The Journal of Nutrition
Nutritional Epidemiology

Higher Intakes of Vegetables and Vegetable-Related Nutrients Are Associated with Lower Endometrial Cancer Risks[1]

Michael Yeh,[2,3] Kirsten B. Moysich,[2] Vijayvel Jayaprakash,[2,3] Kerry J. Rodabaugh,[2] Saxon Graham,[3] John R. Brasure,[3] and Susan E. McCann[2]*

[2]Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, NY 14263; and [3]Department of Social and Preventive Medicine, University at Buffalo, Buffalo, NY 14214

Abstract

A limited number of studies have investigated diet in association with endometrial cancer (EC). We examined the association between intakes of selected food groups and nutrients with EC risk among 541 women with histologically confirmed EC and 541 women with an intact uterus and noncancer diagnoses seen at Roswell Park Cancer Institute between 1982 and 1998. Self-reported dietary and other epidemiologic data were collected by questionnaire. Unconditional logistic regression was used to estimate odds ratios (OR) and 95% CI, adjusting for age, BMI, hormone replacement therapy use, cigarette smoking, lifetime duration of menstruation, and total energy intake. We observed significant inverse associations for women in the highest vs. lowest quartiles of intake of total vegetables (OR, 0.51; 95% CI, 0.34–0.75), vitamin E (OR, 0.44; 95% CI, 0.27–0.70), dietary fiber (OR, 0.60; 95% CI, 0.39–0.94), β-carotene (OR, 0.55; 95% CI, 0.37–0.82), lutein (OR, 0.52; 95% CI, 0.34–0.78), and folate (OR, 0.57; 95% CI, 0.36–0.91). Our results support that vegetables and related nutrients are associated with decreased risk of EC. J. Nutr. 139: 1–6, 2009.

Introduction

Endometrial cancer (EC)[4] is the 7th most common malignancy among women worldwide, with the highest incidence in the United States and Northern Europe (1,2). Known risk factors for EC include increased body mass, history of diabetes mellitus or hypertension, late age at menopause, early menarche, use of exogenous hormone replacement therapy, and nulliparity. Cigarette smoking and use of oral contraceptives also have been associated with decreased risk (2,3).

Prolonged exposure to estrogens is a common link among several known risk factors for EC. Estrogen exposure increases proliferation of endometrial cells, potentially leading to hyperplasia and carcinogenesis. BMI, reproductive factors, diabetes, cigarette smoking, and low levels of physical activity are all risk factors associated with EC that are also associated with circulating estrogen concentrations. Overweight and obesity may elevate concentrations of circulating estrogens because of the increased peripheral aromatization of plasma androstenedione in adipose tissue. Higher BMI is also associated with lower concentrations of plasma sex hormone-binding globulin (SHBG), which may increase free estradiol in the systemic circulation. Early menarche and late menopause may be markers of a prolonged period of estrogen exposure unopposed by progesterone, whereas parity may be protective due to high concentrations of progesterone during pregnancy. Diabetes is hypothesized to elevate androgens and lower SHBG concentrations in the blood, thereby increasing risk. Smoking may upregulate liver enzymes that lead to reduced estrogen concentrations, which may explain the apparent protective associations observed in epidemiologic studies (2). Low levels of physical activity are associated with greater risk, independent of obesity (4).

The relationship between diet and EC risk is not well characterized, although there are plausible mechanisms of action other than those mediated through obesity and diabetes. Many foods contain antioxidant nutrients and anticarcinogenic compounds. Phytoestrogenic compounds such as isoflavones and lignans in fruits and vegetables may also alter sex hormone metabolism (4–7). Dietary fiber affects intestinal microflora that can affect enterohepatic cycling of estrogen conjugates. Some observational studies have shown that vegetarians have higher concentrations of SHBG, lower free plasma estradiol, lower urinary estrogen excretion, and higher fecal estrogen excretion (1,6,8–10).

Previous studies have reported increased EC risks with high total dietary, saturated, and monounsaturated fat intakes (11–14). In general, consumption of foods of animal origin are positively associated with EC in most studies to date (3,15,16), although 1 study suggests that consumption of fatty fish may be inversely associated (17). Some investigators have reported

[1] Author disclosures: M. Yeh, K. B. Moysich, V. Jayaprakash, K. J. Rodabaugh, S. Graham, J. R. Brasure, and S. E. McCann, no conflicts of interest.

[4] Abbreviations used: EC, endometrial cancer; OR, odds ratio; PEDS, Patient Epidemiologic Data Systems; RPCI, Roswell Park Cancer Institute; SHBG, serum hormone binding globulin.

* To whom correspondence should be addressed. E-mail: susan.mccann@roswellpark.org.

