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Antioxidant and DNA methylation-related nutrients and risk of distal colorectal cancer

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Abstract

Objective—To investigate the relationship between antioxidant nutrients (vitamins C and E, β-carotene, selenium) and DNA methylation-related nutrients (folate, vitamins B6 and B12) and distal colorectal cancer risk in whites and African Americans and to examine intakes from food only versus total (food plus dietary supplements) intakes.

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Methods—Data are from the North Carolina Colon Cancer Study-Phase II, a case–control study of 945 distal colorectal cancer (including sigmoid, rectosigmoid, and rectum) cases and 959 controls. In-person interviews captured usual dietary intake and various covariates. Multivariate logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (95% CI).

Results—High intakes of each antioxidant and DNA methylation-related nutrient were significantly associated with lower risk in whites. In African Americans, the highest category of selenium from food only had a marginally significant inverse association with distal colorectal cancer risk (Q4 vs. Q1 OR: 0.55, 95% CI 0.29–1.02). Supplements did not provide additional risk reduction beyond intakes from food.

Conclusions—Our findings provide evidence that antioxidant and DNA methylation-related nutrients may lower the risk of distal colorectal cancer in whites, and selenium may lower risk in African Americans. Optimal micronutrient intakes from food alone may be more beneficial than supplementation.

Keywords

Micronutrients; Colorectal cancer; Race; Dietary supplements; Disparities

Introduction

Colorectal cancer (CRC) is the third most common cancer in the United States [1] and results from a combination of genetic, epigenetic, and environmental factors [2]. Diet is widely believed to play an important role in the development of CRC, and several biological mechanisms provide a theoretical link between micronutrients and reduced risk of CRC [3,4].

Oxidative stress plays a major role in CRC development and progression [5] and results from an excess production of free radicals or insufficient antioxidant defenses [6]. Free radicals are unstable, highly reactive, oxygen-containing molecules that can cause tissue damage. Therefore, the balance between free radicals and antioxidants is critical. Numerous dietary nutrients, such as vitamin C, vitamin E, carotenoids, and selenium, have antioxidant properties [4,7] and protect against the damaging effects of free radicals. In addition to their antioxidant properties, these nutrients may also inhibit tumor development by stimulating the immune system [8] and regulating cell growth [9]. Together, these properties of antioxidant nutrients may help to prevent CRC.

Another well-known process involved in colorectal carcinogenesis is aberrant DNA methylation, which includes global hypomethylation and hypermethylation of CpG islands [10]. DNA hypomethylation, for example, is an early and consistently observed feature in colorectal carcinogenesis [2,11]. It is a result of low levels of S-adenosyl methionine (SAM), and the production of SAM depends on dietary factors such as folate, vitamin B6, and vitamin B12. The main role of folate is to provide one-carbon units in several reactions necessary for DNA methylation and synthesis, while vitamins B12 and B6 serve as cofactors in some of these reactions [12]. Therefore, sustained low levels of these nutrients may lead to disturbances in DNA methylation, synthesis, and repair, possibly influencing colorectal carcinogenesis.

Despite the biological and mechanistic rationale for the hypothesis that these nutrients could reduce the risk of CRC, epidemiological studies have yielded inconsistent results [13-16]. This may in part be due to different methods of diet assessment, or that few studies had complete data on both dietary and supplemental sources of these nutrients. It is particularly important to include intakes from vitamin and mineral supplements, as they contribute

appreciably to micronutrient intakes [17]. Another reason could be that dietary risk factors may differ for proximal and distal tumors in the colorectum. It has been suggested that diet may have a greater influence on the development of distal colon tumors compared to proximal colon tumors. Studies that examined the association between diet and sub-sites of the colorectum reported stronger associations with distal colon cancer for fruits and vegetables [18], alcohol [19], and calcium intake [20]. The different pH levels [21] and bacterial composition [22] of these sites may affect their susceptibility to components of the diet. Furthermore, proximal and distal colon tumors have different clinical features [23] and genetic characteristics [24]. For example, methylation levels in normal mucosa of the proximal and distal colon vary, which could contribute to the effect folate has on these sub-sites [25]. The literature is scarce regarding the relationship between antioxidant and DNA methylation-related nutrients and distal CRC specifically, particularly in African Americans.

In this report, we examined associations of selected micronutrients (from food only and food plus dietary supplements) with risk of distal CRC among white and African American participants. Specifically, we evaluated the relationships between antioxidant nutrients (vitamin C, vitamin E, β-carotene, selenium) and DNA methylation-related nutrients (folate, vitamin B6, vitamin B12) and the risk of distal CRC in a population-based case–control study.

