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Dietary Carbohydrate, Glycemic Index, and Glycemic Load in Relation to Colorectal Cancer Risk in the Women's Health Initiative

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Abstract

Evidence implicating hyperinsulinemia and insulin resistance in the etiology of colorectal cancer suggests that a diet characterized by a high glycemic index and load may increase the risk of this disease, but previous studies have yielded inconsistent results. We assessed the association between intake of total carbohydrates, sugars, fiber, and the glycemic index (GI) and glycemic load (GL) of individual diets, and risk of developing colorectal cancer among 158,800 participants in the Women's Health Initiative (WHI). We used a GI/GL database developed specifically for the WHI food-frequency questionnaire. Over an average of 7.8 years of follow-up, 1,476 incident cases of colorectal cancer were identified. Cox proportional hazards models were used to estimate the association between dietary factors classified by quintiles and risk of colorectal cancer, with adjustment for covariates. Total carbohydrate intake, glycemic index, glycemic load, and intake of sugars and fiber showed no association with colorectal cancer. Analyses by cancer subsite yielded null results, with the exception of a borderline positive association between glycemic load and rectal cancer (HR for the highest vs. lowest quintile 1.84, 95% confidence interval 0.95–3.56, p for trend 0.05). Analyses stratified by tertiles of body mass index and physical activity showed no evidence of effect modification by these factors. Results of this large study do not support of a role of a diet characterized by a high glycemic index or load in colorectal carcinogenesis in postmenopausal women.

Introduction

Evidence implicating hyperinsulinemia and insulin resistance in the etiology of colorectal cancer suggests that a diet characterized by a high glycemic index and glycemic load may increase the risk of this disease [1–4]. Both animal and human studies support an etiological association between hyperinsulinemia and colorectal cancer [2, 3]. In addition, known risk factors for colorectal cancer, including obesity, lack of physical activity, and diabetes, are associated with increased insulin levels and insulin resistance [5, 6]. Furthermore, insulin influences the production of insulin-like growth factor-I (IGF-I), and both insulin and IGF-I enhance mitogenesis and cell proliferation, while inhibiting apoptosis in colonic epithelial cells [2, 3, 7].

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Glycemic index (GI) and glycemic load (GL) provide a means of characterizing foods and diets in terms of their glycemic response [8, 9]. A number of epidemiologic studies have examined the association of GI/GL with risk of colorectal cancer [10–18] and with colorectal adenoma [19, 20]. Two case-control studies and two cohort studies have reported positive associations [10, 11, 13, 14], but most cohort studies have not [12, 15–20]. However, the methodology for establishing GI/GL databases for different food-frequency questionnaires is not well standardized. Thus, the association of GI/GL with risk of colorectal cancer remains unresolved.

Women's Health Initiative (WHI) scientists have developed a GI/GL database using a "rule base" derived from the scientific literature as a guide in assigning a GI to foods listed on the WHI food frequency questionnaire (FFQ) [21]. We utilized this database to examine the association of intake of carbohydrates, glycemic index, glycemic load, and related dietary factors in relation to colorectal cancer and subsites within the colorectum in the WHI Observational Study and Clinical Trial.

Methods and Materials

The Women's Health Initiative is a large, multifaceted study designed to advance understanding of the determinants of major chronic diseases in postmenopausal women [22]. It is composed of a Clinical Trial component (CT) and an Observational Study component (OS). The CT component (n = 68,132) included randomized controlled clinical trials to test the effects of a low-fat dietary pattern, calcium plus vitamin D supplementation, and administration of estrogen alone or estrogen plus progestin on the risk of coronary heart disease, breast cancer, colorectal cancer, and fractures. Utilizing a sample of postmenopausal women, the OS (n = 93,676) was designed to obtain detailed information on a broader range of lifestyle factors and medical history than the clinical trials [23]. Women between the ages of 50 and 79 and representing major racial/ethnic groups were recruited from the general population at 40 clinical centers throughout the United States between 1993 and 1998. Common protocols were followed at all 40 centers. Details of the design and reliability of the baseline measures have been published [22, 24, 25].

The WHI OS included women who were screened for the clinical trial components but were either ineligible or unwilling to be randomized to the HRT or dietary modification components [26]. Due to this circumstance, OS and CT participants differ to some extent on sociodemographic and lifestyle characteristics and medical history. For example, compared to CT participants, OS participants had lower body mass index, were more likely to have used hormone therapy, and had higher mean hours of total physical activity per week.

