

Risk of endometrial cancer in relation to individual nutrients from diet and supplements

Rita K Biel^{1,*}, Ilona Csizmadı^{1,2,3}, Linda S Cook^{1,2,4}, Kerry S Courneya⁵, Anthony M Magliocco^{1,3,6} and Christine M Friedenreich^{1,2,3}

¹Division of Cancer Care, Department of Population Health Research, Alberta Health Services, 1331 – 29 St. N.W., Calgary, Alberta T2N 4N2, Canada: ²Department of Community Health Sciences, Faculty of Medicine, University of Calgary, Calgary, Alberta, Canada: ³Department of Oncology, Faculty of Medicine, University of Calgary, Calgary, Alberta, Canada: ⁴Department of Internal Medicine, NM Health Sciences Center, University of New Mexico, Albuquerque, NM, USA: ⁵Faculty of Physical Education and Recreation, E488 Van Vliet Centre, University of Alberta, Edmonton, Alberta, Canada: ⁶Department of Pathology and Laboratory Medicine, Faculty of Medicine, University of Calgary, Calgary, Alberta, Canada

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Abstract

Objective: Intake of nutrients may influence the risk of endometrial cancer (EC). We aimed to estimate the association of intake of individual nutrients from food and from food plus supplements with EC occurrence.

Design: A population-based case–control study conducted in Canada (2002–2006).

Setting: Nutrient intakes from food and supplements were assessed using an FFQ. Logistic regression was used to estimate EC risk within quartile levels of nutrient intakes.

Subjects: Incident EC cases (n 506) were identified from the Alberta Cancer Registry, and population controls were frequency- and age-matched to cases (n 981).

Results: There existed little evidence of an association with EC for the majority of macronutrients and micronutrients examined. We observed a statistically significant increased risk associated with the highest, compared with the lowest, quartile of intake of dietary cholesterol (multivariable-adjusted OR = 1.51, 95% CI 1.08, 2.11; P for trend = 0.02). Age-adjusted risk at the highest level of intake was significantly reduced for Ca from food sources (OR = 0.73, 95% CI 0.54, 0.99) but was attenuated in the multivariable model (OR = 0.82, 95% CI 0.59, 1.13). When intake from supplements was included in Ca intake, risk was significantly reduced by 28% with higher Ca (multivariable-adjusted OR = 0.72, 95% CI 0.51, 0.99, P for trend = 0.04). We also observed unexpected increased risks at limited levels of intakes of dietary soluble fibre, vitamin C, thiamin, vitamin B₆ and lutein/zeaxanthin, with no evidence for linear trend.

Conclusions: The results of our study suggest a positive association between dietary cholesterol and EC risk and an inverse association with Ca intake from food sources and from food plus supplements.

Keywords
Endometrium
Cancer
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Nutritional supplements

Endometrial cancer (EC) ranks as the fourth most common cancer among women in Canada, with an estimated 4500 women newly diagnosed and 790 estimated deaths from this cancer in 2010⁽¹⁾. Obesity and oestrogen-only menopausal hormone therapy (HT) expose women to higher levels of oestrogen and are well-established risk factors for EC⁽²⁾. Diet may also mediate endogenous oestrogen levels, promoting endometrial carcinogenesis⁽²⁾. A 2007 review concluded that the evidence for an association between diet and EC was 'limited', but 'suggestive' for a decrease in risk with consumption of non-starchy vegetables, particularly cruciferous vegetables, and for an increase in risk with consumption of red meat,

providing rationale for further study of diet in EC aetiology⁽³⁾. A conclusive link with macro- and micronutrients has not been established. Micronutrient intake from food alone may not fully reflect an individual's overall biological micronutrient dose, as vitamins and minerals are also widely consumed as supplements. The prevalence of vitamin/mineral supplement use in Canada was recently estimated to be 47% among women, and a higher 60% among women aged ≥ 51 years⁽⁴⁾. Hence, misclassification among exposure levels has likely impacted the observed dietary associations with EC, contributing to inconsistent findings among studies. Few studies have accounted for these additional nutrient sources through

*Corresponding author: Email Rita.Biel@albertahealthservices.ca

adjustment, through addition to diet or by restriction to non-users of supplements. Only two studies have examined EC risk in association with micronutrient intake from food and supplements combined, examining a limited number of micronutrients^(5,6). To address this gap, we collected information on a wide range of micronutrients from food and supplements through a case-control study of EC.

Methods

Study population

A population-based case-control study of EC risk was conducted in Alberta, Canada, and details of this study have been reported⁽⁷⁾. As part of the present study, information was collected on past-year dietary intake. All participants provided signed informed consent, and ethical approval was obtained from the Alberta Cancer Board and from the University of Calgary. Cases, identified from the Alberta Cancer Registry, comprised women aged 30–79 years with incident, primary-site EC diagnosed in Alberta between 12 September 2002 and 15 February 2006. Controls comprised ≥ 30 -year-old Alberta residents recruited through random digit dialling and frequency-matched to cases 2:1 on the basis of age (± 5 years)⁽⁸⁾. All participants completed in-person interviews and a self-administered diet history questionnaire (DHQ). The participation rate was 67.9% (n 549) for cases and 52.2% (n 1036) for controls. We excluded eleven women because of unsatisfactory interviews, forty-seven women because they did not complete a DHQ and forty women because they reported total daily energy intake values < 2510 kJ (600 kcal)/d (n 33) and > 20920 kJ (5000 kcal)/d (n 7). Thus, 506 cases and 981 controls were included in the present analysis.

Data collection

In-person interviews were conducted and anthropometric measurements were taken. Participants self-reported their past-year dietary intake using a Canadian version of the National Cancer Institute's (NCI) DHQ⁽⁹⁾ following their interview. The cognitively tested DHQ queries frequency and portion size intakes of 124 individual food items. A subset of questions ascertains seasonal food intake, special foods and use or addition of fat. The original US version was validated against biomarkers of energy expenditure and protein intake^(10–12). Because of differences in nutrient fortification⁽¹³⁾, the Canadian DHQ nutrient database was previously modified for use in Canada⁽¹⁴⁾. The 'Diet*Calc' Analysis Program version 1.4.3 (National Cancer Institute, Bethesda, MD, USA) was used to derive nutrient intake variables.

Twenty-seven nutrients were examined in total. Macronutrients included total energy (kJ (kcal)), protein (g), total fat (g), saturated fat (g), monounsaturated fat (g), polyunsaturated fat (g), discretionary fat (g), cholesterol (mg), carbohydrate (g), dietary fibre NDSR (Nutrition

Data Systems for Research; g), insoluble fibre (g) and soluble fibre (g). We examined food and supplement intakes, expressed as daily intakes, of twelve individual micronutrients including vitamin A (retinol equivalents), β -carotene (μg), vitamin C (mg), vitamin D (μg), vitamin E (mg α -tocopherol equivalents), folate (μg dietary folate equivalents (DFE)), thiamin (B_1 ; mg), riboflavin (B_2 ; mg), niacin (mg), vitamin B_6 (mg), vitamin B_{12} (μg) and Ca (mg). Methionine (g) and additional phytochemicals lycopene (μg) and lutein/zeaxanthin (μg) were examined from food sources only. Total folate intake, expressed as DFE, was estimated by accounting for the greater bioavailability of synthetic folic acid compared with naturally occurring food folate⁽¹⁵⁾. Synthetic folic acid was multiplied by 1.7 before this amount was added to naturally occurring food folate to derive total DFE from food or from food and supplements^(15,16).

