Diet, Body Size, Physical Activity, and the Risk of Endometrial Cancer

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ABSTRACT

Endometrial cancer is associated with increased weight and body size, diabetes, and other conditions that may result from an excess in calories or lack of physical activity. Although a few studies have explored the effect of dietary constituents on the risk of endometrial cancer, the nature of the joint association of these constituents and obesity, energy intake, or energy expenditure with risk is unknown. A population-based case-control study was conducted in Hawaii to examine the association of diet, body size, and physical activity with the risk of endometrial cancer. Subjects included 332 histologically confirmed, primary endometrial cancer cases and 511 controls identified between 1985 and 1993. Cases and controls were residents of Oahu, Hawaii who were between 18 and 84 years of age and were from one of the following ethnic groups: Japanese, Caucasian, Native Hawaiian, Filipino, and Chinese. Cases were identified through the Hawaii Tumor Registry and matched to the controls on age (±2.5 years) and ethnicity. In-person interviews, conducted in the subjects' homes, included dietary, reproductive, menstrual, and medical histories and use of exogenous hormones, physical activity, and other lifestyle variables. Weight, girth, and skinfold measurements were taken at the time of the interview. We found a strong dose-response relation of increased body size to the development of endometrial cancer after adjustment for energy intake. The odds ratio (OR) for endometrial cancer among women in the highest quartile of body mass index (BMI; kg/m²) was more than four times that among women in the lowest quartile. Waist, hip, midarm, and wrist girths were positively associated with the estimated risk of endometrial cancer after adjustment for total calories and other nondietary risk factors, although the trends in the ORs were attenuated after adjustment for BMI. Physically active women had a modest reduction in their risk of disease compared with inactive women. Cases consumed a greater percentage of their calories from fat and a lower percentage of their calories from carbohydrates than did controls. Adjustment for BMI reduced the ORs for the highest compared with the lowest quartile of fat calorie intake from 2.0 (95% confidence interval, 1.3–3.2) to 1.6 (95% confidence interval, 1.0–2.6), suggesting that part of the association is explained by obesity. There was a differential effect of fat on endometrial cancer according to BMI. For all components of fat, the associations with endometrial cancer were either minimal or absent among leaner women (i.e., those with BMI below the median), whereas, among more obese women, two-fold differences in risk were observed between women above and below the median of fat intake. Foods that are high in fat and cholesterol, such as red meat, margarine, and eggs, were positively associated with endometrial cancer, whereas cereals, legumes, vegetables, and fruits, particularly those high in lutein, were inversely associated. These findings suggest that women who avoid being overweight and who consume a diet low in plant and animal fats and high in complex carbohydrates are at a reduced risk of endometrial cancer.

INTRODUCTION

Risk factors for endometrial cancer, including reproductive history and the use of exogenous hormones, suggest a hormone dependence for this cancer (1–11). Endometrial cancer is positively associated with obesity and diabetes (2, 5, 7, 8–15), conditions that may result from an excess in energy intake or a deficit in energy expenditure, and that are known to alter endogenous hormone levels (16, 17). Dietary associations suggesting that differences in consumption of various foods and nutrients may underlie some of the observed variation in incidence among populations are beginning to emerge. Ecological studies have shown a positive correlation between per capita fat and animal protein consumption and the incidence of endometrial cancer (18, 19). In a correlational analysis of cancer incidence rates and mean nutrient intakes among five ethnic groups in Hawaii, endometrial cancer was positively related to consumption of saturated and unsaturated fat and animal protein (18). A similar result was found in a large international correlation study of per capita fat consumption and uterine cancer incidence and mortality (19).

Although it now appears that diet may be related to the risk of endometrial cancer (7, 8, 20–22), the specific dietary components involved are still unclear. Few studies have analyzed the effect of dietary constituents on the risk of endometrial cancer and, more particularly, the interaction of these constituents with obesity, energy intake, and physical activity. The major objective of this analysis was to examine the association of dietary factors, especially fat and related foods, with the etiology of endometrial cancer, and to determine the extent to which these associations are influenced by anthropometric variables. We also wished to investigate the relationship of energy intake to endometrial cancer risk and to separate the effect of calories from the effect of fat and other dietary components. Finally, we wanted to characterize the joint effects of dietary and nondietary factors, especially obesity, on risk.

MATERIALS AND METHODS

We conducted a population-based case-control study of endometrial cancer on the island of Oahu, Hawaii, between January 1, 1985, and June 1, 1993. Eligible women were residents of Oahu who were 18–84 years of age and who belonged to one of the five major ethnic groups in Hawaii: Japanese, Caucasian, Native Hawaiian (defined as any part Hawaiian), Filipino, and Chinese. Women with incident, histologically confirmed, primary endometrial cancer (International Classification of Diseases for Oncology code 182.0; Ref. 23) were identified through medical records and pathology reports by the rapid reporting system of the Hawaii Tumor Registry, part of the National Cancer Institute-sponsored Surveillance, Epidemiology, and End Results program (24).