Data Collection

Information was collected at baseline on demographics, medical, reproductive and family history, and lifestyle factors. All baseline information was collected from both CT and OS participants between 1993 and 1998. Weight was assessed at baseline using a calibrated beam balance, and height was assessed with a stadiometer. Physical activity was assessed by computing average weekly metabolic equivalents of moderate and vigorous leisure-time physical activity. Participants completed a self-administered FFQ specifically designed for the WHI that inquired about usual food intake in the previous 3 months. In addition to 122 food and food group items, the FFQ included 19 "adjustment" questions (i.e. fat added at the table and in cooking) and three summary questions. The WHI FFQ has been shown to yield nutrient estimates that are similar to those obtained from short-term dietary recall and recording methods, and test-retest reliability for most nutrients was high [27]. The WHI nutrient database was derived from the University of Minnesota's Nutrition Coordinating

Center database. With the exception of processed meat and glycemic index/glycemic load, the nutrient variables used in these analyses are standard output from the primary database.

Calculation of overall glycemic index and glycemic load

Because GI and GL were not part of the original WHI FFQ dietary database, a GI and GL database was developed and tested for use with this FFQ [21]. Values for the GI of different foods were obtained from international tables [28] or were imputed from foods with similar carbohydrate and fiber contents, when published values were not available. Only foods containing at least 5 g of total carbohydrate per medium portion were assigned a GI value, because small amounts of carbohydrate do not contribute significantly to the total glycemic response. Performance of the database was tested in a random sample of previously completed WHI FFQs. Correlations of GI with potentially collinear variables such as total carbohydrate ($r=.47$, $p<.001$) and total sugars ($r=.38$, $p<0.001$) were statistically significant but modest, indicating that GI is not merely a reflection of closely related nutrients [21].

Ascertainment of colorectal cancer

Clinical outcomes (including cancer diagnosis) were updated annually in the OS and semi-annually in the CT using mail or telephone questionnaires. Self-reports of colorectal cancer were verified by trained physician adjudicators at the Clinical Centers who reviewed medical records and pathology reports [29]. All colorectal cancer diagnoses were then confirmed by blinded review at the WHI Clinical Coordinating Center. Groupings of subsites within the colorectum were classified as: proximal colon (cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure); distal colon (descending colon, sigmoid colon); and rectum, including the rectosigmoid junction [30].

Exclusions

Both OS and CT participants were included in the analysis. We sequentially excluded women missing information on colorectal cancer as an outcome (n = 736), cases of colorectal cancer with histologies other than adenocarcinoma (n = 51), and those with a prior history of colorectal cancer (n = 951), with cancer of the appendix (n = 1), or whose cause of death was recorded as colorectal cancer but who had no report of incident colorectal cancer (n = 55). We further excluded women with extreme energy intakes (<600 or >5000 kcal/d; n = 425) and extreme values for body mass index (<15 kg/m^2 or >50 kg/m^2; n = 789). The resulting data set contained 158,800 women: 1,476 cases and 157,324 non-cases.

Statistical analysis

Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) for the association of total carbohydrate intake, glycemic index, glycemic load, and intake of total sugars, and fiber, with colorectal cancer risk adjusting for colorectal cancer risk factors and potential confounding variables. Quintiles of GI, GL, and other dietary variables of interest were computed based on the distribution in the non-cases. GI and GL were computed in two ways: using total carbohydrate and using an estimate for available carbohydrate (total carbohydrate –total dietary fiber). Two different approaches were used to adjust for total energy intake. First, energy was included as a continuous covariate in the models containing quintiles of carbohydrates, GI, etc. Second, we used the nutrient density method [31], wherein intake of carbohydrate, total sugars, and fiber were divided by the number of kilocalories and the variables so created were then categorized into quintiles.

