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Original Contribution

Dietary Carbohydrate, Glycemic Index, and Glycemic Load in Relation to Risk of Colorectal Cancer in Women

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Diets with a high glycemic index and glycemic load have been hypothesized to be implicated in the etiology of colorectal cancer owing to their potential to increase postprandial glucose and insulin levels. Prospective data on glycemic index and glycemic load in relation to colorectal cancer risk are limited and inconsistent. Therefore, the authors prospectively investigated the associations of dietary carbohydrate, glycemic index, and glycemic load with the incidence of colorectal cancer among 61,433 Swedish women who were free of cancer in 1987–1990 and completed a 67-item food frequency questionnaire. During follow-up through June 2005, 870 incident cases of colorectal adenocarcinoma were diagnosed. Carbohydrate intake, glycemic index, and glycemic load were not associated with risk of colorectal cancer, colon cancer, or rectal cancer. The multivariate hazard ratios for colorectal cancer comparing the highest with the lowest quintile were 1.10 (95% confidence interval: 0.85, 1.44) for carbohydrate intake, 1.00 (95% confidence interval: 0.75, 1.33) for glycemic index, and 1.06 (95% confidence interval: 0.81, 1.39) for glycemic load. Results did not vary by body mass index. The findings from this prospective study do not support the hypothesis that a high carbohydrate intake, a high glycemic index, and a high glycemic load increase the risk of colorectal cancer.

carbohydrates; cohort studies; colorectal neoplasms; diet; glycemic index; prospective studies; Sweden

Abbreviation: CI, confidence interval.

Ample evidence indicates that insulin resistance and associated complications, such as elevated fasting glucose, insulin, insulin-like growth factor-I, and free fatty acid levels, are implicated in colorectal carcinogenesis (1, 2). Risk factors for colorectal cancer, including a high body mass index, visceral adiposity, lack of physical activity, and type 2 diabetes mellitus, are all linked to insulin resistance and hyperinsulinemia (2–4). Furthermore, epidemiologic studies have shown a two- to threefold increased risk of colorectal cancer associated with high blood glucose, insulin, and C-peptide (a marker of insulin secretion) levels (5–7). A recent study found that chronic insulin therapy was related to an elevated risk of colorectal cancer in type 2 diabetes patients (8).

The type and amount of carbohydrates determines an individual's glycemic response to a food or meal. The glycemic index was introduced as a way to quantify the glycemic responses induced by a fixed amount of carbohydrate in various foods (9). A related measure, the dietary glycemic load, is the product of the glycemic index of a food and the amount of carbohydrate in a serving (10). Glycemic load represents both quality and quantity of dietary carbohydrates (10). In healthy individuals, stepwise increases in glycemic load have been shown to predict stepwise

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elevations in postprandial blood glucose and insulin levels (11). Thus, diets with a high glycemic index and glycemic load might increase the risk of colorectal cancer, but results from case-control (12, 13) and cohort (14–17) studies have been inconsistent.

Because of inconsistent findings, we sought to prospectively examine the associations between carbohydrate intake, glycemic index, and glycemic load and the risk of colorectal cancer in the population-based Swedish Mammography Cohort.

MATERIALS AND METHODS

Study cohort

The Swedish Mammography Cohort was established between 1987 and 1990, when 66,651 women (74 percent of the source population) aged 40–76 years and living in central Sweden (Uppsala and Västmanland counties) completed a mailed questionnaire about diet, education, weight, and height (18). A second questionnaire was sent to all 56,030 women who were still alive and residing in the study area in the autumn of 1997; 39,227 women (70 percent) responded to this questionnaire. The study was approved by the Regional Ethical Review Board in Stockholm.

