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High Dietary Glycemic Load is Associated With Increased Risk of Colon Cancer

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Abstract

High dietary glycemic load (GL) has been inconsistently associated with risk of colon cancer. We analyzed data for 1,093 incident cases and 1,589 controls in a population-based case-control study of colon cancer to further clarify the GL-colon cancer relationship. GL was assessed using a self-administered food frequency questionnaire. Cases had a significantly higher GL intake (mean = 136.4, SD = 24.5) than controls (mean = 132.8, SD = 25.2) ($P = 0.0003$). In a multivariate unconditional logistic regression model, the odds ratios (ORs) for colon cancer increased significantly with increasing GL: compared to the bottom quartile of GL, the ORs (95% CI) for the 2nd through the upper quartiles were 1.38 (1.06, 1.80), 1.67 (1.30, 2.13), and 1.61 (1.25, 2.07), respectively ($P_{\text{trend}} < 0.0001$). Stratified analyses showed that the association was more pronounced among older participants [ORs (95% CI) for the 2nd through the upper quartiles were 1.35 (0.91, 2.00), 1.87 (1.29, 2.71), 2.02 (1.39, 2.95), respectively] than among younger participants [ORs were 1.46 (1.02, 2.10), 1.53 (1.09, 2.15), and 1.35 (0.96, 1.91), respectively] ($P_{\text{int}} = 0.02$). Our results provide support for the hypothesis that a diet with high GL increases the risk of colon cancer.

Keywords

glycemic load; diet; insulin resistance; colon cancer; epidemiological

Introduction

Colorectal cancer is the third leading cause of cancer death in the United States, with approximately 143,000 newly diagnosed cases and 52,000 deaths recorded annually (1). Although the etiology of sporadic colon cancer remains largely undetermined, diet and other modifiable risk factors undoubtedly play a significant role (2-4). A number of epidemiological studies have examined the association of dietary GL with the risk of colon cancer, and they have yielded conflicting results. We seek to further clarify the relationship between GL and colon cancer in an incident case-control study based on the Kentucky population, characterized by high incidence of colorectal cancer.

High GL causes an increase in circulating levels of insulin and insulin-like growth factors (IGFs) (4, 5). McKeown-Eyssen (6) and Giovannucci (4) proposed the hyperinsulinemia-colon cancer hypothesis which implies that a diet high in energy and carbohydrates leads to insulin resistance, thus promoting colon carcinogenesis (4, 7, 8). Several case-control studies reported significant association between increased risk of colorectal cancer and high glycemic index (GI) (9-11) and dietary GL (9). Results from prospective cohort studies were less consistent for colorectal cancer (8, 12-19) and adenomas (20, 21), where one study showed significant positive (12) and another significant inverse (17) association between GL and colorectal cancer risk. The rest of the cohort studies have reported no significant associations (8, 13-16, 18, 19). A meta-analysis based on these case-control and cohort studies found that neither GI nor GL were associated with risk of colorectal cancer (22). In contrast, another meta-analysis (23) revealed a statistically significant positive association between high GL intake and colorectal cancer. In this study, we sought to further examine the association between GL and colon cancer risk in a Kentucky population-based case-control study.

Subjects and Methods

Study population

Recruitment of study participants was conducted between April 2003 and December 2010. Cases were identified and recruited through the Kentucky Cancer Registry (KCR) which is a part of the Surveillance, Epidemiology, and End Results (SEER) Program. Cases were defined as individuals diagnosed with histopathologically confirmed incident primary colon cancer. They were registered in the KCR within 6 months of the initial diagnosis and were invited to participate in the study within three months of registration to minimize recall and information biases. Cases were eligible to participate if they 1) had a non-recurrent diagnosis; 2) had no known family history or diagnosis of familial adenomatous polyposis (FAP), hereditary nonpolyposis colorectal cancer (HNPCC), Peutz-Jeghers, or Cowden disease; 3) had no known diagnosis of inflammatory bowel disease such as Crohn's disease or ulcerative colitis; 4) were at least 21 years of age at the time of diagnosis; 5) had contact information listed in the KCR database; 6) were willing to complete two questionnaires. Individuals diagnosed with rectal cancer were excluded.

