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

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The higher incidence of colon cancer in African Americans compared with other US racial/ethnic groups is largely unexplained. This report describes associations of total energy and macronutrients with colon cancer risk in African Americans and Whites from a case-control study in North Carolina between 1996 and 2000. Incident cases of histologically confirmed colon cancer, aged 40–80 years ($n = 613$), and matched controls ($n = 996$) were interviewed in person to elicit information on potential colon cancer risk factors. A validated food frequency questionnaire adapted to include regional foods was used to assess diet over the year prior to diagnosis or interview date. Cases generally reported higher mean daily intakes of total energy and macronutrients and lower dietary fiber consumption than did controls. Total energy intake was positively associated with colon cancer risk in both racial groups and, although there were some differences by race, high intakes of individual energy sources were also generally associated with two- to threefold increases in risk in models not controlled for total energy. However, these associations largely disappeared when total energy was taken into account. A high level of dietary fiber was associated with a statistically significant 50–60% risk reduction in African Americans and a nonsignificant 30% decreased risk in Whites. Alcohol intake was not statistically significantly associated with colon cancer in either racial group. Total energy intake was consistently associated with colon cancer risk, but associations with individual macronutrients varied somewhat by race and by adjustment for energy intake. These findings may provide an explanation for some of the racial differences in colon cancer incidence.

Blacks; colonic neoplasms; confounding factors (epidemiology); diet; energy intake; Whites

Abbreviations: eCarb, nonfiber or "effective" carbohydrate; MET, metabolic equivalent; OR, odds ratio.

Colon cancer is one of the most common malignancies in developed countries (1). In the United States, colon cancer is the second leading cause of cancer death and the third most common cancer among adults, accounting for approximately 15 percent of all cancers diagnosed annually (2, 3). In the year 2001, an estimated 48,100 persons died from colon and rectal cancers and 98,200 new cases were diagnosed (4). There are marked racial/ethnic disparities in colon cancer incidence and mortality: Specifically, African Americans have the highest incidence and mortality from colon cancer of all US racial/ethnic groups (3, 4). For example, between 1990 and 1996, colon and rectal cancer incidence and mortality rates were 50.7 and 23.1 per 100,000, respectively, among African Americans. In comparison, incidence and mortality rates for Whites were 43.9 and 17.4 per 100,000, respectively (3).

The remarkable racial differences in incidence rates for colon cancer are largely unexplained. Clearly, some of these

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disparities are attributable to health care, socioeconomic, behavioral, and cultural differences; however, these factors do not completely explain the diverging trends (5). Moreover, recent evidence suggests that the increase in colon cancer incidence in African Americans does not appear to be attributable to higher rates of screening and early detection (6). Differences in hereditary susceptibility factors, such as polymorphic variations in phase I and phase II carcinogen-metabolizing enzymes and related gene-environment interactions, are plausible explanations that deserve further research. In addition, it is important to uncover prognostic behavioral and lifestyle factors that are potentially modifiable and that may contribute to the higher colon cancer incidence in African Americans.

The wide geographic variations in the incidence of colon cancer and results from international correlational studies that have consistently demonstrated striking changes in incidence with migration strongly suggest an important lifestyle or environmental component to colon cancer risk (7–10). Diet has long been regarded as the most important lifestyle risk factor for colon cancer; in fact, it has been estimated that 12 percent of colon cancer is attributable to consumption of a Western-style diet (10). However, although diet and colon cancer associations have been studied extensively, the impact of many dietary factors on colon carcinogenesis remains unresolved (9–11). Furthermore, associations of diet with colon cancer risk have been rarely examined in African Americans or in population-based studies with an adequate number of African-American participants. To our knowledge, there is only one etiologic study of diet and colon cancer in African Americans, but it was conducted more than 20 years ago and included only 99 cases (12).

The purpose of this report is to investigate whether the impact of diet on colon cancer risk differs by race in a large case-control study in North Carolina with similar numbers of African-American and White cases and controls. This study contributes to the existing body of knowledge in two major ways. First, we present associations of total energy, macronutrient intakes (total carbohydrate, "effective" carbohydrate, protein, total fat, saturated fat, alcohol), and dietary fiber with colon cancer risk, stratified by race (i.e., African American and White). Second, because there is debate in the literature (13, 14) regarding energy adjustment for individual nutrients, we examine these relations using two analytical approaches: one in which risk estimates are adjusted for total energy intake (to assess the effect of *substituting* one nutrient for another without a change in total energy consumption), and another in which total energy is not included in statistical models (which assesses the effect of *adding* a nutrient to the diet).