0022-3166/08 $8.00
Manuscript received September 22, 2008. Initial review completed October 7, 2008. Revision accepted November 3, 2008.
doi:10.3945/jn.108.099960.

inconsistent results, with 1 large cohort study reporting a strong association with only BMI but not with most dietary factors and even a slight decrease in risk associated with saturated fat and animal fat (18). Another study found no association between EC with protein and fats but an inverse association with lactose, dairy foods, and calcium (19). Calcium supplements were associated with decreased risk, whereas iron supplements were associated with higher risk in 1 study (20). Glycemic index and load have also been reported as potential risk factors (21,22).

Diets high in plant-based foods (3,15,20,23,24), especially dark green or yellow vegetables, fresh legumes, alliums (3,23), whole grains (25), pulses, nuts, and seeds (26), appear to be protective, but the magnitude of these associations differs across studies and some have reported no effect (16). Several inquiries have shown an inverse association with EC risk for carotenoids (11,12,14,24,27), but these results are not consistent (16). Given the limited literature and sometimes inconsistent findings, we investigated the association between dietary intake and EC among patients seen at Roswell Park Cancer Institute (RPCI) between 1982 and 1998.

Participants and Methods

This study utilized data obtained from women who received medical care for cancer or a suspicion of cancer at RPCI between 1982 and 1998. Data were available for 541 women, aged 27–96 y, with incident, histologically confirmed endometrial carcinoma. Controls were selected from a pool of 4614 eligible women with an intact uterus seen at RPCI with a suspicion of cancer but without a cancer diagnosis. One control was randomly selected for each case, matched by 5-y age strata, resulting in 541 participants with no history of cancer or hysterectomy.

All participants completed the self-administered Patient Epidemiology Data System (PEDS) questionnaire, a 16-page instrument that assessed family history of cancer; reproductive, health, and medical histories; environmental and occupational exposures; medication and dietary supplements; tobacco use; alcohol consumption; and other potential risk factors. The protocol for the PEDS study was approved by the RPCI Institutional Review Board and all subjects provided informed consent.

As part of PEDS, diet was queried using a 44-item FFQ that assessed usual intake within the several years prior to diagnosis in cases or questionnaire completion in controls. For each food or beverage, a commonly used unit or portion size was specified and participants were asked how often they had consumed that amount of the food. For foods, there were 5 possible responses ranging from never to 5–7 times/wk. For beverages, there were 9 possible responses that ranged from never to >6 drinks/d.

The FFQ was designed to provide an assessment of intakes of fruits and vegetables, cruciferous vegetables, and foods providing good sources of vitamins A, C, and E, and fat and fiber. Because of the brevity of the FFQ, regression weights were used to calculate nutrient intakes. The methods for the derivation of regression weights have been described in detail previously (28,29). Briefly, multiple linear regression was used to identify foods explaining maximal variability in intake of vitamins A, C, and E, and fat and fiber from detailed diet interviews of 293 healthy participants in the Western New York Diet Study (1975–86). Gender- and nutrient-specific regression weights were then derived using dietary data from 1475 male and 780 female control participants of the Western New York Diet Study through multiple linear regression models, with the nutrient as the dependent variable and the foods identified previously as independent variables. The resulting regression coefficients for each food and nutrient were then multiplied by the frequency of use reported on the PEDS FFQ summed across foods to obtain an index of each nutrient (28,30). Nutrient data for the regression weights utilized food composition data primarily from the USDA (31).

Statistical analyses were conducted using SPSS for Windows version 11.0. All tests were 2-sided and were considered significant at $P < 0.05$. Descriptive characteristics of cases and controls were compared using the Student's *t* test for continuous variables (values are means ± SD) and chi-square for categorical variables [values are *n* (%)]. To estimate the association between dietary intake and EC, mean daily intakes of total energy, food groups, and individual nutrients were divided into quartiles using the distributions of the controls. Analyses by food group were limited to total vegetables, cruciferous vegetables, and total fruits due to the brevity of the FFQ. We used unconditional logistic regression to compute odds ratios (OR) and 95% CI for each quartile of intake relative to the lowest quartile, which served as the referent group. Multivariate models were evaluated using the Hosmer-Lemeshow goodness of fit test (32).

In the logistic regression analyses, risks associated with food groups and individual nutrients were calculated adjusting for age, BMI, cigarette smoking, exogenous estrogen use, total menstrual months, and total energy intake, except when calculating risk associated with macronutrients. Because fat, carbohydrates, and protein are major contributors to total energy, we used the remaining 2 macronutrients as adjusting factors for each macronutrient logistic regression model. Tests for trend were performed from the 2-tailed *P*-value of the logistic regression for each continuous nutrient or food group variable.

