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Original Contribution

Dietary Carbohydrate Intake, Glycemic Index, and Glycemic Load and Endometrial Cancer Risk: A Prospective Cohort Study

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Endometrial cancer risk has been directly associated with glycemic load. However, few studies have investigated this link, and the etiological role of specific dietary carbohydrate components remains unclear. Our aim was to investigate associations of carbohydrate intake, glycemic index, and glycemic load with endometrial cancer risk in the US Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. Recruitment took place in 1993–2001. Over a median of 9.0 years of follow-up through 2009, 386 women developed endometrial cancer among 36,115 considered in the analysis. Dietary intakes were assessed using a 124-item diet history questionnaire. Cox proportional hazards models were applied to calculate hazard ratios and 95% confidence intervals. Significant inverse associations were detected between endometrial cancer risk and total available carbohydrate intake (hazard ratio (HR) = 0.66, 95% confidence interval (CI): 0.49, 0.90), total sugars intake (HR = 0.71, 95% CI: 0.52, 0.96), and glycemic load (HR = 0.63, 95% CI: 0.46, 0.84) when women in the highest quartile of intake were compared with those in the lowest. These inverse associations were strongest among overweight and obese women. No associations with endometrial cancer risk were observed for glycemic index or dietary fiber. Our findings contrast with previous evidence and suggest that high carbohydrate intakes and glycemic loads are protective against endometrial cancer development. Further clarification of these associations is warranted.

carbohydrate; dietary fiber; endometrial cancer; glycemic index; glycemic load

Abbreviations: BMI, body mass index; CI, confidence interval; DHQ, Diet History Questionnaire; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; IGF, insulin-like growth factor; PLCO, Prostate, Lung, Colorectal and Ovarian.

Endometrial cancer is a relatively common malignancy affecting women in developed countries (1), where type 1 endometrial tumors have been increasing in incidence (2–4). As such, factors associated with Western lifestyles have been closely linked with endometrial cancer development. It is the female malignancy most highly related to excess body weight (5), yet despite this clear direct association with body size, very few dietary risk factors have been implicated in endometrial cancer etiology (6). In particular, no conclusions were made with respect to carbohydrate and dietary fiber intakes and endometrial cancer risk in the World Cancer Research Fund/American Institute of Cancer Research 2007 global food, nutrition, physical activity, and cancer report (6).

A recent systematic review showed that diets high in glycemic load are directly associated with endometrial cancer development (7). Glycemic load is a carbohydrate-related measure designed to reflect the overall glucose demand of a food over the 2-hour period after consumption; it incorporates both the glycemic index value and the total available carbohydrate content of the usual portion size of the food (8). Glycemic load can therefore be interpreted as a measure of carbohydrate quality and quantity. Glycemic index values rank the glucose demand of the standardized portion size (usually 50 g) of a food in comparison with white bread or glucose over the 2-hour postprandial period. Glycemic index can therefore be viewed as a measure of carbohydrate quality only. Findings from the systematic review

also indicated that a high-glycemic-load diet increases the risk of endometrial cancer with higher body mass index (BMI; weight (kg)/height $(m)^2$), suggesting that BMI may be an effect modifier of the association between glycemic load and endometrial cancer (7). However, only 4 prospective cohort studies were included in the review (9–12). A subsequent study originating from the National Institutes of Health-AARP Diet and Health Study suggested that women with the highest glycemic loads were at a nonsignificantly heightened risk of endometrial cancer (13). In contrast, glycemic index has not been associated with endometrial cancer risk (7, 13), while reports on other carbohydrate components, including sugars, starch, and fiber, have produced conflicting findings (9, 14–16). Because of the relatively small number of studies conducted to date, we sought to investigate the associations of glycemic index, glycemic load, and other dietary carbohydrate components with endometrial cancer risk within a large US prospective study, the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial.

MATERIALS AND METHODS

Study design

The PLCO Cancer Screening Trial is a large population-based trial in which participants have been randomized to undergo screening procedures for the 4 cancer types of interest or to follow their usual medical care practices (17). Recruitment of participants occurred between 1993 and 2001 at 10 study centers throughout the United States: Georgetown University/Lombardi Cancer Center (Washington, DC), Henry Ford Health System (Detroit, Michigan), Marshfield Clinic Research Foundation (Marshfield, Wisconsin), Pacific Health Research and Education Institute (Honolulu, Hawaii), University of Alabama at Birmingham (Birmingham, Alabama), University of Colorado (Denver, Colorado), University of Minnesota (Minneapolis, Minnesota), University of Pittsburgh (Pittsburgh, Pennsylvania), University of Utah (Salt Lake City, Utah), and Washington University School of Medicine (St. Louis, Missouri) (18). Approval for the study was granted by the relevant institutional review boards at all study centers.

