84 to 0.99)	0.92 (0.83 to 1.01)	0.88 (0.79 to 0.96)	.04	.20	.35
Women	1.00	0.90 (0.81 to 0.99)	0.87 (0.79 to 0.96)	0.92 (0.82 to 1.02)	0.85 (0.74 to 0.98)	.12	.07	
Men	1.00	0.98 (0.84 to 1.13)	1.00 (0.86 to 1.16)	0.93 (0.75 to 1.17)	0.93 (0.80 to 1.08)	.15	.88	
Multivariable§								
Total	1.00	0.94 (0.86 to 1.02)	0.93 (0.85 to 1.02)	0.94 (0.86 to 1.03)	0.91 (0.82 to 1.01)	.19	.31	.44
Women	1.00	0.91 (0.83 to 1.01)	0.89 (0.80 to 0.99)	0.95 (0.84 to 1.06)	0.88 (0.76 to 1.02)	.28	.09	
Men	1.00	0.99 (0.85 to 1.15)	1.03 (0.88 to 1.20)	0.93 (0.79 to 1.08)	0.97 (0.82 to 1.14)	.52	.97	
Total fruits								
Number of cases								
Women	862	703	800	760	820			
Men	359	376	385	382	388			
Age-adjusted								
Total	1.00	0.83 (0.76 to 0.90)	0.89 (0.82 to 0.97)	0.83 (0.76 to 0.90)	0.87 (0.80 to 0.95)	.01	.30	.32
Women	1.00	0.77 (0.70 to 0.85)	0.86 (0.78 to 0.95)	0.79 (0.71 to 0.87)	0.85 (0.76 to 0.95)	.04	.26	
Men	1.00	0.98 (0.84 to 1.14)	0.98 (0.83 to 1.16)	0.93 (0.80 to 1.07)	0.93 (0.80 to 1.07)	.13	.43	
Multivariable§								
Total	1.00	0.85 (0.78 to 0.93)	0.93 (0.85 to 1.01)	0.88 (0.80 to 0.95)	0.93 (0.85 to 1.02)	.28	.62	.23
Women	1.00	0.78 (0.71 to 0.87)	0.88 (0.80 to 0.97)	0.82 (0.74 to 0.91)	0.90 (0.80 to 1.00)	.26	.50	
Men	1.00	1.02 (0.87 to 1.18)	1.03 (0.89 to 1.20)	1.00 (0.86 to 1.17)	1.01 (0.86 to 1.18)	.80	.72	
Total vegetables								
Number of cases								
Women	832	798	788	753	776			
Men	375	395	353	384	383			
Age-adjusted								
Total	1.00	0.99 (0.91 to 1.08)	0.94 (0.86 to 1.02)	0.92 (0.85 to 1.00)	0.92 (0.85 to 1.00)	.06	.67	.54
Women	1.00	0.97 (0.88 to 1.07)	0.95 (0.86 to 1.05)	0.90 (0.81 to 0.99)	0.91 (0.82 to 1.00)	.07	.65	
Men	1.00	1.05 (0.88 to 1.25)	0.91 (0.79 to 1.06)	0.99 (0.82 to 1.18)	0.96 (0.83 to 1.11)	.55	.43	
Multivariable§								
Total	1.00	1.00 (0.92 to 1.09)	0.95 (0.87 to 1.03)	0.93 (0.85 to 1.01)	0.94 (0.86 to 1.02)	.17	.91	.99
Women	1.00	0.98 (0.89 to 1.09)	0.95 (0.85 to 1.07)	0.92 (0.82 to 1.02)	0.94 (0.84 to 1.04)	.23	.77	
Men	1.00	1.05 (0.89 to 1.23)	0.91 (0.78 to 1.06)	0.96 (0.82 to 1.12)	0.94 (0.80 to 1.10)	.49	.78	

* *P* values for the tests for trend and the tests for between-studies heterogeneity due to sex were calculated using the Wald test statistic.

† *P* values for the tests for heterogeneity between studies were calculated using the *Q* statistic.

‡ There were three participants who developed colon cancer for whom data on total fruits were missing and one for whom data on total vegetables were missing.

§ Adjusted for body mass index (<23, 23 to <25, 25 to <30, ≥30 kg/m^2); height (men: <1.70, 1.70 to <1.75, 1.75 to <1.80, 1.80 to <1.85, ≥1.85 m; women: <1.60, 1.60 to <1.65, 1.65 to <1.70, 1.70 to <1.75, ≥1.75 m); education (<high school graduate, high school graduate, >high school graduate); physical activity (low, medium, high); family history of colorectal cancer (no, yes); postmenopausal hormone use (premenopausal, never, ever); oral contraceptive use (never, ever); use of nonsteroidal anti-inflammatory drugs (no, yes); multivitamin use (no, yes <6 times/wk, yes ≥6 times/wk, yes missing dose for the Adventist Health Study, Breast Cancer Detection Demonstration Project Follow-up Study, Health Professionals Follow-up Study, Iowa Women's Health Study, New York University Women's Health Study, Nurses' Health Study [a and b], and Women's Health Study; no, yes, for the (Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, Cancer Prevention Study II Nutrition Cohort, Netherlands Cohort Study, and New York State Cohort); smoking habits (never, past [<20, 20 to <40, ≥40 y], current [<25 cigarettes/day and <40 y, ≥25 cigarettes/day and <40 y, <25 cigarettes/day and ≥40 y, ≥25 cigarettes/day and ≥40 y]); red meat intake (quintiles); total milk intake (quartiles); alcohol (0, >0 to <5, 5 to <15, 15 to <30, ≥30 g/day); and total energy (continuous). Age in years and year of questionnaire return were included as stratification variables.

older (n = 3617cases), the corresponding RRs (95% CIs) were 0.92 (0.81 to 1.03) for total fruits and vegetables, 0.93 (0.83 to 1.04) for total fruits and 0.93 (0.83 to 1.04) for total vegetables. The Adventist Health Study and the Prospective Study on Hormones, Diet and Breast Cancer were not included in these and other stratified analyses due to the small number of colon cancer cases in each study. None of the relative risks in Table 2 were appreciably changed when these two studies were excluded.