Dietary assessment

A food frequency questionnaire with 67 and 96 food items was sent to women at baseline and in 1997, respectively. In these questionnaires, women were asked to indicate how often, on average, they had consumed each food over the past year. There were open questions for some commonly consumed foods such as bread and dairy foods. The main difference between the baseline and second food frequency questionnaire was that the second questionnaire included more food items, particularly those for vegetables. Nutrient intakes were computed by multiplying the frequency of consumption of each food by the nutrient content of age-specific portion sizes. Values for the nutrient amounts in foods were obtained from the Swedish Food Administration Database (19). Glycemic load was calculated by multiplying the carbohydrate content of each food by its glycemic index value, multiplying that product by the frequency of consumption, and summing values for all foods. Each unit of glycemic load represents the equivalent of 1 g of carbohydrate from white bread. Glycemic index values were obtained from international tables (20). In addition, we created a variable we termed overall glycemic index by dividing the glycemic load by total carbohydrate intake; this variable represents the overall quality of the carbohydrate consumed for each participant. All dietary variables were adjusted for total energy intake by using the regression-residual method (21).

In a validity study of 129 women from the cohort, the correlation coefficient between the average intakes assessed by four 1-week diet records (3–4 months apart) and the baseline dietary questionnaire was 0.53 for carbohydrate intake. The validity of nutrient intake as assessed by the second food frequency questionnaire has been examined among 248 men in the study area; the correlation coefficient for carbohydrate intake was 0.73 between the dietary questionnaire and the average of fourteen 24-hour recall interviews (22).

Assessment of nondietary factors

On the baseline and second questionnaires, the participants reported their education, weight, and height. The second questionnaire also collected information on family history of colorectal cancer, history of diabetes, physical activity, smoking status and history, and use of aspirin, postmenopausal hormones, and dietary supplements. We calculated body mass index as weight in kilograms divided by the square of height in meters. Pack-years was calculated as the product of reported number of cigarettes smoked per day and the number of years of smoking.

Case ascertainment and follow-up

Incident cases of colorectal cancer were ascertained by computerized record linkage of the study population (using the national registration number assigned to each Swedish resident) with the national and regional Swedish Cancer registers. These cancer registers provide almost 100 percent complete case ascertainment in Sweden (23). Complementary data concerning localization of colonic carcinomas were obtained from the regional colon cancer registry in the study area. Only those women with colorectal adenocarcinomas were included as cases in this study. Proximal colon cancers were defined as tumors occurring from the cecum to the splenic flexure. Distal colon cancers included tumors of the splenic flexure, descending colon, and sigmoid colon. Rectal cancers included tumors of the rectosigmoid junction and rectum. Dates of death for deceased participants and dates of migration were ascertained by linkage to the Swedish Death and Population registers at Statistics Sweden.

Population for analysis

We excluded from the baseline cohort women who were outside the age range of 40−76 years ($n = 165$); those with an erroneous or missing national registration number ($n = 1{,}120$); and those for whom a date on the questionnaire ($n = 608$), date of moving out of the study area ($n = 79$), or date of death ($n = 16$) was lacking. After additional exclusion of women with an implausible total energy intake (i.e., three standard deviations from the $\log_e$-transformed mean energy intake, $n = 793$) and those diagnosed with cancer (other than nonmelanoma skin cancer) prior to baseline ($n = 2{,}437$), the study cohort for our primary analyses consisted of 61,433 women.

For the analyses based on information from the second questionnaire, 36,616 women were eligible after exclusion of those with an erroneous or missing national registration number ($n = 243$), those with an implausible total energy intake on the second dietary questionnaire ($n = 531$), and those diagnosed with cancer between baseline and January 1998 ($n = 1{,}837$).

TABLE 1. Age-standardized baseline characteristics of 61,433 women in the Swedish Mammography Cohort according to quintiles of overall glycemic index and dietary glycemic load in 1987–1990

