Carbohydrates and Colorectal Cancer Risk among Chinese in North America

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Abstract

Previous studies have analyzed total carbohydrate as a dietary risk factor for colorectal cancer (CRC) but obtained conflicting results, perhaps attributable in part to the embedded potential confounder, fiber. The aim of this study was to analyze the nonfiber ("effective") carbohydrate component (eCarb) separately and to test the hypothesis that effective carbohydrate consumption is directly related to CRC risk. The data (473 cases and 1192 controls) were from a large, multicenter, case-control study of Chinese residing in North America. Multivariate logistic regression was used to perform a secondary analysis controlling for age; sex; consumption of fat, fiber, calcium, and total kilocalories; body mass (Quetelet's) index; family history; education; and years in North America. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate risk among subgroups by sex and cancer site. A statistically significant positive association was observed between eCarb consumption and risk of CRC in both men (OR, 1.7 comparing highest with lowest tertile of eCarb consumption; 95% CI, 1.1–2.7) and women (OR, 2.7; 95% CI, 1.5–4.8). As expected, the ORs for total carbohydrate were somewhat lower than those for effective carbohydrate, but the differences were not large. A sex difference in risk by colorectal subsite was observed, with risk concentrated in the right colon for women (OR, 6.5; 95% CI, 2.4–18.4) and in the rectum for men (OR, 2.4; 95% CI, 1.2–4.8). These data indicate that increased eCarb and total carbohydrate consumption are both associated with increased risk of CRC in both sexes, and that among women, relative risk appears greatest for the right colon, whereas among men, relative risk appears greatest for the rectum.

Introduction

CRC,[2] the fourth most common cancer in the world, is largely attributable to environmental, especially dietary, factors (1–4). Recently, a unifying hypothesis has been proposed suggesting that obesity, inactivity, alcohol, and the consumption of a typical Western diet are all associated with the development of insulin resistance and hyperinsulinemia (5–9). Moreover, hyperinsulinemia may stimulate growth of colorectal tumors. Several lines of research support a role for insulin in colorectal carcinogenesis (10–14). Although an excessive carbohydrate intake might not result in abnormally elevated insulin levels in a healthy young person of normal body weight, factors such as age, body mass index, diet, activity, and genetic predisposition among others can all contribute to resistant insulin receptors (5, 15, 16). This resistance can lead to a chronic state of elevated insulin to maintain normal blood glucose levels. Insulin is a powerful anabolic hormone and a known risk factor for several major diseases, including heart disease, non-insulin-dependent diabetes, and hypertension (17); therefore, excess insulin is a concern.

The role of insulin in CRC is a fairly recent area of investigation. The idea is consistent with the normal role of insulin as a growth factor for human colonic mucosal cells, which have both insulin and IGF-I receptors (5, 9, 14, 18). A role for insulin is also supported by prospective studies of human subjects with non-insulin-dependent diabetes mellitus (an insulin-resistant state), in whom an increased risk of CRC has been found (11, 12). Thus insulin, a known growth factor, is a biologically plausible agent in colorectal carcinogenesis, particularly at chronically elevated levels.

The research hypothesis of this study is that "total carbohydrate minus carbohydrate fiber" (hereafter called "effective carbohydrate," *i.e.,* the digestible nonfiber portion of carbohydrate intake that stimulates insulin release) is a significant risk factor for CRC via chronic insulin stimulation. Although some databases may already have the fiber component subtracted, those analyses that are based on total carbohydrate including fiber might be biased toward the null because of the possibly protective effect of the embedded fiber (19), *i.e.,* a negative confounder. Effective carbohydrate consumption may be a variable with a significant impact on health and heretofore not properly controlled for in analyses using a carbohydrate variable that includes fiber.

Received 3/23/01; revised 11/2/01; accepted 11/16/01.
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[2] The abbreviations used are: CRC, colorectal cancer; IGF, insulin-like growth factor; NDF, neutral detergent fiber; OR, odds ratio; CI, confidence interval; QI, Quetelet's index.