The pooled relative risks for colon cancer did not vary substantially according to follow-up period (*P* values for difference between follow-up periods were .40 for total fruits and vegetables, .88 for total fruits, and .57 for total vegetables). For colon cancer

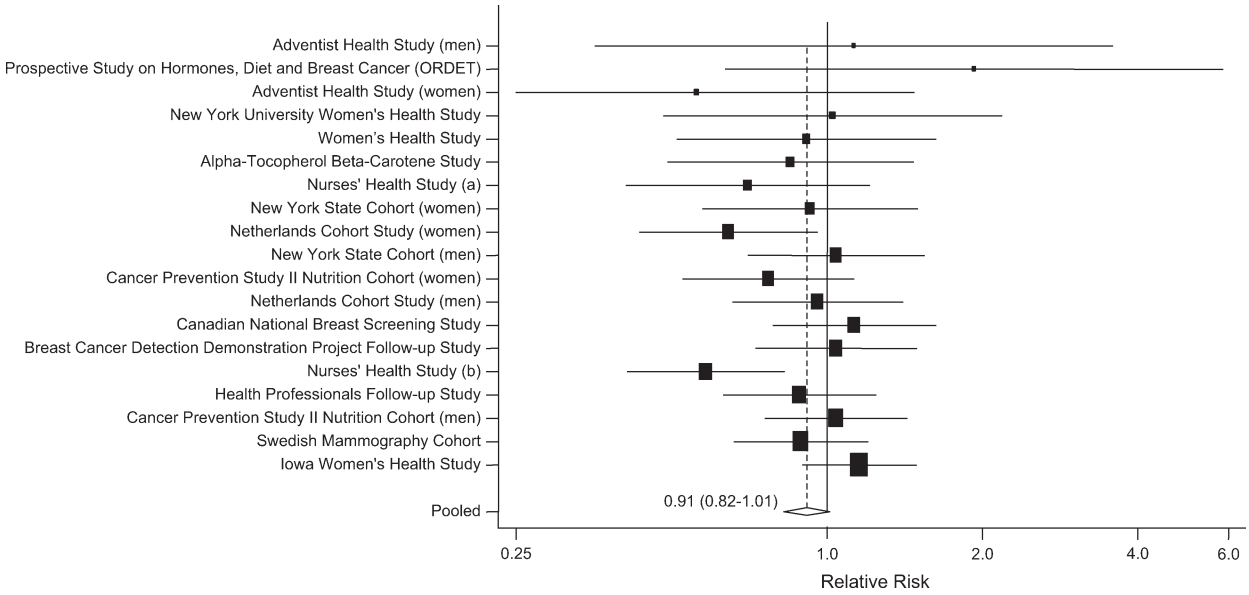

Fig. 1. Study-specific and pooled multivariable relative risks (RR) and 95% confidence intervals of colon cancer according to intake of total fruits and vegetables, quintile 5 versus quintile 1. The **black squares** and **horizontal lines** correspond to the study-specific multivariable relative risks and 95% confidence intervals, respectively. The **area of the black square** reflects the study-specific weight (inverse of the variance). The **diamond** represents the pooled multivariable relative risk and 95% confidence interval. The **solid vertical line** indicates a RR of 1.0.

diagnoses that occurred within the first 5 years of follow-up (n = 2288 cases), the pooled multivariable RRs (95% CIs) comparing the highest with the lowest quintiles of intake were 0.97 (0.79 to 1.18) for total fruits and vegetables, 0.94 (0.77 to 1.14) for total fruits, and 0.97 (0.84 to 1.12) for total vegetables, and for colon cancer diagnoses that occurred at 5 years or later after baseline (n = 3384 cases), the RRs (95% CIs) were 0.89 (0.78 to 1.00) for total fruits and vegetables, 0.92 (0.82 to 1.04) for total fruits, and 0.92 (0.81 to 1.03) for total vegetables. When we restricted the analysis to nonusers of multivitamin supplements, which included 3314 cases (the Canadian National Breast Screening Study and Swedish Mammography Cohort were excluded from these analyses because data on multivitamin supplement use at baseline were not available for all participants), the results were similar to those seen among the whole study population (results not shown).

When fruit and vegetable intakes were categorized using identical absolute cut points (Table 3), the associations for each fruit and vegetable group were similar to those observed when intakes were categorized as quintiles. For example, for total fruits and vegetables, the pooled multivariable RR (95% CI) for intakes of ≥800 g/day compared with <200 g/day was 0.90 (0.77 to 1.05). There was no evidence of heterogeneity between studies and the pooled relative risks were not statistically significantly modified by sex, although the results suggested a stronger inverse association for women than men with total fruits and vegetables and total fruits. As observed in the quintile analyses, the relative risks for the highest compared with the lowest intakes were similar in magnitude across the three food groups (Table 3). The age-standardized incidence rates of colon cancer were 61 per 100 000 person-years among those who consumed <200 g/day of total fruits and vegetables and 54 per 100 000 person-years among those who consumed ≥800 g/day.

When fruits and vegetables were grouped according to botanical definitions (28), the pooled multivariable RRs (95% CIs) for the highest versus the lowest tertiles of intake were 1.00 (0.92 to 1.09) for Compositae, 0.99 (0.93 to 1.06) for Cruciferae, 0.96 (0.89 to 1.03) for Cucurbitaceae, 0.97 (0.90 to 1.03) for Leguminosae, 0.94 (0.86 to 1.02) for Rosaceae, 0.94 (0.88 to 1.01) for Rutaceae, 1.01 (0.94 to 1.08) for Solanaceae, and 0.97 (0.90 to 1.05) for Umbelliferae. For the consumption of green leafy vegetables, the pooled multivariable RR (95% CI) was 0.97 (0.90 to 1.05) for the highest versus the lowest tertile of intake. In the analyses of individual fruits and vegetables, inverse associations were observed for intakes of bananas and spinach (Table 4). Further adjustment for total vegetables did not appreciably change the results for spinach. The association for bananas was similar but no longer statistically significant when the analysis was further adjusted for total fruits (not shown).

In our analyses of population subgroups (i.e., by colon cancer risk factors and by colon site), the results using quintiles of total fruits and vegetables, total fruits, and total vegetables were similar to the results where categories were based on identical absolute cut points. To take advantage of the variation in intakes across the study populations, we present only the results for categories based on identical absolute cut points (Tables 5 and 6). The association between total fruits and vegetables and colon cancer risk did not vary by levels of smoking status, body mass index, and postmenopausal hormone use. However, the association between total fruit and vegetable consumption and colon cancer risk differed by intakes of alcohol ($P_{\text{iteraction}}$ value, test for interaction = .02) and red meat ($P_{\text{iteraction}}$ value, test for interaction = .01). In particular, an inverse association with total fruit and vegetable intakes was apparent among nondrinkers of alcohol and among individuals in the lowest two tertiles of red meat intake (Table 5).

