

Dietary associations in a case-control study of endometrial cancer

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Despite the established role of obesity in the etiology of endometrial cancer, limited data are available from analytical epidemiologic studies on the association of risk with dietary factors. A case-control study of 399 cases and 296 controls conducted in five areas of the United States from 1 June 1987 to 15 May 1990, enabled evaluation of risk related to dietary intakes adjusted for potential confounders. Caloric intake was associated modestly with increased risk (odds ratio [OR] = 1.5, 95 percent confidence interval [CI] = 0.9-2.5 for highest cf lowest quartiles of intake), with the principal contributors being fat and protein calories. After adjustment for other risk factors, including body mass, increased risk was associated with higher intakes of fat. Several components of fat investigated were associated with increased risk, although associations were slightly stronger for saturated fat (OR = 2.1, CI = 1.2-3.7) and oleic acid (OR = 2.2, CI = 1.2-4.0) than for linoleic acid (OR = 1.6, CI = 0.9-2.8). Food-group analyses showed intake of complex carbohydrates—and specifically of breads and cereals—associated with reduced risks (OR = 0.6, CI = 0.4-1.1), whereas animal fat and fried foods were associated with elevated risks (OR = 1.5 and 1.7, respectively). The relations of endometrial cancer with animal fat and complex carbohydrates were independent. No consistent associations were noted for intakes of cholesterol, fiber, vitamins A and C, individual carotenoids, or folate-rich foods. These data imply an etiologic role for a diet rich in total fat and/or animal fat and low in complex carbohydrates with endometrial cancer. These associations are consistent with a hormonal mechanism and were independent of the associations of obesity and other risk factors.

Key words: Carbohydrate, case-control study, diet, endometrial cancer, fat, protein, United States.

Introduction

It is well established that obese women experience elevated rates of endometrial cancer.¹ This association is consistent with a well-recognized effect of estrogenic factors on the risk of this tumor, since obese women

have both an increased capacity for conversion of precursor steroids to estrogens in their peripheral fat tissue and low levels of sex-hormone binding globulin (SHBG), resulting in high levels of free estrogen.^{2,4}

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Dietary factors may relate not only to the development or maintenance of obesity, but may directly influence circulating hormone levels.⁵⁻¹⁰ The extent to which the association of obesity with endometrial cancer is related to dietary intake remains unknown.

Only a limited number of studies have reported on the relation of diet and risk of endometrial cancer. Ecologic studies have suggested total fat^{11,12} and saturated fat¹³ were related to endometrial cancer incidence. Only two analytic studies have evaluated risk related to dietary intake and found increased risk associated with animal fat and protein,¹⁴ high fat food items,¹⁵ and reduced risks associated with whole grain foods¹⁵ and complex carbohydrates.¹⁴ No association with endometrial cancer has been reported for a variety of micronutrients,^{14,16} but reports from two studies indicated lower levels of β -carotene in the blood¹⁷ and diet¹⁵ of cases. In general, these ecologic and analytic studies have been limited by the dietary data or inadequate adjustment for other risk factors, including obesity.

We had the opportunity to evaluate the association of diet and endometrial cancer in a study of 399 cases and 296 controls. The collection of detailed risk-factor information allowed us to assess the role of diet independent of the other major predictors of endometrial cancer risk and the effect of diet in relation to risk from obesity.

Materials and methods

This case-control study was conducted between 1 June 1987 and 15 May 1990 in five areas of the United States: Chicago, IL; Hershey, PA; Irvine and Long Beach, CA; Minneapolis, MN; and Winston-Salem, NC. Details of the study design and interview have been reported elsewhere.^{18,19} Eligible cases were women newly diagnosed with endometrial cancer who were between the ages of 20 and 74 and who resided in defined geographic areas. We attempted to select one community control for each eligible case, matched on five-year age-group, race, and geographic region of residence (telephone exchanges or zip codes). For controls under age 65, random-digit-dialing techniques were utilized,²⁰ whereas older controls were selected using data from the Health Care Financing Administration. Controls who were not at risk for endometrial cancer due to previous hysterectomy were excluded and replaced with other eligible subjects.

Overall, 498 eligible cases were identified, with 434 (87 percent) completing the interview. Of the 304 younger and 180 older eligible controls, 320 (66 percent) completed the interview. The principal reason for nonresponse among controls was refusal (22 percent), with slightly higher nonresponse among older con-

trols. Because of the possible etiologic differences by histologic type, cases with nonepithelial tumors and their matched controls were removed from the analytic sample.

Subjects were interviewed by uniformly trained staff. The interview, averaging 60 min in length, elicited information regarding reproductive and menstrual histories, use of exogenous hormones and contraceptive behavior, demographic factors, physical activity, alcohol use, and diet. Following the interview, another 15 min were devoted to obtaining a variety of anthropometric measurements, which are described in detail elsewhere.²¹

The 60-item food-frequency Block questionnaire²² was administered as part of the interview process. Participants were asked how often, on average, during the past few years, they had consumed a specific food item (e.g., eggs) or group of similar food items (e.g., hamburgers, cheeseburgers, or meat loaf), ignoring any recent changes in diet. Subjects were given cards that described medium portion sizes for each item and asked about their intake relative to this amount. Measuring cups, spoons, and beverage containers also were used in the interview to help establish portion sizes. Frequency of intake was asked in an open-ended format, and verbatim responses and comments were recorded and used for coding purposes.

Subjects with suspect dietary data were eliminated. Of the 405 cases with epithelial cancers and 297 community controls, six cases and one control were removed because of inadequate dietary data (*i.e.*, either more than 10 percent missing frequency on foods or fewer than three food items consumed per day). Thus, the dietary analyses consisted of 399 cases and 296 community controls.