Statistical analyses

Nutrients were natural log transformed and adjusted for total energy using the residual method⁽¹⁷⁾. Unconditional logistic regression analysis was used to estimate OR and 95% CI for the risk of EC within nutrient intake quartiles according to the distribution among controls in age-adjusted and multivariable-adjusted models. If an association with EC was detected, possible effect modification was assessed by stratifying these models by BMI (< 25.0 *v.* ≥ 25.0 kg/m^2), waist circumference (< 88 *v.* ≥ 88 cm) and menopausal status (pre/perimenopausal *v.* postmenopausal) and by examining the interaction terms between nutrient intake exposure levels and these effect modifiers in logistic models. A stratified analysis by HT use was also undertaken to examine postmenopausal women not taking HT compared with those taking only oestrogen plus progesterone (E + P) HT. The following factors were considered as confounders because of their known or suspected associations with both EC risk and diet: age (years), total energy intake (kJ (kcal)/d; as per the residuals-adjusted model, except in the case of modelling total energy intake as an exposure), age at menarche (years), BMI (< 25.0 *v.* 25.0 – 29.9 , ≥ 30.0 kg/m^2), parity (0 *v.* 1–2, more than two pregnancies at ≥ 20 weeks' gestation), education (lower than high school *v.* high school or higher), hypertension history (ever *v.* never), history of type 2 diabetes (ever *v.* never), hormone contraceptive use (never *v.* ever), HT use combined with menopausal status (post/perimenopausal/no HT *v.* post/perimenopausal + oestrogen; post/perimenopausal + E + P; post/perimenopausal + other menopausal hormones; premenopausal), lifetime alcohol consumption (0 drinks *v.* < 1 drink, ≥ 1 drink/d) and smoking (smoker, ex-smoker or current smoker). All covariates were first individually assessed.

Age and total energy intake were included in all models. Nutrient-specific supplement use (yes *v.* no) was included in all micronutrient diet models, except for lycopene, lutein/zeaxanthin and methionine. Covariates were deleted from saturated models using a backward

elimination procedure⁽¹⁸⁾, with the exception of biologically important covariates. A significant change in effect was defined as >10% difference in the point estimate from the saturated model OR. Fully adjusted models included age, total energy intake, age at menarche, BMI, parity, education, hypertension history, hormone contraception use and HT use combined with menopausal status. Model fit was assessed using the Hosmer–Lemeshow goodness-of-fit test⁽¹⁹⁾. Tests for linear trend were conducted for all models of categorized data, with an ordinal-score variable

treated as a continuous variable and all *P* values reported as two-sided. All statistical analyses were performed using the STATA statistical software package version 10.0 (Stata-Corp LP, College Station, TX, USA)⁽⁵¹⁾.

Results

Our study population consisted primarily of Caucasian (96%), postmenopausal (74%) women, 28–79 years of

Table 1 Characteristics of endometrial cancer cases and controls and age-adjusted OR for risk of endometrial cancer with non-dietary risk factors, Alberta, Canada, 2002–2006 (*n* 1487)

Characteristic	Cases (<i>n</i> 506)		Controls (<i>n</i> 981)		Age-adjusted OR	95% CI
	Mean or <i>n</i>	SD or %	Mean or <i>n</i>	SD or %		
Age (years)	58.7	9.2	58.3	10.1	–	–
BMI (kg/m ²)*	32.3	7.9	28.1	5.7	–	–
<25.0	92	18	321	33	1.00	–
25.0–29.9	136	27	357	36	1.32	0.98, 1.80
≥30.0	278	55	302	31	3.20	2.41, 4.25
Waist circumference (cm)†	97.9	18.7	87.5	14.6	–	–
<88	163	32	550	57	1.00	–
≥88	339	68	422	43	2.71	2.16, 3.39
Age at menarche (years)‡	12.3	1.5	12.6	1.5	0.89	0.83, 0.96
Parity (pregnancies at ≥20 weeks' gestation)	2.2	1.5	2.6	1.6	–	–
0	89	18	101	10	1.00	–
1–2	220	43	411	42	0.58	0.42, 0.81
>2	197	40	469	48	0.42	0.30, 0.60
HT use by menopausal status§						
Post/perimenopausal – no HT	283	56	487	50	1.00	–
Post/perimenopausal – E only	19	4	23	2	1.37	0.73, 2.58
Post/perimenopausal – E + P	125	25	322	35	0.66	0.51, 0.85
Post/perimenopausal – other HT	26	5	26	3	1.73	0.98, 3.03
Premenopausal	52	10	116	12	0.85	0.55, 1.30
Hormone contraception use (ever)	308	61	695	71	0.63	0.50, 0.80
Hypertension (ever)*¶	213	42	257	26	2.08	1.65, 2.63
Type 2 diabetes (ever)**	60	12	56	6	2.19	1.49, 3.22
Educational level††						
High school or lower	167	33	273	28	1.00	–
Above high school	339	67	707	72	0.79	0.63, 1.00
Total physical activity (MET × h/week per year)	119.2	32.4	120.1	32.7	–	–
≤96.47	123	24	246	25	1.00	–
>96.47 to ≤117.75	141	28	245	25	1.13	0.83, 1.53
>117.75 to ≤139.90	125	25	245	25	1.00	0.74, 1.36
>139.90 to ≤275.43	117	23	245	25	0.92	0.67, 1.27
Smoking						
Never/fewer than 100 cigarettes	257	51	489	50	1.00	–
Ex-smoker	194	38	369	38	1.00	0.79, 1.25
Current smoker	55	11	123	12	0.86	0.60, 1.22
Total alcohol consumption (drinks/d)‡‡						
0 (non-drinkers)	105	21	149	15	1.00	–
≤1	387	76	804	82	0.69	0.52, 0.91
>1	14	3	28	3	0.72	0.36, 1.44
Supplement use (multivitamin or nutrient-only type)						
No	81	16	120	12	1.00	–
Yes	425	84	861	88	0.72	0.53, 0.98

HT, hormone therapy; E, oestrogen; E + P, oestrogen + progesterone; MET, metabolic equivalents.

*Height and weight self-reported for five cases and five controls, not reported by one control.

†Not reported for four cases and nine controls.

‡Not reported for two cases.

§HT use not reported for one case and six controls.

||Menopausal status not reported in one case and one control.

*¶Not reported in two controls; OR compared with never.

**Not reported in three controls; OR compared with never.

††Not reported in one control.