Interview information was obtained from 356 cases, which represented 66% of the 540 eligible women. Reasons for nonparticipation included physician refusal (1%); patient refusal (14%); and death, inability to locate, language barrier, or psychological reasons usually associated with the illness (19%). For this analysis, we excluded 15 women with malignancies having morphology codes greater than 888 (23) and 9 cases with missing nondietary information, yielding a final sample of 332 cases.

Potential controls were selected randomly from lists of female Oahu residents who were interviewed by the Health Surveillance Program of the Hawaii Department of Health. Each year, the Department of Health identifies a 2% representative sample of all households in the state with a sampling procedure.
FACTORS AFFECTING RISK OF ENDOMETRIAL CANCER

modeled after that of the National Health Survey (25). A total of 1023 women meeting the eligibility criteria who were interviewed by the Department of Health between 1983 and 1993 were contacted to participate in the study. Interviews were obtained for 742 (73%) of these women who were individually matched 2:1 or 3:1 to each case on ethnicity and age (±2.5 years). Reasons for nonparticipation included refusal to be interviewed (18%); inability to locate, mental incompetence, or language barrier (8%); and death or illness (1%). Among interviewed women, 219 were hysterectomized, and 12 were matched to cases who were subsequently excluded, leaving 511 controls with intact uteri available for analysis.

Our trained interviewers conducted the majority (>90%) of interviews in the subjects’ homes. All interviews were administered uniformly, regardless of the location of the interview. The questionnaire included a diet history; reproductive, menstrual and medical histories; and use of exogenous estrogens, physical activity, and other lifestyle practices. The diet history included 250 food items or food groups that were selected from measured food records of representative women in each of the ethnic groups studied (26). Cases were asked about their usual diet during the year prior to diagnosis, whereas controls were asked about their usual diet during the year before the interview. For each food item, we obtained frequency data on the number of times per day, week, month, or year the item was consumed, along with quantitative estimates of the usual amounts consumed. For most items, the subjects selected amounts consumed from color photographs showing three different size portions. These portions were based on the identification of three modes in the distributions of the amounts consumed of the items reported in the measured food records. Specific inquiry was made about added fats and oils, as well as supplements. The dietary data were analyzed using our multiethnic food composition database compiled from several sources (27–30), which includes more than 3000 food items and recipes and more than 95 dietary components. The specific nutrient intakes for each person were computed as the sum of nutrients divided by all foods.

Body measurements taken by the interviewer included body weight by a calibrated digital bathroom scale (Health O Meter) to the nearest 0.1 pound, circumferences by a roll tape (Hoeschtmass) to the nearest 0.1 cm, and skinfolds by a calibrated caliper (Lange) to the nearest 0.1 mm. Waist and hip girths were measured over skin in the majority (53%) of participants. We subtracted 0.2 cm from measurements made over clothes to achieve comparability. Left midarm girth was measured at the midpoint of the left upper arm between the acromion and olecranon processes, left wrist girth was measured at the widest area over the protruding bone, waist girth was measured at the smallest area on the torso (near the umbilicus) at the end of normal expiration, and hip girth was measured at the maximum extension of the buttocks. The average value for two measurements of the triceps skinfold measurement, taken in the posterior of the left midarm, was used in the analysis. A BMI1 was calculated as weight (kg)/height (m)2 to serve as an index of general adiposity, and the ratio of the waist:hip and arm:wrist measurements was used to assess the distribution of body fat.

Analysis of covariance was used to compare the means of log-transformed intakes of nutrients, foods, and body size measurements between cases and controls while adjusting for age, ethnicity, and energy intake (31). Partial Pearson correlations (r) of continuous dietary and nondietary variables adjusting for age and ethnicity were calculated to evaluate colinearity. These means and correlations guided subsequent analyses. The risks associated with different levels of the exposure variables were evaluated by conditional logistic regression modeling case-control status (32). Odds ratios and 95% CIs were computed by exponentiating the coefficients (and the 95% CIs) for the binary indicator variables representing quantiles of the variable of interest. Nondietary adjustment variables included pregnancy history (ever versus never pregnant), oral contraceptive use (at least 1 month versus never or less than one), unopposed estrogen use (at least 1 month versus never or less than 1 month), diagnosis of diabetes (yes versus no), and BMI (in most analyses as a continuous variable).

We used various methods of energy adjustment, including the standard multivariate method (33), in which energy intake is included as a covariate in the regression model; the residual method (34), in which the residuals of nutrient intake regressed on total energy intake are analyzed; and the partition method (35), in which energy intake is partitioned into macronutrient sources, e.g., energy from fat. In some models, we used the nutrient density method for energy adjustment, in which the calories from each macronutrient are divided by total energy to derive the percentage of energy from each macronutrient source. Odds ratios were generally similar for the residual and standard methods, so we present results for the standard method in which energy was introduced as a log-transformed model covariate. In selected analyses, we adjusted separately for log-transformed energy from fat or carbohydrates, instead of total energy, because these indices were less correlated than total energy with the nutrients and foods of interest.

