

Associations of Micronutrients with Colon Cancer Risk in African Americans and Whites: Results from the North Carolina Colon Cancer Study

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Abstract

African Americans have the highest incidence of colon cancer among United States racial/ethnic groups, but these disparities are largely unexplained. This report describes associations of micronutrients with colon cancer risk in African Americans and whites using data from a case-control study in North Carolina. Incident cases of histologically confirmed colon cancer, age 40–80 years ($n = 613$), and matched controls ($n = 996$) were interviewed in person to elicit information on potential colon cancer risk factors. A previously validated food frequency questionnaire adapted to include regional foods was used to assess diet over the year prior to diagnosis or interview date. Micronutrient exposure included food sources and dietary supplements. Multivariate logistic regression models estimated energy-adjusted and non-energy-adjusted odds ratios (ORs). African Americans reported lower mean micronutrient intakes than whites, primarily due to larger contributions from dietary supplements in whites. Controls generally reported higher micronutrient intakes than cases; however, these differences were only statistically significant for whites. In whites, high β -carotene, vitamin C, and calcium intakes were associated with 40–60% reductions in colon cancer risk when contrasting highest to lowest quartiles in both energy-adjusted and non-energy-adjusted models, e.g., OR = 0.4 (95% confidence interval, 0.3–0.6) for the highest quartile of calcium in the energy-adjusted model. In African Americans, vitamins C and E were strongly inversely associated using both statistical approaches: high vitamin E intake was associated with a 70% reduced

risk for colon cancer, and the OR comparing the highest to lowest quartiles of vitamin C was 0.5 (95% confidence interval, 0.3–0.8). Folate and lutein were not statistically significantly associated with colon cancer risk in either racial group. These results suggest that at high intakes, micronutrients commonly found in plant and other foods (in particular, β -carotene, vitamin C, and calcium in whites and vitamins C and E in African Americans) exhibit independent associations consistent with 30–70% reductions in colon cancer risk.

Introduction

Colon cancer is one of the most common malignancies in developed countries (1). It is the second leading cause of cancer death in the United States and the third most common cancer among men and women in the United States, accounting for approximately 15% of all cancers diagnosed annually (2, 3). In the year 2001, an estimated 48,100 persons died from colorectal cancer, and 98,200 new cases were diagnosed (4). Colon cancer incidence and mortality vary markedly by race/ethnicity: specifically, African Americans have higher incidence and mortality from colon cancer compared with other population groups (3, 4). For example, between 1990 and 1996, colon/rectum cancer incidence and mortality rates were 50.7 and 23.1 per 100,000, respectively, among African Americans. Incidence and mortality rates for whites were 43.9 and 17.4 per 100,000, respectively (3).

The racial differences in incidence rates for colon cancer are largely unexplained. Although some of these disparities may be attributed to access to health care and socioeconomic differences, these factors do not completely explain the diverging trends (5). Furthermore, the increase in colon cancer incidence in African Americans does not appear to be explained by higher rates of early detection and screening (6). Differences in inherited susceptibility characteristics such as polymorphic variations in phase I and II carcinogen-metabolizing enzymes and related gene-environment interactions are plausible explanations that warrant further investigation. In addition, it is important to explore prognostic factors that are potentially modifiable in African Americans to decrease the colon cancer burden in this high-risk population.

Epidemiological studies have consistently demonstrated marked changes in the incidence of colon cancer with geography and migration, suggesting an important environmental component to colon cancer risk (7). Dietary factors have been the most extensively studied and are among the most widely accepted etiological risk factors for colon cancer (8, 9). However, despite years of research, the impact of many dietary factors on colon carcinogenesis remains unresolved (8, 9). Moreover, associations of diet with colon cancer risk have rarely been examined in African Americans or in population-

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based studies with an adequate African-American representation. To our knowledge, there is only one etiologic study of diet and colon cancer in African Americans, but it was conducted over 20 years ago and included only 99 cases (10).

Therefore, the purpose of this report is to investigate whether the role of dietary intake in colon cancer risk differs by race in a large case-control study with similar numbers of African-American and white cases and controls. Specifically, we describe associations of selected micronutrients (β -carotene, lutein, vitamin C, vitamin E, folate, and calcium) with colon cancer risk in African Americans and whites enrolled in the NCCCS.²

Materials and Methods

Study Design. The NCCCS is a population-based, case-control study of colon cancer in North Carolina. Study participants were from 33 counties in the central portion of North Carolina, an area that includes rural, suburban, and urban counties with a diverse socioeconomic mix of African Americans and whites. The study was approved by the Institutional Review Board at the University of North Carolina School of Medicine and by equivalent committees at the collaborating hospitals.