Materials and Methods

Study Design. The data are from a case-control study of CRC published in 1990, and the data collection methods are described in detail in the original publication (20). Briefly, data were collected during the study period 1981–1986 from Chinese men and women in North America and China. The study centers included Vancouver, San Francisco, Los Angeles, Ningbo, and Hangzhou. In the three North American centers used in this secondary analysis, there were 473 cases and 1192 controls. The selection criteria were: (*a*) diagnosis of invasive adenocarcinoma of the colon or rectum (International Classification of Diseases for Oncology site codes 153.1–153.9 for colon and 154.0–154.1 for rectum) between January 1, 1981 and December 31, 1986 at age 20 or more years; and (*b*) both parents of Chinese ancestry, defined as Chinese surname, or subject's own assessment of ethnicity. All cases meeting the criteria were selected from the British Columbia Cancer Registry, the San Francisco-Oakland Surveillance, Epidemiology, and End Results Program, and the Los Angeles Cancer Surveillance Program.

Cases. Of the 805 eligible North American patients, 235 died between selection and interview, 91 refused to participate, 58 were too ill or had moved, and 421 (52%) were interviewed. To assess potential bias from loss to interview by death, next of kin were contacted for those who died before being interviewed ($n = 235$), and 52 relatives (22%) knew enough about the subject's lifestyle and agreed to provide a surrogate interview. Data from these interviews showed no significant differences in mean values for CRC risk factors such as family history, physical activity, dietary, demographic, medical, reproductive, and migrant factors; therefore, information from patient and surrogate interviews was pooled, giving data on 473 of the 805 eligible cases (59%).

Controls. Chinese-American population controls were frequency matched to cases by sex, age (at 5-year intervals), and residential location, in an approximately 3:1 ratio. In Vancouver, controls were selected from the Medical Services Plan list of subscribers, matched on school district of residence, whereas in San Francisco and Los Angeles, controls were recruited by house-to-house canvassing of the case's neighborhood. Of 2219 potentially eligible controls, 446 could not be contacted because they were deceased or had moved, 581 refused to participate, and 1192 (54%) were interviewed.

Interviews. The study questionnaire (20) was administered by a trained interviewer in the participant's home, in the language of their choice. The questionnaire covered diet and physical activity, length of residence in North America, body weight and height, as well as demographic, medical, and reproductive factors. The subjects were asked about themselves, including diet and weight at age 21, age 40, and a reference year (the year before diagnosis for cases and the year before interview for controls). To ensure a common protocol, interviewers at all centers were trained by a core group of trainers, and taped interviews were monitored throughout the study. During the study period, investigators from all centers convened at least twice a year to maintain communication and a consistent approach to data collection.

Dietary History. Food items were selected to include the most frequently consumed foods, both Western and Chinese. Participants reported their average frequency of consumption of 84 foods in six food groups: meat, fish, and eggs; dairy; starches and sweets; vegetables; fruits; and beverages. They also reported portion sizes for items consumed more than once a week. Food models were used to simulate Chinese and Western style foods.

Data Coding. A common protocol was used for questionnaire coding and data entry at all study sites. All nutrient intake variables were calculated by combining food frequencies with portion sizes and nutrient values obtained from three sources (21–23). A new variable was created for the current analysis, effective carbohydrate consumption (eCarb), defined as "total carbohydrate grams per day" minus "total fiber grams per day." For this calculation, total fiber was defined as grams per day of both pectin (soluble carbohydrate fiber) and NDF (insoluble carbohydrate fiber). Other independent variables included: age (as a continuous variable); sex ($0 = $ male, $1 = $ female); saturated, monounsaturated, and polyunsaturated fat consumption (g/day); years in North America ($0 = 0$–9, $1 = 10$–19, $2 = 20+$); total kilocalories consumed/day; calcium consumption (mg/day); fiber consumption (g/day of pectin and NDF); QI; and education ($0 = $ less than 12 years, $1 = 12+$ years).