MATERIALS AND METHODS

Study design

The North Carolina Colon Cancer Study 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 (15, 16). 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 case ascertainment system of the North Carolina Central Cancer Registry (17). Other eligibility criteria included the following characteristics: 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 to complete the interview, a North Carolina driver's license or identification card if under the age of 65 years (because similarly aged controls were sampled from driver's license rosters), and permission to contact the primary physician. Diagnoses based on review of pathology slides and reports were confirmed by the study pathologist, and dysplasia was graded as mild, moderate, or severe.

A letter and study description requesting permission to invite the patient to participate in the study were sent to the primary physicians of eligible cases. When permission for contact was obtained, the patient was sent a letter describing the study and 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: records from the North Carolina Division of Motor Vehicles for cases under the age of 65 years and from the Center for Medicare and Medicaid Services (formerly the Health Care Financing Administration) for cases aged 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 fashion similar to that of the cases to schedule in-person interviews.

Completed interviews were obtained from 1,691 participants. Of these, 731 were African American (294 cases, 437 controls) and 957 were White (349 cases, 611 controls). The overall study cooperation rate (interviewed/(interviewed + refused)) was 84 percent for cases and 63 percent for controls. For both cases and controls, the cooperation rates were slightly higher for Whites (89 percent for cases, 64 percent for controls) than for African Americans (79 percent for cases, 61 percent for controls). The study response rate (interviewed/eligible) was 72 percent for cases and 61 percent for controls. Among those eligible to participate, the

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reasons for nonparticipation included the following: refusal (14 percent for cases, 36 percent for controls); physician denial (7 percent for cases); untraceable (1 percent for cases, 1 percent for controls); and not reachable by telephone (6 percent for cases, 1 percent 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 dietary and 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 food frequency questionnaire developed at the National Cancer Institute (18). The food frequency questionnaire was modified by adding 29 foods commonly consumed in North Carolina in order to better assess regional dietary practices in a sample of North Carolinians that included low-income African Americans (19). 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 food frequency questionnaire also included adjustment questions on types of foods used in cooking and preparation techniques and questions relating to restaurant eating, consumption of low-fat foods, fortified beverages, and fats used in cooking, as these variables can have large effects on estimates of fat intake (20). Nutrient intake was calculated by an analytical 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 (18). For these analyses, we examined the following nutrients: total energy; total carbohydrate; nonfiber or "effective" carbohydrate (eCarb = total carbohydrate (g/day) – total fiber (g/day)) (21); protein; total fat; saturated fat; alcohol; and dietary fiber. Participants with reported energy intakes of <800 kcal and >5,000 kcal for men ($n = 10$) and of <600 kcal and >4,000 kcal for women ($n = 22$) were excluded because their food frequency questionnaires were considered to be unreliable (22). Participants with missing values on any of the above dietary variables ($n = 16$) were also excluded from further analyses.

Other participant characteristics

Data were collected on several demographic characteristics including age, sex, education, race, smoking history, physical activity, use of nonsteroidal antiinflammatory drugs over the last 5 years, and first-degree family history of colon cancer. Using a standardized protocol, trained staff measured height and weight at the in-person interview. Height and weight were used to compute body mass index as weight (in kilograms) divided by height (in meters) squared. Body mass index was divided into three categories according to the cutoffs recommended by the Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: "normal," 18.5–24.9; "overweight," 25.0–29.9; and "obese," ≥30.0 (23). Participants in the "underweight" category with body mass indexes of less than 18.5 and those with body mass indexes of more than 50 were not included in these analyses ($n = 36$) as they comprised a very small percentage (<2 percent) of the analytical sample. Physical activity was measured in metabolic equivalent task-minutes per day for combined occupational, nonoccupational, and non-work/weekend activities (including duration, frequency, and intensity) using a modified version of a validated 7-day physical activity recall (24–26).

Because there were very few participants of other races/ethnicity ($n = 8$), these analyses are restricted to Whites and African Americans. After all the exclusions, 1,609 participants remained for these analyses, including 933 Whites (337 cases and 596 controls) and 676 African Americans (276 cases and 400 controls).

Statistical analyses

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. Stratification of results by race was based on statistical testing, suggesting effect modification by race for several of the macronutrients and dietary fiber (data not shown). 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 values for differences were adjusted for participant characteristics, and the dietary factors were also adjusted for total energy intake.