Dietary data were converted into nutrients based on Block's US National Cancer Institute (NCI) program.²³ Intake of nutrients was computed based on the frequency of consumption of each food item and the nutrient content of a small, medium, or large serving. Age- and sex-specific portion sizes and food composition data were obtained from the US National Health and Nutrition Examination Survey II (NHANESII) nutrient database.²⁴ Individual carotenoids were based on updated US Department of Agriculture data and compilations of other sources, and were components in the Block database. Questions regarding intake of alcoholic beverages concerned a different timeframe than those of the dietary questionnaire. Therefore, calories contributed from alcohol were not included in the total calorie estimate. Frequency of consumption of a food group was derived by adding together frequency of intake of individual food items comprising each food group (Appendix). In addition, combination

variables were created to approximate consumption patterns (e.g., diets high in meats and low in vegetables compared with diets low in meats and high in vegetables). For these analyses, low and high intakes were defined as below or above the median for each variable.

Analyses were performed with SAS version 6.0²⁵ and BMDP Statistical Software.²⁶ All nutrients were log-transformed for evaluation of means because of highly skewed distributions. Analysis of covariance was used to derive adjusted mean values of the nutrients and to test differences between cases and controls after adjusting for age. We used Spearman correlation coefficients to evaluate associations among nutrients and food groups. Unconditional logistic regression was used to derive odds ratios (OR, approximations to relative risks) and 95 percent confidence intervals (CI), after adjustment for confounding variables.²⁷

Tests for trend across quartiles were performed by assigning the median nutrient value to each quartile and treating it as a continuous variable. Stratified analyses were conducted for categories of other risk factors to determine the consistency of nutrient associations. Cross-product terms were entered into logistic regression models to test the statistical significance of interactions.

Nutrients were adjusted for energy intake in several ways. Total calories were included in the model for: percent of calories from fat, protein, and carbohydrates; vitamins A and C; carotenoids; and food groups. For those nutrients highly correlated with total calories ($r \geq 0.5$), we utilized a less correlated macronutrient-calorie variable to preclude overadjustment in our models. For example, both protein and fat calories were highly correlated with total calories ($r = 0.9$) and with each other ($r = 0.8$). Similarly, protein and non-protein calories were correlated ($r = 0.9$) as were fat and non-fat calories ($r = 0.7$). Thus, in the analyses of protein and fat calories, we used carbohydrate calories to adjust for the remaining macronutrient calories as this variable was less strongly correlated with protein and fat ($r = 0.7$ and 0.6 , respectively).

The major risk factors identified in this study, after adjustment for each other, included: number of births (OR = 0.3 for ≥ 5 cf 0 births); smoking (OR = 0.4 for current cf never); oral contraceptive usage (OR = 0.4 for ever cf never); alcohol intake (OR = 0.8 for drinkers cf nondrinkers); age at menarche (OR = 3.1 for < 12 cf ≥ 15 years of age); menopausal estrogen usage (OR = 2.2 for ever cf never); body mass index (BMI, weight/height²) (OR = 2.2 for BMI ≥ 28.4 cf < 22.5); upper body obesity (OR = 2.3 for highest cf lowest quartile of waist-to-thigh [WTR] ratio); and years of education (OR = 2.6 for ≥ 16 cf < 12 years). History of

hypertension and gallbladder disease were not related to risk of disease after adjustment for weight, but diabetes was somewhat related (OR = 1.6). Adjustment of nutrient associations for study site, WTR, alcohol intake, age at menarche, and diabetes did not materially change the results presented and were not included as potential confounders in logistic models. Evaluation of the association between nutrients of interest and other risk factors among controls revealed that women reporting diets low in saturated fat and total calories were likely to be older (age 70-79), nulliparous, below the median body mass index, and users of menopausal estrogens. In addition, younger women (age 25-49), current smokers, those with less than 12 years of education, or few births were more likely to report low complex-carbohydrate intakes. Adjustment factors for all analyses therefore included: age (< 40 , 40-49, 50-59, 60-69, 70+); menopausal estrogen usage (ever/never); oral contraceptive usage (ever/never); parity (0, 1, 2, 3, 4, 5+), smoking status (never, former, current); years of education (< 12 , 12, 13-15, 16+); and BMI (< 22.5 , 22.5-24.9, 25.0-28.3, 28.4+). Finer categorization or use of the continuous BMI, weight, or WTR variables resulted in similar findings to those presented.

Results

Cases and controls were comparable on race and age, with a mean age at interview of 59.1 years for cases and 58.0 years for controls. Nutrient analyses of age-adjusted means indicated that cases consumed more calories and higher levels of most dietary constituents than did controls (Table 1).

Dietary intake of cholesterol showed the most marked difference between cases and controls ($P < 0.001$), but intakes of fat, saturated fat, and oleic acid were also higher among cases ($P < 0.01$). Cases reported higher intakes of protein, carbohydrates, linoleic acid, and vitamin C ($P < 0.05$), whereas differences were not statistically significant for fiber and vitamin A ($P = 0.09$ and 0.13 , respectively).

