

## Case–Control Study of the Metabolic Syndrome and Metabolic Risk Factors for Endometrial Cancer

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### Abstract

**Background:** Metabolic syndrome may predict endometrial cancer risk better than diabetes, hypertension, dyslipidemia, dysglycemia, or weight alone, but few studies have examined this issue.

**Methods:** We conducted a population-based case–control study in Alberta, Canada (2002–2006) that included 515 incident endometrial cancer cases and 962 frequency age-matched controls. Data were collected through in-person interviews, anthropometric measurements, and 8-hour fasting bloods drawn either pre- or postsurgery. Bloods were analyzed using quantitative colorimetric or absorbance-based assays (ELISA), specific to metabolic syndrome markers. Metabolic syndrome was defined using harmonized guidelines requiring presence of  $\geq 3$  of the following risk factors: waist circumference  $\geq 88$  cm, triglycerides  $\geq 150$  mg/dL, high-density lipoprotein cholesterol  $< 50$  mg/dL, treatment of previously diagnosed hypertension, and fasting blood glucose  $\geq 100$  mg/dL. OR and 95% CIs for endometrial cancer risk with presence of metabolic syndrome and individual metabolic syndrome components were estimated using logistic regression analysis.

**Results:** Metabolic syndrome was significantly more prevalent among cases (62%) than controls (38%). A statistically significant increased risk for endometrial cancer was observed for metabolic syndrome (OR = 1.53; 95% CI: 1.17–2.00), as well as for some of the individual components of metabolic syndrome including waist circumference  $\geq 88$  cm (OR = 1.57; 95% CI: 1.18–2.08), hypertension (OR = 1.57; 95% CI: 1.18–2.09), and fasting blood glucose  $\geq 100$  mg/dL (OR = 1.31; 95% CI: 1.03–1.67). Some evidence for effect modification by menopausal status and body mass index was also found.

**Conclusion:** Metabolic syndrome is clearly associated with increased endometrial cancer risk.

**Impact:** Targeting the entire metabolic syndrome may optimize endometrial cancer risk reduction. *Cancer Epidemiol Biomarkers Prev*; 20(11); 2384–95. ©2011 AACR.

### Introduction

Endometrial cancer ranks as the most common gynecologic cancer among women in Canada, with an estimated 4,500 women that were newly diagnosed and 790 estimated deaths from this cancer in 2010 (1). Exposure to higher levels of endogenous or exogenous estrogens, plays a major role in endometrial carcinogenesis (2); a process leading to malignant disease with a peak in

incidence after menopause (3). Obesity, a condition that exposes women to higher levels of estrogen produced in adipose tissue, is now considered a "convincing" cause of endometrial cancer based on numerous cohort and case–control studies conducted worldwide (4). Estimates suggest that 28.2% of Canadian women are overweight and an additional 21.0% are obese (5). The rising prevalence of obesity occurring over the past 20 years is expected to continue and will likely result in an increased incidence of endometrial cancer. Other conditions that have been shown to increase endometrial cancer risk independently of obesity, include diabetes mellitus (6, 7) and hypertension (8, 9).

The metabolic syndrome is a cluster of risk factors that includes central adiposity, high blood pressure, elevated blood glucose levels, elevated triglycerides, and low high-density lipoprotein (HDL) cholesterol (10–12). Metabolic syndrome has emerged as a possible clinical condition that predisposes women to endometrial cancer, in addition to weight and other metabolic risk factors such as diabetes, hypertension, insulin resistance, and dysglycemia. Although studies have suggested a relation between individual metabolic syndrome components and

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endometrial cancer (2, 13–15), very few studies have investigated the association with metabolic syndrome itself (16–19). The metabolic syndrome could be a means for identifying those at risk of endometrial cancer who might otherwise be missed or before any one component of metabolic syndrome becomes more advanced. We collected information on different components of the metabolic syndrome in a population-based case–control study of endometrial cancer and examined the role of metabolic dysfunction in endometrial carcinogenesis, as defined by this cluster of risk factors, in addition to examining risk with individual components of the metabolic syndrome.

## Methods

### Study population

Our population-based case–control study of physical activity and endometrial cancer risk was conducted between 2002 to 2006 in Alberta, Canada and has been previously reported in detail (20). We recruited 549 incident, primary endometrial cancer cases through pathology reports from the Alberta Cancer Registry, and 1,036 population-based controls through random digit dialing (21). Cases were women, 30 to 79 years of age, without a history of previous cancer (except nonmelanoma skin cancer). Controls had no history of hysterectomy, endometrial ablation, or previous cancer (except nonmelanoma skin cancer) and were frequency age-matched ( $\pm 5$  years) to cases (2:1 ratio). Participation rates were 67.9% and 52.2% for cases and controls, respectively. We excluded 11 women because of unsatisfactory interviews. Determination of metabolic syndrome for another 83 women was not possible, either because a blood sample was not provided or information was missing for a sufficient number of components that were needed to classify a participant as having metabolic syndrome. However, we were able to include up to 17 of these women in analyses of individual metabolic syndrome components, depending on the component that had complete information. Any women missing information on one or more of the other covariates included in our models were also excluded. Our final analytical sample included 515 cases and 962 controls for the metabolic syndrome analysis. The sample sizes for the analysis of individual metabolic syndrome components varied according to completeness of the data.