Table 3. Pooled multivariable* relative risks (95% confidence intervals) of colon cancer for categories of fruit and vegetable intake based on absolute cut points

	Cutpoint category					*P* value, test for trend†	*P* value, test for between-studies heterogeneity, highest category‡	*P* value, test for between-studies heterogeneity due to sex, highest category†
	1	2	3	4	5			
Total fruits and vegetables§,‖								
Intake category (g/day)	<200	200 to <400	400 to <600	600 to <800	≥800¶			
Median intake (g/day)	142.0	304.0	489.1	681.7	960.1			
No. of cases (women, men)	523, 265	1163, 684	1079, 478	644, 263	492, 200			
Total	1.00	0.90 (0.82 to 0.98)	0.84 (0.75 to 0.93)	0.83 (0.73 to 0.95)	0.90 (0.77 to 1.05)	.06	.46	.28
Women	1.00	0.85 (0.76 to 0.95)	0.83 (0.73 to 0.94)	0.78 (0.66 to 0.91)	0.84 (0.68 to 1.03)	.16	.27	
Men	1.00	1.00 (0.86 to 1.17)	0.85 (0.71 to 1.02)	0.95 (0.76 to 1.20)	1.03 (0.77 to 1.39)	.20	.86	
Total fruits‖								
Intake category (g/day)	<100	100 to <200	200 to <300	300 to <400	≥400			
Median intake (g/day)	55.6	152.1	246.8	344.6	514.3			
No. of cases (women, men)	602, 386	847, 519	839, 410	701, 301	913, 274			
Total	1.00	0.94 (0.86 to 1.02)	0.89 (0.81 to 0.97)	0.98 (0.89 to 1.09)	0.87 (0.77 to 0.97)	.04	.90	.45
Women	1.00	0.87 (0.78 to 0.97)	0.83 (0.74 to 0.93)	0.91 (0.80 to 1.03)	0.84 (0.74 to 0.96)	.08	.58	
Men	1.00	1.06 (0.92 to 1.22)	1.00 (0.85 to 1.18)	1.16 (0.97 to 1.38)	0.93 (0.76 to 1.14)	.23	>.99	
Total vegetables								
Intake category (g/day)	<100	100 to <200	200 to <300	≥300#				
Median intake (g/day)	68.4	146.7	241.6	384.0				
No. of cases (women, men)	918, 339	1437, 751	894, 414	698, 386				
Total	1.00	0.98 (0.89 to 1.07)	0.89 (0.79 to 1.01)	0.96 (0.84 to 1.09)		.24	.33	.93
Women	1.00	0.95 (0.85 to 1.05)	0.92 (0.82 to 1.04)	0.95 (0.81 to 1.11)		.73	.28	
Men	1.00	1.06 (0.88 to 1.28)	0.85 (0.63 to 1.13)	0.98 (0.76 to 1.25)		.11	.33	

* The relative risks were adjusted for the covariates listed in the fourth footnote to Table 2.

† *P* values for the tests for trend and the test for between-studies heterogeneity due to sex were calculated using the Wald test statistic.

‡ *P* values for the tests for heterogeneity between studies were calculated using the *Q* statistic.

§ There were three participants who developed colon cancer for whom data on total fruits were missing and one for whom data on total vegetables were missing.

‖ The Prospective Study on Hormones, Diet and Breast Cancer was not included in this analysis because there were no cases in the reference category.

¶ The Alpha-Tocopherol Beta-Carotene Cancer Prevention Study did not include any cases with total fruit and vegetable intakes exceeding 800 g/day. The participants who were not cases who would have been in this highest category were included in the next highest category.

The Adventist Health Study did not include any cases (men or women) with total vegetable intakes exceeding 300 g/day. The participants who were not cases who would have been in this highest category were included in the next highest category.

Intakes of total fruits and vegetables, total fruits, and total vegetables were not associated with proximal colon cancers but were associated with statistically significant reductions in the risk of distal colon cancer for the highest versus the lowest intakes (Table 6), although the differences in associations by colon site were not statistically significant (*P* value, test for common effects by tumor site in the highest category > .14 for all women and men combined; Table 6). For total fruits and vegetables, the pooled multivariable RR (95% CI) comparing intakes of ≥800 versus <200 g/day were 0.74 (0.57 ot 0.95) for distal colon cancer and 1.02 (0.82 to 1.27) for proximal colon cancer. The suggestive differences in risk estimates for the three food groups by colon site were generally consistent among men and women (Table 6) and also when fruit and vegetable intakes were categorized by quintiles. The pooled multivariable RRs (95% CIs) comparing the highest with the lowest quintile of total fruit and vegetable intake were 0.81 (0.69 to 0.95) for distal colon cancer and 0.98 (0.86 to 1.11) for proximal colon cancer (*P* value, test for common effects by tumor site in the highest quintile = .20). Because of the observed lower risk of distal colon cancer with fruit and vegetable intakes, we reexamined the association between distal colon cancer risk and intakes of botanically defined food groups and green leafy vegetables and observed no statistically significant associations, with the exception of Umbelliferae (pooled multivariable RR = 0.88, 95% CI = 0.79 to 0.99, for the highest versus the lowest tertile of intake). Intakes of bananas

Table 4. Pooled multivariable* relative risks (95% confidence intervals) of colon cancer by category of intake of specific fruits and vegetables