Food sources of vitamin A, β-carotene, and lutein were included as additional continuous model covariates in various analyses, although these are not presented, because differences in the results were slight. We performed a test for linear trend in the logit of risk by comparing twice the difference in log likelihoods for models with and without a trend variable, based on a χ2 distribution with 1 degree of freedom. The trend variable was assigned the median for the appropriate quantile or category. The likelihood ratio test was also used to evaluate the interaction between BMI and selected dietary variables on the risk of endometrial cancer in Table 6. This test compared a no-interaction model containing main effect terms with a fully parameterized model containing all possible interaction terms for the variables of interest.

RESULTS

Matched endometrial cancer case-control sets were similar with respect to age and ethnicity as shown in Table 1. More than one-half of the subjects were of Asian ancestry, one-fourth were Caucasian, and the remaining subjects were of Hawaiian or part-Hawaiian ancestry. Pregnancy and oral contraceptive use were inversely related to the odds ratios for endometrial cancer, and the use of unopposed estrogen and a history of diabetes were positively associated with estimated risk. We found little relation between menopausal status, a history of hypertension, tobacco use, alcohol use, or education (data not shown) and endometrial cancer risk.

Energy intake, particularly from fat, was significantly higher among cases than among controls (Table 2). Cases reported consuming 11% more total calories and 18% more fat calories than did controls. Cases also derived a slightly greater proportion of their calories from fat than controls, and a lower proportion of their calories from carbohydrates. Greater absolute differences in intake between cases and controls were found for unsaturated fat than for saturated fat and for plant fat than for animal fat. Dietary cholesterol was also higher among cases than among controls. Corresponding to their energy intake, endometrial cancer cases weighed more than controls, ing 11% more total calories and 18% more fat calories than did controls. Cases also derived a slightly greater proportion of their calories from fat than controls, and a lower proportion of their calories from carbohydrates. Greater absolute differences in intake between cases and controls were found for unsaturated fat than for saturated fat and for plant fat than for animal fat. Dietary cholesterol was also higher among cases than among controls. Corresponding to their energy intake, endometrial cancer cases weighed more than controls, had higher BMIs, and had greater girth measurements. The ratios of the waist:hip and arm:wrist girths were also higher among cases than controls. Controls reported a longer duration of moderate to heavy nonrecreational physical activity than cases, but there were no differences in reported recreational physical activity.

The estimated risk of endometrial cancer in this population was positively associated with energy intake and body size (Table 3). We found a positive, monotonic trend in the relation of fat calorie consumption to the risk of endometrial cancer, after adjustment for BMI and other confounders. The odds ratio for the highest compared with the lowest quartile of fat calorie consumption declined from 2.0 (95% CI, 1.3–3.1) to 1.6 (95% CI, 1.0–2.6) after adjustment for BMI.

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1 The abbreviations used are: BMI, body mass index; CI, confidence interval.
Table 1 Odds ratios and 95% CIs for endometrial cancer by selected characteristics (Hawaii, 1985–1993)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case (n = 332)</th>
<th>Control (n = 511)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;55</td>
<td>118</td>
<td>205</td>
<td>0.4</td>
</tr>
<tr>
<td>55–64</td>
<td>99</td>
<td>149</td>
<td>0.29</td>
</tr>
<tr>
<td>≥65</td>
<td>115</td>
<td>157</td>
<td>0.31</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japanese</td>
<td>125</td>
<td>203</td>
<td>0.4</td>
</tr>
<tr>
<td>Caucasian</td>
<td>84</td>
<td>117</td>
<td>0.23</td>
</tr>
<tr>
<td>Hawaiian</td>
<td>55</td>
<td>89</td>
<td>0.17</td>
</tr>
<tr>
<td>Filipino</td>
<td>40</td>
<td>63</td>
<td>0.12</td>
</tr>
<tr>
<td>Chinese</td>
<td>28</td>
<td>39</td>
<td>0.1</td>
</tr>
<tr>
<td>Menopausal status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>99</td>
<td>176</td>
<td>0.9 (0.5–1.7)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>233</td>
<td>335</td>
<td>1</td>
</tr>
<tr>
<td>Ever pregnant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>84</td>
<td>60</td>
<td>1.2</td>
</tr>
<tr>
<td>Yes</td>
<td>248</td>
<td>451</td>
<td>0.5 (0.3–0.7)</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>253</td>
<td>328</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>79</td>
<td>183</td>
<td>0.7 (0.4–1.0)</td>
</tr>
<tr>
<td>Unopposed estrogen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>167</td>
<td>344</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>165</td>
<td>167</td>
<td>1.3 (1.0–1.7)</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>287</td>
<td>483</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>45</td>
<td>28</td>
<td>1.4 (0.8–2.5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>196</td>
<td>358</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>136</td>
<td>152</td>
<td>1.1 (0.8–1.6)</td>
</tr>
<tr>
<td>Tobacco use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>211</td>
<td>300</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>121</td>
<td>211</td>
<td>0.5 (0.6–1.2)</td>
</tr>
<tr>
<td>Alcohol use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>254</td>
<td>373</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>78</td>
<td>138</td>
<td>0.9 (0.6–1.4)</td>
</tr>
</tbody>
</table>

