Carotenoids and colon cancer[1–4]

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ABSTRACT

Background: Carotenoids have numerous biological properties that may underpin a role for them as chemopreventive agents. However, except for β-carotene, little is known about how dietary carotenoids are associated with common cancers, including colon cancer.

Objective: The objective of this study was to evaluate associations between dietary α-carotene, β-carotene, lycopene, lutein, zeaxanthin, and β-cryptoxanthin and the risk of colon cancer.

Design: Data were collected from 1993 case subjects with first primary incident adenocarcinoma of the colon and from 2410 population-based control subjects. Dietary data were collected from a detailed diet-history questionnaire and nutrient values for dietary carotenoids were obtained from the US Department of Agriculture–Nutrition Coordinating Center carotenoid database (1998 updated version).

Results: Lutein was inversely associated with colon cancer in both men and women [odds ratio (OR) for upper quintile of intake relative to lowest quintile of intake: 0.83; 95% CI: 0.66, 1.04; $P = 0.04$ for linear trend]. The greatest inverse association was observed among subjects in whom colon cancer was diagnosed when they were young (OR: 0.66; 95% CI: 0.48, 0.92; $P = 0.02$ for linear trend) and among those with tumors located in the proximal segment of the colon (OR: 0.65; 95% CI: 0.51, 0.91; $P < 0.01$ for linear trend). The associations with other carotenoids were unremarkable.

Conclusion: The major dietary sources of lutein in subjects with colon cancer and in control subjects were spinach, broccoli, lettuce, tomatoes, oranges and orange juice, carrots, celery, and greens. These data suggest that incorporating these foods into the diet may help reduce the risk of developing colon cancer. *Am J Clin Nutr* 2000;71:575–82.

KEY WORDS α-Carotene, β-carotene, β-cryptoxanthin, carotenoids, smoking, colon cancer, lutein, lycopene, zeaxanthin, men, women

INTRODUCTION

Carotenoids are pigments found primarily in plants. The predominant carotenoids in plasma are β-carotene, lycopene, lutein, β-cryptoxanthin, and α-carotene (1). Carotenoids, long recognized for their antioxidant properties, are of increasing interest in relation to cancer because of their effect on regulation of cell growth, modulation of gene expression, and, possibly, immune response (2). Because of the many biological properties of carotenoids, the role of carotenoids in modulating the cancer process is of interest, especially because plant foods, the primary dietary source of carotenoids, were shown to be inversely associated with cancer in numerous epidemiologic studies (3–5). The protective properties of plant foods can most likely be attributed to their rich composite of beneficial nutrients and biologically active compounds. However, one of these compounds, β-carotene, has been inconsistently associated with colon cancer (4). Additionally, although other dietary carotenoids were shown to be associated with risk of other cancers (6, 7), their associations with colon cancer are generally unknown.

The purpose of this study was to examine whether dietary carotenoids are associated with colon cancer. We examined the associations of intake of α-carotene, β-carotene, lycopene, lutein, zeaxanthin, and β-cryptoxanthin in conjunction with age at diagnosis and tumor site within the colon because other studies showed these to be important modifiers of dietary associations (8, 9). We also evaluated associations by smoking status, because compounds found in cigarette smoke can deplete carotenoids and alter the body's carotenoid requirements (10).

SUBJECTS AND METHODS

Study population

Study participants were white (91.3%), black (4.2%), or Hispanic (4.4%) and members of the Kaiser Permanente Medical Care Program of Northern California, in an 8-county area in Utah (Davis, Salt Lake, Utah, Weber, Wasatch, Tooele, Morgan, and Summit counties), and in the metropolitan Twin Cities area of Minnesota (Anoka, Carver, Dakota, Hennepin, Ramsey, Scott,

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and Washington counties). A rapid reporting system was used to identify case subjects, and most case subjects were interviewed within 4 mo of diagnosis. Eligibility criteria for case subjects included diagnosis of first primary incident colon cancer [International Classification of Diseases of Oncology (2nd ed) codes 18.0 and 18.2–18.9] between 1 October 1991 and 30 September 1994; age of 30–79 y at the time of diagnosis; and mental competence to complete the interview. Case subjects with cancers of the rectosigmoid junction or rectum (defined as the first 15 cm from the anal opening) and with known familial adenomatous polyposis, ulcerative colitis, or Crohn disease were not eligible. Of the case subjects invited to participate in the study, ≈76% did so. Methods used to recruit control subjects were reported previously and included random selection from Kaiser Permanente membership lists, driver's license lists, Social Security lists, and random-digit dialing (11). Of all control subjects asked to participate, ≈64% did so. Reasons for nonparticipation were described previously (12). A total of 1993 case subjects and 2410 control subjects with complete data were included in the analyses presented. Ethical guidelines for the study were reviewed and approved by local institutional review boards.