Food item	No. of cases	Serving size		Category of intake				*P* value, test for trend†	*P* value, test for between-studies heterogeneity in highest category†,‡
		Quantity	Weight (g)	0	>0 to <1 serving/wk	1 serving/wk to <½ serving/day (or ≥1 serving/wk if highest category)	≥½ serving/day		
Fruits									
Apples, pears, applesauce§,‖,¶	5445	1, ½ cup	138	1.00	1.05 (0.94 to 1.17)	0.98 (0.88 to 1.09)	0.98 (0.88 to 1.10)	.18	.69
Bananas§,‖,#,**	4430	1	114	1.00	0.91 (0.83 to 1.00)	0.84 (0.76 to 0.93)	0.88 (0.78 to 0.99)	.07	.85
Cantaloupe §,‖,¶,††, ‡‡,§§,¶¶,##	3064	¼ melon	134	1.00	0.93 (0.83 to 1.03)	1.03 (0.83 to 1.27)		.86	.23
Grapefruit §,¶,††,‖ ‖,¶¶,##,***	4272	½ fruit	120	1.00	0.95 (0.87 to 1.04)	0.98 (0.89 to 1.07)	0.96 (0.81 to 1.13)	.58	.03
Oranges§,¶,††,‖ ‖,##	4464	1	131	1.00	1.02 (0.94 to 1.11)	0.96 (0.87 to 1.05)	1.00 (0.89 to 1.11)	.43	.63
Peaches§,‖,¶,#,**,‡‡,##	3065	1, ½ cup	87	1.00	0.99 (0.86 to 1.14)	0.93 (0.81 to 1.07)	0.97 (0.75 to 1.24)	.54	.12
Fruit juices	5760	6 oz	190	1.00	0.95 (0.86 to 1.05)	0.92 (0.81 to 1.04)†††	0.96 (0.89 to 1.05)	.92	.79
Vegetables									
Broccoli§,‖,‡‡,##	4433	½ cup	78	1.00	0.91 (0.83 to 0.99)	0.95 (0.85 to 1.05)‡‡‡		.94	.53
Brussels sprouts §,‖,#,**,‖ ‖,¶¶,##	3733	½ cup	78	1.00	0.91 (0.85 to 0.99)	1.03 (0.82 to 1.29)‡‡‡		.83	.10
Cabbage§,‖,††,¶¶	5038	½ cup	68	1.00	1.10 (0.98 to 1.24)	1.08 (0.97 to 1.21)		.42	.31
Carrots§,#,***	5303	½ cup	57	1.00	0.96 (0.85 to 1.08)	0.92 (0.81 to 1.03)	0.87 (0.75 to 1.01)	.16	.59
Lettuce, salad‖ ‖,¶¶,***,§§§	5509	1 cup	56	1.00	1.00 (0.89 to 1.13)	0.89 (0.77 to 1.02)	0.90 (0.79 to 1.03)‡‡‡	.13	.46
Peas, lima beans§,‖,#,**,‡‡,‖ ‖,##	3159	½ cup	80	1.00	0.89 (0.80 to 0.99)	0.90 (0.79 to 1.02)		.52	.71
String beans§,#,**,§§,##	3491	½ cup	68	1.00	0.89 (0.78 to 1.03)	0.93 (0.79 to 1.09)‡‡‡	0.85 (0.65 to 1.09)†††	.37	.71
Spinach§,¶¶,***	5460	½ cup	73	1.00	0.93 (0.86 to 1.00)	0.89 (0.82 to 0.97)‡‡‡		.001	.89
Tomatoes, tomato juice¶,***	5576	1, 4 oz juice	122	1.00	0.94 (0.84 to 1.05)	0.88 (0.79 to 0.99)	0.93 (0.81 to 1.07)	.89	.37
Yams, sweet potatoes§,‖, ¶,††,‡‡,§§,##	3244	½ cup	128	1.00	0.92 (0.81 to 1.04)	0.83 (0.65 to 1.07)		.31	.53
Mature beans and lentils¶	5608	½ cup	131	1.00	0.99 (0.92 to 1.05)	1.00 (0.90 to 1.11)		.64	.91
Potatoes‖ ‖ ‖, ¶¶¶	5504	1 or 1 cup	202	1.00	0.87 (0.75 to 1.02)	0.89 (0.77 to 1.04)	1.02 (0.86 to 1.21)###	.05	.84

* The relative risks were adjusted for the covariates listed in the fourth footnote to Table 2.

† *P* values for the tests for trend were calculated using the Wald test statistic and for the test for between-studies heterogeneity were calculated using the Q statistic.

‡ *P*>.13 for between-studies heterogeneity due to sex in the highest category for each food item.

§ The Adventist Health Study was not included in this analysis because consumption of this item was not measured.

‖ The Prospective Study on Hormones, Diet and Breast Cancer (ORDET) was not included in this analysis because consumption of this item was not measured.

¶ The Alpha-Tocopherol Beta-Carotene Cancer Prevention Study was not included in this analysis because consumption of this item was not measured.

The Breast Cancer Detection Demonstration Project Follow-up Study was not included in this analysis because consumption of this item was not measured.

** The Cancer Prevention Study II Nutrition Cohort was not included in this analysis because consumption of this item was not measured.

†† The Canadian National Breast Screening Study was not included in this analysis because consumption of this item was not measured.

‡‡ The Netherlands Cohort Study was not included in this analysis because consumption of this item was not measured.

§§ The New York State Cohort was not included in this analysis because consumption of this item was not measured.

‖ ‖ The New York University Women's Health Study was not included in this analysis because consumption of this item was not measured.

¶¶ Nurses' Health Study (a) was not included in this analysis because consumption of this item was not measured.

The Swedish Mammography Cohort was not included in this analysis because consumption of this item was not measured.

*** ORDET was not included in this analysis because there were no cases in the reference group.

††† ORDET did not have any cases with intakes in this category and greater (if applicable). The participants who were not cases who would have been in this highest category were included in the next highest category.

‡‡‡ The Alpha-Tocopherol Beta-Carotene Cancer Prevention Study did not include cases with intakes in this category and greater (if applicable). The participants who were not cases who would have been in this highest category were included in the next highest category.

§§§ The New York University Women's Health Study was not included in this analysis because there were no cases in the reference group.

‖ ‖ ‖ Potatoes, not including French fried potatoes or chips.

¶¶¶ The Alpha-Tocopherol Beta-Carotene Cancer Prevention Study was not included in this analysis because there were no cases in the reference group.

The New York University Women's Health Study did not have any cases with intakes in this category. The participants who were not cases who would have been in this highest category were included in the next highest category.

Table 5. Pooled multivariable*relative risks (95% confidence intervals) for total fruit and vegetable intakes by risk factors for colon cancer†

Effect modifier	Category of intake (g/day)				*P* value, test for trend‡	*P* value, test for between-studies heterogeneity, highest category§,‖	*P* value, test for interaction, highest category¶
	<200	200 to <400	400 to <600	≥600			
Smoking#,**							
Never (n = 2219 cases)††	1.00	0.84 (0.71 to 1.00)	0.82 (0.65 to 1.02)	0.79 (0.64 to 0.97)	.53	.42	.99
Past (n = 1908 cases)††	1.00	0.86 (0.70 to 1.05)	0.78 (0.64 to 0.95)	0.85 (0.68 to 1.06)	.09	.89	
Current (n = 912 cases)‡‡	1.00	0.96 (0.78 to 1.16)	0.80 (0.62 to 1.02)	0.80 (0.58 to 1.10)	.11	.40	
Alcohol consumption#							
Nondrinker (n = 1976 cases)§§	1.00	0.78 (0.67 to 0.90)	0.77 (0.64 to 0.92)	0.69 (0.56 to 0.84)	.01	.48	.02
<1 drink/day (n = 2640 cases)	1.00	0.97 (0.84 to 1.11)	0.91 (0.77 to 1.07)	0.93 (0.77 to 1.12)	.62	.74	
≥1 drink/day (n = 945 cases)‖ ‖	1.00	1.13 (0.77 to 1.67)	0.78 (0.58 to 1.04)	1.27 (0.88 to 1.82)¶¶,##	>.99	.95	
Body mass index							
<25kg/m^2 (n = 2591 cases)	1.00	0.88 (0.77 to 1.00)	0.82 (0.70 to 0.95)	0.80 (0.66 to 0.97)	.27	.42	.58
≥25kg/m^2 (n = 2936 cases)	1.00	0.88 (0.73 to 1.07)	0.82 (0.69 to 0.97)	0.88 (0.73 to 1.05)	.16	.39	
Red meat intake							
Tertile 1 (n = 1904 cases)	1.00	0.87 (0.75 to 1.02)	0.82 (0.68 to 0.99)	0.82 (0.64 to 1.05)¶ ¶	.52	.23	.01
Tertile 2 (n = 1970 cases)	1.00	0.86 (0.74 to 1.01)	0.77 (0.64 to 0.93)	0.71 (0.57 to 0.87)	.03	.72	
Tertile 3 (n = 1795 cases)	1.00	0.99 (0.77 to 1.27)	0.93 (0.75 to 1.14)	1.13 (0.84 to 1.54)	.89	.09	
Postmenopausal hormone use among women#,**,***,†††							
Never (n = 1473 cases)	1.00	0.78 (0.62 to 0.99)	0.82 (0.66 to 1.00)	0.73 (0.57 to 0.92)	.27	.67	.10
Past (n = 522 cases)†††	1.00	0.98 (0.69 to 1.37)	1.05 (0.72 to 1.52)	1.22 (0.80 to 1.86)	.42	.70	
Current (n = 283 cases)‡‡‡	1.00	0.71 (0.48 to 1.05)	0.58 (0.37 to 0.92)	0.74 (0.44 to 1.25)	.20	.93	

