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Association of Dietary Quercetin with Reduced Risk of Proximal Colon Cancer

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Abstract

Quercetin is a flavonol that appears to be protective against several cancers, but its possible role in prevention of colorectal cancer is not yet well studied. We evaluated dietary intakes of quercetin and risk of colorectal cancer in a large case-control study conducted in Metropolitan Detroit, MI (n = 2664). The protective effects of quercetin intake, as assessed by food frequency questionnaire, were confined to risk of proximal colon cancer. Stratified analyses showed that the protective effects of quercetin on risk of proximal colon cancer were significant only when fruit intake or the Healthy Eating Index score were high, or when tea intake was low, with odds ratios (OR) for the highest versus the lowest quartile = 0.49, 0.44, and 0.51, respectively. Increased quercetin intake had no protective effects when tea intake was high. Interestingly, increased intake of quercetin was associated with increased risk of distal colon cancer when total fruit intake was low (OR for the highest versus the lowest quartile = 1.99). These results suggest that quercetin can have disparate effects on colon cancer risk depending on whether dietary intakes of fruit or tea are high, and that quercetin had protective effects only on proximal, not distal, colon cancer.

Keywords

diet; quercetin; distal colon cancer; proximal colon cancer; epidemiological

Introduction

Quercetin is a flavonol that is widely distributed in many fruits and vegetables. Quercetin has been reported to account for about 75% of typical U.S. intake of flavonoids (1). Tea, onions and apples with skin are major food sources of quercetin in the U.S. and the Netherlands (1, 2). There are, however, many food sources of quercetin. These include allium vegetables, berries, cucumber, sweet potato, cruciferous vegetables, beans, fruits and even some herbs such as sage, rosemary and oregano (3-8). Although fruits and vegetables are of interest for cancer prevention, epidemiological studies have indicated weak, inverse

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associations of fruit and vegetable intakes with colorectal cancer risk (9, 10). These weak associations might be explained by residual confounding, different risk factors being operative in colonic sub-sites, and possibly by the protective effects of only some subtypes of fruits and vegetables.

The content of micronutrients and bioactive compounds does vary across specific types of vegetables and fruits. It is therefore possible to consume a diet that is high in quercetin but poor in vitamin C, β-carotene and folate. Correlations between dietary intakes of these nutrients and quercetin are reported to be weak with r = 0.3-0.2 (1). Many fruits and vegetables that are low in carotenoids, such as onion, beans, apples, raspberries and citrus, contain relatively high levels of flavonoids (11). In the Finnish diet, for example, vegetables were the major contributor to carotenoid intakes but fruits were the major contributor flavonoid intakes (12). Dietary intakes of quercetin in the U.S. have been reported to be in the range of 6-18 mg/day (1, 13-16). In plasma of un-supplemented individuals, levels of quercetin have ranged from 65 to 1500 ng/ml, which is in the same range as carotenoid levels (17, 18). Carotenoid intakes, however, have been only weakly associated with colorectal cancer risk in observational studies (19, 20), and clinical trials using β-carotene supplementation have not found a chemopreventive effect, making investigation of other plant-based nutrient important (21-23).

There is growing data that quercetin has a potential role in cancer prevention. Consistent and strong associations have been observed for quercetin in reducing the risk of lung cancer (24, 25). There is also growing evidence that quercetin and apple consumption are protective of human colon cancer (24). Experimental models of colon cancer suggest that quercetin can inhibit colon tumor formation *in vivo* and proliferation of colon tumor cells *in vitro* (25-32). Quercetin also reduced high fat diet-induced formation of aberrant crypt foci (33). Site-specific preventive properties of quercetin in the colon unfortunately were not investigated, but quercetin did have some preventive activity in distal colon against chemically-induced tumors (34). Quercetin appears to have anti-inflammatory properties in the colon, which is consistent with preventive effects (29, 35, 36). In addition to a possible role in colon cancer prevention, quercetin may be beneficial in the treatment of colon cancer. Quercetin had synergistic activity with cancer chemotherapeutic agents and appeared to reverse multi-drug resistance (37, 38).