Characteristic	Quintile of glycemic index					Quintile of glycemic load				
	1 (lowest)	2	3	4	5 (highest)	1 (lowest)	2	3	4	5 (highest)
No. of participants	12,189	12,615	12,277	11,991	12,361	12,251	12,327	12,274	12,298	12,283
Mean age (years)	52.0	52.9	53.9	54.5	55.4	50.7	52.0	53.6	55.1	57.1
Mean body mass index*	24.8	24.7	24.6	24.7	24.8	24.7	24.7	24.8	24.8	24.8
Postsecondary education (%)	15.5	13.9	13.2	11.0	9.3	14.0	13.5	12.7	11.7	10.9
Mean daily intake										
Total energy (kcal)	1,536	1,597	1,614	1,619	1,548	1,545	1,597	1,606	1,608	1,554
Alcohol†	4.4	3.9	3.6	3.5	3.3	4.9	4.0	3.5	3.1	2.8
Carbohydrate (g)	224	228	229	230	232	201	218	229	239	256
Cereal fiber (g)	15.4	17.5	18.2	18.4	19.0	14.5	16.6	17.7	18.9	20.6
Folate (μg)	266	246	232	220	203	232	234	235	234	234
Calcium (mg)	1,115	977	909	836	719	1,074	982	919	850	728
Magnesium (mg)	336	327	319	310	296	311	316	318	320	322
Red meat (g)	80	78	77	75	70	93	82	76	70	58

* Weight (kg)/height (m)^2.
† Among drinkers.

Statistical analysis

We used data from the baseline questionnaire in the primary analyses; in secondary analyses, we used data from the second questionnaire. We also conducted analyses by using simple updating of diet. Specifically, colorectal cancer incidence from baseline through 1997 was related to dietary intake from the baseline questionnaire, and outcomes from 1998 through June 2005 were related to dietary intake from the second questionnaire.

For each participant, person-time of follow-up was counted from the date of return of the baseline questionnaire (primary analyses and analyses using simple updating) or January 1998 (secondary analyses) to the date of diagnosis of colorectal cancer, death, migration, or June 30, 2005, whichever occurred first. Participants were classified into quintiles of carbohydrate intake, glycemic index, and glycemic load. We used Cox proportional hazards models (24) stratified by age in months and the year of entry into the cohort to calculate hazard ratios. In multivariate models, we simultaneously adjusted for the following covariates: education (less than high school, high school graduate, or more than high school), body mass index (kg/m^2; <23, 23–<25, 25–<30, or ≥ 30), total energy intake (continuous), and quartiles of intakes of alcohol, cereal fiber, folate, calcium, magnesium, and red meat. In subanalyses using data from the second questionnaire, we examined whether additional adjustment for physical activity, smoking, family history of colorectal cancer, and use of aspirin, postmenopausal hormones, and multivitamin supplements had any effect on the results.

The significance of linear trend across quintiles of dietary exposures was tested by assigning each participant the median value for her quintile and modeling this value as a continuous variable. Because adiposity and physical inactivity can be important determinants of insulin resistance and hyperinsulinemia (25), we hypothesized that these factors could modify the associations of carbohydrate intake, glycemic index, and glycemic load with colorectal cancer risk. We evaluated this hypothesis by conducting analyses stratified by body mass index (<25, 25–<30, or ≥ 30 kg/m^2) and physical activity (below median (≤ 1 hour/week) vs. above median (≥ 2 hours/week)). In addition, we performed analyses stratified by alcohol intake ($<$75th percentile (<4 g/day) vs. $\geq$75th percentile (≥ 4 g/day)) and smoking status (nonsmokers vs. current smokers). Analyses stratified by physical activity and smoking were based on data from the second questionnaire. The likelihood ratio test was used to assess the significance of the interactions terms. The models presented all satisfied the proportional hazards assumption. All statistical procedures were carried out with SAS software, version 9.1 (SAS Institute, Inc., Cary, North Carolina). All p values are two sided.

RESULTS

Baseline characteristics of the study population according to quintiles of glycemic index and glycemic load are presented in table 1. In general, relative to women with a low glycemic index and a low glycemic load, those with a higher glycemic index and glycemic load were older and less likely to have a postsecondary education. They also had higher intakes of carbohydrates and cereal fiber but lower intakes of alcohol, calcium, and red meat. Women with a high glycemic index also had lower intakes of folate and magnesium compared with those with a low glycemic index.