Variables were included in the final models if they were established risk factors for colorectal cancer or if their inclusion altered the parameter estimate for GI or GL by more

than 10%. We entered variables sequentially in the model and retained variables in decreasing order of change in the beta-coefficient for the study variable. The following variables were included in the final model: age (continuous), education (less than high school graduate, high school graduate, some college, college graduate, post college), cigarettes smoked per day (0, 0<–14, 15–24, 25–34, ≥35), body mass index (kg/m^2; continuous), height (cm - continuous), hormone therapy (ever, never), history of diabetes (no, yes), family history of colorectal cancer in a first degree relative (yes, no), total metabolic equivalent-hours/week (MET-h/wk) of physical activity (continuous), OS participant (yes, no) [alternative models substituted Dietary Modification trial: intervention, control, other], and daily intakes of total dietary fiber, energy, and dietary calcium (all continuous). To test for trends in risk with increasing levels of the exposures of interest, we assigned the corresponding median value to each quintile and then fitted the medians as a continuous variable in the risk models. We then evaluated the statistical significance of the corresponding coefficient, using the Wald test [32].

Analyses were carried out in the OS and CT combined with an indicator variable for OS vs. CT participant. Because the OS and the CT populations differ in a number of respects due to the inclusion criteria for the clinical trials [22, 23, 26], and because the interventions in specific clinical trials could have affected the outcome, we repeated the main analyses in the OS and CT separately. We carried out sensitivity analyses: 1) excluding participants in the Dietary Modification trial (leaving 110,413 women, including 998 cases); 2) excluding women with a history of diabetes (leaving 149,421 women, including 1335 cases); and excluding cases of colorectal cancer diagnosed during the first two years of follow-up (leaving 158,453 women, including 1129 cases). Further analyses were carried out for groupings of subsites within the colorectum: proximal colon, distal colon, and rectum. Finally, stratified analyses were performed within tertiles of body mass index and physical activity to detect possible effect modification by these factors.

Results

The distribution of baseline characteristics by quintiles of age- and energy-adjusted glycemic load is given in Table 1. The proportion of women with post-college education, the proportion of never smokers, and mean MET-h/wk of physical activity increased modestly with increasing GL, whereas the proportion of ever users of oral contraceptives and mean body mass index decreased modestly. Intakes of fiber, total carbohydrates, total energy, and total sugars increased substantially, and fat intake decreased with increasing GL.

In multivariable models, total carbohydrate intake, glycemic index, glycemic load, and intake of sugars and fiber showed no association with colorectal cancer, and there were no trends over increasing quintiles (HRs ranged from 0.89 to 1.16, and all 95% confidence intervals included the null value of 1.0) (Table 2). Analyses using the nutrient-density corrected variables yielded similar results (data not shown). In analyses conducted in the OS and CT separately, those excluding participants in the Dietary Modification clinical trial, those excluding women with diabetes, and those excluding cases diagnosed in the first two years of follow-up, none of the adjusted hazard ratios showed any association with colorectal cancer (data not shown).

In analyses stratified by colorectal cancer subsite grouping, no associations or trends were seen for any of the carbohydrate-related variables with cancer of the proximal or distal colon (Table 3). For rectal cancer, increasing GL showed a borderline positive association with risk: HR for highest vs. lowest quintile 1.84 (95% confidence interval 0.95–3.56), p for trend 0.05. The association remained unchanged after exclusion of cases diagnosed during the first

two years of follow-up. None of the other variables showed any association with rectal cancer.

In analyses carried out within strata of body mass index (<25, 25–<30, ≥30) and level of physical activity (MET-h/wk: <3.5, 3.5–<13.5, ≥13.5), there was no suggestion of effect modification (data not shown).

Discussion

The present analysis, based on 7.8 years of follow-up of the Women's Health Initiative Clinical Trial and Observational Study cohorts, showed no suggestion of an association between baseline intake of carbohydrates, glycemic index, glycemic load, or related dietary variables and overall risk of colorectal cancer. Analyses carried out in the OS and the CT separately, in the combined data excluding participants in the DM trial, as well as analyses excluding women with diabetes yielded results similar to those for the entire study population. Glycemic load and related variables showed no association with subsites within the colorectum, with the exception of a borderline positive association of GL with rectal cancer. Finally, no association of any of the study factors was found in analyses stratified on body mass index and physical activity.

Previous studies on this topic have yielded inconsistent, but mostly null, results. Two case-control studies reported significant positive associations of GI and/or GL with colon and colorectal cancer, respectively [10, 11]. Among cohort studies, only that of Higgenbotham et al. [13] showed evidence of a substantial association: hazard ratio of 2.85 (95% CI 1.40–5.80) for the highest versus the lowest quintile of glycemic load in relation to risk of colorectal cancer. Michaud et al. [14] observed much more modest positive associations between relatively high GL and intake of fructose and sucrose and colorectal cancer risk in men but found no associations in women. McCarl and colleagues [15] identified an association between glycemic index and colorectal cancer risk but only in obese women. Five of the seven cohort studies found no overall association [12, 15–18]. Further, neither of two very large cohort studies of colorectal adenoma showed any associations with glycemic index, glycemic load, or carbohydrate intake [19, 20].