Methods

Study design

Data were obtained from the North Carolina Colon Cancer Study-Phase II, which was conducted between May 2001 and September 2006. Subjects were eligible for the study if they resided in one of 33 counties in central and eastern North Carolina, were African American or White, were 40–79 years of age, had a North Carolina driver's license, had no previous diagnosis of colon or rectal cancer, and were able to give informed consent and complete the interview. A randomized recruitment strategy was used to select cases and controls [26]. African Americans were over-sampled to increase their representation in the study. The recruitment probability for African American cases was 1.0 (i.e., all were recruited) and African American controls had a higher recruitment probability than white controls. This study was approved by the institutional review board at the University of North Carolina-Chapel Hill.

Cases

Cases had a primary diagnosis of distal colorectal (including sigmoid, rectosigmoid, and rectum) cancer during the study period. Cases were obtained from the rapid ascertainment system of the North Carolina Central Cancer Registry and diagnoses were confirmed by our study pathologist. Permission was received from the primary physician before contacting cases. There were a total of 1,831 potentially eligible cases identified. Fifty-seven (3%) of these were excluded for physician refusal, and 357 (19%) were found to be ineligible. Of the remaining 1,417 eligible cases, 118 (8%) could not be contacted and 242 (17%) refused; therefore, 1,057 (75%) had an in-person interview. On average, cases were interviewed within 7 months after diagnosis. The overall response rate (number of persons interviewed divided by the total number of eligible persons) for cases was 74% (76 and 70% for white and African American cases, respectively).

Controls

Controls under the age of 65 were identified using lists provided by the North Carolina Division of Motor Vehicles and the Center for Medicaid and Medicare Services for those 65 and older. Controls were selected using a randomized recruitment procedure based on

sampling probabilities within blocks defined by 5-year age group, sex, and race [26]. There were a total of 2,345 potentially eligible controls, but 518 (22%) were found to be ineligible. Of the 1,827 eligible controls identified, 325 (18%) could not be contacted, 483 (26%) refused to be contacted; therefore, 1,019 (56%) were interviewed. The overall response rate for controls was 56% (58 and 46% for white and African American controls, respectively).

The analyses were restricted to those who completed all components of the study (n = 1987). We further excluded 83 participants with implausible values for total energy intake (<800 kcal/day and >5,000 kcal/day for men and <600 kcal/day and >4,000 kcal/day for women) [27]. Therefore, the analytic sample for this report included 1,520 whites (720 cases, 800 controls) and 384 African Americans (225 cases, 159 controls).

Data collection

Trained nurse-interviewers collected all data in participants' home or another convenient location using standard questionnaires. We collected information on age at diagnosis, socioeconomic indicators, household information, physical activity, medical history, non-steroidal anti-inflammatory drug use, smoking history, and first-degree family history of colorectal cancer. Dietary information was obtained by an in-person interview using the 124-item Diet History Questionnaire (DHQ), which was developed and validated by the National Cancer Institute [28–30]. The validation study was done in a nationally representative sample and reported moderate to strong correlations with actual intake for antioxidant nutrients such as vitamin C (r = 0.67 in men and 0.58 in women) and vitamin E (r = 0.30 in men and 0.31 in women), and DNA methylation-related nutrients such as vitamin B6 (r = 0.79 in men and 0.65 in women) [29]. In the present study, participants were asked to recall their intake in the 12 months prior to diagnosis (cases) or interview (controls). There were 10 frequency options for each food, as well as three choices to estimate portion size. Nutrient and total energy intakes were based on the nutrient content of each food item, frequency of consumption, and portion size, and were determined using software provided by the NCI. The DHQ also collected detailed information on the type, dose, and frequency of dietary supplement use. The nutrients of interest for this study were antioxidant nutrients (vitamin C, vitamin E, β-carotene, selenium) and DNA methylation-related nutrients (folate, vitamin B12, vitamin B6) from food and supplements.

Statistical analyses

All analyses were done using SAS 9.1 software (SAS Institute, Inc., Cary, NC). We stratified the analyses by race and compared characteristics of cases and controls. We used chi-square and Wilcoxon rank-sum tests to make these comparisons with regard to categorical and continuous variables, respectively. Each nutrient was categorized into quartiles based on sex-specific cutoffs in controls. Unconditional logistic regression models were used to determine odds ratios (OR) and 95% confidence intervals (95% CI) for the association between nutrient intake and risk of distal CRC. We examined these associations for nutrient intake from foods only, as well as total intake (food plus dietary supplements). Nutrients were examined in separate models. We also examined the relationship between distal CRC risk and all antioxidant nutrients (i.e., the combined intakes of total vitamin C, vitamin E, β-carotene, and selenium) and all DNA methylation-related nutrients (i.e., the combined intakes of total folate, vitamin B6, and vitamin B12). All logistic models included an offset term to adjust for the sampling probability. To assess confounding, the following covariates were tested in a bivariate model with each nutrient: age (continuous), sex, education (less than or equal to high school, some college, college graduate/advanced degree), smoking status (never, current, former), prior BMI (i.e., in the year prior to interview for controls and diagnosis for cases) (normal, overweight, obese), physical activity (quartiles of metabolic equivalent (MET)-minutes/day), first-degree family history of

