

# Dietary Glycemic Load, Carbohydrate, Sugar, and Colorectal Cancer Risk in Men and Women

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## Abstract

Hyperinsulinemia may explain excess colorectal cancer among individuals who are overweight or inactive. Recent studies have observed elevated colorectal cancer risk among individuals with elevated insulin levels 2 hours after oral glucose challenge or with elevated plasma C-peptide levels. The effect of consuming a high glycemic diet on colorectal risk, however, remains uncertain. Two prospective cohort studies, the Nurses' Health Study and the Health Professionals Follow-up Study, contributed up to 20 years of follow-up. After exclusions, 1,809 incident colorectal cancers were available for analyses. Dietary glycemic load (GL) was calculated as a function of glycemic index (postprandial blood glucose response as compared with a reference food), carbohydrate content, and frequency of intake of individual foods reported on food frequency questionnaires. Multivariable Cox proportional hazards models were used to

adjust for potential confounders. Intakes of dietary carbohydrate, GL, overall glycemic index, sucrose, and fructose were not associated with colorectal cancer risk in women. A small increase in risk was observed in men with high dietary GL (multivariate relative risk, 1.32; 95% confidence interval, 0.98-1.79; highest versus lowest quintile), sucrose or fructose (multivariate relative risk, 1.37; 95% confidence interval, 1.05-1.78; highest versus lowest quintile of fructose,  $P = 0.008$ ). Associations were slightly stronger among men with elevated body mass index ( $\geq 25$  kg/m<sup>2</sup>). Results among women were similar after stratifying by body mass index or physical activity. High intakes of GL, fructose, and sucrose were related to an elevated colorectal cancer risk among men. For women, however, these factors did not seem to increase the risk of colorectal cancer. (Cancer Epidemiol Biomarkers Prev 2005;14(1):138-43)

## Introduction

Substantial evidence indicates that hyperinsulinemia may play an important role in colorectal cancer (1, 2). Many of the established risk factors of colorectal cancer, including obesity and physical inactivity, directly influence insulin levels. Several studies have observed elevated risks of colon cancer among those with a history of type 2 diabetes mellitus (3-8). Studies examining insulin levels in blood (using 2-hour insulin test) or plasma C-peptide levels (a marker of insulin secretion) have reported 2- to 3-fold elevated risk of colorectal cancer for those in the highest categories (9-11).

Dietary intake can influence insulin levels, especially among individuals who are insulin resistant due to other factors, such as obesity. Dietary glycemic load (GL), which is a quantitative measure of the glycemic effect of food, has been associated with triglycerides and high-density lipoprotein levels (12-14), as well as the risk of diabetes (15, 16) and heart disease (17). Two case-control studies reported positive associations between intakes of GL and colorectal cancer risk (18, 19). In a recent prospective study, a relative risk (RR) of 2.85 [95% confidence interval (95% CI), 1.40-5.80] was observed for colorectal cancer risk comparing the highest to the lowest quintile of GL intake (20). In another prospective study, GL was not related to colorectal cancer risk, although a slight increase in risk was observed among those with distal colon cancer (21). Moreover, no association was observed between GL, glycemic index (GI), or carbohydrate intake and

the risk of distal colorectal adenoma in the Nurses' Health Study (NHS; ref. 22).

In a recent cross-sectional analysis in the NHS I and II, we observed statistically significant higher plasma C-peptide levels among women with high intakes of fructose and GL (23). To provide additional data on the role of the quality and quantity of carbohydrates on colorectal cancer risk, we examined the association between dietary carbohydrate, sucrose, fructose, GI, and GL and the risk of colon and rectal cancers in two large prospective cohorts with repeated diet measures and up to 20 years of follow-up.