During 963,426 person-years of follow-up (mean, 15.7 years) of 61,433 participants, we ascertained 870 incident

TABLE 2. Multivariate* hazard ratios of colorectal cancer according to quintiles of carbohydrate intake, overall glycemic index, and dietary glycemic load among 61,433 women in the Swedish Mammography Cohort from 1987–1990 through June 2005

	No. of person-years	Colorectal cancer			Colon cancer†			Rectal cancer†		
		No. of cases	HR‡	95% CI‡	No. of cases	HR	95% CI	No. of cases	HR	95% CI
Carbohydrate intake (g/day)										
<211	194,773	155	1.00	Referent	106	1.00	Referent	52	1.00	Referent
211–222	195,598	166	1.01	0.80, 1.27	122	1.10	0.84, 1.45	46	0.80	0.53, 1.20
223–233	191,768	165	0.98	0.77, 1.24	113	1.00	0.75, 1.34	53	0.87	0.58, 1.32
234–245	191,924	185	1.05	0.83, 1.34	114	0.97	0.72, 1.31	71	1.12	0.74, 1.69
≥246	189,363	199	1.10	0.85, 1.44	139	1.14	0.83, 1.57	61	0.94	0.59, 1.50
p-trend			0.45			0.64			0.78	
Glycemic index										
<75.8	192,853	151	1.00	Referent	109	1.00	Referent	45	1.00	Referent
75.8–78.3	199,223	161	0.96	0.76, 1.22	101	0.83	0.62, 1.10	60	1.20	0.80, 1.81
78.4–80.6	192,946	173	0.92	0.72, 1.17	124	0.86	0.64, 1.15	50	0.96	0.61, 1.50
80.7–83.3	187,821	173	0.87	0.67, 1.13	116	0.76	0.55, 1.04	58	1.08	0.68, 1.71
≥83.4	190,583	212	1.00	0.75, 1.33	144	0.84	0.60, 1.18	70	1.32	0.80, 2.17
p-trend			0.55			0.21			0.62	
Glycemic load										
<164	194,565	152	1.00	Referent	111	1.00	Referent	44	1.00	Referent
164–175	196,016	168	0.98	0.78, 1.24	118	0.95	0.72, 1.25	53	1.05	0.69, 1.59
176–186	192,505	156	0.85	0.67, 1.09	100	0.76	0.55, 1.02	56	1.04	0.69, 1.48
187–199	192,033	174	0.89	0.69, 1.14	112	0.77	0.57, 1.04	62	1.09	0.70, 1.71
≥200	188,305	220	1.06	0.81, 1.39	153	0.97	0.70, 1.32	68	1.20	0.74, 1.95
p-trend			0.78			0.66			0.45	

* Multivariate hazard models were stratified by age in months and date of enrollment and included the following: education (less than high school, high school graduate, or more than high school), body mass index (weight (kg)/height $(m)^2$; <23, 23–<25, 25–<30, or ≥30), total energy intake (continuous), and quartiles of intakes of alcohol, cereal fiber, folate, calcium, magnesium, and red meat.

† Seven women who were diagnosed with both colon cancer and rectal cancer were included in analysis of both cancer sites.

‡ HR, hazard ratio; CI, confidence interval.

cases of colorectal adenocarcinoma, including 594 cases of colon cancer (286 proximal colon, 210 distal colon, and 98 cases for which the site in the colon was not specified), and 283 cases of rectal cancer (seven women were diagnosed with both colon and rectal cancer).