The ORs for quartiles of macronutrient variables are presented in Table 2. After adjustment for age, the strongest trend with risk was noted for increasing total calories (P for trend = 0.03). Modestly increased risks were noted for intake of protein calories, fat calories, and percent of calories from fat greater than 32.1. Other risk factors added to the models counter-balanced each other so that adjustment for all potential confounders appeared to have little effect on point estimates. Of interest, BMI had a particularly large impact on many associations. For example, the OR in the highest quartile of protein calories adjusted for other risk factors excluding BMI was 1.8 (CI = 1.0-3.3) and

Table 1. Age-adjusted mean (95% confidence interval) daily nutrient intakes for endometrial cancer cases and community controls

Nutrient (unit)	Cases (No. = 399)	Community controls (No. = 296)
Calories (Kcals) ^a	1,314 (1,267-1,362)	1,227 ^b (1,176-1,280)
Protein (g)	50.7 (48.7-52.6)	47.7 ^b (45.6-49.9)
Carbohydrate (g)	152 (146-158)	143 ^b (137-150)
Fat (g)	55.1 (52.6-57.8)	50.1 ^c (47.5-52.9)
Saturated Fat (g)	19.1 (18.2-20.1)	17.1 ^c (16.1-18.1)
Oleic acid (g)	19.4 (18.5-20.4)	17.6 ^c (16.7-18.6)
Linoleic acid (g)	10.6 (10.0-11.1)	9.6 ^b (9.1-10.3)
Cholesterol (mg)	202 (190-213)	174 ^d (164-188)
Fiber (g)	10.5 (10.0-11.0)	10.0 (9.5-10.5)
Vitamin A (IU)	7,181 (6,802-7,580)	6,688 (6,280-7,122)
Vitamin C (mg)	127 (120-135)	114 ^b (107-122)

^a Excludes calories from alcohol.

^b $P < 0.05$ difference for cases *cf* control group.

^c $P < 0.01$.

^d $P < 0.001$.

changed to 1.4 (CI = 0.7-2.7) after adjustment for BMI. Similarly, in an analysis including age only, the OR in the highest quartile of total calories was 1.6 but decreased to 1.3 with adjustment for BMI. High caloric intake, however, continued to be associated with increased risk (OR = 1.5, CI = 0.9-2.5) after adjustment for the major risk factors, with fat and possibly protein calories contributing to this increased risk. Before and after adjustment for carbohydrate calories, elevated risks were observed for fat calories and, to a lesser extent, protein calories. The variables describing diet composition suggested that risk of disease was related to higher percent fat (P -trend = 0.07 and 0.11 before and after adjustment for calories, respectively) but not to percent of protein or carbohydrates. The ORs for total calories in these models were not altered by adjustment for these percent-macronutrient variables, suggesting independent effects of diet composition and caloric intake.

Risks associated with types of fat, fiber, and cholesterol are shown in Table 3. After adjustment for non-dietary risk factors, cases had higher intakes of saturated fat and oleic acid in all three quartiles above the reference group, with results for linoleic acid being

less strong. After control for carbohydrate calories, the risks associated with high intake of saturated fat and oleic acid were enhanced slightly (P -trend = 0.05 and 0.04, respectively). Women in the highest quartile of cholesterol intake had two times the risk of those in the lowest quartile. Although no trend in risk estimates was apparent with increasing quartiles of cholesterol, a trend test using median values indicated increasing risk as cholesterol intakes increased ($P = 0.01$). Consumption of fiber was not associated with risk, whereas higher consumption of vitamins A and C was associated with elevated risks. Although the risk estimates were elevated, no trends were observed either before or after adjustment for total calories. Further adjustment for intake of saturated fat did not alter the ORs. No associations or trends were observed for individual carotenoids including α - and β -carotene, lutein, cryptoxanthin, xanthins, and lycopene (data not presented).

Because of the strong association of endometrial cancer and obesity in these data²¹ and the influence of BMI on nutrient associations, we attempted to assess whether dietary patterns differed by body mass. After adjustment for weight and other risk factors, carbohydrate calories did not appear to be related differentially to disease among any one body mass group (Table 4). However, total calories, protein and fat calories—and saturated fat, in particular—appeared to be associated more strongly with disease in women with a BMI less than 29 compared with heavier women. Limiting the analysis to the thinnest women (BMI < 23) or to women with intermediate weights (BMI 23-28) resulted in elevated risk estimates for all quartiles above the reference for saturated fat (OR = 2.0, 3.0, 2.2 for BMI < 23 and OR = 5.8, 4.9, 5.0 for BMI 23-28). After women were divided into groups below or above the median weight (69.5 kg), findings were similar to those for BMI. However, carbohydrate calories appeared associated with lower risks in lower-weight women than in heavier women. Fat distribution was a strong predictor of risk and had a positive linear relation with risk in these data,²¹ and so it was of interest to evaluate risk related to dietary intake among women with low and high-risk fat-distribution patterns. Contrary to the finding from body mass, where risk associated with nutritional factors appeared stronger in the women thought to be at low risk of disease, these same factors were stronger in women with upper body obesity (high risk of disease). Women above the median WTR had increased risks associated with protein, fat, and saturated fat, and lower risks associated with carbohydrate calories. No clear trends were noted for women with lower body fat distributions although some elevation in risk estimates was noted for saturated fat. Although results for the nutrient factors

appeared differential by anthropometric strata, none of the interactions was statistically significant. Weight was controlled in these stratified analyses because of possible residual effects of this factor within anthropometric subgroups. In addition, further adjustment for body fat distribution in the BMI and weight stratified analyses did not substantially change results presented.

Evaluation of food patterns utilizing food frequency data also were pursued (Table 5). Analyses adjusted only for age suggested greater consumption of red meat, foods high in animal fat, fried foods, fruit, and citrus fruit among cases. These findings may have resulted from consistent over-reporting by cases or

under-reporting by controls of frequency in this questionnaire. We attempted to compensate for this by adjusting for calories in a simple model with age only (data not presented), yet increased risks persisted for consumption of animal fat and fried foods. These two food groups were associated with the largest and consistently elevated risk-estimates after adjustment for energy and other risk factors, and a clear trend was noted for fried foods (P for trend = 0.08). The increased risk associated with fruit consumption diminished after adjustment for other risk factors.

