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Antioxidants, Carotenoids, and Risk of Rectal Cancer

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Numerous properties suggest that antioxidants and carotenoids may be valuable chemopreventive agents. A population-based case-control study of 952 rectal cancer cases and 1,205 controls from Northern California and Utah was conducted between September 1997 and February 2002. Detailed diet history, medical history, and lifestyle factors interviews were conducted. Dietary antioxidants were not associated with rectal cancer risk in men. For women, relative to the highest level of intake, low intake of dietary lycopene (odds ratio (OR) = 1.7, 95% confidence interval (CI): 1.0, 2.8) or vitamin E (OR = 2.2, 95% CI: 1.1, 4.3) was associated with an increased risk of rectal cancer. Alpha-, beta-, and gamma-tocopherol were associated with an approximate twofold increased risk of rectal cancer in women. Associations were stronger for women aged ≥60 years for vitamin E and tocopherols (alpha-tocopherol OR = 3.6, 95% CI: 1.4, 9.4; gamma-tocopherol OR = 5.3, 95% CI: 2.1, 13.2; delta-tocopherol OR = 1.9, 95% CI: 0.9, 4.0), except for beta-tocopherol, for which risk increased twofold for all women. Associations differed by estrogen status for beta-carotene, lycopene, and vitamin E. These results suggest that vitamin E and lycopene may modestly reduce the risk of rectal cancer in women.

antioxidants; carotenoids; diet; rectal neoplasms

Antioxidants include a variety of vitamins, carotenoids, minerals, and phytochemicals that deactivate free radicals and thereby prevent damage to cellular membranes or genetic material within the cell. Approximately two dozen of the more than 600 fat-soluble plant pigments called carotenoids are found in human blood and tissue (1). Although it is commonly perceived that vitamin E, beta-carotene, and other carotenoids act similarly to antioxidants, their unique biologic activities distinguish them from each other (2, 3). For example, individual antioxidants and carotenoids act differently in different components of the immune system (2, 4) in addition to contributing to cell-to-cell communication, cellular differentiation, and regulation of cell growth (5) or induction of apoptosis (6). Because of these biologic properties, they have been proposed as being potentially important chemopreventive agents that may alter cancer risk.

Epidemiologic studies examining associations between antioxidants, carotenoids, and cancer have produced far from consistent results. Significant associations have been reported for alpha-carotene and lycopene with breast cancer (7); alpha-carotene, beta-carotene, and lycopene with ovarian cancer (8, 9); lycopene with prostate cancer (10, 11); lycopene with colorectal cancer (9); lutein with proximal colon cancer (12); and vitamin E with colon cancer (13–17). On the other hand, some observational studies and clinical trials have shown that beta-carotene supplementation increases the risk of cancer, especially among smokers (18, 19).

In general, it can be concluded that the associations of antioxidants with colorectal cancer are inconsistent, and studies have primarily focused on colon cancer (14, 16, 19–25). However, a few studies have reported associations between antioxidants and carotenoids and rectal cancer (15, 26, 27). These studies can be characterized as having limited carotenoid data (15, 26, 28), usually including only beta-carotene, and imprecise estimates of association since most report that few cases of rectal cancer were available for analysis (27).

Thus, our primary objective was to explore associations of antioxidants and carotenoids with the risk of rectal cancer in a case-control study of adult men and women residents of Utah and Northern California. We investigated potential modification of these associations by age and estrogen status.

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MATERIALS AND METHODS

Study population

Participants in the study were from the Kaiser Permanente Medical Care Program of Northern California (KPMCP) and the state of Utah. All eligible cases within these defined populations were identified and recruited for the study. Cases with a first primary tumor in the rectosigmoid junction or rectum were identified between May 1997 and May 2001 by using a rapid-reporting system. Case eligibility was determined in Northern California by using the Surveillance, Epidemiology, and End Results (SEER) Program Cancer Registries and in Utah by using the Utah Cancer Registry. An online pathology reporting system was searched for rapid ascertainment of rectal cancer cases. In California, cases identified were confirmed through linkage to the Kaiser Permanente Northern California Cancer Registry. To be eligible for the study, cases could not have had a previous colorectal tumor. Cases with known (as indicated on the pathology report) familial adenomatous polyposis, ulcerative colitis, or Crohn's disease were not eligible. In addition to these criteria, participants were required to be between 30 and 79 years of age at the time of diagnosis, English speaking, and mentally competent to complete the interview.