colorectal cancer (yes, no), non-steroidal anti-inflammatory drug use (yes, no), and intakes of alcohol (continuous), fiber (continuous), red meat (continuous), and fruit/vegetables (continuous). Covariates that produced at least a 10% change in any of the nutrient coefficients were considered potential confounders, and a backward-stepwise procedure was done to obtain the final model. Any variable that was a confounder in any model was retained in all models. We considered the other micronutrients as potential confounders, although none met the criteria for confounding. All nutrients were adjusted for total energy intake using the nutrient residual method [27], and all logistic regression models included total energy as a covariate. A linear trend test was conducted using median quartile values among controls, which were incorporated into the logistic regression model as a continuous predictor. We assessed interactions with alcohol for each nutrient by including a cross-product term in each model.

Results

Table 1 presents demographic and lifestyle characteristics of distal CRC cases and respective controls stratified by race. In both whites and African Americans, cases were slightly younger, had a higher mean BMI 1 year ago, and greater total daily energy intakes than their respective controls. Fewer white cases reported using non-steroidal anti-inflammatory drugs compared to controls (35.1 vs. 45.7%, $p < 0.0001$). In African Americans, significantly more cases had a first-degree family history of CRC ($p = 0.03$). In controls, a larger proportion of African Americans were obese and more whites were college graduates.

Mean nutrient intakes for white and African American distal CRC cases and controls are given in Table 2. Nutrient intake was evaluated by the contribution from food sources only and from food and dietary supplements combined. There were significant differences in intake between cases and controls in both racial groups. In general, white cases had *lower* mean nutrient intakes than controls, while African American cases had *higher* nutrient intakes than their respective controls. In both whites and African Americans, total (food plus supplements) mean intakes for most nutrients were significantly different between cases and controls (all p values <0.05). More specifically, white controls had higher intakes of all nutrients, except selenium, compared to white cases; African American cases reported higher consumption of vitamin C, vitamin E, folate, vitamin B6, and vitamin B12 than their respective controls. The contribution of supplements to total selenium intake was negligible in both racial groups. In controls, African Americans reported significantly lower total mean intakes for most nutrients compared to whites, and the higher intakes in whites was mainly due to contributions from dietary supplements. For example, daily vitamin E levels from food sources only in white and African American controls were similar (12.0 mg αTE and 11.1 mg αTE, respectively); however, total vitamin E intake was 103 mg αTE among whites and 47 mg αTE among African Americans.

Tables 3 and 4 give the associations (OR and 95% CI) between distal CRC and nutrients in our study population, stratified by race. Table 3 presents results for antioxidant nutrients (vitamins C and E, β-carotene, and selenium). In whites, the highest quartiles of all nutrients were associated with a statistically significant lower risk of distal CRC compared to the lowest quartile, except for total vitamin E intake. The greatest risk reduction was observed for total β-carotene intake (Q4 vs. Q1 OR: 0.51, 95% CI 0.37–0.70). The ORs for the highest categories of nutrient intake from food only and from total intake were similar for vitamin C, β-carotene, and selenium. For example, the OR for high vitamin C intake from food only was 0.58 (95% CI 0.42–0.80) and 0.59 (95% CI 0.43–0.80) for total vitamin C intake. In whites, the statistically significant ORs of single antioxidant nutrients were stronger than the OR for all antioxidant nutrients combined. In African Americans, high

selenium intake from food had a marginally significant inverse association with distal CRC risk (OR: 0.55, 95% CI 0.29–1.02), and moderately high intakes of total selenium was significantly associated with lower risk (Q3 vs. Q1 OR: 0.45, 95% CI 0.24–0.87). There was evidence of a linear trend for selenium intake from food only and total intake (p_{trend} = 0.02 and 0.04, respectively).

Table 4 gives results for DNA methylation-related nutrients (folate, vitamin B6, vitamin B12). There were significantly lower risks of distal CRC associated with all DNA methylation-related nutrients in whites when contrasting the highest and lowest quartiles of intake, and all tests for linear trend were statistically significant. High intake of vitamin B6 from food in whites had the strongest (52%) reduction in risk (OR: 0.48, 95% CI 0.35–0.67, $p_{trend} < 0.0001$). The OR for all DNA methylation-related nutrients combined was 0.57 (95% CI 0.41–0.80). In African Americans, the highest category of total folate, vitamin B6, and vitamin B12, as well as all DNA methylation-related nutrients combined were suggestive of elevated risk, although odds ratios were not statistically significant. However, the trend analyses in African Americans were positive and statistically significant for total folate (p_{trend} = 0.01) and total vitamin B6 (p_{trend} = 0.04).