We calculated odds ratios and 95 percent confidence intervals from unconditional logistic regression models to ascertain associations of total energy and macronutrient intakes (in quartiles) with colon cancer risk. Offset terms were included in all models to correct for randomized recruitment-sampling fractions (15, 16) and to allow estimation of unbiased odds ratios. This was necessary because we conditioned recruitment on age, sex, and race, in addition to disease status; thus, the odds ratios without the offset term would be biased compared with a traditional design in which recruitment was conditioned on disease status alone. Cutpoints for quartiles of nutrient intakes were determined on the basis of distributions among all controls and race-specific controls. Age (continuous), sex, education (high school, some college, college graduate/advanced degree), body mass index (continuous), smoking history (never, former, current), physical activity (quartiles), first-degree family history of colon cancer (yes, no), use of nonsteroidal antiinflammatory drugs (never, occasionally, regularly), total energy, total fat, dietary fiber, fruits, and vegetables were evaluated as poten-

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TABLE 1. Characteristics of participants with and without colon cancer, by race (*n* = 1,609), North Carolina Colon Cancer Study, 1996–2000*

Participant characteristic†	Whites (*n* = 933)			African Americans (*n* = 676)		
	Cases (*n* = 337)	Controls (*n* = 596)	*p* value‡	Cases (*n* = 276)	Controls (*n* = 400)	*p* value‡
Tumor site (%)						
Proximal	45			49		
Distal	45			42		
Unknown/missing	10			9		
Age (%)						
<55 years	17	14	<0.0001	27	15	<0.0001
55–65 years	29	26		29	26	
≥65 years	54	60		44	58	
Mean years (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	
Body mass index, 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 kg/m^2 (SD)	27.4 (5.3)	27.6 (5.0)	0.10	29.0 (6.1)	29.4 (5.8)	0.18
Body mass index, 1 year 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 kg/m^2 (SD)	28.4 (5.3)	27.6 (4.8)	0.04	30.6 (6.3)	29.4 (5.5)	0.007

Table continues

tial confounding factors. Covariate inclusion was based on whether there was a 10 percent 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 nutrient had a unique set of confounding variables. All odds ratios are reported for energy-adjusted and non-energy-adjusted nutrient intakes. The standard multivariate method was used to adjust for total energy intake; applying other energy adjustment approaches (e.g., the nutrient residual and energy partition models) did not alter the results (14). Statistical tests were two sided, and *p* values less than 0.05 were considered statistically significant. All analyses were performed using SAS version 8.1 software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Demographic and lifestyle characteristics of the study participants, stratified by race and case-control status, are given in table 1. The study sample included 613 cases (276 African Americans) and 996 controls (400 African Americans). African Americans more often had proximal tumors (49 percent vs. 45 percent), while Whites were more likely to have distal tumors (45 percent vs. 42 percent). Among both Whites and African Americans, colon cancer cases were slightly younger than controls, and approximately half of the cases were aged 65 years or older. White cases and controls did not differ significantly by sex; however, African-American cases were more often males, while controls were more often females ($p < 0.02$). For both racial groups, there were no statistically significant differences between cases and controls by educational level, physical activity (metabolic equivalent (MET)-minutes/day), or smoking history; however, the majority of White cases were former smokers (53 percent), while African-American cases were more often never smokers (47 percent). Although cases and controls did not differ by current body mass index, body mass index values from the year prior to diagnosis suggested that cases had lost weight (28.4 vs. 27.4 kg/m^2 for Whites and 30.6 vs.

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TABLE 1. Continued

Participant characteristic	Whites (n = 933)			African Americans (n = 676)		
	Cases (n = 337)	Controls (n = 596)	p value	Cases (n = 276)	Controls (n = 400)	p value
Smoking history (%)						
Never smoker	34	40	0.01	47	45	0.95
Former smoker	53	44		34	35	
Current smoker	13	16		19	21	
Physical activity (MET§-minutes/day) (mean, %)						
1st quartile	1,783 (23)	1,812 (25)	0.50	1,710 (22)	1,712 (25)	0.54
2nd quartile	1,998 (27)	2,006 (25)		1,921 (30)	1,919 (25)	
3rd quartile	2,209 (26)	2,196 (25)		2,120 (28)	2,138 (25)	
4th quartile	2,971 (24)	2,789 (25)		2,936 (19)	2,883 (25)	
Mean MET-minutes/day (SD)	2,255 (558)	2,202 (451)	0.18	2,226 (568)	2,162 (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 (%)¶						
Never	11	7	0.0003	11	7	0.0006
Occasionally	38	28		44	33	
Regularly	51	65		45	60	
Vitamin/mineral supplement use (%)#						
Yes	48	59	0.04	33	43	0.08
No	52	41		67	57	

* All data are for the reference year, which is the year before diagnosis for cases and the year before interview for controls.
† All data are in percentages, except for mean and standard deviation for age and body mass index (current and 1 year ago).
‡ Test for difference between cases and controls after controlling for the other participant characteristics in the table (excluding current body mass index).
§ SD, standard deviation; MET, metabolic equivalent; NSAID, nonsteroid antiinflammatory drug.
¶ "Never," no NSAID use in the past 5 years; "occasionally," used NSAIDs less than three times per week in the past 5 years; "regularly," used NSAIDs three or more times per week in the past 5 years.
# Use of any vitamin or mineral supplement at least once a week over the past year.