### Data collection

Data were collected through in-person interviews using a structured questionnaire and cognitive interviewing methods, in which information on demographic variables and endometrial cancer risk factors including medical history, levels of recreational, occupational and household physical activity, smoking habits, alcohol drinking history, and exogenous hormone use. Three measurements of height, weight, waist, and hip circumference were taken using standardized methods for anthropometric measurements at the time of interview, with the

mean used as the final measurement. Blood was collected after a minimum 8-hour fast, either prior to surgical treatment by hysterectomy or postsurgery and subsequent to interviews for cases whose blood could not be drawn presurgery. Blood was drawn postinterview among controls. A 19-mL blood sample was collected according to a standardized protocol, and samples were processed into blood fractions (serum, plasma, red blood cells, and buffy coat), frozen at  $-80^{\circ}\text{C}$  within 24 hours of collection, and transported for storage to a specimen biorepository at the Tom Baker Cancer Centre, Calgary, Alberta. Ethical approval was obtained from the ethics review boards of the Alberta Cancer Board, the University of Calgary, and all participants provided a signed informed consent.

### Laboratory assays

All assays were carried out at the laboratory of one of the authors (D.C.W.L.) at the University of Calgary by a laboratory technician blinded to the case–control status of the study participants. Batches of case–control sets were constructed in a 2:1 ratio, according to the date of blood collection. Each batch included 4 quality assurance (QA) specimens: a pooled sample of clinical serum specimens from women of a similar age range to the study participants, 1 case and 1 control sample selected at random within the batch, and a case–control pooled sample. Duplicate analyses for the relevant biological metabolic syndrome components were conducted using colorimetric or absorbance-based assays (ELISA) specific to the metabolic syndrome component. Analyses for HDL- and low-density lipoprotein (LDL) cholesterol (K614; BioAssay Systems), triglycerides (10010303; BioAssay Systems), and glucose (10009582; BioAssay Systems) were completed from serum with the exception of 9 samples that were analyzed from plasma because of unavailable serum. Three sets were run per assay plate. The mean intra- and interbatch coefficients of variation (%CVs) for HDL cholesterol were 4.3% and 5.5%, for triglycerides were 1.9% and 3.5%, and for fasting glucose were 3.7% and 4.6%. Total cholesterol was determined from HDL and LDL cholesterol according to the Friedewald standardized formula [total cholesterol = HDL-C + LDL-C + (triglycerides/5); ref. 22].

We also analyzed the blood samples for adiponectin (47-ADPHU-E01; ALPCO Diagnostics), leptin (11-LEPHU-E01; ALPCO Diagnostics), and insulin (HI-11K; LINCO Research) from serum at the same laboratory. The intra- and interbatch %CVs for adiponectin were 4.6% and 5.6%, for leptin were 4.3% and 5.9%, and for insulin were 5.0% and 5.3%.

### Definition of metabolic syndrome

We evaluated 4 different definitions of metabolic syndrome that are currently available for clinical use that have been developed by national or international experts and for which we had the appropriate data: (i) the National Cholesterol Education Program (NCEP)-Adult

Treatment Panel III (10); (ii) the International Diabetes Federation (IDF; ref. 11); (iii) Harmonized metabolic syndrome guidelines (12); and (iv) a modified IDF definition that we created by changing waist circumference cut-point from 80 to 88 cm to align more closely with the definition of abdominal obesity used for North American Caucasian populations (12). The harmonized guidelines define presence of metabolic syndrome as having  $\geq 3$  of the following risk factors: waist circumference  $\geq 88$  cm, triglycerides  $\geq 150$  mg/dL, HDL cholesterol  $< 50$  mg/dL, systolic blood pressure (BP)  $\geq 130$  or diastolic BP  $\geq 85$  mm Hg, or treatment of previously diagnosed hypertension, and fasting plasma glucose  $\geq 100$  mg/dL (12). We classified women as hypertensive in our study if they self-reported having a past or present hypertension diagnosis and taking hypertension medications.

### Statistical analysis

We used unconditional logistic regression to estimate ORs and 95% CIs for developing endometrial cancer in association with presence of metabolic syndrome and individual biological metabolic syndrome components. The individual biological metabolic syndrome components were modeled as meeting the respective cut-point according to the harmonized definition. In the multivariate models, we adjusted for potential confounders selected a priori from the literature and those that introduced more than 15% difference in the point estimate or contributed significantly to the model. We considered the following factors as potential confounders because of important differences observed between cases and controls in univariate analyses: age (years), parity (0 vs. 1–2,  $> 2$  pregnancies  $\geq 20$  weeks gestation), education (high school diploma, non-University certificate, and University degree), age at menarche (years), hormone therapy use type (estrogen, estrogen + progestin, and other hormone therapy), age at menopause (years), history of Type 2 diabetes (ever vs. never), hormone contraception (including both oral and nonoral hormone contraception by shots and implants) use (ever vs. never), history of angina (ever vs. never), history of stroke (ever vs. never), history of thrombosis (ever vs. never), residential status (urban vs. rural), physical activity (MET-hours per week per year), smoking history (ever vs. never), type of smoker (smoker, ex-smoker, and current smoker), and alcohol consumption (grams of ethanol per year over lifetime). Of these factors, age, age at menarche, parity, and hormone therapy use type were included in the final models. For the individual biological components of metabolic syndrome, we also mutually adjusted the components for the other metabolic syndrome components. In addition, the IDF recognizes a number of other parameters including insulin (pmol/mL), adiponectin ( $\mu\text{g/mL}$ ), leptin (ng/mL), TNF- $\alpha$  (pg/mL), C-reactive protein (CRP;  $\mu\text{g/mL}$ ), and interleukin-6 (IL-6; pg/mL) as potentially being related to the metabolic syndrome. They recommend that these factors also be considered in research studies as "platinum standard" components of the meta-

bolic syndrome (11). We, therefore, also included an assessment of the importance of these factors as potential covariates in our models.