Controls were categorically matched to cases by sex and by 5-year age groups. At the Kaiser Permanente Medical Care Program of Northern California, controls were randomly selected from membership lists; in Utah; controls aged 65 years or older were randomly selected from social security lists, and controls younger than age 65 years were randomly selected from driver's license lists. A total of 952 rectal cancer cases and 1,205 matched controls were included in the analyses presented. Response rates were 65.2 percent for cases and 65.3 percent for controls; cooperation rates, or the number of people who participated and we were able to contact, was 73.2 percent for cases and 68.8 percent for controls.

Data collection. Data were collected by trained and certified interviewers using laptop computers. The interview lasted approximately 2 hours. Quality control methods used in the study were the same as those used in the colon cancer study and have been described in detail elsewhere (7, 8).

Diet. Dietary intake was ascertained by using an adaptation of the CARDIA diet history to accommodate yearly seasonal variation and changes in food availability, for example, more low-fat choices (8, 12). Participants were asked to recall foods eaten during the calendar year 2 years prior to diagnosis or selection, the frequency with which they were eaten, the serving size, and whether fats were added in the preparation. Nutrient information was obtained by converting food intake data into nutrient data using the University of Minnesota Nutrition Coding Center nutrient database, version 4.04_30. This version of the database has information on alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein, zeaxanthin, and lycopene (29) as well as complete data on other antioxidants, including alpha-, beta-, gamma-, and delta-tocopherols. Participants were asked whether they used any multivitamins, multivitamins with minerals, single vitamins, single minerals, or other supplements. Participants who responded in the affirmative were asked to report the kind, frequency, and dose of the supplements they used.

Other information. Height was measured at the time of interview, and weight was reported for the 2 and 5 years prior to interview. Body mass index (weight (kg)/height $(m)^2$) was calculated for men and women. Physical activity data were collected by using a detailed physical activity questionnaire (30). "Estrogen status" was determined by a combination of menopausal status and use of hormone replacement therapy. Women who were premenopausal or postmenopausal and reported hormone replacement therapy use within the past 2 years were considered estrogen positive. Postmenopausal women who did not report recent hormone replacement therapy use were considered estrogen negative. Women who reported having a hysterectomy with one ovary removed and were younger than age 57 years were excluded from analysis because menopausal status could not be determined. The estrogen status variable enabled us to use our entire population rather than restrict the analysis to postmenopausal women only. Information also was collected on smoking, reproductive, and medical history.

Statistical methods

Unconditional logistic regression models were used to estimate the risk of rectal cancer associated with dietary carotenoids/antioxidants. Dietary data were first assessed by determining risk across quintiles of intake; quintiles were determined by the sex-specific intake distribution in the control population. We assessed associations both with and without inclusion of supplement information; however, since associations were similar, this paper reports associations for dietary intake without supplement use to make these data more comparable to data reported elsewhere (12, 24, 26–28, 31). In these models, the following variables were included: age at selection, body mass index, physical activity, energy intake, dietary fiber, dietary calcium, and cigarette smoking status. Linear trend was determined by evaluating significance of linear association across the categorized variable. Interaction or effect modification between dietary intake and estrogen status was evaluated as the relative excess risk from interaction on the additive scale (32).

RESULTS

Approximately 14–18 percent of the population were under age 50 years (table 1). Compared with cases, controls had slightly more education, reported more physical activity, had slightly lower body mass index levels, and were more likely to report never having smoked cigarettes. Cases reported higher mean levels of energy intake, while controls reported higher mean levels of calcium intake. Among women, over half of the population reported multivitamin use, while about 40 percent of men reported multivitamin use. In addition, roughly 25 percent of the population reported using vitamin E and vitamin C as a single supplement during the referent year.

