Metabolic syndrome and endometrial cancer risk

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Background: Various studies reported direct associations between endometrial cancer risk and individual components of the metabolic syndrome (MetS), i.e. obesity, diabetes, hypertension, and dyslipidemia, but only a few epidemiological studies considered the association with MetS overall.

Methods: We analyzed data from a case–control study including 454 women with incident endometrial cancer and 798 controls admitted to the same hospitals as cases for acute conditions. Different definitions of MetS were considered, including a combination of self-reported history of diabetes, drug-treated hypertension, drug-treated hyperlipidemia, and various measures of (central) obesity. Odds ratios (ORs) were computed from unconditional logistic regression models, adjusted for major confounding factors.

Results: The multivariate ORs of endometrial cancer were 2.18 for type 2 diabetes, 1.77 for hypertension, 1.20 for hyperlipidemia, between 1.62 and 2.23 for various definitions of central obesity, and 3.83 for women with a body mass index (BMI) > 30 kg/m². The risk of endometrial cancer was significantly increased for subjects with MetS, the ORs ranging between 1.67 and 2.77 when waist circumference was included in MetS definition, and 8.40 when BMI was considered instead.

Conclusions: This study indicates a direct association between various MetS components, besides overweight, with the risk of endometrial cancer.

Key words: diabetes, dyslipidemia, endometrial cancer, hypertension, metabolic syndrome, obesity

introduction

The metabolic syndrome (MetS) is a combination of metabolic disorders, which include central obesity, hyperglycemia, hypertension, and dyslipidemia [1–5]. Initially defined as a risk factor for cardiovascular diseases, MetS has recently been associated to the development of various cancers [6–11].

Several studies reported direct associations between endometrial cancer risk, obesity, and other individual components of MetS [12]. The World Cancer Research Fund defined obesity as a convincing cause of endometrial cancer on the basis of the evidence from at least 25 cohort and 40 case–control studies [13]. Several epidemiological studies reported diabetes to be a risk factor for endometrial cancer, independently from obesity [14–17]. Hypertension has also been positively related to the risk of endometrial cancer [18, 19], while data on dyslipidemia are limited [20, 21].

A few epidemiological studies have considered simultaneously the association between combinations of selected components of MetS and endometrial cancer risk [18, 22–24], again reporting positive associations. However, only scanty data have been made available on the risk of endometrial cancer in relation to MetS. A record linkage study conducted in Milan, and including 20 women with endometrial cancer, defined MetS on the basis of drug prescriptions of conditions related to this syndrome and reported a 60% nonsignificantly increased risk of endometrial cancer [11].

A case–control study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) on 284 women with endometrial cancer found a relative risk of 2.12 [95% confidence interval (CI) 1.51–2.97] for women with MetS and a positive trend in risk with increasing number of Mets components [25].

To evaluate if MetS can be an additional predictor of endometrial cancer to obesity or other single component of MetS, we analyzed data from a case–control study from Italy.

materials and methods

A case–control study on endometrial cancer was conducted between 1992 and 2006 in three Italian areas, including the provinces of Milan and Pordenone, in northern Italy, and the urban area of Naples, in southern Italy [17]. Cases were 454 women (median age 60 years, range 16–79) with...
incident, histologically confirmed endometrial cancer (including both type 1, endometrial cancers, and type 2, serous and clear cell carcinomas) with no previous diagnosis of cancer. Controls were 908 women (median age 61 years, range 19–79) selected among patients admitted to the same network of hospitals for a wide spectrum of nonneoplastic and acute illnesses, of comparable age, study center, and period of enrollment as cases. Women with gynecological or hormone-related conditions, or any condition associated with long-term dietary changes, were not eligible as controls. A subset of 110 patients included in a previous report were excluded, since selective exclusion of diabetic patients was made in that study [26]. Thus, the control group included 798 controls. Controls were admitted for traumatic orthopedic disorders (36%), other orthopedic disorders (32%), acute surgical conditions (9%), and miscellaneous other illnesses, including eye, nose, ear, skin, or dental disorders (23%). Less than 5% of cases and controls approached refusal to be interviewed.

Cases and controls were interviewed during their hospital stay by trained interviewers using a structured questionnaire, including information on sociodemographic characteristics, anthropometric measures, lifestyle habits (e.g. tobacco smoking, alcohol drinking, and dietary habits), personal history of selected medical conditions, family history of cancer, menstrual and reproductive factors, and use of oral contraceptives (OC) and hormone replacement therapy (HRT).

Self-reported information on height and weight at different ages was collected. Waist circumference (2 cm above the umbilicus) was measured by interviewers on 791 women (307 cases and 484 controls). History of medical conditions, including type 2 diabetes, clinical obesity, drug-treated hypertension, and drug-treated or clinical diagnosis of hyperlipidemia, was self-reported and included age at first diagnosis. Diseases whose onset was <1 year before hospital admission were not considered.

