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Null Results in Brief

Cancer Epidemiology, Biomarkers & Prevention

Association between Dietary Energy Density and Risk of Breast, Endometrial, Ovarian, and Colorectal Cancer among Canadian Women

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Abstract

Background: Dietary energy density (DED) is strongly associated with cancer-associated metabolic disorders such as obesity and metabolic syndrome and may thus influence carcinogenesis. However, little is known about its association with cancer. Therefore, we investigated the association of DED with risk of breast, endometrial, ovarian, and colorectal cancers in the Canadian Study of Diet, Lifestyle, and Health.

Methods: We conducted a case–cohort study that included an age-stratified subcohort of 3,120 of the 39,532 female participants who completed self-administered lifestyle and dietary questionnaires at baseline, and in whom, respectively, 922, 188, 104, and 269 incident breast, endometrial, ovarian, and colorectal cancer cases were diagnosed, respectively. We estimated HRs and 95% confidence intervals for the association of DED with risk of these cancers using Cox proportional hazards regression models modified for the case–cohort design.

Results: There was no statistically significant association between DED and risk of breast, endometrial, ovarian, and colorectal cancers.

Conclusions: Our study suggests that DED is not independently associated with risk of breast, endometrial, ovarian, and colorectal cancers among women.

Impact: Further investigation of the association between DED and risk of these cancers in larger prospective studies is warranted, as demonstration of associations may have important implications for primary prevention of these cancers. *Cancer Epidemiol Biomarkers Prev; 27(3); 338–41. ©2017 AACR.*

Introduction

Breast, endometrial, ovarian, and colorectal cancers are among the leading cancers affecting Canadian women (1). The mechanism that underpins the development of these cancers is not completely understood, but epidemiologic and experimental studies suggest that relatively common metabolic disorders such as obesity, diabetes, and the metabolic syndrome are potential risk factors for these cancers (2). These metabolic disorders result partly from poor-quality diets characterized by high intake of nutrient-deficient foods which are high in fats, refined sugars, and alcohol (3, 4). In this regard, dietary energy density (DED), a new indicator of diet quality, has been positively associated with risk of these cancer-associated metabolic disorders (3, 4). Therefore, it is possible that DED may influence carcinogenesis, but very few studies have assessed the association between DED and cancer risk. One recent study found that DED is positively associated with risk of breast cancer (5), but to our knowledge, no studies have been conducted to examine its association with endometrial, ovarian, and colorectal cancers. Nevertheless, given the association of the aforementioned metabolic disorders with risk of these cancers, it is of interest to also determine whether DED influences their risk.

Therefore, we investigated the association between DED and risk of breast, endometrial, ovarian, and colorectal cancers among women in the Canadian Study of Diet, Lifestyle, and Health (CSDLH).

Materials and Methods

The CSDLH, described in detail elsewhere (6), is a prospective cohort study that includes a total of 73,909 participants (34,291 males, 39,618 females) who were recruited between 1992 and 1998. At enrolment, each participant completed a self-administered quantitative food frequency questionnaire that collected information on usual dietary intake of 166 food items over the previous year, and also completed a self-administered lifestyle questionnaire that ascertained information on sociodemographic, anthropometric, and lifestyle factors. For our analyses, the study comprised an age-stratified subcohort of 3,120 women, and 922 and 269 incident invasive breast and colorectal cancer cases, respectively. For endometrial cancer, we excluded women with a history of hysterectomy prior to enrolment in the study, resulting in a subcohort of 3,092 women and 188 incident cases, while for ovarian cancer, we excluded women with a history of bilateral oophorectomy leaving a subcohort of 2,826 women and 104 incident ovarian cancer cases.

Total DED, the exposure of interest, was calculated by dividing the total energy content [kilocalories (kcal)] of reported food intake by the total food weight (gm). All beverages were excluded from the calculation, as the participants' water intake was

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Table 1. Characteristics of study population