Data collection

Data were collected from study participants by trained and certified interviewers using laptop computers. The study questionnaire was pretested on a group of people aged >50 y and living in Utah (randomly selected by using random-digit dialing). The referent period that study participants were asked to recall was the calendar year 2 y before the date of selection (the date of diagnosis for case subjects or date of selection for control subjects). The interview took ≈2 h to complete. Quality-control methods used in the study were described previously (13, 14).

Dietary intake

Dietary intake data were collected by using an adaptation of the validated Coronary Artery Risk Development in Young Adults (CARDIA) diet-history questionnaire (14–16). Participants were asked to report which foods were eaten (using brand names of food items such as fast foods, cookies, crackers, and cereals, when possible), the frequency with which these foods were eaten, and the amount of fat used to prepare other foods. Three-dimensional food models were used to help participants estimate their usual serving size. Cue cards were used to facilitate the consistent identification of foods within broad categories. For items for which many types of food within a category might have been eaten (eg, breakfast cereal), participants were asked to report the 3 most commonly eaten items. As part of the diet history, detailed information was obtained on foods eaten as additions to other foods (eg, sugar added to cereal); standard amounts of additions were assigned per unit of the food item they accompanied. More than 800 separate food items are listed on the CARDIA diet-history questionnaire to enable more accurate values to be obtained for specific foods eaten. Thus, using individual food items rather than major groups allows for assessment of specific foods eaten. Nutrients were calculated by using the Minnesota Nutrition Coordinating Center (NCC) nutrient database (version 19) (17).

Carotenoid data

Part of the adapted CARDIA diet-history questionnaire sought information on the consumption of fruit, vegetables, and other carotenoid-containing foods (eg, dairy products). Fruit, vegetables, and other food items were given separate food codes from the US Department of Agriculture (USDA)-NCC Database for US Foods (1998 updated version) (18). This database was developed through a collaborative effort between the USDA and the NCC that was supported by the National Cancer Institute. Carotenoid values were available for α-carotene, lutein, lycopene, zeaxanthin, and β-cryptoxanthin for 215 raw, canned, frozen, and cooked fruit and vegetables and for foods such as eggs, cheese, and vegetable-containing casseroles, soups, and stews that are sources of carotenoids; zeaxanthin values only were available for 22 foods. A level of confidence was given as to the estimated carotenoid content of each food. Levels of confidence ranged from A (highest) to C (lowest). For many food items, a lower level of confidence was given because data on carotenoid content were available from only one source rather than from multiple sources (M Forman, personal communication, 1999). For some carotenoids, such as zeaxanthin, food data were limited and included only major food sources. Values for β-carotene were obtained from the NCC nutrient database (version 19) for consistency with study data published elsewhere. Because we grouped all cooked greens together on the CARDIA diet-history questionnaire, β-carotene, α-carotene, lutein, lycopene, and zeaxanthin values were calculated for this food category by averaging the contribution of these nutrients from beet greens, collards, kale, turnip greens, and Swiss chard. In addition, all natural cheeses (Cheddar, Swiss, and Monterey jack) were grouped together in the CARDIA diet-history questionnaire. In our analysis we used the carotenoid values for Cheddar cheese because this is the most frequently eaten cheese in the cheese category (19). Because the CARDIA diet-history questionnaire included corn bread, whereas the USDA-NCC carotenoid database listed only cornmeal, the carotenoid content of corn bread was calculated on the basis of the approximate amount of cornmeal used in a corn bread recipe. Foods identified in this study as contributing to carotenoid intakes were based on items reported in the database.

Other data

Other data obtained and used in these analyses were age at the time of diagnosis or selection; body mass index (BMI; in kg/m^2), self-reported for the referent year; the presence or absence of a history of colorectal cancer among first-degree relatives; use of aspirin or other nonsteroidal antiinflammatory drugs (NSAIDs) regularly; usual number of cigarettes smoked; and long-term vigorous leisure-time activity (20). Physical activity at home and at leisure was ascertained by using an adaptation of the validated CARDIA physical activity history (20). Tumor site within the colon was classified as proximal (cecum through transverse colon) or distal (splenic flexure and descending and sigmoid colon).

Statistical analyses

To determine the associations between carotenoid intakes and colon cancer, we calculated odds ratios (ORs) and 95% CIs from unconditional logistic regression models (SAS, SAS Institute, Inc, Cary, NC; BMDP, SPSS Inc, Chicago). In these analyses, total energy intake, dietary folate and fiber intakes, age at selection, sex, BMI, and long-term vigorous physical activity were used as covariates. Differences in associations were evaluated for age (using the median age of the control subjects of 67 y as the cutoff), tumor site, and smoking status (never smoker, ex-smoker, or current smoker).

