NUTRITION AND CANCER, *42*(1), 25–32

Dietary Factors in Relation to Endometrial Cancer: A Nationwide Case-Control Study in Sweden

Paul Terry, Harri Vainio, Alicja Wolk, and Elisabete Weiderpass

Abstract: *The incidence of endometrial cancer varies up to 10-fold between high- and low-incidence regions, suggesting the importance of environmental factors, including diet, in the etiology of this disease. However, few studies have examined the role of diet in the etiology of endometrial cancer. Using unconditional logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI), we analyzed data from a large, case-control study of Swedish-born postmenopausal women aged 50–74 yr (709 cases and 2,887 controls) residing in Sweden between 1994 and 1995. We found no clear association between foods or food groups and endometrial cancer risk, although high consumption of certain foods, such as* Brassica *vegetables, coffee, and legumes, might be associated with small-to-moderate reduced risks of endometrial cancer, while red meat consumption might be associated with a small-to-moderate increased risk. Daily use of calcium supplements appeared to lower endometrial cancer risk (OR = 0.5, 95% CI = 0.3–0.9,* P *for trend = 0.04), especially among women with low calcium intake from dairy products. On the other hand, the use of iron supplements appeared to increase the risk (OR = 1.7, 95% CI = 0.9–3.3,* P *for trend = 0.03). The findings are discussed with respect to previous studies and the possible underlying mechanisms.*

Introduction

Endometrial cancer is the seventh most commonly diagnosed cancer among women worldwide (1). Endometrial cancer occurs three times more frequently in developed countries, where incidence is ~11 per 100,000 per year (1). The incidence of endometrial cancer varies ≥10-fold between high- and low-incidence regions (1), suggesting the importance of environmental factors, including diet, in the etiology of this disease; yet clear associations with dietary factors have been elusive. Fruit and vegetable consumption, for example, has been hypothesized to lower the risk of many cancers, primarily through antioxidative mechanisms (2). However, although fruit and vegetable consumption is one of the most commonly examined dietary factors in relation to endometrial cancer risk, the evidence remains sparse and inconsistent (3–9).

In addition to total fruit and vegetable consumption, other dietary factors have been linked to endometrial cancer, such as dairy products, meat, certain antioxidants (such as vitamins C and E), alcohol, and high-fiber grains (3,10). In addition, certain dietary factors that have been associated with other hormone-responsive cancers, such as breast cancer, may also be relevant to endometrial cancer etiology, including coffee (11), calcium (12–14), alcohol (15), and *Brassica* vegetables (6,16,17). However, these dietary factors have rarely been examined in epidemiological studies of endometrial cancer risk. Therefore, we examined foods, food groups, and supplemental vitamin use in relation to endometrial cancer risk in a large case-control study of women in Sweden.

Methods

The design of our study has been described in detail elsewhere (18). This case-control study was conducted among women aged 50–74 yr, born and residing in Sweden from 1 January 1994 to 31 December 1995. We restricted our study to postmenopausal women with an intact uterus and no previous diagnosis of endometrial or breast cancer. Eligible as case patients (n = 1,055) were women with an incident, primary, histopathologically confirmed endometrial cancer. The case patients were identified through six regional cancer registries in Sweden, which comprise a virtually complete cancer registration system (19). Case women were approached after approval from their physicians.

Control women (n = 4,216) were randomly selected from a continuously updated population register including all residents in Sweden. To coordinate use of resources, most of the control women (n = 2,633) were also subjects in a concomitant breast cancer case-control study that used the same questionnaire (20); 735 control women were separately sam-

P. Terry, A. Wolk, and E. Weiderpass are affiliated with the Department of Medical Epidemiology, Karolinska Institute, Stockholm, Sweden. P. Terry is also affiliated with the Department of Epidemiology and Social Medicine, Albert Einstein College of Medicine, Bronx, NY 10461. H. Vainio and E. Weiderpass are affiliated with the International Agency for Research on Cancer, Lyon, France.

pled after completion of the breast cancer study in March 1995 to ensure that the recruitment period for endometrial cancer case patients and the control women was identical. Thus control women were frequency matched to the expected age distribution of breast or endometrial cancer case patients.