Study Population. Cases and controls were selected using a randomized recruitment approach to achieve approximate frequency matching on age, race, and sex and to enhance the proportion of African Americans (11, 12). Participants were offered a \$25 incentive to take part in the study.

Cases. Persons with a first diagnosis of histologically confirmed invasive adenocarcinoma of the colon between October 1, 1996 and September 30, 2000 were identified through the rapid ascertainment system of the North Carolina Central Cancer Registry (13). Other eligibility criteria included: age of 40–80 years at the time of diagnosis; residence in the 33-county study area in North Carolina; ability to give informed consent and complete the interview; a North Carolina driver's license or identification card if under age 65 years (because controls under age 65 years were sampled from driver's license rosters); and permission to contact from the primary physician. Diagnoses were confirmed by the study pathologist based on review of pathology slides and reports, and dysplasia was graded as mild, moderate, or severe.

A letter and study description were sent to the primary physicians of eligible cases requesting permission to invite the patient to participate in the study. When permission for contact was obtained, the patient was sent a letter describing the study, then called by a race-matched enrollment specialist who explained the study, answered questions, and sought participation. If consent was obtained, the enrollment specialist scheduled an appointment for an in-person interview. Interviews were generally scheduled within 5 months of surgery. White cases were undersampled to increase the proportion of non-white cases in the study population.

Controls. The noninstitutionalized population-based controls were selected from two sources: (a) North Carolina Division of Motor Vehicle records for cases under the age of 65 years; and (b) the Center for Medicare and Medicaid Services (formerly the Health Care Financing Administration) for cases 65 years or older. These listings were used to randomly select potential

controls within the same 5-year age group-, sex-, and race-defined strata. Those identified as eligible controls were contacted in a similar fashion to the cases to schedule in-person interviews.

Completed interviews were obtained from 1691 participants. Of these, 731 were African American (294 cases and 437 controls), and 957 were white (349 cases and 611 controls). The overall study cooperation rate [interviewed/(interviewed + refused)] was 84% for cases and 63% for controls. For both cases and controls, the cooperation rates were slightly higher for whites (89% for cases and 64% for controls) than for African Americans (79% for cases and 61% for controls). The study response rate (interviewed/eligible) was 72% for cases and 61% for controls. Among those eligible to participate, reasons for nonparticipation included refusal (14% for cases and 36% for controls), physician denial (7% for cases), untraceable (1% for cases and 1% for controls), and not reachable by telephone (6% for cases and 1% for controls).

Data Collection. Data were collected in person by trained nurse interviewers at the participant's home or, occasionally, at another convenient location. The questionnaire collected detailed information on several factors that might relate to colon cancer, including diet, lifestyle factors, and medical history. The referent period for the interview was the year prior to diagnosis (cases) or interview date (controls).

Dietary Intake. Nutrient intake was assessed with a modified version of the previously validated 100-item semiquantitative Block FFQ developed at the National Cancer Institute (14). The FFQ was modified by adding 29 foods commonly consumed in North Carolina to better assess regional dietary practices in a sample of North Carolinians that included low-income African Americans (15). In the present study, participants were asked to estimate their usual frequency of consumption of various foods and typical portion sizes for the year prior to diagnosis (for cases) or the year preceding the interview date (for controls). The 1-year period was chosen to account for seasonal variations in dietary intake. Each food item had nine options for frequency (ranging from "never or less than once per month" to "2+ times per day") and three options for portion size. The FFQ also included adjustment questions on cooking methods, food preparation techniques, restaurant eating, and consumption of low-fat foods and fortified beverages because these variables can affect estimates of nutrient intake (16). Nutrient intake was calculated by an analysis program provided by the National Cancer Institute that incorporates the nutrient content of each food item, the consumption frequency, and a portion size based on age (14). For these analyses, we examined selected micronutrients that are reasonably well captured by FFQs: β -carotene; lutein; vitamin C; vitamin E; folate; and calcium (17, 18). Participants with reported energy intakes <800 kcal and >5000 kcal for men ($n = 10$) and <600 kcal and >4000 kcal for women ($n = 22$) were excluded because their FFQs were considered to be unreliable (17). Participants with missing values on any of the above dietary micronutrient variables ($n = 16$) were also excluded from further analyses.