Female PLCO study participants

Women were eligible for enrollment if they were aged ≥55 years and <75 years; had no prior diagnosis of primary or metastatic colon, rectal; lung, or ovarian cancer; had not undergone surgical removal of both ovaries (prior to October 2006), the entire colon, or 1 lung; and had no previous or current use of tamoxifen or raloxifene during the 6 months prior to randomization (prior to April 1999). At recruitment, participants completed a baseline questionnaire that included questions about sociodemographic background, smoking history, personal and family medical histories, anthropometric factors, reproductive factors, medication and hormone use, and recent history of screening examinations for prostate, lung, colorectal, and ovarian cancers.

At baseline, of the 78,216 women recruited, 2,094 had more than 8 missing frequency responses for the dietary questionnaires, 81 had a personal history of endometrial cancer at study recruitment, and 5 had invalid follow-up times and were excluded from analysis. Further exclusion criteria applied to the remaining 76,036 women in this data set (in order) were: noncompletion of the validated Diet History Questionnaire (DHQ) ($n = 15{,}714$), having undergone a hysterectomy prior to study entry ($n = 21{,}974$), having the questionnaire completed by a proxy respondent ($n = 255$), having missing information on height or weight ($n = 457$), and having an extreme (greater than twice the interquartile range) log energy intake or BMI ($n = 428$). A further 201 and 892 women who developed endometrial cancer or were censored from follow-up after study recruitment but prior to completion of the DHQ, respectively, were also excluded. This left 36,115 women for inclusion in this analytical data set.

Participants were followed from the date of DHQ completion to study year 13, December 31, 2009, the date of death, or the date of endometrial cancer diagnosis, whichever came first. The median time elapsed between recruitment/completion of the baseline questionnaire and completion of the DHQ was 3.0 years (interquartile range, 2.9–4.0). Tumors classified as malignant neoplasms of the corpus uteri were considered cases of endometrial cancer (codes C.54–C.55 in the *International Classification of Diseases for Oncology, Third Edition*). The majority of cases included in the study (92.2%) were neoplasms of the endometrium (code C54.1), with the remainder being classified as malignant neoplasms of the corpus uteri or uterus.

Dietary assessment

Respondents who completed the validated 124-food item DHQ were considered in the current dietary analyses of carbohydrate intake, glycemic index, and glycemic load. Comparisons between the DHQ and four 24-hour dietary recalls revealed the deattenuated correlation coefficients for energy-adjusted carbohydrate and fiber intakes in women to be 0.69 and 0.77, respectively (19). Dietary nutrient intakes were calculated by multiplying the daily frequency of each consumed food item by the nutrient value of the sex-specific portion size based on the nutrient database from the US Department of Agriculture's 1994–1996 Continuing Survey of Food Intakes by Individuals (19). In the US Department of Agriculture's food composition tables, total carbohydrate values include both available carbohydrate, including sugars and starches, and dietary fiber. Therefore, dietary fiber intake was subtracted from total carbohydrate intake to obtain a value for total available carbohydrate, as previously described (20). Glycemic index and glycemic load values were assigned to each food using published international tables of values (21), finding the best match possible as previously described (22). Sex- and serving-size-specific glycemic load values were then calculated for 225 nutritionally similar food groups using the weighted mean method (19, 23), and daily glycemic load was calculated according to the frequency of intake. Daily glycemic index was then determined by dividing glycemic load by total available carbohydrate intake and multiplying the result by 100 (22). Total sugars intake was classified as total available carbohydrate intake minus starch intake.

Statistical analysis

Cox proportional hazards models were applied to calculate hazard ratios and 95% confidence intervals for endometrial cancer risk, using person-years of follow-up as the underlying time variable. Glycemic load, total available carbohydrate, and intakes of fiber, starch, and sugars were adjusted for energy intake using the nutrient density method (24). Cox proportional hazards plots were visually inspected to ensure that assumptions were met. Dietary variables were categorized according to energy-adjusted quartiles of intake (except for glycemic index, which was not highly correlated with energy; $r = 0.02$), based on the distribution in the whole analytical cohort. In addition, dietary variables were explored as continuous variables by dividing energy-adjusted intake (except glycemic index) by the difference between the 25th and 75th percentiles, after checking for a normal data distribution.

