Association of Incident Carcinoma of the Endometrium with Body Weight and Fat Distribution in Older Women: Early Findings of the Iowa Women’s Health Study

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ABSTRACT

Previous epidemiological studies have demonstrated that obesity increases endometrial cancer risk two- to 10-fold. To test the hypothesis that abdominal adiposity further increases this relative risk, we conducted a nested case-control study of endometrial cancer incidence in a cohort of 41,873 women ages 55-69 years. Women were recruited by mail and asked to have a friend measure circumferences of several body parts using a tape measure and written instructions. Two-year follow-up for cancer incidence was conducted using a state-wide cancer registry. Compared to random controls (n = 1,274), cases (n = 63) had higher age-adjusted mean values of waist-to-hip circumference ratio (P = 0.10) and trunk-to-limb circumference ratio (waist plus hip circumferences divided by arm plus calf circumferences, P = 0.008). Other anthropometric variables, including current body mass index and current weight, were also greater (P < 0.001) in cases than controls. After accounting for the association with body mass index, neither the waist-to-hip ratio nor the trunk-to-limb ratio remained associated with endometrial cancer incidence (P > 0.40). A 5 kg/m² increase in body mass index was associated with an adjusted relative risk of endometrial cancer incidence of 1.80 [95% CI = 1.46, 2.22] when other significant risk factors, namely age, education level, extended use of exogenous estrogens, and age at menopause, were taken into account. We conclude that endometrial cancer risk is increased in relation to the amount but not the distribution of adiposity. This is in contrast with several other diseases in which, in addition to overall body mass, the distribution of adiposity is also important.

INTRODUCTION

Numerous epidemiological studies have reported that overweight women have a two- to 10-fold increased risk of endometrial cancer (1-6). This has been attributed to elevated levels of endogenous estrogens in overweight versus normal weight women (7).

The health risks of excess weight can be further examined by measurement of fat distribution. For example, the waist-to-hip circumference ratio has been employed as a measure of abdominal adiposity (8-12). Lapidus et al. recently reported a significant univariate correlation between the waist-to-hip ratio and endometrial cancer in a study with only 10 cases, but the association was not significant when body mass index was taken into account (12). We sought to extend these findings, testing the association of abdominal adiposity and endometrial cancer in a prospective, population-based cohort of older women. This report presents the early findings of the study, based on 2 years of follow-up.

MATERIALS AND METHODS

The Iowa Women’s Health Study participants were a random sample of women ages 55 to 69 years listed on the 1985 Iowa driver’s license list. A total of 41,837 women responded to a January, 1986 mail survey, representing a response rate of 42.7%. Based on driver’s license and 1980 census information, we could determine that responders were about 3 months older than nonresponders, were 0.4 kg/m² lighter, and were slightly more likely to live in rural, less affluent counties.

The mail questionnaire inquired about major endometrial cancer risk factors, including education level, history of exogenous hormone use, parity, cigarette smoking, and age at menopause. To identify subjects with prevalent cancer, we asked women to indicate whether they had ever been diagnosed by a physician as having any form of cancer, other than skin cancer. They were also asked to report current height and weight, maximal adult weight, weight 1 year prior to the survey, as well as weight at ages 18, 30, 40, and 50 years. Quetelet body mass index (BMI)² was calculated as weight (kg)/height (m)². To assess body fat distribution, we enclosed a paper tape measure, verified for accuracy, and written instructions for having a friend measure circumferences of the waist (one inch above the umbilicus), hips (maximal protrusion), upper arm (mid-point), and lower leg (maximal mid-calf). The accuracy and reliability of measurements of circumferences, height, and weight by this protocol are good (13).

Follow-up for cancer occurrence in the cohort was performed using the Health Registry of Iowa, part of the National Cancer Institute’s Surveillance, Epidemiology, and End Results Program. To identify incident cases, we performed a computer match on name, zip code, birthdate, and social security number between the 1986-1987 Registry cases and the 41,837 study participants. Social security number was available on all subjects because it is also the Iowa driver’s license number. A total of 69 women in the cohort developed endometrial cancer (ICD-O 182) during the 2 years of follow-up.

Because the number of person-years of observation was very large compared to the number of endometrial cancer cases, we analyzed the data as a nested case-control study (14). Women who at baseline reported (a) prior cancer of any site other than skin and/or (b) prior hysterectomy were excluded from analysis. After these exclusions there were 63 incident endometrial cancer cases for analysis. Controls (n = 1274) were randomly selected, after applying the same exclusion criteria, from the women who had not developed endometrial cancer during follow-up. Subjects who developed nonuterine cancers were eligible for selection as controls if they met the other eligibility criteria.