‡‡Lifetime total alcohol consumption (minimum of six drinks per year) assessed at the time of interview. Participants reported the number of drinks of beer (1 can/glass/bottle = 12 oz/360 ml), wine (1 glass = 5 oz/140 ml) or liquor (1.5 oz/45 ml) consumed per week for each pattern of drinking. Responses were used to estimate alcohol consumption in grams of ethanol per year, and this estimate was converted to number of drinks per day.

Table 2 Daily nutrient intakes reported on the DHQ by cases and controls

Daily intake	Cases (<i>n</i> 506)		Controls (<i>n</i> 981)	
	Mean	SD	Mean	SD
Macronutrients				
Total energy (kJ)*	6730.4	2626.7	6682.3	2620.4
Protein (g)	64.9	25.6	64.8	28.0
Total fat (g)	60.2	30.0	58.8	29.1
Saturated fat (g)	19.3	9.8	19.0	10.0
Monounsaturated fat (g)	22.6	11.9	22.0	11.3
Polyunsaturated fat (g)	13.6	7.5	13.2	7.2
Discretionary fat (g)	47.0	25.0	46.0	24.5
Cholesterol (mg)	218.1	134.7	205.3	111.0
Dietary fibre (g; NDSR)	19.4	8.9	19.5	8.9
Soluble fibre (g; NDSR)	6.7	3.1	6.7	3.0
Insoluble fibre (g; NDSR)	12.6	5.9	12.7	6.0
Carbohydrates (g)	206.0	85.0	203.8	82.2
Micronutrients				
Vitamin A (µg RE)	1381.4	895.2	1390.8	946.4
β-Carotene (µg)	4364.2	3523.4	4419.0	3791.1
Vitamin C (mg)	145.2	88.3	138.7	83.9
Vitamin D (µg)	4.3	2.6	4.3	2.9
Vitamin E (mg ATE)	8.3	4.4	8.1	4.2
Thiamin (mg)	1.3	0.5	1.3	0.5
Riboflavin (mg)	1.6	0.7	1.6	0.7
Niacin (mg)	17.8	7.0	17.6	7.1
Vitamin B ₆ (mg)	1.7	0.7	1.7	0.7
Vitamin B ₁₂ (µg)	4.3	2.8	4.1	2.8
Ca (mg)	787.7	385.1	825.6	460.2
Fe (mg)	11.6	4.6	11.8	4.8
Na (mg)	2569.4	1094.5	2524.6	1060.1
Folate (µg)	316.2	144.3	311.3	140.9
Lycopene (µg; NDSR)	6597.3	7425.4	5941.7	5222.8
Lutein/zeaxanthin (µg; NDSR)	3017.5	3072.2	2928.5	3173.7
Methionine (g; NDSR)	1.4	0.6	1.4	0.6
Selected supplement intake†				
Vitamin A (µg RE)	955.9	563.3	1047.2	764.5
β-Carotene (µg)	191.8	199.2	217.9	259.2
Vitamin C (mg)	251.4	327.4	245.1	351.8
Vitamin D (µg)	8.7	4.5	8.8	4.7
Vitamin E (mg ATE)	43.5	60.4	54.2	66.0
Thiamin (mg)	2.5	2.5	2.7	2.6
Riboflavin (mg)	2.2	1.7	2.3	1.7
Niacin (mg)	21.1	12.2	19.9	11.0
Vitamin B ₆ (mg)	9.2	14.9	10.0	15.5
Vitamin B ₁₂ (µg)	4.8	2.0	4.9	1.9
Ca (mg)	493.3	332.2	513.7	330.7
Fe (mg)	17.3	8.7	16.3	7.6
Folate (µg)	327.3	142.3	327.6	137.8

DHQ, diet history questionnaire; NDSR, Nutrition Data Systems for Research; RE, retinol equivalents; ATE, α-tocopherol equivalents.

*Cases: 1608.6 kJ (627.8 kcal); controls: 1597.1 kJ (626.3 kcal).

†Estimated among users of given supplement; multivitamin or nutrient-only-type source.

age, who were married or had been married previously (96%; Table 1). Risk increased with being overweight or obese (BMI ≥ 25.0 kg/m² *v.* BMI < 25.0 kg/m²), having a waist circumference ≥ 88 cm, having a younger age at menarche and having a history of hypertension or type 2 diabetes. Risk was reduced for women who were more educated, parous, past-year dietary supplement users, ever hormone contraception users or post- or perimenopausal and users of E + P HT (Table 1). Women were generally physically inactive and low alcohol consumers; half of them were never smokers (Table 1). The daily nutrient intakes reported by cases and controls are presented in Table 2. The prevalence of use of any multi-

vitamin or any nutrient-only-type supplement was 84% for cases and 88% for controls. Vitamin C was the most prevalent supplemental nutrient, taken by 69% of cases and 74% of controls.

Macronutrients

We did not find an association with EC for the majority of macronutrients examined, including total energy intake, protein, total fat, saturated fat, carbohydrate and total dietary fibre (Table 3). We observed a 51–59% elevation in risk in the highest quartile of intake of dietary cholesterol, with a statistically significant increasing trend in both age-adjusted and multivariable-adjusted models (OR = 1.59,

Table 3 Age- and multivariable-adjusted OR and 95% CI for risk of endometrial cancer with daily intakes of individual macronutrients