A two-stage recruitment strategy was used to recruit potential cases. First, an eligible case was identified by the KCR staff and contacted via registered letter asking for permission to

be contacted for participation in the study. Second, the contact information of eligible cases was forwarded to the research study staff who contacted each case over the phone to determine eligibility and willingness to participate. A control was defined as an individual who: 1) had no known diagnosis of any cancer (except skin cancer); 2) had no known diagnosis of inflammatory bowel diseases or family history of FAP, HNPCC, Peutz-Jeghers, or Cowden disease; 3) was at least 30 years of age; 4) was willing to complete two questionnaires.

Population controls were recruited through random digit dialing and referrals, as described previously (24). Data on family history of colorectal cancer, lifestyle, and behavioral risk factors for population controls were collected in the same manner as for cases. Among cases that were reached, 70.8% agreed to participate in the study. In controls, among individuals that were reached and determined to be eligible, 66.7% agreed to enroll into the study. All enrolled participants have consented to participate in the study by providing written informed consent.

Data Collection

A self-administered lifestyle risk factor questionnaire developed by the National Cancer Institute Colon Cancer Family Registry (Colon CFR) (<http://bioinformatics.dartmouth.edu/ccfrc/downloads/rfq.pdf>) was mailed to each participant to collect information on demographics and lifestyle risk factors such as smoking, physical activity, body mass index (BMI), income, family history of colorectal cancer, and nonsteroidal anti-inflammatory drug (NSAID) use. The Arizona Food Frequency Questionnaire (AFFQ) (25) was used to collect dietary information. The AFFQ, a validated semi-quantitative 153-item questionnaire, asked participants to fill out how often they usually ate a particular food or used vitamin/mineral supplement a year prior to the colon cancer diagnosis (for cases) or a year prior to participation (for controls) (25). Frequency options included a number of times per day, week, or month and the options for portion size of each food included small, medium, or large (25). During the AFFQ analysis, individual nutrients per day were calculated based on the individual's report of food intake (26). The study was approved by the Institutional Review Boards of the University of Kentucky (Lexington, KY) and Case Western Reserve University/University Hospitals of Cleveland (Cleveland, OH).

Glycemic load

GL was defined as the product of the glycemic index (GI) of a food and the amount of carbohydrates in a serving, representing an approximation of total dietary glycemic effect (8, 13). Total GL was calculated as: $GL \text{ for each food} = (\text{Glycemic Index} / 100) * (\text{Carbohydrate grams} - \text{Fiber grams})$ and total GL for each participant was the sum of the GLs for all individual foods consumed and measured in grams. GI represented a comparison of the glycemic effect of carbohydrate of a particular food to that of an equivalent amount of carbohydrate in a standard amount of white bread or glucose and was based on a table by Foster-Powell et al (27).

Other risk factors

Age was defined as age at diagnosis for the cases and age at the time of questionnaire completion for the controls. Body mass index was calculated based on self-reported weight (kg) two years prior to colon cancer diagnosis (cases)/participation (controls) divided by height in meters squared (kg/m^2). Family history of colorectal cancer was defined as reporting one or more first-degree relatives having colorectal cancer. A regular NSAID use was defined as at least twice a week for 6 months or longer. Calcium intake was calculated based on the sum of calcium intake for all individual foods consumed and measured in mg/day. Vitamin D intake was calculated in the same manner, except the addition of supplemental vitamin D, and measured in IU/day. Recreational physical activity, measured in metabolic equivalents of energy expenditure units (METs), was assessed during 3 time periods (20s, 30s and 40s, and since turning 50) and treated as a continuous variable. Income was defined by five categories: Less than \$15,000, \$15 - \$29,000, \$30 - \$44,000, \$45 - \$69,000, and more than \$70,000. Smoking status was grouped into “never”, “former”, and “current” categories based on self-reported use. A participant was considered to be a smoker if he/she smoked at least one cigarette a day (and/or at least one cigar or one pipe per month) for 3 months or longer.

Statistical analysis

We included 1,589 controls and 1,093 cases in our analyses, excluding 35 individuals with missing values for GL, and 3 individuals with missing data for family history. Overall descriptive statistics as well as statistics stratified by disease status were obtained for each of the continuous explanatory variable when running univariate analyses. Univariate significance of differences between cases and controls was assessed using a t-test (for continuous traits) or a chi-square test (for discrete traits). In case the assumption of normality was violated for a continuous variable, a nonparametric Mann-Whitney U-test was performed to test for difference.