Further adjusted the odds ratios for fat calories by carbohydrate calories (and BMI), but this did not change the results significantly; odds ratios (and 95% CIs) were 1.1 (0.7–1.7), 1.4 (0.9–2.4), and 1.8 (1.0–3.4) for the second through the highest quartile of fat calorie intake. Positive gradients in the odds ratios associated with total calories and protein calories were attenuated substantially by additional adjustment for BMI. Odds ratios increased with a higher percentage of intake in calories from fat and decreased with a higher percentage of intake in calories from carbohydrates.

Table 2 shows a strong dose-response relation between increased body size and the odds ratios for endometrial cancer, even after adjustment for total calories or fat calories, years of education, and menopausal status (data not shown). The odds ratios for endometrial cancer among women in the highest quartile of weight or BMI were more than 4-fold those among women in the lowest quartile. Taller women were not at an increased risk of endometrial cancer after adjustment for weight. The various girth measurements, including waist, hip, midarm, and wrist, were all positively associated with the risk of endometrial cancer after adjustment for total calories and other nondietary risk factors, although only the trend for waist girth remained strong after adjustment for BMI. Triceps skinfold and the ratios of waist:hip and arm:waist appeared unrelated to the odds ratios for endometrial cancer after adjustment for calories and BMI. Women with occupations and other nonrecreational physical activity (e.g., gardening) that was more physically demanding were at reduced risk of endometrial cancer compared to women who were sedentary, even after additional adjustment for education. However, little relation was found for recreational physical activity and the odds ratios for endometrial cancer.

The remaining dietary analyses were adjusted for BMI. Total fat

### Table 2

**Means and SE for the daily intake of selected dietary nutrients and measurements of body size and physical activity among endometrial cancer cases and controls (Hawaii, 1985–1993)**

| Variable (unit)          | Cases (n = 332) | Controls (n = 511) | p
|--------------------------|----------------|--------------------|---
| Nutrient                 |                |                    |   
| Total calories (kcal)    | 1918           | 1785               | 0.01  
| Fat calories (kcal)      | 590            | 570                | 0.04  
| Protein calories (kcal)  | 274            | 272                | 0.54  
| Carbohydrate calories (kcal) | 947          | 970                | 0.02  
| % calories from fat      | 38.7           | 37.1               | 0.02  
| % calories from carbohydrates | 67.4       | 69.3               | 0.04  
| Total fat (g)            | 65.8           | 63.5               | 0.03  
| Saturated fat (g)        | 18.6           | 18.2               | 0.28  
| Unsaturated fat (g)      | 47.1           | 45.1               | 0.01  
| Animal fat (g)           | 26.7           | 26.2               | 0.47  
| Plant fat (g)            | 37.1           | 35.3               | 0.03  
| Cholesterol (mg)         | 204            | 193                | 0.04  
| Carbohydrates (g)        | 237            | 242                | 0.02  
| β-carotene from food (µg) | 3022         | 3366               | 0.01  
| Lutein from food (µg)    | 2047           | 2151               | 0.14  

### Body size

| Height (inches) | 62.6 | 63.3 | 0.07  
| Weight (pounds) | 148  | 130  | <0.0001 
| BMI (kg/m²)     | 26.5 | 23.6 | <0.0001 
| Waist girth (cm) | 86.4   | 79.3  | <0.0001 
| Hip girth (cm)  | 105  | 99   | <0.0001  
| Midarm girth (cm) | 31.2   | 29.0  | <0.0001 
| Wrist girth (cm) | 16.1  | 15.5  | <0.0001  
| Triceps skinfold (cm) | 2.74  | 2.42  | <0.0001 
| Waist:hip ratio  | 0.822 | 0.800 | <0.0001 
| Arm:waist ratio  | 1.95  | 1.88  | <0.0001  

### Physical activity

| Nonrecreational (h) | 2863 | 5321 | 0.06  
| Recreational (h)    | 2574 | 2660 | 0.89  

### Notes

- Adjusted by analysis of covariance for age, ethnicity, and total calories (for nonenergy variables only). Nutrients and foods were log transformed before entry into the model. Means were transformed back into their original units.
- Nine cases and 33 controls were missing girth or skinfold measurements.
- Lifetime estimate from age 15 years.
The intake of unsaturated fat, particularly monounsaturated fat, was more strongly and monotonically related to the estimated risk of endometrial cancer than the intake of saturated fat. Both animal and plant sources of fat were weakly and positively related to the risk of endometrial cancer after adjustment for carbohydrate calories, with a risk of 1.16 (95% CI: 1.0—3.4) in the highest compared with the lowest quartile (Table 4). Adjustment for total calories instead of carbohydrate calories attenuated the odds ratios associated with total fat consumption, probably because of the lower correlation of fat with carbohydrate calories ($r_p = 0.69$) than with total calories ($r_p = 0.90$).