Body mass index (BMI) was computed according to Quetelet’s index (weight/height², kg/m²). MetS was defined as the combination of presence of: (i) type 2 diabetes, (ii) history of drug-treated hypertension (as an alternate indicator of elevated blood pressure), (iii) history of a clinical diagnosis or drug-treated hyperlipidemia [as a proxy indicator of increased low-density lipoprotein/reduced high-density lipoprotein (HDL) cholesterol levels], and (iv) (abdominal) obesity. Using different proposed MetS definitions [5, 27], (abdominal) obesity was defined as a waist circumference >88 cm (MetS 1), waist circumference >88 cm (MetS 2), waist circumference >280 cm or BMI ≥28 kg/m² for women with missing information for waist circumference (MetS 3), waist circumference >88 cm or BMI ≥28 kg/m² for women with missing information for waist circumference (MetS 4), or BMI >30 kg/m² (MetS 5). A summary indicator of MetS was also defined according to the International Diabetes Federation criteria [27], adapted to our data, as the simultaneous presence of (abdominal) obesity plus at least two other components of MetS.

statistical analysis
Odds ratios (ORs) and the corresponding 95% CIs for various MetS definitions were estimated by unconditional multiple logistic regression models [28], including terms for age (quintillennia; categorically), study center (categorically), year of interview (<1999, 1999–2003, and ≥2004; categorically), education (<7, 7–11, and ≥12 years; categorically), age at menarche (<13, 13–14, and ≥15 years; categorically), parity (0, 1, 2, 3, and ≥4 children; categorically), menopausal status (pre/perimenopausal; categorically), and OC and HRT use (ever and never; categorically). Further allowance for tobacco smoking and alcohol consumption did not meaningfully modify any of the risk estimates.

The linear trend for an increase in the number of MetS components was assessed by fitting in the logistic models a continuous variable. Additional models were used to assess the potential modifying effect of selected covariates. To test for interaction, the difference in −2 log likelihood of the models with and without an interaction term was compared with the χ² distribution with 1 df. All statistical analyses were performed with SAS 9.1 statistical software (SAS Institute, Cary, NC).

results
Table 1 gives the distribution of 454 cases of endometrial cancer and 798 controls according to selected variables. Cases and controls had similar distribution according to age, study center, and education. Compared with controls, cases had a lower age at menarche, lower parity, and were more frequently HRT users.

Table 2 shows the distribution of endometrial cancer cases and controls and the corresponding ORs according to the components of MetS. The multivariate OR of endometrial cancer was 2.18 for diabetes, 1.77 for hypertension, and 1.20 for hyperlipidemia. With reference to measures of (central) obesity, the OR was 1.62 for women with waist circumference ≥80 cm, 1.90 for women with waist circumference ≥88 cm, 1.95 for a combined index of waist circumference ≥80 cm or a BMI ≥28 kg/m² when waist circumference was not available.
The definition most strongly associated with endometrial cancer included a BMI >30 kg/m² and at least two among hypertension, diabetes, and hyperlipidemia (OR = 8.40, 95% CI 3.95–17.87). The trend in risk with increasing number of components was also significant for all the MetS definitions.

Excluding obesity from the definition of MetS, the OR for subjects with the other three MetS components was 2.37 (95% CI 1.59–3.53), which became 1.73 (95% CI 1.14–2.64) after adjustment for BMI (data not shown).

Table 4 shows the ORs of endometrial cancer according to the two MetS definitions showing the strongest associations by number of their components in strata of age (<60 and ≥60 years), education (<7 and ≥7 years), and smoking habit (never and ever smokers). For both MetS definitions, the direct associations with endometrial cancer risk were stronger in younger women and those with a lower education, although no significant heterogeneity emerged across strata. Excluding obesity from the definition of the MetS, the OR was 1.10 (95% CI 0.51–2.34) in subjects with a BMI below the median (26.2 kg/m²) and 2.84 (95% CI 1.68–4.81) in those above (data not shown in table).

**Discussion**

The present study supports a direct association between MetS and endometrial cancer risk. The risk increased with the number of components using various definitions of MetS up to a three- to fourfold relative risk in women with three or more components of MetS, when considering waist circumference in its definition, and up to an eightfold relative risk, when considering BMI in its definition.

In line with previous epidemiological data, we observed a strong association between endometrial cancer risk and obesity, as measured by both BMI and waist circumference [13]. Our data also agree with studies reporting an increased risk of endometrial cancer with other components of MetS [22–24, 29]. In particular, our findings are in agreement with those of a case–control study nested within the EPIC cohort [25], and with those from an Italian record linkage study [11]. As in the EPIC study, we found a weaker association when MetS was defined as a cluster of diabetes, hypertension, and hyperlipidemia, which was further reduced after adjustment for BMI and was only found in overweight women. Thus, the key feature of MetS on endometrial carcinogenesis appears to be obesity, although the presence of other MetS components leads to an additional increase in risk.