## Material and Methods

**Study Populations.** Two ongoing cohort studies provided data for our analyses, the Health Professionals Follow-up Study (HPFS) and the NHS I. The HPFS was initiated in 1986 when 51,529 U.S. men ages 40 to 75 years responded to a mailed questionnaire with detailed information on individual characteristics and lifestyle habits. Fifty-eight percent of the men in the HPFS cohort are dentists, and the other professionals include optometrists, osteopaths, podiatrists, pharmacists, and veterinarians. The NHS I was initiated in 1976 when 121,700 female registered nurses ages 30 to 55 years responded to a mailed questionnaire. Information on individual characteristics and habits such as age, marital status, weight, height, medical history, medication use, menopausal status, physical activity, and vitamin use was obtained from the baseline or from follow-up questionnaires. In both cohorts, changes in lifestyle habits and information on disease onset have been obtained biennially since study onset using mailed questionnaires.

For each of the follow-up questionnaires, up to six mailings were sent to nonrespondents. Most of the deaths

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in this cohort were reported by family members or by the postal service in response to the follow-up questionnaires. In addition, the National Death Index was searched for nonrespondents; this method has been shown to have a sensitivity of 98% (i.e., the National Death Index did not identify 2% of deaths; ref. 24).

The 1986 baseline questionnaire mailed to the HPFS cohort included a food frequency questionnaire (FFQ, which was completed by all participants). In NHS I, the dietary questionnaire was included in the 1980 mailing, which was completed by 98,462 participants. We excluded participants with implausibly high or low caloric intake (<500 or >3,500 kcal/d for women; <800 or >4,200 kcal/d for men). In addition, individuals who reported a previous cancer diagnosis (other than nonmelanoma skin cancer), ulcerative colitis, Crohn's disease, or familial polyposis syndrome at baseline were also excluded, which left 83,927 women and 47,422 men eligible for analysis.

**Dietary Assessment.** A 61-item FFQ was mailed to all NHS I participants in 1980, and a 131-item FFQ was mailed to HPFS participants in 1986. Follow-up FFQs were mailed to NHS I in 1984 and 1986 and every 4 years thereafter. The 1984 NHS I FFQ was expanded to include a larger number of food items (116 items) and resembles the HPFS FFQ. The HPFS follow-up FFQs are mailed every 4 years after 1986. In the FFQ, participants are asked to report their average frequency of intake over the previous year for a specified serving size of each food. Individual nutrient intakes are calculated by multiplying the frequency of each food consumed by the nutrient content of the specified portion size [obtained from the U.S. Department of Agriculture (25) and supplemented with information from manufactures] and are summed to include contributions from all foods. Nutrient values are adjusted for total energy intake. Total fructose intake was calculated as free fructose plus fructose from sucrose intake.

The GI is based on the postprandial blood glucose response compared with a reference food. GI values for foods that appear in the FFQ were either obtained from published estimates (26), or from direct testing of food items at the Nutrition Center of the University of Toronto (D. Jenkins). The GI value is calculated by the following formula:

$$GI = \frac{\sum \text{incremental blood glucose under the curve of test food}}{\sum \text{incremental blood glucose area under the curve of reference food}} \times 100\%$$

The GI value for a meal containing mixed foods can be predicted as the weighed mean of the GI values for each of the component foods (27, 28). When GI values vary for a specific food, we use the average GI values (using the same standard reference food) that are most representative of our populations (i.e., values available on North American foods and from healthy individuals, and when possible, from the time period closest to the questionnaire).

Using these GI values, we also calculated the average dietary GL during the past year for each participant by multiplying the carbohydrate content (grams per serving) for each food by its GI value; multiplying that product by the frequency of consumption (servings of that food per day), and summing values for all food items reported:

$$\begin{aligned} \text{Individual dietary GL} &= \text{sum of [GI} \\ &\quad \times (\text{carbohydrate content of food}) \\ &\quad \times (\text{servings of food/d})] \end{aligned}$$

Each unit of GL represents the equivalent of 1 g of carbohydrate from white bread (12). In addition, the overall dietary GI was calculated by dividing GL by the total

amount of carbohydrate; this value represents the overall quality of carbohydrate intake for each participant.