Nutrient exposure quartile	Cases (<i>n</i> 506)	Controls (<i>n</i> 981)	Age-adjusted OR*	95% CI	Multivariable OR†	95% CI
Total energy (kJ)‡						
≤4880.6	122	245	1.00	–	1.00	–
>4880.6 to ≤6230.0	129	246	1.06	0.78, 1.44	1.06	0.74, 1.51
>6230.0 to ≤7875.1	124	244	1.04	0.76, 1.41	1.04	0.68, 1.59
>7875.1 to ≤19318.4	131	246	1.09	0.80, 1.48	1.08	0.56, 2.09
<i>P</i> for trend				0.87		0.97
Protein (g)						
≤53.0	121	246	1.00	–	1.00	–
>53.0 to ≤61.1	144	244	1.21	0.90, 1.63	1.31	0.95, 1.80
>61.1 to ≤68.8	106	246	0.88	0.64, 1.21	0.90	0.64, 1.26
>68.8 to ≤101.2	135	245	1.13	0.83, 1.53	1.10	0.79, 1.52
<i>P</i> for trend				0.90		0.86
Total fat (g)						
≤45.7	123	245	1.00	–	1.00	–
>45.7 to ≤53.5	114	245	0.93	0.68, 1.27	1.01	0.72, 1.41
>53.5 to ≤61.9	131	246	1.07	0.79, 1.45	1.13	0.81, 1.56
>61.9 to ≤120.4	138	245	1.13	0.84, 1.53	1.12	0.80, 1.55
<i>P</i> for trend				0.30		0.39
Saturated fat (g)						
≤14.3	120	245	1.00	–	1.00	–
>14.3 to ≤17.0	120	245	1.01	0.74, 1.37	1.08	0.78, 1.51
>17.0 to ≤20.5	140	245	1.18	0.87, 1.59	1.21	0.87, 1.67
>20.5 to ≤44.3	126	246	1.06	0.78, 1.44	1.06	0.76, 1.49
<i>P</i> for trend				0.51		0.59
Monounsaturated fat (g)						
≤16.9	124	246	1.00	–	1.00	–
>16.9 to ≤20.0	124	245	1.01	0.75, 1.37	1.06	0.76, 1.47
>20.0 to ≤23.4	125	245	1.02	0.75, 1.38	1.01	0.72, 1.40
>23.4 to ≤45.9	133	245	1.09	0.80, 1.47	1.07	0.77, 1.48
<i>P</i> for trend				0.60		0.78
Polyunsaturated fat (g)						
≤9.7	121	245	1.00	–	1.00	–
>9.7 to ≤11.7	130	246	1.06	0.78, 1.44	1.07	0.77, 1.49
>11.7 to ≤13.9	121	244	1.00	0.74, 1.36	0.97	0.70, 1.35
>13.9 to ≤40.1	134	246	1.10	0.81, 1.49	1.11	0.81, 1.54
<i>P</i> for trend				0.64		0.66
Discretionary fat (g)						
≤34.3	118	246	1.00	–	1.00	–
>34.3 to ≤41.3	117	245	1.01	0.74, 1.37	1.06	0.76, 1.48
>41.3 to ≤49.6	141	244	1.21	0.89, 1.64	1.23	0.89, 1.71
>49.6 to ≤101.1	130	246	1.11	0.82, 1.51	1.12	0.80, 1.56
<i>P</i> for trend				0.31		0.36
Cholesterol (mg)						
≤141.2	100	246	1.00	–	1.00	–
>141.2 to ≤179.3	126	245	1.27	0.92, 1.74	1.22	0.87, 1.72
>179.3 to ≤225.4	123	245	1.24	0.90, 1.71	1.29	0.92, 1.82
>225.4 to ≤917.8	157	245	1.59	1.17, 2.16	1.51	1.08, 2.11
<i>P</i> for trend				0.01		0.02
Carbohydrate (g)						
≤171.7	127	245	1.00	–	1.00	–
>171.7 to ≤195.8	128	245	1.01	0.75, 1.37	1.10	0.79, 1.51
>195.8 to ≤215.8	113	245	0.88	0.65, 1.21	0.97	0.70, 1.35
>215.8 to ≤332.0	138	246	1.07	0.79, 1.45	1.11	0.80, 1.54
<i>P</i> for trend				0.86		0.70
Dietary fibre (g; NDSR)						
≤14.8	132	246	1.00	–	1.00	–
>14.8 to ≤18.4	134	245	1.01	0.75, 1.36	1.13	0.82, 1.56
>18.4 to ≤21.9	120	244	0.90	0.66, 1.22	1.06	0.77, 1.48
>21.9 to ≤45.1	120	246	0.88	0.65, 1.20	0.96	0.69, 1.34
<i>P</i> for trend				0.32		0.75
Insoluble fibre (g; NDSR)						
≤9.5	132	246	1.00	–	1.00	–
>9.5 to ≤11.8	129	245	0.97	0.72, 1.31	1.16	0.84, 1.60
>11.8 to ≤14.3	132	245	0.98	0.73, 1.33	1.14	0.82, 1.58
>14.3 to ≤31.5	113	245	0.84	0.61, 1.14	0.95	0.68, 1.34
<i>P</i> for trend				0.30		0.81
Soluble fibre (g; NDSR)						
≤5.1	116	246	1.00	–	1.00	–
>5.1 to ≤6.3	148	244	1.27	0.94, 1.72	1.40	1.01, 1.93
>6.3 to ≤7.5	124	246	1.05	0.77, 1.43	1.20	0.86, 1.68
>7.5 to ≤14.9	118	245	1.00	0.73, 1.36	1.08	0.77, 1.52
<i>P</i> for trend				0.65		0.91

NDSR, Nutrition Data Systems for Research.

*Adjusted for age (years) and total energy intake (kcal/d; except in the case of total energy intake).

†Additionally adjusted for age at menarche (years), BMI (<25.0 v. 25.0–29.9, ≥30.0 kg/m²), parity (0 v. 1–2, >2 pregnancies at ≥20 weeks' gestation), educational level (below high school v. high school or above), hypertension history (ever v. never), hormone contraceptive use (never v. ever), hormone therapy use combined with menopausal status (post/perimenopausal/no hormone therapy v. post/perimenopausal + oestrogen, post/perimenopausal + oestrogen + progesterone, post/perimenopausal + other menopausal hormones and premenopausal), alcohol consumption (0 v. <1 drink, ≥1 drink/d).

‡Quartile cut-off points in kcal: 1166.5, 1489.0, 1882.2 and 4617.2, respectively.

Table 4 Multivariable-adjusted OR and 95% CI for risk of endometrial cancer with cholesterol intake (mg) stratified by menopausal status (*n* 1485), BMI (*n* 1486) and HT use (*n* 876)

	Pre/perimenopausal (<i>n</i> 168)				Postmenopausal (<i>n</i> 1317)			
	Cases (<i>n</i> 52)	Controls (<i>n</i> 116)	Multivariable-adjusted OR*	95% CI	Cases (<i>n</i> 453)	Controls (<i>n</i> 864)	Multivariable-adjusted OR*†	95% CI
Cholesterol (mg)								
≤141.2	21	30	1.00	–	79	186	1.00	–
>141.2 to ≤179.3	31	59	1.61	0.73, 3.54	94	186	1.16	0.79, 1.70
>179.3 to ≤225.4	35	75	2.10	0.98, 4.51	88	170	1.14	0.77, 1.68
>225.4 to ≤917.8	32	72	1.55	0.72, 3.35	125	172	1.51	1.04, 2.20
<i>P</i> for trend			0.24				0.04	
	BMI < 25.0 kg/m ² (<i>n</i> 413)				BMI ≥ 25.0 kg/m ² (<i>n</i> 1073)			
	Cases (<i>n</i> 92)	Controls (<i>n</i> 321)	Multivariable-adjusted OR*	95% CI	Cases (<i>n</i> 414)	Controls (<i>n</i> 659)	Multivariable-adjusted OR*†	95% CI
Cholesterol (mg)								
≤141.2	29	93	1.00	–	71	153	1.00	–
>141.2 to ≤179.3	30	68	1.34	0.70, 2.58	96	177	1.29	0.87, 1.92
>179.3 to ≤225.4	18	86	0.67	0.33, 1.36	105	159	1.69	1.13, 2.52
>225.4 to ≤917.8	15	74	0.65	0.31, 1.35	142	170	2.11	1.44, 3.10
<i>P</i> for trend			0.11				0.00	
	No HT (<i>n</i> 581)				E + P HT (<i>n</i> 295)			
	Cases (<i>n</i> 226)	Controls (<i>n</i> 355)	Multivariable-adjusted OR*	95% CI	Cases (<i>n</i> 76)	Controls (<i>n</i> 219)	Multivariable-adjusted OR*†	95% CI
Cholesterol (mg)								
≤141.2	44	91	1.00	–	20	55	1.00	–
>141.2 to ≤179.3	51	99	1.03	0.60, 1.75	21	54	1.17	0.55, 2.47
>179.3 to ≤225.4	45	82	1.08	0.62, 1.90	15	59	0.68	0.31, 1.50
>225.4 to ≤917.8	86	83	1.79	1.06, 3.00	20	51	1.08	0.50, 2.31
<i>P</i> for trend			0.02				0.80	

HT, hormone therapy; E + P, oestrogen + progesterone.

