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Glycemic load and endometrial cancer risk in a case-control study of Canadian women

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ABSTRACT

Introduction: The evidence for a role of dietary carbohydrate intake with endometrial cancer risk is conflicting. We therefore evaluated the association between glycemic load (GL) and endometrial cancer in a population-based-case control study using a comprehensive quantitative food frequency questionnaire for the estimation of GL.
Methods: Diet in the year before the reference date was assessed with the self-administered Canadian Diet History Questionnaire in 511 cases and 980 controls in Alberta, Canada between 2002 and 2006. Multivariable logistic regression was used to examine the association between GL and endometrial cancer risk, with non-linearity evaluated by the examination of cubic splines.
Results: The risk for endometrial cancer did not change based on GL (for the highest versus lowest quartile, adjusted odds ratio = 0.87, 95% confidence interval = 0.52–1.46), even after the removal of participants previously diagnosed with diabetes ((diabetics n cases = 63, *n* controls = 55 excluded) adjusted odds ratio = 0.77, 95% confidence interval = 0.44–1.36). We observed no evidence of effect modification by Body Mass Index (BMI)(*p*-interaction term = 0.22).
Conclusions: Intake of foods eliciting a glycemic response was not associated with endometrial cancer risk in this population of Canadian women.

1. Introduction

Endometrial cancer is the fourth most common cancer diagnosis among Canadian women [1]. Besides factors that result in prolonged exposure and/or altered levels of circulating and free estrogens such as nulliparity, early age at menarche, late age at menopause, among others [2], the other major risk factors for endometrial cancer are obesity [3] and a history of diabetes [4]. The role of obesity in endometrial cancer etiology is well established and has the strongest effect of any cancer site [5]. As excess body weight increases, insulin sensitivity decreases and insulin regulation is altered. Therefore a diet high in foods that elicit a strong glycemic response may plausibly increase endometrial cancer risk. Dietary glycemic load (GL), which characterizes total dietary-related glucose, and endometrial cancer risk has been examined with varying results observed [6]. Two recent case-control studies, that also included meta-analyses, found no effects (odds ratio (OR) = 1.01 (95% confidence interval (CI) = 0.64–1.61) [6] and OR = 1.15, 95% CI = 0.90–1.48) [7] for elevated quartiles of GL whereas the meta-analyses of predominantly case-control studies suggested an increase in endometrial cancer risk (OR = 1.19 (95% CI = 1.06–1.34) [6] and OR = 1.06 (95% CI = 1.01–1.11 [7])). In contrast, a recent prospective analysis by Coleman et al. showed a reduced risk with increased GL (Hazard Ratio (HR) = 0.63, 95% CI = 0.46–0.84) [8]. These inverse findings conflict with the conclusions on glycemic index and endometrial cancer made in the World Cancer Research Fund's 2013 Continuous Update Project

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Report of Endometrial Cancer. This report estimated a 15% risk increase with a 50 unit increase in GL. These inconsistent findings provide a rationale for further investigation of the role of GL in endometrial cancer risk. The objective of this study was to provide additional empirical evidence regarding the putative association between GL and endometrial cancer risk.

2. Materials and methods

The details of this study have been previously reported [9]. Briefly, incident, histologically-confirmed cases of invasive endometrial cancer were identified from the Alberta Cancer Registry. Cases were Alberta residents, aged 30–79 years, not previously diagnosed with cancer with the exception of non-melanoma skin cancer between 2002 and 2006. Female controls were identified through random digit dialing from available prefixes for the province of Alberta. Controls were frequency-matched to cases on age (±5 years). Participation percentages were 68.3% (552/808) for cases and 52.2% (1036/1984) for controls. Diet in year before the reference date (date of interview for controls, date of diagnosis for cases) was assessed with the National Cancer Institute's self-administered Diet History Questionnaire (DHQ), previously adapted for use in Canada [10]. GL values obtained from the Glycemic Index Table published by Foster-Powell et al. [11] were added to 4200 individual foods that generated the DHQ nutrient database using methods described by Flood et al. [12]. The individual-level average daily GL intake was estimated by summing the GL values across all DHQ items after accounting for item-specific portion size and frequency of intakes reported by participants. Interviewers recorded personal health history, reproductive and menstrual history, exogenous hormone history, family history of cancer, lifetime physical activity patterns, lifetime alcohol consumption history, smoking habits, demographic characteristics and usual adult height and weight at each decade from age 20 to 60 years as well as measured waist and hip circumferences, weight, and height at interview.