Data from previous studies regarding the association of GI and GL with subsites within the colorectum are limited and inconsistent [12, 13, 16, 18]. Our finding of a borderline association of glycemic load with rectal cancer could have occurred by chance, given the large number of comparisons and the fact that none of the other carbohydrate-related variables showed any association with rectal cancer. Unlike McCarl et al. [15], who reported positive associations of GI and GL in women who were obese (BMI ≥30 kg/m^2), we found no evidence of an association when women were stratified by BMI.

Use of data from the WHI to address this question has a number of advantages. First, since colorectal cancer was a primary outcome in the WHI, self-reports of colorectal cancer diagnoses were carefully reviewed and confirmed [29]. Second, detailed information was available on a wide range of confounding variables ascertained at baseline in both the OS and CT, and their reliability was assessed [25]. Third, a special database was created to assign GI and GL values to all foods covered in the WHI FFQ which contained 5 or more grams of carbohydrate [21]. We assessed GL for both total carbohydrate and for available carbohydrate (total carbohydrate less total fiber). Use of available carbohydrate is appropriate, since this is the dietary source of circulating blood glucose, thereby contributing to glycemic impact, or load. However, because total dietary fiber is related to GI and GL and possibly to risk of colorectal cancer, we included fiber as a covariate in our analyses.

Assessment of diet using food frequency questionnaires is subject to measurement error, which could obscure a true association between nutrient intake and disease [33, 34]. Thus, as in previous studies, our results may have been affected by misclassification of intake of carbohydrates and sugars due to errors of recall and changes in diet over time, or greater underreporting of diet in the cases due to higher rates of obesity. Furthermore, estimates of GI and GL from the WHI FFQ are based on composite food groupings (FFQ line items) intended primarily to assess dietary fat. Thus, estimates may not accurately reflect the glycemic effects of the individual foods or of consumption and metabolism of mixed dishes and prepared foods. GI/GL databases are currently incomplete (e.g. for many foods, no GI values are available; some values are derived from small studies or are based on varying test meal values (2-, 3-, 4-hr values). Additionally, there may be misclassification due to random variation in the computed values for GI and GL, and such misclassification would reduce the power to detect an effect. Another potential source of error is that, while we controlled for a large number of potential confounding variables, uncontrolled confounding from dietary or non-dietary factors cannot be ruled out. Finally, serum insulin levels were not available, and, thus, we were unable to investigate an association between serum insulin levels and GI and GL.

One possible explanation for the lack of association between risk of colorectal cancer and a diet characterized by a high glycemic index and load in this study and the majority of previous cohort studies is that eating foods that are high in GI/GL may increase fasting blood glucose levels but that this may not necessarily translate to prolonged elevations in insulin, which appear to drive colorectal cancer risk. This is suggested by the results of a recent analysis of the association of fasting blood levels of glucose and insulin carried out in the WHI OS [4]. In that study, fasting blood glucose was not associated with colorectal cancer risk, whereas insulin was.

In summary, this large study provides no evidence that a diet characterized by a high glycemic index or glycemic load, or by a high intake of carbohydrate or sugars, increases the risk of colorectal cancer in generally healthy postmenopausal women. Our findings are in agreement with those of most of the previous cohort studies on this question.

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Table 1

Baseline distributions of background variables, colorectal cancer risk factors, and dietary constituents by quintile of dietary glycemic load* in the Women's Health Initiative

