Relation of Obesity and Body Fat Distribution to Endometrial Cancer in Shanghai, China


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ABSTRACT

In a case-control study involving 268 cases of endometrial cancer and an equal number of population controls, we assessed the relationship of risk to body weight and fat distribution, examining weight at various ages and current anthropometric measurements. Weight gain during later adulthood and resultant high body masses were important risk predictors, indicating that obesity is an important risk factor, even in an area where the prevalence of obesity and incidence of endometrial cancer are low. Certain fat distribution patterns were related to risk of endometrial cancer independent of general obesity. In particular, fat deposits on the trunk were associated with elevated risks, with the odds ratio for the highest versus lowest quartile of subscapular skinfolds remaining significant even after adjustment for body mass index (odds ratio = 2.9; 95% confidence interval, 1.1-7.3). Central versus peripheral obesity, as measured by the subscapula:triceps ratio, also was related to increased risk, although the association failed to remain significant after adjustment for body mass (highest to lowest quartile, odds ratio = 1.7). In contrast, upper body obesity, as assessed by the waist:thigh ratio, was unrelated to risk. These results support the need for future studies assessing the relationship of hormonal and other biological parameters of fat distribution to assist in identifying causal mechanisms for this tumor.

INTRODUCTION

A variety of studies have linked endometrial cancer to obesity, primarily based on either weight or a body mass index (1). More recently there has been interest in adult weight gain, since this largely reflects changes in body fat (2), and in the distribution of body fat. Of particular interest is whether fat is distributed according to android or male type obesity (fat predominately on the upper body, e.g., nape of the neck, shoulder, chest, abdomen), or gynoid or female type obesity (fat predominately on the lower body, e.g., hips, buttocks, thighs). Android obesity has been related to a variety of hormonal abnormalities, including decreased sex hormone-binding globulin and elevated estradiol and testosterone levels (3, 4).

Although high WHRs, indicative of android obesity, as well as central versus peripheral obesity (fat distributed predominately on the trunk of the body as opposed to the limbs), have been linked to increased risks of breast cancer (5-7), the association of fat distribution with endometrial cancer is unclear. Results from two cohort studies revealed positive relationships of endometrial cancer risk with high waist:hip (8, 9) and skinfold measurements (9), but the associations disappeared after adjustment for body mass index. Two case-control studies showed positive relationships of risk with upper body obesity (10, 11), while another implicated central obesity (12).

In a population-based case-control study of 268 endometrial cancer cases and an equal number of population controls in Shanghai, we examined the association between endometrial cancer and obesity by evaluating weight changes over different age intervals and anthropometric measurements of fat distribution. This geographic area offered a unique opportunity for study, given the low incidence of endometrial cancer and low prevalence of obesity. Previous analyses of other risk factors (e.g., nulliparity and exogenous estrogen use) showed relationships similar to those observed in western populations (13).

MATERIALS AND METHODS

Cases consisted of all residents of the Shanghai metropolitan area between the ages of 18 and 74 years who were newly diagnosed with endometrial cancer during the period April 1, 1988 to January 31, 1990. During this period, a total of 294 cases were identified through the population-based Shanghai Cancer Registry. Interviews were conducted with 268 of these cases (91.2%), with nonresponse due to refusals (n = 2 cases), deaths (n = 13), location difficulties (n = 6), and other miscellaneous problems (n = 5). A total of 98.5% of the cases were histopathologically confirmed. Of these, 76.2% were adenocarcinomas, 6.3% adenosquamous cancers, 13.4% other types, and 4.1% unspecified.

A total of 268 controls were individually matched to the cases on age (within 2 years) through random selections from resident rosters at the Shanghai Residents Registry. Details on the control selection procedures have been described elsewhere (13). Of 278 eligible women randomly identified, 268 (96.4%) were successfully interviewed. One woman was excluded because of a prior hysterectomy, while 9 could not be located.

Subjects were interviewed by trained interviewers at their homes or occasionally in the hospital. Most cases were interviewed shortly after diagnosis, with the mean interval between diagnosis and interview being 3.2 months. The standardized questionnaire, which took slightly over 1 h to administer (mean, 85 min for cases and 71 min for controls), covered demographic characteristics, reproductive events, developmental history, contraceptive practices, family cancer history, personal habits, and diet. The developmental history obtained information on perceptions of weight and height at three different time periods: childhood (ages 10-12), early adolescence (ages 13-16), and later adolescence (ages 17 and 18). With respect to weight, subjects were asked for these three time periods to answer whether, compared to other girls their own age, they were considered thin, moderately thin, of average weight, moderately heavy, or heavy. A similar set of questions was asked with respect to relative height. In addition, information was obtained on height (in cm) at age 20, weight (in kg) at different age periods (20-29, 40-49, 50-59, 60+, 1 year before interview), and heaviest and lightest weights after age 20.

