



## NUTRITIONAL FACTORS AND ENDOMETRIAL CANCER IN ONTARIO, CANADA

Meera G. Jain, PhD, Geoffrey R. Howe, PhD, and Thomas E. Rohan, MD, PhD

The Department of Public Health Sciences, University of Toronto, Ontario, Canada (MGJ, TER), and the Division of Epidemiology, Columbia University, New York, NY (GRH).

### Nutritional Factors and Endometrial Cancer in Ontario, Canada

Despite recent declines in the incidence rate, endometrial cancer remains a major cause of morbidity among women. Most risk factors pertain to reproductive factors and hormone replacement therapy that affect a woman's hormonal milieu.<sup>1,3</sup> There is also a strong association between endometrial cancer and obesity.<sup>4</sup> The fact that diet is associated with both serum hormone levels<sup>5</sup> and obesity<sup>6</sup> — the two important risk factors for endometrial cancer — makes the effect of diet on endometrial cancer particularly relevant.

Most of the epidemiologic data pertaining to the relationship between diet and endometrial cancer derive from ecologic and case-control studies.<sup>7</sup> The ecologic studies routinely implicate fat as a risk factor, yet these studies are unable to establish whether the observed effect is independent of obesity or other known risk factors for endometrial cancer. While there are some reports of elevated risks with consumption of animal fat and decreased risk with carotene intakes, these are not consistently supported by case-control studies and also are not supported by the only cohort study on diet and endometrial cancer reported to date.<sup>8</sup>

The present study was conducted to assess the role of various nutritional factors and obesity on the risk of developing endometrial cancer in Ontario, Canada.

### Materials and Methods

#### Subjects

This study was conducted as part of a larger study on diet, hormones, and endometrial cancer in metropolitan Toronto and the surrounding regions of Halton, Peel, and York, Canada. Patients aged 30 to 79 were identified through the Ontario Cancer Registry (Cancer Care Ontario) where a population-based registry of all cases is maintained from reports submitted on a regular basis from all hospitals in the area. Pathology reports are received at the registry within 6 months of diagnosis for more than 90% of cases occurring in Ontario. Women were eligible for inclusion in the study as cases if they had a histologically confirmed, primary diagnosis of adenocarcinoma, carcinoma, cystadenocarcinoma, or mixed Mullerian carcinoma (8 cases) of the endometrium (ICD9 code 182) and were diagnosed between August 1994 and June 1998. Sixteen of the patients had a second cancer diagnosis of either ovary or breast, but for all these patients, the primary diagnosis was endometrial cancer.

Potential control subjects were matched according to frequency to the patients by age group and by four geographic areas (metropolitan Toronto, Peel, Halton, and York). They were identified by randomly selecting women from property assessment lists maintained by the Ontario Ministry of Finance. These lists contain the age, gender, and address of all residents and are updated twice a year.

*Financial support for this study was provided by the National Cancer Institute of Canada.*

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The lists are organized by census division, and therefore it was possible to select potential controls from the same geographic areas as the cases. For the purpose of the present study, a sample of women residing in these areas was selected, with stratification by 5-year age groups and with frequency distribution by age corresponding to the expected age distribution of the cases. Only women at risk, ie, those with an intact uterus, were eligible for inclusion in the study. We also excluded women who did not have a listed telephone number. The telephone number was searched both by the woman's last name and by residence, using a CD-ROM phone listing. No individual matching of cases and controls was performed. Attempts were made to recruit one control per case.

### *Procedures*

All information was obtained by home interviews conducted by trained female interviewers. The questionnaires consisted of questions on the use of hormone replacement therapy and oral contraceptives, lifestyle and medical history, family history of cancer, reproductive history, dietary habits, body measurements, and physical activity at work, leisure, and home. A photo album consisting of more than 200 color photographs of preparations ever used in Canada and the United States was used to assist subjects' recall of hormone and oral contraceptive use. A validated, quantitative diet history was used to obtain estimates of daily intake of alcohol and a majority of foods found in the Canadian diet.<sup>9</sup>

The diet history contained questions concerning seasonality, usual frequency, and usual amount of consumption of various foods. Quantification was achieved by the use of physical volumetric food models. In reporting intake, patients were asked to address their usual intake to the 1-year pre-diagnosis period, while control subjects were asked to address their intake to the 1 year prior to the interview date. Height and weight were self-reported, but the other body measurements were taken by the interviewers including the chest, waist, hip circumferences, and triceps and subscapular skin-fold thickness. Calorie expenditure was calculated by multiplying the time spent on various physical activities with a standard calorie cost-per-minute value given in tables by James and Schofield.<sup>10</sup>