After adjustment for age only, glycemic index, but not carbohydrate intake or glycemic load, was associated with an increased risk of colorectal cancer. The age-adjusted hazard ratios for the highest compared with the lowest quintile were 0.93 (95 percent confidence interval (CI): 0.75, 1.15) for carbohydrate intake, 1.23 (95 percent CI: 1.00, 1.53) for glycemic index, and 1.04 (95 percent CI: 0.83, 1.28) for glycemic load. The relation between glycemic index and colorectal cancer risk did not remain in multivariate models (table 2). The results for carbohydrate intake, glycemic index, and glycemic load did not change appreciably when we excluded the first 3 years of follow-up. When we categorized data for women into deciles to examine more extreme levels of exposure, the multivariate hazard ratios of colorectal cancer for the highest versus the lowest decile were 1.02 (95 percent CI: 0.71, 1.47) for carbohydrate intake, 1.02 (95 percent CI: 0.69, 1.49) for glycemic index, and 0.90 (95 percent CI: 0.63, 1.31) for glycemic load. Stratifying by cancer site (colon and rectum; table 2) and colon subsite (proximal and distal; table 3) showed no significant associations. Carbohydrate intake, glycemic index, and glycemic load had no significant relation with colorectal cancer regardless of body mass index and alcohol consumption (p-interaction > 0.29 for all).

A total of 266,022 person-years (mean, 7.3 years) and 297 incident colorectal cancer cases were available for the analyses based on data from the second questionnaire. As in the primary analysis, we observed no association between carbohydrate intake or glycemic load and risk of colorectal cancer; the multivariate hazard ratios for the top compared with the bottom quintile were 0.88 (95 percent CI: 0.56, 1.37) for carbohydrate intake and 1.09 (95 percent CI: 0.68, 1.74) for glycemic load. Glycemic index was positively associated with colorectal cancer risk; the multivariate hazard ratio comparing the highest with the lowest quintile of glycemic index was 1.95 (95 percent CI: 1.19, 3.20; p-trend $= 0.01$). This association remained after additional

TABLE 3. Multivariate* hazard ratios of proximal and distal colon cancer according to quintiles of carbohydrate intake, overall glycemic index, and dietary glycemic load among 61,433 women in the Swedish Mammography Cohort from 1987–1990 through June 2005

	Quintile of intake									
	1 (lowest)	2		3		4		5 (highest)		*p*-trend
		HR†	95% CI†	HR	95% CI	HR	95% CI	HR	95% CI	
Carbohydrate intake										
Proximal colon‡	1.00	1.39	0.92, 2.10	1.31	0.86, 2.00	0.99	0.62, 1.56	1.23	0.76, 1.97	0.83
Distal colon‡	1.00	1.00	0.63, 1.58	0.84	0.52, 1.37	1.10	0.67, 1.80	1.51	0.89, 2.56	0.14
Glycemic index										
Proximal colon	1.00	1.19	0.77, 1.84	1.03	0.66, 1.62	0.92	0.57, 1.48	0.97	0.58, 1.63	0.41
Distal colon	1.00	0.61	0.38, 1.00	0.77	0.48, 1.23	0.57	0.34, 0.98	0.81	0.46, 1.40	0.25
Glycemic load										
Proximal colon	1.00	1.28	0.85, 1.92	0.93	0.60, 1.44	0.78	0.49, 1.24	1.00	0.62, 1.62	0.50
Distal colon	1.00	0.74	0.47, 1.17	0.71	0.44, 1.16	0.75	0.45, 1.25	1.18	0.69, 2.00	0.45

* Multivariate hazard models were stratified by age in months and date of enrollment and included the following: education (less than high school, high school graduate, or more than high school), body mass index (weight (kg)/height (m)^2; <23, 23–<25, 25–<30, or ≥30), total energy intake (continuous), and quartiles of intakes of alcohol, cereal fiber, folate, calcium, magnesium, and red meat.

† HR, hazard ratio; CI, confidence interval.

‡ Total number of cases: 286 proximal colon cancer and 210 distal colon cancer.

adjustment for physical activity, smoking status and pack-years of smoking, family history of colorectal cancer, and use of aspirin, postmenopausal hormones, and multivitamin supplements (hazard ratio = 1.92, 95 percent CI: 1.17, 3.16) but was attenuated when we excluded the first 3 years of follow-up (hazard ratio = 1.58, 95 percent CI: 0.88, 2.85). Removing women with diabetes from the analysis slightly strengthened the association between glycemic index and colorectal cancer risk; the multivariate hazard ratio comparing extreme quintiles of glycemic index was 1.70 (95 percent CI: 0.93, 3.11; p-trend = 0.04) after excluding diabetics and the first 3 years of follow-up. The associations of carbohydrate intake, glycemic index, and glycemic load with colorectal cancer risk did not differ appreciably across strata of physical activity or smoking status (p-interaction > 0.26 for all).