In a validity study of 173 women from the NHS I, a FFQ was compared with four 1-week diet records. For individual food items that have high GI values, the correlation coefficients between the average intake assessed by two 1-week diet records completed 6 months apart and the FFQ were as follows: 0.71 for white bread, 0.77 for dark bread, 0.66 for potatoes, 0.84 for orange or grapefruit juice, and 0.56 for noncarbonated fruit drinks (includes fruit-flavored punch; ref. 29). Correlation coefficients for total carbohydrate and sucrose were 0.45 and 0.54, respectively, comparing two 1-week diet records and the FFQ in the same validation study of women (30). Similar correlations were observed in a validation study of men in the HPFS using two 1-week dietary records and comparing to a FFQ ( $r = 0.62$  for energy-adjusted carbohydrate; ref. 31).

**Assessment of Nondietary Factors.** Height, current weight, smoking history, aspirin use, and physical activity were initially reported at baseline or in 1980. Family history of colorectal cancer was ascertained in 1982, 1988, 1992, 1996, and 2000 in the women and in 1986, 1990, 1992, 1996, and 2000 in the men. During follow-up, data on current weight and smoking status were obtained from the biennial mailed questionnaires. We estimated body mass index (BMI) from weight and height ( $\text{kg}/\text{height in m}^2$ ) as a measure of total adiposity. Participants were asked about history of diabetes at baseline and in all subsequent questionnaires.

For physical activity in the NHS I, we derived a score based on questions asked in the 1980 questionnaire. The physical activity variable from the 1980 questionnaire has been shown to predict the risk of noninsulin-dependent diabetes mellitus in this cohort of women (32). In 1986, the questionnaires mailed to the two cohorts included a section assessing physical activity in detail. From these questions, we calculated a weekly physical activity (MET-hour) score by multiplying the time spent on each activity by the typical energy expenditure for that activity expressed in metabolic equivalents (MET). The MET is the caloric expenditure per kilogram of body weight per hour of activity, divided by the equivalent per hour at rest.

The reliability and validity of the assessment of physical activity as used in these two cohorts were tested among 147 participants of NHS II, a similar cohort to NHS I but participants were younger nurses. The correlation between physical activity reported on the questionnaire and that recorded in the four 1-week diaries was 0.62 (33). The validity of the physical activity questionnaire used in the HPFS in 1986 was assessed among 238 randomly selected participants by comparisons with four 1-week activity diaries, four 1-week activity recalls, and resting and postexercise pulse rates (34). The correlation for vigorous physical activity with the activity diaries was 0.58. Vigorous activity assessed by the questionnaire was correlated with resting pulse ( $r = -0.45$ ) and postexercise pulse ( $r = -0.41$ ).

**Identification of Colorectal Cancer Cases.** Participants were asked to report specified medical conditions, including cancers that were diagnosed in the 2-year period between each follow-up questionnaire. Whenever a participant (or next-of-kin for decedents) reported a diagnosis of colorectal cancer, we asked for permission to obtain related medical records or pathology reports. If permission to obtain records was denied, we attempted to confirm the self-reported cancer with an additional letter or phone call to the participant. If the primary cause (or secondary cause) of death as reported by a death certificate was a previously unreported colorectal cancer case, we contacted a family member to obtain permission to retrieve medical records, or in the least to confirm the cancer diagnosis. A physician reviewed the medical records to verify information on histologic type, anatomic location, and stage of the cancer. Colorectal cancers with missing anatomic location

(<15%) were grouped with the colon cancers. In the NHS I, a total of 1,113 colorectal cancer cases (870 colon and 243 rectal) were diagnosed between baseline (1980) and May 31, 2000, and in the HPFS, 696 colorectal cancer cases (561 colon and 135 rectal) were diagnosed between baseline and January 31, 2000.

**Statistical Analysis.** We computed person-time of follow-up for each participant from the return date of the baseline questionnaire to the date of colorectal cancer diagnosis, death from any cause, or the end of follow-up (May 31, 2000 in NHS; January 31, 2000 in HPFS), whichever came first. Incidence rates of colorectal cancer were calculated by dividing the number of incident cases by the number of person-years in each category of dietary exposure. We computed the RR for each of the upper categories by dividing the rates in these categories by the rate in the lowest category.