Participation rates were 75% among case patients (789 of 1,055 eligible) and 79.9% among the control women (3,368 of 4,216 eligible). Nonparticipation was due to refusal in 171 (16.2%) of 1,055 eligible case patients and in 811 (19.2%) of 4,216 eligible control women and to death or poor health in 37 (0.88%) control women. The patients' physicians refused permission to contact an additional 95 (9%) case patients, mostly because of poor health of these patients.

Data Collection

Data were obtained through mailed questionnaires. Participants were asked about their usual consumption of foods 1 yr before cancer diagnosis (cases) or 1 yr before completing the questionnaire (controls), using nine predefined frequency categories that ranged from "never/seldom" to "three or more times per day." The food frequency questionnaire (FFQ) was designed to capture information primarily on the consumption of fruit and vegetables, legumes, high-fiber grains, dairy products, fish, chicken, and meat. There were also additional questions about consumption of alcohol and coffee and use of vitamin supplements. The Pearson correlations between estimates of specific food consumption from a similar FFQ and 4 × 7-day diet records were 0.3–0.6.

Questions were also asked about the use of supplemental vitamins and minerals (never, occasionally, daily), hormone replacement therapy (18), reproductive and medical histories, anthropometric measures, and lifestyle. Among control subjects, 491 (14.3%) of 3,368 failed to return the mailed questionnaire but agreed to a telephone interview including most questionnaire items (except family history of cancer, diet, alcohol consumption, and medical history), and they were excluded from the present analysis; those women were similar to the study participants with respect to the hormonal, reproductive, and lifestyle variables (physical activity and smoking) included in the multivariate models. An additional 80 cases with atypical hyperplasias were excluded (see below). This left 709 cases and 2,877 control subjects available for analysis (68.2% of the 4,216 control subjects eligible). Case patients were not approached by phone, since all who had consented returned the questionnaires.

Histopathological Classification

Histological specimens for the case patients were retrieved from all 35 pathology departments in Sweden participating in the study. These specimens were reviewed by one pathologist (Anders Lindgren), who was blinded to hormone use or to any other exposures of case patients and who reclassified the specimens as endometrial cancers (in total 709) and atypical hyperplasias (n = 80). All analyses in this study included only cases with invasive cancer.

Statistical Methods

As measures of relative risk, odds ratios were computed from unconditional logistic regression models fit by maximum likelihood methods (21). For tests of trend in risk across successive levels of categorical variables, median values of each category were fitted in the risk models as successive integers (22). In addition to adjusting each dietary factor for the other dietary factors, multivariate models adjusted for age, body mass index (BMI), smoking, physical activity, and total food consumption (see Table 2 for details regarding how these variables were categorized).

Results

Baseline characteristics of the study subjects are shown in Table 1. Consumption of *Brassica* vegetables, dairy products, and alcohol was lower in cases than in controls, and use of calcium supplements was less frequent in cases than in controls. Use of iron supplements, in contrast, was higher in cases than in controls. Total fruit and vegetable, high-fiber grain, legume, meat, and coffee consumption and supplemental vitamin E and C use were similar in both groups. Cases were also less likely to smoke than controls and had a lower mean number of children and a lower prevalence of oral contraceptive use. Cases also had a higher median BMI and a higher prevalence of diabetes and hormone replacement use.

A high consumption of *Brassica* vegetables (a median of 1 serving/day compared with 1 serving/wk) was associated with a statistically nonsignificant 20% lower risk (Table 2). There was no statistical interaction between *Brassica* vegetable consumption and smoking. A high coffee consumption (a median 4 cups/day compared with 0.5 cup/day) was associated with a statistically nonsignificant 30% lower risk of endometrial cancer. Foods or food groups that appeared to be unrelated to risk include total fruit and vegetables, total vegetables, non-*Brassica* vegetables, high-fiber grains, legumes, and alcohol. There was a suggestion of increased risk with meat consumption, but relative risk estimates did not show a clear dose-response trend, and statistical significance was lacking.