29.0 kg/m^2 for African Americans). Finally, cases were more likely than controls to have a family history of colon cancer, and they were less likely to have used nonsteroidal antiinflammatory drugs regularly over the previous 5 years or to have used vitamin/mineral supplements during the preceding year (all $p < 0.05$).

Table 2 gives the mean total energy, macronutrient, and fiber intakes among White and African-American colon cancer cases and controls. Because results for "total energy, not including alcohol" and "total energy, including alcohol" were not appreciably different, we used the latter in these analyses. Except for greater alcohol consumption among Whites compared with African Americans (8 vs. 5 g/day), there were no marked differences in the *overall mean* intakes of total energy, macronutrients, or dietary fiber between White and African-American participants. Cases generally reported higher levels of mean daily intakes of total energy and most macronutrients than did controls; however, the extent of the differences varied by race. Specifically, both White and African-American cases reported statistically significantly higher intakes of total energy and alcohol than did their respective controls; however, White cases also reported significantly higher consumption of total carbohydrate (g/day), protein (g/day), and percent energy from fat than did White controls (all $p < 0.05$). In both racial groups, cases reported consuming significantly less dietary fiber than did controls (difference = 1 g/1,000 kcal per day, both $p < 0.05$).

Associations (odds ratios and 95 percent confidence intervals) of total energy, macronutrients, and dietary fiber with colon cancer risk, stratified by race, are given in table 3. There were no appreciable differences in the race-specific odds ratios estimated using quartile cutoffs based on combined intakes from all controls and those estimated using race-specific control intakes, so only the latter are presented here. Results differed markedly according to whether or not the odds ratios were adjusted for total energy, and the associations also varied by race. In Whites, high intakes (i.e., the highest quartiles) of total energy and individual energy sources, including total carbohydrate (g/day), eCarb (g/day), protein (g/day), total fat (g/day), and saturated fat (g/day), were associated with two- to threefold increases in colon cancer risk in models that were not controlled for total energy (all $p < 0.001$). However, when total energy was

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TABLE 2. Mean intakes of total energy and macronutrients among participants with and without colon cancer, by race (*n* = 1,609), North Carolina Colon Cancer Study, 1996–2000*

Total energy or macronutrient	Whites (*n* = 933)					African Americans (*n* = 676)				
	Overall† (mean (SD‡))	Cases (*n* = 337)	Controls (*n* = 596)	Difference (cases – controls)	*p* value§	Overall† (mean (SD))	Cases (*n* = 276)	Controls (*n* = 400)	Difference (cases – controls)	*p* value§
Total energy (kcal/day)	1,891 (658)	2,014	1,821	193	<0.0001	1,845 (768)	1,993	1,742	251	0.001
Macronutrients										
Carbohydrate (g/day)	217 (77)	225	212	13	0.03	214 (89)	228	204	24	0.30
Effective carbohydrate¶ (g/day)	202 (73)	211	197	14	0.08	201 (86)	215	191	24	0.44
Carbohydrate (% energy)	46 (8)	45	47	–2	0.02	47 (7)	46	47	–1	0.31
Protein (g/day)	69 (25)	72	68	4	0.01	65 (28)	69	62	7	0.16
Protein (% energy)	15 (3)	14	15	–1	0.0009	14 (3)	14	14	0	0.18
Saturated fat (g/day)	26 (12)	29	25	4	0.58	26 (13)	29	25	4	0.35
Total fat (g/day)	79 (39)	86	74	12	0.12	79 (32)	85	75	10	0.29
Total fat (% energy)	37 (7)	38	36	2	0.02	38 (7)	38	38	0	0.78
Alcohol (g/day)	8 (18)	10	7	24	0.01	5 (21)	8	3	36	0.02
Dietary fiber (g/1,000 kcal)	8.0 (2.4)	7.3	8.3	–1	<0.0001	7.4 (2.9)	6.8	7.8	–1	0.03

* All data are for the reference year, which is the year before diagnosis for cases and the year before interview for controls.
† Mean intakes among race-specific cases and controls.
‡ SD, standard deviation.
§ Test for difference between cases and controls after controlling for the other participant characteristics in table 1 (excluding current body mass index) and for total energy intake; % energy from carbohydrate, % energy from protein, and % energy from fat not further adjusted for total energy intake.
¶ Effective carbohydrate defined as "total carbohydrate (g/day) – total fiber (g/day)."