Dietary supplement use was assessed with closed-ended questions on the use of multiple vitamins (including antioxidant combinations) and single supplements. Participants were asked, specifically, about duration (years), frequency (days per week), and usual dose (e.g., 100, 250, 500, 750, 1000 mg for vitamin C) of supplements used over the past year. Because supplements contribute a large proportion of micronutrient intakes (18–20), we summed across intakes from food sources and

² The abbreviations used are: NCCCS, North Carolina Colon Cancer Study; OR, odds ratio; CI, confidence interval; FFQ, food frequency questionnaire; BMI, body mass index; NSAID, nonsteroidal anti-inflammatory drug; MET, metabolic equivalent task; α -TE, α -tocopherol equivalents.

dietary supplements to obtain total exposure for all micronutrients.

Other Participant Characteristics. Data were collected on several demographic characteristics including age, sex, education, race, smoking history, physical activity, use of NSAIDs over the last 5 years, and first-degree family history of colon cancer. Trained staff measured height and weight at the in-person interview using a standardized protocol. Height and weight were used to compute BMI as weight (in kilograms) divided by height (in meters) squared. BMI was divided into three categories using the recommended cutoffs by the Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: “normal,” 18.5–24.9 kg/m²; “overweight,” 25.0–29.9 kg/m²; and “obese,” ≥30.0 kg/m² (21). Participants with BMIs of <18.5 or >50 kg/m² (*n* = 36) were excluded because they comprised <2% of the analytic sample. Physical activity during the year prior to diagnosis or interview date was measured in MET-minutes per day for combined occupational, nonoccupational, and non-work/week-end activities (including duration, frequency, and intensity) using a modified version of a validated 7-day physical activity recall (22–24).

Because there were very few participants of other races/ethnicities (*n* = 8), these analyses are restricted to whites and African Americans. After all exclusions, 1609 participants remained for these analyses, including 933 whites (337 cases and 596 controls) and 676 African Americans (276 cases and 400 controls).

Statistical Analyses. Data analyses were performed using SAS 8.1 (SAS Institute Inc., Cary, NC). Descriptive statistics (raw means and percentages) stratified by race (white or African American) and case-control status were used to describe the demographic/health-related characteristics and dietary intakes of the study participants. Logistic regression models were used to determine whether there were statistically significant differences between cases and controls for the participant characteristics and dietary variables under examination (Tables 1 and 2). *P*s for differences were adjusted for participant characteristics, and the dietary factors were also adjusted for total energy intake.

We calculated ORs and 95% CIs from unconditional logistic regression models to ascertain associations between micronutrient intakes (in quartiles) and colon cancer risk. Offset terms were included in all models to correct for randomized recruitment sampling fractions (11, 12) and allow estimation of unbiased ORs. This was necessary because we conditioned recruitment on age, sex, and race, in addition to disease status; thus, the ORs without the offset term will be biased compared with a traditional design in which recruitment is conditioned on disease status alone. Cutpoints for quartiles of micronutrient intakes were determined based on the distributions among all controls and race-specific controls. Age (continuous), sex, education (high school, some college, college graduate/advanced degree), BMI (continuous), smoking history (never, former, current), physical activity (quartiles), first-degree family history of colon cancer (yes, no), NSAID use (never, occasionally, regularly), dietary supplement use (yes, no), total energy, total fat, dietary fiber, fruits, and vegetables were evaluated as potential confounding factors. Covariate inclusion was based on whether there was a 10% or greater alteration in the parameter coefficient of interest. Covariates that met this criterion were included in a model, and a backwards-stepwise procedure was performed to obtain the final model. Each micronutrient had a unique set of confounding variables. All ORs are reported for

energy-adjusted and non-energy-adjusted nutrient intakes. The standard multivariate technique was used to adjust for total energy intake (25); applying other energy adjustment methods (e.g., the nutrient residual model) did not alter the results. Statistical tests were two-sided, and *P*s < 0.05 were considered statistically significant.