Summary Descriptive Statistics. Descriptive statistics were generated using SPSS Version 9.0 (24). All analyses were performed separately by sex. Independent t tests for continuous variables and χ^2 tests for categorical variables were used to examine whether statistically significant differences exist between the cases and the controls in any of the factors being considered for the multivariate model.

Variable Selection. Initially, variables of interest and potential confounders were selected from the data, based on prior information from the literature. The final group of variables was selected by testing for their effect on the estimate of the eCarb OR (25, 26). Total kilocalories consumed, a possible risk factor, was included in the model to control for energy intake not covered by the nutrient variables, using the standard multivariate method (27). Study center, physical inactivity (hours spent sitting/day), and protein consumption were also analyzed for effect on the eCarb OR before being excluded. The variable for income level was missing in 67 cases for men and 78 cases for women; therefore, the variable for education level, which was complete, was selected as a reasonable surrogate for socioeconomic status (28, 29).

Multivariate Logistic Regression Model. The SPSS logistic regression model building procedure (24) was used to build an initial model, using the Likelihood Ratio statistic. Each covariate was tested by removal from the model, and if the eCarb OR was unchanged, the variable was excluded from subsequent models.

Residual values were saved during the regression run to allow checking for outliers and influential points. These were plotted against predicted values, and specific cases were then selected for examination. Two cases were found to have large leverage values (relative influence of an observation on the model's fit), indicating outliers that could affect the results. Additional regression models were done excluding the two outlier cases, but the differences observed did not change the conclusion; therefore, the two cases were included in the final model.

All covariates included in the final model exhibit interaction with the primary variable to some degree, as evidenced by a change in eCarb OR when the variables are removed from the model, but none of the interaction terms reached statistical significance for these data.

The independent variable of interest, eCarb, was categorized into tertiles, based on sex-specific control population cutpoints of "effective" carbohydrate consumption. Tertiles

Table 1 Selected characteristics of North American Chinese CRC cases and controls by sex

	Men		Women	
	Cases (n = 284)	Controls (n = 698)	Cases (n = 189)	Controls (n = 494)
Demographic				
Education				
0–12 yr	67.6%	62.2%	83.6%	76.1%
>12 yr	32.4%	37.8%	16.4%	23.9%
Family history				
Yes	25.7%	17.3%	23.8%	15.6%
No	74.3%	82.7%	76.2%	84.4%
Yr in North America				
0–9 years	22.7%	35.2%	28.6%	39.1%
10–19 years	25.2%	28.7%	30.7%	29.8%
20+ years	52.1%	36.2%	40.7%	31.2%
Consumption[a,b]				
Effective carbohydrates (g/day)[c]	242.1 (95.9)	237.0 (90.0)	208.5 (83.8)	196.3 (69.8)
Fiber, NDF (g/day)	9.5 (5.5)	9.7 (5.8)	8.5 (5.0)	8.7 (4.8)
Fiber, pectin (g/day)	3.2 (1.6)	3.4 (1.7)	3.1 (1.7)	3.2 (1.6)
Calcium (mg/day)	584.5 (312.6)	585.7 (305.8)	487.0 (315.0)	514.0 (302.0)
Protein (g/day)	104.4 (50.2)	93.7 (42.0)	84.7 (42.7)	77.9 (31.8)
Monounsaturated Fat (g/day)	51.1 (23.5)	44.6 (17.6)	40.9 (19.0)	37.6 (15.4)
Polyunsaturated Fat (g/day)	18.3 (6.9)	17.2 (5.9)	16.1 (6.8)	15.4 (5.6)
Saturated fat (g/day)	26.6 (16.0)	21.0 (10.9)	19.3 (12.0)	16.4 (8.2)
kcal/day	2308 (861)	2122 (700)	1885 (739)	1745 (547)
Personal[a]				
Age (yr)	67.6 (12.2)	66.0 (12.2)	63.9 (14.5)	61.7 (14.9)
Quetelet's Index[b]	22.7 (3.4)	22.7 (3.0)	22.2 (3.7)	22.2 (3.3)
Hr spent sitting/day[b]	8.8 (2.7)	8.1 (2.7)	8.3 (2.7)	8.0 (2.6)