taken into account either through adjustment in statistical analyses or by using proportional (i.e., percent energy) values, the individual macronutrients were no longer significantly positively associated with colon cancer risk; in fact, some appeared to have inverse associations (e.g., odds ratio (OR) = 0.5 for percent energy from fat) (data for percent energy from carbohydrate and protein are similar but not shown). In African Americans, eCarb (g/day) was positively associated with colon cancer risk in both energy-adjusted and non-energy-adjusted models (OR = 2.0), while high saturated fat intake was associated with an almost twofold increased risk only in models that did not include total energy. Besides eCarb, only total fat was (inversely) statistically significantly associated with colon cancer in energy-adjusted models (OR = 0.3), and there was a nonsignificant trend for total energy intake (OR = 1.4, 95 percent confidence interval: 0.8, 2.3). Dietary fiber was statistically significantly inversely associated with colon cancer risk in African Americans in both energy-adjusted (OR = 0.5) and non-energy-adjusted (OR = 0.4) models, but the 30 percent risk reduction in Whites was not statistically significant. Alcohol was not statistically significantly associated with colon cancer risk in either racial group; however, two thirds of the participants did not consume alcoholic beverages during the referent period.

DISCUSSION

In this large case-control study of colon cancer in North Carolina with an adequate representation of African Americans and Whites, associations of total energy, various macronutrients, and dietary fiber with colon cancer risk varied to some extent by race and, to a larger extent, by whether or not total energy was included in statistical models. When risk estimates were not adjusted for total energy in Whites, high intakes of total energy and most macronutrients were statistically significantly positively associated with increased risk for colon cancer; however, these associations largely disappeared when total energy was taken into account. In African Americans, high intakes of eCarb (in both models) and saturated fat (in models not controlled for total energy) significantly increased colon cancer risk, while high dietary fiber consumption was statistically significantly associated with reduced risk. These results suggest that individual sources of energy may not be independently associated with colon cancer beyond the risk explained by total energy.

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The results for total energy intake in White participants are in agreement with several previous case-control investigations, which generally found positive associations between total energy and colon cancer risk (27–31). However, prospective studies have usually reported null or weak associations (32–34). Thus, it has been suggested that the findings from case-control studies may be due to methodological bias, such as a combination of selective participation or recall of past diet (9). Nonetheless, a positive association between total energy and colon cancer is in agreement with mechanistic evidence that caloric restriction reduces cancer incidence in rodents and colorectal cell proliferation in humans (35–37).

Overall, our findings for individual energy sources (fat, protein, and carbohydrate) in Whites are similar to those from other epidemiologic investigations. More specifically, our non-energy-adjusted results are similar to those from many case-control studies in which the role of energy intake was not taken into account (9, 10, 38–41), while our adjusted findings mirror those from prospective investigations and case-control studies in which risk estimates were controlled for total energy (9, 10, 29, 42–46). For example, a combined analysis of 13 case-control studies by Howe et al. (47) showed no association between the intake of total fat or saturated fat and colon cancer risk after adjustment for total energy intake. Similarly, a recent Italian case-control study found no significant associations between different types of fat and colon cancer after control for total energy, although the association for saturated fat was positive (48). In contrast, dietary fat was found to be a significant risk factor for colon cancer in an earlier study in which adjustment was not made for total energy intake (38). The epidemiologic evidence for an association of protein with colon cancer is inconsistent, primarily because it is difficult to separate the data on protein from those of fat and total energy (9, 49). Our finding of a positive association between "effective" carbohydrate or eCarb (i.e., the digestible nonfiber portion of carbohydrate) and colon cancer is in agreement with recent work by Borugian et al. (21) in North American Chinese. These results are bolstered by a research hypothesis suggesting that a high refined carbohydrate diet may increase glycemic overload and result in a compensatory increase in blood insulin, which is a growth factor of the human colonic mucosa (50, 51). In fact, recent studies have associated high levels of insulin and insulin growth factor, as well as a high glycemic index (which is an indicator of the dietary insulin demand) and glycemic load, with increased risk for colon cancer (37, 50–53). However, other studies do not support this hypothesis (50, 54).

Many correlational and case-control studies provide evidence of a linear inverse association between dietary fiber and colon cancer risk in Whites (9, 55–58); however, prospective studies have been equivocal (59, 60). Although the association in our study was not statistically significant, the trend suggested that dietary fiber may decrease colon cancer risk. It is worth noting, however, that recent intervention trials have failed to demonstrate that a high-fiber diet of 3–4 years' duration reduces the incidence or recurrence of adenomatous polyps, which are important colon cancer precursors (61–63). Finally, as with other nutrients, epidemiologic studies have reported either an increased risk, particularly for beer consumption (64, 65), or no association (66, 67) between total alcohol intake and colon cancer. The absence of a significant association in the present study may be partly due to the fact that only one third of the participants reported consuming alcoholic beverages.