TABLE 1
Characteristics of subjects with or without colon cancer

	Men			Women		
	Case subjects	Control subjects	*P*	Case subjects	Control subjects	*P*
Daily dietary intake						
Energy						
(kJ)	11 510 ± 5096[1]	11 092 ± 5008		8644 ± 3820	8330 ± 3590	
(kcal)	2751 ± 1218	2651 ± 1197	0.04	2066 ± 913	1991 ± 858	0.06
Dietary fiber (g)	26.5 ± 12.7	27.0 ± 12.6	0.36	22.8 ± 10.4	22.9 ± 10.2	0.85
Folate (μg)	421 ± 208	422 ± 201	0.97	347 ± 156	352 ± 159	0.47
Carotenoids (μg)						
α-Carotene	1043 ± 1186	1174 ± 1413	0.05	1194 ± 1283	1236 ± 1383	0.47
β-Carotene	5950 ± 6808	6001 ± 5036	0.84	6173 ± 5106	5998 ± 5042	0.44
Lutein	1050 ± 1136	1177 ± 1394	0.01	1211 ± 1296	1232 ± 1114	0.70
Lycopene	6408 ± 6835	6581 ± 7778	0.56	5622 ± 6134	5672 ± 6462	0.86
Zeaxanthin	161 ± 115	164 ± 122	0.56	153 ± 110	155 ± 107	0.70
β-Cryptoxanthin	176 ± 186	172 ± 167	0.57	169 ± 163	166 ± 152	0.68
Physical activity score	6.9 ± 3.0	7.5 ± 3.1	<0.01	5.9 ± 3.0	6.4 ± 3.0	<0.01
BMI (kg/m^2)	28.1 ± 4.6	27.0 ± 4.3	<0.01	27.1 ± 6.0	26.4 ± 5.4	<0.01
NSAID[2] users						
Yes	416 (37.9)[3]	606 (47.0)	<0.01	329 (36.8)	544 (48.6)	<0.01
No	683 (62.1)	684 (53.0)		565 (63.2)	576 (51.4)	
Family history of colorectal cancer						
Yes	177 (16.1)	110 (8.5)	<0.01	133 (14.9)	118 (10.5)	<0.01
No	922 (83.9)	1180 (91.5)		761 (85.1)	1002 (89.5)	
Smoking status						
Never smoker	336 (30.6)	485 (37.6)	<0.01	487 (54.6)	636 (56.8)	0.61
Exsmoker	599 (54.6)	620 (48.1)		271 (30.4)	321 (28.7)	
Current smoker	162 (14.8)	185 (14.3)		134 (15.0)	163 (14.5)	

[1] $\bar{x}$ ± SD.
[2] Nonsteroidal antiinflammatory drug.
[3] *n*; % in parentheses.

RESULTS

Except for lutein and α-carotene in men, there were no significant differences between case and control subjects in mean intakes of carotenoids (**Table 1**). The top 10 contributors of α-carotene to the diet were carrots, apples, winter squash, beef stew and soup, tomatoes, mixed vegetables, green peas, vegetable juice, cantaloupe, and chicken and vegetable stir-fry. For β-carotene, the major contributors were carrots, sweet potatoes, cantaloupe, spinach, beef stew and mixed dishes, broccoli, romaine lettuce, tomato and vegetable juices, winter squash, and Cheddar cheese. Spinach, broccoli, lettuce, tomatoes, carrots, oranges and orange juice, celery, greens, and eggs were the major contributors of lutein. Lycopene was obtained primarily from tomatoes (including tomato juice, tomato soup, ketchup, and vegetable soups), vegetable juice, watermelon, grapefruit, lasagna, pizza, mixed dishes, apricots, and persimmons. Zeaxanthin was contributed primarily by oranges and orange juice, lettuce, romaine, green peas, eggs, spinach, corn, peaches, carrots, and corn bread. The major contributors of β-cryptoxanthin were oranges and orange juice, peaches, papayas, mangoes, watermelon, nectarines, fruit cocktail, plums, grapefruit, and black olives. Significant differences between case and control subjects were observed for both men and women in amount of physical activity, BMI, NSAID use, and family history of colorectal cancer among first-degree relatives.

Lutein intake was significantly associated with colon cancer in persons in whom cancer was diagnosed before the age of 67 y (**Table 2**). Additionally, for this group there was a significant inverse linear trend with increasing lutein intake. Intakes of α-carotene, β-carotene, lycopene, zeaxanthin, and β-cryptoxanthin were not significantly associated with colon cancer. There were no meaningful differences in detected associations between men and women.

Evaluation of associations between carotenoid intakes and colon cancer by site of tumor within the colon showed that a high intake of lutein was inversely associated with risk of proximal tumors (**Table 3**). None of the other carotenoids was significantly associated with colon cancer, although there were suggestions that a high intake of β-carotene slightly increased the risk of colon tumors.

Assessment by smoking status showed that lutein intake was more strongly associated with risk of colon cancer in current smokers than in subjects who had never smoked, although, given that there were few current smokers, we were limited in our ability to detect a significant association (**Table 4**). The *P* value for the interaction between age, lutein intake, and smoking status was 0.15. None of the other carotenoids was significantly associated with colon cancer within any of the categories of smoking status, although there were suggestions of an increased risk among smokers who consumed high amounts of β-carotene.