After adjustment for covariates, low intakes of lycopene (odds ratio = 1.7, 95 percent confidence interval: 1.0, 2.8; p for linear trend = 0.01) and vitamin E (odds ratio = 2.2, 95

TABLE 1. Description of the population studied to assess associations of antioxidants and carotenoids with risk of rectal cancer, Northern California and Utah, 1997–2002

	Men				Women			
	Cases		Controls		Cases		Controls	
	No.	%	No.	%	No.	%	No.	%
Age (years)								
<50	76	13.6	94	14.0	71	18.1	84	15.8
50–59	150	26.8	166	24.7	98	24.9	138	25.9
60–69	201	36.0	239	35.5	118	30.0	153	28.8
70–79	132	23.6	174	25.8	106	27.0	157	29.5
p value		0.01				0.70		
Race								
White, non-Hispanic	446	80.2	544	82.2	321	83.6	455	86.0
Hispanic	41	7.4	51	7.7	31	8.1	40	7.6
African American	23	4.1	33	5.0	15	3.9	17	3.2
Asian	39	7.0	32	4.8	14	3.7	15	2.8
Native American	7	1.3	2	0.3	3	0.8	2	0.4
p value		0.14				0.80		
Educational level								
Less than high school	57	10.2	76	11.3	47	12.0	51	9.6
High school	125	22.4	126	18.7	101	25.7	144	27.1
College	278	49.7	323	48.1	195	49.6	255	47.9
Graduate school	99	17.7	147	21.9	50	12.7	82	15.4
p value		0.16				0.45		
Physical activity level								
No vigorous activity	175	31.3	150	22.3	157	40.0	167	31.4
1–2 hours/week	212	37.9	264	39.2	151	38.4	221	41.5
≥3 hours/week	172	30.8	259	38.5	85	21.7	144	27.1
p value		0.01				0.02		

Table continues

percent confidence interval: 1.1, 4.3; *p* for linear trend = 0.04) were associated with an increased risk of rectal cancer in women. No association of lutein, beta-carotene, vitamin C, or selenium from dietary sources with risk of rectal cancer was found for either men or women (table 2). Vitamin supplement use was not associated significantly with rectal cancer in women or men (data not shown).

The association between vitamin E and rectal cancer was stronger for women aged 60 years or older than for younger women (quintile 5 vs. quintile 1 odds ratio = 3.5, 95 percent confidence interval: 1.5, 8.5; *p* for interaction = 0.05 (table 3)). Associations with lycopene, beta-carotene, vitamin C, and selenium did not vary by age for men or women.

Further assessment of types of vitamin E showed that all forms except delta-tocopherol were associated with a decreased risk of rectal cancer in women (table 4), but not men (data not shown in table). Assessment of tocopherols by age showed that beta-tocopherol was associated with rectal cancer in both younger and older women, while other forms of tocopherols were associated with rectal cancer in older women only. At the lowest level of intake, alpha-tocopherol was associated with a 3.6-fold (95 percent confidence interval: 1.4, 9.4) increased risk, gamma-tocopherol was associated with a 5.3-fold (95 percent confidence interval: 2.1, 13.2) increased risk, and delta-tocopherol was associated with a 1.9-fold (95 percent confidence interval: 0.9, 4.0) increased risk.

Given the gender-specific associations observed with some antioxidants and carotenoids, we evaluated the associations for women by estrogen status. We found no differences in the associations of lutein, vitamin C, and selenium by estrogen status. However, estrogen status appeared to modify the associations of beta-carotene, lycopene, and vitamin E with rectal cancer in women (table 5). The combined effect of being estrogen negative and having low intakes of lycopene, beta-carotene, and vitamin E was greater than any of these factors independently. For lycopene and vitamin E, lower dietary intakes were associated with approximately a threefold increase in risk of rectal cancer in estrogen-negative women relative to estrogen-positive women with high intakes; for beta-carotene, there was an approximate twofold increase in risk of rectal cancer in estrogen-negative women.