The main hypothesis tested was that measures of fat distribution representing abdominal and trunkal adiposity were significantly associated with endometrial cancer incidence after accounting for the known association with BMI. Two measures of fat distribution were used: the waist-to-hip circumference ratio and a trunk-to-limb circumference ratio, computed as the sum of the waist and hip circumferences divided by the sum of the upper arm and lower leg circumferences. This ratio is similar to the “central obesity index” defined by Hiramatsu et al. (15). Data were initially examined comparing age-adjusted means of anthropometric variables using analysis of covariance. Variables were normally distributed. Odds ratios were calculated from stratified analyses in which anthropometric variables were trichotomized at tertile cutoffs of the entire distribution. Odds ratios were age-adjusted by the Mantel-Haenszel method (16) using 5-year groupings. Ninety-five % confidence intervals for the summary odds ratios were test based (17). Unconditional multiple logistic regression was employed for multivariate modelling. First, separate two-factor models were constructed using age and each anthropometric characteristic as independent vari-
was unrelated to endometrial cancer, and weights reported for circumference ratio (Table I). The mean waist-to-hip ratio was not significantly higher in cases than controls (P = 0.10). Height was unrelated to endometrial cancer, and weights reported for

RESULTS

The subjects were aged 55-69 years at baseline, and 99% were white. Follow-up was approximately 2 years. On average, women who developed endometrial cancer had significantly greater values ($P < 0.01$) for BMI, weight, maximal adult weight, waist and hip circumference, and the trunk-to-hip circumference ratio (Table 1). The mean waist-to-hip ratio was not significantly higher in cases than controls ($P = 0.10$). Height was unrelated to endometrial cancer, and weights reported for earlier ages were less strongly related to endometrial cancer risk than current or maximal adult weights. The product moment correlation between BMI and waist-to-hip ratio was 0.42, between BMI and the trunk-to-limb circumference ratio was 0.43, between BMI and weight was 0.91, and between waist-to-hip ratio and the trunk-to-limb circumference ratio was 0.43.

Table 1 shows that, adjusted for age, the endometrial cancer risks were associated with one standard deviation increases in the waist-to-hip ratio (0.98 (0.74, 1.30) and 0.84 (0.60, 1.18), respectively. However, neither of these two fat distribution variables (entered as continuous variables) were 0.09 and 0.008, respectively. The P values for trend indicated that a linear fit was sufficient for each anthropometric variable. Two-factor logistic regression models using each anthropometric variable and age as continuous predictor variables.

Table 2 shows that, adjusted for age, the endometrial cancer risk was related to nonanthropometric characteristics, Iowa women, ages 55-69

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n = 63)</th>
<th>Controls (n = 1274)</th>
<th>Age-adjusted* odds ratio (95% CI)</th>
<th>P value for trend*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index (kg/m²)</td>
<td>&lt;24.31</td>
<td>15 422 1.00</td>
<td>(0.27-1.37)</td>
<td>0.000</td>
</tr>
<tr>
<td>Waist circumference (in)</td>
<td>&lt;31.5</td>
<td>15 417 1.00</td>
<td>(0.71-3.25)</td>
<td>0.000</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>&lt;0.7914</td>
<td>14 424 1.00</td>
<td>(0.44-1.92)</td>
<td>0.000</td>
</tr>
<tr>
<td>Trunk-to-limb circumference ratio</td>
<td>&lt;2.673</td>
<td>11 406 1.00</td>
<td>(0.88-3.36)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

4.08* Haensel, et al.

5.0-77.5 Age

6.73-3.052 1.85 (0.88-3.88) 0.008

>3.052 27 390 2.50 (1.25-5.03) 0.008

* Age-adjusted by analysis of covariance.

** Waist circumference + hip circumference divided by arm circumference + leg circumference.

Table 3 shows the risk of endometrial cancer in relation to nonanthropometric characteristics, Iowa women, ages 55-69

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Age-adjusted* odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parity</td>
<td>1.00</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>1.74 (1.04, 2.90)</td>
</tr>
<tr>
<td>Age at menopause (years)</td>
<td>47 to 51 0.96 (0.43, 2.10) &gt;51 1.71 (0.82, 3.58)</td>
</tr>
<tr>
<td>Age at menopause (years)</td>
<td>12-13 1.29 (0.59, 2.82) &gt;13 0.69 (0.28, 1.69)</td>
</tr>
<tr>
<td>Exogenous estrogen use</td>
<td>Never 1.00 (0.31, 2.00) ≥5 years 3.45 (1.68, 7.04)</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Low 1.00 Medium 0.61 (0.32, 1.15) High 0.53 (0.27, 1.06)</td>
</tr>
<tr>
<td>Education level</td>
<td>&lt; High school graduate 1.00 High school graduate 1.42 (0.62, 2.37) &gt; High school graduate 1.84 (0.83, 4.07)</td>
</tr>
<tr>
<td>First degree relative with cancer of uterus</td>
<td>No 1.00 (0.34, 14.9) Yes 2.26 (0.34, 14.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>No 1.00 (0.34, 14.9) Yes 2.26 (0.34, 14.9)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>No 1.00 (0.69, 4.08) Yes 1.68 (0.69, 4.08)</td>
</tr>
</tbody>
</table>

6.829

* Age-adjusted by 5-year groupings using the Mantel-Haenszel method.