Stratification of the population on the basis of their family history of colorectal cancer (data not shown in table) showed inverse associations for lutein intake among subjects without a family history of colorectal cancer (OR for upper quintile relative to lower quintile of intake: 0.82; 95% CI: 0.64, 1.05; *P* = 0.02 for linear trend); lutein was not inversely associated

TABLE 2
Associations between carotenoids and colon cancer[1]

	Median intake	All subjects		Subjects <67 y of age		Subjects ≥67 y of age	
		OR (95% CI)	*P* for linear trend	OR (95% CI)	*P* for linear trend	OR (95% CI)	*P* for linear trend
	μg						
α-Carotene[2]							
Low quintile (*n* = 452 cases, 481 controls)	165	1.00		1.00		1.00	
Quintile 2 (*n* = 377 cases, 483 controls)	442	0.87 (0.72, 1.06)		0.77 (0.59, 1.01)		0.99 (0.75, 1.31)	
Quintile 3 (*n* = 383 cases, 482 controls)	786	0.88 (0.73, 1.07)		0.70 (0.54, 0.92)		1.13 (0.86, 1.49)	
Quintile 4 (*n* = 424 cases, 482 controls)	1302	0.98 (0.81, 1.20)		0.77 (0.58, 1.01)		1.29 (0.97, 1.71)	
High quintile (*n* = 357 cases, 482 controls)	2636	0.88 (0.71, 1.09)	0.58	0.82 (0.60, 1.12)	0.16	0.96 (0.71, 1.30)	0.52
β-Carotene[3]							
Low quintile (*n* = 402 cases, 482 controls)	1889	1.00		1.00		1.00	
Quintile 2 (*n* = 378 cases, 482 controls)	3204	1.03 (0.85, 1.25)		0.87 (0.66, 1.16)		1.23 (0.93, 1.61)	
Quintile 3 (*n* = 377 cases, 482 controls)	4678	1.00 (0.82, 1.22)		0.75 (0.57, 1.00)		1.34 (1.01, 1.78)	
Quintile 4 (*n* = 419 cases, 482 controls)	6829	1.14 (0.93, 1.40)		0.97 (0.72, 1.30)		1.36 (1.02, 1.81)	
High quintile (*n* = 408 cases, 482 controls)	11 399	1.18 (0.94, 1.49)	0.10	1.05 (0.75, 1.48)	0.72	1.34 (0.96, 1.85)	0.06
Lutein[4]							
Low quintile (*n* = 451 cases, 480 controls)	300	1.00		1.00		1.00	
Quintile 2 (*n* = 433 cases, 485 controls)	565	0.95 (0.78, 1.14)		0.66 (0.50, 0.88)		1.28 (0.99, 1.65)	
Quintile 3 (*n* = 374 cases, 481 controls)	830	0.82 (0.68, 1.00)		0.68 (0.51, 0.91)		0.96 (0.73, 1.27)	
Quintile 4 (*n* = 373 cases, 482 controls)	1290	0.82 (0.67, 1.00)		0.65 (0.48, 0.87)		0.98 (0.74, 1.31)	
High quintile (*n* = 362 cases, 482 controls)	2395	0.83 (0.66, 1.04)	0.04	0.66 (0.48, 0.92)	0.02	0.99 (0.71, 1.38)	0.44
Lycopene[5]							
Low quintile (*n* = 405 cases, 482 controls)	1017	1.00		1.00		1.00	
Quintile 2 (*n* = 399 cases, 483 controls)	2411	1.00 (0.82, 1.21)		1.06 (0.80, 1.42)		0.97 (0.75, 1.26)	
Quintile 3 (*n* = 396 cases, 481 controls)	4117	1.00 (0.82, 1.21)		1.10 (0.83, 1.46)		0.92 (0.71, 1.21)	
Quintile 4 (*n* = 396 cases, 482 controls)	6719	0.96 (0.79, 1.17)		1.05 (0.79, 1.40)		0.91 (0.69, 1.19)	
High quintile (*n* = 397 cases, 482 controls)	13 072	0.96 (0.79, 1.19)	0.66	0.99 (0.74, 1.34)	0.96	0.96 (0.72, 1.29)	0.59
Zeaxanthin[6]							
Low quintile (*n* = 439 cases, 481 controls)	43	1.00		1.00		1.00	
Quintile 2 (*n* = 370 cases, 480 controls)	91	0.87 (0.72, 1.06)		0.68 (0.51, 0.89)		1.10 (0.84, 1.44)	
Quintile 3 (*n* = 404 cases, 491 controls)	135	0.94 (0.77, 1.14)		0.83 (0.63, 1.09)		1.07 (0.81, 1.46)	
Quintile 4 (*n* = 402 cases, 478 controls)	194	0.94 (0.77, 1.15)		0.85 (0.63, 1.14)		1.03 (0.79, 1.36)	
High quintile (*n* = 378 cases, 480 controls)	301	0.92 (0.73, 1.15)	0.68	0.83 (0.60, 1.15)	0.75	0.99 (0.72, 1.36)	0.82
β-Cryptoxanthin[7]							
Low quintile (*n* = 400 cases, 478 controls)	18	1.00		1.00		1.00	
Quintile 2 (*n* = 357 cases, 385 controls)	72	0.92 (0.75, 1.12)		0.84 (0.64, 1.11)		1.00 (0.76, 1.33)	
Quintile 3 (*n* = 420 cases, 484 controls)	131	1.08 (0.89, 1.31)		1.00 (0.76, 1.31)		1.18 (0.89, 1.55)	
Quintile 4 (*n* = 436 cases, 481 controls)	206	1.15 (0.95, 1.40)		1.01 (0.76, 1.34)		1.32 (1.01, 1.74)	
High quintile (*n* = 380 cases, 482 controls)	350	1.02 (0.83, 1.27)	0.08	0.98 (0.72, 1.34)	0.34	1.08 (0.80, 1.46)	0.12