TABLE 1. Continued

	Men				Women			
	Cases		Controls		Cases		Controls	
	No.	%	No.	%	No.	%	No.	%
Body mass index*								
<25	135	24.3	164	244	174	44.6	231	44.0
25–29	224	40.1	290	43.2	90	23.1	151	28.8
>30	197	35.4	218	32.4	126	32.3	143	26.9
p value		0.50				0.09		
Cigarette smoking status								
Current smoker	118	21.2	103	15.3	67	17.1	86	16.2
Former smoker	229	40.3	272	43.2	93	23.7	118	22.2
Never smoker	209	37.6	297	44.2	232	59.2	328	61.6
p value		0.01				0.75		
Energy intake (kcal/day)†	2,955 (60.7)		2,862 (55.4)		2,409 (56.3)		2,269 (48.4)	
p value		0.26				0.06		
Fiber intake (g/day)†	27.6 (0.59)		28.6 (0.54)		24.4 (0.63)		24.8 (0.54)	
p value		0.18				0.67		
Calcium intake (mg/day)†	1,227 (31.1)		1,245 (28.4)		1,040 (28.6)		1,075 (24.5)	
p value		0.68				0.35		
Multivitamin supplement use	204	36.5	296	44.0	205	52.2	297	55.8
p value		<0.01				0.27		
Single supplement use								
Vitamin E	108	19.3	173	25.7	111	28.2	153	28.8
p value		<0.01				0.86		
Vitamin C	141	25.2	210	31.2	126	32.1	176	33.1
p value		<0.02				0.74		
Beta-carotene	18	3.2	22	3.3	12	3.1	28	5.3
p value		0.96				0.10		
Selenium	11	2.0	9	1.3	8	2.0	16	3.0
p value		0.38				0.36		
Antioxidant	13	2.3	27	4.0	10	2.5	31	5.8
p value		0.10				0.02		

* Weight (kg)/height (m)^2.
† Values are presented as mean (standard error).

DISCUSSION

High intakes of dietary lycopene and vitamin E were associated with a modest reduction in risk of rectal cancer in women, but not men. The association between vitamin E and rectal cancer varied by the type of tocopherol being assessed. Age and estrogen status appeared to modify the relations of antioxidants and carotenoids with rectal cancer in women.

These results add to those from previous studies that point to a modest reduction in risk of rectal cancer associated with high dietary and supplemental sources of vitamin E (15, 26, 33). We found that the highest dietary intakes of vitamin E were associated with a decreased risk of rectal cancer in women. Bostick et al. (16) reported significant associations between colon cancer and total vitamin E intake (diet and supplements in a cohort of older women), but associations were stronger for women aged 55–59 versus 60–64 years. A study of incident rectal cancer found no association with dietary vitamin E for men or women (26). Many explanations are possible for the differences observed, including different levels of vitamin E reported, different sources of vitamin E in the diet, and type of tocopherol being eaten; differences in the proportion of the population using supplements and the dosage of supplements could exist as well as differences in other factors that could modify associations, including age and estrogen status of the population being studied.

Assessment of various forms of tocopherols was informative. Low levels of beta-tocopherol were associated with an increased risk for both younger and older women, while low levels of alpha- and gamma-tocopherol were associated with a strong increased risk for older women. Delta-tocopherol

TABLE 2. Associations between intake of dietary carotenoids and antioxidants and rectal cancer risk, Northern California and Utah, 1997–2002