TABLE 1 Descriptive characteristics of EC cases and controls[1]

	Cases	Controls
n	541	541
Age, *y*	63.3 ± 11.1	63.2 ± 11.1
BMI, *kg/m²*	30.0 ± 8.2	25.7 ± 5.4
Weight,[2] *kg*	78.6 ± 21.5	67.4 ± 14.4
Age at menarche, *y*	13.7 ± 10.1	13.4 ± 7.8
Parity[2]	2.3 ± 1.8	2.7 ± 2.1
Age at first pregnancy, *y*	19.6 ± 9.9	20.6 ± 9.3
Age at first birth, *y*	19.6 ± 10.3	20.8 ± 9.9
Age at menopause,[2] *y*	48.2 ± 15.6	42.1 ± 19.4
Total menstrual months,[2] *mo*	406.7 ± 77.5	394.3 ± 77.2
Oral contraceptive use,[2] *n (%)*		
Yes	68 (12.6)	101 (18.7)
No	473 (87.4)	440 (81.3)
Ever pregnant, *n (%)*		
Yes	439 (81.1)	457 (84.5)
No	102 (18.9)	84 (15.5)
IUD use, *n (%)*		
Yes	27 (5.0)	33 (6.1)
No	514 (95.0)	508 (93.9)
Estrogen or DES, *n (%)*		
Yes	116 (21.4)	106 (19.6)
No	425 (78.6)	435 (80.4)
Smoking,[2] *n (%)*		
Current	47 (8.7)	78 (14.4)
Never	333 (61.7)	296 (54.8)
Former	160 (29.6)	166 (30.7)
Education,[2] *n (%)*		
<8th grade	28 (5.2)	23 (4.3)
8th grade	43 (8.0)	33 (6.1)
Some high school	82 (15.2)	66 (12.2)
High school graduate	200 (37.1)	180 (33.3)
Some college	106 (19.7)	112 (20.7)
College graduate	80 (14.8)	126 (23.3)
Family income,[2] *n (%)*		
<$25,000	403 (77.6)	372 (70.3)
≥$25,000	116 (22.4)	157 (29.7)

[1] Values are means ± SD.
[2] $P < 0.05$.
[3] Values are *n* (%); χ^2 for differences in categorical variables between cases and controls.

TABLE 2 OR and 95% CI for the association of EC with monthly frequency of fruits, total vegetables, and cruciferous vegetables

	Case	Control	OR[1] (95%CI)	*P*-trend
Total vegetables		*n*		
Q1 (≤42/mo)	168	133	1.00	0.001
Q2 (43–66/mo)	144	137	0.78 (0.55–1.11)	
Q3 (67–93/mo)	116	130	0.63 (0.44–0.91)	
Q4 (≥94/mo)	113	141	0.51 (0.34–0.75)	
Total cruciferous vegetables				
Q1 (≤6.4/mo)	129	132	1.00	0.09
Q2 (6.5–10/mo)	145	138	0.97 (0.68–1.39)	
Q3 (11–24/mo)	155	136	1.18 (0.82–1.69)	
Q4 (≥25/mo)	112	135	0.77 (0.52–1.13)	
Total fruit				
Q1 (≤27/mo)	110	135	1.00	0.87
Q2 (28–46/mo)	141	135	1.22 (0.84–1.76)	
Q3 (47–69/mo)	148	131	1.31 (0.91–1.90)	
Q4 (≥70/mo)	142	140	1.10 (0.74–1.62)	

[1] Values are OR and 95% CI; adjusted for age, BMI (continuous variable), exogenous estrogen use, smoking, total menstrual months, and total energy.

Results

We compared descriptive statistics of the study participants using standard statistical methods (**Table 1**). Compared with controls, cases tended to have higher body weight, increased BMI, and later age at menopause. Controls were more likely than cases to have >12 y of education, higher family income, used oral contraceptives, and smoked cigarettes.

We also examined the association of EC with nondietary risk factors, adjusted for age (data not shown). Consistent with previous literature, EC was positively associated with BMI (OR, 2.46; 95% CI, 1.91–3.16; BMI, ≥25 vs. <25) and inversely associated with years of education (OR, 0.74; 95% CI, 0.56–0.97; ≥12 y vs. <12), cigarette smoking (OR, 0.75; 95% CI, 0.59–0.96; ever vs. never smoking), and oral contraceptive use (OR, 0.62; 95% CI, 0.44–0.86; ever vs. never). Weak, but not significant, inverse associations were observed with later age at menarche (OR, 0.79; 95% CI, 0.62–1.02; ≥13 y vs. <13 y; $P < 0.10$) and pregnancy history (OR, 0.73; 95% CI, 0.53–1.02; ever vs. never pregnant; $P < 0.10$).