We did not observe any statically significant interactions between alcohol intake and any of the nutrients (data not shown). There was, however, a marginally significant interaction between alcohol and folate from food only (p = 0.06).

Discussion

In this large population-based case–control study, each antioxidant nutrient was associated with reduced distal CRC risk in whites, and there was an inverse trend in risk for selenium intake in African Americans. Inverse associations with DNA methylation-related nutrients were only observed in whites, and there were significant positive linear trends for total folate and total vitamin B6 in African Americans.

There were notable differences in mean nutrient intakes between whites and African Americans. In general, African American controls reported lower mean intakes than white controls, primarily due to the greater contribution to intake from dietary supplements in whites. The prevalence of any dietary supplement use in the last 12 months among our control population was 72% in whites and 53% in African Americans. It has been estimated that approximately 50–70% of non-institutionalized US adults take dietary supplements in the form of multivitamin/mineral or singlenutrient supplements [17,31], and Radimer et al. [17] also noted that supplement use patterns differ by race. Therefore, it is necessary to collect detailed information on supplement use when assessing the effect of micronutrients on disease risk, especially in racially diverse populations.

Findings in this present study for whites are consistent with the hypotheses that dietary antioxidants may reduce the risk of distal CRC. Our results are in agreement with other observational studies reporting significant inverse associations for dietary antioxidant intake and colon [32-35] and rectal cancer [33]. Kune and colleagues reported colon and rectal cancer risk reductions for high intakes of vitamin C, vitamin E, and selenium [33], and elevated risk of rectal cancer has been observed for low vitamin E intakes in women [36]. On the contrary, there was no effect of vitamin E on colon cancer in the Women's Health Study clinical trial [37], and a large population-based case–control study reported no association between β-carotene intake and proximal or distal colon cancer [38]. Most of the current evidence has been limited to non-African American populations; however, in a previous case–control study Satia-Abouta et al. noted significant inverse associations with colon cancer for high intakes of β-carotene, vitamin C, and vitamin E in African Americans

[34]. We did not observe any statistically significant risk estimates for antioxidant nutrients in African Americans in the present study.

We also found intakes of DNA methylation-related nutrients to be associated with reduced risk of distal CRC in whites. Results are conflicting regarding the effect of folate on CRC development. In a recent report of the Netherlands Cohort Study, the authors did not find folate to be significantly associated with CRC risk in men or women [39]. Null findings have also been reported for folate and colon cancer [34,40-42]. The most recent report from the World Cancer Research Fund/American Institute for Cancer Research indicated that there is only limited suggestive evidence that folate reduces the risk of CRC [43]. Epidemiologic studies of vitamin B6 and B12 are limited in comparison with studies on folate intake. The present study is in agreement with findings from an Australian case–control study in which there was a statistically significant lower risk of colon and rectal cancer for the highest categories of vitamin B6 and B12 intake [33]. On the other hand, two large prospective studies observed an elevated risk of rectal cancer in women for high intake of vitamin B6 [39,41]. These discrepant findings may be due to inherent biases in case–control studies, the method of dietary assessment, or variation in intakes of these micronutrients. We did not observe interactions with alcohol for any of these DNA methylation-related nutrients, although alcohol is a known to interact with these nutrients [44]. This may be because the average alcohol intake in our study population (8 g/day) was much lower than the level at which alcohol intake has been shown to be associated with elevated CRC risk (≥30 g/day) [19].

The reasons why the associations between micronutrients and distal CRC differ for whites and African Americans are not totally clear. Surprisingly, the odds ratios for high total intakes of vitamin C and all DNA methylation-related nutrients suggested elevated risk of distal CRC in African Americans, although they were not significant. This direct association may be due to the source of these nutrients; however, after controlling for fruit and vegetable consumption there was still a non-significant positive association with risk. Due to our small sample of African Americans, we may have missed other statistically significant associations, and this small sample size may also have led to unstable estimates. We did, however, observe a significant inverse trend for selenium, and positive trends for total folate and total vitamin B6. Results from other epidemiologic studies with adequate African American representation are needed to confirm (or dispute) these findings.