The study design was modified after 7 months of data collection to additionally include collection of a variety of anthropometric measurements. Anthropometric measurements were taken for 162 cases and 95 controls, either at the time of interview or at a subsequent visit. The
average interval between diagnosis and measurements was 8.3 months, with 41.3% of the cases being measured within 6 months of diagnosis. A requirement for subjects to be measured in lightweight loose clothing and lack of heating during winter months resulted in a number of anthropometric measurements being delayed. Standing height and sitting height were measured to the nearest 0.1 cm by using a pocket stadiometer. Girth measurements, recorded to the nearest 0.1 cm, were taken with a cloth tape, with any worn clothing lifted so that measurements could be taken directly over skin. Midarm circumference was measured at the midpoint of the arm between the acromion and olecranon process. Waist circumference was measured at the level of the umbilicus. Hip girth was not taken because of concerns that this measurement would be offensive to subjects. Midthigh circumference was measured midway between the greater trochanter of the femur and the proximal border of the patella (lateral edge). Skinfolds were measured to the nearest 0.1 mm by using Tanner-Whitehouse skinfold calipers. Triceps skinfolds were measured on the posterior midline of the arm at the same level identified for the midarm circumference. The subscapular skinfold site was identified by locating the area just below the inferior angle of the scapula. The suprapatellar skinfold site was located about 2 cm above the proximal edge of the patella. All limb circumferences and skinfolds were measured on the right side of the body. All measurements were taken twice and a tolerance of difference was given for each measurement (1.0 cm for standing and sitting height and waist and midthigh circumferences; 0.2 cm for midarm circumference; 0.2 cm for triceps and suprapatellar skinfolds; 0.3 cm for subscapular skinfold). A third measurement was taken if the difference of the first two measurements was in excess of the tolerance. The means of the replicates were used in analyses. Only self-reported weight was obtained in this study. Body mass indices and summations of skinfolds (subscapular plus triceps plus suprapatellar) were used to reflect general obesity. A STR was calculated to measure central versus peripheral obesity and a WTR to measure upper body obesity.

Relative risks, as estimated by odds ratios, were used to evaluate associations of the anthropometry variables with endometrial cancer risk. Subjects were divided into four categories by using the quartile distribution of anthropometry variables of the controls. Adjustment for confounding variables was accomplished by using multivariate logistic regression techniques (14), deriving maximum likelihood estimates of adjusted odds ratios and 95% confidence intervals. Because of missing values for several anthropometry variables, we broke the case-control pairing in order to keep the maximum number of subjects in the analysis. Thus, an unconditional logistic regression model was used, with age always included in the model as a continuous variable. Several models using conditional logistic regression showed results similar to those obtained from the unconditional analyses, confirming the appropriateness of this latter approach. Tests for trend in the logistic analysis were obtained by categorizing the exposure variable and treating the scored variable as a continuous variable.

RESULTS

The relationship of endometrial cancer risk to a variety of nonanthropometric factors is shown in Table 1. Cases and controls were similarly distributed with respect to age (respective means of 56.0 and 56.4 years), education, and income. Cases were much more likely than controls to have never been pregnant, to have later ages at menopause, to have no history of use of oral contraceptives, and to have histories of irregular menstruation or diabetes. There was no difference with respect to a history of hypertension. Only three cases versus no controls reported prior use of menopausal estrogens. Of the various risk factors identified, only adjustment for number of pregnancies (categorized as 0, 1–3, >3) substantially changed the estimates of the anthropometric variables, so that only number of pregnancies and age (the matching factor) were considered as potential confounders. Additional adjustment for other risk factors, including age at menopause, diabetes, or irregular menstruation, failed to substantially alter results.

Odds ratios for endometrial cancer according to quartiles of recalled height, recent weight, and body mass index are summarized in Table 2. Cases tended to be taller than controls, but neither the point estimate for the highest quartile nor the trend
Table 3 Odd ratios of endometrial cancer associated with body mass index during different periods

Women whose weight reflected weight within 2 years of diagnosis were excluded from analyses, e.g., women aged 42 or less were excluded from analyses of weight at ages 40-49 (12 cases, 6 controls); women aged 52 or less were excluded from analyses of weight at ages 50-59 (21 cases, 20 controls); and women aged 62 or less were excluded from analyses of weight at ages 60-69 (23 cases, 23 controls).