In our investigations of plant food groups and EC, we found a significantly reduced risk of EC in the highest quartile of total vegetable intake (OR, 0.51; 95%, CI 0.34–0.75) with a strong inverse dose-response trend (*P*-trend = 0.001). However, there were no consistent associations with intakes of either cruciferous vegetables and fruit examined separately (**Table 2**).

EC risk was not associated with the highest compared with lowest quartiles of any of the macronutrients examined (**Table 3**). However, significant inverse linear trends were observed with polyunsaturated fat intake and a borderline significant positive trend with saturated fat intakes.

Consistent with the findings for total vegetable intakes, significant inverse associations were observed in the highest intake quartiles of vitamin E (OR, 0.44; 95% CI, 0.27–0.70; *P*-trend < 0.001), dietary fiber (OR, 0.60; 95% CI, 0.39–0.94; *P*-trend = 0.02), β-carotene (OR, 0.55; 95% CI, 0.37–0.82; *P*-trend = 0.002), lutein (OR, 0.52; 95% CI, 0.34–0.78; *P*-trend = 0.001), and folate (OR, 0.57; 95% CI, 0.36–0.91) (**Table 4**). Although the quartile-specific estimates were not significant, there were inverse trends with vitamin C and α-carotene. Unexpectedly, vitamin D intake was significantly associated with increased risk in the highest quartile of intake.

TABLE 3 OR and 95% CI for the association of EC with daily macronutrient intake

	Cases	Controls	OR[1] (95%CI)	*P*-trend
Total energy, *kJ/d*		*n*		
Q1 (≤5694)	121	135	1.0	0.14
Q2 (5695–7352)	128	135	1.04 (0.72–1.50)	
Q3 (7353–9257)	142	136	1.15 (0.80–1.64)	
Q4 (≥9258)	150	135	1.27 (0.89–1.82)	
Carbohydrates, *g/d*				
Q1 (≤169)	125	135	1.0	0.09
Q2 (170–220)	140	135	1.07 (0.74–1.56)	
Q3 (221–273)	134	136	0.87 (0.58–1.31)	
Q4 (≤274)	142	135	0.85 (0.51–1.40)	
Protein, *g/d*				
Q1 (≤57)	121	134	1.0	0.92
Q2 (58–75)	118	136	1.00 (0.68–1.48)	
Q3 (76–97)	140	136	1.26 (0.81–1.96)	
Q4 (≥98)	162	135	1.40 (0.75–2.59)	
Total fat, *g/d*				
Q1 (≤49)	124	135	1.0	0.22
Q2 (50–64)	102	135	0.86 (0.58–1.28)	
Q3 (65–87)	160	136	1.37 (0.89–2.09)	
Q4 (≥88)	155	135	1.21 (0.67–2.21)	
Saturated fat, *g/d*				
Q1 (≤16)	111	135	1.0	0.05
Q2 (17–23)	111	135	0.97 (0.65–1.44)	
Q3 (24–33)	160	136	1.60 (1.05–2.43)	
Q4 (≥34)	159	135	1.51 (0.84–2.68)	
Monounsaturated fat, *g/d*				
Q1 (≤14)	113	133	1.0	0.29
Q2 (15–19)	109	136	0.91 (0.62–1.35)	
Q3 (20–27)	167	137	1.45 (0.95–2.19)	
Q4 (≥28)	152	135	1.26 (0.71–2.23)	
Polyunsaturated fat, *g/d*				
Q1 (≤7)	124	134	1.0	0.01
Q2 (8,9)	137	136	1.05 (0.72–1.54)	
Q3 (10–12)	152	134	1.11 (0.74–1.67)	
Q4 (≥13)	128	137	0.85 (0.51–1.41)	
Cholesterol, *mg/d*				
Q1 (≤230)	120	135	1.0	0.76
Q2 (231–307)	116	135	0.90 (0.61–1.31)	
Q3 (308–446)	162	136	1.34 (0.89–2.00)	
Q4 (≥447)	143	135	1.09 (0.65–1.85)	

[1] Values are OR and 95% CI; adjusted for age, BMI, exogenous estrogen use, smoking, total menstrual months, and total energy (except for estimates with energy intake); fats were adjusted for total protein and carbohydrates; proteins were adjusted for total fat and carbohydrates; carbohydrates were adjusted for total fat and total protein.