In minimally adjusted models, we included energy intake (log kcal/day) and age at completion of the DHQ (years) as covariates. For potential confounders, the mode was imputed for missing or unknown values for education ($n = 58$; <0.2%), history of diabetes ($n = 181$; <0.5%), age at menarche ($n = 57$; <0.2%), age at menopause ($n = 324$; <0.9%), use of hormone replacement therapy ($n = 212$; <0.6%), and use of oral contraceptives ($n = 20$; <0.1%). In multivariable-adjusted models, additional confounders included ethnicity (non-Hispanic white, non-Hispanic black, Asian, or other), age at menarche (<12, 12–13, or ≥14 years), age at menopause (<50 years vs. ≥50 years), oral contraceptive use (ever/never), and BMI (<18.5, 18.5–<25, 25–<30, or ≥30). Other potential confounders that were tested but did not significantly influence results ($P > 0.25$ in models) and therefore were not included in the models were history of diabetes, study center, education, height, parity, hormone replacement therapy, personal history of endometriosis, personal history of uterine fibroid tumors, alcohol intake, physical activity level, and smoking status. In further models, the nutrient density method was also used to evaluate possible confounding effects of other macronutrients (24), and these energy-adjusted intakes were used to assess correlations between nutrients using Pearson's partial correlation coefficient. *P* values for trend across quartiles were estimated by assigning the median intake value for the quartile to each person and including this as a continuous variable in the hazards model. We also conducted analyses stratified a priori to explore effect modification for tertiles (data not shown because of limited statistical power) and continuous increments of dietary intake and endometrial cancer risk by BMI category. Tests for interaction were conducted by including an additional multiplicative variable for BMI and dietary intake in the regression model in tertile analysis and by means of the Wald test for continuous analysis. Stratified analysis was also performed for endometrial adenocarcinomas only and according to time to diagnosis for cases diagnosed during the first 2, 2–4, and >4 years of follow-up. All statistical analysis was conducted using Intercooled Stata, version 11 (StataCorp LP, College Station, Texas).

RESULTS

Over a median follow-up period of 9.0 years, 386 women developed endometrial cancer among 36,115 women included in this analysis (corresponding to a total of 305,360 person-years of follow-up). Characteristics of participants are displayed according to quartile of energy-adjusted glycemic load in Table 1. Persons with the highest dietary glycemic loads were slightly older and less likely to be Caucasian, to be obese, to have a college or postgraduate education, to be a current or former smoker, and to have used oral contraceptives, but they reported undertaking vigorous physical activity more frequently than women with the lowest glycemic loads, although activity levels were unknown for more than half of participants. History of diabetes, use of hormone replacement therapy, parity, and ages at menarche and menopause were largely similar across categories of glycemic load.

As shown in Table 2, women with the highest energy-adjusted glycemic loads also had higher intakes of available carbohydrate, starch, total sugars, and fiber and a higher glycemic index but lower intakes of total energy, fat, saturated fat, protein, and alcohol compared with counterparts with lower glycemic loads.

Results from Cox proportional hazards regression analysis of carbohydrate intake and endometrial cancer risk are displayed in Table 3. After adjustment for confounders, total available carbohydrate was strongly inversely associated with endometrial cancer risk when the highest quartile of intake was compared with the lowest (hazard ratio (HR) = 0.66, 95% confidence interval (CI): 0.49, 0.90; *P* for trend = 0.01) and in continuous analysis. Similar risk reductions were observed for glycemic load and endometrial cancer (quartile 4 vs. quartile 1: HR = 0.63, 95% CI: 0.46, 0.84; *P* for trend = 0.002). Similar or potentially stronger inverse associations were detected when the nutrient density method of energy adjustment was not applied to the analysis (see Web Table 1, available at http://aje.oxfordjournals.org/). No clear pattern of association between glycemic index and endometrial cancer risk was observed in either minimally adjusted models or fully adjusted models. The similar results seen for endometrial cancer risk and energy-adjusted glycemic load and energy-adjusted total available carbohydrate reflect their very high correlation ($r = 0.94$). Neither dietary glycemic load nor available carbohydrate was highly correlated with glycemic index after adjustment for energy intake ($r = 0.34$ and $r = 0.004$, respectively). After energy adjustment, dietary glycemic load was also highly correlated with intakes of fat ($r = -0.67$) and saturated fat ($r = -0.56$) and was moderately correlated with intakes of dietary fiber ($r = 0.31$) and protein ($r = -0.35$). Similar patterns were seen for correlations between energy-adjusted available carbohydrate and other nutrients. In multivariable-adjusted models, further adjustments for energy-adjusted total fat, saturated fat, fiber, or protein intake did not alter the associations seen for glycemic load or total available carbohydrate intake and endometrial cancer risk (data not shown).