R Rs adjusted for potential confounders were estimated using Cox proportional hazards models stratified on age in years. In these models, we included covariates that have been previously associated with colorectal cancer in the cohorts, using previously defined categories (35); these include BMI, physical activity, smoking (pack-years of smoking before age 30), family history of colorectal cancer, height, alcohol intake, history of colonoscopy or sigmoidoscopy, and dietary intakes of folate, calcium, processed meats, and beef, pork or lamb as a main dish. In addition, we adjusted for aspirin use in men (36) and women (37), and menopausal status and postmenopausal hormone use in women. All *P*s are based on two-sided tests. We did tests for trend by assigning the median value to each category and modeling this variable as a continuous variable.

We did additional analyses using the 1984 dietary questionnaire as baseline for the NHS I (because the 1984 FFQ had more food items), and separately, using cumulative updating of the dietary exposures with follow-up data (1984, 1986, 1990, and 1994 in the NHS I and 1990 and 1994 in the HPFS; ref. 38).

## Results

Age, height, BMI, calcium, and total caloric intake did not vary appreciably across quintiles of dietary GL in either cohort (Table 1). Men and women with higher GL were less likely to smoke, consumed less alcohol and total fat, but had higher intakes of carbohydrate and folate (Table 1). Other baseline characteristics varied differently by cohort; for example, exercise level did not vary across GL in the women but was positively associated with dietary GL in the men (Table 1).

No associations were observed for dietary carbohydrate, GL, GI, sucrose, or fructose and the risk of colorectal cancer in the NHS I (Table 2). In the HPFS, men with higher intakes of GL, sucrose or fructose had a slightly elevated risk of colorectal cancer (Table 2). R Rs in the age-adjusted models were not elevated (data not shown), but these estimates were confounded by alcohol intake; adding alcohol intake to the multivariate model accounted for almost all of the change in the risk estimate. The multivariate RR for a 10-unit increment in GL was 1.03 (95% CI, 1.00-1.06) in men and 1.05 (95% CI, 0.98-1.12) in women.

In men, associations between GL and sucrose intakes were more apparent for rectal cancer risk (Table 2). For fructose intake, the increase in risk was stronger for colon cancer (Table 2). When stratifying by colon site (proximal and distal), no statistically significant associations were observed in either cohort (Table 3).

Although we did not control for diabetes in the multivariate models in Tables 2 and 3, adding this variable did not change the estimates. Removing diabetics from the analyses slightly strengthened the association between fructose intake and risk of colorectal cancer in men (R Rs for the top four quintile: 1.04, 1.21, 1.29, and 1.40). We observed no associations for the dietary factors of interest in either cohort when repeating the analyses using cumulative updating of dietary

**Table 1. Baseline characteristics according to quintile of energy-adjusted GL among NHS cohort participants and HPFS participants**

Characteristics	NHS (quintiles of GL*)			HPFS (quintiles of GL*)		
	1	3	5	1	3	5
No. individuals	16,776	16,782	16,735	9,476	9,499	9,444
Glycemic load (mean)	76	119	175	127	177	230
Age (y)	47	47	47	54	54	54
Height (in.)	65	65	64	70	70	70
BMI (kg/m <sup>2</sup> )	24	24	25	26	26	25
Exercise <sup>†</sup>	3.2	3.2	3.0	18	21	24
Current smokers (%)	35	26	27	17	8.5	5.4
Pack-years of cigarettes <sup>‡</sup>	7.5	6.9	6.8	12	11	11
Family history (%)	8.0	7.8	8.0	7.9	8.3	8.9
Endoscopy history (%)	15	15	15	27	28	29
Diabetes (%)	2.6	2.5	2.0	4.1	3.0	2.2
Aspirin use (%)	51	51	51	30	29	28
Mean daily intake						
Calories (kcal)	1,552	1,583	1,536	1,957	2,024	1,930
Total fat (g) <sup>§</sup>	82	70	57	82	73	58
Carbohydrate (g) <sup>§</sup>	108	156	201	179	235	292
Protein (g) <sup>§</sup>	84.8	77.1	64.7	99.8	93.3	83.4
Alcohol (g)	12	5.4	3.1	23	9.3	4.3
Total calcium (mg) <sup>§</sup>	696	775	674	868	910	911
Total folate (μg) <sup>§</sup>	344	372	378	435	476	539
Red meat (servings/wk) <sup>¶</sup>	3.8	2.5	1.5	2.5	1.8	2.1
Cereal fiber (g)	1.6	2.6	2.9	3.8	5.8	8.2
RGI	68	73	78	72	76	79