*Adjusted for age (years) and total energy intake (kJ (kcal)), age at menarche (years), BMI (<25.0 v. 25.0–29.9, ≥30.0 kg/m²), parity (0 v. 1–2, >2 pregnancies at ≥20 weeks' gestation), educational level (below high school v. high school or above), hypertension history (ever v. never), hormone contraceptive use (never v. ever), alcohol consumption (0 drink v. <1 drink, ≥1 drink/d).

†If further adjusted for use of HT (lowest to highest quartile of cholesterol intake): OR = 1.14 (95% CI 0.78, 1.67), 1.16 (95% CI 0.78, 1.72) and 1.48 (95% CI 1.02, 2.16).

Table 5 Multivariable-adjusted OR and 95% CI for risk of endometrial cancer with daily intakes of individual micronutrients from diet alone and diet with supplements

Nutrient exposure quartile	Diet alone*				Diet with supplementst				
	Cases (n 506)	Controls (n 981)	Multivariable OR	95% CI	Nutrient exposure quartile	Cases (n 506)	Controls (n 981)	Multivariable OR	95% CI
Vitamin A (RE)									
≤838·6	120	246	1·00	–	≤1115·5	136	245	1·00	–
>838·6 to ≤1115·1	119	244	0·97	0·70, 1·36	>1115·5 to ≤1800·1	127	246	0·98	0·71, 1·34
>1115·1 to ≤1603·0	150	246	1·30	0·94, 1·79	>1800·1 to ≤2380·2	127	245	1·11	0·80, 1·53
>1603·0 to ≤8028·0	117	245	1·03	0·74, 1·45	>2380·2 to ≤9135·3	116	245	0·95	0·68, 1·32
<i>P</i> for trend				0·44	<i>P</i> for trend				0·97
β-Carotene (μg)									
≤2122·7	121	246	1·00	–	≤2258·0	112	246	1·00	–
>2122·7 to ≤3302·5	117	244	1·01	0·73, 1·41	>2258·0 to ≤3438·4	117	244	0·95	0·68, 1·32
>3302·5 to ≤5199·5	147	245	1·22	0·89, 1·69	>3438·4 to ≤5371·0	147	246	1·21	0·88, 1·67
>5199·5 to ≤28673·0	121	246	1·14	0·81, 1·59	>5371·0 to ≤28673·1	120	245	1·10	0·79, 1·53
<i>P</i> for trend				0·27	<i>P</i> for trend				0·32
Vitamin C (mg)									
≤87·6	108	246	1·00	–	≤131·8	136	246	1·00	–
>87·6 to ≤124·4	131	244	1·25	0·90, 1·75	>131·8 to ≤185·5	107	244	0·90	0·64, 1·25
>124·4 to ≤167·0	129	246	1·20	0·86, 1·68	>185·5 to ≤374·7	153	246	1·28	0·94, 1·76
>167·0 to ≤478·2	138	245	1·45	1·04, 2·03	>374·7 to ≤2465·7	110	245	0·84	0·60, 1·17
<i>P</i> for trend				0·05	<i>P</i> for trend				0·84
Vitamin D (μg)									
≤2·4	126	245	1·00	–	≤4·4	133	246	1·00	–
>2·4 to ≤3·4	117	246	0·88	0·63, 1·22	>4·4 to ≤10·2	132	245	1·07	0·77, 1·47
>3·4 to ≤5·1	139	245	1·10	0·80, 1·52	>10·2 to ≤14·0	116	244	0·97	0·70, 1·34
>5·1 to ≤18·1	124	245	0·98	0·71, 1·36	>14·0 to ≤33·1	125	246	1·08	0·78, 1·50
<i>P</i> for trend				0·74	<i>P</i> for trend				0·78
Vitamin E (mg ATE)									
≤6·2	127	245	1·00	–	≤7·9	133	246	1·00	–
>6·2 to ≤7·3	128	246	1·08	0·78, 1·49	>7·9 to ≤15·2	147	244	1·17	0·85, 1·60
>7·3 to ≤8·5	115	245	1·01	0·73, 1·41	>15·2 to ≤66·6	136	245	1·13	0·82, 1·55
>8·5 to ≤18·7	136	245	1·18	0·85, 1·62	>66·6 to ≤324·4	90	246	0·74	0·52, 1·04
<i>P</i> for trend				0·41	<i>P</i> for trend				0·13
Folate (μg DFE)									
≤277·6	133	246	1·00	–	≤329·9	125	245	1·00	–
>277·6 to ≤322·5	97	245	0·80	0·57, 1·12	>329·9 to ≤591·8	139	246	1·14	0·82, 1·57
>322·5 to ≤377·6	140	245	1·14	0·83, 1·57	>591·8 to ≤987·7	111	244	0·95	0·68, 1·32
>377·6 to ≤851·3	136	245	1·18	0·85, 1·63	>987·7 to ≤1551·0	131	246	1·18	0·85, 1·64
<i>P</i> for trend				0·12	<i>P</i> for trend				0·54
Thiamin (mg)									
≤1·1	119	246	1·00	–	≤1·3	139	245	1·00	–
>1·1 to ≤1·2	108	244	0·93	0·66, 1·30	>1·3 to ≤2·2	130	246	0·85	0·62, 1·17
>1·2 to ≤1·4	161	245	1·49	1·09, 2·04	>2·2 to ≤2·9	123	244	0·92	0·67, 1·27
>1·4 to ≤2·5	118	246	1·01	0·72, 1·41	>2·9 to ≤9·7	114	246	0·83	0·60, 1·16
<i>P</i> for trend				0·30	<i>P</i> for trend				0·38
Riboflavin (mg)									
≤1·3	142	246	1·00	–	≤1·6	138	246	1·00	–
>1·3 to ≤1·5	97	244	0·66	0·47, 0·92	>1·6 to ≤2·6	133	245	1·07	0·78, 1·48
>1·5 to ≤1·7	136	246	1·00	0·73, 1·37	>2·6 to ≤3·5	130	245	1·12	0·82, 1·55