Results

Table 1 gives baseline demographic and lifestyle characteristics of study participants, stratified by race and case-control status. African Americans more often had proximal tumors (49% versus 45%), whereas whites were more likely to have distal tumors (45% versus 42%). Among both whites and African Americans, colon cancer cases were slightly younger than controls, and approximately half of the cases were 65 years or older. White cases and controls did not differ significantly by sex; however, African-American cases were more often males, whereas controls were more often females (*P* < 0.02). For both racial groups, there were no statistically significant differences between cases and controls by education level, physical activity (MET-minutes/day), or smoking history; however, the majority of white cases were former smokers (53%), whereas African-American cases were more often current smokers (47%). Although cases and controls did not differ by current BMI, BMI values from the year prior to diagnosis suggested that cases had lost weight (28.4 versus 27.4 kg/m² for whites and 30.6 and 29.0 kg/m² for African Americans). Finally, cases were more likely than controls to have a family history of colon cancer but were less likely to have used NSAIDs regularly over the previous 5 years or to have used vitamin/mineral supplements during the preceding year (all *P* < 0.05).

Mean micronutrient intakes (food sources only and diet plus supplements) among white and African-American colon cancer cases and controls are given in Table 2. With the exception of β-carotene and lutein, African Americans reported lower total mean intakes of micronutrients than whites; however, for most nutrients, the higher intakes in whites were primarily due to contributions from dietary supplements. For example, mean daily vitamin E intake from foods plus supplements was 81 mg α-TE for white cases but only 32 mg α-TE for African-American cases; however, reported mean intakes from diet alone were similar for both groups (approximately 9 mg α-TE). There were modest differences in micronutrient intakes between cases and controls, but the extent of the differences varied by race. Specifically, although mean intakes among African-American controls tended to be somewhat higher than those for African-American cases, these differences did not reach statistical significance for any of the micronutrients examined, except for vitamin E. In contrast, white controls consistently reported significantly higher micronutrient intakes than white cases (all *P* < 0.05, except for vitamin E).

Table 3 gives energy- and non-energy-adjusted associations (ORs and 95% CI) of the micronutrients with colon cancer risk, stratified by race. ORs for intakes from food sources alone were not appreciably different (although they were slightly weaker) from the diet plus supplement estimates, so only the latter are presented here. In addition, there were no marked differences in race-specific ORs estimated using quartile cut-offs based on combined intakes from all controls (data not shown) and those estimated using race-specific control intakes. Overall, slightly stronger associations were observed for energy-adjusted ORs than for ORs not adjusted for total energy, and all micronutrients were inversely associated with risk if the association was statistically significant. Among whites, those in

Table 1 Baseline characteristics of NCCCS participants with and without colon cancer, by race (n = 1609)^a

Participant characteristic ^b	Whites (n = 933)			African Americans (n = 676)		
	Cases (n = 337)	Controls (n = 596)	P ^c	Cases (n = 276)	Controls (n = 400)	P ^c
Age (%) (yrs)						
<55	17	14	<0.0001	27	15	<0.0001
55–65	29	26		29	26	
≥65	54	60		44	58	
Mean ± SD	65.1 (9.7)	66.1 (9.3)	<0.0001	62.3 (10.3)	66.0 (9.5)	0.0002
Sex (%)						
Males	56	55	0.23	48	44	0.02
Females	44	45		52	56	
Education (%)						
≤High school	57	48	0.17	72	70	0.20
Some college	20	24		18	17	
College graduate/Advanced degree	23	27		9	13	
BMI (%)—Current						
Normal (18–24.9 kg/m ²)	36	31	0.08	25	24	0.38
Overweight (25–29.9 kg/m ²)	37	44		39	35	
Obese (≥30 kg/m ²)	28	25		36	42	
Mean ± SD (kg/m ²)	27.4 (5.3)	27.6 (5.0)	0.10	29.0 (6.1)	29.4 (5.8)	0.18
BMI (%)—1 yr ago						
Normal (18–24.9 kg/m ²)	28	31	0.65	13	20	0.13
Overweight (25–29.9 kg/m ²)	42	43		42	39	
Obese (≥30 kg/m ²)	30	26		45	42	
Mean ± SD (kg/m ²)	28.4 (5.3)	27.6 (4.8)	0.04	30.6 (6.3)	29.4 (5.5)	0.07
Smoking history (%)						
Never smoker	13	16	0.01	19	21	0.95
Former smoker	53	44		34	35	
Current smoker	34	40		47	45	
Physical activity (MET-minutes/day) (%)						
1 st quartile	23	25	0.50	22	25	0.54
2 nd quartile	27	25		30	25	
3 rd quartile	26	25		28	25	
4 th quartile	24	25		19	25	
Mean ± SD (MET-minutes/day)	2255 (558)	2202 (451)	0.18	2226 (568)	2162 (526)	0.99
Family history of colon cancer (%)						
Yes	22	9	<0.0001	17	10	0.003
No	78	91		83	90	
NSAID use over the past 5 years ^d (%)						
Never	11	7	0.0003	11	7	0.0006
Occasionally	38	28		44	33	
Regularly	51	65		45	60	
Vitamin/mineral supplement use ^e (%)						
Yes	48	59	0.04	33	43	0.08
No	52	41		67	57	