Daily intakes of most nutrients were calculated using the food tables given in the Canadian Nutrient File, 1997 version.<sup>11</sup> Specific estimates of carotenoids ( $\alpha$ -carotene,  $\beta$ -carotene, lycopene, cryptoxanthin, and lutein) were obtained on the basis of USDA-NCI carotenoid food-composition database on more than 2,400 fruits and vegetables and multi-ingredient foods containing fruits and vegetables.<sup>12,13</sup> In all, 22 nutrients were examined for this analysis (total energy, protein, carbohydrate, total fat, saturated fat, monounsaturated fat, linoleic acid, linolenic acid, animal fat, total dietary fiber, insoluble fiber, cereal fiber, fruit fiber, vegetable fiber, vitamin C, vitamin E, total vitamin A, folic acid,  $\beta$ -carotene, lycopene, lutein, and

cryptoxanthin). Nutrients from vitamin supplements were also calculated separately and then added to the total dietary nutrients. In addition, foods were grouped into 142 food groups according to the food grouping criteria used by the National Food Consumption Survey classification system<sup>14</sup> and a few groups based on the classification described by Smith et al.<sup>15</sup> These food groups were further collapsed together to obtain gram intakes per day of food groups for these analyses. These food groups included grains (breads, pasta, breakfast cereals, muffins, pies, cakes, crackers, pancakes), fruit (citrus fruit, berries, and all other fruits), vegetables (green, leafy, root vegetables, tomatoes, tomato or vegetable soup, and other vegetables), green vegetables, milk (all kinds), cheeses, red meat (all beef, pork, veal, lamb, game, meat stews, meat soups), chicken, fish, beans (beans, lentils, nuts, seeds), tea, coffee, and absolute amount of total alcohol from all alcoholic drinks.

Permission to contact was obtained from the physicians of 968 (87%) of the 1,113 potentially eligible patients and for whom a contact was made with the physician. For 145 cases, the physicians either refused to give permission or were not able to receive permission from the cases. Of the 968 patients, 78 were further excluded because they lived outside of the study area. From the remaining 890 patients, 43 were ineligible due to language, age, and inability to answer questions, and 62 could not be contacted due to death or wrong address. Of the 785 eligible cases remaining, we

interviewed 552 women (70%), while 233 (30%) refused or were too sick to be interviewed.

Of the 2,428 potential controls we attempted to contact, 1,039 were ineligible (403 women had had a hysterectomy, 391 were unable to be contacted, and 245 women either had died, had language difficulty, or were too sick to participate). Of 1,389 eligible women, 563 (41%) were interviewed, and 826 (59%) refused to be interviewed (of whom 421 com-

pleted a screening questionnaire). The women who refused to participate in the control group had a mean age of 63 years and an average of 2 children; 15% of them were current smokers, 21% had post high school education, and 14% reported ever using Premarin (Wyeth-Ayerst Laboratories, Radnor, Penn). The mean age, average number of children, history of smoking, and use of premarin were similar in the participating and nonparticipating controls except for a lower level of education

among the nonparticipants (60% reported post high school education in the interviewed controls). Details of the association between hormone replacement therapy and endometrial cancer are described in a separate publication.<sup>16</sup>

### Statistical Methods

All nutrients (not foods) were log converted and adjusted for total energy by the residual method described by Willett and Stampfer<sup>17</sup> and more recently

Table 1. — Distribution of Cases and Controls by Selected Risk Factors: Endometrial Cancer Study, Ontario 1994-1998

| Risk Factor                              | Category/Unit         | Number of Cases With Risk Factor (Total Cases = 552) | Number of Controls With Risk Factor (Total Controls = 562) | OR (95% CI) <sup>a</sup>      |
|--|-----------------------|--|--|-------------------------------|
| Post high school education               | Yes <i>cf</i> No      | 276  | 337  | 0.67 (0.53-0.85) <sup>b</sup> |
| Ever smoked                              | Yes <i>cf</i> No      | 220  | 223  | 1.01 (0.79-1.28)              |
| Age at menarche                          | ≥13 yrs <i>cf</i> <13 | 308  | 356  | 0.73 (0.58-0.93) <sup>c</sup> |
| Regular periods                          | No <i>cf</i> Yes      | 70   | 66   | 1.09 (0.76-1.56)              |
| Missed periods >3 months in life         | Yes <i>cf</i> No      | 82   | 60   | 1.46 (1.02-2.08) <sup>d</sup> |
| Number of pregnancies                    | >0 <i>cf</i> 0        | 465  | 496  | 0.71 (0.50-1.00) <sup>d</sup> |
| Number of live births                    | >0 <i>cf</i> 0        | 432  | 471  | 0.70 (0.51-0.94) <sup>c</sup> |
| Used oral contraceptives                 | Yes <i>cf</i> No      | 226  | 287  | 0.66 (0.52-0.83) <sup>b</sup> |
| Age at menopause (only women 48 or over) | Per 1 year increase   | 462  | 452  | 1.04 (1.01-1.07) <sup>c</sup> |
| Body weight                              | Per 10 kg             | 552  | 562  | 1.36 (1.25-1.48) <sup>b</sup> |
| Weight gain since age 21                 | Per 10 kg             | 539  | 551  | 1.37 (1.24-1.51) <sup>b</sup> |
| Body mass index                          | >25 <i>cf</i> ≤25     | 391  | 298  | 2.15 (1.68-2.76) <sup>b</sup> |
| Exercise calories                        | >0 <i>cf</i> 0        | 466  | 503  | 0.64 (0.45-0.91) <sup>c</sup> |
| Calories spent at job                    | >0 <i>cf</i> 0        | 238  | 263  | 0.86 (0.68-1.09)              |
| Cancer in family                         | Yes <i>cf</i> No      | 321  | 307  | 1.15 (0.91-1.46)              |
| Diabetes history                         | Yes <i>cf</i> No      | 73   | 29   | 2.80 (1.79-4.38) <sup>b</sup> |
| Age                                      | Per 5 yrs             | 552  | 562  | 1.02 (0.96-1.08)              |
| Hormone replacement therapy              | Per 3 yrs use         | 552  | 562  | 1.21 (1.12-1.31) <sup>b</sup> |
| Combined estrogen/progestogen            | Per 3 yrs use         | 552  | 562  | 1.12 (1.00-1.25) <sup>d</sup> |