Characteristics	Subcohort[a] $n = 3,120$	Breast cancer cases $n = 922$	Colorectal cancer cases $n = 269$	Endometrial cancer		Ovarian cancer	
				Subcohort $n = 2,636$	Cases $n = 180$	Subcohort $n = 2,826$	Cases $n = 104$
Age (years)							
Median (IQR)	59 (48–71)	53 (44–64)	65 (52–72)	59 (48–71)	55 (47–65)	58 (48–70)	55 (44–65)
BMI							
Median (IQR)	23.7 (21.5–26.3)	23.7 (21.7–26.5)	23.9 (21.9–26.2)	23.6 (21.5–26.3)	25.4 (23.5–30.3)	23.6 (21.5–26.3)	23.6 (21.5–26.9)
Educational status *n* (%)							
High school or less	75 (2.4)	23 (2.2)	11 (4.1)	57 (2.1)	2 (1.1)	64 (2.3)	4 (3.9)
Post-secondary/some college	1820 (58.3)	605 (57.4)	146 (54.3)	1526 (57.9)	99 (55.0)	1649 (58.1)	55 (52.3)
Graduate school	1225 (39.3)	427 (40.5)	112 (41.6)	1053 (40.0)	79 (43.9)	1124 (39.6)	45 (43.3)
Family history of breast cancer *n* (%)							
Yes	314 (10.1)	143 (13.5)	–	265 (10.1)	18 (10.0)	285 (10.1)	11 (10.6)
No	2806 (89.9)	912 (86.5)	–	2371 (90.0)	162 (90.0)	2541 (89.9)	93 (89.4)
Smoking status *n* (%)							
Never	1687 (54.1)	576 (54.6)	138 (51.3)	1424 (54.0)	105 (58.3)	1524 (53.9)	45 (43.3)
Former	1217 (39.0)	403 (38.2)	111 (41.3)	1030 (39.1)	60 (33.3)	1104 (39.1)	51 (49.0)
Current	211 (6.8)	75 (7.1)	19 (7.1)	177 (6.7)	13 (7.2)	194 (6.9)	8 (7.7)
Missing	5 (0.2)	1 (0.1)	1 (0.1)	5 (0.2)	2 (1.1)	4 (0.1)	0 (0.0)
Physical activity							
Median (IQR)	13.5 (1.4–27.1)	13 (5.3–25.8)	11.8 (3.3–23.0)	13.5 (4.0–26.8)	11.2 (5.7–25.7)	14.0 (4.3–27.5)	12.4 (4.2–25.1)
Hormone therapy use *n* (%)							
Yes	1079 (34.4)	334 (31.7)	–	727 (27.8)	59 (32.8)	846 (29.9)	40 (38.5)
No	2055 (65.6)	721 (68.3)	–	1909 (72.4)	121 (67.2)	1980 (70.1)	64 (61.5)
Age at menopause							
Median (IQR)	50 (45–52)	50 (45–53)	–	50 (48–53)	51(48–53)	50 (46–52)	50 (44–52)
DED (kcal/g)							
Median (IQR)	1.3 (1.1–1.5)	1.3 (1.1–1.5)	1.3 (1.1–1.5)	1.3 (1.1–1.5)	1.3 (1.2–1.5)	1.3 (1.1–1.5)	1.3 (1.1–1.5)

[a]Subcohort for breast and colorectal cancer.

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Table 2. Associations between DED and risk of breast, endometrial, ovarian, and colorectal cancers among women from the Canadian Study of Diet, Lifestyle, and Health

Characteristics	No. of cases	HR (95% CI[a])	HR (95% CI[b])
Breast cancer			
Continuous (per unit score)		0.95 (0.73–1.23)	0.93 (0.71–1.22)
Quintiles			
1	190	1.00	1.00
2	152	0.78 (0.57–1.07)	0.76 (0.55–1.04)
3	181	0.89 (0.65–1.23)	0.87 (0.63–1.21)
4	209	1.31 (0.97–1.78)	1.33 (0.98–1.81)
5	190	0.91 (0.66–1.26)	0.88 (0.64–1.23)
P_{trend}		0.34	0.37
Endometrial cancer			
Continuous (per unit score)		1.04 (0.65–1.68)	1.04 (0.64–1.71)
Quintiles			
1	27	1.00	1.00
2	41	1.41 (0.74–2.68)	1.32 (0.68–2.54)
3	40	1.69 (0.88–3.23)	1.64 (0.83–3.21)
4	39	1.66 (0.84–3.26)	1.70 (0.86–3.38)
5	33	1.33 (0.67–2.65)	1.30 (0.64–2.62)
P_{trend}		0.30	0.30
Ovarian cancer			
Continuous (per unit score)		0.86 (0.43–1.70)	0.88 (0.44–1.76)
Quintiles			
1	18	1.00	1.00
2	19	1.47 (0.66–3.26)	1.55 (0.68–3.53)
3	25	1.27 (0.56–2.87)	1.38 (0.60–3.18)
4	15	1.05 (0.44–2.53)	1.01 (0.41–2.53)
5	27	1.49 (0.67–3.30)	1.63 (0.73–3.67)
P_{trend}		0.58	0.51
Colorectal cancer[c]			
Continuous (per unit score)		0.96 (0.71–1.30)	0.96 (0.71–1.30)
Quintiles			
1	55	1.00	1.00
2	45	0.73 (0.50–1.07)	0.70 (0.47–1.03)
3	56	0.92 (0.64–1.32)	0.89 (0.62–1.30)
4	68	1.12 (0.78–1.61)	1.12 (0.77–1.61)
5	45	0.98 (0.68–1.41)	0.98 (0.68–1.41)
P_{trend}		0.37	0.34

[a]Stratified by age at entry and adjusted for age at menarche, educational level, breastfeeding, smoking status, BMI, parity, family history, age at menopause, oral contraceptive use, physical activity level, alcohol intake.