### Table 4: Odds ratios for endometrial cancer by quartile ($Q$) of daily intake of nutrients (Hawaii, 1985-1993)

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>$Q_1$</th>
<th>$Q_2$</th>
<th>$Q_3$</th>
<th>$Q_4$</th>
<th>$P$ for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total fat</td>
<td>1.13</td>
<td>1.4</td>
<td>1.8</td>
<td>0.04</td>
<td>1.0</td>
</tr>
<tr>
<td>Saturated fat</td>
<td>1.3</td>
<td>1.0</td>
<td>2.4</td>
<td>0.03</td>
<td>1.2</td>
</tr>
<tr>
<td>Unsaturated fat</td>
<td>1.0</td>
<td>1.4</td>
<td>2.1</td>
<td>0.02</td>
<td>1.0</td>
</tr>
<tr>
<td>Monounsaturated fat</td>
<td>1.0</td>
<td>1.3</td>
<td>2.3</td>
<td>0.009</td>
<td>1.0</td>
</tr>
<tr>
<td>Polyunsaturated fat</td>
<td>1.0</td>
<td>1.4</td>
<td>1.7</td>
<td>0.04</td>
<td>1.0</td>
</tr>
<tr>
<td>Animal fat</td>
<td>1.3</td>
<td>1.1</td>
<td>2.0</td>
<td>0.11</td>
<td>1.3</td>
</tr>
<tr>
<td>Plant fat</td>
<td>1.0</td>
<td>1.5</td>
<td>1.8</td>
<td>0.02</td>
<td>1.0</td>
</tr>
<tr>
<td>Plant protein</td>
<td>1.1</td>
<td>1.2</td>
<td>1.5</td>
<td>0.19</td>
<td>1.0</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>1.1</td>
<td>1.6</td>
<td>2.2</td>
<td>0.006</td>
<td>1.1</td>
</tr>
<tr>
<td>Vitamin A from food</td>
<td>0.5</td>
<td>0.6</td>
<td>0.6</td>
<td>0.16</td>
<td>0.5</td>
</tr>
<tr>
<td>$\beta$-carotene from food</td>
<td>0.5*</td>
<td>0.5*</td>
<td>0.6</td>
<td>0.07</td>
<td>0.5*</td>
</tr>
<tr>
<td>Lycopene from food</td>
<td>0.7</td>
<td>0.8</td>
<td>1.1</td>
<td>0.01</td>
<td>0.7</td>
</tr>
<tr>
<td>Lutein from food</td>
<td>0.5*</td>
<td>0.6*</td>
<td>0.6</td>
<td>0.02</td>
<td>0.5*</td>
</tr>
<tr>
<td>Vitamin C from food</td>
<td>0.6</td>
<td>0.7</td>
<td>0.6</td>
<td>0.10</td>
<td>0.6*</td>
</tr>
<tr>
<td>$\alpha$-tocopherol from food</td>
<td>0.7</td>
<td>0.8</td>
<td>0.6</td>
<td>0.24</td>
<td>0.8</td>
</tr>
<tr>
<td>Vitamin B$_6$ from food</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.15</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*Adjusted by conditional multiple logistic regression for the following unmatched covariates: pregnancy history; oral contraceptive pill use; unopposed estrogen use; history of diabetes; oral contraceptive pill use; and one of the following variables: total calories, carbohydrate calories, or fat calories.

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odds ratios were reduced after adjustment for total calories. There was little association of animal protein or plant protein consumption with risk. We found a strong, positive trend of increasing odds ratios by quartile of cholesterol consumption: women in the highest intake quartile had an estimated risk of 2.2 (95% CI, 1.2—4.1) compared with women in the lowest intake quartile after adjustment for carbohydrate calories, with only slight attenuation of the risks after adjustment for total calories and fat or carbohydrate calories (Table 5). We found a positive dose-response relation of beef and other red meat to the risk of endometrial cancer after adjustment for energy (total calories).

Dietary micronutrient consumption was generally inversely related to the odds ratios for endometrial cancer, although we found few strong, monotonic gradients of risk. The estimated risk of endometrial cancer associated with the lowest intake quartile for dietary lutein was almost twice that of the other quartiles (Table 4). There was little relation between endometrial cancer and the intakes of vitamin D, folacin, vitamin B₁₂, zinc, copper, iron, calcium, or selenium (data not shown).

We examined the association of several foods and food groups with the risk of endometrial cancer after adjustment for energy (total calories and fat or carbohydrate calories) and other confounders (Table 5). We found a positive dose-response relation of beef and other red meat to the risk of endometrial cancer after adjustment for carbohydrate calories, with only slight attenuation of the risks after adjustment for total calories. Estimated risks for endometrial cancer among women in the highest compared to the lowest quartile of red meat consumption were 2.1 (95% CI, 1.2—3.6) after adjustment for carbohydrate calories and 2.0 (95% CI, 1.1—3.7) after adjustment for total calories. We found an inverse relation of poultry intake with the...
risk of endometrial cancer, which persisted after additional adjustment for β-carotene or lutein (data not shown). The consumption of dairy products was not associated with risk. A positive, monotonic trend in risk was found for the intake of fats and oils, especially margarine, even after adjustment for total calories. Egg consumption was also positively related to the development of endometrial cancer.