[a] Data are presented as means (SD).
[b] Data are for reference year, which is the year before diagnosis for cases and the year before interview for controls.
[c] Total carbohydrate (not shown separately) equals effective carbohydrate plus pectin and NDF.

Table 2 Association between tertile of effective carbohydrate consumption and CRC risk among North American Chinese by sex

	Grams/day	Cases	Controls	OR	95% CI
Men		284	696		
1st tertile[a]	0–192	92	232	1.0	
2nd tertile	193–255	91	232	1.3	(0.9–1.9)
3rd tertile	256+	101	232	1.7	(1.1–2.7)
Women		189	495		
1st tertile[a]	0–160	56	165	1.0	
2nd tertile	161–216	55	165	1.3	(0.8–2.1)
3rd tertile	217+	78	165	2.7	(1.5–4.8)

[a] First tertile is reference category, adjusted for age, education, family history, QI, years in North America, total kilocalories consumed, and intake of fat, calcium, and fiber.

were used to categorize the primary variable to allow analysis by sex and cancer site, given the study sample size. Education and years in North America were also categorized, whereas remaining independent variables were analyzed as continuous variables to conserve degrees of freedom in the model. Analysis of the interaction terms used the same coding used for testing confounding.

Results

Descriptive Statistics. Table 1 compares cases and controls separately by sex on selected demographic variables and other potential confounders. These data show that on average, CRC cases eat more of everything than controls do, except fiber and calcium. With respect to carbohydrates, both men and women consume more effective carbohydrate than controls, but the difference was only statistically significant among the women. Cases also eat less fiber of both types than controls, but only consumption of pectin by the men approaches statistical significance. Level of inactivity as measured by hours sitting/day was greater in cases than in controls but was statistically significant only in the men. Another important difference between cases and controls of both sexes is the number of years they have lived in North America. Among men, 52.1% of cases have lived in North America >20 years, whereas only 36.2% of controls have been in North America that long. The difference in women is similar (40.7% compared with 31.2%) and also statistically significant.

Differences in Risk by Sex. Table 2 shows the confounder-adjusted ORs for sex-specific tertiles of eCarb consumption. The multivariate logistic regression model controlled for known confounders: age (at diagnosis for cases, at interview for controls); QI; years of education; family history; years in North America; total kilocalories consumed; and nutrient consumption variables for the reference year (1 year before diagnosis for

Table 3 Association between tertile of effective carbohydrate consumption and CRC risk among North American Chinese by cancer site and sex

	Controls	Right			Left			Rectal		
		Cases	OR	95% CI	Cases	OR	95% CI	Cases	OR	95% CI
Men[a]	697	53			114			105		
1st tertile[b]	232	15	1.0		40	1.0		31	1.0	
2nd tertile	233	21	1.8	(0.8–4.0)	36	1.1	(0.7–1.9)	33	1.5	(0.8–2.7)
3rd tertile	232	17	1.3	(0.5–3.4)	38	1.6	(0.9–3.1)	41	2.4	(1.2–4.8)
Women[c]	494	45			60			75		
1st tertile[b]	165	10	1.0		22	1.0		21	1.0	
2nd tertile	166	14	2.7	(1.0–7.0)	17	1.0	(0.5–2.1)	21	1.2	(0.6–2.4)
3rd tertile	163	21	6.5	(2.3–18.4)	21	1.7	(0.7–4.0)	33	2.7	(1.2–6.2)

[a] Twelve male cases were missing cancer site indicators.
[b] First tertile is reference category, adjusted for age, education, family history, QI, years in North America, total kilocalories consumed, and intake of fat, calcium, fiber.
[c] Nine female cases were missing cancer site indicators.