We assessed effect modification by age at menarche (years), hormone contraceptive use (ever vs. never), age (years), hormone therapy use combined with menopausal status (peri/postmenopausal/no hormone therapy vs. peri/postmenopausal + estrogen; peri/postmenopausal + estrogen + progestin; peri/postmenopausal + other menopausal hormone therapy; premenopausal), and menopausal status (pre-/peri- vs. postmenopausal) alone. Women were classified as premenopausal if they were menstruating, pregnant, lactating, or self-identified as premenopausal and menstruating within 6 months of diagnosis/reference date. They were categorized as perimenopausal if they self-reported that they were "going through the change of life" at their diagnosis/reference date with the last menstrual period less than 12 months before diagnosis/reference date, were aged 40 to 49 years and using menopausal hormones, or 50 to 59 years and using menopausal hormones for less than 2 years. They were classified as postmenopausal if they were aged 60 or older or self-identified as postmenopausal with the last menstrual period 12 or more months before diagnosis/reference date, or 50 to 59 years and using menopausal hormones for 2 or more years, or unknown. Of these, menopausal status was found to be an effect modifier for metabolic syndrome, given the statistically significant interaction between metabolic syndrome and menopausal status ( $P = 0.031$ ). Although body mass index (BMI) was not a statistically significant effect modifier ( $P = 0.500$ ), we did stratify the results by BMI to examine the role of obesity in the association between metabolic syndrome and endometrial cancer. We chose not to adjust our models for BMI a priori to avoid over adjustment for the very effect of interest but rather examined models stratified by BMI to observe the influence of this strong risk factor for endometrial cancer on its association with metabolic syndrome.

Final model fit was assessed using the Hosmer–Lemeshow goodness of fit test (23). All statistical analyses were done using Stata software version 10.1 (StataCorp).

### Results

As previously reported (20), our study population was 58 years old on average at the time of interview, mainly married (96%), Caucasian (96%), well educated (74% had greater than high school education), and postmenopausal (74%). They were generally physically inactive, low alcohol consumers, and half were nonsmokers ( $< 100$  cigarettes smoked in their lifetimes). For this study, we present the participant characteristics by menopausal status (Table 1). The proportions of cases with levels of triglycerides, HDL cholesterol, fasting blood glucose, and waist circumference corresponding to the cut-offs for metabolic syndrome were relatively similar between pre-/perimenopausal women and postmenopausal women.

**Table 1.** Characteristics of endometrial cancer cases and population-based controls, by menopausal status, Alberta, Canada, 2002–2006 (*n* = 1,477)

Characteristic mean (SD) or <i>n</i> (%)	Pre/Perimenopausal ( <i>n</i> = 383)		Postmenopausal ( <i>n</i> = 1,094)	
	Cases ( <i>n</i> = 121)	Controls ( <i>n</i> = 262)	Cases ( <i>n</i> = 394)	Controls ( <i>n</i> = 700)
Age, y	48.0 (6.5)	46.4 (6.5)	61.9 (7.4)	62.8 (7.2)
Pregnancies $\geq$ 20 wk gestation				
0	38 (31.4)	40 (15.3)	54 (13.7)	50 (7.1)
1–2	61 (50.4)	130 (49.6)	160 (40.6)	274 (39.1)
>2	22 (18.2)	92 (35.1)	180 (45.7)	376 (53.7)
Age at menopause, y			50.0 (4.9)	50.1 (4.1)
Ever hormone therapy use	10 (8.3)	18 (6.9)	168 (42.6)	353 (50.4)
Estrogen only	0 (0.0)	2 (0.8)	20 (5.1)	23 (3.3)
Estrogen + progestin	5 (4.1)	10 (3.8)	126 (32.0)	310 (44.3)
Other hormone therapy	5 (4.1)	6 (2.3)	22 (5.6)	20 (2.9)
Ever had Type 2 diabetes	11 (9.1)	4 (1.5)	51 (12.9)	47 (6.7)
Body mass index, kg/m <sup>2</sup>	33.51 (8.6)	27.7 (5.7)	31.9 (7.8)	28.2 (5.5)
Weight, kg	89.1 (23.7)	74.7 (16.4)	83.5 (20.8)	73.5 (15.0)
Waist circumference, cm	100.3 (18.4)	85.8 (14.5)	97.1 (18.9)	87.9 (14.4)
Waist circumference $\geq$ 88 cm	85 (70.8)	98 (37.7)	260 (66.5)	313 (44.8)
Triglyceride, mg/dL	152.2 (99.1)	106.8 (70.4)	144.9 (97.9)	126.6 (83.0)
Triglyceride $\geq$ 150 mg/dL	44 (36.4)	46 (17.6)	136 (34.8)	181 (26.0)
HDL cholesterol, mg/dL	35.3 (12.7)	39.4 (12.9)	38.0 (12.8)	40.3 (13.1)
HDL cholesterol <50 mg/dL	109 (90.1)	208 (79.4)	331 (84.0)	557 (79.6)
Ever diagnosed and treated for hypertension	18 (14.9)	18 (6.9)	144 (36.6)	154 (22.0)
Fasting glucose, mg/dL	123.3 (45.3)	109.1 (37.6)	122.3 (43.0)	115.8 (46.1)
Fasting glucose $\geq$ 100 mg/dL	77 (63.6)	130 (49.6)	258 (65.5)	400 (57.1)
Insulin, pmol/L per mL	65.0 (55.6)	39.3 (30.5)	57.2 (45.0)	40.0 (28.7)
Adiponectin, $\mu$ g/mL	10.1 (5.1)	13.8 (7.4)	14.5 (8.5)	18.1 (9.5)
Leptin, ng/mL	56.6 (42.8)	34.8 (25.5)	52.9 (38.4)	38.6 (30.4)