*cf* = compared with  
<sup>a</sup> Unadjusted odds ratios and 95% confidence intervals  
<sup>b</sup>  $P \leq .001$   
<sup>c</sup>  $P \leq .01$   
<sup>d</sup>  $P \leq .05$

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detailed by Hu et al.<sup>18</sup> A value of 0.01 was assigned to 0 values for nutrients before their conversion into log values. Since nutrients expressed as residuals have an unfamiliar scale, a back transformation was made by adding the mean values as a constant and then taking the antilog. Foods and nutrients of interest were classified into quartiles or other suitable categories, based on their distribution among controls, and were treated as separate models. Odds ratios (ORs) and 95% confidence intervals (CIs) for the association between foods, nutrients, and risk of endometrial cancer were obtained from unconditional (since no individual matching was done for control selection) logistic regression models.<sup>19</sup> Analyses were performed first by simpler models that included total energy and the nutrient of interest and then by multivariate analyses adjusting for covariates of importance in the etiology of endometrial cancer. However, since the ORs from the second set of analyses did not differ appreciably from the ORs obtained by the simpler models, only the results of the multivariate analyses are presented. Multivariate models included total energy, age (years), body weight, ever smoked (No/Yes), history of diabetes (No/Yes), use of oral contraceptives (No/Yes), use of hormone replacement therapy (No/Yes), university education (No/Yes), live births (No/Yes), age at menarche (13 or less). Except for age and smoking, all others variables remained significant in all models. Tests for linear trend over categories were performed.

## Results

Results are based on 552 cases and 562 controls. One control was excluded due to insufficient data. The mean age of patients at diagnosis was 61.7 years (SD 9.8) compared with 61.3 years (SD 10.2) among the controls at the time of interview. Both groups had a similar distribution by 5-year age categories. Patients had significantly less education, fewer number of pregnancies and live born children, earlier age at menarche, later age at natural menopause, higher body weights, greater gain in body weight since the age of 21 years, less oral contraceptive use, greater use of hormone replacement therapy, and a greater likelihood of a history of diabetes (Table 1). The risk of endometrial cancer increased 1.36 times for every 10-kg increase in body weight (OR 1.36, 95% CI 1.25-1.48) and the risk was twice as high in women with a body mass index (BMI) >25 as in women with a BMI of ≤25 (OR 2.15, 95% CI 1.68-2.76). For a small number of women older than 48 years who were still having natural periods, we assigned age at menopause equal to their age to avoid missing subjects in the regression analyses. The increase in risk associated with late age at menopause persisted even after inclusion of these subjects in the analyses (OR per 1 year = 1.03, 95% CI 1.01-1.05). We did not find a significant effect of ever vs never smoking. Comparison of mean intakes of energy-adjusted nutrients indicated that patients consumed significantly more calories ( $P<0.001$ ) and slightly higher total

fat ( $P=.07$ ) than control subjects, but no differences were found in the intakes of other nutrients.

The ORs for quartiles of macronutrients and micronutrients are presented in Table 2. The strongest trend with risk was noted for increasing total energy intake ( $P$  for trend = .007). A modest increase in risk was observed with total fat intake of over 46 g, but there was no increasing trend over categories. Fat probably contributed to the increased risk observed with total energy; no effect of protein or carbohydrate was observed. The ORs for total energy in models were not altered by adjustment for protein, carbohydrate, or fat, suggesting an independent effect of energy intake. All potential confounders (age, body weight, smoking, diabetes, oral contraceptives, hormone replacement therapy, education, number of live born, and age at menarche) appeared to have little effect on point estimates. Higher intakes of animal fat increased the risk and also showed a significant trend over categories ( $P$  for trend = .03).