As shown in Table 3, the inverse association between carbohydrate intake and endometrial cancer risk appeared to be attributable to total sugars intake (quartile 4 vs. quartile 1: HR = 0.71, 95% CI: 0.52, 0.96) rather than starch intake. In further analysis, when the associations between endometrial cancer risk and carbohydrate as individual monosaccharides or disaccharides were explored, no associations were detected for fructose intake (quartile 4 vs. quartile 1: HR = 0.89, 95% CI: 0.66, 1.21); however, sucrose intake was protective (quartile 4

Table 1. Characteristics of Women in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial According to Energy-adjusted Quartile of Glycemic Load, United States, 1993–2001

Characteristic	Energy-adjusted Quartile of Glycemic Load[a]							
	Quartile 1 (*n* = 9,029)		Quartile 2 (*n* = 9,029)		Quartile 3 (*n* = 9,029)		Quartile 4 (*n* = 9,028)	
	No.	%[b]	No.	%	No.	%	No.	%
Median age at DHQ completion, years	64		65		65		66	
Race/ethnicity								
Non-Hispanic white	8,545	94.6	8,537	94.6	8,354	92.5	7,746	85.8
Non-Hispanic black	183	2.0	182	2.0	245	2.7	477	5.3
Asian	145	1.6	195	2.2	296	3.3	672	7.4
Other	156	1.7	115	1.3	134	1.5	133	1.5
Body mass index[c]								
<18.5	85	0.9	97	1.1	92	1.0	126	1.4
18.5–<25	3,726	41.3	3,690	40.9	3,730	41.3	4,265	47.2
25–<30	3,046	33.7	3,149	34.9	3,194	35.4	2,965	32.8
≥30	2,172	24.1	2,093	23.2	2,013	22.3	1,672	18.5
Education								
Less than high school	337	3.7	335	3.7	374	4.1	478	5.3
High school/12 years	3,249	36.0	3,121	34.6	3,155	34.9	3,104	34.4
Some college/post-high school	2,185	24.2	2,376	26.3	2,442	27.1	2,597	28.8
College/postgraduate	3,258	36.1	3,197	35.4	3,058	33.9	2,849	31.6
Smoking status								
Never smoker	3,944	43.7	5,027	55.7	5,408	59.9	5,729	63.5
Former smoker	3,870	42.9	3,247	36.0	2,995	33.2	2,663	29.5
Current smoker	1,215	13.5	755	8.4	626	6.9	636	7.0
History of diabetes								
No	8,581	95.0	8,574	95.0	8,621	95.5	8,623	95.5
Yes	448	5.0	455	5.0	408	4.5	405	4.5
Age at menarche, years								
<12	1,768	19.6	1,642	18.2	1,709	18.9	1,642	18.2
12–13	4,926	54.6	5,085	56.3	4,972	55.1	4,878	54.0
≥14	2,335	25.9	2,302	25.5	2,348	26.0	2,508	27.8

Table continues

vs. quartile 1: HR = 0.64, 95% CI: 0.47, 0.88). There was no evidence of a protective association between dietary fiber intake and endometrial cancer risk. Similar results were evident when analysis was restricted to endometrial adenocarcinomas only (Web Table 2).

Table 4 shows results from stratified analysis of continuous measures of dietary variables (categorical data are not shown because of limited statistical power) and endometrial cancer risk by BMI category. The previously observed inverse associations between total available carbohydrate, glycemic load, and total sugars intake and endometrial cancer risk appeared to be strongest for overweight persons (and obese persons, for total sugars only), although tests for interaction were not statistically significant. The nonsignificant associations of glycemic index and starch and dietary fiber intakes with endometrial cancer risk were not markedly altered by varying BMI categories. In further analysis, there was no evidence of the protective associations for total available carbohydrate, total sugars, and glycemic load attenuating over time (data not shown).

DISCUSSION

Analysis from the PLCO Cancer Screening Trial demonstrated that total available carbohydrate and glycemic load were significantly inversely associated with endometrial cancer risk. Inverse associations were stronger for total sugars intake than for starch intake, and this relationship was particularly evident in overweight and obese women. Glycemic index and dietary fiber intake were not related to endometrial cancer risk in this study population.