Discussion

Studies on dietary patterns and risk of EC to date have found positive associations with higher intakes of total fat, saturated fat, polyunsaturated fat, protein from animal sources, and many foods of animal origin (11–15). Despite these findings, the evidence for specific dietary components as potential risk factors remains limited, as several investigators have reported inconsistent results from large observational studies (16,18,19,33). In

TABLE 4 OR and 95% CI for the association of EC with daily micronutrient intake

	Cases	Controls	OR[1] (95%CI)	*P*-trend
Vitamin C, *mg/d*		*n*		
Q1 (≤116)	149	135	1.0	0.02
Q2 (117–179)	143	135	0.99 (0.70-1.41)	
Q3 (180–250)	122	136	0.78 (0.54-1.13)	
Q4 (≥251)	127	135	0.73 (0.49-1.10)	
Vitamin D,[2] *IU/d*				
Q1 (≤107)	105	135	1.0	0.06
Q2 (108–233)	137	135	1.25 (0.85-1.82)	
Q3 (234–390)	119	136	1.16 (0.78-1.72)	
Q4 (≥391)	180	135	1.78 (1.14-2.76)	
Vitamin E (total), *mg/d*				
Q1 (≤5.2)	158	134	1.0	<0.001
Q2 (5.3–6.7)	110	135	0.57 (0.39-0.83)	
Q3 (6.8–9.7)	160	137	0.71 (0.48-1.04)	
Q4 (≥9.8)	113	135	0.44 (0.27-0.70)	
Dietary fiber, *g/d*				
Q1 (≤16)	136	135	1.0	0.02
Q2 (17–23)	152	134	1.06 (0.74-1.51)	
Q3 (24–32)	138	136	0.80 (0.55-1.17)	
Q4 (≥33)	115	136	0.60 (0.39-0.94)	
Retinol, $\mu g/d$				
Q1 (≤417)	136	135	1.0	0.07
Q2 (418–631)	133	135	0.92 (0.64-1.32)	
Q3 (632–1112)	125	136	0.86 (0.58-1.27)	
Q4 (≥1113)	147	135	0.85 (0.56-1.30)	
α-Carotene, $\mu g/d$				
Q1 (≤489)	141	135	1.0	0.02
Q2 (490–935)	161	135	1.10 (0.77-1.56)	
Q3 (936–1776)	137	136	0.88 (0.61-1.27)	
Q4 (≥1777)	102	135	0.69 (0.47-1.02)	
β-Carotene, $\mu g/d$				
Q1 (≤3439)	165	135	1.0	0.002
Q2 (3440–5698)	127	135	0.72 (0.51-1.03)	
Q3 (5699–8681)	141	136	0.71 (0.50-1.02)	
Q4 (≥8682)	108	135	0.55 (0.37-0.82)	
Cryptoxanthin, $\mu g/d$				
Q1 (≤4)	101	135	1.0	0.50
Q2 (5–61)	122	135	1.33 (0.91-1.95)	
Q3 (62–250)	155	136	1.36 (0.95-1.96)	
Q4 (≥251)	163	135	1.42 (0.98-2.04)	
Lycopene, $\mu g/d$				
Q1 (≤2601)	140	135	1.0	0.34
Q2 (2602–4279)	124	135	0.87 (0.61-1.25)	
Q3 (4280–6620)	122	136	0.80 (0.56-1.16)	
Q4 (≥6621)	155	135	1.01 (0.69-1.46)	
Lutein, $\mu g/d$				
Q1 (≤2926)	149	135	1.0	0.001
Q2 (2927–4279)	132	135	0.61 (0.43-0.88)	
Q3 (4280–6620)	131	136	0.69 (0.48-0.99)	
Q4 (≥6621)	129	135	0.52 (0.34-0.78)	
Folate, $\mu g/d$				
Q1 (≤288)	149	135	1.0	0.01
Q2 (289–371)	132	135	0.74 (0.51-1.07)	
Q3 (372–473)	131	136	0.69 (0.46-1.01)	
Q4 (≥474)	129	135	0.57 (0.36-0.91)	

our study, higher total vegetable intakes were associated with decreased risk of EC, although no clear associations were seen with higher intake of cruciferous vegetables and fruit. Similarly, we observed inverse associations with nutrients strongly related to plant-based diets, such as vitamins C and E, carotenoids, folate, and dietary fiber. Our results are consistent with studies suggesting that diets rich in vegetables and nutrients associated with these foods are associated with lower risk.

There are plausible biologic mechanisms of action for the inverse associations between individual micronutrients and EC risk. Antioxidant micronutrients such as carotenoids (3,11–14,34,35) and vitamin E (36) neutralize reactive oxygen species and may protect against free radical damage involved in carcinogenesis. Folate is a necessary component for synthesis and methylation of DNA, which plays an important role in maintaining normal cellular functions (37). Especially relevant to EC, observational studies in vegetarian compared with omnivore women suggest that diet can modify circulating concentrations of sex hormones in plasma, including decreased estradiol and estrone concentrations (9,10,38). Higher dietary fiber and lower fat intakes have also been shown to modify plasma sex hormone concentrations, including lower serum estrone and 17β estradiol concentrations (39–42). Decreasing intake of dietary fat is also associated with reduced serum estrogen concentrations, and high-fiber, low-fat diets have been hypothesized to reduce the risk of breast cancer and EC. However, interventional studies have yielded inconsistent results about the relationship between high-fiber, low-fat diets and serum estrogen (43). In the present data, we observed significant inverse associations with vegetable intake and dietary fiber, which is consistent with the hypothesis that a diet high in vegetables may modify EC risk by altering sex hormone metabolism.