Table 5 Continued

Nutrient exposure quartile	Diet alone*				Diet with supplement†				
	Cases (n 506)	Controls (n 981)	Multivariable OR	95% CI	Nutrient exposure quartile	Cases (n 506)	Controls (n 981)	Multivariable OR	95% CI
>1.7 to ≤3.6	131	245	0.94	0.69, 1.29	>3.5 to ≤8.3	105	245	0.84	0.60, 1.17
<i>P</i> for trend				0.74	<i>P</i> for trend			0.42	
Niacin (mg)									
≤14.4	120	246	1.00	–	≤17.8	146	246	1.00	–
>14.4 to ≤16.6	122	244	1.28	0.92, 1.78	>17.8 to ≤30.9	121	244	0.82	0.59, 1.13
>16.6 to ≤18.9	127	245	1.16	0.83, 1.60	>30.9 to ≤37.6	119	245	0.91	0.66, 1.26
>18.9 to ≤32.9	137	246	1.18	0.86, 1.63	>37.6 to ≤102.7	120	246	0.84	0.61, 1.15
<i>P</i> for trend				0.44	<i>P</i> for trend			0.39	
Vitamin B ₆ (mg)									
≤1.3	107	246	1.00	–	≤1.7	129	246	1.00	–
>1.3 to ≤1.6	128	245	1.28	0.92, 1.78	>1.7 to ≤3.0	131	244	1.06	0.77, 1.47
>1.6 to ≤1.8	135	244	1.16	0.83, 1.60	>3.0 to ≤3.9	122	245	1.07	0.77, 1.48
>1.8 to ≤3.2	136	246	1.18	0.86, 1.63	>3.9 to ≤68.7	124	246	1.07	0.77, 1.48
<i>P</i> for trend				0.05	<i>P</i> for trend			0.71	
Vitamin B ₁₂ (μg)									
≤2.8	115	246	1.00	–	≤3.5	106	245	1.00	–
>2.8 to ≤3.5	111	244	0.97	0.70, 1.36	>3.5 to ≤6.1	137	245	1.29	0.92, 1.79
>3.5 to ≤4.5	144	246	1.21	0.87, 1.67	>6.1 to ≤9.2	137	245	1.45	1.04, 2.02
>4.5 to ≤47.9	136	245	1.09	0.79, 1.51	>9.2 to ≤47.9	126	246	1.23	0.88, 1.72
<i>P</i> for trend				0.37	<i>P</i> for trend			0.19	
Ca (mg)									
≤559.2	153	246	1.00	–	≤767.0	168	245	1.00	–
>559.2 to ≤717.4	115	244	0.81	0.59, 1.12	>767.0 to ≤1075.4	117	246	0.76	0.56, 1.05
>717.4 to ≤938.5	123	245	0.86	0.62, 1.18	>1075.4 to ≤1453.2	116	245	0.75	0.54, 1.03
>938.5 to ≤2463.7	115	246	0.82	0.59, 1.13	>1453.2 to ≤3176.0	105	245	0.72	0.51, 0.99
<i>P</i> for trend				0.28	<i>P</i> for trend			0.04	
Fe (mg)									
≤9.7	120	245	1.00	–	≤11.2	126	245	1.00	–
>9.7 to ≤11.1	130	246	1.20	0.87, 1.65	>11.2 to ≤16.3	116	245	0.84	0.60, 1.17
>11.1 to ≤12.7	122	245	1.05	0.75, 1.46	>16.3 to ≤28.8	116	246	0.93	0.67, 1.29
>12.7 to ≤21.8	126	245	1.05	0.75, 1.46	>28.8 to ≤55.6	148	245	1.19	0.87, 1.64
<i>P</i> for trend				0.99				0.21	
Lycopene (μg)									
≤3244.8	103	245	1.00	–	N/A				
>3244.8 to ≤4509.7	141	246	1.36	0.98, 1.89					
>4509.7 to ≤6302.7	125	245	1.29	0.92, 1.81					
>6302.7 to ≤57 216.5	137	245	1.31	0.94, 1.82					
<i>P</i> for trend				0.19					
Lutein/zeaxanthin (μg)									
≤1446.2	116	245	1.00	–	N/A				
>1446.2 to ≤2095.3	134	246	1.27	0.92, 1.76					
>2095.3 to ≤3006.8	111	244	1.03	0.73, 1.44					
>3006.8 to ≤32 400.0	145	246	1.42	1.02, 1.97					
<i>P</i> for trend				0.11					

Table 5 Continued

Nutrient exposure quartile	Diet alone*			Diet with supplementst				
	Cases (n 506)	Controls (n 981)	Multivariable OR	95% CI	Cases (n 506)	Controls (n 981)	Multivariable OR	95% CI
Methionine (g)								
≤ 1.1	123	246	1.00					
> 1.1 to ≤ 1.3	138	245	1.16	0.84, 1.59				
> 1.3 to ≤ 1.5	103	244	0.84	0.60, 1.17				
> 1.5 to ≤ 2.6	142	246	1.08	0.78, 1.48				
P for trend				0.90				
								N/A

RE, retinol equivalents; ATE, α -tocopherol equivalents; DFE, dietary folate equivalents; N/A, not applicable.

*Diet-only models adjusted for age (years), total energy intake (kJ (kcal)/d), nutrient-specific supplement use (no v. yes, except for lycopene, lutein/zeaxanthin and methionine), age at menarche (years), BMI (<25.0 v. 25.0–29.9, ≥30.0 kg/m²), parity (0 v. 1–2, >2 pregnancies at ≥20 weeks gestation), educational level (below high school v. high school or above), hypertension history (ever v. never), hormone contraceptive use (never v. ever), hormone therapy use combined with menopausal status (post/perimenopausal/no hormone therapy v. post/perimenopausal + oestrogen, post/perimenopausal + oestrogen + progesterone, post/perimenopausal + other menopausal hormones and premenopausal) and alcohol consumption (0 drink v. <1 drink, ≥1 drink/d).

†Diet and supplement models adjusted for the same covariates as diet-only models, except for nutrient-specific supplement use.

95% CI 1.17, 2.16, *P* for trend = 0.01; OR = 1.51, 95% CI 1.08, 2.11, *P* for trend = 0.02, respectively). BMI modified the association at the highest levels of cholesterol intake and EC (*P* for interaction = 0.01 and 0.00). We observed an 80–211% statistically significant elevation in risk at the highest level of cholesterol intake for women whose BMI was defined as overweight or obese (BMI ≥ 25.0 kg/m²; OR = 2.11, 95% CI 1.44, 3.10) but not for normal-weight women (BMI < 25.0 kg/m²; Table 4). A similar pattern of significantly increased risk was observed with waist circumference ≥ 88 cm (OR = 2.07, 95% CI 1.32, 3.25; results not shown). We found no statistical interaction between cholesterol intake and menopausal status. However, when models were stratified, risks remained statistically significantly elevated among postmenopausal women in the highest quartile of cholesterol intake (OR = 1.51, 95% CI 1.04, 2.20, *P* for trend = 0.04). The association with cholesterol was also strengthened among postmenopausal women who were non-users of HT (OR = 1.79, 95% CI 1.06, 3.00, *P* for trend = 0.02) at the highest level of intake when it was examined in models assessing no HT and E + P HT use.