In the present study, we evaluated the effects of quercetin on risks of both proximal and distal colon cancers in a case-control study that was conducted in Detroit, MI. This Detroit study provided data on dietary intakes from the Block 98.2 Food Frequency Questionnaire (FFQ) on 2664 cases and matched controls (39). The ability to evaluate proximal and distal colon cancer risk separately in this study was important since these colonic subsites have distinct biological origins and characteristics (40-45). We also evaluated the effects of quercetin on colon cancer subsites stratified by consumption of fruits, vegetables, and tea since these are the major food sources of quercetin. Pooled analyses of cohort studies have indicated that black tea consumption is not protective of colon cancer while fruit and vegetable intake may modestly protect against distal colon cancer (10, 46). It was therefore important to determine the effects of quercetin on risk of colon cancer when intakes of tea, fruit or vegetables were either low or high.

Subjects and Methods

This study was approved by Wayne State University Human Investigation Committee and all subjects gave written informed consent to participate in the study. Details concerning the eligibility, ascertainment, recruitment and characteristics of the study subjects as well as dietary assessment and sample collection procedures in the parent study are described

elsewhere (39). In brief, eligible study subjects were residents in the Metropolitan Detroit Tri-County area (Wayne, Oakland and Macomb counties), between 45 and 80 years of age at time of ascertainment, with a working telephone and no prior history of any invasive cancer, in-situ colorectal cancer or colectomy. Eligible colorectal cancer cases were histologically diagnosed between January 1, 2003 and September 30, 2005, and were identified through the Metropolitan Detroit Cancer Surveillance System. Population controls were selected through random digit dialing and frequency matched to the cases on age, gender, race and county of residence. The cases and controls were well balanced on age, race and county of residence, but gender-matching was incomplete (50% and 57% females in the cases and controls, respectively). Distal colon cancer was defined as that occurring from the descending colon to the rectum, and proximal colon cancer was defined as that occurring from the cecum to the splenic flexure. The subjects were interviewed over the telephone using structured questionnaires regarding their usual diet, and other risk factors for colorectal cancer for a time-period preceding cancer diagnosis (approximately 2 years prior to the interview). Specifically, a validated semi-quantitative food frequency questionnaire (FFQ), Block 98.2 (Block Dietary Data Systems, Berkeley, CA), was used to estimate daily nutrient (including quercetin) intake. The Healthy Eating Index-1996 (HEI) was calculated as part of the FFQ data analysis using 10 food categories: meeting the five major serving recommendations from the Food Guide Pyramid, dietary variety, and intakes of total fat, saturated fat, cholesterol and sodium (47). The residual method described by Willett and Stampfer was chosen as the primary strategy to calculate energy-adjusted nutrient intake (48). The present study included a total of 1163 cases and 1501 controls who completed the study and provided information about basic covariates required for statistical analysis.

Statistical analysis

Dietary predictors for quercetin intake were assessed by means of Spearman correlation coefficients. Dietary quercetin intake was grouped into quartiles based on distributions of the cases and controls combined and the means and proportions of selected subjects' characteristics were calculated according to these quartiles. Unconditional logistic regression models (49) were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) associated with dietary quercetin intake for all colorectal cancer combined, as well as for distal (from the descending colon to the rectum) and proximal (from the cecum to the splenic flexure) colorectal cancer separately. The lowest quartile of quercetin intake was used as the reference category to calculate ORs, and tests for linear trend in the logit of risk associated with ordinal quercetin intake were performed using median intake of each quartile. Because of the unbalanced gender matching, we first calculated bi-variate (gender-adjusted) ORs. Then, additional covariates were selected from established risk factors for colorectal cancer. They were tested one at a time in a model that included basic demographic variables, age, gender and educational levels. Those variables showing an association at the $p \leq 0.10$ level were included to estimate multivariable ORs. Non-dietary covariates included in the final model were age, gender, educational level, family history of colorectal cancer, regular (≥ 3 times per week for 6 months or longer) non-steroidal anti-inflammatory drug (NSAID) use, body mass index in kg/m^2), and physical activity index in their 30s, which was the weighted sum of time the subject spent per 24 hours on physical activity as described previously (50). Next, dietary covariates not directly associated with quercetin intake, i.e., red meat and total (dietary and supplemental) calcium were included in the model. Finally, we added dietary covariates closely correlated with quercetin, i.e., dietary fiber, carotenoids and folate, as well as total fat intake which is known to increase quercetin absorption (51-53), to the model one at a time.