The proportion of women with a history of hypertension or diabetes was highest among postmenopausal cases (37% and 13%, respectively).

We compared the proportion of participants having metabolic syndrome according to these 4 definitions and the results did not differ appreciably; the kappa interrater agreement was 89.5% between harmonized and IDF, 96.6% between harmonized and ATP III, and 86.6% between IDF and ATP III, 93.3% between harmonized and the modified IDF, 88.3% between IDF and modified IDF and 91.6% between ATP III and the modified IDF. The prevalence of metabolic syndrome in our population ranged from 40% to 51% overall, with a higher range in proportion of 56% to 66% among endometrial cancer cases (Table 2). The proportion of women with metabolic syndrome as defined by the harmonized guidelines was significantly greater among cases (62%) than controls (38%) and was associated with a 2.5-fold increase in endometrial cancer risk (multivariable-adjusted OR = 2.58; 95% CI: 2.05–3.24; Table 3). This increase in risk was attenuated to a 50% increase but remained statistically significant with adjustment for adiponectin, leptin, and insulin (multivariable-adjusted OR = 1.53; 95% CI: 1.17–2.00; Table 3). The magnitude of the risk increase was

similar with the other definitions of metabolic syndrome that were considered, with statistically significant ORs ranging from 2.41 to 2.77 for the more parsimonious multivariable model and 1.46 to 1.66 for the multivariable model that included adiponectin, leptin, and insulin as covariates (Table 3). Endometrial cancer risk also increased with most of the individual components of the metabolic syndrome, including a waist circumference  $\geq$ 88 cm (multivariable-adjusted OR = 2.24; 95% CI: 1.75–2.87; OR = 1.57; 95% CI: 1.18–2.08), ever being diagnosed and treated for hypertension (multivariable-adjusted OR = 1.75; 95% CI: 1.32–2.32; 1.57; 95% CI: 1.18–2.09), and having an impaired fasting blood glucose level  $\geq$ 100 mg/dL (multivariable-adjusted OR = 1.39; 95% CI: 1.09–1.76; OR = 1.31; 95% CI: 1.03–1.67; Table 3).

Endometrial cancer risk associated with the metabolic exposures examined was modified by menopausal status (Table 4). Among the 1,094 postmenopausal women in our study, risk remained significantly elevated with metabolic syndrome according to the harmonized definition (multivariable-adjusted OR = 1.61; 95% CI: 1.18–2.21). Within the postmenopausal group, risk also increased with individual components, including a waist circumference  $\geq$ 88 cm (multivariable-adjusted OR = 2.01; 95% CI: 1.51–2.68),

**Table 2.** Proportion of metabolic syndrome by definition and menopausal status, case-control study of endometrial cancer, Alberta, Canada

Definition risk factors	Metabolic syndrome definition		
	Harmonized (n = 1,477)	ATP III (n = 1,476)	IDF (n = 1,467)
Waist circumference	≥88 cm (population and country specific definition)	≥88 cm	≥80 cm (women of Europids ethnic group)
Triglyceride levels	≥150 mg/dL	≥150 mg/dL	≥150 mg/dL
HDL cholesterol	<50 mg/dL	<50 mg/dL	<50 mg/dL
Blood pressure or hypertension	Systolic BP ≥130 or diastolic BP ≥85 mm Hg or treatment of previously diagnosed hypertension	Systolic BP ≥130 or diastolic BP ≥85 mm Hg	Systolic BP ≥130 or diastolic BP ≥85 mm Hg or treatment of previously diagnosed hypertension
Fasting glucose	≥100 mg/dL	≥110 mg/dL	≥100 mg/dL or previously diagnosed type 2 diabetes
Number of criteria	3 or more of the above	3 or more of the above	WC necessary and any 2 of the above
Menopausal status <sup>a</sup>			
Pre/peri			
Cases	73 (60.3)	69 (57.0)	80 (66.7)
Controls	71 (27.1)	64 (24.4)	94 (36.1)
Total	144 (37.6)	133 (34.7)	174 (45.8)
Post			
Cases	245 (62.2)	229 (58.3)	255 (65.2)
Controls	296 (42.3)	272 (38.9)	323 (46.4)
Total	541 (49.4)	501 (45.8)	578 (53.2)
Total			
Cases	318 (61.7)	298 (58.0)	335 (65.6)
Controls	367 (38.1)	336 (34.9)	417 (43.6)
Total	685 (46.4)	634 (42.9)	752 (51.3)

<sup>a</sup>Sample size for each stratum reflects the harmonized definition.