Reduced risks were noted for consumption of complex carbohydrates, and cereals and grains, although

Table 2. Odds ratios (OR) and 95% confidence intervals (CI) for endometrial cancer associated with daily intakes of macronutrients

Nutrient (cut-points)	Cases	Controls	OR ^a	OR ^b	OR	(CI)
Calories						
Q1 (< 975 Kcals)	83	74	1.0	1.0		
Q2 (975-1,247)	92	74	1.1	1.2		
Q3 (1,248-1,560)	99	74	1.3	1.2		
Q4 (> 1,560)	125	74	1.6 ^c	1.5		
Protein calories						
Q1 (< 147 Kcals)	83	74	1.0	1.0	1.0 ^d	
Q2 (147-199)	105	74	1.3	1.3	1.4	(0.8-2.4)
Q3 (200-250)	88	74	1.1	1.1	1.1	(0.6-2.0)
Q4 (> 250)	123	74	1.6 ^c	1.4	1.4	(0.7-2.7)
Fat calories						
Q1 (< 344 Kcals)	85	74	1.0	1.0	1.0 ^d	
Q2 (344-465)	89	74	1.1	1.1	1.2	(0.7-1.9)
Q3 (466-634)	111	74	1.4	1.6	1.7	(1.0-2.9)
Q4 (> 634)	114	74	1.4	1.4	1.5	(0.8-2.7)
Carbohydrate calories						
Q1 (< 463 Kcals)	94	74	1.0	1.0	1.0 ^d	
Q2 (463-598)	90	74	0.9	0.9	0.8	(0.4-1.3)
Q3 (599-758)	103	74	1.1	0.9	0.7	(0.4-1.3)
Q4 (> 758)	112	74	1.2	1.2	0.9	(0.5-1.6)
% Calories from protein						
Q1 (< 13.7)	118	74	1.0	1.0	1.0 ^e	
Q2 (13.7-15.5)	81	74	0.7	0.6	0.6	(0.4-1.0)
Q3 (15.6-17.2)	84	74	0.7	0.6	0.6	(0.4-1.0)
Q4 (> 17.2)	116	74	1.0	1.0	1.0	(0.6-1.6)
% Calories from fat						
Q1 (< 32.2)	83	74	1.0	1.0	1.0 ^e	
Q2 (32.2-37.7)	107	74	1.3	1.2	1.1	(0.7-1.9)
Q3 (37.8-43.4)	105	74	1.3	1.4	1.3	(0.8-2.2)
Q4 (> 43.4)	104	74	1.3	1.6	1.5	(0.9-2.4)
% Calories from carbohydrates						
Q1 (< 40.4)	90	74	1.0	1.0	1.0 ^e	
Q2 (40.4-46.9)	126	74	1.4	1.2	1.2	(0.7-1.9)
Q3 (47.0-52.5)	96	74	1.0	0.9	0.9	(0.5-1.5)
Q4 (> 52.5)	87	74	0.9	0.8	0.8	(0.5-1.4)

^a Adjusted for age-group.

^b Adjusted for age-group, BMI, current smoking, years of education, number of births, ever oral-contraceptive use, ever menopausal-estrogen use.

^c Confidence interval does not include 1.00.

^d Further adjusted for carbohydrate calories.

^e Further adjusted for non-carbohydrate calories.

^f Further adjusted for total calories.

the trends were not significant (P trend = 0.12 and 0.15, respectively). The components of cereals and grains were similar to those for complex carbohydrates excluding the contributions from vegetables (Appendix). Addition of either complex carbohydrates or breads and cereals to a model including animal fat resulted in similar risk estimates to those presented. No associations were observed for dairy foods, cruciferous vegetables, or folate-rich foods. Inconsistent, nonsignificant results were observed for 'poultry + fish,' and a red meat to 'poultry + fish' ratio (data not shown). However, this questionnaire was limited in the component food items for these food groups. For example, the

'poultry + fish' group consisted of only three line items (fried chicken; baked, stewed, or broiled chicken or turkey; and fried fish or fish sandwich).

Combination variables were created to better describe dietary patterns. Increased risk was noted for consumption of high animal fat together with low complex carbohydrates (OR 1.6, CI = 0.9-2.7), compared with low animal fat and high complex carbohydrates. However, evaluation of the interaction of these two nutrients indicated this risk was no larger than would be expected from adding the separate risks for these dietary variables. Evaluation of risk associated with combined effects of percent fat and percent

Table 3. Odds ratios (OR) and 95% confidence intervals (CI) for endometrial cancer associated with daily intakes of fats, cholesterol, fiber, and vitamins