Risks associated with various types of fat and fiber are also presented in Table 2. Consumption of total dietary fiber was not associated with risk, whereas higher consumption of fruit fiber was associated with an increase in risk (OR for highest quartile 1.34, 95% CI 0.92-1.95), but no significant trends were observed. A higher intake of vegetable fiber was associated with a significant decrease in risk (OR for highest quartile

0.64, 95% CI 0.44-0.91). Risk estimates associated with various vitamins from dietary sources and sup-

plements did not exhibit any particular patterns. Although there was a significant lowering of risk

in the third quartile of vitamin E intake (OR for highest quartile 0.61, 95% CI 0.43-0.88), there was

Table 2. — Odds Ratios (95% CI)<sup>a</sup> for Endometrial Cancer by Categories of Nutrient Intake (n = 1,114, Cases = 552, Controls = 562, Canada 1994-1998)

| Dietary Factor <sup>b</sup> | Number of Cases per Quartile <sup>c</sup> | Quartile of Intake <sup>d</sup> |                               |                               |                               | P for Trend |
|-----------------------------|---|---------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------|
|                             |   | 1 (low) <sup>e</sup>            | 2                             | 3                             | 4 (high)                      |             |
| <b>Macronutrients:</b>      |   |                                 |                               |                               |                               |             |
| Total energy                | 114, 121, 145, 172                        | 1.00                            | 1.02 (0.71-1.47)              | 1.29 (0.90-1.85)              | 1.54 (1.08-2.20) <sup>f</sup> | .007        |
| Carbohydrate                | 134, 148, 141, 129                        | 1.00                            | 1.03 (0.73-1.48)              | 1.03 (0.72-1.47)              | 0.96 (0.67-1.39)              | .83         |
| Protein                     | 149, 151, 127, 125                        | 1.00                            | 1.01 (0.72-1.43)              | 0.85 (0.60-1.21)              | 0.78 (0.54-1.11)              | .11         |
| Total fat                   | 112, 161, 131, 148                        | 1.00                            | 1.32 (0.93-1.88)              | 1.00 (0.69-1.44)              | 1.21 (0.84-1.83)              | .65         |
| Saturated fat               | 123, 152, 131, 146                        | 1.00                            | 1.26 (0.89-1.80)              | 0.96 (0.67-1.38)              | 1.22 (0.85-1.75)              | .57         |
| Mono-unsaturated fat        | 132, 127, 133, 160                        | 1.00                            | 0.87 (0.61-1.25)              | 0.89 (0.63-1.28)              | 1.08 (0.76-1.53)              | .63         |
| Linoleic acid               | 137, 126, 126, 163                        | 1.00                            | 0.97 (0.68-1.38)              | 0.95 (0.67-1.37)              | 1.14 (0.81-1.61)              | .48         |
| Linolenic acid              | 147, 132, 134, 139                        | 1.00                            | 1.00 (0.70-1.41)              | 0.93 (0.65-1.33)              | 1.02 (0.72-1.46)              | .99         |
| Animal fat                  | 95, 156, 141, 160                         | 1.00                            | 1.63 (1.13-2.35) <sup>g</sup> | 1.45 (1.00-2.11) <sup>f</sup> | 1.66 (1.15-2.40) <sup>g</sup> | .03         |
| Dietary fiber               | 141, 145, 164, 102                        | 1.00                            | 0.97 (0.68-1.38)              | 1.06 (0.75-1.49)              | 0.71 (0.49-1.03)              | .14         |
| Insoluble fiber             | 133, 162, 133, 124                        | 1.00                            | 1.27 (0.90-1.80)              | 1.03 (0.72-1.48)              | 0.92 (0.64-1.33)              | .43         |
| Cereal fiber                | 135, 128, 141, 148                        | 1.00                            | 0.95 (0.66-1.36)              | 0.98 (0.69-1.40)              | 1.03 (0.72-1.47)              | .83         |
| Fruit fiber                 | 106, 168, 141, 137                        | 1.00                            | 1.56 (1.09-2.24) <sup>g</sup> | 1.33 (0.92-1.93)              | 1.34 (0.92-1.95)              | .31         |
| Vegetable fiber             | 162, 139, 139, 112                        | 1.00                            | 0.88 (0.62-1.25)              | 0.84 (0.59-1.18)              | 0.64 (0.44-0.91) <sup>g</sup> | .02         |
| <b>Micronutrients:</b>      |   |                                 |                               |                               |                               |             |
| Vitamin C                   | 154, 131, 148, 119                        | 1.00                            | 1.01 (0.71-1.43)              | 1.10 (0.78-1.56)              | 0.87 (0.61-1.24)              | .59         |
| Vitamin C with supplements  | 150, 130, 135, 137                        | 1.00                            | 0.90 (0.63-1.28)              | 0.96 (0.67-1.36)              | 1.01 (0.71-1.44)              | .90         |
| Vitamin E                   | 152, 138, 111, 151                        | 1.00                            | 0.84 (0.60-1.20)              | 0.61 (0.43-0.88) <sup>g</sup> | 0.87 (0.62-1.23)              | .22         |
| Vitamin E with supplements  | 147, 121, 132, 152                        | 1.00                            | 0.71 (0.50-1.02)              | 0.78 (0.55-1.11)              | 0.91 (0.64-1.29)              | .70         |
| Vitamin A                   | 136, 135, 139, 142                        | 1.00                            | 1.04 (0.73-1.49)              | 1.14 (0.80-1.62)              | 1.04 (0.73-1.48)              | .71         |
| Vitamin A with supplements  | 136, 130, 149, 137                        | 1.00                            | 0.98 (0.69-1.41)              | 1.15 (0.81-1.63)              | 0.98 (0.69-1.40)              | .86         |
| Folic acid                  | 143, 155, 119, 135                        | 1.00                            | 1.17 (0.83-1.65)              | 0.88 (0.62-1.26)              | 0.96 (0.67-1.36)              | .46         |
| β-carotene                  | 147, 117, 147, 141                        | 1.00                            | 0.88 (0.62-1.26)              | 1.07 (0.76-1.52)              | 0.99 (0.69-1.40)              | .81         |
| β-carotene with supplements | 144, 117, 148, 143                        | 1.00                            | 0.89 (0.62-1.27)              | 1.12 (0.79-1.59)              | 1.02 (0.72-1.45)              | .62         |
| Lycopene                    | 150, 144, 122, 136                        | 1.00                            | 0.88 (0.62-1.25)              | 0.81 (0.57-1.15)              | 0.85 (0.60-1.21)              | .32         |
| Lutein                      | 146, 157, 136, 113                        | 1.00                            | 1.21 (0.86-1.71)              | 0.95 (0.67-1.36)              | 0.80 (0.56-1.15)              | .13         |
| Cryptoxanthin               | 144, 137, 120, 151                        | 1.00                            | 1.06 (0.75-1.51)              | 0.96 (0.67-1.38)              | 1.23 (0.86-1.74)              | .36         |