[1] Adjusted for age, sex, BMI, energy intake, dietary fiber and folate intake, physical activity, use of nonsteroidal antiinflammatory drugs, and family history of colorectal cancer. OR, odds ratio.
[2] Cutoffs for men: 291, 557, 944, and 1651 μg; cutoffs for women: 316, 649, 1077, and 1888 μg.
[3] Cutoffs for men: 2538, 3884, 5484, and 8476 μg; cutoffs for women: 2579, 3884, 5610, and 8370 μg.
[4] Cutoffs for men: 411, 658, 975, and 1522 μg; cutoffs for women: 468, 739, 1090, and 1816 μg.
[5] Cutoffs for men: 1809, 3425, 5604, and 9564 μg; cutoffs for women: 1661, 2976, 4896, and 8332 μg.
[6] Cutoffs for men: 70, 113, 168, and 240 μg; cutoffs for women: 71, 111, 162, and 226 μg.
[7] Cutoffs for men: 47, 100, 164, and 262 μg; cutoffs for women: 44, 101, 168, 261 μg.

with risk in subjects with a family history of colorectal cancer (OR for upper relative to lower quintile of intake: 1.05; 95% CI: 0.53, 2.10; *P* = 0.42 for linear trend). There were suggestions of a higher risk of colon cancer in persons with a family history of colorectal cancer if they consumed diets high in β-carotene (OR for upper relative to lower quintile of intake: 1.93; 95% CI: 0.93, 4.02; *P* = 0.16 for linear trend) and lycopene (OR for upper relative to lower quintile of intake: 1.83; 95% CI: 0.96, 3.52; *P* = 0.04 for linear trend). Neither β-carotene (OR for upper relative to lower quintile of intake: 1.11; 95% CI: 0.86, 1.42; *P* = 0.26 for linear trend) nor lycopene (OR for upper relative to lower quintile of intake: 0.91; 95% CI: 0.73, 1.13; *P* = 0.26) was associated with increased risk in persons without a family history of colorectal cancer.

DISCUSSION

Our results suggest that high intakes of lutein may be protective against colon cancer in men and women. An inverse association with lutein intake was observed for all subjects, especially those who were younger when their cancer was diagnosed and those with proximal tumors. The inverse association with high intakes of lutein was stronger for subjects who currently smoked

TABLE 3
Associations between carotenoids and colon cancer by tumor site[1]