Micronutrients

We did not observe an association with EC for most micronutrients (Table 5). A reduced risk was detected for dietary intake of riboflavin (multivariable-adjusted OR = 0.66, 95% CI 0.47, 0.92) in the second, compared with the lowest, quartile of intake, but risk was unchanged for the remaining intake levels and there was no evidence for linear trend. Risk was reduced in the highest quartile of vitamin E intake from food and supplements in the age-adjusted model (OR = 0.66, 95% CI 0.48, 0.91, *P* for trend = 0.01) but was attenuated in the multivariable-adjusted model (OR = 0.74, 95% CI 0.52, 1.04, *P* for trend = 0.13). Age-adjusted risk accounting for supplement use at the highest level of intake was significantly reduced for Ca from food sources (OR = 0.73, 95% CI 0.54, 0.99, *P* for trend = 0.07) but was attenuated in the multivariable-adjusted model (OR = 0.82, 95% CI 0.59, 1.13, *P* for trend = 0.28). The strongest association observed was for total combined Ca intake (from both food and supplements), in which we observed a statistically significant 28–40% reduced risk associated with the highest exposure level (multivariable-adjusted OR = 0.72, 95% CI 0.51, 0.99, *P* for trend = 0.04). In an analysis of Ca intake from food, restricted to supplement non-users (*n* 196 cases, *n* 300 controls), using quartile cut-off points among non-supplement-using controls we found a statistically significant reduced risk for EC (OR = 0.52, 95% CI, 0.30, 0.93, *P* for trend = 0.07). We observed unexpected increased risks at limited levels of intake of dietary soluble fibre, vitamin C, thiamin, vitamin B₆ and lutein/zeaxanthin and vitamin B₁₂ from food plus supplements (Table 5). There was no evidence for linear trend being associated with these increased risks, except for vitamin B₆ (*P* for trend = 0.05).

Discussion

In this population-based case-control study that had detailed assessments of food and supplement use, we did not find increased risks associated with most macronutrients, including total fat and saturated fat, but did find an association between decreased risks and some micronutrient intakes. Our findings are not corroborated by previous research, which has generally suggested a relationship between increased EC risks and higher intakes of total fat^(20–26), saturated fat^(5,20,22,27) and animal fat^(5,20,25,26,28). A meta-analysis reported statistically significant increased risks of 24–72% for total fat, 28–49% for saturated fat and 34–78% for animal fat⁽²⁹⁾. Two studies have since found an association between non-statistically significant increased risk and higher total fat intake^(30,31) and one found no association⁽³²⁾. Meanwhile, our results are consistent with the Women's Health Initiative Dietary Intervention Trial, a study that aimed to reduce fat intake to <20% of total energy intake from a baseline of $\geq 32\%$ and found no change in EC incidence among postmenopausal women⁽³³⁾.

The most pronounced finding among the macronutrients was a statistically significant increased risk of 51–59% at the highest level of cholesterol intake. The association between dietary cholesterol and EC has been assessed in nine previous case-control studies^(20,22–25,28,31,32,34) with mixed results: three found statistically significant increased risks^(20,24,32), but the remaining six found non-significant reduced risks^(23,25), no association⁽³⁴⁾ or non-significant increased risks^(22,28,31). A pooled analysis of six of these studies reported a non-statistically significant increased risk of 35–39% with higher cholesterol intake⁽²⁹⁾. Studies of serum cholesterol have shown similar mixed results^(35–41).

Our results are consistent with the increased EC risk observed for dietary cholesterol from pooled estimates. Although most cholesterol is produced by the liver, prolonged intake of dietary saturated fat and cholesterol raises the average serum cholesterol concentration, as well as levels of LDL cholesterol and HDL cholesterol⁽⁴²⁾. Individual serum cholesterol response to intake of dietary cholesterol seems to be dependent on genetic susceptibility⁽⁴²⁾, which may, in part, contribute to mixed results from observational studies. The role of cholesterol in endometrial carcinogenesis is biologically plausible, as cholesterol and oestrogen are physiologically interconnected. Cholesterol is the founding substrate in steroid hormone synthesis⁽⁴³⁾ and can be converted to oestrogen via metabolic pathways; thus, increased levels of cholesterol may influence EC risk by increasing bioavailable oestrogen synthesis. Meanwhile, in postmenopausal women, circulating cholesterol levels are decreased as a result of oestrogen therapy⁽⁴⁴⁾. Further, oestrogen stimulates LDL receptor activity; hence, premenopausal women have lower LDL cholesterol levels, which increase after menopause⁽⁴⁵⁾. During premenopause, oestrogen production occurs in the ovaries and circulating oestrogen levels are tightly regulated; hence, any influence of

cholesterol on oestrogen levels may be marginal⁽⁴⁶⁾. Since endogenous oestrogen production after menopause occurs primarily in adipose tissue⁽⁴⁶⁾, the relative influence of cholesterol on oestrogen bioavailability is greater than that before menopause. In addition, the oestrogen in HT users may overwhelm any effect of cholesterol. Our finding of a stronger increased risk with dietary cholesterol among postmenopausal women, particularly those not exposed to HT, and among overweight and obese women, is consistent with this hypothesis and suggests that cholesterol may be more influential after menopause. Alternatively, the highest sources of cholesterol among food groups in our questionnaire were, as expected, red meat (including higher fat beef, veal and pork), eggs, poultry and high-fat dairy. Hence, the increased risk with cholesterol may also reflect intake of animal foods that also increase EC risk⁽⁴⁷⁾.

Numerous observational studies have reported on the influence of dietary micronutrients in EC aetiology^(5,6,20,21,23–26,28,30,31,34,48–53); two were cohort studies^(6,48) and the rest were case-control studies. Reduced risks have been observed for dietary intake of vitamin C^(20,21,23,30,51,52), β -carotene^(20,23,30,31,51–53) or other carotenoids^(20,23,28,31,50,53), as well as for intakes of vitamin A^(20,21,30), folate^(23,31), Ca^(25,34), vitamins E^(5,31), D and B₁₂⁽⁵⁴⁾ and lycopene⁽⁴⁸⁾. Pooled analyses suggest a reduced risk with intakes of β -carotene (12%) and vitamins C (15%) and E (9%) from food⁽⁵⁵⁾. A hospital-based case-control study in Korea examined pre-operative levels of plasma micronutrients and found significantly reduced risks associated with higher concentrations of plasma β -carotene and lycopene (OR = 0.12, 95% CI 0.03, 0.48 and OR = 0.15, 95% CI 0.04, 0.61, respectively)⁽⁵⁶⁾. Overall, the evidence from dietary studies is mixed, which may be explained by misclassification of exposure levels or by confounding by unmeasured supplement use. The benefits of supplements on cancer risk are inconclusive; supplements are currently not recommended for cancer prevention⁽³⁾. A recent meta-analysis of randomized controlled trials showed no benefit of antioxidant supplementation on cancer risk but found that supplementation with β -carotene can increase cancer risk and mortality among smokers⁽⁵⁷⁾. Of the observational studies that have examined any supplement use and EC^(5,6,28,30,58), one showed a reduced risk with B-only vitamins and a reduced risk with multivitamin use that was further decreased with increasing duration of use⁽³⁰⁾. Another study found a reduced risk with Ca and an increased risk with Fe supplementation⁽⁵⁸⁾. The Women's Health Initiative concluded that there was no significant association of EC with multivitamin use; however, there was a marginal, but non-significant, increased risk with longer duration of use⁽⁵⁹⁾.