It is interesting to note that for all DNA methylation-related nutrients and vitamin E in whites, the risk reduction was greater for intake from food sources only compared to total intake (food plus supplements). Other studies have reported null effects of supplement use on colorectal cancer [45,46] and adenomas [47,48]. For example, compared to the placebo, 1 mg/day of folic acid did not reduce the risk of colorectal adenomas, the precursor to colon and rectal cancer, and actually increased the risk of advanced adenomas in the Aspirin/Folate Polyp Prevention Study [48]. There are several possible explanations for these findings. One reason may relate to the dual effect of folate, depending on dosage and time of exposure. While adequate folate intake may suppress tumor development, excessive intake may not offer additional benefit or even enhance carcinogenesis, especially when there are pre-existing lesions [49]. These disparate findings may also reflect the different chemical structures and biological pathways of natural folate and synthetic folic acid. Folic acid is more bioavailable and therefore more readily absorbed than natural folate found in food [50]. However, high circulating levels of unmetabolized folic acid may reduce the immune response against carcinogenic cells by reducing the amount of natural killer cells [50]. When considering intake from foods versus supplements, it is important to note that foods can contain the synthetic form of the nutrient due to fortification. For example, mandatory fortification in the United States resulted in an average total folate intake of approximately

400 μg/day among supplement non-users, with only about 200 μg/day being naturally occurring folate and 200 μg/day being folic acid in fortified foods [51,52].

Clinical trials have also found no evidence for associations of vitamin C, vitamin E, or *β*-carotene with reduced risk of CRC [45,46]. One trial reported a significant inverse association of vitamin E supplementation and colon cancer risk, but there was no statistically significant association with rectal cancer [46]. Therefore, these supplements may have different effects on proximal and distal sites in the colon. Also, at high concentrations, vitamins C and E may exert pro-oxidant effects, and thereby promote oxidative DNA damage. Our study results suggest that nutrient intake from dietary supplements may not help reduce distal CRC risk, and that intake from food sources alone may be more relevant for risk reduction. This could be because supplement use may only benefit those with suboptimal nutrient intakes, while providing no benefit for those with adequate intakes. In our study, the mean intake of these micronutrients from food alone in whites and African Americans was above the daily recommended intakes [53]. In addition, other compounds of natural foods such as phytochemicals and fiber may be chemopreventive and act in synergy with these nutrients to reduce distal CRC risk, and it is likely that past and long-term supplement use may be associated with risk as opposed to recent use. Currently, the overall evidence for recommending supplements for CRC is weak [54].

A major strength of this study was our large sample size, especially for a study of distal colorectal cancer. This allowed us to observe associations that would be undetectable in studies with fewer participants. All data were collected in-person by trained nurse-interviewers, thereby minimizing the potential for misclassification. We collected detailed information on dietary supplement use to include in our assessment of total nutrient intake. Our study is among the first reports of micronutrient intake and distal CRC risk in African Americans.

There are some limitations worth noting. Our study was subject to potential biases in case–control studies such as recall bias. It is possible that there was differential recall between cases and controls. Differential response rates between cases and controls, as well as between whites and African Americans, could have biased our results. There was also the potential of measurement error; however, the diet history questionnaire has been validated [29,30], although not in African American populations. We cannot exclude the possibility of chance findings due to multiple testing and the possibility of residual confounding.

In summary, the present findings add to the evidence that dietary antioxidants (vitamin C, vitamin E, *β*-carotene, selenium) and DNA methylation-related nutrients (folate, vitamin B6, vitamin B12) are associated with lower risk of distal colorectal cancer in whites. Our results also support the hypotheses of mechanisms by which these nutrients may play a role in preventing colorectal cancer. Our findings suggest that the associations between these nutrients and distal colorectal cancer may differ between whites and African Americans. This stresses the importance of examining these associations by race in large racially diverse samples. Furthermore, intakes from dietary supplements appeared to attenuate the risk reduction in whites for some nutrients, suggesting that optimal intakes of these nutrients from food sources alone may be sufficient to lower risk of distal colorectal cancer.

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Table 1

Characteristics (means and standard deviations, percents) of cases and controls in the North Carolina Colon Cancer Study-Phase II (2001–2006), by race

	Whites (n = 1,520)		African Americans (n = 384)	
	Cases (n = 720)	**Controls (n = 800)**	**Cases (n = 225)**	**Controls (n = 159)**
Sex (%)				
Male	58.3	60.5	52.4	52.2
Age (years) (%)				
40–49	19.2	12.1	21.3	17.5
50–59	27.5	26.6	29.2	22.7
60–69	31.5	34.4	33.8	41.6
70–79	21.8	27.0	15.7	18.2
Mean(SD)	59.6 (10.3)	61.7 (9.8)	58.0(10.0)	60.3(9.8)
Education (%)				
≤ High school	50.3	39.0	61.8	58.5
Some college	25.1	25.9	22.2	25.8
College graduate/advanced degree	24.6	35.1	16.0	15.7
Body mass index (1 year ago) (%)				
Normal (18.5–24.9 kg/m^2)	22.7	30.3	17.4	18.1
Overweight (25.0–29.9 kg/m^2)	38.8	40.7	31.6	36.2
Obese (≥ 30.0 kg/m^2)	38.5	29.0	50.9	45.6
Mean(SD)	29.2 (6.3)	28.0 (5.5)	31.6 (7.7)	29.9 (6.5)
Physical activity (MET-min/day[a]) (%)				
Quartile 1	25.7	24.9	30.2	28.9
Quartile 2	25.5	23.8	24.5	28.9
Quartile 3	20.5	26.6	17.0	17.4
Quartile 4	28.6	24.7	28.3	24.8
Mean(SD)	2,250.0 (661.8)	2,152.7 (473.4)	2,178.4 (545.5)	2,152.8 (494.2)
Total energy intake (kcal/day)				
Mean(SD)	2,245.9 (826.2)	2,143.0 (790.9)	2,423.6 (953.3)	2,207.7 (891.6)
Smoking status (%)				
Current smoker	15.6	13.5	22.7	17.0

