Research Article

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Metabolic Syndrome and Risk of Endometrial Cancer in the United States: A Study in the SEER–Medicare Linked Database

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Abstract

Background: Metabolic syndrome and its component feature, central obesity, are associated with endometrial cancer risk. It remains unclear whether associations with the other metabolic factors that comprise metabolic syndrome are independent of the obesity–endometrial cancer association. Furthermore, the link with specific endometrial cancer subtypes remains ill-defined, despite evidence of etiologic heterogeneity among these tumors.

Methods: In a case–control study within the SEER–Medicare linked database, we examined whether metabolic factors, individually or combined, were associated with endometrial cancer. Cases ($n = 16{,}323$) were women diagnosed with endometrial cancer from 1993 through 2007. Controls ($n = 100{,}751$) were a 5% sample of female Medicare enrollees residing in the same SEER registry area as cases. Metabolic syndrome was defined using ICD-9-CM codes from inpatient/outpatient diagnoses 1 to 3 years before case diagnosis and a comparable time period in controls. ORs and 95% confidence intervals (CI) were estimated using logistic regression.

Results: Endometrial cancer risk was associated with metabolic syndrome [OR (95% CI): 1.39 (1.32–1.47)] and its component factors: overweight/obesity [1.95 (1.80–2.11)], impaired fasting glucose [1.36 (1.30–1.43)], high blood pressure [1.31 (1.25–1.36)], and high triglycerides [1.13 (1.08–1.18)]. After adjusting for overweight/obesity, the increased risks associated with the metabolic syndrome factors remained. Heterogeneity of associations by subtype were not identified ($P_{\text{heterogeneity}} = 0.82$).

Conclusions: Among women age 65 and older in the United States, metabolic syndrome, and its component factors, increased endometrial cancer risk similarly across endometrial cancer subtypes.

Impact: Strategies to reduce the prevalence of metabolic syndrome factors might have a favorable effect on endometrial cancer incidence. *Cancer Epidemiol Biomarkers Prev; 24(1); 261–7. ©2015 AACR.*

Introduction

Endometrial cancer is the most common cancer of the female reproductive tract and the fourth most common cancer in women in the developed world (1). Adult overweight/obesity is one of the strongest risk factors for endometrial cancer (2–6), accounting for approximately 40% of endometrial cancer incidence in developed countries (2). As many as 60% of obese women suffer from related health problems including hypertension, insulin resistance, and dyslipidemia, which increases risk of endometrial cancer as well as other tumors and chronic diseases (7). The prevalence of metabolic syndrome in the United States (according to National Cholesterol Education Program/Adult Treatment Panel III criteria) has been estimated at 23% among nondiabetics in the Third National Health and Nutrition Examination Survey (NHANES; ref. 8). Evidence has begun to link metabolic syndrome to certain types of cancer (9–15). Recent reports have directly associated metabolic syndrome with endometrial cancer (16–20). Diabetes (both type I and type II) has also been related to an increased risk of endometrial cancer (5, 6). Furthermore, other metabolic risk factors, such as hypertension and hyperglycemia, have also been associated with increased endometrial cancer risk, especially among overweight and obese women (4, 6). However, it remains unclear whether endometrial cancer associations with the metabolic factors that comprise metabolic syndrome are independent of the obesity–endometrial cancer association.

Of the six studies evaluating metabolic syndrome and endometrial cancer published to date (14, 16–20), one reported results by type I and II tumors (20) and two made statements about the consistency of the associations between overall and type I tumors (17) or across type I and II tumors (16), without reporting data. Given heterogeneity in the obesity–endometrial cancer associations by subtype (3, 21–24) and the hypothesis that specific subtypes are more hormonally dependent than others (25), it is plausible that metabolic syndrome associations might also differ across endometrial cancer subtypes.

To further clarify the relationship between metabolic syndrome, its component factors, and endometrial cancer risk, we utilized data from the Surveillance, Epidemiology and End Results (SEER)–Medicare linked database, which provides information on medical conditions recorded in inpatient and outpatient encounters at the time of and preceding cancer diagnoses.

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The large size of this database allowed us to evaluate the independence of various parameters of metabolic syndrome as well as to determine whether associations varied according to the presence of obesity, one of the primary components of metabolic syndrome and the strongest risk factor for endometrial cancer to date. In addition, we were able to evaluate whether metabolic syndrome was differentially associated with risk dependent on various clinical parameters of the endometrial cancer, including histology and grade of the tumors, characteristics that have recently been shown to affect relationships with other established risk factors (21, 22, 26).