Occasional or daily use of multivitamins was not associated with endometrial cancer risk, nor was the use of supplemental vitamin C or E (Table 3). Daily use of calcium supplements was associated with a statistically significant 50% decreased risk of endometrial cancer, although occasional use showed an apparently aberrant nonsignificant increased risk. Examining this association over strata of dairy consumption (which is a major source of calcium) revealed that the inverse association with calcium supplements was limited to individuals with low dairy consumption (Table 3).

Table 1. Baseline Characteristics of Study Subjects

Characteristics	*n* (cases/controls)	Cases	Controls
Dietary factors, servings/wk (median ± SD)			
Total fruit and vegetables	627/2,560	22.0 ± 13.7	22.0 ± 14.4
Brassica vegetables	662/2,705	2.2 ± 3.2	2.5 ± 4.2
Non-*Brassica* vegetables	682/2,796	8.0 ± 6.4	8.0 ± 6.2
Total fruit	679/2,750	9.0 ± 8.0	9.5 ± 8.5
Dairy products	698/2,874	35.0 ± 20.0	39.0 ± 23.7
Coffee	709/2,870	21.0 ± 14.3	21.0 ± 13.8
High-fiber grains	604/2,515	4.1 ± 4.7	4.0 ± 4.8
Legumes	657/2,708	1.1 ± 1.6	1.2 ± 2.1
Meat	657/2,708	12.0 ± 14.0	12.0 ± 12.8
Alcohol, g/day	704/2,859	1.9 ± 4.1	2.1 ± 3.8
Use of dietary supplements, %			
Multivitamins	683/2,796	30.8	28.2
Vitamin C	680/2,776	31.3	32.2
Vitamin E	683/2,796	11.0	11.2
Calcium	680/2,776	7.9	9.9
Iron	683/2,796	7.9	5.6
Age, yr (median)	709/2,877	66.0	64.0
Smoking, % >1 yr	709/2,877	34.0	42.8
Body mass index, kg/m^2 (median)	709/2,868	26.6	24.9
Parity, no. of children (mean)	709/2,876	1.9	2.1
Diabetes, %	709/2,874	11.7	5.7
Oral contraceptive use, %	692/2,765	20.4	32.1
Estrogen replacement therapy use, potency %[a]			
Low	705/2,856	19.9	11.1
Medium	680/2,801	13.4	5.0
Medium with continuous progestins	675/2,779	5.0	7.1
Medium with cyclic progestins	675/2,782	11.6	9.3

a: See Ref. 18 for details.

This association was observed among users and nonusers of multivitamins. In contrast, the association with dairy products did not vary according to calcium supplement use (data not shown). Use of iron supplements was positively associated with risk in a dose-response fashion. The positive association with iron supplement use did not vary across strata of exogenous hormone use, BMI, or consumption of major food groups. Age-adjusted results were similar to multivariate-adjusted results. Results were also similar after additional adjustment for parity (nulliparous, 1 or 2 children, ≥3 children), physical activity between ages 18–30 (never, >1 h/wk, 1–2 h/wk, >2 h/wk), hormonal contraceptive use (ever/never), exogenous hormone use (ever or never use of low-potency estrogens, medium-potency estrogens, medium-potency estrogens with continuous progestins, and medium-potency estrogens with cyclic progestins), age at menarche (>12 yr, 12–14 yr, <14 yr), age at last birth (in quartiles), alcohol consumption (quartiles), and history of hypertension (yes/no).

Discussion

In our large, population-based, case-control study, we did not observe any strong association between specific foods or food groups and endometrial cancer risk in the study population as a whole. However, daily use of calcium supplements appeared to lower endometrial cancer risk, particularly among women with low calcium intake from dairy products. Iron supplement use appeared to increase the risk.