	Men					Women			
	Cases (no.)	Controls (no.)	OR*,†	95% CI*		Cases (no.)	Controls (no.)	OR†	95% CI
Lutein (μg)					Lutein (μg)				
>4,518	97	134	1.0		>4,571	77	106	1.0	
>3,023–≤4,518	121	135	1.1	0.7, 1.6	>3,216–≤4,571	66	107	0.8	0.5, 1.3
>2,234–≤3,023	112	134	1.0	0.6, 1.5	>2,404–≤3,216	72	106	0.8	0.5, 1.4
>1,497–≤2,234	115	136	1.0	0.6, 1.5	>1,492–≤2,404	99	106	1.2	0.7, 1.9
≤1,497	114	134	0.9	0.5, 1.5	≤1,492	79	107	0.9	0.5, 1.7
Lycopene (μg)					Lycopene (μg)				
>16,806	118	134	1.0		>14,208	76	106	1.0	
>10,111–≤16,806	110	135	0.9	0.6, 1.3	>8,869–≤14,208	65	106	0.9	0.6, 1.4
>6,489–≤10,111	114	135	0.9	0.6, 1.4	>5,714–≤8,869	63	107	1.0	0.6, 1.6
>3,673–≤6,489	105	135	0.9	0.6, 1.3	>3,136–≤5,714	90	106	1.5	0.9, 2.3
≤3,673	112	134	0.9	0.6, 1.4	≤3,136	99	107	1.7	1.0, 2.8
Beta-carotene (μg)					Beta-carotene (μg)				
>7,493	104	134	1.0		>7,294	73	106	1.0	
>4,894–≤7,493	105	136	0.9	0.6, 1.3	>4,876–≤7,294	65	108	0.8	0.5, 1.3
>3,252–≤4,894	131	134	1.0	0.7, 1.6	>3,483–≤4,876	78	106	1.0	0.6, 1.6
>2,137–≤3,252	100	134	0.8	0.5, 1.2	>2,308–≤3,483	88	105	1.2	0.7, 1.9
≤2,137	119	135	0.9	0.5, 1.4	≤2,308	89	107	1.1	0.6, 1.9
Vitamin E (mg)					Vitamin E (mg)				
>18.8	116	136	1.0		>16.5	78	106	1.0	
>13.9–≤18.8	111	135	1.0	0.7, 1.5	>12.1–≤16.5	79	105	1.4	0.8, 2.2
>10.8–≤13.9	107	135	1.0	0.6, 1.6	>9.3–≤12.1	78	109	1.4	0.8, 2.5
>7.7–≤10.8	112	135	1.1	0.6, 1.8	>6.6–≤9.3	72	108	1.5	0.8, 2.8
≤7.7	113	132	1.1	0.6, 1.9	≤6.6	86	104	2.2	1.1, 4.3
Vitamin C (mg)					Vitamin C (mg)				
>245.1	106	134	1.0		>227.6	85	106	1.0	
>185–≤245.1	74	136	0.7	0.4, 1.0	>169–≤227.6	72	106	0.8	0.5, 1.2
>135.6–≤185	127	134	1.1	0.8, 1.7	>132.3–≤169	73	107	0.7	0.4, 1.1
>87–≤135.6	135	136	1.1	0.7, 1.7	>91.2–≤132.3	79	106	0.7	0.4, 1.2
≤87	117	133	1.0	0.6,1.5	≤91.2	84	107	0.7	0.4, 1.3
Selenium (μg)					Selenium (μg)				
>236.3	119	134	1.0		>168.3	89	107	1.0	
>164–≤236.3	118	135	1.0	0.7, 1.4	>126.4–≤168.3	86	106	1.0	0.6, 1.6
>132.4–≤164	88	135	0.7	0.5, 1.1	>99.1–≤126.4	76	108	0.9	0.6, 1.6
>95.5–≤132.4	141	134	1.1	0.7, 1.8	>77.7–≤99.1	60	103	0.8	0.5, 1.4
≤95.5	93	135	0.7	0.4, 1.2	≤77.7	82	108	1.1	0.6, 2.0

* OR, odds ratio; CI, confidence interval.

† Odds ratios were adjusted for age, body mass index, physical activity level, cigarette smoking status, energy intake, calcium intake, and fiber intake.

had a much weaker effect than other forms of tocopherols on the risk for older women. In a review of tocopherols and colon cancer (34), it was suggested that alpha- and gamma-tocopherols both may be important in the prevention of colon cancer, although alpha-tocopherol is usually studied. Alpha-tocopherol, present in relatively high concentrations in plasma compared with other forms of tocopherol, may reduce lipid peroxidation in cellular membranes. Gamma-tocopherol, on the other hand, is high in Western diets and is preferentially secreted into the intestine and fecal material. Antioxidants in fecal material may be effective in preventing DNA damage in epithelial cells lining the colon (34). It has