Materials and Methods

Data sources

We used the SEER–Medicare linked database to define a case–control study with cases identified via the SEER registries and information on exposure ascertained through the SEER–Medicare linked claims data. The SEER registries utilized in this study include 17 areas covering approximately 28% of the U.S. population. For each cancer case, the SEER data include month and year of diagnosis, cancer site, histology, extent of disease, initial treatment, and sociodemographic information (age, race, Hispanic ethnicity, and marital status).

The SEER–Medicare database links Medicare claims data to the SEER registry data for patients with cancer aged 65 and older and for a sample of patients without cancer. Medicare is the primary health insurer for approximately 97% of individuals aged 65 years and older in the United States. The Health Care Financing Administration (HCFA), which has a master enrollment file for all persons eligible for Medicare, collects information on all claims for inpatient hospitalizations, outpatient hospital services, physician services, and hospice care for persons with fee for service coverage. Medicare hospitalization data contain up to ten Clinical Modification of the International Classification of Diseases revision 9 (ICD-9-CM) diagnostic codes and six ICD-9 CM procedures codes. Medicare outpatient hospital services files, physician claims, and hospital files contain both ICD-9 CM diagnoses as well as Current Procedural Terminology (CPT)-4 for all billed claims. All files contain fields for dates of services. Linkage details were described elsewhere and include 94% of all patients in the SEER database (27).

Study population

Using the SEER–Medicare linked database, we identified all women with endometrial cancer (ICD-9 site 54.1 or 54.9) diagnosed from 1993 through 2007 (n = 57,892). A comparison group of noncancer controls (n = 490,674) was selected from a 5% random sample of Medicare beneficiaries residing in the geographic areas of the SEER registries. Controls were assigned an index date using a random number generator. Of these, 16,323 cases and 100,751 noncancer controls satisfied our inclusion criteria for the study. To ensure that we include both cases and controls with equivalent ascertainment of exposure information, we selected only those with continuous enrollment in Medicare parts A and B for at least the three years before cancer diagnosis or the randomly selected index date for noncancer controls. Cases and controls were excluded for the following reasons: enrollment in a Medicare HMO plan within 3 years of diagnosis or index date (n = 11,091 cases, 96,646 controls), enrollment in Medicare part A and part B for less than 3 years before diagnosis or index date (n = 27,179 cases, 194,515 controls), enrolled in Medicare for reasons other than age (n = 2,319 cases, 23,122 controls), or age at diagnosis or index date less than 65 or greater than 89 (n = 651 cases, 14,718 controls). Cases were further excluded if they had missing information on month of diagnosis (n = 178), or endometrial cancer diagnosed only from autopsy or death certificate (n = 151). Controls were also excluded if they had not lived in the geographic area of the SEER registries by their index date (n = 4,221), or if they had ever had a hysterectomy according to Medicare claims data (ICD-9-CM: 68.3-68.9; n = 26,845).

Metabolic syndrome and its component factors

The ICD-9-CM code and corresponding medical conditions that were used to define metabolic syndrome are provided in Supplementary Table S1. There was no specific ICD-9-CM code for elevated waist circumference/central adiposity before 2001, therefore a medical record indication of overweight, obesity, or morbid obesity served as a proxy for this exposure during the entire time period, and the code for central adiposity was included in this definition from 2001 to 2007. Because of the very low frequency of medical record indication of low high-density lipoprotein (HDL) cholesterol, this condition was not evaluated as an independent risk factor for endometrial cancer; it was however used as a component to define metabolic syndrome. Metabolic factors were identified between 1 and 3 years before either case diagnosis or index date for noncancer controls. We excluded diagnoses of metabolic syndrome factors in the year before diagnosis date or index date to avoid potential differential assessment of exposure resulting from an increased number of medical encounters in the year preceding cancer diagnosis.