Table 4 Comparison of ORs using total carbohydrate with those using effective carbohydrate

	Controls	Right colon			Left colon			Rectum		
		Cases	OR	95% CI	Cases	OR	95% CI	Cases	OR	95% CI
Males										
Total Carb[a]	698	53			114			105		
1st tertile[b]	233	17	1.0		39	1.0		34	1.0	
2nd tertile	233	19	1.5	(0.7–3.2)	37	1.3	(0.7–2.1)	29	1.2	(0.6–2.1)
3rd tertile	232	17	1.1	(0.4–2.9)	38	1.7	(0.9–3.2)	42	2.3	(1.1–4.5)
e-Carb	698	53			114			105		
1st tertile[b]	232	15	1.0		40	1.0		31	1.0	
2nd tertile	234	21	1.8	(0.8–4.0)	36	1.1	(0.7–1.9)	33	1.5	(0.8–2.7)
3rd tertile	232	17	1.3	(0.5–3.4)	38	1.6	(0.9–3.1)	41	2.4	(1.2–4.8)
Pectin (g/day)			0.9	(0.6–1.2)		0.8	(0.6–1.0)		0.9	(0.8–1.2)
NDF (g/day)			1.0	(0.9–1.1)		1.1	(1.0–1.1)		1.0	(0.9–1.1)
Females										
Total Carb	494	45			60			75		
1st tertile	165	11	1.0		24	1.0		22	1.0	
2nd tertile	166	15	2.2	(0.9–5.6)	18	0.8	(0.4–1.7)	21	1.2	(0.6–2.5)
3rd tertile	163	19	4.6	(1.6–13.1)	18	1.2	(0.5–2.9)	32	2.6	(1.1–6.1)
e-Carb	494	45			60			75		
1st tertile	165	10	1.0		22	1.0		21	1.0	
2nd tertile	166	14	2.7	(1.0–7.0)	17	1.0	(0.5–2.1)	21	1.2	(0.6–2.4)
3rd tertile	163	21	6.5	(2.3–18.4)	21	1.7	(0.7–4.0)	33	2.7	(1.2–6.2)
Pectin (g/day)			0.7	(0.5–1.0)		1.2	(0.8–1.8)		1.3	(1.0–1.7)
NDF (g/day)			1.0	(0.9–1.1)		1.0	(0.9–1.1)		0.9	(0.9–1.0)

[a] Total carbohydrate = effective carbohydrate plus pectin plus NDF; e-Carb, effective carbohydrate.
[b] First tertile is reference category. Models are adjusted for age, education, family history, QI, years in North America, total kilocalories, and intake of fat, calcium, fiber.

cases and 1 year before interview for controls) including saturated fat, monounsaturated fat, polyunsaturated fat, calcium, and fiber (pectin and NDF). A dose-response pattern was observed for both sexes, with an increasing risk from the lowest to the highest tertile of eCarb consumption. The women showed a greater risk over that interval (OR, 2.7; 95% CI, 1.5–4.8) than the men (OR, 1.7; 95% CI, 1.1–2.7).

Differences in Risk by Anatomical Site. A further finding is revealed in Table 3 where sex-specific risk, which looked fairly similar overall, is split into the component cancer sites: right or proximal colon (cecum, ascending, hepatic flexure, transverse, and splenic flexure); left or distal colon (descending and sigmoid); and rectum. The women are most at risk of right colon cancer (OR, 6.5; 95% CI, 2.3–18.4, for highest tertile of eCarb consumption compared with lowest tertile), whereas the men show no significant elevated risk in the right colon. For the other sites, the differences between men and women are smaller, with fairly wide CIs.