TABLE 3. Association of levels of intake of antioxidants and carotenoids with rectal cancer risk,* by women's age, Northern California and Utah, 1997–2002

	<60 years				≥60 years			
	Cases (no.)	Controls (no.)	OR†,‡	95% CI†	Cases (no.)	Controls (no.)	OR‡	95% CI
Lutein								
High	41	48	1.0		36	58	1.0	
Intermediate	105	143	0.9	0.5, 1.6	132	176	0.9	0.5, 1.5
Low	23	31	0.8	0.4, 2.1	56	76	0.7	0.3, 1.6
Lycopene								
High	45	60	1.0		31	46	1.0	
Intermediate	100	127	1.3	0.8, 2.2	118	192	0.9	0.4, 1.6
Low	24	35	1.3	0.6, 2.7	75	72	1.6	0.8, 3.1
Beta-carotene								
High	41	46	1.0		32	60	1.0	
Intermediate	100	127	0.8	0.4, 1.5	132	188	1.0	0.6, 1.9
Low	24	35	0.7	0.3, 1.5	60	62	1.3	0.6, 2.8
Vitamin E								
High	45	41	1.0		33	65	1.0	
Intermediate	102	149	0.8	0.4, 1.5	127	173	2.2	1.2, 4.2
Low	22	32	1.0	0.4, 2.7	64	72	3.5	1.5, 8.5
Vitamin C								
High	42	48	1.0		43	58	1.0	
Intermediate	95	129	0.8	0.4, 1.5	129	129	0.7	0.4, 1.1
Low	32	45	0.8	0.3, 1.8	190	190	0.7	0.3, 1.4
Selenium								
High	49	41	1.0		40	66	1.0	
Intermediate	101	147	0.6	0.3, 1.1	121	170	1.4	0.8, 2.4
Low	19	34	0.5	0.2, 1.4	63	74	1.7	0.8, 3.6

* Collapsed quintiles: high, top quintile; intermediate, quintiles 2–4; low, bottom quintile.
† OR, odds ratio; CI, confidence interval.
‡ Odds ratios were adjusted for body mass index, physical activity level, cigarette smoking status, energy intake, calcium intake, and fiber intake.

long been hypothesized that fecal bacteria contribute to colon cancer risk by producing carcinogens or procarcinogens (35). It is possible that gamma-tocopherol is involved in reducing the risk of rectal cancer via this mechanism.

Although we found no previous reports of the association of lycopene with the risk of rectal cancer, dietary lycopene has been associated with other cancers whose etiology is thought to have a hormonal basis, including breast, ovarian, and prostate cancer (7, 8, 10, 11). Cramer et al. (8) reported an inverse association of lycopene with the risk of ovarian cancer, predominantly among postmenopausal women. Similarly, in the present study, the highest intakes of lycopene were associated with a decreased risk of rectal cancer in women only, and the association was stronger for estrogen-negative women. It has been suggested that the actions of higher levels of prooxidant catechol estrogens prior to menopause could be countered by the free-radical-quenching activity of lycopene (7). Differences in associations detected for studies including serum and dietary lycopene could be explained by their poor correlation (36) and by variability in the bioavailability of lycopene (1) and interactions among carotenoids and other nutrients (37). Other possibilities for the detected association include up-regulation of the cytochrome P450 enzyme system (38) and of the proteins that enable cell-to-cell communication at high levels of lycopene intake (39, 40).

Findings from the present study conflict with previous reports of an inverse association of beta-carotene with rectal cancer (15, 27); with the highest intake of beta-carotene, a 46 percent reduction in risk was reported for Chinese (27) and a 68 percent reduction in risk was reported for Italians (15). Our findings are more consistent with those from the Australian case-control study in which no significant associations were detected (28). To our knowledge, others have not examined the associations between rectal cancer and beta-carotene by hormone replacement therapy use or estrogen status. However, in our study, for estrogen-negative women versus estrogen-positive women, the lowest intakes of beta-

TABLE 4. Associations between forms of tocopherols and rectal cancer in women, Northern California and Utah, 1997–2002