	Baseline glycemic load				
Variables	**Quintile 1 (N = 31,414) 247,061 pyrs**	**Quintile 2 (N = 31,551) 249,459 pyrs**	**Quintile 3 (N = 31,508) 250,538 pyrs**	**Quintile 4 (N = 31,019) 251,819 pyrs**	**Quintile 5 (N = 31,019) 251,497 pyrs**
Education (% post college)	23.6	28.2	30.4	31.8	31.9
Ever used hormone therapy (%)	43.9	41.8	41.8	42.2	44.4
Never smokers (%)	48.6	49.6	51.3	52.2	53.3
Family history of colorectal cancer (%)	14.6	14.9	15.1	15.4	15.2
History of diabetes (%)	7.1	6.0	5.4	5.1	5.4
Age (mean)	63.1	63.3	63.4	63.3	63.0
Height (cm - mean)	161.7	162.0	162.1	162.0	161.4
Body mass index (wt/ht^2) (mean)	29.0	28.1	27.7	27.3	27.0
Total MET-h/wk# (mean)	9.2	11.0	12.0	12.9	14.5
Dietary intake (means)					
Glycemic load (mean)	47.3	72.6	91.2	112.5	160.0
Total energy (kcal/day)	910.6	1279.2	1539.1	1832.7	2492.3
Fiber (g/day)	10.8	13.8	15.8	17.8	20.9
Total carbohydrates (g/day)	140.2	171.4	194.3	219.7	272.5
Total sugars (g/day)	63.1	80.4	93.6	108.0	138.9
Total fat (g/day)	78.7	68.4	61.1	53.2	38.0
Protein (g/day)	71.3	69.9	68.5	66.5	59.8
Fruit (medium servings/day)	0.9	1.5	1.9	2.3	2.4
Vegetables (medium servings/day)	1.8	2.1	2.2	2.3	2.4
Calcium (mg/day)	691.2	765.2	816.9	866.9	916.8

*All values are age- and energy-adjusted, except for age and energy, respectively.

#Total metabolic equivalent-hours/week.

Table 2

Multivariable hazard ratios and 95% confidence intervals for the association of intake of total carbohydrates, glycemic index, glycemic load, and related variables with colorectal cancer in the Women's Health Initiative.

Quintiles of dietary intake	No. cases	Person-years	Multivariable adjusted*	
			HR	95% CI
Total carbohydrates (g/day)				
<131.6	337	242,053	1.00 (reference)	
131.6–171.4	283	246,919	0.85 (0.71–1.01)	
171.4–209.2	301	248,173	0.96 (0.79–1.18)	
209.2–260.1	302	248,817	0.97 (0.76–1.23)	
260.1+	247	245,657	0.89 (0.64–1.25)	
Ptrend			*0.97*	
Glycemic index**				
<49.4	273	245,001	1.00 (reference)	
49.4–51.6	284	246,981	1.04 (0.87–1.24)	
51.6–53.3	293	247,579	1.06 (0.89–1.27)	
53.3–55.4	304	247,015	1.09 (0.91–1.30)	
55.4+	316	245,042	1.10 (0.92–1.32)	
Ptrend			*0.27*	
Glycemic load** (g/day)				
<62.4	323	241,998	1.00 (reference)	
62.4–81.9	294	247,053	0.94 (0.79–1.12)	
81.9–100.7	304	248,043	1.07 (0.88–1.29)	
100.7–126.6	281	249,138	1.01 (0.81–1.27)	
126.6+	268	245,386	1.11 (0.82–1.49)	
Ptrend			*0.47*	
Total sugars (g/day)				
<58.8	321	243,189	1.00 (reference)	
58.8–79.9	301	247,495	0.99 (0.83–1.17)	
79.9–101.0	288	248,220	1.00 (0.83–1.20)	
101.0–129.7	277	248,551	1.01 (0.82–1.24)	
129.7+	283	244,163	1.16 (0.91–1.49)	
Ptrend			*0.34*	
Total fiber (g/day)				
<9.9	307	241,810	1.00 (reference)	
9.9–13.3	348	246,971	1.16 (0.96–1.39)	
13.3–16.7	267	248,569	0.92 (0.72–1.18)	
16.7–21.2	289	248,736	1.10 (0.80–1.50)	
21.2+	259	245,532	1.06 (0.67–1.70)	
Ptrend			*0.97*	

*The following variables were included in the multivariable model: age (continuous), education (less than high school graduate, high school graduate, some college, college graduate, post college), cigarettes smoked per day (0, 0<–14, 15–24, 25–34, ≥35), body mass index (continuous),

height (continuous), hormone replacement therapy (ever, never), history of diabetes (no, yes), family history of colorectal cancer in a first degree relative (yes, no), total metabolic equivalent-hours per week from physical activity (continuous), Observational Study participant (yes, no), and intakes of total fiber, energy (kcal), and dietary calcium (all continuous).

** Based on available carbohydrate.

Table 3

Hazard ratios and 95% confidence intervals for the association of intake of total carbohydrates, glycemic index, glycemic load, and related variables with subsites within the colorectum in the Women's Health Initiative.