Metabolic syndrome variables were created on the basis of two definitions. The first, as suggested by the US National Cholesterol Education Program Adult Treatment Panel III (NCEP-III), was defined as the presence of at least three of the following conditions: central adiposity/elevated waist circumference, hypertension, high triglycerides, low HDL cholesterol, and impaired fasting glucose (including type II diabetes), based on the ICD-9-CM and CPT codes summarized in Supplementary Table S1. The second, as described by the International Diabetes Foundation (IDF), was defined as the presence of central adiposity/elevated waist circumference plus any two of the other factors [impaired fasting glucose (including type II diabetes), hypertension, low HDL cholesterol, high triglycerides]. As mentioned above overweight/obesity as defined through the ICD-9-CM codes defined in Supplementary Table S1 served as a proxy for central adiposity/elevated weight circumference in these definitions. Furthermore, the ICD-9-CM code for "dysmetabolic syndrome" (277.7) was instituted in 2001 and this code was 100% accounted for using either categorization of metabolic syndrome (NCEP-III or IDF) and was therefore not presented.

Statistical analysis

We separately evaluated the association between metabolic syndrome and the individual components of metabolic syndrome and endometrial cancer using logistic regression analyses. The multivariable logistic regression models included the following *a priori* adjustment factors: diagnosis date (index date in noncancer controls), age (continuous), race/ethnicity (white, black, Hispanic, Asian, other/unknown), SEER registry, and tobacco use as indicated in the medical record (yes/no; defined using ICD-9-CM codes: V15.82, 305.1, 989.84). Additional adjustment

for the severity of comorbidities as captured via the Charlson comorbidity index (low, moderate, severe) did not change effect estimates and therefore was not included in the final adjusted models. We evaluated potential effect modification of the association between the individual components of metabolic syndrome and endometrial cancer by overweight/obesity using a cross-product term and further adjusted the multivariable models evaluating the individual components of metabolic syndrome for the variable overweight/obesity, to determine whether they were independently related to risk.

We evaluated the association between metabolic syndrome and its component factors with endometrial cancer subtypes by constructing separate logistic regression models comparing each case subtypes to the entire non–case-control group. Given recent studies suggesting variation in risk factors across specific histologic subtypes (21, 28), we evaluated associations separately for low grade (grade 1 and 2) endometrioid, high grade (grade 3) endometrioid, adenocarcinoma, mucinous, serous, clear cell, carcinosarcoma, sarcoma, and "other" endometrial cancer subtypes. Case-only data were used in a baseline category logistic regression model with low-grade endometrioid tumors as the reference to test for heterogeneity of the metabolic syndrome association across endometrial cancer subtypes. We report both the *P* value for heterogeneity from this model as well as the *P* value for the pairwise comparison with low-grade endometrioid tumors. We also provide analyses by type I/II tumors for comparison with prior studies.

All statistical tests were two-sided with an α of 0.05. Statistical analyses were performed using SAS version 9.2 (SAS Institute).

Results

Table 1 shows selected factors of the study population. The majority of cases and controls were white and nonsmokers. The severity of comorbidities, as captured via the Charlson comorbidity index, was similar between the two groups.

The endometrial cancer associations with individual components of metabolic syndrome as well as associations with metabolic syndrome as defined by the NCEP-III and the IDF definitions are summarized in Table 2. As mentioned previously, because of the very low frequency of medical record indication of low HDL cholesterol (<1%), this condition was not evaluated as an independent risk factor for endometrial cancer. Among noncases, the prevalence of metabolic conditions evaluated ranged from 3.4% for overweight/obesity to 63.2% for high blood pressure. The prevalence of metabolic syndrome was 9.9% among noncases using the NCEP-III definition, and 2.1% using the IDF definition.

Among the individual components of metabolic syndrome, overweight/obesity, as captured in the medical records, was

Table 1. Selected characteristics of endometrial cancer cases and controls, SEER–Medicare (1993–2007)

	Controls (*N* = 100,751)		Cases (*N* = 16,323)	
	Mean	SD	Mean	SD
Age, y	77	6.0	76	5.7
Race/ethnicity	*n*	%	*n*	%
White	87,845	87.2	14,750	90.4
Black	6,500	6.5	978	6.0
Hispanic	1,538	1.5	159	1.0
Asian	2,580	2.6	206	1.3
Other/unknown	2,288	2.3	230	1.4
Registry at diagnosis				
San Francisco	4,321	4.3	832	5.1
Connecticut	8,499	8.4	1,665	10.2
Detroit	9,592	9.5	1,756	10.8
Hawaii	1,281	1.3	169	1.0
Iowa	9,437	9.4	1,893	11.6
New Mexico	3,086	3.1	441	2.7
Seattle	6,355	6.3	1,304	8.0
Utah	2,990	3.0	563	3.4
Atlanta	4,100	4.1	549	3.4
San Jose	2,739	2.7	494	3.0
Los Angeles	7,509	7.5	1,522	9.3
Rural Georgia	342	0.3	32	0.2
Greater California	12,659	12.6	1,654	10.1
Kentucky	7,338	7.3	770	4.7
Louisiana	5,548	5.5	541	3.3
New Jersey	14,955	14.8	2,138	13.1
Tobacco use				
No	97,926	97.2	15,982	97.9
Yes	2,825	2.8	341	2.1
Charlson comorbidity score				
Low (0–2)	92,012	91.3	15,192	93.1
Moderate (3–5)	7,879	7.8	1,037	6.4
Severe (6+)	860	0.9	94	0.6