**Table 3.** Age-adjusted and multivariable ORs and 95% CIs for risk of endometrial cancer with individual components of the metabolic syndrome and metabolic syndrome defined according to harmonized guidelines (2009; *n* = 1,477)

Component	Cases ( <i>n</i> = 515)	Controls ( <i>n</i> = 962)	Age-adjusted <sup>a</sup> OR (95% CI)	Multivariable <sup>b</sup> OR (95% CI)	Multivariable <sup>c</sup> OR (95% CI)
Waist circumference $\geq 88$ cm <sup>d</sup>	343	411	2.32 (1.82–2.96)	2.24 (1.75–2.87)	1.57 (1.18–2.08)
Triglyceride $\geq 150$ mg/dL <sup>e</sup>	179	227	1.19 (0.92–1.54)	1.23 (0.94–1.60)	0.97 (0.74–1.29)
High-density lipoprotein $< 50$ mg/dL	434	757	1.06 (0.78–1.46)	1.07 (0.78–1.47)	0.92 (0.66–1.27)
Ever diagnosed and treated for hypertension	158	169	1.74 (1.32–2.29)	1.75 (1.32–2.32)	1.57 (1.18–2.09)
Fasting blood glucose $\geq 100$ mg/dL	331	527	1.43 (1.13–1.81)	1.39 (1.09–1.76)	1.31 (1.03–1.67)
Metabolic syndrome (harmonized)	318	367	2.62 (2.10–3.27)	2.58 (2.05–3.24)	1.53 (1.17–2.00)
Metabolic syndrome (IDF)	335	417	2.45 (1.96–3.07)	2.41 (1.92–3.04)	1.46 (1.12–1.90)
Metabolic syndrome (ATP III)	298	336	2.58 (2.07–3.22)	2.56 (2.04–3.21)	1.56 (1.20–2.03)
Metabolic syndrome (modified IDF)	285	296	2.82 (2.26–3.53)	2.77 (2.21–3.49)	1.66 (1.26–2.19)

<sup>a</sup>Adjusted for age ( $\gamma$ ), age<sup>2</sup> ( $\gamma^2$ ).<sup>b</sup>The individual components of the metabolic syndrome have been mutually adjusted, age at menarche (years), number of pregnancies  $\geq 20$  wks gestation (0, 1, and  $> 1$ ), type of hormone therapy (estrogen + progestin, and other HT).<sup>c</sup>Additionally adjusted for adiponectin ( $\mu\text{g/mL}$ ), insulin (pmol/L per mL), leptin (ng/mL).<sup>d</sup>Waist circumference missing for 4 cases, 4 controls.<sup>e</sup>Triglycerides missing for 3 cases, 4 controls.

ever having hypertension (multivariable-adjusted OR = 1.89; 95% CI: 1.40–2.55), and fasting blood glucose  $\geq 100$  mg/dL (multivariable-adjusted OR = 1.35; 95% CI: 1.02–1.77). Among pre-/perimenopausal women, a stronger nearly 2-fold increased risk (multivariable-adjusted OR = 1.96; 95% CI: 1.09–3.50) and a nearly 3-fold increased risk (OR = 2.98; 95% CI: 1.77–5.03) were found with metabolic syndrome and having a waist circumference  $\geq 88$  cm, respectively.

We stratified our results by BMI to assess the influence of obesity, a strong risk factor for endometrial cancer, on the associations with metabolic syndrome and individual metabolic components (Table 5). Although we did not find statistical evidence for interaction by BMI, we observed that risk was elevated with presence of metabolic syndrome across all BMI categories but became statistically nonsignificant among normal-weight women (multivariable OR = 1.84; 95% CI: 0.92–3.67). Although limited by sample size, the most pronounced finding from these stratified results revealed a 5-fold increased risk among normal-weight women with a waist circumference  $\geq 88$  cm.

## Discussion

In this comprehensive population-based case-control study of Alberta women, we found statistically significant 1.5- to nearly 3-fold increased risks of endometrial cancer with all metabolic syndrome definitions examined. We also observed evidence for increased risk of endometrial cancer associated with metabolic syndrome components, including having a higher waist circumference  $\geq 88$  cm, ever being diagnosed and treated for hypertension, and having an elevated fasting blood glucose level ( $\geq 100$  mg/dL).

Metabolic syndrome was originally recognized as a cluster of risk factors that better predicted cardiovascular disease and diabetes incidence, than simple BMI or obesity measures (24). Whereas excess weight substantially increases risk, not all overweight/obese people manifest these diseases, although a proportion of normal-weight people do. Excess weight is an established risk factor for endometrial cancer, however, although studies have suggested a relation between individual components of metabolic syndrome and endometrial cancer, very little research has been conducted to determine whether metabolic syndrome better predicts endometrial cancer risk than weight (25), diabetes (6, 7), hypertension (8, 9), dyslipidemia, or dysglycemia alone (14–18, 26, 27). In this study, we were also able to examine 4 different definitions of metabolic syndrome that were all associated with an elevated endometrial cancer risk. The largest increased risk was for the modified IDF definition that used a more appropriate cut-point for central adiposity (a waist circumference of 88 rather than 80 cm) for this study population and, in so doing, recognized the importance of elevated waist circumference as a key endometrial cancer risk factor.