^a All data are for the reference year, which is the year before diagnosis for cases and the year before the interview for controls.

^b All data are in percentages, except for mean ± SD for age and BMI (current and 1 year ago).

^c Test for difference between cases and controls after controlling for the other participant characteristics in the table (excluding current BMI) and for total energy intake.

^d Never, no NSAID use in the past 5 years; occasionally, used NSAIDs less than 3 times/week in the past 5 years; regularly, used NSAIDs 3 or more times/week in the past 5 years.

^e Use of any vitamin or mineral supplement at least once a week over the past year.

the highest quartiles of β -carotene, vitamin C, and calcium intakes had statistically significantly lower (40–60%) colon cancer risk than those in the lowest quartiles, regardless of the statistical model examined. For example, the OR comparing the highest quartile of calcium to the lowest in the energy-adjusted model was 0.4 (95% CI, 0.3–0.6; $P < 0.0001$). In African Americans, vitamins C and E had strong inverse associations using both statistical approaches: vitamin E was associated with a 70% lower risk for colon cancer (OR, 0.3; 95% CI, 0.1–0.6); whereas the energy-adjusted OR contrasting the highest to lowest quartiles of vitamin C was 0.5 (95% CI, 0.3–0.8). Folate and lutein were not statistically significantly associated with colon cancer risk in either whites or African Americans.

Discussion

In this large case-control study of colon cancer in North Carolina with an adequate representation of whites and African Americans, high intakes of β -carotene, vitamin C, vitamin E, and calcium were inversely related to colon cancer status. However, the associations differed somewhat by race: calcium was statistically significantly inversely associated only in whites; vitamin E was inversely associated only in African Americans; and associations with energy-adjusted β -carotene and vitamin C were seen in both racial groups.

To our knowledge, this is the first published investigation of micronutrients with colon cancer risk in African Americans. Overall, African-American colon cancer cases and controls

Table 2 Mean intakes of micronutrients among NCCCS participants with and without colon cancer, by race (n = 1609)^a

Micronutrient	Whites (n = 933)					African Americans (n = 676)				
	Overall ^b Mean ± SD	Cases (n = 337)	Controls (n = 596)	Difference (cases-controls)	P ^c	Overall ^b Mean ± SD	Cases (n = 276)	Controls (n = 400)	Difference (cases-controls)	P ^c
β -Carotene ($\mu\text{g/day}$)										
From foods + supplements	4222 (4721)	3453	4657	-1204	0.0001	4333 (3447)	4188	4433	-245	0.35
From foods only	3095 (2373)	2728	3303	-575	0.0001	3894 (2785)	3834	3936	-102	0.23
Lutein ($\mu\text{g/day}$) ^d	2580 (2960)	2313	2730	-417	0.02	4341 (3798)	4373	4319	54	0.64
Vitamin C (mg/day)										
From foods + supplements	248 (353)	204	273	-69	0.005	163 (217)	140	178	-38	0.22
From foods only	96 (55)	92	99	-7	0.02	94 (55)	96	93	3	0.92
Vitamin E (mg α -TE/day)										
From foods + supplements	100 (169)	81	111	-30	0.18	46 (116)	32	56	-24	0.05
From foods only	9.3 (4.3)	9.5	9.2	0.3	0.14	8.9 (4.7)	9.0	8.8	0.2	0.02
Folate ($\mu\text{g/day}$)										
From foods + supplements	449 (237)	422	465	-43	0.05	358 (212)	357	359	-2	0.75
From foods only	292 (116)	287	295	-8	0.001	260 (118)	267	255	12	0.45
Calcium (mg/day)										
From foods + supplements	941 (511)	869	981	-112	0.001	672 (384)	673	671	2	0.24
From foods only	741 (344)	719	754	-35	0.0005	590 (306)	614	573	41	0.61

^a All data are for the reference year, which is the year before diagnosis for cases and the year before the interview for controls.