Because the Block Food Frequency questionnaire (version 98.2) does not provide food-specific quercetin intake, additional analyses were performed by stratifying the subjects by intake level of major sources of dietary quercetin, i.e., fruits, vegetables and tea, to explore if the sources of quercetin influenced the association with colorectal cancer. Furthermore, to examine the inter-relationship between quercetin intake and general healthy eating lifestyle (as measured by Healthy Eating Index (HEI) score) in colorectal cancer risk (54), ORs were further calculated for quartiles of quercetin and HEI stratified by the median of the other. These stratified analyses were based on multivariable models that included non-dietary covariates.

Results

Table 1 summarizes the characteristics of the study subjects according to quercetin intake levels. Persons with the highest quercetin intakes tended to be female, college graduates, non-smokers and races other than African American. There were no clear linear relationships with age, total energy intake, physical activity and body mass index. Percent calories from fat were lower with high quercetin intakes, but high HEI scores and intakes of vegetables, fruit, tea, fiber, folate and carotenoids were found with increasing quercetin intake. The foods with the strongest correlations to quercetin intake were tea servings/week (Spearman r=0.650), fruit servings/day (r=0.475), fiber g/day (0.433), carotenoids μg/day (r=0.396), vegetables servings/day (r=0.362), folate μg/day (r=0.328) and vegetable soup servings/week (r=0.323). Mean intakes of quercetin were 8.47 mg/day for controls (n=1501, SD 6.42) and 8.20 in cases (n=1163, SD 6.53) (p=0.157). Mean intakes in cases with proximal cancer were lower than in cases with distal cancer (7.63 vs. 8.63 mg/day, respectively, p=0.012).

Quercetin intake was inversely associated with risk of proximal but not distal colorectal cancer in the analyses adjusted for gender (Table 2). This association was weakened by further adjustment for fiber or folate. The protective effect of quercetin on proximal colon cancer risk remained significant after adjustment for carotenoid intakes, perhaps since many fruits and vegetables high in carotenoids are not high in flavonoids. With regard to risk of distal colorectal cancer, intake of quercetin had no significant effect in the models adjusted for demographic factors. After adjustment for dietary fiber and folate, however, increased quercetin intake was significantly associated with increased distal colorectal cancer risk (Table 2). The adjustment for folate and fiber may minimize the contribution of fruits and vegetables to quercetin intakes, leaving tea as the major source of quercetin.

The effects of quercetin intake on site-specific colorectal cancer risk were also evaluated when stratifying by intakes of fruit, vegetables and tea (Table 3). Average intake in the low and high consumption groups were 0.53 vs. 2.05 servings/day for fruits , 2.00 vs. 5.06 servings/day for vegetable and 0.08 and 7.66 cups/week for tea, respectively. Increased quercetin intake was protective against proximal colon cancer risk when fruit intake was at or above 1 serving/day or when tea intake was low. For distal colorectal cancer, increased quercetin intake increased risk, but only when intake of fruit was low.

Finally, we evaluated the inter-relationship between quercetin intake and the Healthy Eating Index (HEI) on colorectal cancer risk (Table 4). When the HEI score was high, increased quercetin intake was associated with reduced risk of proximal colon cancer (p=0.003). When the HEI score was low, increased quercetin intake increased distal colorectal cancer risk but this did not reach statistical significance (p=0.078). This was similar to the effects of fruit intake. When stratified by quercetin intake, increased HEI score was protective against colorectal cancer only when quercetin intake was high. This protective trend with increasing

quartiles of HEI score was evident on both proximal (p=0.012) and distal (p=0.055) colorectal cancer, but the trend was not quite significant for distal colon cancer.