We did not find any clear association between total fruit and/or total vegetable consumption and endometrial cancer risk. Fruit and vegetable consumption has been variably associated with endometrial cancer risk in the few early case-control studies (3), perhaps as a result of the different methodologies employed and the different categories of fruit and vegetables studied. However, more recent studies have continued to show mixed results. For example, two recent case-control studies (5,7) found inverse associations with the consumption of vegetables, but not fruit. Another case-control study found inverse associations with total fruit and vegetables, but not dark-green vegetables (9). The two prospective cohort studies that examined the association between diet and endometrial cancer risk found no association for plant foods (8) or for micronutrients found in fruit and vegetables (4).

The reasons for the inconsistent results for fruit and vegetable consumption are not clear. The possibility of recall bias in some of the case-control studies is suggested by the null results of the two prospective cohort studies. As in most of the previous case-control studies, those cohort studies adjusted relative risk estimates for potentially confounding factors,

Table 2. Odds Ratios of Endometrial Cancer According to Dietary Factors[a,b]

	Dietary Factors Quartiles				*P* for Trend[c]
	1	2	3	4	
Total fruit and vegetables					
Median consumption/wk	9.9	18	25	37	
No. of cases	153	161	166	147	
Age-adjusted OR (95% CI)	1.0 (Ref)	1.1 (0.9–1.4)	1.1 (0.9–1.5)	1.0 (0.8–1.3)	0.91
Multivariate OR (95% CI)[d]	1.0 (Ref)	1.0 (0.7–1.4)	1.2 (0.9–1.6)	0.9 (0.7–1.2)	0.73
Total fruit					
Median consumption/wk	2.5	7.5	13	21	
No. of cases	173	183	168	155	
Age-adjusted OR (95% CI)	1.0 (Ref)	1.1 (0.9–1.4)	1.0 (0.8–1.2)	0.9 (0.7–1.2)	0.33
Multivariate OR (95% CI)[d]	1.0 (Ref)	1.1 (0.8–1.4)	1.0 (0.7–1.2)	0.9 (0.7–1.2)	0.35
Brassica vegetables					
Median consumption/wk	0.8	1.6	3.4	7.4	
No. of cases	177	172	166	147	
Age-adjusted OR (95% CI)	1.0 (Ref)	0.9 (0.8–1.2)	0.9 (0.7–1.1)	0.8 (0.7–1.0)	0.10
Multivariate OR (95% CI)[d]	1.0 (Ref)	1.0 (0.7–1.3)	0.9 (0.6–1.2)	0.8 (0.6–1.1)	0.13
Non-*Brassica* vegetables					
Median consumption/wk	2.9	6.5	9.5	15	
No. of cases	165	164	166	187	
Age-adjusted OR (95% CI)	1.0 (Ref)	1.0 (0.8–1.3)	1.0 (0.8–1.3)	1.2 (0.9–1.5)	0.21
Multivariate OR (95% CI)[d]	1.0 (Ref)	1.0 (0.7–1.3)	1.0 (0.8–1.5)	1.1 (0.8–1.5)	0.28
Dairy products (milk, yogurt, cheese)					
Median consumption/wk	5	14	21	35	
No. of cases	171	151	171	205	
Age-adjusted OR (95% CI)	1.0 (Ref)	1.1 (0.9–1.4)	0.9 (0.7–1.1)	0.9 (0.7–1.1)	0.20
Multivariate OR (95% CI)[d]	1.0 (Ref)	1.0 (0.8–1.3)	0.9 (0.7–1.2)	0.9 (0.7–1.2)	0.30
Coffee					
Median consumption/wk	4	11	22	30	
No. of cases	250	167	137	155	
Age-adjusted OR (95% CI)	1.0 (Ref)	0.9 (0.6–1.2)	0.8 (0.6–1.0)*	0.7 (0.5–1.0)*	0.10
Multivariate OR (95% CI)[d]	1.0 (Ref)	0.9 (0.6–1.3)	0.8 (0.6–1.1)	0.7 (0.5–1.0)	0.19
High-fiber grains					
Median consumption/wk	0.1	2.1	6.0	9.0	
No. of cases	141	144	154	165	
Age-adjusted OR (95% CI)	1.0 (Ref)	1.0 (0.8–1.3)	1.1 (0.9–1.5)	1.0 (0.8–1.3)	0.64
Multivariate OR (95% CI)[d]	1.0 (Ref)	0.9 (0.7–1.2)	1.2 (0.8–1.6)	1.0 (0.7–1.3)	0.66
Legumes (peas, beans, lentils, soy)					
Median consumption/wk	0.4	0.9	1.5	3.1	
No. of cases	187	162	146	162	
Age-adjusted OR (95% CI)	1.0 (Ref)	0.9 (0.7–1.2)	0.8 (0.6–1.0)*	0.9 (0.7–1.1)	0.19
Multivariate OR (95% CI)[d]	1.0 (Ref)	0.8 (0.6–1.0)	0.7 (0.5–1.0)*	0.8 (0.6–1.1)	0.37
Meat (all types)					
Median consumption/wk	4	8	16	24	
No. of cases	118	256	111	195	
Age-adjusted OR (95% CI)	1.0 (Ref)	1.2 (0.9–1.5)	1.2 (0.9–1.7)	1.2 (1.0–1.6)	0.18
Multivariate OR (95% CI)[d]	1.0 (Ref)	1.2 (0.9–1.6)	1.3 (0.9–1.8)	1.3 (1.0–1.8)	0.11