<table>
<thead>
<tr>
<th>Weight/height (^2)</th>
<th>Cases</th>
<th>Controls</th>
<th>OR*</th>
<th>95% CI</th>
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<tr>
<td>At ages 20-29</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;19.0</td>
<td>60</td>
<td>63</td>
<td>1.0</td>
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<tr>
<td>19.1-20.8</td>
<td>77</td>
<td>65</td>
<td>1.3</td>
<td>0.8-2.1</td>
</tr>
<tr>
<td>20.9-22.0</td>
<td>36</td>
<td>60</td>
<td>0.6</td>
<td>0.4-1.1</td>
</tr>
<tr>
<td>≥22.1</td>
<td>87</td>
<td>65</td>
<td>1.5</td>
<td>0.9-2.4</td>
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<tr>
<td>Trend test</td>
<td></td>
<td></td>
<td>P</td>
<td>0.37</td>
</tr>
<tr>
<td>At ages 40-49</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20.3</td>
<td>52</td>
<td>59</td>
<td>1.0</td>
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</tr>
<tr>
<td>20.4-21.8</td>
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<td>58</td>
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<td>0.5-1.6</td>
</tr>
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<td>21.9-24.0</td>
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<td>1.2</td>
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<tr>
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<td>60</td>
<td>1.6</td>
<td>0.9-2.6</td>
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<tr>
<td>Trend test</td>
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<td></td>
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<td></td>
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<td>46</td>
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<tr>
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<td>50</td>
<td>1.0</td>
<td>0.6-2.1</td>
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<tr>
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<td>41</td>
<td>46</td>
<td>1.2</td>
<td>0.7-2.4</td>
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<tr>
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<td>46</td>
<td>2.5</td>
<td>1.4-4.5</td>
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<tr>
<td>Trend test</td>
<td></td>
<td></td>
<td>P</td>
<td>&lt;0.01</td>
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<tr>
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<td></td>
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<td>16</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
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<td>1.0</td>
<td>0.3-2.9</td>
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<tr>
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<td>14</td>
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<td>0.3-3.2</td>
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<tr>
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<td>29</td>
<td>17</td>
<td>2.4</td>
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<tr>
<td>Trend test</td>
<td></td>
<td></td>
<td>P</td>
<td>0.05</td>
</tr>
</tbody>
</table>

* Adjusted for age and number of pregnancies.

Quetelet's index at all adult ages was associated with increased risk. The association was most striking after age 50, with an OR at ages 50-59 of 2.5 (95% CI, 1.4-4.5) for women in the highest versus lowest quartile of Quetelet's index. The corresponding OR was only 1.5 (95% CI, 0.9-2.4) at ages 20-29.

Attempts were made to assess whether the effect of Quetelet's index at an early age could be explained by Quetelet's index at later ages and vice versa. Trends became difficult to interpret because of small numbers of subjects in some cells. However, using women in the lowest quartile of Quetelet's index at ages 20-29 and 50-59 as the referent, significantly high risks were observed for those with large body mass at both ages (OR = 3.5; 95% CI, 1.5-8.3) as well as those with large body mass only at older ages (OR = 6.8; 95% CI, 1.8-25.5).

Effects of weight changes across different age intervals are presented in Table 4. Weight gain or loss, within 2.5 kg, was defined as constant weight and was used as the referent group. Weight gain of more than 7.5 kg from ages 20-29 to 40-49 and from ages 40-49 to 50-59 was related to increased risk, with ORs of 1.7 (95% CI, 0.7-2.5) and 2.0 (95% CI, 1.1-3.7), respectively. Weight gain from ages 50-59 to age 60 or older, however, was not related to an increased risk, although based on relatively small numbers of subjects. Weight loss during all age periods was related to slight, but nonsignificant, increases in risk. Compared to women achieving their maximum weight prior to age 40, women who reached their heaviest weight at ages 50-55 and 56 years or older had ORs of 1.6 (95% CI, 1.0-2.6) and 1.3 (0.8-2.3), respectively (data not shown).

Table 5 presents associations with various anthropometric measurements. After adjustment for age and number of pregnancies, standing height was related to increased risk, with an OR of 2.0 (95% CI, 0.9-4.3) for women in the highest versus lowest quartile. This association became weak and no longer significant after adjustment for weight 1 year before diagnosis. Sitting height was also related to increased risk, with the OR after adjustment for age and number of pregnancies being 3.0 for the highest versus lowest quartile (95% CI, 1.3-7.0). However, the ratio of sitting to standing height, suggested as reflecting nutritional status during childhood, was not related to risk, either before or after adjustment for weight.