We identified no significant association between dietary fiber and endometrial cancer risk in either categorical or continuous analysis. This contrasts with results from a meta-analysis of case-control studies, in which Bandera et al. (25) found

Table 1. Continued

Characteristic	Energy-adjusted Quartile of Glycemic Load[a]							
	Quartile 1 (*n* = 9,029)		Quartile 2 (*n* = 9,029)		Quartile 3 (*n* = 9,029)		Quartile 4 (*n* = 9,028)	
	No.	%[b]	No.	%	No.	%	No.	%
Age at menopause, years								
<50	3,039	33.7	2,939	32.6	3,016	33.4	3,106	34.4
≥50	5,990	66.3	6,090	67.5	6,013	66.6	5,922	65.6
Median no. of livebirths	3		3		3		3	
Use of oral contraceptives								
Never use	3,469	38.4	3,981	44.1	4,369	48.4	4,616	51.1
Ever use	5,560	61.6	5,048	55.9	4,660	51.6	4,412	48.9
Use of hormone replacement therapy								
Never use	3,303	36.6	3,515	38.9	3,651	40.4	3,823	42.4
Former use	4,182	46.3	4,013	44.5	3,793	42.0	3,641	40.3
Current use	1,544	17.1	1,501	16.6	1,585	17.6	1,564	17.3
Vigorous physical activity, hours/week								
<1	1,487	16.5	1,282	14.2	1,200	13.3	1,193	13.2
1–4	1,932	21.4	1,985	22.0	1,933	21.4	1,766	19.6
>4	844	9.4	873	9.7	906	10.0	924	10.2
Unknown	4,766	52.8	4,889	54.2	4,990	55.3	5,145	57.0

Abbreviation: DHQ, Diet History Questionnaire.

[a] Cutpoints for energy-adjusted quartiles of glycemic load were as follows: quartile 1, <57.8 units/1,000 kcal/day; quartile 2, 57.8–<65.2 units/1,000 kcal/day; quartile 3, 65.2–<72.6 units/1,000 kcal/day; quartile 4, ≥72.6 units/1,000 kcal/day.

[b] Percentages may not total 100 because of rounding.

[c] Weight (kg)/height (m)^2.

Table 2. Median Daily Nutrient Intakes of Women in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial According to Energy-adjusted Quartile of Glycemic Load, United States, 1993–2001

Median Daily Nutrient Intake	Energy-adjusted Quartile of Glycemic Load[a]			
	Quartile 1 (*n* = 9,029)	Quartile 2 (*n* = 9,029)	Quartile 3 (*n* = 9,029)	Quartile 4 (*n* = 9,028)
Energy, kcal	1,501	1,474	1,399	1,300
Total available carbohydrate, g/1,000 kcal	99.0	116.4	128.5	145.2
Glycemic index, units	52.2	53.0	53.5	54.5
Glycemic load, units/1,000 kcal	52.3	61.7	68.6	78.2
Starches, g/1,000 kcal	39.9	46.3	49.5	52.3
Total sugars, g/1,000 kcal	56.8	70.1	78.9	92.4
Sucrose, g/1,000 kcal	18.4	23.1	26.1	29.8
Fructose, g/1,000 kcal	8.8	11.6	13.8	17.9
Fiber, g/1,000 kcal	7.6	9.9	12.0	15.5
Total fat, g/1,000 kcal	42.1	37.1	33.1	27.2
Saturated fat, g/1,000 kcal	12.9	11.4	10.1	8.1
Protein, g/1,000 kcal	40.8	39.9	38.5	35.1
Alcohol, g	4.2	1.5	0.8	0.4

[a] Cutpoints for energy-adjusted quartiles of glycemic load were as follows: quartile 1, <57.8 units/1,000 kcal/day; quartile 2, 57.8–<65.2 units/1,000 kcal/day; quartile 3, 65.2–<72.6 units/1,000 kcal/day; quartile 4, ≥72.6 units/1,000 kcal/day.

