

Dietary Energy Density, Glycemic Load, Glycemic Index, and Risk for Endometrial Cancer in the CPS-II Nutrition Cohort

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Abstract

Background: The glycemic potential and energy density (ED) of diet may influence endometrial cancer risk. Although glycemic load (GL) is considered a probable risk factor for endometrial cancer, no studies have evaluated the association of total dietary ED with risk.

Methods: We evaluated associations of ED, GL, and glycemic index (GI) with postmenopausal endometrial cancer incidence. Analyses included 30,997 postmenopausal women from the Cancer Prevention Study II Nutrition Cohort with no previous history of cancer or diabetes, who provided information on diet, lifestyle, and medical history in 1999 and were followed for cancer incidence through June 2013. Multivariable-adjusted HRs and 95% confidence intervals were estimated for quartiles (Q) of total dietary ED, GL, and GI in relation to endometrial cancer incidence using Cox proportional hazards regression models.

Results: During a median follow-up time of 13.6 years, 425 endometrial cancer cases were identified. Median dietary ED was 1.5 kcal/g [interquartile range (IQR) = 1.3–1.7 kcal/g]. Median (IQR) GL and GI were 113.7 (100.5–126.8) and 52.5 (50.4–54.5), respectively. After adjustment for age, use of hormone replacement therapy, physical activity, and body mass index (kg/m²), neither ED, GL, nor GI were associated with endometrial cancer risk.

Conclusions: We found no associations of ED, GL, or GI with endometrial cancer risk.

Impact: These results do not support an association between total dietary ED, GL, or GI and risk of postmenopausal endometrial cancer. *Cancer Epidemiol Biomarkers Prev*, 27(1); 113–5. ©2017 AACR.

Introduction

There is growing interest in the role of dietary factors related to energy balance in endometrial cancer etiology. The association between energy density (ED), an estimate of energy per unit of food (kcal/g; ref. 1), and endometrial cancer risk has not been studied. Glycemic index (GI) reflects the difference in glycemic response between consumption of a food compared with glucose. Glycemic load (GL) reflects carbohydrate quality and quantity. GI and GL could influence cancer risk through effects on insulin and glucose metabolism, adiposity, and related conditions (2). The World Cancer Research Fund/American Institute for Cancer Research concluded that GL (but not GI) is a probable cause of endometrial cancer (3). The lack of convincing evidence may be due to inconsistencies in results among prospective studies and other methodologic concerns. The ability to update hysterectomy status and censor during follow-up is important for minimizing bias, especially if hysterectomy rates differ by GL or related factors (e.g., adiposity). Residual confounding by smoking, which is inversely associated with endometrial cancer risk, is another potential concern

(4, 5). Finally, type II diabetes (T2D) is a risk factor for endometrial cancer. Cohort participants with prevalent T2D may have already made changes to lower carbohydrate (GL) intakes. At least one study (4) observed that GL was lower in women with T2D and positively associated with risk only among women without baseline T2D (4). Careful consideration of these potential sources of bias is necessary when examining associations of ED, GL, and GI with risk.

Materials and Methods

The American Cancer Society established the Cancer Prevention Study II Nutrition Cohort (CPS-II NC) in 1992 (6). In 1999, 73,641 CPS-II NC women completed a 152-item food frequency questionnaire (FFQ; 17–19). We excluded women who completed no subsequent surveys ($n = 1,741$), had a history of any cancer prior to 1999 (except nonmelanoma skin cancer; $n = 13,633$), were perimenopausal, premenopausal, of unknown menopausal status ($n = 189$), had an unverified self-reported cancer ($n = 38$), reported implausible dietary data [very low (<500 kcal/day) or high (>3,500 kcal/day) energy intakes or missing FFQ sections ($n = 1,255$)], or reported having a hysterectomy ($n = 22,452$) or diabetes ($n = 3,336$), leaving 30,997 women in this analysis.

Endometrial cancer cases (ICD 10:C54.1 and C55; ICD 9:179 and 182) were identified through self-report on follow-up questionnaires and verified via medical records or linkage with state registries or the National Death Index. Person-years of follow-up were computed from completion of the 1999 FFQ to the date of last return of a subsequent biennial questionnaire, reported hysterectomy, diagnosis of endometrial cancer, death, or June 30, 2013.

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Table 1. Characteristics of eligible CPS-II NC participants by quartile (Q4 vs. Q1) of ED, GL, and GI (*n* = 30,996)