a: ORs, odds ratios; CI, confidence interval.

b: Statistical significance is as follows: *, $P < 0.05$.

c: All *P* values are from 2-sided tests.

d: In addition to adjusting each dietary factor for the other dietary factors, multivariate models adjusted for age (as a continuous variable), body mass index (in quartiles defined among controls), smoking (ever >1 yr, never), physical activity (never, >1 h/wk, 1–2 h/wk, >2 h/wk), prevalence of diabetes (yes, no), fatty fish consumption (quartiles), and quintiles of total food consumption (estimated by summing all food items in the food frequency questionnaire).

such as age, smoking, BMI, and hormonal factors. It is also possible that certain categories of fruit and vegetables are more important than others in endometrial cancer etiology. Among the major fruit and vegetable categories in our data, only the consumption of *Brassica* vegetables (mostly green, white, and Chinese cabbage, broccoli, and cauliflower) was inversely associated with risk, although the association was neither strong nor statistically significant. One can speculate that *Brassica* vegetables may lower endometrial cancer risk because of their beneficial effect on estrogen metabolism. Among postmenopausal women, *Brassica* vegetable consumption significantly increased the ratio of 2-hydroxyestrone to 16α-hydroxyestrone in urine (16), which might be inversely associated with the risk of hormone-responsive can-

Table 3. Odds Ratios of Endometrial Cancer According to Vitamin/Mineral Supplement Use[a]

	Supplement Use			*P* for Trend[b]
	Never	Occasionally	Daily	
Multivitamin supplement use				
No. of cases	474	89	122	
Age-adjusted OR (95% CI)	1.0 (Ref)	1.1 (0.9–1.5)	1.1 (0.9–1.4)	0.37
Multivariate OR (95% CI)[c]	1.0 (Ref)	1.0 (0.7–1.4)	1.0 (0.8–1.4)	0.80
Vitamin C supplement use				
No. of cases	472	154	61	
Age-adjusted OR (95% CI)	1.0 (Ref)	1.0 (0.8–1.3)	0.8 (0.6–1.1)	0.38
Multivariate OR (95% CI)[c]	1.0 (Ref)	0.9 (0.7–1.2)	0.8 (0.6–1.2)	0.30
Vitamin E supplement use				
No. of cases	606	38	37	
Age-adjusted OR (95% CI)	1.0 (Ref)	0.9 (0.6–1.3)	1.0 (0.7–1.4)	0.77
Multivariate OR (95% CI)[c]	1.0 (Ref)	0.7 (0.4–1.2)	1.3 (0.8–1.9)	0.53
Iron supplement use				
No. of cases	626	35	19	
Age-adjusted OR (95% CI)	1.0 (Ref)	1.6 (0.6–4.1)	1.4 (0.8–2.4)	0.04
Multivariate OR (95% CI)[c]	1.0 (Ref)	1.4 (0.4–4.6)	1.7 (0.9–3.3)	0.03
Calcium supplement use				
No. of cases	627	30	24	
Age-adjusted OR (95% CI)	1.0 (Ref)	1.2 (0.6–2.5)	0.6 (0.4–0.9)*	0.04
Multivariate OR (95% CI)[c]	1.0 (Ref)	1.5 (0.6–3.5)	0.5 (0.3–0.9)*	0.04
Calcium supplement use (dairy consumption below median)				
No. of cases	323	21	10	
Age-adjusted OR (95% CI)	1.0 (Ref)	2.4 (0.9–5.8)	0.4 (0.2–0.8)*	0.05
Multivariate OR (95% CI)[c]	1.0 (Ref)	2.4 (0.7–6.9)	0.3 (0.1–0.7)†	0.01
Calcium supplement use (dairy consumption above median)				
No. of cases	302	9	14	
Age-adjusted OR (95% CI)	1.0 (Ref)	0.3 (0.1–1.8)	0.8 (0.5–1.5)	0.30
Multivariate OR (95% CI)[c]	1.0 (Ref)	0.4 (0.1–2.9)	0.8 (0.4–1.5)	0.39