Differences in eCarb and Total Carbohydrate Variable Results. Table 4 shows the effect of using total carbohydrate consumption in place of eCarb consumption as the primary variable in this analysis. The major subclassifications of carbohydrate fiber [pectin (soluble fiber) and NDF (insoluble fiber)] are also shown to illustrate the heterogeneity of the fiber component itself. These fiber variables are presented in continuous form because of the difficulty in comparing categorized nested subcomponents of such different relative sizes as fiber and eCarb (30).

The men show similar or slightly lower ORs for total carbohydrate compared with eCarb. Consistent with this result, pectin and NDF exhibit neutral or weakly protective effects for the men. The women show a similar pattern for the left colon and rectum, but for the right colon, the difference is more marked, perhaps attributable in part to the stronger protective effect of pectin for women. An interesting finding relates to the female rectum and also but more weakly to the female left colon, where pectin is a risk factor rather than a protective factor.

Discussion

Overview. The results show a statistically significant increased risk of CRC associated with increased consumption of carbohydrates. Results for total and effective carbohydrates were similar, with a slightly higher risk associated with eCarb consumption. As reported in the original study, other highly significant predictors of CRC included age, saturated fat intake, calcium intake, and years in North America, especially if >20 years. Sex was an important factor, with women having a greater carbohydrate-associated risk overall, as well as a much greater site-specific risk in the right colon than men, although relatively wide CIs mean these results must be interpreted with caution.

The data indicate about a 2-fold increase in risk of CRC for those with high intake of effective carbohydrates (highest tertile) *versus* those with low intake (lowest tertile), after controlling for potential confounders. This observed result gives support to our *a priori* hypothesis that increased consumption of effective carbohydrate is associated with increased risk of CRC. Although the differences in risk between total and effective carbohydrate consumption are not large, they are compatible with expectations in terms of direction. When the cancer sites are considered together, men and women appear similar in their response to carbohydrate consumption. The observed site-specific differences between the sexes, however, suggest possible differences in etiology for right and left colon cancers that are consistent with women's higher incidence of right colon tumors (31, 32). Given the male-female difference in incidence by subsite, it is likely that one or more risk factors might also exhibit differences such as those observed in this study.

The study results must be interpreted with caution, however, in light of the selection of one ethnic group (Chinese) for the study population. Chinese were specifically targeted because of the relatively low incidence of CRC among Chinese living in China compared with Chinese living in North America. It is possible, however, that people of Chinese ancestry may be either more or less sensitive than other ethnic groups to the effects of dietary carbohydrates, potentially affecting generalizability of this analysis.

Although this study supports recent work on carbohydrates and insulin resistance, the current results are not consistent with all previous studies of carbohydrates. This may be partly explained by the novel treatment of carbohydrate in this study, *i.e.*, to subtract the fiber portion before analysis, something that other studies may not have done. Fiber, as in whole grains for example, is thought to modulate the glycemic response (33–35). The observed sex and cancer site differences in the OR of pectin suggest that some fiber components may further confuse carbohydrate analysis by being a risk factor in some circumstances and a protective factor in other circumstances. Also, some previous studies have focused on sucrose consumption (36) with risk ratios similar to those we observed. Because sucrose is only a fraction of digestible carbohydrate, however, studying it in isolation from starch consumption may increase the likelihood of a null result.

One inconsistency of the female right colon result with existing literature is that components of the Western lifestyle such as diet and activity have been associated more often with left colon and rectal cancer than with right colon cancer. This may be explained partly by the preponderance of male subjects used in studies and the increased likelihood that a male pattern might predominate in published study results. It could also be attributable to the multifactorial nature of "Western lifestyle" and the difficulties of studying any one component without some residual confounding. A second inconsistency relates to the nonsignificant interaction term for QI and also the lack of effect on eCarb OR for physical inactivity, both of which might be expected to interact strongly with carbohydrate consumption. This may be related to limited variability in the study population for these characteristics, as shown in Table 1.