Table 2. ORs and 95% CIs for the association between metabolic syndrome and endometrial cancer, SEER–Medicare

	Noncases (*N* = 100,751) *n* (%)	All cases (*N* = 16,323) *n* (%)	OR[a] (95% CI)	Additionally adjusted for overweight/obesity OR[b] (95% CI)	Mutually adjusted model OR[c] (95% CI)
Metabolic conditions					
Overweight/obesity	3,390 (3.4)	1,107 (6.8)	1.95 (1.80–2.11)	—	1.77 (1.63–1.92)
Impaired fasting glucose	20,568 (20.4)	4,320 (26.5)	1.36 (1.30–1.43)	1.38 (1.31–1.44)	1.25 (1.19–1.31)
High blood pressure	63,703 (63.2)	11,129 (68.2)	1.31 (1.25–1.36)	1.28 (1.23–1.33)	1.21 (1.15–1.26)
Low HDL cholesterol	279 (0.3)	58 (0.4)	—	—	—
High triglycerides	30,354 (30.1)	6,155 (37.7)	1.13 (1.08–1.18)	1.11 (1.07–1.16)	1.03 (0.99–1.08)
Metabolic syndrome[d]					
NCEP-III	9,930 (9.9)	2,505 (15.3)	1.39 (1.32–1.47)	1.21 (1.14–1.29)	
IDF	2,105 (2.1)	753 (4.6)	2.03 (1.84–2.23)	1.17 (0.99–1.38)	

[a]ORs adjusted for diagnosis date, age, race/ethnicity, registry area, and tobacco use.

[b]ORs adjusted for diagnosis date, age, race/ethnicity, registry area, tobacco use, and overweight/obesity.

[c]ORs adjusted for diagnosis date, age, race/ethnicity, registry area, tobacco use, overweight/obesity, impaired fasting glucose, high blood pressure, and high triglycerides.

[d]NCEP-III: US National Cholesterol Education Program Adult Treatment Panel III defines metabolic syndrome as the presence of at least three of the following conditions: central adiposity/elevated waist circumference, hypertension, high triglycerides, low HDL cholesterol, and impaired fasting glucose; IDF: International Diabetes Foundation defines metabolic syndrome as the presence of central adiposity/elevated waist circumference plus any 2 of the other factors (impaired fasting glucose, hypertension, low HDL cholesterol, and high triglycerides).

associated with an almost doubling of endometrial cancer risk [OR: 1.95; 95% confidence interval (CI): 1.80–2.11; Table 2]. Impaired fasting glucose (OR: 1.36; 95% CI: 1.30–1.43), high blood pressure (OR: 1.31; 95% CI: 1.25–1.36), and high triglycerides (OR: 1.13; 95% CI: 1.08–1.18) were also individually associated with increased risk of endometrial cancer. The individual associations of impaired fasting glucose, high blood pressure, and high triglycerides with endometrial cancer were not significantly modified by overweight/obesity ($P_{interaction}$: 0.19, 0.48, 0.53, respectively). After adjusting for overweight/obesity, the independent associations between impaired fasting glucose (OR: 1.38; 95% CI: 1.31–1.44), high blood pressure (OR: 1.28; 95% CI: 1.23–1.33), high triglycerides (OR: 1.11; 95% CI: 1.07–1.16), and endometrial cancer risk remained. In the mutually adjusted analysis, overweight/obesity (OR: 1.77; 95% CI: 1.63–1.92), impaired fasting glucose (OR: 1.25; 95% CI: 1.19–1.31), and high blood pressure (OR: 1.21; 95% CI: 1.15–1.26), were all independently associated with endometrial cancer risk.