* The relative risks were adjusted for the covariates listed in the fourth footnote to Table 2.

† The Adventist Health Study and The Prospective Study on Hormones, Diet and Breast Cancer were not included in the analyses of effect modification because of sparse stratum-specific case numbers.

‡ *P* values for the tests for trend were calculated using the Wald test statistic.

§ *P*>.12 for between-studies heterogeneity due to sex in the highest category for each effect modifier (not including postmenopausal hormone use), except for tertile 1 of red meat intake (*P* = .03).

‖ *P* values for the tests for heterogeneity between studies were calculated using the *Q* statistic.

¶ *P* values for the tests for interaction between the effect modifier and fruit and vegetable intake were calculated using the Wald test statistic.

The New York University Women's Health Study was not included in this analysis because this variable was not measured.

** The Swedish Mammography Cohort was not included in this analysis because this variable was not measured.

†† The Alpha-Tocopherol Beta-Carotene Cancer Prevention Study was not included in this stratum because all participants in this cohort were current smokers.

‡‡ The Women's Health Study was not included in this stratum because few cases were current smokers.

§§ The Alpha-Tocopherol Beta-Carotene Cancer Prevention Study was not included in this stratum because few cases were nondrinkers.

‖‖ The Swedish Mammography Cohort was not included in this stratum because few cases drank more than one drink per day.

¶¶ The Alpha-Tocopherol Beta-Carotene Cancer Prevention Study did not include any cases with total fruit and vegetable intakes exceeding 600 g/day in this stratum. The participants who were not cases who would have been in this highest category were included in the next highest category.

The Netherlands Cohort Study was not included in this stratum because few cases currently used postmenopausal hormones.

*** The Canadian National Breast Screening Study was not included in this analysis because this variable was not measured.

††† The New York State Cohort was not included in this analysis because this variable was not measured.

‡‡‡ The Nurses' Health Study (a) was not included in this stratum because there were no cases in the reference group.

Table 6. Pooled multivariable* relative risks (95% confidence intervals) of distal and proximal colon cancers† for categories of fruit and vegetable intake‡

	Cutpoint category					*P* value, test for trend§	*P* value, test for between-studies heterogeneity, highest category‖,¶	*P* value, test for common effects by tumor site, highest category#
	1	2	3	4	5			
Total fruits and vegetables (g/day)	<200	200 to <400	400 to <600	600 to <800	≥800**			
No. of cases distal (women, men)	167, 111	433, 294	421, 203	239, 120	170, 82			
No. of cases proximal (women, men)	278, 136	608, 323	555, 230	344, 177	280, 106			
Total								
Distal	1.00	0.93 (0.80 to 1.09)	0.84 (0.71 to 0.99)	0.78 (0.63 to 0.97)	0.74 (0.57 to 0.95)	.02	.40	.14
Proximal	1.00	0.86 (0.75 to 0.99)	0.80 (0.69 to 0.94)	0.86 (0.71 to 1.03)	1.02 (0.82 to 1.27)	.57	.76	
Women								
Distal	1.00	0.88 (0.69 to 1.12)	0.83 (0.67 to 1.03)	0.67 (0.51 to 0.88)	0.68 (0.47 to 0.97)	.02	.24	.30
Proximal	1.00	0.80 (0.66 to 0.97)	0.78 (0.64 to 0.95)	0.84 (0.67 to 1.04)	0.95 (0.74 to 1.23)	.77	.60	
Men								
Distal	1.00	0.98 (0.77 to 1.24)	0.85 (0.64 to 1.11)	1.01 (0.71 to 1.42)	0.92 (0.58 to 1.44)	.48	.90	.62
Proximal	1.00	0.98 (0.79 to 1.22)	0.85 (0.65 to 1.11)	0.91 (0.65 to 1.29)	1.24 (0.81 to 1.92)	.54	.87	
Total fruits (g/day)	<100	100 to <200	200 to <300	300 to <400	≥400			
No. of cases distal (women, men)	210, 162	303, 218	313, 185	290, 136	315, 109			
No. of cases proximal (women, men)	309, 200	459, 258	443, 186	352, 139	502, 129			
Total								
Distal	1.00	0.93 (0.81 to 1.07)	0.92 (0.79 to 1.07)	1.06 (0.90 to 1.25)	0.77 (0.64 to 0.93)	.06	.64	.45
Proximal	1.00	0.96 (0.85 to 1.09)	0.86 (0.76 to 0.98)	0.95 (0.82 to 1.09)	0.91 (0.77 to 1.06)	.24	>.99	
Women								
Distal	1.00	0.86 (0.72 to 1.03)	0.83 (0.69 to 1.01)	0.96 (0.78 to 1.17)	0.69 (0.55 to 0.87)	.04	.64	.21
Proximal	1.00	0.92 (0.79 to 1.07)	0.84 (0.72 to 0.98)	0.88 (0.74 to 1.05)	0.91 (0.76 to 1.10)	.53	.98	
Men								
Distal	1.00	1.03 (0.83 to 1.28)	1.07 (0.85 to 1.35)	1.27 (0.97 to 1.65)	0.94 (0.70 to 1.28)	.82	.74	.94
Proximal	1.00	1.05 (0.86 to 1.27)	0.91 (0.72 to 1.14)	1.11 (0.85 to 1.44)	0.89 (0.66 to 1.20)	.22	.87	
Total vegetables (g/day)	<100	100 to <200	200 to <300	≥300				
No. of cases distal (women, men)	326, 154	521, 312	330, 168	254, 176				
No. of cases proximal (women, men)	456, 149	741, 357	490, 205	379, 201				
Total								
Distal	1.00	0.88 (0.78 to 1.00)	0.73 (0.62 to 0.86)	0.82 (0.68 to 0.98)		.01	.69	.15
Proximal	1.00	1.02 (0.88 to 1.18)	1.04 (0.85 to 1.28)	1.07 (0.88 to 1.29)		.66	.23	
Women								
Distal	1.00	0.90 (0.77 to 1.04)	0.79 (0.65 to 0.96)	0.81 (0.65 to 1.02)		.06	.58	.44
Proximal	1.00	0.94 (0.80 to 1.11)	0.99 (0.78 to 1.26)	1.00 (0.81 to 1.22)		.67	.37	
Men								
Distal	1.00	0.90 (0.66 to 1.22)	0.64 (0.44 to 0.93)	0.83 (0.61 to 1.15)		.10	.50	.23
Proximal	1.00	1.24 (0.96 to 1.60)	1.22 (0.77 to 1.92)	1.36 (0.85 to 2.18)		.78	.17	

* The relative risks were adjusted for the covariates listed in the fourth footnote to Table 2.