NOTE: All variables (except age) are age-standardized; mean values are presented for continuous variables and percentages are shown for categorical variables.

\*Quintile cut points NHS: <93, 93-111, 112-127, 128-148, >148; quintile cut points HPFS: <147, 147-167, 168-185, 186-206, >206.

<sup>†</sup>Exercise in NHS is in hours per week and in METs/week for the HPFS.

<sup>‡</sup>Pack-years are calculated for current and past smokers before age 30.

<sup>§</sup>Energy-adjusted nutrient values.

<sup>¶</sup>Beef, pork, or lamb as main dish.

**Table 2. Multivariate relative risk of colorectal cancer in relation to intakes of GL, GI, carbohydrate, and fructose in the NHS (1980-2000) and HPFS (1986-2000)**

	Quintiles of intake					95% CI*	P
	1	2	3	4	5		
<b>GI</b>							
<b>Men</b>							
Index/d <sup>†</sup>	69	74	76	78	82		
Colorectal (n = 683)	1.0	1.06	1.09	1.08	1.14	0.88-1.48	0.33
Colon (n = 552)	1.0	1.11	1.16	1.13	1.13	0.84-1.51	0.40
Rectal (n = 131)	1.0	0.91	0.85	0.89	1.21	0.68-2.15	0.65
<b>Women</b>							
Index/d <sup>†</sup>	65	71	74	77	81		
Colorectal (n = 1,096)	1.0	0.84	1.02	1.00	1.08	0.87-1.34	0.27
Colon (n = 858)	1.0	0.82	1.10	1.04	1.06	0.83-1.36	0.29
Rectal (n = 238)	1.0	0.91	0.75	0.88	1.14	0.73-1.78	0.70
<b>GL</b>							
<b>Men</b>							
Load/d	131	158	177	195	223		
Colorectal	1.0	1.13	1.36	1.36	1.32	0.98-1.79	0.04
Colon	1.0	1.07	1.42	1.32	1.25	0.88-1.25	0.11
Rectal	1.0	1.32	1.07	1.48	1.61	0.82-3.17	0.17
<b>Women</b>							
Load/d	80	103	119	137	167		
Colorectal	1.0	1.03	1.10	0.91	0.89	0.71-1.11	0.15
Colon	1.0	1.06	1.08	0.79	0.89	0.69-1.15	0.11
Rectal	1.0	0.93	1.19	1.40	0.87	0.52-1.44	0.95
<b>Carbohydrate</b>							
<b>Men</b>							
g/d	182	214	234	256	288		
Colorectal	1.0	1.11	1.21	1.24	1.27	0.93-1.72	0.11
Colon	1.0	1.05	1.23	1.22	1.21	0.85-1.71	0.20
Rectal	1.0	1.31	1.09	1.29	1.45	0.73-2.38	0.34
<b>Women</b>							
g/d	110	137	155	174	202		
Colorectal	1.0	1.07	1.11	0.94	0.87	0.68-1.11	0.15
Colon	1.0	1.07	1.09	0.88	0.86	0.65-1.13	0.14
Rectal	1.0	1.09	1.18	1.18	0.91	0.53-1.55	0.78
<b>Sucrose</b>							
<b>Men</b>							
g/d	26	36	44	53	67		
Colorectal	1.0	1.15	1.19	1.40	1.30	0.99-1.69	0.03
Colon	1.0	1.18	1.20	1.36	1.25	0.93-1.68	0.13
Rectal	1.0	1.07	1.21	1.62	1.47	0.81-2.66	0.11
<b>Women</b>							
g/d	17	26	33	41	55		
Colorectal	1.0	1.05	0.98	0.98	0.89	0.72-1.11	0.10
Colon	1.0	1.17	1.00	0.98	0.99	0.78-1.26	0.49
Rectal	1.0	0.69	0.90	0.97	0.62	0.39-0.99	0.17
<b>Fructose</b>							
<b>Men</b>							
g/d	29	40	48	56	72		
Colorectal	1.0	1.02	1.19	1.26	1.37	1.05-1.78	0.008
Colon	1.0	1.01	1.25	1.25	1.38	1.03-1.86	0.02
Rectal	1.0	1.13	0.99	1.28	1.31	0.72-2.38	0.33
<b>Women</b>							
g/d	22	33	41	50	68		
Colorectal	1.0	0.94	0.93	0.80	0.87	0.71-1.07	0.20
Colon	1.0	0.92	0.88	0.80	0.86	0.68-1.09	0.15
Rectal	1.0	1.03	1.15	0.81	0.92	0.59-1.44	0.47