Discussion

The present study suggests that quercetin may have a site-dependent effect on risk of colorectal cancer, with protection in the proximal but not distal colon (Table 2). This is of clinical relevance since proximal colon cancer is associated with higher mortality than distal cancer (55, 56). Patients with proximal colon cancer tend to be older and have more advanced cancer at diagnosis than patients with distal colon cancer (42, 57). This difference is likely a combination of several factors such as those stemming from region-specific differences in biology and/or to limitations of screening methodology. Proximal and distal colon cancers arise from different molecular pathways, and these two regions of the colon have different embryonic origins (40-44). During development, patterns of gene expression also differentiate proximal and distal colon (45). It is therefore not surprising that preventive agents might have differential activity against proximal and distal colon cancers. For example, in a Japanese study, omega 3 polyunsaturated fatty acids decreased proximal colon cancer risk but increased distal colon cancer risk (58). Sulindac in the mouse model likewise exhibits opposite effects in the two regions of the colon, being protective in the distal colon and increasing risk in proximal colon (59). Prudent diets, calcium and vitamin D have been shown to be protective against distal colon cancer only (10, 60, 61).

A limited number of other epidemiological studies have reported data for quercetin and risk of colorectal cancer. Several large studies reported no association of quercetin intake with colon cancer risk, but risk in sub-sites of the colon were not examined (14, 62, 63). One large case control in Italy did find a significant protective effect of flavonol and flavone intakes on colorectal cancer risk (64). In the Polyp Prevention Trial, a high intake of total flavonols was associated with decreased risk of advanced adenoma recurrence (OR 0.24) (65). Interestingly, a population-based case-control study in the United Kingdom showed that non-tea flavonol intake and non-tea quercetin intake were inversely associated with colon but not rectal cancer risk (66).

In the present study, we were able to evaluate subsite-specific effects of quercetin and to control for various food sources of quercetin. The results showed a significant protective effect of quercetin in the proximal colon when fruit intake was high or tea intake was low (Table 3). Although other nutrients present in the foods together with quercetin could be responsible for this, the major source of quercetin would be fruits and vegetables when tea intake is low. In the distal colon, cancer risk increased with higher quercetin intake when fruit intake was low, suggesting that quercetin intake from tea might have different effects than quercetin from fruit. However, these effects could be due to other chemical compounds in tea that are independent of quercetin content. In fact, tea intake itself was positively associated with the risk distal colon cancer in the Detroit study (P=0.005, data not shown), and an increased risk of colon cancer with tea consumption was also reported in a pooled analysis of cohort studies (46). Although green tea has perhaps more potential for prevention of colon cancer, intakes of green tea in the U.S. are low (1, 2).

The potential protective association of quercetin with proximal colon cancer was considerably attenuated in the multivariable models which included dietary covariates. The effect was most pronounced when dietary fiber was included in the model (Table 2). This may be accounted for by the fact that dietary fiber showed the strongest positive correlation (r=0.433) with quercetin intake and a strong inverse association with colorectal cancer risk overall in these study subjects (P<0.001), whereas carotenoids and folate had weaker correlations with quercetin (r=0.396 and 0.328, respectively) and their relations with

colorectal cancer risk were nonexistent (p=0.974) or weak (p=0.086), respectively. Thus, it is possible that the protective effect of quercetin was primarily attributable to the simultaneous intake of dietary fiber, as the inverse association with dietary fiber remained significant (p=0.003) for all cancer combined and distal cancer or was stronger than that with quercetin (p=0.144) for proximal cancer when they were entered in the model simultaneously. Fiber from foods has been shown to have protective effects on risk of colon cancer (67). On the other hand, because of the relatively strong co-linearity between these two dietary intakes, it may be difficult to disentangle both effects. Nevertheless, the results from Table 4 are intriguing, since quercetin may exert protective effect against proximal colon cancer only in the context of a healthy diet. In other words, it could be hypothesized that adding quercetin to a poor quality diet as a supplement might not be a good strategy for colorectal cancer prevention. Also, the results suggest that a healthy diet that incorporates quercetin rich foods may help in reducing the risk of colorectal cancer.