	Whites (*n* = 1,520)		African Americans (*n* = 384)	
	Cases (*n* = 720)	**Controls (*n* = 800)**	**Cases (*n* = 225)**	**Controls (*n* = 159)**
Former smoker	47.3	48.7	38.2	42.1
Never smoker	37.1	37.8	39.1	40.9
NSAID use (%)[b]				
Yes	35.1	45.7	24.4	22.8
First-degree family history of CRC (%)				
Yes	13.2	11.3	11.8	5.2

[a] Metabolic equivalent minutes per day; cutoffs for men: 1,875, 2,046, and 2,499 MET- min/day; cutoffs for women: 1,860, 1,980, and 2,193 MET-min/day

[b] Greater than or equal to 15 non-steroidal anti-inflammatory drugs (NSAID) per month in the past 5 years

Table 2

Mean (standard deviation) nutrient intakes of participants in the North Carolina Colon Cancer Study-Phase II (2001–2006), by case/control status and race

Nutrient	Whites (*n* = 1,520)			African Americans (*n* = 384)			
	Cases (*n* = 720)	Controls (*n* = 800)	p^a	Cases (*n* = 225)	Controls (*n* = 159)	p^a	p^b
Vitamin C (mg/day)							
From foods only	132 (82)	146 (77)	<0.0001	183 (107)	152 (86)	0.003	0.76
From foods + supplements	266 (314)	313 (346)	<0.0001	259 (228)	215 (212)	0.001	0.0004
Vitamin E (mg αTE[c]/day)							
From foods only	11.5 (5.5)	12.0 (6.2)	0.38	11.9 (6.0)	11.1 (5.0)	0.35	0.14
From foods + supplements	79 (133)	103 (153)	0.0003	56 (122)	47 (91)	0.05	<0.0001
β-Carotene (μg/day)							
From foods only	3,881 (2,610)	4,595 (3,012)	<0.0001	5,794 (4,637)	5,247 (4,233)	0.31	0.30
From foods + supplements	4,185 (2,712)	4,945 (3,077)	<0.0001	6,042 (4,678)	5,426 (4,277)	0.21	0.75
Selenium (μg/day)							
From foods only	104 (41)	105 (43)	0.81	112 (51)	107 (50)	0.42	0.91
From foods + supplements	105 (41)	106 (44)	0.75	112 (50)	108 (49)	0.45	0.94
Folate (μg/day)							
From foods only	433 (157)	450 (176)	0.14	483 (206)	432 (177)	0.02	0.20
From foods + supplements	619 (262)	665 (270)	0.002	649 (280)	549 (252)	0.0004	<0.0001
Vitamin B6 (mg/day)							
From foods only	2.1 (0.8)	2.2 (0.9)	0.08	2.3 (1.0)	2.1 (0.9)	0.01	0.14
From foods + supplements	4.8 (8.1)	5.6 (9.0)	0.0004	4.3 (5.9)	3.7 (5.9)	0.001	<0.0001
Vitamin B12 (μg/day)							
From foods only	5.4 (3.2)	5.7 (3.3)	0.06	6.5 (5.2)	6.2 (4.7)	0.20	0.62
From foods + supplements	8.2 (4.3)	8.8 (4.3)	0.004	9.0 (5.9)	7.9 (5.5)	0.01	0.0004

[a] Based on Wilcoxon rank-sum test for comparisons between race-specific cases and controls

[b] Based on Wilcoxon rank-sum test for comparisons between white and African American controls

[c] α-Tocopherol equivalents

Table 3

Multivariate odds ratios (OR) and 95% confidence intervals for the association of distal colorectal cancer with antioxidant nutrients, by race (North Carolina Colon Cancer Study-Phase II, 2001–2006)