† Proximal colon cancers include tumors from the cecum to the splenic flexure; distal colon cancers include tumors in the descending and sigmoid colon.

‡ The Adventist Health Study and The Prospective Study on Hormones, Diet and Breast Cancer were not included in the analyses by colon site because of sparse stratum-specific case numbers.

§ *P* values for the tests for trend were calculated using the Wald test statistic.

‖ *P* values for the tests for heterogeneity between studies were calculated using the *Q* statistic.

¶ *P*>.11 for between-studies heterogeneity due to sex in the highest category for each food group.

P values for the test for common effects by tumor site were calculated using the Wald test statistic.

** The Alpha-Tocopherol Beta-Carotene Cancer Prevention Study did not include any cases with total fruit and vegetable intakes exceeding 800 g/day. The participants who were not cases who would have been in this highest category were included in the next highest category.

and spinach were not statistically significantly associated with distal colon cancer risk (results not shown).

Discussion

In this pooled analysis of data from 14 prospective cohort studies, increasing fruit and vegetable intakes were not associated with colon cancer risk overall, though the lowest intakes were associated with an elevation in risk. This pattern of association was consistent whether examined by study-specific quintiles or categories based on identical absolute intakes across studies. An inverse association was more apparent among nondrinkers of alcohol and among low consumers of red meat. Green leafy vegetables, botanically defined fruit and vegetable groups, and most specific fruits and vegetables, except bananas and spinach, were not associated with colon cancer risk. When examined by colon site, the inverse association for fruits and vegetables was limited to cancers of the distal colon, although the risk estimates for distal and proximal colon cancer were not statistically significantly different. Results for each fruit and vegetable group were generally consistent between men and women.

The relationship between fruit and vegetable intakes and the risk of colon cancer has been examined in many previous studies (1,3). For total vegetables, 75% of the results reported in 22 case–control studies suggested that colon cancer risk was reduced by at least 20% for those in the highest compared with the lowest intake category, with 33% of the estimates indicating that the reduction in risk exceeded 50%. For total fruits, the results have been less consistent among 19 case–control studies; 48% of the risk estimates suggested at least a 20% reduction in risk and only 11% showed more than a 50% lower risk for the highest versus the lowest intakes. Among five prospective cohort studies that were not included in this pooled analysis because they did not meet our inclusion criteria (36–40), only three studies have reported associations for total fruits and/or total vegetables (38–40), among which inverse associations with colon cancer risk were suggested for total vegetable intake in one study (39) and for total fruit intake (among women only) in another study (38).

Analyzing specific foods and food groups may identify particular components of fruits and vegetables that are associated with risk, and these associations could be diluted in an analysis of total fruits and vegetables. Associations for cruciferous and green vegetable intakes and the risk of colon cancer have been reported in more than 15 studies each, with most studies suggesting inverse associations (1). Other specific food groups for which associations with colon cancer risk have been reported with less frequency are legumes, allium vegetables, and citrus fruits, and the reported associations for these groups have been inconsistent across studies. Few studies have reported associations for individual fruits and vegetables. Spinach intake (41–43) has been consistently associated with a reduced risk of colon cancer and a lower risk with banana consumption has been observed in some (42,44) but not all (43,45) studies. To our knowledge, separate evaluation of distal and proximal colon cancers has been conducted in relatively few studies (41,46–50).

The suggestive reductions in colon cancer risk observed in our multivariable analyses, ranging from 6%–9% for the highest versus the lowest quintiles of total fruit and vegetable, total fruit, and total vegetable intakes, are much weaker than those observed in most previous studies, particularly for total vegetables. Differential misclassification of fruit and vegetable intakes or differential participation rates between cases and controls may have led to biased relative risk estimates in the case–control studies. Also, in light of the stronger inverse associations that we observed for distal versus proximal colon cancers, the differences between our results and previous case–control studies may reflect differences in the distribution of colon cancers by site. In our pooled analysis that included studies with follow-up periods up to 2003, more proximal compared with distal colon cancers occurred. This site distribution is consistent with the trend over the past several decades of an increasing incidence of proximal colon cancers with a corresponding decrease in distal colon cancers (6,51). In contrast, most previous case–control studies were conducted in earlier time periods, and among the studies that provided colon site distributions (41,42,44,46–48,50,52,53), colon cancers were more frequent in the distal compared with the proximal colon, except among women only in one study (50).

Research in embryology, physiology, and epidemiology supports the notion that cancers of the proximal and distal colon may have different etiologies (5–7). Recent evidence shows that two distinct kinds of genetic instability contribute to carcinogenesis in the colon; chromosomal instability occurs more often in distal colon cancers, whereas microsatellite instability predominates in proximal colon cancers (6,7). Diet has been hypothesized to have more of a role in distal versus proximal colon cancers (54).

Fruits and vegetables are rich in many nutrients and bioactive compounds, such as vitamins, carotenoids, folate, and fiber, that may have cancer-preventive properties (55). Nutrients that detoxify or deactivate carcinogens may act to prevent chromosomal instability whereas nutrients that function to regulate cell cycle progression and apoptosis may prevent the growth of chromosomally unstable cells. Other than bananas and spinach, we did not identify any specific food or food group that was more strongly associated with colon cancer risk that would suggest a role for a particular class of bioactive compounds. Rather, our results for total fruits and total vegetables separately did not greatly differ from one another, suggesting that potential synergy between the numerous bioactive compounds in fruits and vegetables could contribute to this modest inverse association (56).