a: Statistical significance is as follows: *, $P < 0.05$; †, $P < 0.01$.

b: All *P* values are from 2-sided tests.

c: In addition to adjusting each dietary factor for the other dietary factors, multivariate models adjusted for age (as a continuous variable), body mass index (in quartiles defined among controls), smoking (ever >1 yr, never), physical activity (never, >1 h/wk, 1–2 h/wk, >2 h/wk), prevalence of diabetes (yes, no), fatty fish consumption (quartiles), and quintiles of total food consumption (estimated by summing all food items in the food frequency questionnaire).

cers. In agreement with this finding and with previous animal experiments, indole-3-carbinol found in *Brassica* vegetables was recently found to exert a tamoxifen-like antagonism of the estrogen receptor signaling pathway (23). Indole-3-carbinol was also shown to arrest the growth of human breast cancer cells (24) and to induce apoptosis in various cell types (25). Moreover, a class of phytochemical, isothiocyanates (ITCs), which are found in *Brassica* vegetables, have shown inverse associations with lung cancer and colon cancer (26,27). Because the protective effect of ITCs is predominantly seen among subjects who are predicted to metabolize ITCs more slowly on the basis of deletion of glutathione *S*-transferase (GST) genes that eliminate these compounds from the body, it may be that the eventual preventive effect of *Brassica* vegetables could more clearly be seen only after stratification according to GST genotypes.

Our data do not support an association between the consumption of high-fiber grains and endometrial cancer risk. Three of the most recent case-control studies of diet and endometrial cancer show mixed results for dietary fiber (5,7,10). One of these studies (7) found an inverse association for total dietary fiber, whereas another (5) found no association with fiber from grains or fruit (but found an inverse association with vegetable fiber). In contrast, another study found an inverse association mainly with cereal fiber intake (10). Four earlier case-control studies also showed mixed results regarding whole grains and fiber (3). One cohort study (4) found no association between fiber intake and endometrial cancer risk.

One advantage of our study is the relatively high intake of cereal fiber in Sweden (28). Our null results are, therefore, not likely a result of a low or narrow range of intake of fiber and whole grains. On the other hand, since our data on high-fiber grains were limited to the three richest sources of fiber in the Swedish diet (29), breakfast cereal (such as musli), high-fiber breads, and wheat fiber, some misclassification of this exposure is likely due to other fiber-containing food items not included in our questionnaire.

We found intake of legumes to be weakly associated with endometrial cancer risk. Soybeans, as well as whole grains (30), are rich in phytoestrogens, which have been hypothesized to lower the risk of hormone-responsive cancers (31). Tofu, from soybeans, was found to reduce the risk in a previous case-control study (10). However, legumes were not as-

sociated with risk in a case-control study from Canada (5) or in a case-control study from China (32), although the intake of tofu was not specifically examined. The consumption of soy and soy products in our own data was extremely low. Therefore, our results for legumes, and those of the Canadian and Chinese studies, do not necessarily apply to soy consumption.