	Quintile of intake													*p* for linear trend
	High		4			3			2			Low			
	Value	OR*,†	Value	OR	95% CI*	Value	OR	95% CI	Value	OR	95% CI	Value	OR	95% CI	
Alpha-tocopherol (IU)	>13.3				9.8, 13.2			7.4, 9.7			4.5, 7.3	<5.5			
Cases/controls (no.)	74/106		81/105			77/106			71/108			90/107			
Everyone		1.0		1.4	0.9, 2.3		1.5	0.9, 2.6		1.5	0.8, 2.8		2.2	1.1, 4.3	0.05
Aged <60 years		1.0		1.0	0.5, 2.1		0.9	0.4, 2.1		0.8	0.3, 2.0		1.1	0.4, 3.0	0.88
Aged ≥60 years		1.0		1.8	0.9, 3.5		2.2	1.0, 4.7		2.5	1.1, 5.9		3.6	1.4, 9.4	0.01
Beta-tocopherol (IU)	>0.51				0.38, 0.51			0.28, 0.37			0.19, 0.27	<0.19			
Cases/controls (no.)	71/105		71/105			65/109			91/102			95/111			
Everyone		1.0		1.3	0.8, 2.1		1.2	0.7, 2.1		2.0	1.2, 3.4		2.1	1.2, 3.9	<0.01
Aged <60 years		1.0		1.5	0.7, 3.0		1.4	0.6, 3.1		2.5	1.1, 5.6		2.1	0.8, 5.3	0.06
Aged ≥60 years		1.0		1.2	0.6, 2.2		1.0	0.5, 2.1		1.6	0.8, 3.2		2.0	0.9, 4.3	0.06
Gamma-tocopherol (IU)	>24.4				20.9, 24.4			15.2, 20.8				<10.2		10.2, 15.1	
Cases/controls (no.)	86/105		65/106			82/109			74/106			86/106			
Everyone		1.0		1.1	0.7, 1.8		1.5	0.9, 2.4		1.6	0.9, 2.9		2.4	1.3, 4.5	<0.01
Aged <60 years		1.0		0.6	0.3, 1.3		0.8	0.4, 1.6		0.7	0.3, 1.6		1.1	0.4, 2.7	0.77
Aged ≥60 years		1.0		1.9	0.9, 3.6		2.9	1.4, 6.0		3.5	1.5, 8.1		5.3	2.1, 13.2	<0.01
Delta-tocopherol (IU)	>6.2				43, 6.2			2.9, 4.2			1.9, 2.8	<1.9			
Cases/controls (no.)	76/108		76/108			76/106			67/112			80/99			
Everyone		1.0		0.9	0.6, 1.4		1.0	0.7, 1.6		1.0	0.6, 1.5		1.5	0.9, 2.5	0.17
Aged <60 years		1.0		0.9	0.5, 1.7		0.9	0.5, 1.7		0.9	0.2, 1.1		1.1	0.5, 2.5	0.66
Aged ≥60 years		1.0		0.9	0.5, 1.7		1.2	0.7, 2.4		1.4	0.7, 2.7		1.9	0.9, 4.0	0.03

* CI, confidence interval; OR, odds ratio.

† All odds ratios were adjusted for age, body mass index, physical activity level, cigarette smoking status, energy intake, calcium intake, and fiber intake.

TABLE 5. Interaction between estrogen status and levels of intake of lycopene, beta-carotene, and vitamin E, Northern California and Utah, 1997–2002

	Positive estrogen status				Negative estrogen status				*p* for interaction*
	Cases (no.)	Controls (no.)	OR†,‡	95% CI†	Cases (no.)	Controls (no.)	OR‡	95% CI	
Lycopene									
High	47	73	1.0		28	33	1.6	0.8, 3.1	0.12
Intermediate	132	195	1.2	0.8, 2.0	86	124	1.4	0.8, 2.4	
Low	36	65	1.2	0.6, 2.2	63	42	3.2	1.7, 6.0	
Beta-carotene									
High	46	73	1.0		26	33	1.4	0.7, 2.8	0.17
Intermediate	131	189	1.0	0.6, 1.6	100	130	1.2	0.7, 2.0	
Low	38	71	0.7	0.4,1.4	51	36	2.0	1.0, 4.0	
Vitamin E									
High	45	64	1.0		32	42	1.2	0.6, 2.2	0.17
Intermediate	132	208	1.3	0.7, 2.2	97	114	1.9	1.1, 3.5	
Low	38	61	1.7	0.8, 3.6	48	43	3.0	1.4, 6.5	