NOTE: Multivariate RRs are relative risks adjusted for age, family history of colon cancer, prior endoscopy screening, aspirin use, height, BMI, pack-years of smoking before age 30, physical activity, and intakes of cereal fiber, alcohol, calcium, folate, processed meat and beef, pork or lamb as main dish.

\*95% CI for q5 versus q1.

<sup>†</sup>Intakes are provided for medians of quintiles.

exposures, or when using 1984 as baseline for the NHS I cohort (data not shown).

We considered whether menopausal status and hormone use altered the association between the dietary variables in Table 2 and colorectal cancer risk in women. Among

premenopausal women, an association between carbohydrate intake and colorectal cancer risk was apparent (multivariate RR, 2.03; 95% CI, 1.01-4.06, highest versus lowest quintile), but no associations were observed for dietary GL, fructose or sucrose intake. No associations were observed for any of the dietary variables in postmenopausal women when stratifying on hormone use (never, past, and current use).

The effect of diet on insulin response may vary across strata of BMI or physical activity as these two factors can be strong determinants of insulin resistance, which can magnify the adverse influence of a high GL. We examined this possibility by stratifying our analyses into two BMI and physical activity strata, separately. In men, the multivariate RR for colorectal cancer for the highest versus lowest quintile of fructose intake was 1.47 (95% CI, 1.05-2.07) in the elevated BMI strata (BMI  $\geq 25$  kg/m<sup>2</sup>). No association was apparent in the low BMI strata (multivariate RR, 1.09; 95% CI, 0.69-1.71 for extreme quintile comparison of fructose intake). Stratifying by BMI resulted in a similar pattern for GL and sucrose intakes in men. In contrast, no clear pattern emerged across quintiles of GL, sucrose, or fructose when stratifying on physical activity level. The BMI and physical activity stratified analyses in the NHS yielded no associations (data not shown).

In a recent study by Ma et al. (9) an interaction was reported between plasma C-peptide and alcohol intake in men (RR, 3.9; 95% CI, 1.3-11.7 for high C-peptide and high alcohol intake versus low C-peptide and low alcohol intake). Given these findings, there is a possibility that alcohol exacerbates the effect of consuming a high GL or sugar diet. We examined this in men and observed that among those with elevated alcohol intake ( $\geq 20$  g/d), the risk of colorectal cancer increased across quintiles of GL, sucrose, fructose and carbohydrate intakes (*P*s for tests of trend = 0.008, 0.02, 0.01, and 0.04, respectively). In this strata of alcohol drinkers ( $\geq 20$  g/d), the RR for the highest quintile of GL was 2.11 (95% CI, 0.79-5.63), compared with the lowest quintile in that strata. In contrast, trends were weak between dietary intakes of glucose load or sugar and risk of colorectal cancer among men with low alcohol consumption (data not shown). Among women with a high alcohol intake ( $\geq 20$ g/d), elevated GL, sucrose, or fructose intakes were associated with slightly higher risks of colorectal cancer, although these were not statistically significant (highest versus lowest quintile: multivariate RRs, 1.29; 95% CI, 0.58-2.90 for GL; multivariate RR, 1.39; 95% CI, 0.62-3.10 for sucrose intake; multivariate RR, 1.56; 95% CI, 0.79-3.06 for fructose intake).