Table 3. Risk of Endometrial Cancer in Relation to Quartile of Dietary Carbohydrate Intake Among Women in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, United States, 1993–2001

Carbohydrate and Quartile of Intake	No. of Controls	No. of Cases	Age- and Energy-adjusted		Multivariable-adjusted[a]	
			HR	95% CI	HR	95% CI
Total available carbohydrate, g/1,000 kcal/day						
Q1 (<109.1)	8,921	108	1.00		1.00	
Q2 (109.1–<122.6)	8,919	110	1.00	0.77, 1.31	1.00	0.77, 1.31
Q3 (122.6–<136.1)	8,930	99	0.90	0.68, 1.18	0.91	0.69, 1.19
Q4 (≥136.1)	8,959	69	0.62	0.46, 0.85	0.66	0.49, 0.90
P for trend[b]				0.002		0.01
Continuous measure[c]	35,729	386	0.80	0.70, 0.91	0.82	0.72, 0.93
Glycemic index, units/day						
Q1 (<51.1)	8,940	89	1.00	1.00	1.00	
Q2 (51.1–<53.3)	8,911	118	1.31	0.99, 1.72	1.29	0.98, 1.70
Q3 (53.3–<55.4)	8,939	90	0.99	0.74, 1.33	0.97	0.72, 1.30
Q4 (≥55.4)	8,939	89	0.98	0.73, 1.31	0.94	0.70, 1.26
P for trend				0.49		0.34
Continuous measure	35,729	386	0.95	0.86, 1.05	0.94	0.85, 1.04
Glycemic load, units/1,000 kcal/day						
Q1 (<57.8)	8,911	118	1.00		1.00	
Q2 (57.8–<65.2)	8,929	100	0.83	0.64, 1.09	0.82	0.63, 1.07
Q3 (65.2–<72.6)	8,934	95	0.79	0.60, 1.03	0.78	0.59, 1.02
Q4 (≥72.6)	8,955	73	0.60	0.44, 0.81	0.63	0.46, 0.84
P for trend				0.001		0.002
Continuous measure	35,729	386	0.80	0.71, 0.91	0.81	0.72, 0.92
Starches, g/1,000 kcal/day						
Q1 (<39.7)	8,928	100	1.00		1.00	
Q2 (39.7–<46.6)	8,934	95	0.94	0.71, 1.24	0.92	0.69, 1.22
Q3 (46.6–<53.7)	8,932	97	0.95	0.72, 1.25	0.92	0.69, 1.21
Q4 (≥53.7)	8,935	94	0.91	0.68, 1.20	0.90	0.67, 1.19
P for trend				0.53		0.46
Continuous measure	35,729	386	0.99	0.87, 1.11	0.99	0.87, 1.12

Table continues

significant 20%–30% reduced risks of endometrial cancer for women with the highest dietary fiber intakes. However, our nonsignificant findings corroborate those from the only prospective case-cohort study identified in that systematic review (25) and 2 further prospective studies originating from the European Prospective Investigation into Cancer and Nutrition (EPIC) (9) and Nurses' Health Study (26) cohorts. This suggests that fiber intake is not related to endometrial cancer risk and perhaps that dietary measurement error may have influenced the results seen in previous case-control studies.

No evidence of an association between glycemic index and endometrial cancer risk was identified either, which is consistent with null findings from previous work (7, 13). However, the surprising observation that a high glycemic load was inversely associated with endometrial cancer risk in the PLCO Trial challenges previous conclusions from systematic reviews and meta-analyses (7, 27–29). Additionally, total available carbohydrate intake was strongly associated with a reduced risk of endometrial cancer. Conversely, the majority of investigations to date have shown no significant links between carbohydrate intake and endometrial cancer risk (10, 11, 30, 31). In the current study, glycemic load was very highly correlated with total available carbohydrate intake. Nonetheless, similar correlations were observed between glycemic load and total carbohydrate intake in EPIC (9), which found positive associations between these dietary factors and endometrial cancer risk, in contrast to the current study findings.

We examined total sugars and starches in an attempt to further clarify the inverse association between total available carbohydrate intake and endometrial cancer risk in the PLCO Trial. The protective association was stronger for total sugars intake than for starch intake, and this was attributed to sucrose