<sup>a</sup> Multivariate ORs were adjusted for total energy, age (yrs), body weight, ever smoked (No/Yes), history of diabetes (No/Yes), used oral contraceptives (No/Yes), used hormone replacement therapy (No/Yes), university education (No/Yes), live births (No/Yes), age at menarche (>13 or less).

<sup>b</sup> All nutrients were energy adjusted by residual method.

<sup>c</sup> Listed from low to high quartile, respectively. The number of controls were almost evenly distributed among categories.

<sup>d</sup> The quartile cutpoints for daily nutrient intakes were as follows: total energy, 1436, 1805, 2235 kcal; carbohydrate, 240.3, 268.2, 296.5 g; protein, 64.7, 72.9, 82.6 g; total fat, 46.0, 56.8, 66.3 g; monounsaturated fat, 17.4, 21.6, 26.4 g; linoleic acid, 5.9, 7.2, 9.0 g; linolenic acid, 0.8, 1.1, 1.6 g; animal fat, 22.1, 32.9, 44.0 g; dietary fiber, 17.2, 22.1, 27.5 g; cereal fiber, 4.8, 7.2, 10.5 g; fruit fiber, 3.4, 6.0, 8.9 g; vegetable fiber, 6.63, 9.30, 12.83 g; vitamin C, 130.4, 185.1, 251.4 mg; vitamin C with supplements, 163.9, 240.6, 414.0 mg; vitamin E, 5.5, 11.1, 17.5 mg; vitamin E with supplements, 8.2, 16.0, 37.8 mg; vitamin A, 7157, 10486, 15561 IU; vitamin A with supplements, 7967, 12261, 18059 IU; folic acid, 267.9, 332.3, 398.3 μg; β-carotene, 3268, 4971, 7342 μg; β-carotene with supplements, 3281, 4989, 7393 μg; lycopene, 2634, 5200, 9583 μg; lutein, 1322, 2354, 3918 μg; cryptoxanthin, 30.6, 67.3, 118.3 μg.

<sup>e</sup> Reference category for all models.

<sup>f</sup> P ≤ .05

<sup>g</sup> P ≤ .01

no dose response relationship across different level of intake. Intake of supplemental vitamins C, E, A, or  $\beta$ -carotene did not alter the risk estimates appreciably.

Risk estimates associated with various food groups (Table 3) also show that while risk increases with higher intakes of fruit (OR for highest quartile 1.29, 95% CI 0.88-1.89), it decreases with higher consumption of vegetables (OR for highest quartile 0.65, 95% CI 0.44-0.96), particularly the green vegetables (OR for highest quartile 0.73, 95% CI 0.51-1.04). Consistent with the observation of an increased risk

with animal fat, risk increased with higher consumption of red meats and chicken, two main sources of animal fat. However, no significant trends were observed for these meats. ORs were higher with higher consumption of grains and cereals, but no trends were observed. Higher intakes of alcohol from beverages were associated with a lower OR (OR for highest category 0.72, 95% CI 0.52-0.99) and a significant trend across categories ( $P$  for trend = .04).