There are several mechanisms by which quercetin could function to prevent proximal colon cancer. Most nutrient absorption occurs in the small intestine, but there is still some nutrient absorption in the colon with the proximal colon being exposed to more luminal nutrients than the distal colon. Querectin in the luminal contents could reduce oxidative damage, decrease formation of advanced glycation end products and chelate iron (68-70). In addition, quercetin has been shown to function as an epigenetic regulator (71). Tumors of the proximal colon are known to have a much higher prevalence of be microsatellite-instability, which is derived from gene silencing, and could therefore be more susceptible to the preventive effects of agents with epigenetic effects such as quercetin (72, 73).

One of the limitations of this study is that the Block Food Frequency Questionnaire does not specifically ask about onion intake. Nutrient intakes for the Block 98.2 FFQ were calculated at the food level, not the ingredient level, and quercetin intake from soups and stews was captured. In the present study, however, the median total quercetin intake was 6 mg/day, which is lower than in most studies. Mean and median estimates have ranged from 9-18 mg/day using the Harvard FFQ (1, 13, 14). In a case-control study of lung cancer using a brief version of the Block FFQ, estimates of quercetin intake were similar to ours. In the Multi-ethnic cohort in Hawaii using a population-specific FFQ that also does not ask about onion intake, median intake of quercetin was about 10 mg/day (15, 16). In addition to differences between studies due to the nature of the questionnaire and the populations studied, differences will arise due to the database used for nutrient composition and to the assumptions made in the calculations. The present results are best interpreted for quercetin intakes from foods other than onions. Here, quercetin was significantly inversely associated with risk of proximal colon cancer only when fruit intake or the HEI score was high. In this case, more of the quercetin intake would be from fruit versus tea. In addition, fruit contains fiber and fiber has been shown to increase bioavailability of quercetin via increased hydrolysis of glycosides (74).

We acknowledge the limitations of this case-control study that have been discussed elsewhere in detail, including the possibility of self-selection bias, volunteer bias and/or recall bias (75, 76). To address these concerns, we adjusted for factors potentially indicative of these biases in statistical analyses and used structured, not open-ended questionnaires to collect information. Yet, it is possible that unmeasured factors may have confounded the analysis. Other flavonoids that are present along with quercetin in fruits, vegetables and tea could account for the present observations. Bioavailability of nutrients including flavonoids is known to vary depending on food preparation methods, which is not accounted for with the food frequency questionnaire. In addition, we are aware of the likelihood that some of the associations observed in this study may be chance findings due to multiple comparisons, particularly for stratified analyses, and that caution should be excised in interpreting the

results of any posterior analyses such as that in this study. Strengths of the study include the large sample size, investigation of different quercetin food sources and the ability to evaluate effects of diet on cancer in different regions of the colon. The results were statistically significant despite use of an FFQ, a dietary assessment method that can attenuate diet-disease associations (77).

In summary, the relationships between quercetin intake and colon cancer were complex. Importantly, the effects of quercetin differed for proximal and distal colon cancer. The effects also appeared to differ by food sources of quercetin. There were inverse associations between quercetin from fruits and vegetables and proximal cancer risk, whereas quercetin intake primarily from tea was positively associated with risk of distal cancer. We suggest that this should be investigated more fully in animal models where it might be possible to separate the effects of quercetin per se from the effects of the foods which contain quercetin along with other components.

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Abbreviations

(CI)	confidence interval
(FFQ)	food frequency questionnaire
(HEI)	Healthy Eating Index
(NSAID)	non-steroidal anti-inflammatory drug
(ORs)	odds ratios
(Q)	quartile