Sources of starch and simple carbohydrates, such as rice, sweets, and other desserts, were generally unrelated to risk. However, women with diets high in vegetables and fruit, as well as cereals and pasta, major sources of dietary fiber in this population, were at significantly reduced risk of endometrial cancer. Adjustment of the odds ratios for vegetables or fruits by fat calories or total calories did not change the results, suggesting an independent association of these food groups with endometrial cancer risk. Although we found inverse relationships for the consumption of several vegetable groups, the inverse trend in the odds ratios for all vegetables combined was stronger than for any vegetable group or particular vegetable. In addition to all fruits, the consumption of peers reduced the risk of endometrial cancer substantially, with strong negative interactions (i.e., departure from additivity in the coefficients) between BMI and lutein or any of the other micronutrients in Table 4 on the risk of endometrial cancer.

In this analysis, we attempted to distinguish between the independent effects of the amount of body fat and its distribution on endometrial cancer risk. Measurements of the circumference of the waist and the risk of endometrial cancer was limited to women above the 50th percentile of BMI and total caloric intake; the effect of energy intake on the risk of endometrial cancer was limited to women above the 50th percentile of BMI. A similar negative interaction was found for sources of dietary fat, especially unsaturated fats and fats from plant sources. For example, high consumption of plant fat was associated with a 2-fold (4.0 divided by 1) increase in risk among women with a high BMI, whereas high plant fat consumption was not associated with an increased risk among women with a low BMI. We found no statistical interactions (i.e., departure from additivity in the coefficients) between BMI and lutein or any of the other micronutrients in Table 4 on the risk of endometrial cancer.

In addition to BMI, we also modeled the joint effects of the dietary and the nondietary risk factors in this study. There was no interaction between unopposed estrogen use and any of the dietary variables. Using women with a low intake of calories from fat and no estrogen use as the reference category, odds ratios were 3.5 (95% CI, 2.0—6.3) for women with a high intake of calories from fat who used estrogens, 3.0 (95% CI, 1.9—4.7) for women with a low intake of calories from fat who used estrogens, and 1.9 (95% CI, 1.2—2.8) for women with a high intake of calories from fat who did not use estrogens.

**DISCUSSION**

In this analysis, we attempted to distinguish between the independent effects of the amount of body fat and its distribution on endometrial cancer risk. Measurements of the circumference of the waist and

### Table 6 Odds ratios and 95% CIs for the joint association of BMI (kg/m²) and energy, fat, and cholesterol intake with the risk of endometrial cancer (Hawaii, 1985–1993)

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Daily intake (g)</th>
<th>BMI &lt;23.6 (95% CI)</th>
<th>Odds ratio (95% CI)</th>
<th>p^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy Total</td>
<td>≤65.2</td>
<td>1</td>
<td>1.9 (1.2–3.0)</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>&gt;65.2</td>
<td>1</td>
<td>3.0 (1.9–4.8)</td>
<td>0.05</td>
</tr>
<tr>
<td>Fat</td>
<td>≤928</td>
<td>1</td>
<td>2.1 (1.3–3.3)</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>&gt;928</td>
<td>1</td>
<td>4.3 (2.6–7.0)</td>
<td>0.13</td>
</tr>
<tr>
<td>Protein</td>
<td>≤272</td>
<td>1</td>
<td>2.3 (1.5–3.7)</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>&gt;272</td>
<td>1</td>
<td>3.3 (2.1–5.2)</td>
<td>0.15</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>&gt;928</td>
<td>1</td>
<td>2.1 (1.3–3.3)</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>≤928</td>
<td>0.86 (0.5–1.4)</td>
<td>2.8 (1.8–4.4)</td>
<td>0.15</td>
</tr>
<tr>
<td>Fat and protein</td>
<td>≤880</td>
<td>1</td>
<td>1.9 (1.2–3.1)</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>&gt;880</td>
<td>1.1 (0.7–1.8)</td>
<td>3.8 (2.4–6.1)</td>
<td>0.15</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>≤18.5</td>
<td>1</td>
<td>2.3 (1.5–3.7)</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>&gt;18.5</td>
<td>1.0 (0.6–1.7)</td>
<td>2.8 (1.5–4.7)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

---

^a Adjusted by conditional multiple logistic regression for the following unmatched covariates: pregnancy history, oral contraceptive pill use, unopposed estrogen use, and history of diabetes.

^b Based on the likelihood ratio test comparing models with and without an interaction term.

^c Reference category.