Metabolic syndrome, as defined by both NCEP-III and IDF criteria, was associated with an increased risk of endometrial cancer (NCEP-III OR: 1.39; 95% CI: 1.32–1.47, IDF OR: 2.03; 95% CI: 1.84–2.23). Adjustment for overweight/obesity caused a slight attenuation in the association with metabolic syndrome using the NCEP-III criteria (OR: 1.21; 95% CI: 1.14–1.29), while the endometrial cancer association with metabolic syndrome using the IDF definition was attenuated substantially (OR: 1.17; 95% CI: 0.99–1.38).

Overweight/obesity was associated with increased risk of all endometrial cancer subtypes (ORs ranged from 1.67 to 2.71; $P_{heterogeneity} = 0.82$; Table 3). Impaired fasting glucose was associated with significantly increased risks of all endometrial cancer subtypes except for mucinous carcinomas and sarcomas. However, based on the *P* value for heterogeneity there was no difference across the impaired fasting glucose–endometrial cancer subtype associations ($P_{heterogeneity} = 0.35$). Likewise, high blood pressure was associated with significantly increased risks of all endometrial cancer subtypes except for serous and "other" tumors. The high blood pressure–endometrial cancer subtype associations did not show significant heterogeneity ($P_{heterogeneity} = 0.12$). We did observe heterogeneity across cancer subtypes for high triglycerides ($P_{heterogeneity} < 0.01$), risks of low-grade endometrioid, adenocarcinoma, serous, and mucinous tumors were all increased with high triglycerides.

Metabolic syndrome, as defined by the NCEP-III criteria, was associated with increased risk for all endometrial cancer subtypes except for carcinosarcomas (OR: 1.14; 95% CI: 0.94–1.38) and sarcomas (OR: 1.34; 95% CI: 0.94–1.92). There was little evidence for heterogeneity across the metabolic syndrome–endometrial cancer subtype associations ($P_{heterogeneity} = 0.82$). Metabolic syndrome, as defined by the IDF criteria, was associated with increased risk of all endometrial cancer subtypes (ORs ranged

Table 3. ORs and 95% CIs for the association between metabolic syndrome and endometrial cancer subtype, SEER–Medicare