Analysis of skinfold measurements showed that fat deposits on the trunk (subscapular area) of the body were related to higher risks than those on peripheral areas. Thus, the comparison of the highest to lowest quartile values of subscapular skinfolds resulted in an OR of 3.2 (95% CI, 1.4-7.0). Similar
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comparisons for triceps and suprapatellar skinfolds resulted in ORs of 2.0 (95% CI, 0.9–4.0) and 2.6 (95% CI, 1.2–5.8), respectively (data not shown). A significant trend \( (P = 0.02) \) was observed for the subscapular skinfolds even after adjustment for Quetelet’s index (based on weight 1 year before diagnosis).

The summation of the three skinfold measurements (triceps, subscapular, suprapatellar) was used to assess general obesity (data not shown). This summed value, however, provided no stronger effect of the association between obesity and endometrial cancer than did the individual skinfolds or weight alone. The OR was 2.3 (95% CI, 1.1–4.7) for the highest versus lowest quartile of total skinfolds.

The association between endometrial cancer risk and central versus peripheral obesity was evaluated by the subcapular:triceps skinfold ratio. After adjustment for age and number of pregnancies, women in the highest quartile of STR had an OR of 2.2 (95% CI, 1.0–4.8) compared to those in the lowest quartile. Although no longer significant after adjustment for recent Quetelet’s index, the OR remained elevated \( (OR = 1.7; 95\% CI, 0.8–3.7) \).

The effect of STR was observed only among women with low values of Quetelet’s index. The OR of the highest to lowest quartile of STR was 1.8 (95% CI, 0.5–5.9) for women with Quetelet’s index values below the median and 1.1 (95% CI, 0.3–3.8) for women with higher values. Waist:thigh circumference ratio, calculated to measure upper body obesity, was not related to risk, either before or after adjustment for recent Quetelet’s index.

More cases than controls reported a self-defined family history of obesity, with an OR of 3.2 (95% CI, 1.4–7.5) after adjustment for age, number of pregnancies, and Quetelet’s index. Six cases but no controls reported more than one obese relative.

DISCUSSION

Obesity has been consistently reported to be associated with endometrial cancer risk \( (1) \), with most studies conducted in western countries. Shanghai women in the present study were generally much thinner than western women (average weight of 57.6 kg, with a range from 34 to 93 kg) and few would have been defined as obese by other criteria. For example, the lower distribution of our upper quartile of body mass index weight/height\(^{1.5} \) would be equivalent to only the third quartile of a recent American study \( (12) \). Despite these differences, we observed a 2.5-fold increased risk of endometrial cancer associated with the highest versus lowest quartile of weight. The association between weight and endometrial cancer appeared to be strongest in relation to weight gain during late adulthood.

The effect of body mass on endometrial cancer appeared independent of other conditions that have been related both to obesity and to endometrial cancer \( (e.g., \) diabetes, hypertension, irregular menstruation). Although the underlying mechanism is unknown, the effect of excess fat on endometrial cancer may be mediated through endogenous hormones. Body fat increases with age \( (15) \), weight change in adulthood is mainly attributable to fat deposits \( (2) \), and adipose tissue is the primary extragonadal site for estrone production by aromatization of androstenedione \( (16) \). Among the hormonal changes associated with obesity are increased production rates of androgens, increased peripheral conversion of androgens to estrogens, and decreased levels of progesterone and sex hormone-binding globulin \( (17) \). The conversion of androstenedione to estrone also increases as a function of aging \( (18) \). Increased exposure to endogenous estrogens unopposed simultaneously by progestogens in obese women, especially in the elderly, may stimulate mitotic activity of endometrial cells \( (19) \), leading to hyperplasia and subsequent neoplasia \( (17) \).

Blitzer et al. \( (20) \) found an increased risk of endometrial cancer among women with teenage obesity, with the highest risk among women with a history of both teenage and current obesity. However, Le Marchand et al. \( (21) \) failed to demonstrate an association with endometrial cancer risk, using information on adolescent weight obtained through a computer linkage with existent historical data. Similarly, we failed to observe that excess relative weight during childhood or adolescence was related to risk, although these measures of perceived weight must be interpreted cautiously, due to the possibility of inaccurate or selective recall. Further support for a central effect of weight at older ages derived from findings of stronger relationships with higher weights at older ages.