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Table 1

Characteristics of study subjects according to quartiles of quercetin intake

Characteristics	Quercetin intake (mg/day) quartiles			
	Q1 (0-4.32) N=666	**Q1 (4.33-6.30) N=666**	**Q3 (6.31-10.28) N=666**	**Q4 (>10.28) N=666**
	Proportions			
Males	55.26%	45.50%	43.69%	38.59%
African American	32.88%	27.63%	26.13%	18.92%
College graduates	21.77%	28.38%	29.73%	31.53%
Current smokers	33.03%	19.16%	14.63%	15.69%
Regular alcohol use	22.52%	17.42%	20.42%	15.62%
NSAID use[a]	24.32%	29.13%	27.33%	29.73%
Multivitamin use	42.49%	48.80%	61.56%	60.81%
	Means			
Age	60.68	63.39	63.43	63.55
Body mass index	28.92	28.82	28.58	28.15
Physical activity index age 30-39	35.41	34.22	35.17	36.05
Physical activity index last 2 years	31.20	30.62	31.06	31.46
Total calorie intake (kcal/day)	2477.95	2044.32	2165.59	2374.94
Calories from fat (%)	39.50	37.60	36.80	36.13
Trans fatty acids (g/day)	8.59	8.01	7.41	7.11
Omega-3 fatty acids (g/day)	2.00	2.09	2.12	2.10
Total calcium (mg/day)	911.59	1037.27	1105.30	1194.51
Red Meat (servings/week)	12.33	8.99	8.70	9.18
Dietary fiber (g/day)	16.00	19.16	21.16	23.13
Dietary folate (mcg/day)	448.80	518.13	553.09	581.31
Carotenoids (mcg/day)	3466.32	4614.40	5914.06	6786.00
Tea (cups per week)	0.22	0.58	2.01	10.29
Fruits (servings/day)	0.89	1.39	1.85	2.22
Vegetable (servings/day)	2.78	3.23	4.11	4.78
Healthy Eating score	55.27	62.91	65.28	67.25

[a]NSAID: non-steroidal anti-inflammatory drug, use was defined as at least three times a week for 6 months or more.

Table 2

Odds ratios and 95% confidence intervals for colorectal cancer according to quartile levels of dietary quercetin intake

Cases/controls	Covariates adjusted	Quercetin intake (mg/day) quartiles				Trend P-value
		Q1 (< 4.33)	Q2 (4.33-6.30)	Q3 (6.31-10.28)	Q4 (≥ 10.29)	
Controls		347	400	365	389	
All cases		319	266	301	277	
	Gender	1.00	0.74 (0.60-0.92)	0.93 (0.75-1.15)	0.81 (0.65-1.01)	0.289
	All non-dietary factors[a]	1.00	0.76 (0.61-0.95)	0.98 (0.78-1.22)	0.88 (0.71-1.11)	0.816
	All non-dietary+ partial dietary (#3)[c]	1.00	0.80 (0.64-1.00)	1.05 (0.84-1.32)	0.95 (0.76-1.20)	0.726
	#3 + Total fat	1.00	0.79 (0.63-0.99)	1.04 (0.83-1.30)	0.93 (0.74-1.18)	0.872
	#3 + Dietary fiber	1.00	0.84 (0.67-1.05)	1.15 (0.91-1.45)	1.08 (0.85-1.37)	0.197
	#3 + Dietary carotenoids	1.00	0.79 (0.63-1.00)	1.04 (0.82-1.30)	0.94 (0.74-1.19)	0.876
	#3 + Dietary folate	1.00	0.80 (0.64-1.01)	1.06 (0.84-1.33)	0.96 (0.76-1.22)	0.663
Proximal[b]		148	114	125	96	
	Gender	1.00	0.67 (0.51-0.89)	0.81 (0.61-1.07)	0.59 (0.44-0.79)	0.004
	All non-dietary factors	1.00	0.66 (0.49-0.88)	0.83 (0.62-1.12)	0.63 (0.47-0.86)	0.026
	All non-dietary+ partial dietary (#3)	1.00	0.71 (0.53-0.95)	0.91 (0.68-1.23)	0.70 (0.51-0.95)	0.097
	#3 + Total fat	1.00	0.70 (0.52-0.94)	0.90 (0.67-1.21)	0.68 (0.50-0.93)	0.074
	#3 + Dietary fiber	1.00	0.73 (0.54-0.98)	0.97 (0.71-1.32)	0.76 (0.55-1.05)	0.273
	#3 + Dietary carotenoids	1.00	0.69 (0.51-0.93)	0.86 (0.64-1.17)	0.65 (0.47-0.90)	0.038
	#3 + Dietary folate	1.00	0.70 (0.52-0.94)	0.89 (0.66-1.21)	0.68 (0.49-0.94)	0.083
Distal[b]		169	150	174	181	
	Gender	1.00	0.80 (0.62-1.05)	1.02 (0.79-1.33)	1.02 (0.79-1.33)	0.366
	All non-dietary factors	1.00	0.84 (0.64-1.10)	1.10 (0.84-1.43)	1.13 (0.87-1.47)	0.113
	All non-dietary+ partial dietary (#3)	1.00	0.88 (0.67-1.16)	1.17 (0.89-1.53)	1.20 (0.92-1.57)	0.053
	#3 + Total fat	1.00	0.88 (0.67-1.15)	1.15 (0.88-1.51)	1.18 (0.90-1.55)	0.077
	#3 + Dietary fiber	1.00	0.93 (0.71-1.22)	1.29 (0.98-1.70)	1.39 (1.04-1.84)	0.005
	#3 + Dietary carotenoids	1.00	0.89 (0.68-1.17)	1.18 (0.90-1.56)	1.23 (0.93-1.62)	0.047
	#3 + Dietary folate	1.00	0.90 (0.68-1.18)	1.20 (0.91-1.58)	1.25 (0.95-1.64)	0.034