	Endometrioid grade 1–2 ($n = 5,516$)		Endometrioid grade 3 ($n = 1,478$)		Adenocarcinoma ($n = 5,219$)		
	n (%)	OR[a] (95% CI)	*n* (%)	OR[a] (95% CI)	*n* (%)	OR[a] (95% CI)	
Metabolic conditions							
Overweight/obesity	435 (7.9)	2.08 (1.86–2.34)	106 (7.2)	1.93 (1.56–2.38)	277 (5.3)	1.89 (1.64–2.17)	
Impaired fasting glucose	1,551 (28.1)	1.36 (1.27–1.46)	400 (27.1)	1.28 (1.14–1.45)	1,160 (22.2)	1.33 (1.24–1.44)	
High blood pressure	3,877 (70.3)	1.33 (1.25–1.42)	1,055 (71.4)	1.37 (1.22–1.55)	3,349 (64.2)	1.40 (1.31–1.50)	
High triglycerides	2,431 (44.1)	1.20 (1.13–1.28)	608 (41.1)	1.11 (0.99–1.24)	1,558 (29.9)	1.22 (1.14–1.31)	
Metabolic syndrome[b]							
NCEP-III	987 (17.9)	1.42 (1.31–1.53)	260 (17.6)	1.40 (1.21–1.61)	561 (10.8)	1.41 (1.27–1.56)	
IDF	303 (5.5)	2.09 (1.83–2.40)	73 (4.9)	2.02 (1.57–2.59)	165 (3.2)	1.99 (1.67–2.38)	
	Serous ($n = 1,111$)		**Clear cell ($n = 291$)**		**Mucinous ($n = 206$)**		
	n (%)	OR[a] (95% CI)	*n* (%)	OR[a] (95% CI)	*n* (%)	OR[a] (95% CI)	
Metabolic conditions							
Overweight/obesity	76 (6.8)	1.85 (1.45–2.36)	17 (5.8)	1.68 (1.01–2.77)	17 (8.3)	2.71 (1.63–4.49)	
Impaired fasting glucose	336 (30.2)	1.45 (1.27–1.67)	86 (29.6)	1.39 (1.07–1.81)	48 (23.3)	1.21 (0.87–1.69)	
High blood pressure	744 (67.0)	1.12[c] (0.98–1.28)	210 (72.2)	1.42 (1.09–1.85)	149 (72.3)	1.74 (1.27–2.38)	
High triglycerides	439 (39.5)	1.19 (1.05–1.36)	104 (35.7)	1.06 (0.82–1.38)	80 (38.8)	1.42 (1.05–1.92)	
Metabolic syndrome[b]							
NCEP-III	192 (17.3)	1.41 (1.19–1.67)	50 (17.2)	1.46 (1.06–2.02)	33 (16.0)	1.69 (1.14–2.50)	
IDF	61 (5.5)	2.29 (1.74–3.01)	13 (4.5)	2.03 (1.15–3.60)	15 (7.3)	4.06[c] (2.36–6.99)	
	Carcinosarcoma ($n = 912$)		**Sarcoma ($n = 237$)**		**Other ($n = 816$)**		
	n (%)	OR[a] (95% CI)	*n* (%)	OR[a] (95% CI)	*n* (%)	OR[a] (95% CI)	*P*-het
Metabolic conditions							
Overweight/obesity	64 (7.0)	1.87 (1.43–2.45)	17 (7.2)	1.89 (1.14–3.13)	64 (7.8)	2.07 (1.58–2.71)	0.82
Impaired fasting glucose	245 (26.9)	1.20 (1.03–1.40)	59 (24.9)	1.16 (0.85–1.57)	255 (31.3)	1.43 (1.23–1.67)	0.35
High blood pressure	638 (70.0)	1.23 (1.06–1.43)	165 (69.6)	1.33 (1.00–1.78)	571 (70.0)	1.09 (0.93–1.28)	0.12
High triglycerides	311 (34.1)	0.89[c] (0.76–1.03)	84 (35.4)	0.92 (0.69–1.22)	322 (39.5)	0.93[c] (0.80–1.08)	< 0.01
Metabolic syndrome[b]							
NCEP-III	137 (15.0)	1.14 (0.94–1.38)	39 (16.5)	1.34 (0.94–1.92)	151 (18.5)	1.31 (1.08–1.58)	0.82
IDF	37 (4.1)	1.58 (1.12–2.24)	13 (5.5)	2.17 (1.22–3.85)	49 (6.0)	2.34 (1.72–3.17)	0.31

[a]ORs adjusted for diagnosis date, age, race/ethnicity, registry area, and tobacco use.

[b]NCEP-III: US National Cholesterol Education Program Adult Treatment Panel III defines metabolic syndrome as the presence of at least three of the following conditions: central adiposity/elevated waist circumference, hypertension, high triglycerides, low HDL cholesterol, and impaired fasting glucose; IDF: International Diabetes Foundation defines metabolic syndrome as the presence of central adiposity/elevated waist circumference plus any 2 of the other factors (impaired fasting glucose, hypertension, low HDL cholesterol, and high triglycerides).

[c]*P* <0.05 for pairwise comparison with low-grade (1 or 2) endometrioid-type tumors.

Table 4. ORs and 95% CIs for the association between metabolic syndrome and type I/II endometrial cancer, SEER–Medicare

	Type I ($n = 12,956$)		Type II ($n = 1,402$)		
	n (%)	OR[a] (95% CI)	*n* (%)	OR[a] (95% CI)	$P_{heterogeneity}$
Metabolic conditions					
Overweight/obesity	869 (6.7)	1.97 (1.81–2.15)	93 (6.6)	1.82 (1.46–2.28)	0.39
Impaired fasting glucose	3,339 (25.8)	1.36 (1.29–1.42)	422 (30.1)	1.44 (1.28–1.63)	0.27
High blood pressure	8,801 (67.9)	1.35 (1.30–1.42)	954 (68)	1.17 (1.04–1.32)	0.06
High triglycerides	4,895 (37.8)	1.17 (1.12–1.23)	543 (38.7)	1.17 (1.04–1.31)	0.83
Metabolic syndrome[b]					
NCEP-III	1,936 (14.9)	1.41 (1.32–1.50)	242 (17.3)	1.42 (1.22–1.65)	0.58
IDF	580 (4.5)	2.03 (1.83–2.26)	74 (5.3)	2.24 (1.74–2.88)	0.53

[a]ORs adjusted for diagnosis date, age, race/ethnicity, registry area, and tobacco use.