* *p* for interaction from the additive scale.
† OR, odds ratio; CI, confidence interval.
‡ All odds ratios were adjusted for age, body mass index, physical activity level, cigarette smoking status, energy intake, calcium intake, and fiber intake.

carotene were associated with a twofold greater risk of rectal cancer. Beta-carotene exposure has been linked to production of reactive oxygen species in the colon that may act in either a prooxidant or antioxidant capacity, depending on the cellular environment (5). It is also possible that the association of beta-carotene with rectal cancer is through regulation of cell growth. Availability of beta-carotene as a precursor to vitamin A and the maintenance of cell integrity may be more important for estrogen-positive women, since estrogen may increase cell proliferation.

As in other studies (27, 33), we observed no association between dietary or supplemental vitamin C and rectal cancer. However, inverse associations between vitamin C and rectal cancer have been reported for New York women (26) and Italian men and women (15).

Of interest is the gender-specific associations we noted. Among women, the strongest associations were found for older women, who could, on the surface, appear to be hormonally more similar to men. However, in assessing other risk factors and gender differences in colon cancer, we observed that associations with body mass index were more similar for premenopausal women and men than for postmenopausal women and men (41). We hypothesize that androgens function similarly to estrogen in some disease pathways. Our observation of gender-specific associations between carotenoids and colorectal cancer have some support in the literature. Differences in associations between antioxidants and risk of colon cancer (17), rectal cancer (26, 28), and colorectal cancer (15) between men and women have been noted before. Furthermore, associations of retinol and rectal cancer for men and women reported by Potter and McMichael (28), although not significant, were in opposite directions. Other studies of smaller size (27) have not examined gender-specific associations, but failure to examine them does not preclude their existence.

Both age and estrogen appeared to modify the associations of lycopene and vitamin E with risk of rectal cancer. However, age and estrogen status are tightly related, making it difficult to evaluate whether their influences are independent or whether estrogen status influences the relation of age to risk of rectal cancer. Inadequate power hampered our efforts to clearly distinguish this issue; however, the association of lycopene with hormone-sensitive cancers (7, 8, 10, 11) certainly points to the plausibility of an independent influence of estrogens, as do the gender-specific associations.

Strengths of the study include the large number of cases of rectal cancer, comprehensive assessment of diet using a quantitated diet history, a comprehensive carotenoid database (29) used to calculate carotenoid exposure, and the quality control procedures we used to collect data. Classification of women according to estrogen status enabled us to study both pre- and postmenopausal women. However, despite the large sample size, we were limited in our ability to conduct statistical tests for significant interactions when stratifying by estrogen status or to further stratify by supplement use in gender-specific associations. The CARDIA dietary history has previously been shown to be a valid measure of vitamin A use in White men and women (11). Recall bias cannot be ruled out as a contributor to the present findings. However, since our referent period for dietary data was the calendar year 2 years prior to diagnosis or selection and we noted significant associations, the referent period appears to be appropriate for vitamin E, lycopene, and beta-carotene. If other antioxidants or carotenoids operate at a different stage in the carcinogenic process, we could have missed other potentially important associations.

In summary, this study supports the hypothesis that some antioxidants and carotenoids are modestly associated with a reduction in the risk of rectal cancer. However, the most important associations appear to be restricted to women and, in some instances, are further modified by age. Of interest is the observed effect modification by estrogen status. Further investigation into how estrogens might influence lycopene and vitamin E is needed. Given previously reported associations by others that lycopene is associated with hormonal cancers such as prostate, ovarian, and breast cancer, this could be an informative area of research into diet and cancer etiology.

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