Body fat distribution, especially upper body obesity as measured by the WHR, has been related to endometrial cancer risk \( (8–11) \), although in several studies the effect disappeared after adjustment for body mass index \( (8, 9) \). Although we were unable to directly assess this specific relationship, we did not observe an association of risk with the waist:thigh circumference ratio, a measure used in some studies to assess upper versus lower body obesity \( (22, 23) \). However, several other measures of fat distribution appeared to indicate that a centralized distribution of fat was an important determinant of risk. In particular, fat located on the trunk area \( (subcapula) \) was related to the
highest risk, and this association remained significant after adjustment for overall obesity. Fat located on other parts of the body, especially the arm (triceps), was much less related to risk. Central versus peripheral obesity, as measured by the STR, also appeared related to increased risk, although the trend was no longer significant after adjustment for Quetelet’s index ($P = 0.23$). Austin et al. (12) found central obesity to be significantly related to endometrial cancer risk independent of body mass index, but there was no separate effect of WHR. Upper body obesity has been reported to be associated with higher levels of testosterone and lower levels of sex hormone-binding globulin and progesterone (3). It is unclear whether a biological difference exists between central and upper body obesity, and the interchangeable use of these terms in the literature to reflect fat distribution further complicates interpretation of our findings. It has been reported that WHR and STR are weakly correlated (24), and in our study the correlation coefficient of WTR and STR was only 0.16. In addition, WHR and STR have been reported to be independent predictors of gallbladder disease as well as endometrial cancer (12, 25). Given the lack of a strong correlation between WHR or WTR and STR, it would appear that these measures may reflect different patterns of fat deposition and perhaps different endocrine profiles and consequences. Further research is needed to define the health risks and hormonal mechanisms associated with central versus upper body obesity and with various anthropometric measurements.

Height has been related to the risk of endometrial cancer in several studies (21, 26–28), but another study (29) found no such effect. In our study, measurements of standing height and sitting height were both related to an excess risk of endometrial cancer, although self-reported height was not significantly related, possibly due to poor recall. The standing-sitting height ratio, which has been proposed as a reflection of childhood growth patterns, was not related to any elevation in risk. Although height has been linked to cancers of the breast (30) and perhaps prostate (31), the relationship to endometrial cancer remains unclear.

Several limitations of this study should be addressed before causal inferences can be made. (a) The validity of information on height and weight must be questioned. Height was a stronger risk factor when measurements were considered, possibly reflecting the fact that measured height was available on only a sample of subjects. However, differences may have also reflected the tendency of women to overestimate their height. This was somewhat more pronounced among controls, which would have biased risks associated with reported heights toward the null, unless unique degenerative changes associated with aging were involved. More concerns are apparent with respect to weight associations, especially since this information was based on self-reports. Unfortunately, we were unable to directly assess this potential bias in our study. It would appear unlikely that the association of endometrial cancer with obesity, as assessed by reported weight, was grossly distorted, since using the summation of measured skinfolds as a measure of obesity provided similar results. (b) Anthropometric measurements were available for only 60% of the cases and 35% of the controls, leading to concerns that the measured women might be a selected group that differed from the target population. Measured women were comparable to unmeasured women with respect to most risk factors, including weight, body mass index, and number of pregnancies, although they were somewhat older (1.8 years). (c) There was some delay between the time of diagnosis and when measurements were actually taken. The average time interval from diagnosis to measurement was 8.3 months for cases. There were, however, no appreciable differences in body circumferences or skinfolds for cases whose measurements were taken within 6 months of diagnosis compared with those whose measurements were taken later. (d) Possible errors in anthropometric measures should be kept in mind. However, the interviewers were kept blind of the specific study hypotheses (e.g., effects of fat distribution), and each interviewer was required to measure both cases and controls. Since measurement error is likely to be nondifferential, the association between anthropometric measurements and endometrial cancer risk would, if anything, be likely to be underestimated.

In summary, this study found that, despite a low prevalence of obesity among Chinese women, weight gain, particularly during later adulthood, and resultant high body masses were associated with increases in the risk of endometrial cancer. The distribution of body fat appeared to have an independent effect, with high risks associated with fat located on the trunk of the body. These findings infer a relationship of endometrial cancer risk to positive energy balance, emphasizing the need for further studies to clarify the role of energy intake (including diet composition) and energy expenditure (physical activity). Standardized measurements for fat distribution, along with the assessment of hormonal and other biological parameters, are also needed to assist in identifying causal mechanisms for this tumor.

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