Quintiles	Proximal colon (N= 798)		Distal colon (N= 351)		Rectal cancer (n = 303)	
	HR*	95% CI	HR*	95% CI	HR*	95% CI
Total carbohydrates (g/day)						
<131.6	1.00 (reference)		1.00 (reference)		1.00 (reference)	
131.6–171.4	0.78 (0.61–0.99)		0.85 (0.59–1.24)		0.93 (0.62–1.40)	
171.4–209.2	0.82 (0.62–1.08)		0.92 (0.60–1.41)		1.29 (0.82–2.02)	
209.2–260.1	0.77 (0.55–1.07)		0.99 (0.60–1.64)		1.42 (0.82–2.44)	
260.1+	0.78 (0.49–1.25)		0.66 (0.32–1.37)		1.33 (0.62–2.85)	
Ptrend	*0.28*		*0.93*		*0.15*	
Glycemic index**						
<49.4	1.00 (reference)		1.00 (reference)		1.00 (reference)	
49.4–51.6	1.07 (0.84–1.36)		1.04 (0.73–1.49)		1.00 (0.67–1.49)	
51.6–53.3	1.10 (0.87–1.41)		1.13 (0.79–1.62)		0.84 (0.55–1.28)	
53.3–55.4	1.02 (0.79–1.32)		1.01 (0.70–1.47)		1.24 (0.84–1.83)	
55.4+	1.17 (0.90–1.51)		0.95 (0.64–1.41)		1.07 (0.71–1.62)	
Ptrend	*0.45*		*0.90*		*0.35*	
Glycemic load** (g/day)						
<62.4	1.00 (reference)		1.00 (reference)		1.00 (reference)	
62.4–81.9	0.86 (0.68–1.10)		0.94 (0.65–1.35)		1.12 (0.75–1.67)	
81.9–100.7	0.93 (0.71–1.21)		1.14 (0.77–1.71)		1.33 (0.86–2.06)	
100.7–126.6	0.82 (0.60–1.12)		1.08 (0.67–1.73)		1.51 (0.92–2.50)	
126.6+	0.86 (0.56–1.31)		1.11 (0.59–2.11)		1.84 (0.95–3.56)	
Ptrend	*0.41*		*0.50*		*0.05*	
Total sugars (g/day)						
<58.8	1.00 (reference)		1.00 (reference)		1.00 (reference)	
58.8–79.9	0.94 (0.75–1.19)		1.20 (0.85–1.69)		1.23 (0.85–1.76)	
79.9–101.0	0.91 (0.71–1.16)		1.00 (0.67–1.45)		1.06 (0.72–1.58)	
101.0–129.7	0.98 (0.76–1.25)		1.21 (0.84–1.76)		1.39 (0.94–2.05)	

Quintiles	Proximal colon (N= 798)		Distal colon (N= 351)		Rectal cancer (n = 303)	
	HR*	95% CI	HR*	95% CI	HR*	95% CI
129.7+	0.95	(0.73–1.24)	1.15	(0.77–1.72)	1.26	(0.82–1.93)
Ptrend	*0.81*		*0.38*		*0.24*	
Total fiber (g/day)						
<9.9	1.00	(reference)	1.00	(reference)	1.00	(reference)
9.9–13.3	1.09	(0.84–1.40)	1.00	(0.69–1.46)	1.34	(0.90–1.97)
13.3–16.7	0.97	(0.71–1.32)	0.84	(0.53–1.33)	0.93	(0.57–1.54)
16.7–21.2	1.03	(0.71–1.49)	1.07	(0.61–1.85)	0.86	(0.46–1.60)
21.2+	1.20	(0.73–1.95)	0.97	(0.46–2.05)	0.88	(0.39–2.01)
Ptrend	*0.97*		*0.94*		*0.39*	

* The following variables were included in the multivariable model: age (continuous), education (less than high school graduate, high school graduate, some college, college graduate, post college), cigarettes smoked per day (0, 0<–14, 15–24, 25–34, ≥35), body mass index (continuous), height (continuous), hormone replacement therapy (ever, never), history of diabetes (no, yes), family history of colorectal cancer in a first degree relative (yes, no), total metabolic equivalents per week from physical activity (continuous), Observational Study participant (yes, no), and intakes of total fiber, energy (kcal), and dietary calcium (all continuous).

** Based on available carbohydrate.