[b]Also adjusted for BMI.

[c]Not adjusted for age at menarche, breastfeeding, parity, menopausal status, oral contraceptive use, hormone therapy use. Also adjusted for red/processed meat intake, dairy intake, folate.

unknown. The endpoints of interest were incident breast, endometrial, ovarian, and colorectal cancers. Incident cancer cases were ascertained via record linkage to the Canadian Cancer Registry and to the Ontario Cancer Registry.

Cox proportional hazards regression was used to estimate HRs and 95% confidence intervals for the association of DED with risk of reproductive cancers (breast, endometrial, and ovarian) and colorectal cancer, adjusting for education, smoking status, physical activity, alcohol intake, and BMI in all models. Models for reproductive cancers were additionally adjusted for age at menarche, parity, breastfeeding, menopausal status, HRT use, oral contraceptive use, and family history of breast cancer in a first-degree relative, while colorectal cancer was additionally adjusted for red/processed meat intake, dairy intake, folate, and folate. The statistical analyses were conducted using Stata 14.1 (StataCorp).

Results

Median DED in the study population at baseline was similar for both subcohort members and cases (1.3 kcal/g; Table 1). After adjusting for potential confounders, we found no associations between DED and risk of breast, endometrial, ovarian, or colorectal cancer among women (Table 2).

Discussion

Despite the relatively strong associations that have been observed between DED and cancer-associated metabolic disorders (3, 4), in this study, there was no evidence to support independent associations between DED and risk of breast, endometrial, ovarian, and colorectal cancers with or without adjustment for BMI. Contrary to our results, one large prospective study reported a positive association between DED and risk of breast cancer ($n = 2{,}509$ breast cancer cases; ref. 5). To our knowledge, the associations between DED and endometrial, ovarian, and colorectal cancers have not been previously studied. Our null results for endometrial and ovarian cancer may be due in part to the relatively small number of cases. Errors in the DED estimates resulting from recall and reporting biases may also have contributed to our findings. In addition, the food coding database may not have fully accounted for water loss during cooking, which may impact the energy density of a food (7). Nonetheless, an

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association between DED and risk of breast, endometrial, ovarian and colorectal cancers should not be ruled out, as DED is strongly correlated with metabolic disorders such as obesity and metabolic syndrome which may generate chronic inflammation, oxidative stress, and other processes that predispose to carcinogenesis (2). Therefore, further investigations in larger cohort studies are warranted, as the results of such research may have important implications for the primary prevention of these cancers.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: R. Arthur, T.E. Rohan
Development of methodology: R. Arthur, T.E. Rohan
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): V. Kirsh, T.E. Rohan
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): R. Arthur, T.E. Rohan
Writing, review, and/or revision of the manuscript: R. Arthur, V. Kirsh, T.E. Rohan
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): R. Arthur, V. Kirsh, T.E. Rohan
Study supervision: T.E. Rohan

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References

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]; 2013. Available from: http://globocan.iarc.fr/Default.aspx.
2. Gallagher EJ, LeRoith D. Epidemiology and molecular mechanisms tying obesity, diabetes, and the metabolic syndrome with cancer. Diabetes Care 2013;36 (Suppl 2):S233–9.
3. Mendoza JA, Drewnowski A, Christakis DA. Dietary energy density is associated with obesity and the metabolic syndrome in U.S. adults. Diabetes Care 2007;30:974.
4. Hingle MD, Wertheim BC, Neuhouser ML, Tinker LF, Howard BV, Johnson K, et al. Association between dietary energy density and incident type 2 diabetes in the Women's Health Initiative. J Acad Nutr Diet 2017;117:778–85.
5. Hartman TJ, Gapstur SM, Gaudet MM, Shah R, Flanders WD, Wang Y, et al. Dietary energy density and postmenopausal breast cancer incidence in the cancer prevention study II nutrition cohort. J Nutr 2016;146:2045–50.
6. Rohan TE, Soskolne CL, Carroll KK, Kreiger N. The Canadian Study of Diet, Lifestyle, and Health: design and characteristics of a new cohort study of cancer risk. Cancer Detect Prev 2007;31:12–7.
7. Ledikwe JH, Blanck HM, Khan LK, Serdula MK, Seymour JD, Tohill BC, et al. Dietary energy density determined by eight calculation methods in a nationally representative United States Population. J Nutr 2005;135:273–8.

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AACR American Association for Cancer Research

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