Table 3. Continued

Carbohydrate and Quartile of Intake	No. of Controls	No. of Cases	Age- and Energy-adjusted		Multivariable-adjusted[a]	
			HR	95% CI	HR	95% CI
Total sugars, g/1,000 kcal/day						
Q1 (<61.2)	8,924	105	1.00		1.00	
Q2 (61.2–<73.9)	8,918	110	1.04	0.80, 1.36	1.07	0.82, 1.40
Q3 (73.9–<87.8)	8,929	101	0.95	0.72, 1.25	0.98	0.75, 1.29
Q4 (≥87.8)	8,958	70	0.67	0.49, 0.90	0.71	0.52, 0.96
P for trend				0.007		0.02
Continuous measure	35,729	386	0.79	0.69, 0.91	0.81	0.71, 0.93
Fiber, g/1,000 kcal/day						
Q1 (<8.8)	8,938	91	1.00		1.00	
Q2 (8.8–<10.9)	8,926	103	1.12	0.85, 1.49	1.12	0.84, 1.49
Q3 (10.9–<13.3)	8,936	93	1.02	0.76, 1.36	1.03	0.77, 1.36
Q4 (≥13.3)	8,929	99	1.08	0.81, 1.44	1.13	0.85, 1.51
P for trend				0.76		0.53
Continuous measure	35,729	386	0.99	0.87, 1.14	1.02	0.89, 1.17

Abbreviations: CI, confidence interval; HR, hazard ratio; Q, quartile.

[a] Adjusted for age at completion of the Diet History Questionnaire (years), body mass index (weight (kg)/height (m)^2; <18.5, 18.5–<25, 25–<30, or ≥30), age at menarche (<12, 12–13, or ≥14 years), age at menopause (<50 years vs. ≥50 years), race/ethnicity (non-Hispanic white, non-Hispanic black, Asian, or other), oral contraceptive use (ever/never), and energy intake (calculated by the nutrient density method, except for glycemic index, and including log kcal/day in the model).

[b] *P* values for trend were estimated by assigning the median intake value for the quartile to each person and including this as a continuous variable in the model.

[c] Continuous intakes were calculated by dividing the energy-adjusted intake (except glycemic index) by the difference between the 75th and 25th percentiles.

intake. This contrasts with EPIC, which found a significant 36% increased risk of endometrial cancer per 50-g/day increment in total sugars intake (9). Few other studies have examined carbohydrate constituents in relation to endometrial cancer risk, with some reporting largely nonsignificant associations (14, 15), while another study observed direct associations with sucrose intake (32). Thus, it is unclear why glycemic load and total carbohydrate and sugars intakes were inversely related to endometrial cancer risk in our study. There is some evidence that a high-fat diet can increase the risk of developing endometrial cancer (33, 34), but this is certainly not conclusive, as other studies have observed no associations (14, 35) or indeed have found inverse associations for animal and saturated fat intakes and endometrial carcinogenesis (30). In our explorations, intake of dietary fat, including saturated fat, could not explain the inverse associations seen for glycemic load and available carbohydrate in the present analysis.

We had postulated that a high-glycemic-load diet may increase endometrial cancer risk via hyperinsulinemia and the insulin-like growth factor (IGF) system (36). Hyperinsulinemia has been shown to lower concentrations of IGF-binding protein, thereby increasing levels of insulin-like growth factor 1 (IGF-1), which inhibits apoptosis and sex hormone-binding globulin synthesis and stimulates cell proliferation and sex steroid synthesis, promoting tumor development (37). However, perhaps the results from the current study should not have been entirely unexpected. Free IGF-1 concentrations have been inversely related to endometrial adenocarcinoma development in a US prospective study, despite illustrating a strong positive association between hyperinsulinemia and risk, especially among overweight and obese participants (38). Moreover, the inverse association between IGF-1 and endometrial cancer risk was also strongest among overweight and obese women, rather than normal-weight women (38). The authors proposed that the seemingly paradoxical association may have been due to a lack of connection between circulating IGF-1 concentrations and those found in uterine cells (38). Since dietary carbohydrate factors are thought to affect IGF concentrations (39), it is plausible that these factors may explain the inverse associations with endometrial cancer risk in the current study, but they do not explain the lack of consistency with positive associations seen in other studies. However, these observations require confirmation before further speculation on the potential underlying mechanisms involved.

There is overwhelming evidence of a dose-response relationship between BMI and the risk of endometrial cancer (6, 40–42). Alternatively, overweight and obese persons are known to underreport total energy consumption in dietary assessments (43), so we cannot rule out the possibility that differential underreporting of energy intake in these women may have exaggerated the observed associations. It is also plausible that methodological issues regarding glycemic load calculations may explain the discrepancy between our findings and published data; however,

Table 4. Multivariable-adjusted Association between Energy-adjusted Dietary Factors and Risk of Endometrial Cancer Among Women in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, by Body Mass Index Category, United States, 1993–2001