[a]Non-dietary covariates included age, gender, physical activity at age 30-39, body mass index, family history of colorectal cancer, highest education achieved, and NSAID use.

[b] Distal colon: from the descending colon to the rectum; proximal colon: from the cecum to the splenic flexure.

[c] Dietary covariates in model #3 include non-quercetin associated items, red meat and total calcium intake

Table 3

Odds ratios and 95% confidence intervals for colorectal cancer according to quartile levels of quercetin intake (Q1 by major food sources of quercetin (fruits, vegetable and tea)[a]

	Fruit servings		**Vegetable servings**		**Tea**	
	< 1/day	**≥ 1 day**	**< 3/day**	**≥ 3/day**	**< 1cup /week**	**≥ 1 cup/week**
Controls	456	1045	630	871	867	634
All Cases	361	802	538	625	673	490
Q1	1.00 -	1.00 -	1.00 -	1.00 -	1.00 -	1.00 -
Q2	0.82 (0.57-1.18)	0.60 (0.44-0.82)	0.67 (0.50-0.90)	0.93 (0.65-1.32)	0.82 (0.64-1.05)	0.51 (0.28-0.93)
Q3	1.32 (0.87-2.00)	0.72 (0.53-0.97)	0.86 (0.61-1.20)	1.20 (0.86-1.67)	0.88 (0.67-1.17)	0.94 (0.54-1.62)
Q4	1.63 (1.04-2.58)	0.62 (0.46-0.84)	0.94 (0.66-1.34)	1.01 (0.72-1.40)	0.64 (0.40-1.01)	0.81 (0.48-1.38)
Trend P	0.015	0.063	0.907	0.944	0.067	0.590
Proximal	168	315	238	245	295	188
Q1	1.00 -	1.00 -	1.00 -	1.00 -	1.00 -	1.00 -
Q2	0.67 (0.41-1.07)	0.59 (0.40-0.88)	0.53 (0.36-0.78)	1.04 (0.64-1.68)	0.76 (0.55-1.05)	0.34 (0.16-0.72)
Q3	1.20 (0.71-2.02)	0.68 (0.46-1.00)	0.65 (0.41-1.01)	1.29 (0.82-2.03)	0.81 (0.56-1.18)	0.63 (0.32-1.24)
Q4	1.31 (0.79-2.36)	0.49 (0.32-0.73)	0.60 (0.37-0.98)	0.90 (0.56-1.44)	0.51 (0.26-1.00)	0.47 (0.25-0.91)
Trend P	0.256	0.006	0.075	0.381	0.044	0.346
Distal	192	482	297	377	373	301
Q1	1.00 -	1.00 -	1.00 -	1.00 -	1.00 -	1.00 -
Q2	0.98 (0.63-1.52)	0.61 (0.43-0.88)	0.82 (0.57-1.18)	0.88 (0.58-1.33)	0.88 (0.65-1.19)	0.69 (0.33-1.45)
Q3	1.44 (0.87-2.37)	0.76 (0.53-1.07)	1.09 (0.73-1.63)	1.14 (0.78-1.68)	0.95 (0.68-1.33)	1.25 (0.63-2.46)
Q4	1.99 (1.17-3.39)	0.74 (0.52-1.05)	1.30 (0.86-1.97)	1.11 (0.76-1.63)	0.79 (0.46-1.34)	1.21 (0.63-2.35)
Trend P	0.006	0.725	0.096	0.347	0.435	0.115