## Discussion

We observed a 27% to 37% increase in the risk of colorectal cancer with increasing intakes of carbohydrate, GL, sucrose or fructose in men (*P*s for test of trend were significant for all except carbohydrate intake) but no associations were observed in women. No statistically significant associations were observed for distal or proximal cancer in either gender. In the NHS I, stratifying by BMI, physical activity, or hormone use did not change the associations. In men, stratifying by BMI led to slightly stronger associations for those who were overweight (BMI  $\geq 25$ ) and weaker associations for those with normal weight.

Although a recent cohort study observed no association for dietary GL and colorectal cancer (21), another cohort study (20) and two previous case-control studies reported elevated risks of colorectal cancer with higher intake of GL (18, 19). RRs for high versus low intake of GL ranged between 1.7 and 2.9 in these studies (18-20). A number of studies have also reported significantly elevated risks of colorectal cancer for individuals with a high, compared with low, sucrose intake (39-44). The associations between dietary sucrose and

**Table 3. Multivariate RR of colon cancer by site in relation to intakes of GL, GI, carbohydrate, and fructose in the NHS (1980-2000) and HPFS (1986-2000)**

	Quintiles of intake					95% CI*	P
	1	2	3	4	5		
<b>GI</b>							
<b>Men</b>							
Proximal (n = 227) <sup>†</sup>	1.0	0.96	1.15	1.18	0.99	0.63-1.57	0.72
Distal (n = 228)	1.0	1.30	1.09	1.01	1.06	0.67-1.68	0.91
<b>Women</b>							
Proximal (n = 403) <sup>†</sup>	1.0	0.85	1.19	1.15	1.11	0.77-1.58	0.27
Distal (n = 326)	1.0	0.81	1.02	0.92	0.91	0.63-1.34	0.82
<b>GL</b>							
<b>Men</b>							
Proximal	1.0	0.97	1.35	1.06	1.10	0.64-1.88	0.67
Distal	1.0	1.01	1.22	1.15	0.87	0.51-1.49	0.85
<b>Women</b>							
Proximal	1.0	1.06	0.96	0.58	0.77	0.53-1.11	0.02
Distal	1.0	0.90	1.14	0.89	0.90	0.60-1.36	0.59
<b>Carbohydrate</b>							
<b>Men</b>							
Proximal	1.0	1.17	1.26	1.09	1.11	0.64-1.93	0.81
Distal	1.0	0.88	0.99	1.01	0.86	0.50-1.47	0.73
<b>Women</b>							
Proximal	1.0	1.06	0.95	0.67	0.63	0.42-0.95	0.01
Distal	1.0	1.04	1.25	1.10	0.95	0.61-1.50	0.85
<b>Sucrose</b>							
<b>Men</b>							
Proximal	1.0	1.18	1.16	1.49	1.17	0.73-1.89	0.41
Distal	1.0	1.12	1.09	1.23	1.14	0.72-1.79	0.54
<b>Women</b>							
Proximal	1.0	0.93	0.79	0.75	0.73	0.51-1.03	0.04
Distal	1.0	1.60	1.31	1.23	1.34	0.89-2.02	0.60
<b>Fructose</b>							
<b>Men</b>							
Proximal	1.0	0.97	1.25	1.33	1.19	0.74-1.91	0.31
Distal	1.0	1.14	1.15	1.07	1.30	0.82-2.04	0.34
<b>Women</b>							
Proximal	1.0	1.09	0.98	0.70	0.83	0.58-1.17	0.06
Distal	1.0	0.70	0.79	0.85	0.79	0.55-1.14	0.48

NOTE: Multivariate RRs are relative risks adjusted for age, family history of colon cancer, prior endoscopy screening, aspirin use, height, BMI, pack-years of smoking before age 30, physical activity, and intakes of cereal fiber, alcohol, calcium, folate, processed meat and beef, pork or lamb as main dish.