^d After additional adjustment for total calories.
the circumference of the hips provided us with a quantitative measure of regional fat distribution. In agreement with other studies of body fat distribution (10—15), we found a strong, positive dose-response relation of waist girth to risk that was independent of BMI and caloric intake. However, the waist:hip ratio was not strongly associated with risk after adjustment for BMI. This lack of an association has been reported by other investigators (10—12) and may have resulted, in part, from the correlation between BMI and the waist:hip ratio ($r_p = 0.42$), as discussed by Schapira et al. (12). It would appear that overall obesity, not abdominal fatness, is important to the etiology of endometrial cancer among these subjects.

The association of obesity with the risk of endometrial cancer suggests that diet, especially energy intake, may be an underlying cause of this malignancy. Our findings are only partially supportive of this notion. The positive association of energy intake with the risk of endometrial cancer was specific to dietary fat: there was little association of protein calories or carbohydrate calories with risk after controlling for BMI. Furthermore, a dose-response relation of various sources of fats and oils, particularly monounsaturated fats and cholesterol, to the risk of endometrial cancer was independent of energy source (total calories or carbohydrate calories) and BMI. Although there were clearly effects of both diet and BMI on endometrial cancer development, we found a negative statistical interaction between BMI and several sources of energy and fat in the diet. Thus, at least part of the effect of nutrient overconsumption on the risk of endometrial cancer may be mediated by being overweight.

An interaction of BMI with nutrient intakes was examined by Potischman et al. (21) in a multicenter case-control study in the United States that included 399 cases and 296 controls and used an abbreviated 60-food item version of the Block dietary questionnaire (37). In contrast to our results, these investigators found that the effect of dietary variables on risk was stronger among thinner women than among heavier women. They postulated that thinner women may be more susceptible to the effects of diet because they have less estrogen production from adipose tissue to compete with dietary precursors of this steroid. Although we showed stronger dietary associations among heavier women, it is possible that differences in our findings may be artifactual, resulting from small subgroups. Potischman et al. (17) and Austin et al. (13) have reported that circulating levels of androgens and estrogens, although related to risk, do not explain the association of BMI with endometrial cancer. This raises the possibility of non-hormonal mechanisms for the association of adiposity with the risk of endometrial cancer that may be influenced by diet.

This is the first epidemiological investigation of endometrial cancer with sufficient dietary detail to examine the association of major animal and plant sources of fats and oils with the development of disease. In a previous analysis of these data (36), we showed that diets high in fiber and rich in legumes (especially soybeans) and whole-grain foods decreased the risk of endometrial cancer. In this analysis, saturated, as well as monounsaturated and polyunsaturated fats, were related to increased cancer risk. Women consuming a greater percentage of their calories from fat were at higher risk of endometrial cancer compared to women with a low-fat diet, whereas women who obtained their calories predominantly from carbohydrate sources were at reduced risk. Foods that are high in fat, such as red meat and margarine, were also positively associated with endometrial cancer, whereas the consumption of vegetables and fruits lowered risk. Dose-response relationships were stronger and more likely to be monotonic for the foods and food groups than for the nutrients we analyzed, implying that a combination of dietary factors, rather than specific differences in nutrient intake, might be the basis for the variation in endometrial cancer incidence in this population.

These dietary findings are consistent with most earlier investigations of diet and endometrial cancer. Using a 12-item food frequency questionnaire, La Vecchia et al. (7) showed an increased intake of high-fat foods and a reduced intake of whole grains, fruits, and green vegetables among 206 endometrial cancer cases compared to hospital controls in northern Italy. Levi et al. (8) administered a more detailed 50-item food frequency questionnaire to 274 endometrial cancer cases and 572 controls in Switzerland and Italy. They reported a positive association of energy intake and the frequency of intake of meats, eggs, beans, or peas with the risk of endometrial cancer, and an inverse association with the consumption of whole-grain bread and pasta, as well as fresh vegetables and fruits. Although the positive association of peas and beans with risk is contrary to our finding, it may have resulted from the limited food list and lack of adequate control for energy intake. Results from a case-control study of 268 cases and 268 controls conducted in Shanghai (20) suggest that animal sources of dietary fat and protein, rather than energy intake, are important determinants of endometrial cancer. Data on the consumption of 63 foods were obtained from a quantitative food frequency questionnaire. Our results were not completely consistent with this finding: we found that fat from both animal sources (especially red meat) and plant sources (especially margarine) were risk factors for disease. In agreement with our results, Potischman et al. (21) reported an increased risk of endometrial cancer associated with oleic and linoleic acids. In contrast, in a case-control study of 168 endometrial cancer cases and 334 controls in Birmingham, AL, Barbone et al. (22) found no association between animal or vegetable fat and the risk of endometrial cancer using the 116-food item Willett questionnaire (38). It is possible that ethnic differences between the various studies may explain some of the contradictory findings. Also, few studies of diet and endometrial cancer included information about added fats and oils, important sources of fat calories in our population.