In each of the analyses where an inverse association was suggested, the observed relative risks for the highest versus the lowest intakes were generally modest. Thus, although we adjusted for several covariates, we cannot rule out uncontrolled confounding by an unknown and unmeasured factor or residual confounding due to measurement error in the covariates. Also, our results, particularly for distal colon cancer, may reflect uncontrolled confounding by prior colorectal cancer screening, if individuals with the highest fruit and vegetable intakes compared with the lowest intakes were more likely to have been screened for colorectal cancer and had their screen-detected adenomatous polyps (precursor lesions to colon cancer) removed. Data on screening practices were not available in most studies. On the other hand, we also cannot rule out measurement error in the assessment of fruit and vegetable consumption. Thus, the observed relative risks may represent

attenuated estimates. For instance, we used only baseline dietary information, which may be subject to greater misclassification than dietary information from multiple questionnaires throughout follow-up. Also, we were unable to correct for measurement error because most studies did not evaluate the validity of total fruit and total vegetable intakes. Furthermore, if fruit and vegetable intakes during childhood, adolescence, or early adulthood are more important determinants of colon cancer risk, than intakes in later adulthood then our analysis of adult diet may not have captured the relevant exposure period.

In our analysis, in which multiple studies were combined, exposure misclassification could also arise depending on whether fruit and vegetable intakes were modeled as study-specific quantiles or as categories in which cut points were defined by identical absolute intakes across studies. With the study-specific quantile approach, true differences in intakes across studies are not accounted for, and this may result in exposure misclassification when pooling the results. On the other hand, misclassification could also occur in the analyses of absolute intake categories because varying intakes across studies may be due to differences in questionnaire design. However, our results for colon cancer overall, and for proximal and distal colon cancers separately, were consistent regardless of how intakes were analyzed.

This study had several strengths, including the fact that we prospectively examined 14 cohorts from North America and Europe with a wide range of fruit and vegetable intakes. By conducting a pooled analysis, we were able to define fruit and vegetable intakes, and other covariates, in a standardized manner across studies, thus minimizing heterogeneity between studies due to differences in exposure and covariate definitions. We examined several specific foods and food groups that have not been consistently reported in previous studies. By including more than 5800 colon cancer cases in our analysis, we were able to conduct analyses by sex and according to colon site with greater statistical power than would be possible for any individual cohort. This large sample size further allowed us to evaluate whether associations were modified by other colon cancer risk factors.

In summary, the consumption of fruits and vegetables was not strongly associated with the risk of colon cancer overall but was inversely associated with the risk of distal colon cancer. Diets plentiful in fruits and vegetables remain important given these findings and the benefits that have been observed for other health outcomes, including cardiovascular disease (57) and some other cancers (3).

References

(1) Smith-Warner SA, Genkinger J, Giovannucci E. Fruit and vegetable intake and cancer. In: Heber D, Blackburn GL, Go VL, Milner J, editors. Nutritional oncology. 2 ed. Burlington (MA): Elsevier; 2006. p. 97–173.

(2) World Cancer Research Fund, American Institute for Cancer Research Expert Panel (J.D. Potter, Chair). Food, nutrition and the prevention of cancer: a global perspective. Washington (DC): American Institute for Cancer Research; 1997.

(3) Vainio H, Bianchini F, editors. Fruit IARC, vegetables. IARC handbooks of cancer prevention. Lyon (France): IARC Press; 2003.

(4) Riboli E, Norat T. Epidemiologic evidence of the protective effect of fruit and vegetables on cancer risk. Am J Clin Nutr 2003;78(Suppl)559S–69S.

(5) Bufill JA. Colorectal cancer: evidence for distinct genetic categories based on proximal or distal tumor location. Ann Intern Med 1990;113:779–88.

(6) Iacopetta B. Are there two sides to colorectal cancer? Int J Cancer 2002;101:403–8.

(7) Gervaz P, Bucher P, Morel P. Two colons-two cancers: paradigm shift and clinical implications. J Surg Oncol 2004;88:261–6.

(8) Singh PN, Fraser GE. Dietary risk factors for colon cancer in a low-risk population. Am J Epidemiol 1998;148:761–74.

(9) Pietinen P, Malila N, Virtanen M, Hartman TJ, Tangrea JA, Albanes D, et al. Diet and risk of colorectal cancer in a cohort of Finnish men. Cancer Causes Control 1999;10:387–96.

(10) Flood A, Velie EM, Chaterjee N, Subar AF, Thompson FE, Lacey JV Jr, et al. Fruit and vegetable intakes and the risk of colorectal cancer in the Breast Cancer Detection Demonstration Project follow-up cohort. Am J Clin Nutr 2002;75:936–43.

(11) Terry P, Jain M, Miller AB, Howe GR, Rohan TE. Dietary intake of folic acid and colorectal cancer risk in a cohort of women. Int J Cancer 2002;97:864–7.

(12) McCullough ML, Robertson AS, Chao A, Jacobs EJ, Stampfer MJ, Diver R, et al. A prospective study of whole grains, fruits, vegetables, and colon cancer risk. Cancer Causes Control 2003;14:959–70.

(13) Michels KB, Giovannucci E, Joshipura KJ, Rosner BA, Stampfer MJ, Fuchs CS, et al. Prospective study of fruit and vegetable consumption and incidence of colon and rectal cancers. J Natl Cancer Inst 2000;92: 1740–52.

(14) Steinmetz KA, Kushi LH, Bostick RM, Folsom AR, Potter JD. Vegetables, and fruit colon cancer in the Iowa Women's Health Study. Am J Epidemiol 1994;139:1–15.

(15) Voorrips LE, Goldbohm RA, van Poppel G, Sturmans F, Hermus RJ, van den Brandt PA. Vegetable and fruit consumption and risks of colon and rectal cancer in a prospective cohort study: The Netherlands Cohort Study on diet and cancer. Am J Epidemiol 2000;152:1081–92.

(16) Bandera EV, Freudenheim JL, Marshall JR, Zielezny M, Priore RL, Brasure J, et al. Diet and alcohol consumption and lung cancer risk in the New York State Cohort (United States). Cancer Causes Control 1997;8: 828–840.

(17) Kato I, Akhmedkhanov A, Koenig K, Toniolo PG, Shore RE, Riboli E. Prospective study of diet and female colorectal cancer: the New York University Women's Health Study. Nutr Cancer 1997;28:276–81.

(18) Sieri S, Krogh V, Muti P, Micheli A, Pala V, Crosignani P, et al. Fat and protein intake and subsequent breast cancer risk in postmenopausal women. Nutr Cancer 2002;42:10–17.

(19) Terry P, Giovannucci E, Michels KB, Bergkvist L, Hansen H, Holmberg L, et al. Fruit, vegetables, dietary fiber, and risk of colorectal cancer. J Natl Cancer Inst 2001;93:525–33.

(20) Lin J, Zhang SM, Cook NR, Rexrode KM, Liu S, Manson JE, et al. Dietary intakes of fruit, vegetables, and fiber, and risk of colorectal cancer in a prospective cohort of women (United States). Cancer Causes Control 2005;16:225–33.

(21) Potter JD. Nutrition and colorectal cancer. Cancer Causes Control 1996; 7:127–46.