We used unconditional logistic regression models where all known and potential confounders were evaluated for percent changes to the estimated effects of GL. Confounders were evaluated one at a time with all other covariates in the model using a 15% change in estimated OR as the criterion for inclusion in the final models. Final multivariable models were adjusted for age at reference, parity, hormone therapy and menopausal status, rural residential status (vs. urban), weight at reference, waist circumference, co-morbidities (Type II diabetes, hypertension, thrombosis, pulmonary embolism, myocardial infarction, angina pectoris, stroke, high cholesterol), fiber intake and total caloric intake. We also evaluated if energy adjustment using the residuals method influenced this association. We tested the effects of the residuals from a model of caloric intake regressed on both linear and non-linear variables for glycemic load. We examined the distribution of GL and characterized respondents based on quartiles of exposure among controls. A three-knot restricted cubic spline was also evaluated for GL to examine potential non-linearity in the association. We conducted a sensitivity analysis excluding those reporting a history of diabetes (n cases = 63, n controls = 55). We then examined effect modification by body mass index (BMI, kg/m^2) as a proxy for obesity as a continuous variable and by categories (<25, 25–30, >30).

3. Results

The demographic and relevant covariates from this population are presented in Table 1. Late age at menarche, peri- and

Table 1
Demographic and lifestyle characteristics of the study population by case and -control status, Alberta, Canada, 2001–6, (n = 1491).

Variable	Cases (n = 511)	Controls (n = 980)
	N and (%) or median and (25th, 75th percentile)	N and (%) or median and (25th, 75th percentile)
Age at reference (yr)	59 (53, 65)	59 (52, 66)
Age at menarche (yr)	12 (11, 13)	12.5 (12, 13)
Age at menopause (yr)	50 (48, 53)	50 (48, 53)
BMI (kg/m^2)	31.0 (26.4, 36.3)	27.2 (24.0, 31.0)
Waist-to-hip ratio (0.1 increments)	8.5 (7.9, 8.9)	8.1 (7.6, 8.6)
Nulliparous (vs. multiparous)	87 (17.0%)	97 (9.9%)
Pre-menopause (vs. peri and post)	51 (10.0%)	114 (11.6%)
Peri-menopause (vs. pre and post)	65 (12.7%)	153 (15.6%)
Post-menopause (vs. pre and peri)	395 (77.3%)	713 (72.8%)
Ever HT (post-menopause only)	175 (34.3%)	374 (38.2%)
HT & Menopause		
Peri & post, no HT (referent category)	285 (55.8%)	492 (50.2%)
Peri & post, estrogen only	20 (3.9%)	25 (2.6%)
Peri & post, estrogen and progestin	129 (25.4%)	323 (33.0%)
Peri & post, other hormones	26 (5.1%)	26 (2.7%)
Pre-menopausal	51 (10.0%)	114 (11.6%)
Smoke type		
Non-smoker	259 (50.7%)	490 (50.0%)
Current smoker	69 (13.5%)	125 (12.8%)
Ex smoker	163 (31.9%)	345 (35.2%)
Occasional	20 (3.9%)	20 (2.0%)
Ever hormonal contraceptive	380 (74.4%)	771 (78.7%)
MET-hrs/wk of lifetime total physical activity	101.0 (79.4, 127.7)	105.2 (83.01, 129.4)
Comorbidities combined (Type II diabetes, hypertension, thrombosis, pulmonary embolism, myocardinal infarction, angina pectoris, stroke, high cholesterol)		
0	212 (41.5%)	568 (58.0%)
1	175 (34.3%)	281 (28.7%)
2	91 (17.8%)	73 (7.5%)
3+	33 (6.5%)	58 (5.9%)
Glucose (mg/dL)	113.9 (90.7, 144.6)	103.7 (84.7, 134.9)
Insulin (mIU/L)	6.6 (4.2, 10.9)	4.8 (3.3, 7.2)
Calories	1482 (1158.2, 1892.6)	1482 (1147.9, 1880.4)
Mean daily ethanol intake from any alcoholic beverage	3.9 (1.2, 9.7)	4.9 (1.9, 11.3)

Abbreviations: yr = years, BMI = body mass index, HT = hormone therapy, MET = metabolic equivalent of task.