To examine whether carbohydrate intake, glycemic index, and glycemic load close in time to colorectal cancer diagnosis is important, we used simple updating of diet. In these analyses, the multivariate hazard ratios of colorectal cancer comparing extreme quintiles were 1.12 (95 percent CI: 0.87, 1.45; p-trend = 0.33) for carbohydrate intake, 1.26 (95 percent CI: 0.96, 1.66; p-trend = 0.25) for glycemic index, and 1.11 (95 percent CI: 0.85, 1.44; p-trend = 0.34) for glycemic load.

DISCUSSION

In this large, population-based cohort of Swedish women, we observed no association between carbohydrate intake, glycemic index, or glycemic load and risk of colorectal cancer. Although there was a statistically significant positive association between glycemic index and colorectal cancer risk in a subanalysis with 7.3 years of follow-up of women who completed a follow-up questionnaire, this relation was weakened after excluding the first 3 years of follow-up.

Results from previous studies of glycemic index and glycemic load have been inconsistent. Our findings are broadly in agreement with results from two large prospective cohort studies of Canadian (14) and US (16) women with up to 20 years of follow-up, in which neither glycemic index nor glycemic load was associated with colorectal cancer risk. However, another cohort study of US women, with 174 colorectal cancer cases and 7.9 years of follow-up (15), and two case-control studies (12, 13) reported a statistically significant increase in colorectal cancer risk associated with a high glycemic index and/or a high glycemic load. In the Health Professionals Follow-up Study with 14 years of follow-up (16), men in the highest quintile of glycemic load had a non-significant elevated risk of colorectal cancer (relative risk = 1.32, 95 percent CI: 0.98, 1.78) compared with men in the lowest quintile. In the Iowa Women's Health Study (17), there was no overall association of glycemic index or glycemic load with colorectal cancer risk; however, a high glycemic index and a high glycemic load were associated with a statistically significant increased risk of colorectal cancer among obese women (body mass index ≥30 kg/m^2).

This study has several strengths. One is the large sample size, which enabled us to examine associations according to subsites in the colorectum and across strata of body mass index with reasonably high statistical power. Second, the prospective design eliminated recall bias, which could be of concern in case-control studies. Third, the virtually complete follow-up of the study population minimized the possibility that our findings were biased by differential loss to follow-up. Finally, in subanalysis using data from a follow-up questionnaire, many putative colorectal cancer risk factors could be controlled for, although these adjustments had minimal impact on the results. A potential limitation of any

study is that dietary intakes are measured with error, which will inevitably lead to some degree of misclassification of exposures and to an underestimation of any true relation. Moreover, the glycemic index values of some foods are currently based on results reported in only one or two studies, and those studies often had small sample sizes (20). Therefore, misclassification in our study could also be caused by random variation in the estimated glycemic index values.

The glycemic index was developed to rank foods according to their effects on postprandial blood glucose and, consequently, insulin concentrations. However, some foods (e.g., protein- and fat-rich foods) have been shown to elicit insulin responses that are not proportional to their glycemic responses (26). An insulin index of foods may improve the accuracy of estimating the insulin response induced by consumption of different foods (26). At present, the number of foods that have been analyzed for their insulin index is limited.

In summary, although available evidence implicates hyperglycemia and hyperinsulinemia in colorectal cancer etiology, the results from this prospective study do not indicate an association between increasing glycemic load, which has been shown to predict postprandial blood glucose and insulin concentrations (11), and the risk of colorectal cancer in women. We also found no increase in colorectal cancer risk associated with a high carbohydrate intake or a high glycemic index. Future studies should examine the insulin index of foods in relation to cancer risk.

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