We had hypothesized that physically active women would be at reduced risk of endometrial cancer, because they would be leaner and would have lower circulating estrogen levels than inactive women (39). In agreement with Sturgeon et al. (40), our results suggest a modest inverse association between nonrecreational physical activity and risk that was independent of BMI and energy intake but little association between recreational physical activity risk. Levi et al. (41) and Shu et al. (42) have also reported a decreased risk of endometrial cancer associated with occupational activity and housekeeping. It is possible that occupational activities are more accurately recalled than recreational activities, although we do not have any data to support this notion. Table 3 shows a much broader range of responses for nonrecreational activities than recreational activities, enabling us to distinguish more easily among exposure strata. As noted by other investigators (40, 41), physical activity is difficult to quantify adequately, so these results will need confirmation.

The observed associations of obesity, diet, and physical activity with the risk of endometrial cancer may result from alterations in estrogen or androgen metabolism among cases. Obese women have an increased capacity to convert testosterone and androstenedione (the latter an androgen that is produced in the ovaries, the adrenal gland, and fatty tissue) to estrone and estradiol by cytochrome P450 aromatase (43). In obese postmenopausal women, androstenediolide levels may be sufficient to produce substantial amounts of estrogen, thereby inducing mitosis in endometrial cells (17). Overweight women also have lower levels of sex hormone-binding globulin, resulting in greater amounts of biologically available estrogen (44). In contrast, vegetarian women who have lower rates of endometrial cancer also have reduced levels of free estrogen and higher levels of serum hormone-binding globulin compared to omnivorous women (45). Dietary fiber may decrease enterohepatic recirculation of estrogen, increase the elimination of estrogen by the fecal route, and reduce...
intestinal reabsorption of estrogen (46—48). Plant compounds (phytoestrogens) may also reduce endometrial cancer risk by competing with estrogen for receptor sites (49). Polysaturated fatty acids, such as arachidonic acid, can be converted to prostaglandin, which can activate P450 aromatase conversion of androstenedione to estrone (43). Cholesterol can also be converted to androgens and estrogens through a variety of metabolic pathways (50).

Aside from effects on steroid hormones, there are a large number of other plausible mechanisms for a relation of diet to the risk of endometrial cancer. Increased dietary intake of fat and cholesterol (51) and decreased intake of antioxidants (52) may be associated with increased oxidant stress reflected in higher levels of cholesterol oxidation products. In a pilot study, we found that plasma levels of cholesterol β-epoxide were significantly higher among endometrial cancer cases than controls (53). Unsaturated lipids, such as ω-linolenic and oleic acids, but not saturated fats, inhibit carotene-stimulated gap-junctional communication (54). Lutein increases in vitro levels of connexin43 (55), an important gap-junctional protein, and inhibits neoplastic transformation (56). Finally, plant products, including phenols, terpenes, organosulfides, isothiocyanates, indoles, and protease inhibitors may reduce cancer risk through a variety of functions. For example, several plant phenolics can inhibit the production of prostaglandins from the metabolism of arachidonic acid (57).

A limitation of this and other analyses of the relation of diet to disease is the high intercorrelation of the dietary macronutrients. Our results are in agreement with other studies (7, 20, 21) in showing a positive association of energy intake from fat with risk, but it was difficult to distinguish fat from calories in the dietary models. The age- and ethnicity-adjusted correlations of energy and various fats ranged from 0.81 for animal fat to 0.90 for total fat. Fat calories showed a more clear dose-response relationship with the risk of disease than calories from other sources, although protein calories were also positively associated. We attempted to reduce the problem of colinearity of the macronutrient variables by alternatively adjusting for carbohydrate calories, as suggested by Potischman et al. (21). After adjustment for carbohydrate calories, we found an enhanced relation between several types of fat and disease. However, it was impossible to distinguish among the fat sources to determine the best-fitting model of risk.

Prentice et al. (58) have discussed homogeneity in dietary intakes and measurement error as the two most important limitations for studies of diet and disease. An advantage of our study was the broad range of dietary intakes among our population, increasing the odds ratios between extreme categories of the nutrients and foods of interest. For example, the heterogeneity in fat intake is reflected in the means for the extreme quartiles, 22% compared with 42% of energy. We have focused considerable attention on validating our dietary assessment method against food records (59), and we have demonstrated that our dietary data are reproducible (60, 61). It is unlikely that cases would systematically over- or underestimate the consumption of the many foods included in our questionnaire, although we have no means of examining this possibility. Our interviewers were trained in standardized probing methods that minimized inter-interviewer variation. Information was elicited on a large number of food items, and special questions concerning food preparation, seasonal items, and use of fresh foods were also included.

In conclusion, women with diets high in energy and fat and low in complex carbohydrates, including vegetables, fruits, cereals, and grains, were at increased risk of endometrial cancer. These dietary associations were at least partially independent of body size, an important risk factor in this study. Dietary fat appears to have a direct relationship to the risk of endometrial cancer that is not completely mediated by energy intake. The public health implications of our study are consistent with those of other studies of diet and specific cancers. Women with balance in energy intake and expenditure who reduce the fat and increase the intake of complex carbohydrates in their diets may experience a 2- to 4-fold reduction in their risk of endometrial cancer.

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