We also observed positive trends for saturated fat and a significant inverse trend for polyunsaturated fat. Dorgan et al. (43) reported a significant inverse association with plasma estradiol and estrone in the luteal phase of the menstrual cycle with the ratio of polyunsaturated:saturated fat, after adjusting for energy. Our findings are consistent with the hypothesis that a low-fat, high-fiber diet may be protective against EC through its effects on steroid hormones.

Unexpectedly, vitamin D was associated with increased risk in our study. Possible reasons for this unexpected association could be related to several factors. High intake of vitamin D may be attributed to greater consumption of fortified dairy foods, eggs, and organ meats, which also contain saturated fat. Vitamin D plays a key role in calcium metabolism, and animal studies suggest that it is necessary for estrogen biosynthesis in the ovary. Vitamin D receptor-null female mice have low concentrations of circulating estradiol and decreased aromatase expression. A high-calcium diet was shown to increase aromatase activity in vitamin D receptor-null mice (44–46). On the other hand, serum

TABLE 4 ***Continued***

	Cases	Controls	OR[1] (95%CI)	*P*-trend
Calcium, *mg/d*				
Q1 (≤570)	125	135	1.0	0.19
Q2 (571–927)	134	135	0.95 (0.65-1.39)	
Q3 (928–1380)	102	136	0.86 (0.58-1.29)	
Q4 (≥1381)	180	135	1.44 (0.90-2.30)	

[1] Values are OR and 95% CI; adjusted for age, BMI, HRT, smoking, total menstrual months, and total energy.
[2] 1 IU = 0.025 μg.

vitamin D concentrations and dietary intake of calcium and dairy foods have been found to be inversely associated with insulin resistance in several observational studies. Women with Type 2 diabetes are more likely to be deficient in vitamin D compared with controls with no history of diabetes. Other studies have found inverse associations between adiposity, body weight, and dietary calcium intake (45). Thus, the role of calcium and vitamin D in EC risk is unclear, because both are involved in many cellular processes, including estrogen biosynthesis, glucose metabolism, fatty acid metabolism, and regulation of body weight.

Strengths of this study include the relatively large sample size and available information on important covariates such as exogenous hormone use and reproductive factors. However, there are several limitations of our study that should be noted. As with any hospital-based, case-control study, selection bias may be present due to the possibility that individuals seeking medical care may have characteristics and exposures that are not comparable to the general population. Our hospital-based controls sought care at RPCI for nonneoplastic conditions and may have modified their diets as a result of various medical problems. Although we were able to control for several important covariates, there was no reliable data on hypertension and diabetes besides a binary (yes/no) variable on the self-reported PEDS questionnaire. Due to the large amount of missing data for these variables, as well as the problem of self-reporting for disease processes that may be present in the absence of clinical symptoms, we excluded these potential covariates from the analysis. Diseases such as diabetes can also affect dietary patterns when patients attempt to heed medical advice to modify their intake. On the other hand, many of these factors could also affect intake in the hospital-based controls, which would attenuate the true associations between dietary components and EC. In fact, our findings were consistent with much of the previous literature, suggesting that selection bias was not an important issue in this study.

Measurement error on the FFQ is a concern common to observational studies of diet. This can be attributed to limited recall of consumption or serving size, omission of certain foods, and changes in participants' dietary patterns over time. Such random measurement error in dietary assessment can lead to nondifferential misclassification, which would also tend to underestimate any true associations. Also, we used a 44-item FFQ and intake of nutrients not directly measured from the food list were calculated using regression weights. Compared with the Harvard Semiquantitative FFQ and the National Cancer Institute Health Habits and History FFQ, the 44-item questionnaire yielded somewhat different estimates of total energy and fat, whereas vitamins A and C, dietary fiber, and carotenoid estimates were comparable to the longer instruments (29,30). Although it is likely that some measurement error occurred in the estimation of dietary intake, it is unlikely that the dietary assessment of the cases differed systematically from that of the controls.

Because diet is a modifiable risk factor, a more detailed understanding of dietary components and patterns may be useful in developing population-based preventive strategies for EC. Our study provides additional evidence that diet may play an important role in the etiology of EC and that a vegetable-rich diet may have a protective effect. In summary, the findings of this investigation are consistent with most observational studies on diet and EC to date. Further studies will help identify specific dietary components, intake patterns, and biological mechanisms that contribute to risk.