[a]Non-dietary covariates included age, gender, physical activity age 30-39, body mass index, family history of colorectal cancer, highest education achieved, and NSAID use. Table 2 has definitions of colorectal subsites and quercetin quartiles.

Table 4

Odds ratios (OR) and 95% confidence intervals (CI) for colorectal cancer according to quartile levels of quercetin intake (Q1-Q4) by stratified by Healthy Eating Index score and according to quartiles of Healthy Eating Index Score stratified by quercetin intake[a].

Quercetin quartile	Healthy Eating Score (HEI)[b]		HEI quartile	Quercetin intake (g/day)	
	≤ 63	> 63		≤ 6.305	> 6.305
Controls	737	764	Controls	747	754
All cases	615	548	All cases	585	578
Q1	1.00 -	1.00 -	Q1	1.00 -	1.00 -
Q2	0.66 (0.49-0.88)	0.85 (0.58-1.24)	Q2	0.88 (0.67-1.17)	0.80 (0.56-1.15)
Q3	1.13 (0.84-1.52)	0.85 (0.58-1.24)	Q3	1.20 (0.88-1.63)	0.75 (0.53-1.07)
Q4	1.08 (0.79-1.49)	0.77 (0.53-1.12)	Q4	0.59 (0.42-0.83)	0.59 (0.42-0.83)
Trend P	0.204	0.234	Trend P	0.632	0.002
Proximal[c]	256	227	Proximal	262	221
Q1	1.00 -	1.00 -	Q1	1.00 -	1.00 -
Q2	0.59 (0.40-0.87)	0.67 (0.41-1.07)	Q2	0.75 (0.51-1.10)	0.66 (0.41-1.06)
Q3	1.11 (0.75-1.65)	0.59 (0.36-0.94)	Q3	1.18 (0.79-1.75)	0.61 (0.38-0.97)
Q4	0.89 (0.57-1.37)	0.44 (0.27-0.72)	Q4	0.92 (0.58-1.45)	0.46 (0.29-0.73)
Trend P	0.902	0.003	Trend P	0.901	0.012
Distal[c]	357	317	Distal	319	355
Q1	1.00 -	1.00 -	Q1	1.00 -	1.00 -
Q2	0.71 (0.50-1.00)	1.10 (0.67-1.79)	Q2	0.98 (0.70-1.37)	0.89 (0.58-1.35)
Q3	1.13 (0.79-1.60)	1.21 (0.75-1.95)	Q3	1.22 (0.85-1.76)	0.85 (0.56-1.29)
Q4	1.25 (0.86-1.80)	1.24 (0.77-2.00)	Q4	0.64 (0.40-1.02)	0.69 (0.47-1.03)
Trend P	0.078	0.380	Trend P	0.352	0.055

[a] Non-dietary covariates included age, gender, physical activity age 30-39, body mass index, family history of colorectal cancer, highest education achieved, and NSAID use.

[b] Quartiles (Q1-Q4) of the scores are <=54, 55-63, 64-71 and >=72, respectively; ORs for Q2-Q4 in the overall population are 0.88, 1.00,a and 0.73 (P =0.024) for all colorectal cancer, 0.73,0.87,0.65 (P=0.019) for proximal cancer and 0.98,1.08, and 0.79 (P=0.160) for distal cancer, respectively.

[c] Distal colon: from the descending colon to the rectum; proximal colon: from the cecum to the splenic flexure.