We know of only one study in African Americans with which to compare our findings. In a study of 99 African-American colorectal cancer cases and 280 matched controls in San Francisco, Dales et al. (12) found that, compared with controls, colon cancer cases were more likely to report high consumption of saturated fat-rich foods (defined as "at least 5 percent saturated fat content") and less frequent consumption of foods high in dietary fiber (defined as "at least 0.5 percent fiber content"). However, these differences did not reach statistical significance after control for potential confounding variables, but they showed a consistent dose-response pattern. Similarly, we found that, among African-American participants, saturated fat was associated with a twofold increased colon cancer risk (in non-energy-adjusted models), while dietary fiber was significantly associated with reduced risk regardless of the statistical approach examined. Our finding supports the fiber hypothesis put forth by Burkitt (68) based on observations that diseases of the bowel, including colon cancer, were rare in Africans whose diet was high in fiber. Thus, the results of these two case-control studies conducted more than 20 years apart suggest that a high fiber-low saturated fat dietary pattern may reduce colon cancer risk in African Americans. Further research is needed to determine whether specific types of dietary fiber and/or a diet rich in many types of fiber confers protection against colon cancer and whether high saturated fat consumption independently increases colon cancer risk in African Americans.

The reasons why results differed by race are not entirely clear. Overall mean intakes of the nutrients examined here did not differ appreciably by race, which reduces the possibility that race-specific intakes of some nutrients were too low to allow the detection of significant associations. Furthermore, racial differences remained after we combined all control intakes and estimated race-specific odds ratios using global quartile cutoffs (data not shown), suggesting that differences in the range of intake values between Whites and African Americans are not the likely explanation for the differences in risk. In addition, there was no effect modification by sex or tumor site in the combined sample (data not shown). Nonetheless, one possible explanation for the differences by race could be higher levels of obesity in African Americans compared with Whites (table 1), as obesity has been associated with increased risk for colon cancer (69, 70). Specifically, if the effect of obesity on colon cancer risk is modulated primarily through abdominal fat (70), controlling only for body mass index (as in this study) may not fully explain the possible effects of obesity. Results from future investigations in both African Americans and Whites are needed to further elucidate associations of various nutrients with colon cancer risk in these population groups.

Undoubtedly, one of the most striking findings from this study relates to the differences between energy-adjusted and non-energy-adjusted odds ratios. In general, adjustment for

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TABLE 3. Associations (adjusted odds ratios) of total energy and macronutrients with colon cancer risk, by race (*n* = 1,609), North Carolina Colon Cancer Study, 1996–2000*

Total energy or macronutrient†	Whites (*n* = 933)						African Americans (*n* = 676)					
	No. of cases	Median intake/day in controls	Energy adjusted‡		Not adjusted for energy§		No. of cases	Median intake/day in controls	Energy adjusted		Not adjusted for energy	
			OR¶	95% CI¶	OR	95% CI			OR	95% CI	OR	95% CI
Total energy (kcal/day)												
1st quartile (referent)	65	1,135			1.0		54	1,032			1.0	
2nd quartile	76	1,570			1.4	0.9, 2.2	55	1,415			0.9	0.5, 1.5
3rd quartile	67	1,936			1.3	0.7, 2.2	65	1,806			1.0	0.6, 1.6
4th quartile	129	2,546			2.2	1.1, 4.5	102	2,542			1.4	0.8, 2.3
p for linear trend					0.12						0.19	
Carbohydrate (g/day)												
1st quartile (referent)	62	130	1.0		1.0		52	116	1.0		1.0	
2nd quartile	92	183	1.1	0.7, 1.8	1.7	1.1, 2.5	59	168	1.0	0.6, 1.8	1.2	0.7, 2.0
3rd quartile	73	228	0.9	0.5, 1.5	1.7	1.1, 2.6	64	215	0.9	0.5, 1.7	1.2	0.7, 2.0
4th quartile	109	296	0.8	0.4, 1.6	2.8	1.8, 4.4	100	298	0.8	0.3, 1.9	1.6	0.8, 3.0
p for linear trend			0.41		<0.0001				0.56		0.22	
Effective carbohydrate# (g/day)												
1st quartile (referent)	64	121	1.0		1.0		49	106	1.0		1.0	
2nd quartile	85	170	1.1	0.7, 1.7	1.5	1.0, 2.2	61	155	1.3	0.8, 2.2	1.3	0.8, 2.2
3rd quartile	76	212	0.9	0.5, 1.5	1.7	1.1, 2.6	64	199	1.4	0.8, 2.3	1.4	0.8, 2.3
4th quartile	111	276	0.8	0.4, 1.6	2.7	1.7, 4.2	101	281	2.0	1.2, 3.2	2.0	1.2, 3.2
p for linear trend			0.43		<0.0001				0.01		0.01	
Protein (g/day)												
1st quartile (referent)	71	42	1.0		1.0		55	37	1.0		1.0	
2nd quartile	84	59	1.2	0.7, 1.8	1.6	1.0, 2.4	67	51	0.9	0.5, 1.5	1.1	0.6, 1.8
3rd quartile	81	74	1.1	0.5, 1.9	1.8	1.1, 2.8	52	65	0.6	0.3, 1.1	0.8	0.4, 1.3
4th quartile	101	94	1.1	0.6, 2.1	2.9	1.7, 4.7	101	90	0.8	0.3, 1.8	1.2	0.6, 2.4
p for linear trend			0.82		<0.0001				0.31		0.93	
Total fat (g/day)												
1st quartile (referent)	66	40	1.0		1.0		59	41	1.0		1.0	
2nd quartile	65	63	0.9	0.6, 1.4	1.1	0.7, 1.7	52	58	0.6	0.3, 1.0	0.7	0.4, 1.2
3rd quartile	72	79	1.0	0.6, 1.6	1.4	0.9, 2.1	69	79	0.5	0.3, 1.0	0.9	0.5, 1.5
4th quartile	134	110	1.3	0.6, 2.5	2.8	1.8, 4.2	95	118	0.3	0.1, 0.8	1.2	0.7, 1.9
p for linear trend			0.92		<0.0001				0.02		0.34	