Multivariate unconditional logistic regression models (28) were used to assess the association of GL with risk of colon cancer controlling for potential confounders. GL was adjusted for energy intake using the nutrient residual model, where the GL residuals, calculated by regressing log of GL on log of total energy intake, were treated as an independent variable (29). First, the odds ratios (ORs) and their corresponding 95% confidence intervals (CI) were estimated in a base model adjusted for age, gender, race, and family history, where residuals of the GL were categorized into quartiles. The fully adjusted model was further adjusted for total energy intake, total dietary fiber intake, vitamin D intake, body mass index, physical activity, income, and smoking. Calcium intake and NSAIDs were not included in the fully adjusted model since univariate analyses did not show statistically significant differences between cases and controls. We further investigated potential effect modifications by age, gender, BMI, and physical activity. We first performed stratified analyses by age (age < 63 vs. age ≥ 63, median age for the cases), gender (male vs. female), BMI (BMI < 30 vs. BMI ≥ 30), and physical activity (light as MET < 3, moderate as MET 3-6, and vigorous as MET > 6). Second, we tested for interactions, by including a cross-product term between GL and each of these categorized variables (age, gender, BMI, and physical activity) in the logistic regression model. Linear

trend analysis was performed based on the ordinal scale of GL. There were 236 participants with missing information on physical activity but were kept in the final model since our sensitivity analysis showed no appreciable differences in GL-colon cancer association with or without adjustment for physical activity. All *P* values were two-sided with α -level 0.05, and all analyses were conducted using SAS software (version 9.2; SAS Institute, Inc., Cary, NC, USA).

Results

In comparison to controls, cases had higher total caloric intake, higher values for GL, total dietary fiber intake, and calcium intake (Table 1). Cases also reported lower intake of vitamin D and lower METs compared to controls (Table 1). Cases were more likely to be male, were more likely to have reported a positive family history of colorectal cancer and less likely to be regular NSAID users comparing to controls (Table 1). Cases were older, had higher BMI, were less likely to earn an income of greater than 70,000 dollars (21.1% among cases vs. 31.1% among controls), and less likely to be a non-smoker comparing to a control population (Table 1). Study participants were predominantly Caucasians (93.8%) which is consistent with the general population of Kentucky.

The fully-adjusted multivariate unconditional logistic regression model revealed a statistically significant association between the energy-adjusted dietary GL and the risk of colon cancer ($P = 0.0002$) (Table 2). In the model when the continuous variable of residuals of log of GL was categorized into quartiles, there was a 61% increase in risk of colon cancer among participants in the highest quartile of dietary GL compared to the participants in the lowest (referent) quartile (OR = 1.61; 95% CI: 1.25 - 2.07). There was also evidence for a linear trend ($P_{\text{trend}} < 0.0001$).

Age, gender, BMI, and physical activity were further evaluated for potential effect modification. The GL was significantly associated with an increased risk of colon cancer among those 63 years or older (OR = 1.35; 95% CI: 0.91 – 2.00 for the 2nd quartile, OR = 1.87; 95% CI: 1.29 – 2.71 for 3rd quartile, OR = 2.02; 95% CI: 1.39 – 2.95 for 4th quartile, $P_{\text{trend}} < 0.0001$). In contrast, a linear trend was not present among those younger than 63 years in the fully-adjusted model ($P_{\text{trend}} = 0.08$). Test for multiplicative interaction was statistically significant ($P_{\text{int}} = 0.02$).

A statistically significant positive association between GL and colon cancer was also observed among both men ($P = 0.02$) and women ($P = 0.006$). However, tests for interaction showed no evidence for effect modifications by gender ($P_{\text{int}} = 0.76$), by BMI ($P_{\text{int}} = 0.08$), or by physical activity ($P_{\text{int}} = 0.79$).

Discussion

A high GL diet was hypothesized to increase risk of colon cancer. Indeed, our study revealed a 61% increase in colon cancer risk comparing the highest versus the lowest quartile of dietary GL among participants. Further, there was an effect modification by age with a two-fold statistically significant increase of risk for high GL intake among older participants, but not among younger participants.

Previous studies on association of GL with colorectal cancer have yielded mixed results. Our overall results were similar to a prospective cohort study of women (12) and a case-control study from Italy (9), where both have reported a statistically significant positive association between the dietary GL and colorectal cancer risk. Three other cohort studies on women found a slight positive, but not statistically significant, association between the highest quintile of GL and colorectal cancer (14, 16, 18). In contrast, other cohort studies reported a non-significant protective association between GL and colorectal cancer in women (13, 15, 19), while analysis of multiethnic cohort (17) revealed a statistically significant reduction in colorectal cancer risk among women in the highest quintile of GL.