Characteristics	ED		GL		GI	
	Q1 (<1.28)	Q4 (≥1.66)	Q1 (<100.47)	Q4 (≥126.82)	Q1 (<50.43)	Q4 (≥54.48)
Mean (SD) age (y)	68.8 (6.3)	67.9 (6.3)	67.3 (6.1)	69.0 (6.3)	68.2 (6.2)	68.1 (6.2)
Mean (SD) height (in)	64.5 (2.6)	64.6 (2.5)	64.7 (2.5)	64.4 (2.5)	64.6 (2.6)	64.4 (2.5)
Mean (SD) BMI (kg/m ²)	24.7 (4.4)	26.0 (5.0)	25.8 (4.8)	24.7 (4.4)	25.3 (4.6)	25.4 (4.8)
Mean (SD) waist circumference (cm)	82.8 (12.4)	87.1 (13.0)	85.6 (12.9)	83.8 (12.8)	84.3 (12.7)	85.3 (12.8)
Mean (SD) adult weight gain (lbs)	23.5 (25.4)	32.9 (29.4)	29.9 (27.4)	25.1 (25.6)	27.1 (27.0)	29.1 (28.5)
Mean (SD) total energy (kcal/d)	1,517 (450)	1,716 (534)	1,627 (505)	1,585 (478)	1,616 (498)	1,587.7 (480)
Mean (SD) beverage energy (kcal/d)	255 (151)	259 (161)	264 (169)	263 (154)	275 (164)	239 (152)
Mean (SD) fat (% of energy)	25.8 (5.8)	34.3 (6.5)	36.3 (6.4)	23.7 (4.3)	32.4 (7.6)	27.9 (6.1)
Mean (SD) fiber (g/1,000 kcal/d)	14.3 (3.1)	8.8 (2.0)	9.7 (2.5)	12.9 (3.4)	11.5 (3.5)	10.9 (2.9)
Physical activity/week (% none)	3.9	7.1	5.0	4.8	4.4	5.4
Education (% >HS)	96.1	95.5	96.1	95.2	96.0	95.6
Race/ethnicity (% Caucasian)	96.9	98.6	98.4	97.3	98.4	97.6
Age at menarche (% <12)	79.7	83.5	82	82.2	80.8	82.9
Age at menopause (% ≥50)	71.8	67.8	68.9	70.1	70.1	69.1
HRT use (% current)	3.4	2.9	3.4	3.3	3.6	2.9
Oral contraceptive use (% ever)	38.7	39.5	46.2	34.3	40.8	39.1
Smoking (% current)	2.5	8.3	7.8	3.0	4.8	5.2
Parity (% nulliparous)	10.1	10.5	9.9	10.6	10.0	10.4
Family history (% yes)	2.7	2.7	2.7	2.5	2.7	2.3

*Spearman correlation coefficients between total dietary ED with GL and GI were -0.20 and 0.31, respectively, and between GL and GI were 0.60. ED was calculated without beverages.

Statistical analyses were performed using SAS version 9.4. Multivariable-adjusted HRs and 95% confidence intervals (CIs) were estimated for quartiles of dietary ED, GL, and GI using Cox proportional hazards regression models with the lowest category (Q₁) as the referent. These models are stratified by individual age and adjusted for hormone replacement therapy (HRT) use (never, current, former, or missing use of estrogen or combined HRT), detailed smoking history, age at menarche, parity, age at menopause, oral contraceptive use, and physical activity. Final models were evaluated with and without body mass index (BMI; kg/m²) as a continuous variable. Other potential covariates included in Table 1 were considered but did not confound associations. Linear trends were assessed by assigning the median value from each quartile of the exposures and modeling this as a continuous variable. The Cox proportional hazards assumption was tested for each dietary variable, and no violations were observed. Interactions by BMI, HRT, and physical activity with dietary variables were assessed by including each factor and its cross-product term

with quartile of diet variables in separate multivariable models using the likelihood ratio test. Results from two-sided χ^2 tests were considered statistically significant at *P* < 0.05.

Results

During a median follow-up of 13.6 years, 425 endometrial cancer cases were identified. Median dietary ED was 1.5 kcal/g [interquartile range (IQR) = 1.3–1.7 kcal/g]. Median (IQR) GL and GI were 113.7 (100.5–126.8) and 52.5 (50.4–54.5), respectively. Participants who consumed higher ED diets were more likely to have higher BMI, larger waist circumference, and greater adult weight gain, and diets higher in total energy and fat (Table 1). They were also more likely to be current smokers and more sedentary. In contrast, GL and GI were generally inversely associated with these lifestyle characteristics.

We found no associations of ED, GL, or GI with endometrial cancer risk (Table 2). Furthermore, there was no evidence of

Table 2. Association between dietary ED, GL, and GI and incidence of endometrial cancer among 30,996 women in CPS-II NC^a

	Cases (<i>n</i>)	Person-years	Multivariable ^b	Multivariable + BMI ^b
ED (kcal/g)				
<1.28	114	93,743	1.00	1.00
1.28–<1.46	107	95,522	0.94 (0.72–1.22)	0.92 (0.70–1.20)
1.46–<1.66	97	92,571	0.88 (0.67–1.16)	0.81 (0.62–1.08)
≥1.66	107	95,427	0.95 (0.72–1.24)	0.87 (0.66–1.14)
<i>P</i> _{trend}			0.65	0.25
GL				
<100.47	109	94,492	1.00	1.00
100.47–<113.70	115	94,453	0.99 (0.76–1.30)	1.00 (0.77–1.31)
113.70–<126.82	113	94,390	1.00 (0.77–1.31)	1.01 (0.77–1.33)
≥126.82	89	93,929	0.78 (0.59–1.04)	0.83 (0.62–1.11)
<i>P</i> _{trend}			0.10	0.25
GI				
<50.43	111	94,167	1.00	1.00
50.43–<52.49	112	94,470	1.01 (0.77–1.31)	1.05 (0.81–1.38)
52.49–<54.48	100	94,571	0.90 (0.69–1.18)	0.90 (0.68–1.19)
≥54.48	102	94,057	0.93 (0.71–1.21)	0.98 (0.74–1.29)
<i>P</i> _{trend}			0.46	0.66

^aValues are multivariable-adjusted RRs (95% CIs) unless otherwise indicated.

^bStratified by age and adjusted for smoking status, intensity and time since quitting, age at menarche, age at menopause, parity, HRT use, oral contraceptive use, and physical activity.

statistical interactions with BMI, physical activity, or HRT use (not shown).

Discussion

These results do not support an association between ED and postmenopausal endometrial cancer risk. Our null results for GL and GI are consistent with those of the two largest endometrial cancer studies, the NIH-AARP ($n = 1,041$ cases; ref. 5) and the European Prospective Investigation into Cancer and Nutrition cohorts ($n = 710$ cases; ref. 7).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.M. Hodge

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