^b Mean intakes among race-specific cases and controls.

^c Test for difference between cases and controls after controlling for the other participant characteristics in Table 1 (excluding current BMI) and for total energy intake.

^d Intakes are from food sources (FFQ) only.

reported lower intakes of micronutrients than their white counterparts. This is primarily attributable to a higher contribution from dietary supplements in whites, as the intakes from food sources alone were not markedly different (Table 2). Thus, with the increasing prevalence of dietary supplement use in United States populations (26), our findings highlight the importance of collecting information on supplement use when studying associations of micronutrients with disease risk. These findings also show that there are racial differences in patterns of supplement use.

The reasons why some nutrients appeared to reduce colon cancer risk in whites but not in African Americans and *vice versa* are not entirely clear. One possibility is that intakes of some nutrients were too low, even in the highest quartiles, for us to observe significant associations. This may be the case with calcium, for which intakes in whites were considerably higher than in African Americans (Tables 2 and 3). Also, if vitamin and mineral supplement use has an independent effect on cancer risk, racial differences in supplement use patterns may partially explain some of the differences in nutrient-colon cancer associations between African Americans and whites. To our knowledge, no other study has reported such a strong association between vitamin E and colon cancer as we report here for African Americans (70% risk reduction). Furthermore, these differences remained after we combined all control intakes and estimated race-specific ORs using global quartile cutoffs (data not shown), suggesting that differences in range of intakes between whites and African Americans (Table 2) do not explain the disparate findings. It is possible that this and other findings in this report may be due in part to collinearity between micronutrients and foods of which they are constituents (e.g., fruits and vegetables); however, we controlled for the effects of other micronutrients and fruit and vegetable intake in these analyses.

Results from this study are consistent with hypotheses that dietary antioxidants (β -carotene, vitamin C, and vitamin E) may reduce risk of colon cancer. In addition to their antioxidant properties, carotenoids (e.g., β -carotene and lutein) are of increasing interest in relation to colon cancer because of their

possible effects on cell growth regulation, modulation of gene expression, and enhancement of immune response (27–29). The results also lend support to the notion that high calcium intake may reduce risk of colon cancer, perhaps due to the ability of calcium to reduce epithelial proliferation of the colon mucosa and bind bile and free fatty acids (8, 30, 31).

Our findings are also in agreement with a number of studies that have reported inverse associations between these micronutrients and colon cancer risk (30–40). In particular, high intakes of β -carotene (29, 32–35), vitamin C (32–34), vitamin E (32–34, 36), and calcium (32–34, 37–39) have been inversely associated with colon cancer risk in several cohort, case-control, and intervention studies. In addition, randomized clinical trial data suggest that calcium is associated with reduced recurrence of colonic adenomas, which are important precursors of colon cancer (30). However, relationships of these dietary factors with colon cancer risk from analytic epidemiological studies have been inconsistent because results have varied depending on the study design, participant characteristics, dietary assessment method, dietary *versus* non-dietary micronutrient sources, and stage of colon cancer at diagnosis (8, 9, 41).

Nonetheless, it is rather surprising that we did not observe a meaningful association of folate with risk of colon cancer because plausible biological mechanisms exist (7, 42), and numerous investigations have demonstrated an inverse relationship (43–45), including one cohort study of women (46). However, in an earlier study, Giovannucci *et al.* (47) reported that men in the highest quintile of dietary folate intake did not have reduced risk (relative risk, 0.85; 95% CI, 0.54–1.39), and in two more recent case-control studies (34, 48), folate was not associated with colon cancer risk. In addition, there are possible interactions between folate and polymorphisms in the 5,10-methylene-tetrahydrofolate reductase gene that may modulate the association of folate with colon cancer risk (49, 50). The potential role of lutein in colon carcinogenesis has rarely been studied, and to our knowledge, there is only one published report examining this relationship in humans. In contrast to our findings, Slattery *et al.* (51) reported that lutein was associated