Dietary Factor and Body Mass Index[a] Category	No. of Controls	No. of Cases	Hazard Ratio[b,c]	95% Confidence Interval	*P* for Interaction[d]
Total available carbohydrate					
18.5–<25	15,296	115	0.89	0.71, 1.13	0.55
25–<30	12,236	118	0.74	0.59, 0.94	
≥30	7,802	148	0.82	0.66, 1.01	
Glycemic index					
18.5–<25	15,296	115	0.90	0.75, 1.08	0.37
25–<30	12,236	118	0.83	0.69, 1.00	
≥30	7,802	148	1.05	0.89, 1.23	
Glycemic load					
18.5–<25	15,296	115	0.87	0.70, 1.10	0.31
25–<30	12,236	118	0.71	0.56, 0.89	
≥30	7,802	148	0.85	0.69, 1.05	
Starches					
18.5–<25	15,296	115	0.95	0.76, 1.19	0.22
25–<30	12,236	118	0.90	0.71, 1.13	
≥30	7,802	148	1.07	0.88, 1.37	
Total sugars					
18.5–<25	15,296	115	0.91	0.71, 1.17	0.29
25–<30	12,236	118	0.77	0.60, 0.99	
≥30	7,802	148	0.78	0.63, 0.98	
Fiber					
18.5–<25	15,296	115	1.05	0.83, 1.33	0.15
25–<30	12,236	118	1.07	0.83, 1.38	
≥30	7,802	148	0.96	0.75, 1.23	

[a] Weight (kg)/height (m)^2.
[b] Hazard ratio for continuous increments of intake, calculated by dividing the energy-adjusted intake (except glycemic index) by the difference between the 75th and 25th percentiles.
[c] Adjusted for age at completion of the Diet History Questionnaire (years), body mass index (continuous), age at menarche (<12, 12–13, or ≥14 years), age at menopause (<50 years vs. ≥50 years), race/ethnicity (non-Hispanic white, non-Hispanic black, Asian, or other), oral contraceptive use (ever/never), and energy intake (calculated by the nutrient density method, except for glycemic index, and including log kcal/day in the model).
[d] Estimated by means of the Wald test.

this would not account for the inverse associations between total carbohydrate and sugars intakes and endometrial cancer risk. Moreover, the same method was applied in the study by George et al. (13); therefore, it may be that there are different underlying food sources at any given value of dietary glycemic index or glycemic load in the data from the PLCO Trial compared with previous studies. If this were the case, different dietary patterns with the same overall dietary glycemic index and glycemic load values might explain the divergent effects of carbohydrate quality observed between studies. It is also possible that residual confounding from unmeasured factors may have influenced the results shown or that some findings were due to chance. For example, we were unable to fully test adjustment for physical activity level, which has a protective role in endometrial carcinogenesis (44) but was unknown for 55% of women in our data set. Note that a large proportion of women in the original trial had undergone a hysterectomy and were subsequently excluded from the analyses. Although it was necessary to exclude these women since they were not at risk of endometrial cancer, they may have had different dietary habits, which in turn may have influenced the associations seen. However, the prevalence of women with hysterectomies in the PLCO Trial is broadly in line with the prevalences seen nationally in the United States for women aged 55–74 years (45, 46); therefore, this should have had a minimal impact on the representativeness of women in the PLCO Trial.

Strengths of the current study include its large sample size and prospective design, making it unlikely that any associations seen were attributable to reverse causation and that subclinical cancer may have contributed to changes in the dietary habits of cases. The dietary questionnaire has been shown to assess total carbohydrate and fiber intakes of women residing in the United States with fair validity and reproducibility (19), and a rigorous method was used to assign glycemic index and glycemic load values to foods, primarily using data on American foods where possible (22).

There are some limitations of the current analysis. Dietary questionnaire data were self-reported, which may have incorporated some measurement error from participants' overemphasizing healthy eating patterns and underestimating intakes of unhealthier foods. A large number of women ($n = 15,714$) were excluded because they had not completed the validated DHQ, and it is possible that this may have introduced some respondent bias. In addition, dietary intake was assessed only once at baseline; therefore, we were unable to account for subsequent changes in diet. There was also limited statistical power to examine interactions between dietary factors and endometrial cancer risk by BMI stratum.

In conclusion, high glycemic load, available carbohydrate, and total sugars intake were significantly inversely related to endometrial cancer risk in the PLCO Trial. Further studies are needed to determine whether the results seen in the PLCO Trial are atypical or whether the relationship of glycemic load and total carbohydrate and sugars intakes with endometrial cancer risk is not straightforward and varies in different population groups.

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