Obesity is associated to endometrial cancer risk through increased levels and availability of serum estrogens [30]. An additional biological mechanism, which may explain MetS role on endometrial carcinogenesis, is insulin resistance [6, 31]. A contributor to the development of insulin resistance is an excess of circulating fatty acids, derived from adipose tissue triglyceride stores [31]. Hyperinsulinaemia leads to an increase in insulin-like growth factor 1 (IGF-1), which in turn stimulates endometrial cell proliferation [32–35]. Hyperinsulinemia and IGF-1 are key regulators of energy metabolism and growth [36]; they may also increase endogenous estrogen levels and lead to a decrease in circulating levels of sex hormone-binding globulin [12]. Available data, however, indicate only a limited effect of the IGF system on endometrial cancer risk [37]. Furthermore, adiponectin, a protein secreted by adipocytes, can reduce insulin resistance [38], and low adiponectin has been related to both diabetes and endometrial cancer risk [39]. Hypertension has an
independent, though moderate association with endometrial cancer risk [17, 30]. The biological mechanism linking hypertension to endometrial cancer remains unclear but has been related to the insulin resistance, too [40].

Even if expert groups agreed on the core components of MetS, they provided different clinical criteria for its definition [4]. We defined MetS in different ways, considering obesity as a waist circumference ≥80 cm as recommended by the European Group for the study of Insulin Resistance [1], a waist circumference >88 cm as proposed by the National Cholesterol Education Program—Third Adult Treatment Panel [2], or a BMI >30 kg/m² as suggested by the World Health

Table 3. Distribution of 454 women with endometrial cancer and 798 controls, and corresponding ORs with 95% CIs, according to various definitions of the MetS and the number of their components. Italy, 1992–2006

<table>
<thead>
<tr>
<th>Indicator of MetS</th>
<th>Ca:Co MetS 1b</th>
<th>Ca:Co MetS 2c</th>
<th>Ca:Co MetS 3d</th>
<th>Ca:Co MetS 4e</th>
<th>Ca:Co MetS 5f</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>260:444 1b</td>
<td>264:452 1b</td>
<td>387:745 1b</td>
<td>394:757 1b</td>
<td>412:784 1b</td>
</tr>
<tr>
<td>Yes</td>
<td>47:40 1.67 (0.99–2.81)</td>
<td>43:32 1.98 (1.14–3.44)</td>
<td>67:51 2.36 (1.55–3.61)</td>
<td>60:39 2.77 (1.74–4.40)</td>
<td>42:10 8.40 (3.95–17.87)</td>
</tr>
</tbody>
</table>

Table 4. ORs and corresponding 95% CIs of endometrial cancer according to the number of components of two definitions of the MetS in strata of selected covariates. Italy, 1992–2006

<table>
<thead>
<tr>
<th>Number of MetS components</th>
<th>ORa (95% CI)</th>
<th>Education (years)</th>
<th>Smoking habit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;7</td>
<td>≥7</td>
</tr>
<tr>
<td>Cases:controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MetS 4b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>207:357</td>
<td>247:439</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.75 (1.13–2.73)</td>
<td>1.34 (0.85–2.11)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.72 (2.67–16.91)</td>
<td>3.29 (1.74–6.24)</td>
<td></td>
</tr>
<tr>
<td>MetS 5d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1.79 (1.13–2.82)</td>
<td>1.33 (0.89–2.01)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.96 (1.31–2.96)</td>
<td>1.15 (0.71–1.86)</td>
<td></td>
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<tr>
<td></td>
<td>18.84 (9.42–72.23)</td>
<td>5.70 (2.62–13.43)</td>
<td></td>
</tr>
</tbody>
</table>

*aEstimates from logistic regression model adjusted for age, study center, year of interview, education, at menarche, parity, menopausal status, oral contraceptive use, and hormone replacement therapy use.

*bMetS was defined as diabetes, hypertension, hyperlipidemia, and waist circumference ≥80 cm.

*cMetS was defined as diabetes, hypertension, hyperlipidemia, and waist circumference >88 cm.

*dMetS was defined as diabetes, hypertension, hyperlipidemia, and waist circumference ≥80 cm or BMI ≥28 kg/m² for women with missing information for waist circumference.

*eMetS was defined as diabetes, hypertension, hyperlipidemia, and waist circumference >88 cm or BMI ≥30 kg/m² for women with missing information for waist circumference.

*fMetS was defined as diabetes, hypertension, hyperlipidemia, and BMI ≥30 kg/m².

*gMetS was defined as the simultaneous presence of obesity plus at least two other components of the following: diabetes, hypertension, and hyperlipidemia.

hReference category.

OR, odds ratio; CI, confidence interval; MetS, metabolic syndrome; Ca:Co, cases:controls; BMI, body mass index.
Our study shows a significant trend between number of MetS components and endometrial cancer risk. The key component of MetS in endometrial carcinogenesis appears to be overweight, but diabetes, hypertension, and hyperlipidemia play additional independent roles, leading to a substantial excess risk for women with MetS.

In conclusion, our study shows a significant trend between number of MetS components and endometrial cancer risk. The key component of MetS in endometrial carcinogenesis appears to be overweight, but diabetes, hypertension, and hyperlipidemia play additional independent roles, leading to a substantial excess risk for women with MetS.