\*95% CI for q5 versus q1.

<sup>†</sup>Numbers of proximal plus distal cases do not add up to colon cancer cases in Table 2 because colon cases include those for which we could not identify subsite.

colorectal cancer risk were substantially stronger among individuals with low physical activity and elevated BMI in one study (18).

We have previously shown, in a subset of healthy women from the NHS I, that our variable for GL (estimated from the FFQs) predicts fasting plasma triacylglycerol and high-density lipoprotein levels better than total carbohydrate intake does (12). The association between triacylglycerol levels and GL was even stronger among women with BMI >25 kg/m<sup>2</sup> (12), indicating that overweight women are particularly susceptible to the quality of the carbohydrates they consume, probably because of some degree of insulin resistance. Recently in the NHS I cohort, we observed an elevated risk of pancreatic cancer with a higher GL, which was stronger among women with BMI ≥ 25 kg/m<sup>2</sup> (45). Glycemic load intake has also been strongly associated with the risk of diabetes and coronary heart disease in the NHS I (15-17). These findings indicate that we are able to measure GI and load with the FFQs in these cohorts, and that our null findings are unlikely the result of substantial measurement error.

Although mean GL and carbohydrate intakes were lower in women than in men, the range of intake was similar. In addition, the mean and range of GL among women in this

study were similar to those reported in the Women's Health Study, where a significant positive association was reported (20). Therefore, it is unlikely that our null findings in women result from a narrow range of GL intake.

In a recent study in the NHS I, GL and fructose were positively associated with plasma C-peptide levels (23). In the present study, fructose intake was most strongly associated with risk in men, supporting the insulin hypothesis. We did not, however, find any associations in women. There are several possible reasons for the gender differences. One possibility is that men may be more susceptible to insulin, based on stronger associations with obesity, particularly central obesity, in men than in women. Another explanation may be that alcohol intake increases susceptibility to dietary factors that influence insulin levels (as suggested by our findings); in which case men would be at higher risk than women (in these cohorts) because they drink more alcohol (Table 1). Finally, the findings in men may be due to chance.

Overall, our results suggest that the glycemic response to diet may not play a major role in colorectal cancer. The GI was developed to rank foods based on their response to blood glucose concentrations. However, postprandial insulin responses are not always proportional to blood glucose concentrations or to a meal's carbohydrate content (46). Insulinotropic factors, such as protein- and fat-rich foods, may induce substantial insulin secretion despite producing relatively small blood glucose responses (47, 48). In a study comparing glucose to insulin response to foods, the authors reported that although the two scores were highly correlated, the glycemic response accounted for only 23% of the variability in insulinemia (46). The findings suggest that an "insulin index of foods" might help increase the accuracy of estimating the insulin response. Given that insulin has been shown to increase tumor growth in the colonic epithelial cells *in vitro* studies, as well as in rats (49), and hyperinsulinemia is a risk factor for colorectal cancer (9-11), insulin is likely to be an important factor.

The strengths of this study include a prospective design, detailed information on diet, and data on many potential risk factors of colorectal cancer. The prospective design precluded recall bias, which may have limited previous case-control studies. In addition, by including data from two large cohorts, we were able to examine results for men and women and had sufficiently large numbers of cases to examine the data by cancer site.

In summary, we observed a slight increase in colorectal risk for dietary GL and sugar intakes in men, but not in women. The associations were slightly stronger among men with elevated BMI, but stratifying by BMI, physical activity or hormone use did not change the associations among women. Future studies should examine foods that closely predict insulin secretion rather than glycemic response.

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