Nutrient quartiles	Median intake/day in controls	Whites (*n* = 1,520)			African Americans (*n* = 384)		
		No. of cases	OR	95% CI	No. of cases	OR	95% CI
Vitamin C (mg) (food only)[a]							
Q1	70	257	1.00		38	1.00	
Q2	112	171	1.10	0.81–1.48	40	1.29	0.66–2.53
Q3	154	155	0.65	0.47–0.89	58	1.37	0.70–2.69
Q4	235	137	0.58	0.42–0.80	89	1.36	0.72–2.57
P for linear trend			<0.0001			0.43	
Vitamin C (mg) (food + supplements)[b]							
Q1	89	79	1.00		51	1.00	
Q2	155	152	0.73	0.54–0.99	47	0.85	0.46–1.57
Q3	221	217	0.59	0.43–0.81	66	1.15	0.62–2.12
Q4	641	641	0.59	0.43–0.80	61	1.42	0.72–2.81
P for linear trend			0.0007			0.20	
Vitamin E (mg *α*TE) (food only)[c]							
Q1	6.3	197	1.00		56	1.00	
Q2	9.3	139	0.99	0.73–1.35	48	0.64	0.35–1.16
Q3	12.3	207	0.74	0.54–1.02	61	0.70	0.37–1.32
Q4	17.9	177	0.65	0.48–0.89	60	0.74	0.38–1.43
P for linear trend			0.0021			0.35	
Vitamin E (mg *α* TE) (food + supplements)[d]							
Q1	8.2	185	1.00		71	1.00	
Q2	16.7	202	0.94	0.68–1.31	58	0.68	0.36–1.29
Q3	31.8	181	0.88	0.64–1.22	67	1.73	0.88–3.40
Q4	296.2	152	0.80	0.57–1.10	29	1.01	0.47–2.19
P for linear trend			0.20			0.87	
β-Carotene (μg) (food only)[e]							
Q1	1,820	260	1.00		50	1.00	

Nutrient quartiles	Median intake/day in controls	Whites (n = 1,520)			African Americans (n = 384)		
		No. of cases	OR	95% CI	No. of cases	OR	95% CI
Q2	3,235	199	0.69	0.51–0.93	55	0.86	0.44–1.67
Q3	4,774	143	0.50	0.36–0.69	36	0.34	0.33–1.23
Q4	7,644	118	0.52	0.38–0.71	84	0.93	0.51–1.70
P for linear trend			<0.0001			0.83	
β-Carotene (μg) (food + supplements)[f]							
Q1	2,065	254	1.00		52	1.00	
Q2	3,554	196	0.69	0.51–0.94	56	0.74	0.39–1.38
Q3	5,152	144	0.47	0.34–0.65	34	0.74	0.37–1.49
Q4	8,008	126	0.51	0.37–0.70	83	0.96	0.52–1.76
P for linear trend			<0.0001			0.94	
Selenium (μg) (food only)[g]							
Q1	58	170	1.00		53	1.00	
Q2	91	187	1.17	0.87–1.58	44	1.35	0.72–2.53
Q3	119	196	0.74	0.54–1.01	56	0.56	0.29–1.08
Q4	158	167	0.55	0.39–0.77	72	0.55	0.29–1.02
P for linear trend			<0.0001			0.02	
Selenium (μg) (food + supplements)[h]							
Q1	59	170	1.00		52	1.00	
Q2	93	181	1.19	0.88–1.60	44	1.41	0.75–2.64
Q3	120	199	0.80	0.58–1.09	58	0.45	0.24–0.87
Q4	159	170	0.56	0.40–0.79	71	0.64	0.34–1.21
P for linear trend			0.0001			0.04	
All antioxidant nutrients (mg) (food + supplements)[i]							
Q1	106	222	1.00		54	1.00	
Q2	191	189	0.77	0.56–1.04	51	1.02	0.56–1.83
Q3	291	159	0.72	0.52–0.98	82	1.18	0.66–2.12
Q4	893	150	0.67	0.49–0.92	38	1.32	0.62–2.79
P for linear trend			0.06			0.44	

Adjusted for age, sex, education, BMI, family history of CRC, non-steroidal anti-inflammatory drug use, and total energy

[a] Cutoffs for men: 96, 135, and 184 mg; cutoffs for women: 91, 127, and 183 mg

[b] Cutoffs for men: 125, 179, and 285 mg; cutoffs for women: 122, 183, and 300 mg

[c] Cutoffs for men: 9, 11, and 15 mg; cutoffs for women: 7, 9, and 13 mg

[d] Cutoffs for men: 12, 27, and 40 mg; cutoffs for women: 11, 27, and 164 mg

[e] Cutoffs for men: 2,632, 3,958, and 6,122 μg; cutoffs for women: 2,360, 4,026, and 5,835 μg

[f] Cutoffs for men: 2,865, 4,301, and 6,349 μg; cutoffs for women: 2,728, 4,283, and 6,230 μg