Only two studies have examined the risk of EC in relation to micronutrient intake from food and supplements combined^(5,6). Jain *et al.*^(5,6) found no association with vitamin C intake in a case-cohort analysis⁽⁶⁾ and found a significant reduced risk with vitamin E (OR = 0.61, 95% CI 0.43, 0.88)

in a case-control study that examined vitamins C, E and A and β -carotene from food plus supplements⁽⁵⁾.

We found a statistically significant 28–38% reduction in EC risk with Ca intake when dietary and supplemental sources were combined. Dietary Ca intake has been assessed in four previous hospital-based case-control studies^(25,28,34,52), and supplemental Ca has been assessed in one hospital-based⁽²⁸⁾ and one population-based case-control study⁽⁵⁸⁾. Dietary Ca reduced EC risk by 52–61% in two studies^(25,34) and Ca supplements reduced risk by 50%, which became 70% among women whose dairy intake was below the median⁽⁵⁸⁾. The other study reported a non-significant reduced risk with ever use⁽²⁸⁾. Because of a lack of intervention and cohort studies of Ca intake, and because of high heterogeneity between estimates, a review of these studies concluded that evidence to date is too sparse and inconclusive⁽⁶⁰⁾. Our study supports the hypothesis that Ca from food and from supplementation lowers EC risk. The strengthened reductions in risk that we observed in our analysis restricted to non-users of supplemental Ca suggest that dietary Ca is important in EC risk reduction, which may reflect better dietary Ca absorption. Dietary Ca, especially from dairy foods, is important in energy metabolism and can help maintain a healthy body weight⁽⁶¹⁾. Greater weight and fat loss have been observed in randomized trials for groups with high-dairy supplementation^(62–65). These findings are still inconclusive, however, as a review of randomized controlled trials of Ca supplementation and body weight revealed no association⁽⁶⁶⁾. Ca supplementation may be beneficial only in populations with low baseline Ca intake⁽⁶⁷⁾. For cancer prevention, Ca may act through vitamin D, a nutrient with anti-neoplastic potential, as it is highly correlated and metabolically tied to vitamin D. Vitamin D plays a role in cellular growth and differentiation through vitamin D receptors that are present in endometrial tissue^(68,69). Our analysis did not reveal an association with dietary intake of vitamin D; however, circulating serum levels of 25-hydroxyvitamin D may be more relevant in cancer prevention since a substantial portion of vitamin D is derived from the sun. A recent nested case-control study of 830 cases and 992 controls from seven cohorts, however, found no association between circulating 25-hydroxyvitamin D and EC⁽⁷⁰⁾.

We observed a reduced risk within the second quartile of riboflavin intake in our study, suggesting that riboflavin may play a role in EC risk reduction. Riboflavin is being investigated in cancer aetiology because of its role in folate metabolism⁽⁷¹⁾. Minimum adult requirements are between 0.5 and 0.8 mg/d and urinary excretion increases at intakes of 1.1–1.6 mg/d⁽⁴⁵⁾. Since risk was not reduced at higher levels in our study, our results would be consistent with riboflavin bioavailability, suggesting that adequate levels may provide benefit. We observed unexpected increased risks with dietary soluble fibre, vitamin C, thiamin, vitamin B₆ and lutein/zeaxanthin and with combined vitamin B₁₂ intakes. Detection of risks at limited levels of intake for

these nutrients, an absence of linear trend and the presence of multiple comparisons suggest that these may be chance findings. Our results for vitamins B₆ and B₁₂ might be reflective of meat intake, as higher intake of meat, particularly of red meat, has been associated with an increased risk for EC⁽⁴⁷⁾. Adjustment for meat intake attenuated these associations only marginally, but there could be residual confounding. The increased risk we observed for vitamin C from diet is in contrast to the results from other studies^(20,21,23,30,51,52) and could suggest something about foods high in vitamin C. A hypothesis suggesting that grapefruit intake, through inhibition of the cytochrome P450 3A4 enzyme system, can affect oestrogen metabolism, leading to higher levels of circulating oestrogen and increased breast cancer risk, was examined in the Multi-ethnic Cohort Study⁽⁷²⁾. We were unable to examine grapefruit intake with respect to the observed association with vitamin C because it was not assessed separately from intake of other citrus fruits in our questionnaire.

Although our assessments of associations among non-users of the given supplemental nutrient were limited by sample size, restriction caused the detected association to be attenuated towards the null for thiamin and vitamin B₆ and it lost statistical significance for vitamin C. Risk was also attenuated and became non-significant for lutein/zeaxanthin among non-users of any supplements. Meanwhile, the results for dietary Ca were strengthened with restriction to non-users of supplemental Ca. Our results highlight that misclassification on exposure and possible confounding by supplement use are issues in studies of dietary nutrients and disease risk, leading to potentially spurious associations when these additional nutrients are not accounted for. Restriction to non-users of given supplements in the analysis may provide additional insight into detected associations. Future studies should incorporate measures of supplement use in addition to dietary assessment.

The population-based design, large sample size and comprehensive information on a wide range of risk factors are the strengths of our study. We were also able to evaluate the influence of supplement use combined with dietary sources of micronutrients, which has been carried out in only a limited number of previous studies^(5,6). Limitations in dietary assessment are recognized, as is the possibility of recall bias because of the retrospective dietary assessment. Any random measurement error associated with reporting past dietary exposures tends to attenuate associations⁽⁷³⁾. Nevertheless, we were able to detect statistically significant associations, with evidence for linear trend, for some of these dietary and supplemental exposures; however, our estimates are likely to be conservative. The supplemental exposure variables from our questionnaire summarized exposure from all forms of supplements; hence, we could not evaluate risk for nutrients derived from multivitamins in relation to individual vitamins. Further, the potential for confounding by other nutrients in multivitamins also exists. Another limitation was our low control response rate, which

we addressed by comparing our sample to a larger sample of Alberta women from the Canadian Community Health Survey Cycle 2·2 to evaluate possible selection bias. From this comparison we found that the control group was somewhat more educated than the base population but was otherwise similar with regard to age, height, weight and BMI⁽⁷⁾.

In summary, our study is supportive of a positive association between dietary cholesterol and EC risk. Risk was reduced with intake of Ca from food sources and from food plus supplements. Prospective studies of detailed dietary intakes of nutrients from food and supplements and biomarkers of nutritional and metabolic status are needed to confirm the roles of overall diet and specific nutrients in EC risk and provide additional insight into mechanisms that may underlie a true impact.

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