[b]NCEP-III: US National Cholesterol Education Program Adult Treatment Panel III defines metabolic syndrome as the presence of at least three of the following conditions: central adiposity/elevated waist circumference, hypertension, high triglycerides, low HDL cholesterol, and impaired fasting glucose; IDF: International Diabetes Foundation defines metabolic syndrome as the presence of central adiposity/elevated waist circumference plus any 2 of the other factors (impaired fasting glucose, hypertension, low HDL cholesterol, and high triglycerides).

from 1.58 to 4.06; $P_{heterogeneity} = 0.31$). In pairwise comparisons, the association between metabolic syndrome and mucinous tumors (OR: 4.06; 95% CI: 2.36–6.99) was significantly higher than the metabolic syndrome–low-grade endometrioid tumors association (OR: 2.09; 95% CI: 1.83–2.40, *P* value for pairwise comparison = 0.04). There was no evidence of heterogeneity in the metabolic syndrome associations across type I and II subtypes (Table 4).

Discussion

In this large population-based study of older women in the United States, we report an increased risk of endometrial cancer associated with metabolic syndrome with consistent associations across endometrial cancer histologic subtypes. Endometrial cancer was also associated with impaired fasting glucose, high blood pressure, and high triglycerides independent of the association with overweight/obesity. Given the reliance on Medicare claims data to identify metabolic syndrome and its factors, we were not able to evaluate waist circumference as an independent endometrial cancer risk factor. Among the metabolic factors evaluated, the largest increased risk was associated with the proxy variable for elevated waist circumference, namely the diagnosis codes for overweight, obesity, central adiposity, and morbid obesity that were captured in the medical records. This finding is consistent with studies that directly measured waist circumference (16, 19) or utilized measured BMI as a proxy for elevated waist circumference in their metabolic syndrome definition (17).

Metabolic syndrome has been assessed in relation to endometrial cancer in six prior studies. In a study utilizing linked pharmaceutical and cancer registry data, Russo and colleagues report an elevated, albeit not statistically significant, risk of endometrial cancer with metabolic syndrome defined on the basis of combined prescription patterns (14). In a pooled analysis of seven cohort studies in northern Europe (cohort ~290,000 women, 917 endometrial cancer cases), Bjorge and colleagues reported increased risk of endometrial cancer per unit increase in metabolic syndrome score [RR (95% CI), 1.37 (1.28–1.46)], which was calculated using the sum of *Z*-scores for measured BMI, blood pressure, glucose, total cholesterol, and triglycerides, quantified in prediagnostic specimens (primarily nonfasting; ref. 17). With the exception of total cholesterol, the individual component factors (BMI, blood pressure, glucose, and triglycerides) were positively associated with endometrial cancer risk, with associations persisting for blood pressure, glucose, and triglycerides in models adjusted for BMI (17). Furthermore, BMI and glucose remained positively associated with endometrial cancer risk in the mutually adjusted model including all five component factors (17). Bjorge and colleagues reported similar results in analyses restricted to type I tumors, but did not report additional subtype analyses (17). A nested case–control study (284 cases/546 controls) within the EPIC cohort reported a doubling in risk of endometrial cancer with metabolic syndrome using the NCEP-III criteria (OR = 2.12; IDF OR = 1.67), with the largest increased risk for component factor central obesity (waist circumference $\geq$ 88 cm; ref. 16). The remaining metabolic syndrome component factors quantified in prediagnostic specimens were not associated with increased endometrial cancer risk in the mutually adjusted model (16). Furthermore, the authors reported finding similar results across type I and II tumors (16). In a large population-based, case–control (515 cases/962 controls) study in Alberta, Canada, Friedenreich and colleagues reported an increased risk of endometrial cancer with both NCEP-III (OR = 2.56) and IDF definitions (OR = 2.77). They also observed increased endometrial cancer risk for individual components of metabolic syndrome including elevated waist circumference, hypertension, and elevated fasting glucose in models that mutually adjusted for the other metabolic syndrome components (19). However, the individual component factors were quantified in cases at the time of surgery, and therefore not independent of disease status. The remaining studies included two hospital-based case–control studies. The first, conducted in China (942 cases/1721 controls), reported an increased risk of endometrial cancer with metabolic abnormalities (defined as at least 1 of 8 metabolic abnormalities) and consistent associations across type I and II tumors (20). The second, conducted in Italy (454 cases/798 controls)reported increased endometrial cancer risk associated with metabolic syndrome defined as self-reported BMI $\geq$ 30 kg/m^2 in combination with at least 2 of 3 self-reported factors (hypertension, diabetes, and hyperlipidemia; ref. 18).