Table 3 Associations (adjusted ORs) of micronutrients with colon cancer risk in the NCCCS, by race (n = 1609)^a

Micronutrient ^{b,c}	Whites (n = 933)				African Americans (n = 676)			
	No. of cases	Median intake/ day in controls	OR (95% CI)		No. of cases	Median intake/ day in controls	OR (95% CI)	
			Energy- adjusted ^d	Not adjusted for energy ^e			Energy- adjusted ^d	Not adjusted for energy ^e
β-Carotene (μg/day)								
1 st quartile (reference)	113	1403	1.0	1.0	85	1385	1.0	1.0
2 nd quartile	88	2672	0.8 (0.5–1.1)	0.8 (0.6–1.2)	67	2978	0.7 (0.4–1.1)	0.7 (0.5–1.1)
3 rd quartile	84	4087	0.8 (0.5–1.3)	0.8 (0.6–1.3)	58	4286	0.4 (0.3–0.7)	0.6 (0.4–1.0)
4 th quartile	51	7396	0.5 (0.3–0.9)	0.5 (0.3–0.9)	66	7545	0.6 (0.3–0.9)	0.8 (0.5–1.3)
<i>P</i> for linear trend			0.05	0.02			0.009	0.24
Lutein (μg/day)^f								
1 st quartile (reference)	89	531	1.0	1.0	61	972	1.0	1.0
2 nd quartile	94	1291	1.1 (0.8–1.7)	1.2 (0.8–1.8)	84	2475	1.3 (0.8–2.2)	1.5 (0.9–2.4)
3 rd quartile	88	2524	1.1 (0.7–1.7)	1.1 (0.7–1.7)	59	4413	0.7 (0.4–1.2)	0.8 (0.5–1.3)
4 th quartile	62	5067	0.8 (0.5–1.3)	0.8 (0.5–1.3)	72	8197	1.2 (0.7–2.0)	1.3 (0.8–2.2)
<i>P</i> for linear trend			0.56	0.42			0.80	0.98
Vitamin C (mg/day)								
1 st quartile (reference)	115	59	1.0	1.0	87	46	1.0	1.0
2 nd quartile	97	105	0.8 (0.6–1.2)	0.9 (0.6–1.3)	70	93	0.7 (0.4–1.1)	0.7 (0.5–1.2)
3 rd quartile	74	163	0.7 (0.5–1.1)	0.7 (0.5–1.1)	63	132	0.6 (0.4–1.0)	0.7 (0.5–1.1)
4 th quartile	51	644	0.5 (0.3–0.8)	0.5 (0.3–0.8)	56	250	0.5 (0.3–0.8)	0.6 (0.4–0.9)
<i>P</i> for linear trend			0.005	0.002			0.002	0.03
Vitamin E (mg α-TE/day)								
1 st quartile (reference)	82	6	1.0	1.0	75	5	1.0	1.0
2 nd quartile	116	11	1.0 (0.7–1.6)	1.5 (1.0–2.3)	77	9	0.6 (0.4–1.0)	0.7 (0.5–1.2)
3 rd quartile	77	30	1.0 (0.6–1.5)	1.1 (0.8–1.8)	75	14	0.5 (0.3–0.9)	0.7 (0.4–1.1)
4 th quartile	61	296	0.9 (0.6–1.5)	1.0 (0.6–1.6)	49	140	0.3 (0.1–0.6)	0.3 (0.1–0.6)
<i>P</i> for linear trend			0.77	0.69			0.0004	0.002
Folate (μg/day)								
1 st quartile (reference)	104	196	1.0	1.0	66	147	1.0	1.0
2 nd quartile	98	325	0.8 (0.5–1.2)	1.1 (0.7–1.6)	71	240	1.1 (0.7–1.9)	1.2 (0.7–1.9)
3 rd quartile	71	572	0.6 (0.4–1.0)	0.7 (0.5–1.1)	79	369	1.2 (0.7–2.2)	1.4 (0.8–2.4)
4 th quartile	64	741	0.8 (0.5–1.2)	0.9 (0.6–1.4)	60	642	0.9 (0.5–1.6)	1.0 (0.6–1.8)
<i>P</i> for linear trend			0.11	0.29			0.70	0.94
Calcium (mg/day)								
1 st quartile (reference)	110	456	1.0	1.0	68	304	1.0	1.0
2 nd quartile	90	710	0.7 (0.5–1.0)	0.8 (0.6–1.2)	72	492	0.9 (0.5–1.5)	1.0 (0.6–1.6)
3 rd quartile	77	1001	0.5 (0.3–0.7)	0.7 (0.5–1.1)	65	678	0.8 (0.4–1.3)	1.0 (0.5–1.4)
4 th quartile	60	1691	0.4 (0.3–0.6)	0.6 (0.4–0.8)	71	1143	0.6 (0.3–1.1)	0.8 (0.4–1.4)
<i>P</i> for linear trend			<0.0001	0.003			0.08	0.35