[g] Cutoffs for men: 88, 115, and 148 μg; cutoffs for women: 61, 80, and 101 μg

[h] Cutoffs for men: 88, 115, and 148 μg; cutoffs for women: 61, 80, 103 μg

[i] Cutoffs for men: 149, 225, and 435 mg; cutoffs for women: 149, 237, and 493 mg

Table 4

Multivariate odds ratios (OR) and 95% confidence intervals for the association of distal colorectal cancer with DNA methylation-related nutrients, by race (North Carolina Colon Cancer Study-Phase II, 2001–2006)

Nutrient quartiles	Median intake/day in controls	Whites (*n* = 1,520)			African Americans (*n* = 384)		
		No. of cases	OR	95% CI	No. of cases	OR	95% CI
Folate (μg) (food only)[a]							
Q1	272	188	1.00		55	1.00	
Q2	372	189	0.82	0.60–1.10	42	0.65	0.35–1.22
Q3	484	177	0.61	0.45–0.84	43	0.88	0.45–1.73
Q4	641	166	0.50	0.36–0.69	85	1.08	0.58–2.00
P for linear trend			<0.0001			0.62	
Folate (μg) (food + supplements)[b]							
Q1	321	193	1.00		55	1.00	
Q2	531	195	0.67	0.49–0.93	53	0.87	0.49–1.54
Q3	753	167	0.78	0.58–1.05	56	2.71	1.41–5.20
Q4	961	165	0.62	0.45–0.86	61	1.59	0.72–3.25
P for linear trend			0.01			0.01	
Vitamin B6 (mg) (food only)[c]							
Q1	1.3	179	1.00		49	1.00	
Q2	1.8	184	0.80	0.591.08	42	1.12	0.61–2.04
Q3	2.3	211	0.69	0.51–0.94	53	1.38	0.73–2.60
Q4	3.1	146	0.48	0.35–0.67	81	1.53	0.81–2.91
P for linear trend			<0.0001			0.16	
Vitamin B6 (mg) (food + supplements)[d]							
Q1	1.5	192	1.00		54	1.00	
Q2	2.6	206	0.78	0.57–1.07	59	1.09	0.62–1.91
Q3	3.8	172	0.91	0.67–1.23	59	1.65	0.87–3.13
Q4	5.1	150	0.55	0.40–0.77	53	1.93	0.90–4.14
P for linear trend			0.003			0.04	
Vitamin B12 (μg) (food only)[e]							
Q1	2.5	183	1.00		52	1.00	

Nutrient quartiles	Median intake/day in controls	Whites (n = 1,520)			African Americans (n = 384)		
		No. of cases	OR	95% CI	No. of cases	OR	95% CI
Q2	4.3	209	0.98	0.72–1.32	50	1.40	0.74–2.62
Q3	6.2	179	0.66	0.48–0.90	50	1.27	0.62–2.61
Q4	9.5	149	0.59	0.42–0.81	73	0.79	0.44–1.42
P for linear trend			0.0002			0.30	
Vitamin B12 (μg) (food + supplements)[f]							
Q1	3.3	207	1.00		55	1.00	
Q2	6.9	183	0.86	0.63–1.16	61	0.89	0.49–1.60
Q3	9.8	185	0.91	0.67–1.23	43	1.56	0.81–3.02
Q4	13.5	145	0.61	0.44–0.84	66	1.13	0.59–2.15
P for linear trend			0.005			0.41	
All DNA methylation-related nutrients (mg) (food + supplements)[g]							
Q1	1.9	190	1.00		52	1.00	
Q2	3.2	208	0.81	0.60–1.11	59	0.96	0.55–1.69
Q3	4.6	169	0.90	0.66–1.21	62	1.68	0.89–3.16
Q4	6.2	153	0.57	0.41–0.80	52	1.66	0.77–3.58
P for linear trend			0.003			0.07	

Adjusted for age, sex, education, BMI, family history of CRC, non-steroidal anti-inflammatory drug use, and total energy

[a] Cutoffs for men: 358, 460, and 585 μg; cutoffs for women: 292, 368, and 466 μg

[b] Cutoffs for men: 456, 675, 864 μg; cutoffs for women: 361, 610, and 790 μg

[c] Cutoffs for men: 1.7, 2.2, 2.8 mg; cutoffs for women: 1.3, 1.7, and 2.3 mg

[d] Cutoffs for men: 2.2, 3.4, and 4.4 mg; cutoffs for women: 1.8, 3.2, and 4.1 mg

[e] Cutoffs for men: 4.0, 5.8, and 8.2 μg; cutoffs for women: 2.7, 4.0, 5.6 μg

[f] Cutoffs for men: 5.6, 9.3, and 12.1 μg; cutoffs for women: 4.2, 7.9, and 10.2 μg

[g] Cutoffs for men: 2.6, 4.1, and 5.3 mg; cutoffs for women: 2.2, 3.8, and 5.0 mg

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