**Table 4.** Age-adjusted and multivariable ORs and 95% CI for risk of endometrial cancer with individual components of the metabolic syndrome and metabolic syndrome defined according to harmonized guidelines, by menopausal status (*n* = 1,477)

Component <sup>a</sup>	Pre/perimenopausal ( <i>n</i> = 383)				Postmenopausal ( <i>n</i> = 1,094)			
	Cases <sup>a</sup>	Controls	Age adjusted OR (95% CI)	Multivariable <sup>b</sup> OR (95% CI)	Cases	Controls	Age-adjusted OR (95% CI)	Multivariable <sup>c</sup> OR (95% CI)
Waist circumference $\geq 88$ cm <sup>d</sup>	35	162	3.22 (1.95–5.32)	2.98 (1.77–5.03)	260	313	2.08 (1.57–2.74)	2.01 (1.51–2.68)
Ever diagnosed and treated for hypertension	18	18	1.11 (0.51–2.39)	0.87 (0.39–1.96)	144	154	1.87 (1.39–2.51)	1.89 (1.40–2.55)
Triglyceride $\geq 150$ mg/dL <sup>e</sup>	44	46	1.60 (0.91–2.79)	1.77 (0.98–3.20)	136	181	1.11 (0.83–1.49)	1.15 (0.85–1.55)
High-density lipoprotein $< 50$ mg/dL	109	208	1.39 (0.67–2.87)	1.56 (0.74–3.28)	331	557	1.00 (0.70–1.42)	0.95 (0.67–1.37)
Fasting plasma glucose $\geq 100$ mg/dL	77	130	1.48 (0.92–2.38)	1.54 (0.93–2.53)	258	400	1.41 (1.07–1.84)	1.35 (1.02–1.77)
Metabolic syndrome <sup>f</sup> (harmonized)	73	71	4.03 (2.55–6.36)	1.96 (1.09–3.50)	245	296	2.29 (1.77–2.95)	1.39 (1.03–1.89)

<sup>a</sup>All models for MetS components were mutually adjusted. Some individuals have missing values: Pre/perimenopausal 3 missing (*n* = 380); postmenopausal 12 missing (*n* = 1,082). Total *N* = 1,462.

<sup>b</sup>Adjusted for age (*y*), age at menarche (*y*), number of pregnancies  $\geq 20$  wks gestation (0, 1–2, and  $>2$ ).

<sup>c</sup>Additionally adjusted for type of hormone replacement therapy (estrogen, estrogen + progestin, and other HT).

<sup>d</sup>Waist circumference missing for 1 case, 1 control in premenopausal category; 1 control in perimenopausal category; 3 cases, 2 controls in postmenopausal category.

<sup>e</sup>Triglycerides missing for 3 cases, 4 controls in postmenopausal category.

<sup>f</sup>MetS (harmonized) additionally adjusted for adiponectin ( $\mu\text{g/mL}$ ), insulin ( $\text{pmol/L}$  per mL), leptin ( $\text{ng/mL}$ ) in the multivariable-adjusted model.

**Table 5.** Age-adjusted and multivariable ORs and 95% CIs for risk of endometrial cancer with metabolic syndrome defined according to harmonized guidelines, by BMI ( $n = 1,477$ )

Component <sup>b</sup>	BMI <25 ( $n = 406^a$ )			BMI 25–29.9 ( $n = 490^a$ )			BMI > 30 ( $n = 579^a$ )		
	Cases	Controls	Multivariable <sup>c</sup> OR (95% CI)	Cases	Controls	Multivariable <sup>c</sup> OR (95% CI)	Cases	Controls	Multivariable <sup>c</sup> OR (95% CI)
Waist circumference > 88 cm <sup>d</sup>	6	3	5.09 (1.04–24.95)	69	133	1.69 (1.11–2.59)	270	274	1.17 (0.50–2.74)
Ever diagnosed and treated for hypertension	13	28	1.51 (0.70–3.23)	35	55	1.90 (1.11–3.22)	114	89	1.77 (1.20–2.60)
Triglyceride >150 mg/dL <sup>e</sup>	17	33	1.44 (0.69–2.98)	40	80	1.16 (0.71–1.88)	123	113	1.14 (0.79–1.64)
High-density lipoprotein <50 mg/dL	64	213	0.89 (0.52–1.52)	115	291	1.05 (0.59–1.86)	261	260	1.29 (0.70–2.36)
Fasting plasma glucose >100 mg/dL	55	162	1.25 (0.76–2.06)	136	354	1.22 (0.79–1.88)	285	294	1.55 (1.07–2.24)
Metabolic syndrome (harmonized) <sup>f</sup>	17	29	1.84 (0.92–3.67)	68	125	2.04 (1.33–3.11)	233	212	1.71 (1.13–2.58)

<sup>a</sup>Sample size based on metabolic syndrome (harmonized), sample size BMI < 25,  $n = 405$ , BMI 25–29.9,  $n = 486$  and BMI > 30,  $n = 570$  for individual components.