Literature Cited

1. Purdie DM, Green AC. Epidemiology of endometrial cancer. Best Pract Res Clin Obstet Gynaecol. 2001;15:341–54.
2. Persson I. Estrogens in the causation of breast, endometrial and ovarian cancers: evidence and hypotheses from epidemiological findings. J Steroid Biochem Mol Biol. 2000;74:357–64.
3. Goodman MT, Hankin JH, Wilkens LR, Lyu LC, McDuffie K, Liu LQ, Kolonel LN. Diet, body size, physical activity, and the risk of endometrial cancer. Cancer Res. 1997;57:5077–85.
4. Shu XO, Hatch MC, Zheng W, Gao YT, Brinton LA. Physical activity and risk of endometrial cancer. Epidemiology. 1993;4:342–9.
5. Cline JM, Hughes CL Jr. Phytochemicals for the prevention of breast and endometrial cancer. Cancer Treat Res. 1998;94:107–34.
6. Hale GE, Hughes CL, Cline JM. Endometrial cancer: hormonal factors, the perimenopausal "window of risk," and isoflavones. J Clin Endocrinol Metab. 2002;87:3–15.
7. Cassidy A. Potential risks and benefits of phytoestrogen-rich diets. Int J Vitam Nutr Res. 2003;73:120–6.
8. Lampe JW. Health effects of vegetables and fruit: assessing mechanisms of action in human experimental studies. Am J Clin Nutr. 1999;70: S475–90.
9. Shultz TD, Leklem JE. Nutrient intake and hormonal status of premenopausal vegetarian Seventh-day Adventists and premenopausal nonvegetarians. Nutr Cancer. 1983;4:247–59.
10. Goldin BR, Adlercreutz H, Gorbach SL, Warram JH, Dwyer JT, Swenson L, Woods MN. Estrogen excretion patterns and plasma levels in vegetarian and omnivorous women. N Engl J Med. 1982;307:1542–7.
11. Levi F, Franceschi S, Negri E, La Vecchia C. Dietary factors and the risk of endometrial cancer. Cancer. 1993;71:3575–81.
12. Barbone F, Austin H, Partridge EE. Diet and endometrial cancer: a case-control study. Am J Epidemiol. 1993;137:393–403.
13. Littman AJ, Beresford SA, White E. The association of dietary fat and plant foods with endometrial cancer (United States). Cancer Causes Control. 2001;12:691–702.
14. La Vecchia C, Decarli A, Fasoli M, Gentile A. Nutrition and diet in the etiology of endometrial cancer. Cancer. 1986;57:1248–53.
15. Jain MG, Howe GR, Rohan TE. Nutritional factors and endometrial cancer in Ontario, Canada. Cancer Control. 2000;7:288–96.
16. Shu XO, Zheng W, Potischman N, Brinton LA, Hatch MC, Gao YT, Fraumeni JF Jr. A population-based case-control study of dietary factors and endometrial cancer in Shanghai, People's Republic of China. Am J Epidemiol. 1993;137:155–65.
17. Terry P, Wolk A, Vainio H, Weiderpass E. Fatty fish consumption lowers the risk of endometrial cancer: a nationwide case-control study in Sweden. Cancer Epidemiol Biomarkers Prev. 2002;11:143–5.
18. Jain MG, Rohan TE, Howe GR, Miller AB. A cohort study of nutritional factors and endometrial cancer. Eur J Epidemiol. 2000;16: 899–905.
19. Salazar-Martinez E, Lazcano-Ponce E, Sanchez-Zamorano LM, Gonzalez-Lira G, Escudero-De Los Rios P, Hernandez-Avila M. Dietary factors and endometrial cancer risk. Results of a case-control study in Mexico. Int J Gynecol Cancer. 2005;15:938–945.
20. Terry P, Vainio H, Wolk A, Weiderpass E. Dietary factors in relation to endometrial cancer: a nationwide case-control study in Sweden. Nutr Cancer. 2002;42:25–32.
21. Augustin LSA, Gallus S, Bosetti C, Levi F, Negri E, Franceschi S, Dal Maso L, Jenkins DJA, Kendall CWC, et al. Glycemic index and glycemic load in endometrial cancer. Int J Cancer. 2003;105:404–7.
22. Folsom AR, Demissie Z, Harnack L. Glycemic index, glycemic load, and incidence of endometrial cancer: the Iowa women's health study. Nutr Cancer. 2003;46:119–24.
23. Tao MH, Xu WH, Zheng W, Gao YT, Ruan ZX, Cheng JR, Xiang YB, Shu XO. A case-control study in Shanghai of fruit and vegetable intake and endometrial cancer. Br J Cancer. 2005;92:2059–64.
24. McCann SE, Freudenheim JL, Marshall JR, Brasure JR, Swanson MK, Graham S. Diet in the epidemiology of endometrial cancer in western New York (United States). Cancer Causes Control. 2000;11:965–74.
25. Kasum CM, Nicodemus K, Harnack LJ, Jacobs DR Jr, Folsom AR., Iowa Women's Health Study.Whole grain intake and incident endometrial cancer: the Iowa Women's Health Study. Nutr Cancer. 2001;39: 180–6.