Table continues

total energy intake tended to attenuate associations of individual macronutrients with colon cancer risk. Therefore, it is worth discussing why it is necessary or important to adjust risk estimates for total energy and the circumstances under which energy adjustment may not be appropriate.

Nutrient intake can affect disease risk through *additive* or *substitution* effects. Additive effects reflect the consequence of adding a nutrient to the diet (i.e., absolute changes), while energy-adjusted nutrient estimates are used to evaluate the impact of substituting one nutrient for another without a change in total energy intake (i.e., dietary composition). Another rationale for energy adjustment is statistical confounding because, in many instances, total energy is associated with both the exposure (e.g., a macronutrient) and the disease of interest (e.g., colon cancer). Finally, some researchers have suggested that, when self-report instruments are used, energy-adjusted nutrient estimates are more biologically relevant because they tend to have stronger associations with biochemical measures of diet than absolute intakes (71, 72).

In spite of its potential advantages, energy adjustment raises several concerns. First, it is a considerable challenge to separate the distinct effects of individual energy sources and total energy when both variables are in a statistical model, given that the two measures are usually very highly correlated, as in this study, for example, total fat (Pearson's

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TABLE 3. Continued

Total energy or macronutrient	Whites (n = 933)						African Americans (n = 676)					
	No. of cases	Median intake/day in controls	Energy adjusted		Not adjusted for energy		No. of cases	Median intake/day in controls	Energy adjusted		Not adjusted for energy	
			OR	95% CI	OR	95% CI			OR	95% CI	OR	95% CI
Total fat (% kcal)												
1st quartile (referent)	64	28	1.0		1.0		60	30	1.0		1.0	
2nd quartile	75	34	0.7	0.5, 1.2	0.7	0.5, 1.2	67	37	0.8	0.5, 1.3	1.0	0.6, 1.6
3rd quartile	92	39	0.7	0.4, 1.1	0.7	0.4, 1.1	76	41	0.8	0.4, 1.3	0.9	0.5, 1.5
4th quartile	106	44	0.5	0.3, 0.8	0.5	0.3, 0.8	69	45	0.7	0.4, 1.1	0.8	0.5, 1.3
p for linear trend			0.009		0.009				0.24		0.32	
Saturated fat (g/day)												
1st quartile (referent)	67	13	1.0		1.0		58	12	1.0		1.0	
2nd quartile	69	20	0.9	0.6, 1.4	1.1	0.7, 1.7	49	19	0.6	0.3, 1.0	0.8	0.5, 1.3
3rd quartile	71	27	0.8	0.5, 1.4	1.2	0.8, 1.8	66	26	0.7	0.4, 1.3	1.2	0.8, 2.0
4th quartile	130	37	1.2	0.6, 2.2	2.6	1.7, 4.0	102	41	0.6	0.2, 1.3	1.9	1.2, 3.1
p for linear trend			0.68		<0.0001				0.38		0.002	
Alcohol (kcal/day)**												
Nondrinker (referent)	206	0	1.0		1.0		215	0	1.0		1.0	
Drinker	131	70	0.9	0.7, 1.2	0.9	0.7, 1.2	61	60	0.9	0.6, 1.5	1.1	0.7, 1.7
p for linear trend			0.37		0.50				0.82		0.64	
Dietary fiber (g/1,000 kcal)												
1st quartile (referent)	133	5.3	1.0		1.0		114	4.8	1.0		1.0	
2nd quartile	85	7.0	0.8	0.5, 1.1	0.8	0.5, 1.1	70	6.7	0.7	0.4, 1.1	0.6	0.4, 0.9
3rd quartile	68	8.7	0.7	0.5, 1.1	0.7	0.5, 1.1	46	8.0	0.5	0.3, 0.8	0.4	0.2, 0.6
4th quartile	51	11.8	0.7	0.4, 1.2	0.7	0.4, 1.2	46	10.9	0.5	0.3, 0.9	0.4	0.2, 0.6
p for linear trend			0.14		0.14				0.001		<0.0001	

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

† Cutoffs based on intakes among race-specific control participants.