Possible Mechanisms. When insulin is present in abnormally high concentrations, it can react with other receptors because receptor binding is a function of both affinity and concentration. In contrast to its blood glucose regulation role, insulin is believed to act through IGF-I receptors in its mitogenic effect on colonic carcinoma cells *in vitro* (10, 14). The mitogenic signal transduction may be mediated by *p21ras* (13), an important proto-oncogene in colon carcinogenesis. The wide range of effects seen with hyperinsulinemia is consistent with a general pattern such as cross-reaction with other receptor types. Insulin also increases the availability of IGF-I, an independent risk factor (18, 37), by down-regulating IGF binding proteins (38, 39).

Insulin may also act indirectly through its role in the production and regulation of sex steroid hormones (40, 41). In the last three decades, evidence for a hormonal role in colorectal carcinogenesis has accumulated. The bile acid mechanism developed by McMichael and Potter (42–46) suggests that sex differences in the bile acid metabolic profile are relevant to the preponderance of right colon tumors in women compared with men. One possible way that carbohydrate intake might interact with colonic bacteria and secondary bile acid production is via the intermediary of female reproductive hormones, either directly by potentiation of sex hormone production (both estrogen and testosterone), or indirectly by inhibition of sex hormone binding globulin production (40). These actions of insulin would result in higher plasma concentrations of free estrogen available to act at the tissue level.

The eCarb Variable. Regarding the use of eCarb as a variable in place of total carbohydrate, only a small difference in OR might be expected because of the small amount of fiber relative to total carbohydrate consumed and the heterogeneity of the fiber component (47), which this study does not address. In addition, this analysis used crude categorizations, both in terms of carbohydrate subcomponents and also in the use of tertiles of consumption. Although they are not large, the differences observed between eCarb and total carbohydrate analyses are potentially important in dietary research, where ORs are typically modest, and the effects of even small differences are magnified by the universal nature of diet as an exposure. Additional research is needed on the nature and effects of carbohydrate subcomponents. It is possible that simple subtraction of fiber from total carbohydrate may underestimate the potentially greater effect of 1 additional g of fiber/day, compared with 1 g of nonfiber carbohydrate; therefore, the difference between the results using eCarb and those using total carbohydrate may be greater than those observed in this study.

When energy intake is associated with disease, it is important to use a measure of nutrient intake that is independent of total energy. In this study, the effect of total energy consumption was controlled by inclusion of kilocalories consumed/day in the multivariate model. The eCarb variable, therefore, can be interpreted as the nutrient effect, independent of the effects of total energy and fat consumption covariates. One complexity of this approach is that the interpretation of the coefficient for the kilocalories consumed variable changes from total energy to total energy independent of the nutrients in the model, which in this case are carbohydrate and fat.

Glycemic index, if used as the primary variable in this study, might provide more information about the speed of carbohydrate digestion. Glycemic index, however, was not used here because it presents significant additional measurement challenges. Glycemic index may be influenced by a variety of environmental factors such as freshness, method of cooking, other foods eaten at the same time, and industrial processes such as gelatinization (34, 48), about which accurate data were not collected.

Four main conclusions arise from this study: (*a*) increased carbohydrate consumption is associated with increased risk of CRC in both men and women. The risk ratio associated with high levels of effective carbohydrate consumption compared with low levels is 1.7 for men and 2.7 for women when all cancer sites are considered together; (*b*) carbohydrate and especially effective carbohydrate should now be considered important potential risk factors in future research; (*c*) right colon, left colon, and rectal cancers should be considered separately where possible because it appears from these data that the dietary etiological factors may differ by site; and (*d*) excess carbohydrate consumption may pose a special risk of right colon cancer for women. The results of this analysis support the *a priori* hypothesis of increased risk of CRC attributable to increased effective carbohydrate consumption and also provide direction for new work on possible sex-specific, carbohydrate-associated cancer risks in the female right colon.

Acknowledgments

We thank Emily Baptiste and Jennifer Kelly for secretarial and administrative support.

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