<sup>b</sup>All models for MetS components were mutually adjusted. Some individuals have missing values: Pre/perimenopausal 3 missing ( $n = 380$ ); Postmenopausal 12 missing ( $n = 1,082$ ). Total  $N = 1,461$ .

<sup>c</sup>Adjusted for age ( $\gamma$ ), age<sup>2</sup> ( $\gamma^2$ ), age at menarche ( $\gamma$ ), number of pregnancies > 20 weeks gestation (0, 1–2, and >2), type of hormone replacement therapy (estrogen, estrogen + progestin, and other HT).

<sup>d</sup>Waist circumference missing 1 case, 1 control in premenopausal category, 1 control in perimenopausal category; 3 cases and 2 controls in postmenopausal category.

<sup>e</sup>Triglycerides missing 3 cases, 4 controls in postmenopausal category.

<sup>f</sup>MetS (harmonized) additionally adjusted for adiponectin ( $\mu\text{g/mL}$ ), insulin ( $\text{pmol/mL}$ ), leptin ( $\text{ng/mL}$ ).



The most recent Canadian estimates for the prevalence of metabolic syndrome are from the Canadian Heart Health Surveys (1986–1992) that included 18,945 adult participants 20 to 74 years of age. In these surveys, the prevalence of metabolic syndrome was estimated as 13.8% among women in Western Canada, ranging from 12.2% in urban settings to 18.7% in rural areas (28). United States estimates of metabolic syndrome from the National Health and Nutrition Examination Surveys are 30.6% among women 40 to 59 years that increased to 46.1% for those 60 or more years of age, respectively (29). Given the older age range of our study participants, higher average BMI levels, and the established increased risk for endometrial cancer associated with obesity, diabetes, and hypertension, the higher prevalence of metabolic syndrome of 39.5% to 51.3% observed in our study population compared with national estimates for Canada was expected, and it is closer to United States estimates for this age group.

Metabolic syndrome as a cluster of risk factors has only been assessed with regard to endometrial cancer risk in 5 previous studies (16–19, 30). The largest study conducted by Bjorge and colleagues (16) included 917 endometrial cancer cases from a total of 287,320 participants pooled from 7 European cohorts, with an average follow-up of 10 years. These investigators found a statistically significant 37% increased risk per unit increase in metabolic syndrome score, constructed by adding individual z-scores computed for BMI, blood pressure, glucose, cholesterol, and triglycerides, standardized separately for subcohorts and for fasting time (16). A nested case-control study within the EPIC cohort (17) concluded that metabolic syndrome was directly associated with endometrial cancer, with an approximate doubling in risk observed depending on which definition of metabolic syndrome was used [relative risk (RR) = 1.68; 95% CI: 1.23–2.31 for the IDF definition and OR = 2.12; 95% CI: 1.51–2.97 for the NCEP definition]. The EPIC study investigators also observed that endometrial cancer risk increased with a higher number of metabolic syndrome factors present (3 factors present OR = 2.57; 95% CI: 1.52–4.32, 4 or 5 factors present OR = 2.95; 95% CI: 1.60–5.45;  $P_{\text{trend}} < 0.0001$ ; ref. 17). A hospital-based case-control study from Italy revealed that the metabolic syndrome definition most strongly associated with endometrial cancer included a BMI  $>30$  kg/m<sup>2</sup> and at least 2 of hypertension, diabetes, and hyperlipidemia (OR = 8.40; 95% CI: 3.95–17.87; ref. 18). This risk was 2.37 (95% CI: 1.59–3.53) for the other 3 metabolic syndrome components when obesity was excluded from the metabolic syndrome definition. This Italian study also found a significant trend in risk with increasing number of components for all metabolic syndrome definitions examined (18). One small study from China found that central obesity, higher triglycerides, lower HDL-C, and abnormal plasma glucose were independent risk factors for endometrial cancer, in addition to metabolic syndrome (19). Lastly, a study in Norway by Furberg and Thune found

a nearly 2-fold nonstatistically significant elevated risk with a cluster of metabolic abnormalities, although they excluded obesity from their metabolic syndrome definition (14).

The link between higher endometrial cancer risk and central adiposity, history of hypertension, and history of diabetes as single risk factors has been well established (9). A limited number of studies have also examined the association between risk of endometrial cancer and levels of blood glucose or blood lipids individually, including several cohort (14, 16, 17, 26) and case-control studies (15, 18, 27). Most of these studies were limited in that the blood samples collected were nonfasting. Among these studies, the most consistent finding has been an elevated risk of endometrial cancer with higher levels of triglycerides (15, 16, 26) and high blood glucose levels (14–16). The increased risks with elevated triglycerides have been in the order of 25% to 230% (15, 16, 26). When adjusted for BMI, the association with triglycerides is often attenuated (16, 26), suggesting that a large part of this association is mediated by obesity. The increased risks with high glucose were in the order of 41% to 245%, when examined by increasing quintile or quartile (14, 16), and nearly 400% for those whose levels exceeded 6.1 mmol/L versus those whose level did not exceed 6.1 mmol/L (15). Studies of serum cholesterol have shown mixed results (15, 26, 27, 31–34). One study found a nonsignificant elevation in risk with higher serum cholesterol levels, but only for cancers diagnosed within 2 years of follow-up after serum cholesterol determination, and no association for cancers diagnosed after 2 years (31). Among other studies, some showed an increased risk (15, 33), no association (17, 26, 34, 35), and an inverse association (14, 27, 32). In summary, glucose, triglycerides, and hypertension have thus far been found to be the primary important contributors to increased risk for endometrial cancer among the individual metabolic syndrome components (14, 16, 19, 26). Our study results are consistent with previous associations observed for history of hypertension and elevated blood glucose.