We report an increased risk of endometrial cancer associated with metabolic syndrome and its component factors with little heterogeneity in OR estimates across histologic subtypes. Our results corroborate previous studies reporting an increased risk of endometrial cancer associated with metabolic syndrome. Pooled analyses have evaluated the overweight/obese BMI–endometrial cancer association across specific histologic subtypes; however, to our knowledge, no comparable evaluation of metabolic syndrome and histologic subtype has been reported. Our study is the first to report the association between metabolic syndrome and its component factors across endometrial cancer subtypes,

with enough cases to evaluate rarer subtypes, including clear cell and mucinous tumors. We report a stronger increased risk of mucinous tumors compared with low-grade endometrioid tumors using the IDF metabolic syndrome definition, which warrants further investigation. There is some concern about potential confounding by overweight/obesity, given that the presence of other metabolic abnormalities could be directly related to obesity; however, adjusting for overweight/obesity did not substantively attenuate risk estimates for the other metabolic component factors evaluated in the current study or in other study populations (16, 19).

Study strengths include the large sample size and that SEER registries maintained 95% completeness of cases ascertainment with yearly data quality control checks. Although the SEER–Medicare data had a number of strengths, several limitations constrain the generalizability and interpretation of our results. First, the identification of metabolic factors based on Medicare claims data avoid recall bias related to self-reported measurements; however, underascertainment of certain exposures is unavoidable. Medicare files capture 100% coverage for claims, outpatient visits, and hospitalizations for patients aged 65 years and older with continuous enrollment in Medicare part A and part B; however, the prevalence of overweight, obesity, central adiposity, and tobacco use are almost certain underestimates. As a result of the underascertainment of overweight/obesity in this study, the prevalence of metabolic syndrome is also an underestimate. Furthermore, the observed difference in prevalence of NCEP-III defined metabolic syndrome compared with the prevalence of IDF defined metabolic syndrome is due to the low prevalence of overweight/obesity and it being a necessary factor in the IDF definition. The most recent estimate of the prevalence of metabolic syndrome from NHANES, based on NCEP-III criteria, reported that 56.8% of female population 60 years of age and older have metabolic syndrome (29), compared with a prevalence of 15.1% among controls in the current study during the same time period (1999–2006). Given that we excluded exposure information captured in the year before cancer diagnosis or index date, it is likely that the misclassification of exposure is nondifferential with respect to case status, with low sensitivity and high specificity, thus our observed ORs are underestimates of the expected associations. On the basis of comparisons with the other published studies using the NCEP-III and IDF criteria to define metabolic syndrome our OR estimates are comparable, albeit underestimates (19). Second, our findings are restricted to women aged 65 years and older and are not generalizable to younger populations. Third, although we attempted to exclude controls with prior hysterectomy, the reliance on medical billing likely resulted in inclusion of women with prior hysterectomy in the control group. On the basis of Behavioral Risk Factor Surveillance System data, the prevalence of obesity was shown to be higher among women with a prior hysterectomy (30); thus, inclusion of these women in the reference group likely also resulted in an underestimate of the expected association. Finally, reproductive factors, like menopausal hormone therapy use, age at menopause, and parity, were not captured in the Medicare claims data. However, adjustment for these factors in other studies did not substantively change the effect estimates (16, 19).

In summary, the results of this population-based study indicated that metabolic syndrome is a significant risk factor for endometrial cancer with consistent associations across endometrial cancer subtypes. The increased risk of mucinous endometrial cancer with metabolic syndrome as defined by the IDF criteria observed in the current study requires replication in additional study populations. Strategies to reduce the prevalence of metabolic syndrome factors might have a favorable effect on the incidence of endometrial cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: B. Trabert, N. Wentzensen
Development of methodology: B. Trabert
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): B. Trabert
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): B. Trabert, L.A. Brinton, M. Sherman, N. Wentzensen
Writing, review, and/or revision of the manuscript: B. Trabert, L.A. Brinton, A. Felix, M. Sherman, N. Wentzensen, H. Yang
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): B. Trabert
Study supervision: B. Trabert

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