Nutrient (cut-points)	Cases	Controls	OR ^a	OR ^b	OR	(CI)
Saturated fat						
Q1 (< 12 g)	71	74	1.0	1.0	1.0 ^d	
Q2 (13-18)	99	73	1.4	1.7 ^c	1.8	(1.0-2.9)
Q3 (19-25)	108	75	1.6 ^c	1.9 ^c	2.1	(1.2-3.6)
Q4 (> 25)	121	74	1.9 ^c	1.9 ^c	2.1	(1.2-3.7)
Oleic acid						
Q1 (< 13 g)	71	74	1.0	1.0	1.0 ^d	
Q2 (14-19)	110	74	1.6 ^c	1.9 ^c	2.0	(1.2-3.3)
Q3 (20-25)	95	74	1.4	1.7 ^c	1.9	(1.1-3.3)
Q4 (> 25)	123	74	1.8 ^c	2.0 ^c	2.2	(1.2-4.0)
Linoleic acid						
Q1 (< 7 g)	87	73	1.0	1.0	1.0 ^d	
Q2 (8-10)	96	74	1.1	1.1	1.1	(0.6-1.7)
Q3 (11-14)	87	75	1.0	1.0	1.0	(0.6-1.8)
Q4 (> 14)	129	74	1.6 ^c	1.6 ^c	1.6	(0.9-2.8)
Cholesterol						
Q1 (< 123 mg)	86	74	1.0	1.0	1.0 ^d	
Q2 (123-177)	91	74	1.1	1.4	1.5	(0.9-2.4)
Q3 (178-245)	68	74	0.9	0.8	0.8	(0.5-1.5)
Q4 (> 245)	154	74	2.0 ^c	1.9 ^c	2.0	(1.2-3.3)
Fiber						
Q1 (< 7.7 g)	79	72	1.0	1.0	1.0 ^d	
Q2 (7.7-10.1)	98	76	1.2	0.9	0.8	(0.5-1.3)
Q3 (10.2-13.6)	140	73	1.7	1.4	1.2	(0.7-2.0)
Q4 (> 13.6)	82	75	1.0	0.9	0.7	(0.4-1.3)
Total vitamin A						
Q1 (< 4,531 IU)	68	74	1.0	1.0	1.0 ^f	
Q2 (4,531-6,803)	115	74	1.7 ^c	1.6 ^c	1.6	(0.9-2.6)
Q3 (6,804-9,692)	101	74	1.5	1.5	1.4	(0.8-2.4)
Q4 (> 9,692)	115	74	1.7 ^c	1.6 ^c	1.5	(0.8-2.5)
Total vitamin C						
Q1 (< 76 mg)	63	74	1.0	1.0	1.0 ^f	
Q2 (77-125)	123	74	1.9 ^c	1.7 ^c	1.6	(1.0-2.7)
Q3 (126-180)	105	74	1.7 ^c	1.2	1.1	(0.6-1.9)
Q4 (> 180)	108	74	1.7 ^c	1.5	1.3	(0.7-2.2)

^a Adjusted for age-group.

^b Adjusted for age-group, BMI, current smoking, years of education, number of births, ever oral-contraceptive use, ever menopausal estrogen use.

^c Confidence interval does not include 1.00.

^d Further adjusted for carbohydrate calories.

^e Further adjusted for non-carbohydrate calories.

^f Further adjusted for total calories.

Table 4. Odds ratios (OR) and 95% confidence intervals (CI) for endometrial cancer by body mass index (BMI), weight, and waist-to-thigh ratio (WTR) group^{a,b}

Quartiles within group	Total calories	Protein calories ^c	Fat calories ^c	Saturated fat ^c	Carbohydrate calories ^d
BMI < 29					
Q2	1.4 (0.8-2.6)	1.6 (0.8-3.0)	1.4 (0.8-2.7)	2.9 (1.5-5.5)	0.9 (0.5-1.7)
Q3	1.5 (0.8-2.8)	1.3 (0.6-2.7)	2.1 (1.1-4.1)	3.1 (1.6-6.3)	0.7 (0.4-1.5)
Q4	1.8 (0.9-3.3)	2.5 (1.1-5.7)	1.9 (0.9-3.9)	2.8 (1.3-6.0)	0.7 (0.3-1.4)
BMI ≥ 29					
Q2	0.8 (0.3-2.2)	1.4 (0.5-4.0)	0.9 (0.3-2.5)	0.8 (0.3-2.2)	0.4 (0.2-1.1)
Q3	0.9 (0.3-2.2)	1.0 (0.4-2.8)	1.5 (0.5-4.3)	1.4 (0.5-3.9)	0.7 (0.3-2.0)
Q4	1.3 (0.5-3.2)	0.7 (0.2-2.4)	1.3 (0.4-4.2)	1.2 (0.4-3.5)	0.9 (0.3-2.7)
≤ Median weight					
Q2	1.2 (0.6-2.4)	2.1 (1.0-4.3)	1.7 (0.8-3.5)	2.4 (1.2-5.0)	0.5 (0.3-1.1)
Q3	1.5 (0.7-2.9)	1.7 (0.7-3.8)	3.5 (1.7-7.2)	3.9 (1.8-8.5)	0.5 (0.2-1.1)
Q4	1.9 (0.9-3.7)	3.2 (1.2-8.2)	2.6 (1.1-6.0)	3.0 (1.3-6.8)	0.4 (0.2-1.1)
> Median weight					
Q2	1.3 (0.6-2.9)	1.0 (0.4-2.3)	0.8 (0.4-1.9)	1.5 (0.6-3.4)	0.9 (0.4-2.1)
Q3	1.1 (0.5-2.5)	1.0 (0.4-2.4)	1.0 (0.4-2.4)	1.6 (0.6-3.9)	0.9 (0.4-2.1)
Q4	1.5 (0.7-3.2)	0.8 (0.3-2.1)	1.1 (0.4-2.9)	1.7 (0.7-4.4)	1.2 (0.5-2.9)
≤ Median WTR					
Q2	1.1 (0.5-2.3)	1.1 (0.5-2.4)	0.9 (0.4-1.9)	1.8 (0.8-3.8)	1.1 (0.5-2.5)
Q3	1.5 (0.7-3.1)	0.7 (0.3-1.7)	1.1 (0.5-2.5)	1.7 (0.7-3.8)	1.4 (0.6-3.0)
Q4	1.5 (0.7-3.2)	1.0 (0.4-2.7)	1.0 (0.4-2.5)	1.3 (0.5-3.1)	1.5 (0.6-3.8)
> Median WTR					
Q2	1.5 (0.7-3.4)	1.4 (0.6-3.3)	1.4 (0.6-3.3)	2.0 (0.9-4.7)	0.4 (0.2-0.9)
Q3	1.1 (0.5-2.3)	1.6 (0.6-4.0)	2.8 (1.1-6.7)	3.0 (1.2-7.3)	0.4 (0.2-1.1)
Q4	1.7 (0.8-3.6)	2.1 (0.7-5.7)	2.4 (0.9-6.3)	3.8 (1.4-10)	0.4 (0.1-1.0)

^a No. = 205 and 223 cases and controls, respectively, with BMI < 29; 194 and 73 with BMI ≥ 29; 179 and 169 below median weight (69.5 kg); 220 and 126 above median weight; 165 and 161 below median WTR (1.8); 213 and 112 above median WTR.