	Proximal		Distal	
	OR (95% CI)	*P* for linear trend	OR (95% CI)	*P* for linear trend
α-Carotene				
Low quintile (*n* = 223 proximal, 221 distal, 481 control)	1.00		1.00	
Quintile 2 (*n* = 187 proximal, 175 distal, 483 control)	0.90 (0.71, 1.14)		0.81 (0.64, 1.03)	
Quintile 3 (*n* = 192 proximal, 175 distal, 482 control)	0.93 (0.73, 1.18)		0.79 (0.62, 1.01)	
Quintile 4 (*n* = 195 proximal, 220 distal, 482 control)	0.97 (0.76, 1.24)		0.96 (0.75, 1.22)	
High quintile (*n* = 175 proximal, 180 distal, 482 control)	0.96 (0.74, 1.25)	0.20	0.82 (0.62, 1.07)	0.45
β-Carotene				
Low quintile (*n* = 187 proximal, 198 distal, 482 control)	1.00		1.00	
Quintile 2 (*n* = 206 proximal, 173 distal, 482 control)	1.22 (0.96, 1.56)		0.90 (0.70, 1.11)	
Quintile 3 (*n* = 195 proximal, 172 distal, 482 control)	1.20 (0.93, 1.54)		0.87 (0.67, 1.11)	
Quintile 4 (*n* = 204 proximal, 204 distal, 482 control)	1.27 (0.99, 1.65)		1.04 (0.80, 1.34)	
High quintile (*n* = 180 proximal, 224 distal, 482 control)	1.30 (0.96, 1.75)	0.09	1.16 (0.87, 1.54)	0.23
Lutein				
Low quintile (*n* = 228 proximal, 209 distal, 480 control)	1.00		1.00	
Quintile 2 (*n* = 227 proximal, 195 distal, 485 control)	1.01 (0.80, 1.27)		0.89 (0.70, 1.14)	
Quintile 3 (*n* = 187 proximal, 175 distal, 481 control)	0.84 (0.66, 1.08)		0.80 (0.62, 1.03)	
Quintile 4 (*n* = 184 proximal, 182 distal, 482 control)	0.84 (0.65, 1.08)		0.83 (0.64, 1.07)	
High quintile (*n* = 146 proximal, 210 distal, 482 control)	0.65 (0.51, 0.91)	< 0.01	0.99 (0.75, 1.32)	0.68
Lycopene				
Low quintile (*n* = 202 proximal, 195 distal, 482 control)	1.00		1.00	
Quintile 2 (*n* = 222 proximal, 167 distal, 483 control)	1.15 (0.91, 1.45)		0.85 (0.66, 1.09)	
Quintile 3 (*n* = 187 proximal, 198 distal, 481 control)	1.00 (0.78, 1.27)		1.00 (0.79, 1.28)	
Quintile 4 (*n* = 188 proximal, 197 distal, 482 control)	0.99 (0.78, 1.27)		0.95 (0.74, 1.21)	
High quintile (*n* = 173 proximal, 214 distal, 482 control)	0.95 (0.73, 1.23)	0.40	1.02 (0.79, 1.32)	0.62
Zeaxanthin				
Low quintile (*n* = 223 proximal, 207 distal, 481 control)	1.00		1.00	
Quintile 2 (*n* = 188 proximal, 174 distal, 480 control)	0.95 (0.71, 1.14)		0.83 (0.65, 1.06)	
Quintile 3 (*n* = 197 proximal, 190 distal, 491 control)	0.94 (0.74, 1.20)		0.91 (0.71, 1.16)	
Quintile 4 (*n* = 194 proximal, 200 distal, 478 control)	0.94 (0.73, 1.20)		0.96 (0.75, 1.24)	
High quintile (*n* = 170 proximal, 200 distal, 480 control)	0.85 (0.64, 1.13)	0.42	0.97 (0.73, 1.29)	0.88
β-Cryptoxanthin				
Low quintile (*n* = 201 proximal, 190 distal, 478 control)	1.00		1.00	
Quintile 2 (*n* = 157 proximal, 190 distal, 485 control)	0.84 (0.65, 1.14)		1.00 (0.79, 1.28)	
Quintile 3 (*n* = 208 proximal, 199 distal, 484 control)	1.14 (0.89, 1.45)		1.02 (0.80, 1.30)	
Quintile 4 (*n* = 215 proximal, 210 distal, 482 control)	1.22 (0.95, 1.55)		1.12 (0.87, 1.43)	
High quintile (*n* = 191 proximal, 182 distal, 482 control)	1.14 (0.88, 1.49)	0.04	0.94 (0.72, 1.23)	0.30

[1] Adjusted for age, sex, BMI, energy intake, dietary fiber and folate intake, physical activity, use of nonsteroidal antiinflammatory drugs, and family history of colorectal cancer. OR, odds ratio.

cigarettes than for subjects who had never smoked, although given that few subjects reported currently smoking, we were limited in our ability to detect significant interactions between smoking and carotenoid intakes.

Carotenoids can be classified into hydrocarbon carotenoids (including β-carotene, α-carotene, and lycopene) and oxycarotenoids (xanthophylls), which include lutein, zeaxanthin, and β-cryptoxanthin (21). Some of the carotenoids, such as β-carotene, α-carotene, and β-cryptoxanthin, are precursors to vitamin A and are converted to retinol in the body. Carotenoids have different biological activities that may influence how they are associated with different types of cancer. β-Carotene was shown to be effective in protecting lipid membranes from damage by free radicals, lycopene was found to be the most efficient singlet oxygen quencher of the carotenoids, and lutein and zeaxanthin are generally more effective than β-carotene as scavengers of oxygen radical species (22–26). Studies showed that the position of the carotenoid in the cell membrane can influence how it acts (25). For instance, β-carotene and lycopene can react efficiently only with radicals generated in the inner part of the membrane, whereas the less hydrophobic structures of lutein and zeaxanthin enable them to also react with free radicals in the aqueous phase of membranes. Thus, it appears that lutein and zeaxanthin are more effective membrane-based protective antioxidants than are β-carotene and lycopene and, as such, can increase membrane integrity. This action may in turn influence permeability of tissue to oxygen and other molecules.

Carotenoids have biological activities other than those associated with their function as antioxidants. Carotenoids without provitamin A activity, such as lutein and zeaxanthin, were shown to have antimutagenic and anticarcinogenic properties (25–28). A study by Le Marchand et al (27) showed that plasma lutein explained the largest portion of the variance in cytochrome P450 1A2, an activator of procarcinogens. Although lutein was inversely associated with cytochrome P450 1AA, lycopene was directly associated with this procarcinogen. Another property of carotenoids that may influence their association with the carcinogenic process is their ability to enhance immune functions and to facilitate cellular communication (28).