We found some support for our a priori hypothesis that coffee consumption might reduce the risk of endometrial cancer, possibly through increasing sex hormone-binding globulin (11). Although a previous case-control study did not observe an altered risk with coffee consumption (9), the relatively wide range of coffee consumption in Sweden (33) suggests the possibility that an inverse association might exist only at very high levels of intake.

We found a 30% increased risk with high meat consumption, although a dose-response trend and statistical significance were lacking. The results of previous case-control studies of meat consumption are mixed, with some showing positive associations (3,32) and others showing no association (3,5,7). Cohort studies, of which there are few, have found no association with meat consumption. Saturated fat intake was not associated with risk in the Canadian Breast Screening Study (4), nor was total meat or red meat associated with risk in the Iowa Women's Health Study (8). In the latter study, however, high consumption of "processed meat and fish" appeared to increase the risk. We previously found an inverse association with fatty fish, but not other types of fish (34). We also found no association between alcohol consumption and endometrial cancer risk (35). Three other previous case-control studies (7,9,36) and a prospective cohort study (4) also found no association with alcohol consumption although alcohol consumption in our study, as well as in the previous studies, was not high. Therefore, an increased risk with high alcohol consumption (e.g., >2 drinks/day) cannot be ruled out.

The consumption of high-calcium dairy products was not clearly associated with endometrial cancer risk in our data, although a small reduction in risk with high consumption was suggested. Weak inverse associations were also observed in several previous case-control studies (5,13,14), but others found no association (3,37). However, examining calcium supplement use, we found a significant inverse association with endometrial cancer risk; stratified analysis revealed an association only among women with low dairy consumption. Previous studies have not generally examined the association specifically with calcium intake, although a case-control study from Greece (38) found that, of all the examined dietary micronutrients, only calcium was significantly inversely associated with endometrial cancer risk. However, explanations other than a true causal association can be suggested. For example, women who like dairy products might respond to a threat of osteoporosis with a greater intake of these foods, while women who do not like dairy foods might use calcium supplements instead. This might explain the lower risk for calcium supplement users among women with low dairy consumption. However, from a biological perspective, the mechanisms by which calcium may exert chemopreventive effects are not fully clear. Calcium is a pivotal regulator of a wide variety of cell functions in its role as a major second messenger (39–41). The absorption and metabolism of calcium are carefully regulated by vitamin D. Epidemiological studies of vitamin D and calcium have indicated that these nutrients may reduce the risk of several types of cancer, including cancer of the breast (12). Further studies are warranted to verify that this preventive effect of calcium could also be expanded to cancer of the endometrium.

Supplemental use of multivitamins, vitamin C, or vitamin E was not related to endometrial cancer risk in our data, although the statistically nonsignificant 20% lower risk among women taking daily vitamin C supplements can be viewed as offering weak support for a beneficial effect. The results of previous studies that examined vitamin C are sparse and mixed (3,5,7). Although one recent case-control study found no association with vitamin C from diet or supplements (5), another study found an inverse association with total vitamin C intake (7).

We found a positive association between use of iron supplements and endometrial cancer risk. As with calcium supplements and supplement use in general, the proportion of women taking iron supplements was relatively low. Iron intake has received scant attention in relation to endometrial cancer risk, although a previous case-control study found a statistically nonsignificant 30% increased risk with every 2-mg increase in dietary intake. We can speculate that women who take iron supplements have intense bleedings during perimenopausal years. These bleedings may be a marker for estrogenic proliferation of the endometrium, a risk factor for endometrial cancer (42), or even a sign of undiagnosed endometrial cancer (43). In either of these cases, if it is assumed that measures of postmenopausal iron supplement use indeed reflect earlier (perimenopausal) use, daily iron supplement use could be a marker for endometrial cancer risk rather than a cause. However, it has been suggested that excess iron may facilitate the occurrence of cancer; e.g., patients with hereditary hemochromatosis are at high risk of developing liver cancer as well as cancer in nonhepatic organs (44).