Body weight had a particularly significant association with the risk for endometrial cancer in our data

but not on nutrients (Pearson's correlations of  $<0.2$  between BMI and major nutrients). However, because of the strong association of obesity with endometrial cancer, we conducted a separate analysis stratified by BMI (body weight, kg/height, meter<sup>2</sup>) (Table 4). Total energy intake was associated with an increase in risk in both groups of women (ie, women with BMI  $\leq 25$  or  $>25$ ). Similarly, vegetable intake was associated with a decrease in risk irrespective of BMI, the  $P$  value being more significant in the  $>25$  BMI group, reflecting a larger sample size in this group. Risk estimates for all other

Table 3. — Odds Ratios (95% CI)<sup>a</sup> for Endometrial Cancer by Categories of Food Groups (n = 1,114, Cases = 552, Controls = 562, Canada 1994-1998)

| Dietary Factor <sup>b</sup> | Number of Cases per Quartile <sup>c</sup> | Quartile of Intake <sup>d</sup> |                               |                               |                               | $P$ for Trend |
|-----------------------------|---|---------------------------------|-------------------------------|-------------------------------|-------------------------------|---------------|
|                             |   | 1 (low) <sup>e</sup>            | 2                             | 3                             | 4 (high)                      |               |
| Grains and cereals          | 101, 155, 142, 154                        | 1.00                            | 1.53 (1.06-2.21) <sup>f</sup> | 1.30 (0.88-1.91)              | 1.34 (0.87-2.05)              | .35           |
| Fruits                      | 113, 153, 133, 153                        | 1.00                            | 1.56 (1.09-2.25) <sup>f</sup> | 1.30 (0.90-1.89)              | 1.29 (0.88-1.89)              | .41           |
| Vegetables                  | 138, 134, 147, 133                        | 1.00                            | 0.86 (0.60-1.23)              | 0.85 (0.59-1.22)              | 0.65 (0.44-0.96) <sup>f</sup> | .04           |
| Beans                       | 138, 125, 131, 158                        | 1.00                            | 1.01 (0.70-1.45)              | 0.93 (0.65-1.34)              | 1.05 (0.73-1.51)              | .90           |
| Green vegetables            | 165, 143, 106, 138                        | 1.00                            | 0.87 (0.62-1.23)              | 0.62 (0.43-0.89) <sup>g</sup> | 0.73 (0.51-1.04)              | .03           |
| Red meat                    | 107, 147, 129, 169                        | 1.00                            | 1.25 (0.87-1.80)              | 1.01 (0.69-1.46)              | 1.21 (0.83-1.77)              | .55           |
| Fish                        | 135, 140, 136, 141                        | 1.00                            | 1.09 (0.77-1.55)              | 1.02 (0.71-1.47)              | 0.97 (0.67-1.40)              | .79           |
| Chicken                     | 116, 156, 129, 151                        | 1.00                            | 1.54 (1.08-2.21) <sup>f</sup> | 1.16 (0.81-1.68)              | 1.23 (0.85-1.78)              | .65           |
| Milk                        | 136, 149, 117, 150                        | 1.00                            | 1.04 (0.73-1.48)              | 0.78 (0.54-1.12)              | 0.86 (0.59-1.24)              | .21           |
| Cheese                      | 125, 147, 130, 150                        | 1.00                            | 1.05 (0.73-1.49)              | 0.98 (0.68-1.41)              | 0.94 (0.65-1.37)              | .68           |
| Tea                         | 139, 215, 92, 106 <sup>c</sup>            | 1.00                            | 1.21 (0.87-1.68)              | 1.17 (0.79-1.73)              | 0.99 (0.68-1.45)              | .90           |
| Coffee                      | 87, 197, 140, 128 <sup>c</sup>            | 1.00                            | 0.80 (0.54-1.18)              | 1.18 (0.78-1.79)              | 0.68 (0.45-1.04)              | .30           |
| Alcohol                     | 329, 115, 108 <sup>c,h</sup>              | 1.00                            | 0.85 (0.63-1.18)              | 0.72 (0.52-0.99) <sup>f</sup> | none                          | .04           |

<sup>a</sup> Multivariate ORs were adjusted for total energy, age (yrs), body weight, ever smoked (No/Yes), history of diabetes (No/Yes), used oral contraceptives (No/Yes), used hormone replacement therapy (No/Yes), university education (No/Yes), live births (No/Yes), age at menarche ( $>13$  or less).

<sup>b</sup> No energy adjustment by residual method.

<sup>c</sup> Listed from low to high quartile respectively. The number of controls were almost evenly distributed among categories except for tea, coffee and the three categories of alcohol.