^b All models adjusted for age, ever estrogen usage, ever oral contraceptive usage, number of births, current smoking, education and weight (continuous).

^c Further adjusted for carbohydrate calories.

^d Replaced carbohydrate calories with non-carbohydrate calories.

carbohydrate, saturated fat and fiber, red meat and fruit, red meat and 'poultry + fish' consumption did not demonstrate a group at substantially increased or decreased risk.

Discussion

In this study, we observed that endometrial cancer was associated with high intakes of: total calories; fat calories and percent calories from fat; saturated fat and oleic acid; animal fat; and fried foods. Some elevation of risk was noted for high intakes of cholesterol, vitamin A, and vitamin C. Reduced risks were observed for consumption of complex carbohydrates, particularly cereals and grains, and no associations were noted for intake of carotenoids, fiber, fruits, vegetables, cruciferous vegetables, or folate-rich foods.

The possibility of bias due to the response rate among controls was of concern in this study. We evaluated some key findings among the younger and older controls, since the response rate was higher in the younger control group (76.3 percent). Results from

these analyses indicated that the nutrient effects were not restricted to one age-group. Further, analyses of other risk factors in this study¹⁸ were consistent with other studies published previously, suggesting that the effect of this bias would be minimal. Our findings were congruent with ecologic and analytic studies that had suggested endometrial cancer was associated with higher fat,^{11,12,15} saturated fat,¹³ animal fat and protein,¹⁴ and lower complex carbohydrate consumption.¹³⁻¹⁵ In contrast to a protective role suggested for a carotene index in one study,¹⁵ we did not observe any association between carotenoids and endometrial cancer. The association between fried foods and endometrial cancer risk had been reported previously.¹⁴ There may be some alteration of the food composition due to high-temperature cooking or the effect may reflect the fact that these foods are high in fat or saturated fat content (Appendix). It was not possible to distinguish the independent effects of fried foods and animal fats as these variables were correlated ($r = 0.60$).

As in any dietary study, we were concerned about the dietary methodology. In this study and another

Table 5. Odds ratios (OR) and 95% confidence intervals (CI) for endometrial cancer associated with weekly intakes of food groups

Food group ^a	Cases	Controls	OR ^b	OR ^c	OR ^d	(CI)
All meats						
Q1 (<5.1)	88	74	1.0	1.0	1.0	—
Q2 (5.1-7.6)	106	74	1.2	1.2	1.2	(0.7-1.9)
Q3 (7.7-10.8)	97	74	1.1	1.1	1.0	(0.6-1.6)
Q4 (> 10.8)	108	74	1.3	1.2	1.0	(0.6-1.7)
Red meats						
Q1 (<2.9)	74	67	1.0	1.0	1.0	—
Q2 (2.9-5.2)	110	79	1.3	1.4	1.3	(0.8-2.2)
Q3 (5.3-8.0)	96	74	1.2	1.2	1.1	(0.6-1.9)
Q4 (> 8.0)	119	76	1.5	1.6*	1.3	(0.8-2.4)
Animal fat						
Q1 (<7.5)	69	73	1.0	1.0	1.0	—
Q2 (7.5-12.0)	95	72	1.4	1.5	1.5	(0.9-2.6)
Q3 (12.1-18.9)	118	75	1.8*	1.7*	1.6	(0.9-2.8)
Q4 (> 18.9)	117	76	1.7*	1.7*	1.5	(0.8-2.7)
Fried foods						
Q1 (<1.5)	76	74	1.0	1.0	1.0	—
Q2 (1.5-2.9)	90	72	1.2	1.2	1.2	(0.7-2.0)
Q3 (3.0-4.9)	103	71	1.5	1.4	1.3	(0.8-2.2)
Q4 (> 4.9)	130	79	1.6*	1.8*	1.7	(1.0-2.9)
High-fat snacks/desserts						
Q1 (<2.6)	97	70	1.0	1.0	1.0	—
Q2 (2.6-6.1)	110	78	1.0	1.1	1.0	(0.6-1.6)
Q3 (6.2-10.5)	98	73	1.0	1.0	0.9	(0.5-1.5)
Q4 (> 10.5)	94	75	0.9	0.9	0.7	(0.4-1.2)
Dairy foods						
Q1 (<6.0)	90	72	1.0	1.0	1.0	—
Q2 (6.0-10.5)	104	75	1.1	1.0	1.0	(0.6-1.6)
Q3 (10.6-17.6)	86	75	0.9	0.9	0.8	(0.5-1.3)
Q4 (> 17.6)	119	74	1.3	1.4	1.2	(0.7-2.0)
Complex carbohydrates						
Q1 (<13.9)	100	73	1.0	1.0	1.0	—
Q2 (13.9-18.9)	104	75	1.0	0.9	0.8	(0.5-1.4)
Q3 (19.0-23.9)	93	73	0.9	0.8	0.7	(0.4-1.2)
Q4 (> 23.9)	102	75	1.0	0.9	0.7	(0.4-1.2)
Cereals and grains						
Q1 (<9.6)	108	74	1.0	1.0	1.0	—
Q2 (9.7-12.7)	77	73	0.7	0.6	0.6	(0.3-1.0)
Q3 (12.8-17.2)	106	72	1.0	0.8	0.7	(0.4-1.1)
Q4 (> 17.2)	108	77	0.9	0.8	0.6	(0.4-1.1)
Fruit						
Q1 (<8.5)	71	74	1.0	1.0	1.0	—
Q2 (8.5-14.7)	101	73	1.4	1.2	1.2	(0.7-1.9)
Q3 (14.8-21.9)	114	75	1.5	1.2	1.1	(0.7-1.9)
Q4 (> 21.9)	113	74	1.5	1.2	1.1	(0.6-1.9)
Citrus fruit						
Q1 (<2.1)	75	73	1.0	1.0	1.0	—
Q2 (2.1-7.0)	129	73	1.7*	1.6*	1.6	(1.0-2.6)
Q3 (7.1-8.5)	76	75	1.0	0.8	0.8	(0.4-1.3)
Q4 (> 8.5)	119	75	1.5	1.2	1.1	(0.6-1.8)
Vegetables						
Q1 (<11.1)	98	73	1.0	1.0	1.0	—
Q2 (11.1-15.8)	88	75	0.9	0.9	0.8	(0.5-1.3)
Q3 (15.9-21.0)	103	74	1.0	0.9	0.8	(0.5-1.4)
Q4 (> 21.0)	110	74	1.1	1.1	1.0	(0.6-1.6)