The strengths of our study include its large size and the assessment of information on a wide range of potentially confounding lifestyle factors, including many factors related to endogenous and exogenous hormones. In addition, we were able to examine relatively high intake ranges of certain dietary factors, such as dairy foods, cereal fiber (28), and coffee (33) due to consumption patterns common in Sweden. However, the method of assessing diet in our study has limitations. The correlations between estimates of food consumption from a similar FFQ and 7-day diet records were 0.3–0.6, indicating an imperfect relative ranking of individuals according to the studied foods (45). Nondifferential misclassification would tend to attenuate true associations. Furthermore, we assumed that our FFQ, which asked about diet during the preceding year, captured the relative ranking of subjects with respect to long-term diet. The validity of this assumption is supported

by Goldbohm et al. (46), who observed a high consistency of within-subject dietary patterns over five successive annual assessments using an FFQ. In addition, it can be argued that face-to-face interviews, compared with mailed questionnaires, would be less likely to result in measurement error, for example, due to a more uniform interpretation of questions.

Recall bias is possible in our data, since we assessed exposure retrospectively. There are some arguments against such bias, for example, the null association for total fruit and vegetable consumption, arguably among the dietary factors most likely to be perceived as beneficial for health among the public. However, the mean time between diagnosis and interview for cases was 8.4 ± 4.6 mo, giving cases time to have changed their diets and potentially have their recall influenced by this change.

The possibility of selection bias exists in the fact that some potential cases (25%) and controls (32%) declined to participate in our study or provide dietary information. For example, if fruit and vegetable consumption was lower among participating control subjects than among nonparticipating control subjects, a true inverse association with fruit and vegetable consumption might be weakened or masked. A similar result is possible if fruit and vegetable consumption was lower among nonparticipating case subjects than among participating case subjects. Although we know of no important differences in dietary intake according to participation in previous studies, we cannot rule out selection bias in our data. Furthermore, although we did adjust our relative risk estimates for a wide range of potentially confounding factors, including hormonal factors and other known risk factors for endometrial cancer, there may be unidentified factors (including dietary factors) that might have influenced the associations in our data.

We adjusted relative risk estimates for the potentially confounding effect of total energy intake through total food intake. This method does not, by itself, provide complete control for total energy intake, although the limitations of the FFQ might also preclude the complete assessment of total energy intake. However, the main determinants of variation in total energy intake are physical activity and BMI (47), and adjustment for these variables did not attenuate the calculated odds ratios in our study but, rather, the opposite. Furthermore, total energy intake was not associated with endometrial cancer risk in the two prospective cohort studies that examined the association (4,8), or in a case-control study after simultaneous adjustment for BMI (9). Although it is not clear that energy intake is related to endometrial cancer risk, we cannot rule out the possibility of some residual confounding by energy after the adjustment for BMI, physical activity, and total food consumption.

In conclusion, the results of this study do not support any strong association between the studied foods or food groups and endometrial cancer risk. High consumption of coffee, legumes, and *Brassica* vegetables might lower endometrial cancer risk, and high consumption of meat might increase the risk. Although these dietary factors may not be strong predictors of risk individually, they may represent broader dietary patterns that reflect several dietary exposures working together (48). To date, no study has examined dietary patterns in relation to endometrial cancer risk.

Daily use of calcium supplements appeared to lower endometrial cancer risk, especially among women with low calcium intake. In contrast, the use of iron supplements appeared to increase the risk. However, iron supplement use might be a marker for endometrial cancer rather than an etiologic factor. Given the scarcity of studies of diet in relation to endometrial cancer risk, further investigations are warranted.

Acknowledgments and Notes

Address correspondence to P. Terry, Dept. of Epidemiology and Social Medicine, Albert Einstein College of Medicine, 1300 Morris Park Ave., 13th Fl., Bronx, NY 10461. Phone: (718) 430-3038. FAX: (718) 430-8653. E-mail: pterry@aecom.yu.edu.

Submitted 22 August 2001; accepted in final form 25 October 2001.

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