<sup>d</sup> The quartile cutpoints for daily food intakes were as follows: grains and cereals, 158, 228, 438 g; fruits, 229, 387, 555 g; vegetables, 271, 422, 633 g; beans, 2.5, 11.8, 28.3 g; green vegetables, 30, 51, 83 g; red meat, 15, 31, 53 g; fish, 7.6, 18.3, 35.6 g; chicken, 9.2, 20.1, 33.4 g; milk, 84, 223, 413 g; cheese, 5.3, 14.0, 29.1 g; tea categories, 0, 250, 500,  $>500$  g; coffee categories, 0, 250, 500,  $>500$  g; alcohol categories, 0, 1.2, 8.3 g of absolute alcohol;

<sup>e</sup> Reference category for all models.

<sup>f</sup>  $P \leq .05$

<sup>g</sup>  $P \leq .01$

<sup>h</sup> The distribution of alcohol was not suitable for quartiles.

foods and nutrients examined were not particularly different across the two strata of BMI.

We performed a separate analysis after excluding the 8 cases of mixed Mullerian tumors. However, since the ORs and CIs did not change appreciably, the results presented here include all cases.

## Discussion

The results of this study show that endometrial cancer risk increased in association with obesity and high intakes of total energy and animal fat. A nonsignificant elevation of risks was observed for high intakes of fruit, fiber from fruit, chicken, and grains and cereals. Reduced risks were observed

with high consumption of vegetables, vegetable fiber, vitamin E, and alcohol. No associations were observed for carbohydrates, proteins, total fat and major fatty acids, dietary fiber, cereal fiber, insoluble fiber, vitamin C, vitamin A, folic acid,  $\beta$ -carotene, lycopene, lutein, cryptoxanthin, red meats, fish, beans, milk, cheese, tea, and coffee. The associations observed in the study were independent of total energy intake and most nondietary risk factors (age, body weight, education, parity, age at menarche, and history of smoking, diabetes, use of oral contraceptives, and use of hormone replacement therapy).

In considering the validity of our findings, it is reassuring that the ORs for the association of obesity, reproductive history, hormone use,

etc, are similar to previous reports.<sup>1,16</sup> Although several studies have shown a lower risk of endometrial cancer in smokers, the association is mainly seen in postmenopausal women or heavy and current smokers, with the relative risks in ever vs never smokers being closer to null, as seen in our study.<sup>2</sup> In addition, the possibility of any bias due to the response rate among controls seems unlikely as the age, number of live children born, smoking, and the use of Premarin was similar among respondents and nonrespondents. The nonrespondents were less educated than respondents. Examination of the mean values of total energy by education level in our cases and controls showed no significant differences ( $P=.17$ ). Our dietary questionnaire has been validated previ-

Table 4. — Odds Ratios (95% CI)<sup>a</sup> for Endometrial Cancer by Daily Intakes of Selected Nutrients and Food Groups, Stratified by Body Mass Index (n = 1,114, Cases = 552, Controls = 562, Canada 1994-1998)

| Dietary Factor <sup>b</sup> | Units per Day | All Subjects                  | BMI $\leq 25$ (kg/m <sup>2</sup> ) | BMI $>25$ (kg/m <sup>2</sup> ) |
|-----------------------------|---------------|-------------------------------|------------------------------------|--------------------------------|
|                             |               | (552 Cases/562 Controls)      | (161 Cases/264 Controls)           | (391 Cases/298 Controls)       |
| Total energy                | 799 kcal      | 1.28 (1.10-1.48) <sup>c</sup> | 1.28 (0.99-1.65)                   | 1.28 (1.06-1.53) <sup>c</sup>  |
| Total fat                   | 20 g          | 1.12 (0.95-1.33)              | 1.08 (0.83-1.41)                   | 1.16 (0.93-1.45)               |
| Saturate fat                | 12 g          | 1.19 (0.96-1.46)              | 1.05 (0.76-1.45)                   | 1.30 (0.97-1.75)               |
| Animal fat                  | 22 g          | 1.18 (0.98-1.41)              | 1.14 (0.85-1.54)                   | 1.18 (0.93-1.48)               |
| Vitamin C                   | 120 mg        | 0.95 (0.81-1.11)              | 1.05 (0.81-1.35)                   | 0.91 (0.75-1.11)               |
| Vitamin E                   | 12 mg         | 0.93 (0.82-1.05)              | 1.06 (0.88-1.27)                   | 0.87 (0.74-1.03)               |
| Dietary fiber               | 10 g          | 0.89 (0.75-1.05)              | 1.03 (0.79-1.35)                   | 0.85 (0.68-1.06)               |
| Fruit fiber                 | 5.5 g         | 1.00 (0.86-1.18)              | 1.24 (0.93-1.66)                   | 0.91 (0.75-1.10)               |
| Vegetable fiber             | 6.2 g         | 0.87 (0.75-1.01)              | 0.91 (0.71-1.17)                   | 0.89 (0.74-1.07)               |
| Fruit                       | 100 g         | 0.99 (0.95-1.04)              | 1.06 (0.98-1.16)                   | 0.96 (0.91-1.01)               |
| Vegetable                   | 100 g         | 0.94 (0.90-0.98) <sup>c</sup> | 0.96 (0.89-1.02)                   | 0.94 (0.89-1.00) <sup>d</sup>  |
| Green vegetable             | 100 g         | 0.90 (0.72-1.14)              | 1.18 (0.75-1.87)                   | 0.83 (0.63-1.09)               |
| Alcohol                     | 12 g          | 0.98 (0.91-1.06)              | 0.85 (0.67-1.07)                   | 1.00 (0.91-1.10)               |