Continued...

Table 5. Continued

Food group ^a	Cases	Controls	OR ^b	OR ^c	OR ^d	(CI)
Cruciferous vegetables						
Q1 (< 1.0)	101	72	1.0	1.0	1.0	—
Q2 (1.0-1.7)	85	72	0.8	0.9	0.9	(0.5-1.4)
Q3 (1.8-3.1)	123	78	1.1	1.2	1.1	(0.7-1.8)
Q4 (> 3.1)	90	74	0.9	0.9	0.8	(0.5-1.3)
Folate-rich foods						
Q1 (< 6.4)	91	74	1.0	1.0	1.0	—
Q2 (6.4-10.7)	93	73	1.0	0.8	0.8	(0.5-1.3)
Q3 (10.8-15.9)	101	75	1.1	0.9	0.9	(0.5-1.4)
Q4 (> 15.9)	114	74	1.2	1.1	0.9	(0.6-1.6)

^a Quartile cut-points in times per week.

^b Adjusted for age-group.

^c Adjusted for age-group, BMI, ever estrogen usage, ever oral-contraceptive usage, number of births, current smoking, education.

^d Further adjusted for total calories.

^e Confidence interval does not include 1.00.

comparable endometrial cancer study conducted in China,¹⁴ cases reported higher intakes of most nutrients and foods than did controls. Although we cannot exclude the possibility of reporting bias in these studies, it is of interest that increased risk was related to fat intake, particularly from animal sources, in both the US and Chinese studies.

We utilized the 60-item Block questionnaire because this abbreviated questionnaire can rank individuals adequately and requires only 15-20 min rather than 30-35 min for the more detailed questionnaire.²² The reduced questionnaire produces lower absolute estimates of calories and macronutrients, yet these estimates correlate well with values from the expanded questionnaire ($r = 0.96-0.98$).²² Thus, although some estimates are lower, the ranking of individuals should be satisfactory. In addition, percent of calories from fat are comparable to other dietary instruments as the reduced questionnaire yields similar estimates to those from multiple diet records.²²

It was not surprising that 'total calories' was related to risk of disease, as cases appeared to consume slightly higher amounts of most nutrients compared with controls. Evaluation of mean caloric intakes within strata of BMI showed that cases consumed more calories at every level of BMI and that caloric intake increased in conjunction with BMI (data not presented). Adjustment for calories was problematic, however, as most nutrients were correlated with total calories ($r \geq 0.7$), and macronutrient calorie variables were correlated with each other ($r = 0.6-0.8$). Thus, it was difficult to disentangle increased total consumption of foods from increased intake of particular nutrients. The possibility of residual confounding using the macronutrient calorie variables, or even total calories cannot be excluded. Given the homogeneity of dietary intakes in this study and the inherent drawbacks with any energy

adjustment method, we were reassured by the congruence of our findings with other reports as well as with results between the nutrient and food group analyses that employed different methods of energy adjustment.

The consistency of our results among the percent fat, total fat, saturated fat, and animal fat calories initially appeared incongruous with the finding of increased risk associated with the typically vegetable-associated fats, *i.e.*, oleic and linoleic acids. These fatty acids in the nutrient database are markers for mono- and polyunsaturated fats in the diet. Interestingly, an international analysis¹² showed that, among seven cancers investigated, monounsaturated fat was associated only with cancer of the endometrium. In our study, oleic and linoleic acid were correlated with saturated fat ($r = 0.95, 0.73$, respectively). We did not assess intakes of specific oils, which would be expected to be major contributors and sources of variance to the fatty acid indices. An analysis of principal contributors to our fatty acid indices demonstrated that meats contributed substantially to both the saturated fat and oleic acid indices (25 percent and 27 percent of the total), while added fats (margarine and mayonnaise/salad dressing) made less of a contribution. Thus, without other information on the major sources of unsaturated fats in the diet (*i.e.*, oils), we cannot disentangle effects of component fats with these data.