TABLE 4
Associations between carotenoids and colon cancer by smoking status[1]

	Never smokers		Exsmokers		Current smokers	
	OR (95% CI)	*P* for linear trend	OR (95% CI)	*P* for linear trend	OR (95% CI)	*P* for linear trend
α-Carotene						
Low quintile (*n* = 172 never, 191 ex, 88 current)	1.00		1.00		1.00	
Quintile 2 (*n* = 133 never, 174 ex, 69 current)	0.75 (0.55, 1.01)		1.03 (0.77, 1.39)		0.87 (0.56, 1.37)	
Quintile 3 (*n* = 161 never, 179 ex, 42 current)	0.85 (0.64, 1.16)		0.99 (0.73, 1.33)		0.66 (0.39, 1.11)	
Quintile 4 (*n* = 185 never, 179 ex, 59 current)	1.04 (0.77, 1.40)		0.95 (0.70, 1.29)		0.94 (0.57, 1.56)	
High quintile (*n* = 172 never, 147 ex, 38 current)	0.88 (0.64, 1.22)	0.84	0.87 (0.62, 1.22)	0.38	1.00 (0.54, 1.84)	0.85
β-Carotene						
Low quintile (*n* = 160 never, 169 ex, 72 current)	1.00		1.00		1.00	
Quintile 2 (*n* = 161 never, 164 ex, 61 current)	1.04 (0.77, 1.40)		0.93 (0.72, 1.33)		1.14 (0.70, 1.87)	
Quintile 3 (*n* = 159 never, 168 ex, 49 current)	0.99 (0.73, 1.34)		1.06 (0.77, 1.46)		0.82 (0.49, 1.37)	
Quintile 4 (*n* = 164 never, 194 ex, 60 current)	1.07 (0.78, 1.46)		1.16 (0.84, 1.60)		1.21 (0.71, 2.07)	
High quintile (*n* = 179 never, 175 ex, 54 current)	1.14 (0.80, 1.62)	0.51	1.16 (0.80, 1.67)	0.26	1.35 (0.70, 2.60)	0.45
Lutein						
Low quintile (*n* = 184 never, 177 ex, 90 current)	1.00		1.00		1.00	
Quintile 2 (*n* = 117 never, 202 ex, 53 current)	0.99 (0.75, 1.32)		1.04 (0.77, 1.41)		0.60 (0.36, 0.97)	
Quintile 3 (*n* = 152 never, 168 ex, 52 current)	0.85 (0.63, 1.15)		0.81 (0.60, 1.11)		0.70 (0.42, 1.17)	
Quintile 4 (*n* = 160 never, 164 ex, 48 current)	0.91 (0.67, 1.24)		0.74 (0.53, 1.02)		0.69 (0.40, 1.18)	
High quintile (*n* = 150 never, 159 ex, 53 current)	0.91 (0.65, 1.29)	0.45	0.81 (0.63, 1.03)	0.06	0.56 (0.31, 1.03)	0.12
Lycopene						
Low quintile (*n* = 174 never, 176 ex, 55 current)	1.00		1.00		1.00	
Quintile 2 (*n* = 163 never, 182 ex, 52 current)	0.99 (0.74, 1.32)		1.03 (0.77, 1.38)		0.93 (0.55, 1.58)	
Quintile 3 (*n* = 165 never, 170 ex, 60 current)	0.99 (0.74, 1.33)		1.00 (0.74, 1.35)		1.07 (0.63, 1.83)	
Quintile 4 (*n* = 160 never, 173 ex, 62 current)	0.87 (0.65, 1.18)		1.10 (0.81, 1.50)		1.00 (0.59, 1.70)	
High quintile (*n* = 161 never, 169 ex, 67 current)	0.92 (0.67, 1.25)	0.41	1.12 (0.81, 1.56)	0.43	0.84 (0.49, 1.45)	0.65
Zeaxanthin						
Low quintile (*n* = 176 never, 177 ex, 85 current)	1.00		1.00		1.00	
Quintile 2 (*n* = 132 never, 179 ex, 59 current)	0.66 (0.48, 0.90)		1.16 (0.86, 1.56)		0.80 (0.50, 1.28)	
Quintile 3 (*n* = 169 never, 181 ex, 54 current)	0.77 (0.57, 1.04)		1.18 (0.87, 1.60)		0.85 (0.51, 1.41)	
Quintile 4 (*n* = 171 never, 177 ex, 52 current)	0.78 (0.58, 1.06)		1.17 (0.85, 1.59)		0.86 (0.50, 1.45)	
High quintile (*n* = 175 never, 156 ex, 46 current)	0.87 (0.62, 1.23)	0.72	0.99 (0.70, 1.41)	0.90	0.82 (0.43, 1.59)	0.58
β-Cryptoxanthin						
Low quintile (*n* = 146 never, 168 ex, 85 current)	1.00		1.00		1.00	
Quintile 2 (*n* = 140 never, 157 ex, 60 current)	0.76 (0.55, 1.05)		1.07 (0.79, 1.45)		0.85 (0.54, 1.34)	
Quintile 3 (*n* = 161 never, 201 ex, 57 current)	0.85 (0.62, 1.16)		1.21 (0.91, 1.63)		1.34 (0.82, 2.21)	
Quintile 4 (*n* = 201 never, 184 ex, 50 current)	0.94 (0.69, 1.28)		1.34 (0.99, 1.82)		1.32 (0.78, 2.23)	
High quintile (*n* = 175 never, 160 ex, 44 current)	0.81 (0.58, 1.12)	0.76	1.24 (0.89, 1.73)	0.06	1.34 (0.73, 2.44)	0.18