<sup>a</sup> Multivariate ORs were adjusted for total energy, age (years), body weight, ever smoked (No/Yes), history of diabetes (No/Yes), used oral contraceptives (No/Yes), used hormone replacement therapy (No/Yes), university education (No/Yes), live births (No/Yes), age at menarche (>13 or less).

<sup>b</sup> Nutrients were energy adjusted by residual method, foods were not.

<sup>c</sup>  $P \leq .01$

<sup>d</sup>  $P \leq .05$

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ously<sup>9</sup> and shows reasonable correlations with food records for various nutrient intakes and a satisfactory ranking of individuals. The fact that the patients reported a higher calorie consumption despite a greater body weight than controls minimizes the possibility of any systematic overreporting by patients since it is generally known that overweight persons tend to underreport their energy intake.

Endometrial cancer has shown strong positive correlations with being overweight,<sup>1,7,20</sup> and our results are consistent with the previous evidence. A plausible biological mechanism by which obesity may increase the risk of endometrial cancer is through increased aromatization of androstenedione to estrone in adipose tissue.<sup>21</sup>

Our findings are consistent with previous analytic studies that suggested that endometrial cancer is associated with higher energy intake<sup>22-25</sup> and animal fats.<sup>24</sup> Some previous case-control<sup>26,27</sup> and cohort<sup>8</sup> studies did not find any positive association with energy intake. The discrepancy between studies could be due to differences in dietary assessment methods, analytical approaches used, and the population characteristics themselves. The effect of animal fats was mirrored by intakes of red meats and chicken but not by saturated fats, various fatty acids, milk, cheese, or fish, as sources of animal fats. Although meats accounted for a large percent of oleic and linoleic acid in the diet of our subjects, no effect of these fatty acids was observed. The effect of energy

intake persisted across categories of BMI and was found to be stronger among heavier women. This was partly a reflection of a larger sample size in the >25 BMI category. Since heavy women have larger stores of adipose tissue and the resulting increased estrogen production and free circulating estrogen from that source, excessive energy intake may have resulted in a more pronounced adverse effect on the risk of endometrial cancer. This difference by BMI category was not consistent with a previous report where the effect of energy was stronger for women below a BMI of 29.<sup>23</sup> Similar to those of Potischman et al,<sup>23</sup> our results show that diet does not influence the risk associated with obesity and that dietary factors may explain some risk that is not directly related to obesity.

Data on vegetable and fruit intake have been inconsistent from various studies. We found a protective effect of vegetables, particularly from green vegetables. This effect of vegetables has been reported by others.<sup>25,28</sup> We attempted to explain this effect of vegetables by examining the effect of various nutrients contributed from them such as fiber, vitamin C, vitamin A, carotenoids, and folic acid. However, except for the fiber from vegetable sources, no other factor was significantly associated with the decrease in risk of endometrial cancer. It is possible that in addition to these known components of vegetables, there are other helpful constituents of vegetables that impart this beneficial effect. Although carotenoids

have been reported to be associated with a decreased risk,<sup>25,26,28</sup> we did not find any such effect from dietary or supplemental carotenes. Previous reports did not use the newer food tables on carotenes utilized by us and that may explain some of the discrepancy between our results.

The relationship of alcohol and endometrial cancer has been investigated in some previous studies.<sup>25,28-33</sup> All but one<sup>28</sup> of the seven studies reported either no association or a protective effect of alcohol intake. Our results are consistent with a protective effect of alcohol, OR=0.72 (95% CI, 0.52-0.99) for intake of >8.3 g of absolute alcohol per day. However, this effect was not observed when alcohol intake was examined as a continuous variable (OR=0.98). The relationship between alcohol consumption and levels of female sex hormones has been investigated in several studies. However, results are inconsistent, ranging from an inverse association or no association to a positive association.<sup>7</sup> In studies where alcohol consumption was reported to be inversely associated with serum estrone and estradiol and total estrogen levels,<sup>34,35</sup> the association disappeared after adjustment of BMI and other endometrial cancer risk factors.

## Conclusions

Our study supports previous reports of an increase in risk of endometrial cancer associated with obesity, total energy and ani-

mal fat, and a decrease in risk with vegetable intake. Although hormone-related mechanisms of action seem most plausible, other potential mechanisms of action such as the beneficial impact of vegetables on immunocompetence and further on carcinogenesis merit consideration.<sup>36</sup>

*Appreciation is expressed to Cancer Care Ontario and various physicians for help in identifying cases for the study.*

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