It is believed that the association between obesity and endometrial cancer risk is mediated by the increased endogenous hormone production and possibly higher free-estrogen concentrations.^{1,28} The risk related to BMI was not altered by adjustment for nutrients. Although some dietary associations were affected by adjustment for BMI, associations persisted after adjustment for BMI, weight, or WTR. Of particular interest, risk associated with saturated fat persisted

after adjustment for BMI and was found to be consistently stronger among thinner women (BMI < 29 or weight below median) than among obese women. Since thin women would not have the stores of adipose tissue and resulting estrogen production from that source, they may be more susceptible to effects of dietary factors. In addition, our results suggest that diet does not influence the risk associated with obesity, and that dietary factors may explain some risk which is not related directly to obesity. In support of this, Austin and co-workers²⁹ noted higher serum estrogens and androstenedione levels among endometrial cancer cases after adjustment for BMI, suggesting additional mechanisms of altered hormone metabolism beyond those associated with obesity.

The observed increased risk associated with total fat and saturated fat in our study may be due to alterations in estrogen metabolism among cases. A variety of dietary studies have demonstrated nutritional influences on hormone levels. Observational and intervention studies have shown higher levels of plasma estrone,^{6,30,31} estradiol,^{6-9,30-34} and prolactin^{5,35} among women consuming a high-fat or omnivorous diet compared with those consuming a low-fat or vegetarian-style diet. Further, total fat intake has been correlated positively with total plasma estrogens,³² estrone and estradiol,³⁰ and prolactin levels⁸ and negatively related to SHBG.^{8,9} Goldin and coworkers³⁶ also reported a positive correlation between intake of saturated fat and fecal β -glucuronidase activity, suggesting increased uptake of estrogens through enterohepatic circulation. Similarly, supplementation with dietary wheat-bran has been shown to decrease plasma estradiol and estrone concentrations and has been associated with reductions in fecal β -glucuronidase activity.¹⁰ In addition to an effect of lowering levels of circulating estrogens, fiber from grains has been correlated positively with SHBG levels,^{10,37} which would cause further reductions in biologically available estradiol. Although unlikely, we cannot exclude the possibility that some of these findings on diet and hormone levels may have been due to concomitant differences in weight noted in many studies. Nonetheless, our observed increased risk of endometrial cancer associated with high intakes of total fat and saturated fat, and low intakes of breads and cereals may be mediated by circulating estrogen levels. Although other effects of this dietary pattern may influence risk, the established epidemiologic risk factors all support a hormonal mechanism of risk enhancement.

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APPENDIX. Food group components

Meat

Hamburgers, cheeseburgers, or meat loaf; beef such as steaks or roast; beef stew or pot pie; liver; pork such as pork chops or roasts; fried chicken; baked, stewed, or broiled chicken or turkey; fried fish or fish sandwiches; spaghetti, lasagna, or pasta with tomato sauce; hot dogs; ham or lunch meats; bacon; sausage.

Red meat

Hamburgers, cheeseburgers or meat loaf; beef such as steaks or roasts; beef stew or pot pie; liver; pork such as pork chops or roasts; spaghetti, lasagna, or pasta with tomato sauce; hot dogs; ham or lunch meats; bacon; sausage.

Animal fat

Hamburgers, cheeseburgers, or meat loaf; beef such as steaks or roasts; beef stew or pot pie; pork such as pork chops or roasts; fried chicken; spaghetti, lasagna, or pasta with tomato sauce; hot dogs; ham or lunch meats;

beans such as baked beans, kidney beans or in chili; cheese; eggs; bacon; sausage; butter; ice cream; whole milk.

Fried foods

French fries or fried potatoes; hamburgers, cheeseburgers or meat loaf; liver; fried chicken; fried fish or fish sandwiches; bacon; sausage.

High-fat snacks and desserts

French fries or fried potatoes; salty snacks like chips or popcorn; ice cream; pie; doughnuts, cookies, cakes, or pastry; chocolate candy.

Dairy

Cheese or cheese spreads; butter; ice cream; whole milk; 2% milk; skim milk, 1% milk or buttermilk; milk in coffee or tea; cream or half-and-half in coffee or tea.

Complex carbohydrates

Carrots or mixed vegetables containing carrots; peas; french fries and fried potatoes; baked, boiled, or mashed potatoes; sweet potatoes or yams; rice; beans such as baked beans, kidney beans, or in chili; cooked cereals; high fiber cereals such as shredded wheat or bran cereal; white bread, rolls, or crackers including sandwiches and bagels; dark breads such as wheat, rye, or pumpernickel; corn bread, corn muffins, corn tortillas, or grits.

Cereals and grains

Rice; cooked cereals; high fiber cereals such as shredded wheat or bran cereal; highly fortified cereals; other cold cereals such as Rice Krispies or Corn Flakes; white bread, rolls, or crackers including sandwiches and bagels; dark breads such as whole wheat, rye, or pumpernickel; corn bread, corn muffins, corn tortillas, or grits.

All fruit

Orange or grapefruit juice; other fruit or fortified fruit drinks; oranges; grapefruit; cantaloupe in season; apples or applesauce; bananas.

Citrus

Orange or grapefruit juice; oranges; grapefruit.

Vegetables

Carrots or mixed vegetables containing carrots; broccoli; peas; spinach; mustard greens, turnip greens or collards; cole slaw, cabbage or sauerkraut; tomatoes; green salad; vegetable soup; french fries or fried potatoes; baked, boiled, or mashed potatoes; sweet potatoes or yams; beans such as baked beans, kidney beans, or in chili.

Cruciferous vegetables

Broccoli; cole slaw, cabbage or sauerkraut; mustard greens, turnip greens or collards.

Folate-rich foods

Orange or grapefruit juice; oranges; grapefruit; cantaloupe in season; spinach; mustard greens, turnip greens or collards; beans such as baked beans, kidney beans, or in chili; liver; peanuts or peanut butter.