The risk of developing colorectal cancer increases with age, with men being at higher risk compared to women (30). Interestingly, we found a two-fold increase in cancer risk associated with a high GL diet in older participants, but only a modest and non-significant increase in risk in younger participants. To date, there are no other published studies on association of GL with colon cancer stratified on age.

We also found a statistically significant positive association between GL and risk of colon cancer among non-obese and in individuals engaged in vigorous physical activity, although tests for interaction were not statistically significant due to our somewhat limited sample size. A study by Strayer (19) performed two analyses to assess the effects of BMI and physical activity on GL-colon cancer association: 1) within strata of a combined variable of BMI and physical activity level; and 2) as effect modifiers, and had found that increase in GL was associated with reduced colon cancer risk among overweight/less active group (OR = 0.67; 95% CI: 0.34 – 1.31, $P_{\text{trend}} = 0.02$). Overweight/less active group showed the strongest inverse point estimate of GL-colon cancer association out of four strata: normal BMI/high physical activity, normal BMI/low physical activity, overweight/high physical activity, and overweight/low physical activity. In contrast, one case-control and three cohort studies showed evidence for significant association between GL and colorectal cancer in participants with the BMI ≥ 25 (9, 12, 14, 15), while three studies found either no effect modification by BMI or no association between GL and colorectal cancer within BMI categories (8, 13, 18).

There are a few limitations in our study. Recall bias on AFFQ or questions from risk factor questionnaire (family history, NSAID use, physical activity, income, and smoking) cannot be eliminated. However, GL is not a representation of a single food, but a composite score derived from all carbohydrate-containing foods. It is thus unlikely cases would tend to over-estimate GL than the controls. Recall bias if any, would thus likely to be non-differential and tend to bias the association toward the null. The Arizona Food Frequency questionnaire has been tested for reliability and validity (25, 26, 31). Despite well known methodological limitations, food frequency questionnaire is useful and allows for the ranking of individuals according to their intake of glycemic load with sufficient reliability and validity (32, 33). In particular, two recent studies evaluated reproducibility and validity of dietary GI and GL among Swedish men (34) and among Dutch men and women (35). In study by Levitan et al, reproducibility, measured by intraclass correlations between the two FFQ taken 1 year apart, was 0.66 (95% CI: 0.56, 0.75) for dietary GI, 0.61 (95% CI: 0.50, 0.71) for dietary GL, and 0.61 (95% CI: 0.50, 0.71) for carbohydrate (34). Relative validity, measured with Pearson

correlations between the FFQs and 1-week diet records taken 6 months apart, was 0.62 (95% CI: 0.45, 0.74) for dietary GI, 0.77 (95% CI: 0.56, 0.88) for dietary GL, and 0.76 (95% CI: 0.55, 0.88) for carbohydrate after adjustment for within-person variation in the FFQs and diet records (34). Study on Dutch cohort had reproducibility of 0.78 for GI and 0.74 for GL, and validity of 0.63 for both GI and GL (35).

Some of the enrolled unscreened controls could have undiagnosed colon cancer or polyps (24). However, this would occur infrequently, and exclusion of these participants would cause the OR estimates to move away from the null (24). While every effort was made to obtain a representative control sample of the entire state, non-response bias cannot be excluded (36). If present, it would probably underestimate the risk and affect generalizability of the study. To minimize this bias, all analyses were adjusted for well-known confounders. Another limitation was the generalizability of our results to other racial groups due to majority of the population being Caucasian (24).

In summary, our overall results show that high GL increases risk of colon cancer, providing indirect evidence supporting the hyperinsulinemia/colon cancer hypothesis. However, due to an observed significant association of GL and colon cancer in non-obese and in vigorous physical activity groups, perhaps GL is an ineffective measure of insulin response. In fact, although many epidemiological studies utilize dietary GL in measuring of the glucose response and insulin demand, the common assumption that increase in insulin response is proportional to the postprandial glycemia does not hold true (19, 22, 37-39). Thus, future studies are warranted to examine association of insulin index, in addition to GI and GL, with colon cancer risk.

In summary, our study provides additional evidence in support of diet high in GL being associated with increase in colon cancer risk. Thus, consuming a low GL diet could be a possible intervention in reducing colon cancer risk.