(22) Wei EK, Giovannucci E, Wu K, Rosner B, Fuchs CS, Willett WC, et al. Comparison of risk factors for colon and rectal cancer. Int J Cancer 2004;108:433–42.

(23) Smith-Warner S, Spiegelman D, Ritz J, Albanes D, Beeson W, Bernstein L, et al. Methods for pooling results of epidemiologic studies: the pooling project of prospective studies of diet and cancer. Am J Epidemiol 2006; 163:1053–64.

(24) Pennington JAT. Bowes and Church's food values of portions commonly used. 17 ed. New York: Lippincott-Raven; 1998.

(25) Goldbohm RA, van den Brandt PA, Brants HA, van't Veer P, Al M, Sturmans F, et al. Validation of a dietary questionnaire used in a large-scale prospective cohort study on diet and cancer. Eur J Clin Nutr 1994; 48:253–65.

(26) Flagg EW, Coates RJ, Calle EE, Potischman N, Thun MJ. Validation of the American Cancer Society Cancer Prevention Study II Nutrition Survey Cohort food frequency questionnaire. Epidemiology 2000;11: 462–8.

(27) Newby PK, Hu FB, Rimm EB, Smith-Warner SA, Feskanich D, Sampson L, et al. Reproducibility and validity of the Diet Quality Index Revised as assessed by use of a food-frequency questionnaire. Am J Clin Nutr 2003; 78:941–9.
(28) Smith SA, Campbell DR, Elmer PJ, Martini MC, Slavin JL, Potter JD. The University of Minnesota Cancer Prevention Research Unit vegetable and fruit classification scheme (United States). Cancer Causes Control 1995;6:292–302.
(29) Cox DR. Regression models and life-tables. J R Stat Soc (B) 1972;34: 187–220.
(30) SAS Institute. SAS/STAT software: the PHREG procedure: preliminary documentation. Cary (NC): SAS Institute; 1991.
(31) Rothman K. Modern epidemiology. Boston (MA): Little Brown and Company; 1986.
(32) Prentice RL. A case-cohort design for epidemiologic cohort studies and disease prevention trials. Biometrika 1986;73:1–11.
(33) DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
(34) Cochran WG. The combination of estimates from different experiments. Biometrics 1954;10:101–29.
(35) Stram DO. Meta-analysis of published data using a linear mixed-effects model. Biometrics 1996;52:536–44.
(36) Heilbrun LK, Nomura A, Hankin JH, Stemmermann GN. Diet and colorectal cancer with special reference to fiber intake. Int J Cancer 1989; 44:1–6.
(37) Hirayama T. Life-style mortality: a large-scale census-based cohort study in Japan. In: Wahrendorf J, editors. Contributions to epidemiology and biostatistics. Basel: Karger; 1990. p. 1–133.
(38) Shibata A, Paganini-Hill A, Ross RK, Henderson BE. Intake of vegetables, fruits, beta-carotene, vitamin C and vitamin supplements and cancer incidence among the elderly: a prospective study. Br J Cancer 1992;66:673–9.
(39) Thun MJ, Calle EE, Namboodiri MM, Flanders WD, Coates RJ, Byers T, et al. Risk factors for fatal colon cancer in a large prospective study. J Natl Cancer Inst 1992;84:1491–500.
(40) Hsing AW, McLaughlin JK, Chow WH, Schuman LM, Co Chien HT, Gridley G, et al. Risk factors for colorectal cancer in a prospective study among U.S. white men. Int J Cancer 1998;77:549–53.
(41) Young TB, Wolf DA. Case-control study of proximal and distal colon cancer and diet in Wisconsin. Int J Cancer 1988;42:167–75.
(42) Deneo-Pellegrini H, De Stefani E, Ronco A. Vegetables, fruits risk of colorectal cancer: a case-control study from Uruguay. Nutr Cancer 1996;25: 297–303.
(43) Franceschi S, Parpinel M, La Vecchia C, Favero A, Talamini R, Negri E. Role of different types of vegetables and fruit in the prevention of cancer of the colon, rectum, and breast. Epidemiology 1998;9:338–41.
(44) Deneo-Pellegrini H, Boffetta P, De Stefani E, Ronco A, Brennan P, Mendilaharsu M. Plant foods and differences between colon and rectal cancers. Eur J Cancer Prev 2002;11:369–75.
(45) Tuyns AJ, Kaaks R, Haelterman M. Colorectal cancer and the consumption of foods: a case-control study in Belgium. Nutr Cancer 1988;11:189–204.
(46) Slattery ML, Sorenson AW, Mahoney AW, French TK, Kritchevsky D, Street JC. Diet colon cancer: assessment of risk by fiber type and food source. J Natl Cancer Inst 1988;80:1474–80.
(47) Steinmetz KA, Potter JD. Food-group consumption and colon cancer in the Adelaide case-control study. I. Vegetables and fruit. Int J Cancer 1993;53:711–9.
(48) Inoue M, Tajima K, Hirose K, Hamajima N, Takezaki T, Hirai T, et al. Subsite-specific risk factors for colorectal cancer: a hospital-based case-control study in Japan. Cancer Causes Control 1995;6:14–22.
(49) Shannon J, White E, Shattuck AL, Potter JD. Relationship of food groups and water intake to colon cancer risk. Cancer Epidemiol Biomarker Prev 1996;5:495–502.
(50) Slattery ML, Potter JD, Coates A, Ma K-N, Berry TD, Duncan DM, et al. Plant foods colon cancer: an assessment of specific foods and their related nutrients (United States). Cancer Causes Control 1997;8:575–90.
(51) Bonithon-Kopp C, Benhamiche AM. Are there several colorectal cancers? Epidemiological data. Eur J Cancer Prev 1999;8(Suppl 1):S3–12.
(52) Benito E, Obrador A, Stiggelbout A, Bosch FX, Mulet M, Munoz N, et al. A population-based case-control study of colorectal cancer in Majorca. I. Dietary factors. Int J Cancer 1990;45:69–76.
(53) Peters RK, Pike MC, Garabrandt D, Mack TM. Diet and colon cancer in Los Angeles County, California. Cancer Causes Control 1992;3:457–73.
(54) McMichael AJ, Potter JD. Host factors in carcinogenesis: certain bile-acid metabolic profiles that selectively increase the risk of proximal colon cancer. J Natl Cancer Inst 1985;75:185–91.
(55) Lampe JW. Health effects of vegetables and fruit: assessing mechanisms of action in human experimental studies. Am J Clin Nutr 1999; 70(Suppl):475S–90S.
(56) Liu RH. Potential synergy of phytochemicals in cancer prevention: mechanism of action. J Nutr 2004;134(Suppl):3479S–85S.
(57) Ness AR, Powles JW. Fruit and vegetables, and cardiovascular disease—a review. Int J Epidemiol 1997;26:1–13.

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