[1] Adjusted for age, sex, BMI, enery intake, dietary fiber and folate intake, physical activity, use of nonsteroidal antiinflammatory drugs, and family history of colorectal cancer. OR, odds ratio.

Enger et al (29) showed that β-carotene may be more protective against the development of colonic adenomas than other dietary carotenoids. It is possible that dietary carotenoids work at different steps in the disease pathway. If the observation by Enger et al is true, β-carotene may work at early stages of tumor development, whereas lutein may work at later stages in the disease process. The focus of this study was on the late stage of disease, given that the referent period was the 2–3 y before diagnosis, and so may have prevented our detection of other important carotenoids in the complicated pathway to cancer.

The requirement for oxidant defenses varies by oxidant stress. Although many factors can contribute to host oxidant stress, cigarette smoking is one that may be more easily measured in epidemiologic studies. The effect of carotenoids in smokers has been the focus of some clinical trials. β-Carotene was the targeted carotenoid supplement for these trials and was shown to increase risk of lung and colorectal cancer in heavy smokers in 2 trials (30, 31) and to have no effect on cancer risk in another (32). In the present study, we observed the strongest protective effect of dietary lutein in subjects who were current smokers and a slight increase in risk associated with β-carotene. The Australian Polyp Study also showed that β-carotene was associated with higher risk of recurrence of large polyps (33).

These data suggest that persons whose cancer is diagnosed when they are younger have greater protection from higher intakes of lutein. The reason for this observation, similar to that of other studies that showed stronger dietary associations with colon cancer for younger persons, is not clear (4–6). We can only speculate as to the reason for this age-specific association. It is possible that dietary factors, whether increasing or decreasing risk, eliminate the most susceptible persons at an early age. At older ages, other, perhaps intrinsic, biological processes are more important. It is also possible that long-term dietary intake is of primary importance and that diet reported during the referent period of younger persons more closely resembles long-term dietary patterns than it does in older persons. Still another possi-

bility for the age-specific associations detected is simply that younger people recall their diets more accurately than do older people. Inaccurate recall of dietary patterns in older study participants could result in attenuated associations.

Several factors should be considered in interpretation of these results. Although the database used is the most comprehensive carotenoid database of which we are aware, it is possible that individual variation in carotenoid values could occur if a more comprehensive database were used. Likewise, for some carotenoids, such as zeaxanthin, the data are more limited than for others. This could result in measurement error, making the detection of associations difficult. This study relied on dietary intake as the indicator of carotenoid status. Although correlations between dietary and plasma values are fairly high (34), conversion of carotenoids in the diet to a more active form depends on need as well as on other dietary factors, including low amounts of fat (absorption is reduced markedly at fat intakes <20% of energy) and fiber. We adjusted for fiber in our analyses because fiber intake was independently associated with colon cancer and could confound these results. Adjustment for fat intake did not alter the findings. However, few subjects in this study consumed a diet containing <20% of energy as fat. Furthermore, as shown in the tables, after adjustment for fiber, lutein was still inversely associated with colon cancer.

In this study, lutein was the only carotenoid that appeared to be inversely associated with colon cancer. Lutein is found primarily in broccoli and dark-green vegetables such as spinach and lettuce. These foods contain other biologically active ingredients and were found in some studies to be inversely associated with colon cancer (35). However, adjustment for broccoli in this study did not alter the observed associations. Additionally, foods that are high in folate are often the same foods in which lutein is found. However, in this study we observed an inverse association for lutein after adjustment for folate, but not a significant protective effect of folate with or without adjustment for lutein for the whole study population.

In summary, data from this study suggest that lutein may protect against colon cancer. There are biological reasons to support this finding. Although data from other epidemiologic studies are generally lacking, the relatively consistent inverse associations between intake of plant foods, especially vegetables, and colon cancer may be relevant because dietary lutein is obtained almost entirely from vegetables. The findings reinforce the hypothesis that plant foods, perhaps specific kinds, are beneficial in reducing the risk of colon cancer.

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