^a All data are for the reference year, which is the year before diagnosis for cases and the year before the interview for controls.

^b Cutoffs based on intakes among control participants of the same race.

^c Except for lutein, micronutrient exposure is based on intakes from food sources plus dietary supplements.

^d Adjusted for total energy when total energy met criteria for covariate inclusion. Other potential confounders examined include age, sex, education, BMI (1 year ago), smoking history, physical activity, family history of colon cancer, NSAID use, vitamin/mineral supplement use, fat, dietary fiber, calcium, folate, fruits, and vegetables. Variables were included in the final models based on a ≥10% alteration in the parameter coefficient of interest. The set of confounders in the logistic models varied for each micronutrient.

^e Not adjusted for total energy. Potential confounders examined include age, sex, education, BMI (1 year ago), smoking history, physical activity, family history of colon cancer, NSAID use, vitamin/mineral supplement use, fat, dietary fiber, calcium, folate, fruits, and vegetables. Variables were included in the final models based on a ≥10% alteration in the parameter coefficient of interest. The set of confounders in the logistic models varied for each micronutrient.

^f Intakes from food sources (FFQ) only.

with 10–40% reductions in colon cancer risk in a large case-control study, with a stronger effect for proximal tumors and those in whom tumors were diagnosed at a younger age. Results from other epidemiological studies are needed to clarify these relationships.

This study had a number of strengths. We had a large sample size, which allowed us to observe associations that would be undetectable in smaller studies. We also used a detailed interviewer-administered questionnaire, which permitted the collection of comprehensive information on diet and other colon cancer risk factors, thereby reducing the potential for misclassification (52). Most importantly, our study is among the first published reports of micronutrients and colon cancer in a diverse sample of African Americans and whites recruited from the same geographic area.

The study also had some limitations. As in other case-control studies, there is potential for recall and selection bias.

Because exposure information was collected after diagnosis of the disease, differential dietary recall between cases and control could bias results. Controls may have agreed to join this study because of an interest in health and may therefore have healthier dietary and physical activity habits, a pattern that may exaggerate differences with the case group beyond what might have been seen with truly comparable controls (52). Response rates were comparable with those reported in other studies (53, 54); however, because controls had lower cooperation rates than cases, selection bias should be considered when interpreting these results. Estimates of nutrient intakes from a FFQ are not precise (17, 18), and there is always the potential for measurement error; however, the FFQ used in this study has been validated (in comparison with biomarkers and more extensive methods of assessing dietary intake) for the nutrients examined here (55, 56). It is also possible that the 1-year referent period on which dietary data were based is insufficient

if more remote diet (*e.g.*, 5–10 years) has a stronger influence on colon cancer risk. Finally, although we controlled for a wide range of potential confounding factors, the possibility for residual confounding remains. Carefully designed prospective studies using biologically based measures of various dietary exposures are needed to obviate these limitations in future studies.

In conclusion, results from this study add to the growing body of evidence suggesting that micronutrients (in particular, β -carotene, vitamin C, vitamin E, and calcium) commonly found in plant and other foods may reduce risk for colon cancer. The associations with β -carotene and calcium were robust in whites, and vitamins C and E were associated with a statistically significantly reduced risk in African Americans, regardless of the statistical model examined. The possibility that these findings may reflect problems of collinearity between micronutrients or other limitations of the data cannot be completely eliminated. Nonetheless, our findings strongly suggest that at high intakes, these micronutrients exhibit independent associations in both whites and African Americans consistent with 30–70% reductions in colon cancer risk.

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