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SZ helped with data collection, performed data analysis, and wrote the manuscript; CLT advised on statistical analysis, data interpretation, and provided feedback on manuscript; TCT took an active role in the development of overall research plan, and provided access to KCR registry; LL was the Principal Investigator of the project, and was responsible for project conception, development of overall research design, study oversight, data collection and interpretation, and had primary responsibility for final content. All authors read and approved the final manuscript. The work was conducted at Case Western Reserve University, Cleveland, Ohio and University of Kentucky Markey Cancer Control Program, Lexington, Kentucky. None of the authors had any financial or personal relationships with organizations sponsoring the research at the time the research was conducted, nor had any other conflicts of interest. This manuscript has not been published or submitted simultaneously for publication elsewhere.

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Abbreviations

AFFQ	Arizona Food Frequency Questionnaire
BMI	body mass index
FAP	Familial Adenomatous Polyposis
GI	glycemic index
GL	glycemic load
HIPAA	Health Insurance Portability and Accountability Act
HNPCC	Hereditary Non-Polyposis Colorectal Cancer
IGF	insulin-like growth factor
IU	International Units
KCR	Kentucky Cancer Registry
MET	metabolic equivalents of energy expenditure units
NSAID	nonsteroidal anti-inflammatory drug
SEER	Surveillance, Epidemiology, and End Results

Table 1
Descriptive characteristics of the Kentucky colon cancer study

Variable	Controls (n = 1,589)	Cases (n = 1,093)	P-value ¹
Mean total caloric intake (kcal/day) (SD)	1940.1 (1042.6)	2142.3 (1251.9)	< 0.0001
Mean total dietary fiber (g) (SD)	20.7 (11.9)	21.2 (13.0)	0.26
Mean calcium intake (mg/day) (SD)	986.6 (562.6)	996.2 (600.9)	0.67
Mean vitamin D intake (IU/day) (SD)	416.4 (343.5)	388.0 (340.1)	0.03
Mean glycemic load adj. for energy ² (SD)	132.8 (25.2)	136.4 (24.5)	0.0003
Glycemic load (%)			
1st quintile	407 (25.6)	208 (19.0)	0.0003
2nd quintile	350 (22.0)	232 (21.2)	
3rd quintile	422 (26.6)	333 (30.5)	
4th quintile	410 (25.8)	320 (29.3)	
Sex (%)			
Male	553 (34.8)	528 (48.3)	< 0.0001
Female	1036 (65.2)	565 (51.7)	
Mean age (yrs) (SD)	61.1 (10.3)	62.4 (10.3)	0.001
Age (%)			
< 63	861 (54.2)	515 (47.1)	0.0003
63	728 (45.8)	578 (52.9)	
Mean BMI (kg/m ²) (SD)	28.3 (6.4)	29.5 (6.2)	< 0.0001
Body Mass Index (%)			
underweight (< 18.5 kg/m ²)	8 (0.5)	5 (0.5)	< 0.0001
normal (18.5 - 24.99 kg/m ²)	482 (31.1)	243 (22.9)	
overweight (25 - 29.99 kg/m ²)	596 (38.4)	394 (37.1)	
obese (≥ 30 kg/m ²)	466 (30.0)	421 (39.6)	
Missing	37	30	
Family history of colorectal cancer (%)			
Yes	416 (26.2)	385 (35.2)	< 0.0001
No	1173 (73.8)	708 (64.8)	
Race (%)			
African American	84 (5.3)	41 (3.8)	0.17
Caucasian	1477 (93.0)	1034 (94.6)	
Other	28 (1.8)	18 (1.7)	
Regular NSAID use (%)			
< 6 months	596 (44.0)	429 (46.4)	0.27
> 6 months	758 (56.0)	496 (53.6)	
Missing	235	168	
Mean lifetime physical activity (MET) (SD)	11.7 (9.0)	10.2 (7.9)	< 0.0001
Physical Activity (%)			
Light ³	153 (10.4)	134 (13.7)	0.02

Variable	Controls (n = 1,589)	Cases (n = 1,093)	P-value ¹
Moderate ³	245 (16.7)	179 (18.3)	
Vigorous ³	1069 (72.9)	666 (68.0)	
Missing	122	114	
Income (%)			
< \$15,000	156 (10.5)	143 (13.8)	< 0.0001
\$15,000 - 29,000	273 (18.4)	236 (22.7)	
\$30,000 - 44,000	284 (19.1)	226 (21.7)	
\$45,000 - 69,000	313 (21.0)	216 (20.8)	
\$70,000	462 (31.1)	219 (21.1)	
Missing	101	53	
Smoking status (%)			
Current	234 (14.8)	138 (12.8)	< 0.0001
Former	624 (39.3)	524 (48.5)	
Nonsmoker	728 (45.9)	419 (38.8)	
Missing	3	12	

¹ P-value for *t*-test for continuous variables and for χ^2 -test for categorical variables.