** 95% confidence interval for the odds ratio.
This study confirmed findings of previous epidemiological studies that overweight women have a substantially increased risk of carcinoma of the endometrium (1-6). However, we have extended those findings by showing that the distribution of body fat does not seem to contribute additionally to endometrial cancer risk. This confirms the findings of Lapidus et al. which were based on only 10 endometrial cancer cases (12). It is, therefore, the degree of adiposity and not its distribution that increases endometrial cancer risk. This is in contrast with several other diseases where fat distribution is important, such as diabetes mellitus (8, 9), hypertension (8, 10), cardiovascular disease (10, 11), and gallbladder disease (8).

The increased risk of endometrial cancer with obesity is believed to relate to higher production rates and concentrations of endogenous estrogens (7), in particular nonprotein bound estradiol. Increased estrogen exposure leads to endometrial proliferation, which may be a necessary condition for the development of at least some endometrial carcinomas. Because women with abdominal adiposity have significantly reduced concentrations of sex hormone binding globulin (19), we hypothesized that they would therefore have increased nonprotein bound estradiol and estrone, which is the estrogen with the highest serum concentration and is most easily measured in postmenopausal women. However, we found no relation between abdominal adiposity and serum total estradiol, nonprotein bound estradiol, or estrone in a sample of postmenopausal women, despite lower sex hormone binding globulin. In contrast, total and nonprotein bound estradiol concentrations were significantly and positively correlated with body mass. Abdominal adiposity seems to be associated with a relatively more androgenic profile in women (19). This may explain why only overall adiposity, but not abdominal adiposity, is associated with endometrial cancer risk.

These findings for endometrial cancer contrast the association between abdominal adiposity and breast cancer incidence found in this sample of women. The waist-to-hip ratio was positively associated with breast cancer incidence. In addition, there was effect modification by both age and BMI, such that younger and lighter women with abdominal adiposity were not at increased risk of breast cancer, whereas older and heavier women with abdominal adiposity had over a twofold increase in risk. The association of WHR with breast cancer but not endometrial cancer may relate to a different role of endogenous sex hormones in promotion of each neoplasm. Estrogens unopposed by progesterone increase endometrial cancer risk; whereas either estrogens alone (20), estrogens plus progesterone (20), or even androgens (21) may contribute to breast cancer risk.

The methodological drawbacks of this study warrant consideration. The circumanferences were self-measured, but they have sufficient reliability (test-retest correlations > 0.85) and accuracy not to invalidate our conclusions (13). The survey response rate was 43%. However, nonresponders and responders were not appreciably different on several variables (see “Materials and Methods”), and low response could bias these findings only in the unlikely event that associations differed between responders and nonresponders. Follow-up was through a cancer registry and in this early report was only of 2 years’ duration. It is possible that surveillance by local physicians for endometrial cancer differs between obese and nonobese women; however, it seems unlikely that medical surveillance would be related to fat distribution. Finally, although the number of endometrial cancer cases were relatively few, the statistical power of this study should have been sufficient to detect an adjusted relative risk of abdominal adiposity of at least 1.6 at a P < 0.10, if it had existed. The accumulation of additional cases through continued follow-up of this cohort will allow us to test for weaker effects of fat distribution in the future.

In addition to excess weight, age, extended use of estrogen...
replacement therapy, age at menopause, and education level, all were positively and independently associated with endometrial cancer incidence, confirming previous reports (1–6). Associations of hypertension and diabetes mellitus with endometrial cancer were explained by an association with greater body mass. Many investigators have found parity (6) and cigarette smoking (22, 23) negatively and independently associated with endometrial cancer. Univariate associations of these factors were also evident in this study, but they were not independent of other risk factors. Moreover, smoking did not modify the effect of overweight on endometrial cancer risk as has been previously reported (23). A possible explanation for the lack of effect of overweight on endometrial cancer risk as has been of other risk factors. Moreover, smoking did not modify the effect of overweight on endometrial cancer risk as has been previously reported (23). A possible explanation for the lack of association between excess adiposity and endometrial cancer: cases and two control groups from North Carolina. Am. J. Epidemiol., 114: 497-506, 1981.

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