26. Petridou E, Kedikoglou S, Koukoulomatis P, Dessypris N, Trichopoulos D. Diet in relation to endometrial cancer risk: a case-control study in Greece. Nutr Cancer. 2002;44:16–22.
27. Negri E, La Vecchia C, Franceschi S, Levi F, Parazzini F. Intake of selected micronutrients and the risk of endometrial carcinoma. Cancer. 1996;77:917–23.
28. Byers T, Marshall J, Fiedler R, Zielezny M, Graham S. Assessing nutrient intake with an abbreviated dietary interview. Am J Epidemiol. 1985;122:41–50.
29. McCann SE, Trevisan M, Priore RL, Muti P, Markovic N, Russell M, Chan AW, Freudenheim JL. Comparability of nutrient estimation by three food frequency questionnaires for use in epidemiological studies. Nutr Cancer. 1999;35:4–9.
30. McCann SE, Moysich KB, Mettlin C. Intakes of selected nutrients and food groups and risk of ovarian cancer. Nutr Cancer. 2001;39:19–28.
31. USDA, Agricultural Research Service. USDA National Nutrient Database for Standard Reference. Nutrient Data Laboratory Home Page [cited 2008 16 Oct]. Available from: http://www.ars.usda.gov/ba/bhnrc/ndl.
32. Hosmer DW, Lemeshow S. Applied logistic regression. New York: John Wiley & Sons; 1989.
33. Zheng W, Kushi LH, Potter JD, Sellers TA, Doyle TJ, Bostick RM, Folsom AR. Dietary intake of energy and animal foods and endometrial cancer incidence. The Iowa Women's Health Study. Am J Epidemiol. 1995;142:388–94.
34. Mares-Perlman JA, Millen AE, Ficek TL, Hankinson S. The body of evidence to support a protective role for lutein and zeaxanthin in delaying chronic disease. Overview. J Nutr. 2002;132:S518–24.
35. Young AJ, Lowe GM. Antioxidant and prooxidant properties of carotenoids. Arch Biochem Biophys. 2001;385:20–7.
36. Schneider C. Chemistry and biology of vitamin E. Mol Nutr Food Res. 2005;49:7–30.
37. Davis CD, Uthus EO. DNA methylation, cancer susceptibility, and nutrient interactions. Exp Biol Med (Maywood). 2004;229:988–95.
38. Bennett FC, Ingram DM. Diet and female sex hormone concentrations: an intervention study for the type of fat consumed. Am J Clin Nutr. 1990;52:808–12.
39. Adlercreutz H, Fotsis T, Bannwart C, Hamalainen E, Bloigu S, Ollus A. Urinary estrogen profile determination in young Finnish vegetarian and omnivorous women. J Steroid Biochem. 1986;24:289–96.
40. Bagga D, Ashley JM, Geffrey SP, Wang HJ, Barnard RJ, Korenman S, Heber D. Effects of a very low fat, high fiber diet on serum hormones and menstrual function. Implications for breast cancer prevention. Cancer. 1995;76:2491–6.
41. Rose DP, Lubin M, Connolly JM. Effects of diet supplementation with wheat bran on serum estrogen levels in the follicular and luteal phases of the menstrual cycle. Nutrition. 1997;13:535–9.
42. Frische EJ, Hutchins AM, Martini MC, Thomas W, Slavin JL. Effect of flaxseed and wheat bran on serum hormones and lignan excretion in premenopausal women. J Am Coll Nutr. 2003;22:550–4.
43. Dorgan JF, Reichman ME, Judd JT, Brown C, Longcope C, Schatzkin A, Forman M, Campbell WS, Franz C, et al. Relation of energy, fat, and fiber intakes to plasma concentrations of estrogens and androgens in premenopausal women. Am J Clin Nutr. 1996;64:25–31.
44. Lamberg-Allardt C. Vitamin D in foods and as supplements. Prog Biophys Mol Biol. 2006;92:33–8.
45. Harkness LS, Bonny AE. Calcium and vitamin D status in the adolescent: key roles for bone, body weight, glucose tolerance, and estrogen biosynthesis. J Pediatr Adolesc Gynecol. 2005;18:305–11.
46. Kinuta K, Tanaka H, Moriwake T, Aya K, Kato S, Seino Y. Vitamin D is an important factor in estrogen biosynthesis of both female and male gonads. Endocrinology. 2000;141:1317–24.