‡ Adjusted for total energy when total energy met the criteria for covariate inclusion. Other potential confounders that were examined include age, sex, education, body mass index (year prior to diagnosis), smoking history, physical activity, family history of colon cancer, nonsteroidal antiinflammatory drug 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 nutrient.

§ Not adjusted for total energy. Potential confounders that were examined include age, sex, education, body mass index (1 year ago), smoking history, physical activity, family history of colon cancer, nonsteroidal antiinflammatory drug 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 nutrient.

¶ OR, odds ratio; CI, confidence interval.

Effective carbohydrate defined as "total carbohydrate (g/day) – total fiber (g/day)."

** Two thirds of participants did not report consuming alcohol.

r = 0.90–0.93) and total carbohydrate (r = 0.88–0.93). This is because the collinearity that exists between these rather unreliably measured variables can result in unstable and, hence, uninterpretable models (73, 74). Furthermore, because of these high correlations, a very large study sample is needed to separate independent associations. In fact, Wacholder et al. have suggested that "it is not possible with any energy-adjustment method to address the distinct questions of whether intake of total energy or a separate macronutrient causes disease" (73, p. 849). A second potential problem relates to possible underreporting of diet, particularly in the case groups: If cases selectively underreport their intakes of fat, carbohydrate, and/or protein, adjusting for total energy could conceal their true effects because total energy is derived from these macronutrients. Finally, because there is ample evidence that total energy intake is poorly estimated by most self-report instruments, particularly food frequency questionnaires (22, 75, 76), it is not clear that control for total energy in statistical models actually adjusts for true energy intake.

Nonetheless, in this study, energy-adjusted and proportional (i.e., percent energy) risk estimates suggest that macronutrients have no independent effects on colon cancer risk beyond that explained by total energy, while non-

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energy-adjusted odds ratios tended to suggest positive (i.e., unfavorable) associations for most macronutrients. Because of these differences in risk estimates and because it is unclear whether the energy-adjusted or non-energy-adjusted estimates are more appropriate, we present both sets of results in this report. Unfortunately, this is not often done in nutritional epidemiologic studies. It is quite likely that some of the conflicting findings in the literature are due to differences in whether and how total energy is taken into account. We agree with several other researchers (72, 77, 78) that knowledge of both the addition and substitution effects of various nutrients improves our understanding of the relations between nutrition and disease. Possibly, the presentation of both statistical approaches in future studies may contribute to resolving some of the contradictory results often seen in diet and cancer research.

There are several strengths to our study. Most notably, this is among the first published reports examining the associations of total energy and various macronutrients with colon cancer risk in a diverse sample of African Americans and Whites recruited from the same geographic area. We also had a large sample size, which allowed us to observe associations that may not be detectable in smaller studies. Finally, our data were collected with 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 (79).

Several possible limitations of this study also warrant consideration. First, as in other case-control studies, there is potential for methodological (selection and recall) bias. Controls may have agreed to join this study because of an interest in health and may therefore have healthier dietary and physical activity habits than the general population. These patterns may exaggerate differences with the case group beyond what might have been seen with truly comparable controls (79). Response rates were comparable with those reported in other studies (80, 81); however, selection bias should be considered when interpreting these results. Given that exposure information was collected after diagnosis of the disease, differential recall between cases and controls could bias results; in particular, cases may recall dietary exposures differently from controls because of the presence of their illness and/or symptoms. Second, estimates of nutrient intakes from a food frequency questionnaire are not precise (22, 75, 76), and there is always the potential for measurement error; however, the food frequency questionnaire used in this study has been calibrated (in comparison with more extensive methods of measuring dietary intake) for the nutrients examined here (82, 83). Nonetheless, it is important to note that the measurement error from food frequency questionnaires often attenuates estimates of disease risk and reduces statistical power to detect their significance; thus, it is possible that important diet-colon cancer associations may not have been observed in this study (72). Third, the 1-year referent period on which exposure data (including dietary intake) were based would not be appropriate to correctly determine associations if remote diet (i.e., 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 due to unknown, uncontrolled, or imperfectly measured variables remains. Prospective investigations using biologically based measures of various dietary exposures are needed to obviate these limitations.

In conclusion, the results of our case-control study suggest that total energy intake may be positively associated with colon cancer risk in African Americans and Whites. However, associations with individual sources of energy (carbohydrate, protein, and fat) varied by race and by whether or not total energy intake was taken into account. The findings from this study may provide an explanation for some of the racial differences in colon cancer incidence.

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