Among postmenopausal women, we observed a 60% to 230% elevated endometrial cancer risk with metabolic syndrome, and the associations remained statistically significantly elevated for higher waist circumference, hypertension, and impaired fasting blood glucose. Meanwhile, among premenopausal women, the strong 4-fold increased risk that was attenuated to a 2-fold increase after adjustment for adiponectin, leptin, and insulin seemed to be driven by having a higher waist circumference, as risks for other components were not statistically significant. Our results suggest that metabolic syndrome influences endometrial cancer risk in the premenopausal stage, and this risk carries through to postmenopause, particularly as women accumulate unhealthy levels of metabolic markers with age beyond an increased waist circumference. The NHANES III study of 3,240 women showed that in older women

having elevated glucose as one of the metabolic syndrome components was strongly associated with risk of all cause mortality (36).

After menopause, adipose tissue is the primary source of endogenous estrogen; hence, the relative influence of blood cholesterol on estrogen bioavailability may be greater. A 2-fold association (OR = 2.06; 95% CI: 1.1–4.0;  $P_{\text{trend}} = 0.01$ ) for blood cholesterol levels with endometrial cancer risk found in a hospital-based case-control study (27) became 4-fold (OR = 4.15; 95% CI: 1.8–9.7;  $P_{\text{trend}} = 0.002$ ) among older women 55 or more years of age, suggesting that the influence of cholesterol is more influential after menopause. An analysis of LDL cholesterol in this study revealed no association overall but a 3-fold increase in risk among these older women (OR = 3.06; 95% CI: 1.3–7.0;  $P_{\text{trend}} = 0.01$ ; ref. 27). We did not, however, find any association with HDL cholesterol in our study, overall or by menopausal status, but this result could be attributable to the subfraction of HDL of cholesterol examined.

Epidemiologic studies have investigated obesity, adiposity, body fat distribution, and endometrial cancer risk (13, 35, 37–61). The association with overall obesity and adiposity is classified as "convincing" (25), with relative risks ranging from 2 to 10. Although the association with body fat distribution is less consistent (43–46, 48, 50, 51, 54, 58), there is sufficient evidence to suggest that central adiposity is also an important predictor of risk. The importance of body fat distribution was further highlighted in our BMI-stratified analysis. As BMI and waist circumference are closely related measures, one reflecting body size and the other body fat distribution, classification of individuals in our study on elevated BMI in many cases produced the same groupings as for elevated waist circumference. We observed elevated endometrial cancer risk with presence of metabolic syndrome across all BMI categories, but the increased risks became nonstatistically significant among normal-weight women. The most pronounced elevation in risk, although limited by sample size, was a 5-fold increase in risk for women who were normal weight according to BMI (BMI <25) but had abdominal obesity.

This existing study population provided a unique resource for examining the association between metabolic syndrome and metabolic components and endometrial cancer. Strengths of our study include the relatively large case population, very detailed prediagnosis epidemiologic data on endometrial cancer risk factors, the direct anthropometric measurements that were taken in person, comprehensive examination of covariates including insulin, leptin, and adiponectin levels, and the ability to examine metabolic syndrome as a cluster of risk factors according to international definitions. We obtained a minimum 8-hour fasting blood samples in our study, with relatively high response to blood sampling; therefore, the blood results for triglycerides, glucose and total cholesterol, and HDL-C are reliable and were not influenced by recent food intake. Some limitations should be considered when evaluating our results. It is acknowledged that the

presence of disease during blood sampling may have influenced levels of serum lipids from tumor effects. Single blood sample measurements may not fully reflect long-term circulating levels, and there may be considerable biological variation, even in fasting samples, for markers such as triglycerides, cholesterol, and glucose. Blood samples were analyzed within 2 to 5 years of initial storage, some concentrations of metabolic syndrome markers could degrade over time, but there is little reason to believe that results could be affected considerably by long-term storage. Our low control response rate in this study has been previously reported and was addressed by comparing our sample with a sample of Alberta women from the Canadian Community Health Survey Cycle 2.2 to evaluate possible selection bias. The results of that comparison found that the control group was somewhat more educated but otherwise similar to the base population (20) on variables such as age, height, weight, and BMI.

In conclusion, our study provides strong evidence for a role of the metabolic syndrome in endometrial cancer risk. Endometrial cancer risk increases with presence of metabolic syndrome, and the association with obesity and central adiposity plays a considerable role in this association, particularly for premenopausal women. Recommendations to reduce endometrial cancer should continue to encourage women to maintain a healthy weight, particularly reducing abdominal adiposity and should include targeting metabolic syndrome as an earlier indicator of risk.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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