² Glycemic load was adjusted for energy intake with nutrient residual model.

³ Light intensity (< 3 metabolic equivalents (METs)); Moderate intensity (3-6 METs); Vigorous intensity (> 6 METs).

Table 2
Odds ratios (ORs) and 95% confidence intervals (95% CI) of colon cancer by quartiles of energy-adjusted dietary glycemic load (Full Adjustment)

	Quartile				P_{trend}^1	P_{int}^2
	1	2	3	4		
Dietary glycaemic load						
No. cases/controls	208/407	232/350	333/422	320/410		
3OR (95% CI)	1.00 (ref)	1.38 (1.06 - 1.80)	1.67 (1.30 - 2.13)	1.61 (1.25 - 2.07)	<0.0001	
Age < 63 (n = 1376)						
3OR (95% CI)	1.00 (ref)	1.46 (1.02 - 2.10)	1.53 (1.09 - 2.15)	1.35 (0.96 - 1.91)	0.08	0.02
Age ≥ 63 (n = 1306)						
3OR (95% CI)	1.00 (ref)	1.35 (0.91 - 2.00)	1.87 (1.29 - 2.71)	2.02 (1.39 - 2.95)	<0.0001	
Male (n = 1081)						
3OR (95% CI)	1.00 (ref)	1.26 (0.84 - 1.89)	1.40 (0.96 - 2.03)	1.46 (0.98 - 2.16)	0.05	0.76
Female (n = 1601)						
3OR (95% CI)	1.00 (ref)	1.47 (1.03 - 2.09)	1.89 (1.35 - 2.64)	1.68 (1.20 - 2.34)	0.002	
BMI < 30 (n = 1795)						
3OR (95% CI)	1.00 (ref)	1.35 (0.96 - 1.89)	1.70 (1.25 - 2.32)	1.77 (1.30 - 2.42)	0.0002	0.08
BMI ≥ 30 (n = 887)						
3OR (95% CI)	1.00 (ref)	1.43 (0.93 - 2.18)	1.61 (1.07 - 2.43)	1.35 (0.89 - 2.05)	0.12	
MET < 3 (n = 287)						
3OR (95% CI)	1.00 (ref)	0.88 (0.39 - 1.99)	1.75 (0.79 - 3.86)	1.31 (0.61 - 2.80)	0.23	0.79
MET ≥ 3 - 6 (n = 424)						
3OR (95% CI)	1.00 (ref)	0.87 (0.45 - 1.71)	1.59 (0.86 - 2.94)	1.30 (0.71 - 2.36)	0.18	

Quartile					
	1	2	3	4	
MET > 6 (n = 1735)					
³ OR (95% CI)	1.00 (ref)	1.65 (1.21 - 2.26)	1.68 (1.26 - 2.25)	1.78 (1.32 - 2.40)	¹ P _{trend} ² 0.0004

¹ P-values for trend were obtained from two-sided Chi-square tests.

² P-values for interaction were obtained from two-sided Chi-square tests. Test for interactions was conducted by including an interaction term between GL and the group of interest (age, gender, BMI, and physical activity) into the logistic regression model.

³ ORs (95% CI) for colon cancer risk (categorical energy-adjusted dietary glycemic load) adjusted by unconditional logistic regression for energy intake (kcal), total dietary fiber (g), vitamin D intake, age (y), body mass index (kg/m²), gender, family history of colon cancer (yes, no), race (Caucasian, African-American, other), physical activity (METs), income (< \$15,000, \$15-29,000, \$30-44,000, \$45-69,000, > \$70,000), and smoking (never, former, current). In addition to 38 individuals excluded, we also excluded 303 individuals due to missing values for body mass index and physical activity. Missing values for income and smoking variables were included in the analysis by creating an extra dummy variable for these missing values.