



Metabolic syndrome and risk of ovarian and fallopian tube cancer in the United States: An analysis of linked SEER–Medicare data

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HIGHLIGHTS

- Metabolic syndrome was not a strong risk factor for ovarian cancer, but its component factors were associated with risk.
- High triglycerides were associated with increased risks for high-grade ovarian cancers, across histologic subtype.
- In agreement with other studies, we found high blood pressure was associated with increased risk for endometrioid tumors.

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ABSTRACT

Objective: To clarify associations between metabolic syndrome, its components, and ovarian cancer risk.

Methods: Using a case-control study within the U.S.-based Surveillance, Epidemiology and End Results (SEER)–Medicare linked database, we examined metabolic syndrome, its components (obesity, impaired fasting glucose, hypertension, HDL cholesterol, triglycerides), and ovarian/fallopian tube cancer risk. Cases ($n = 16,850$) were diagnosed with cancer between age 68–89 from 1994 through 2013. Controls ($n = 281,878$) were Medicare enrollees without these cancers living in registry areas. We estimated adjusted odds ratios (OR) and 95% confidence intervals (CI) with logistic regression.

Results: Women with metabolic syndrome had reduced ovarian cancer risk compared to women not meeting the diagnostic criteria (OR 0.86, CI 0.82–0.89). Having one or two syndrome components was associated with increased risk, but having ≥ 3 was not, when compared to women without any components. Impaired fasting glucose, which was highly prevalent among those with metabolic syndrome, was associated with reduced risk (OR 0.90, CI 0.87–0.93). Hypertension and high triglycerides, the most prevalent components among women without metabolic syndrome, were associated with increased risks (OR 1.08, CI 1.04–1.12; OR 1.05, CI 1.01–1.08, respectively).

Conclusions: Specific metabolic syndrome components may have modest associations with ovarian cancer. These associations varied in direction and the prevalence of the components influenced the overall association between metabolic syndrome and ovarian cancer. Evaluating metabolic syndrome as a composite exposure could be misleading in ovarian cancer research, but further study of the syndrome components is warranted.

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1. Introduction

Ovarian cancer is the fifth leading cause of cancer mortality among women within the United States (U.S.) and its etiology remains poorly understood [1]. Age is arguably the strongest risk predictor; as such, identifying modifiable factors associated with ovarian cancer risk would improve our etiologic knowledge and potentially reduce incidence rates.

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Almost half of women aged 60 years and older in the U.S. are estimated to have metabolic syndrome [2]. Owing to the increasing prevalence of metabolically unhealthy adults and our evolving understanding of the role of energy balance in carcinogenesis [3], it is not surprising that metabolic syndrome, the signs used to diagnose it (central adiposity/elevated waist circumference, high blood pressure, high triglycerides, low high-density lipoprotein [HDL] cholesterol, and/or impaired fasting glucose) [4], and their treatments, are garnering interest in ovarian cancer research.

Study designs, exposure assessments, and findings vary greatly across these analyses. To our knowledge, only three studies report on metabolic syndrome and ovarian cancer risk—reaching different

conclusions [5–7]. Meta-analyses indicate obesity is likely not a risk factor for postmenopausal ovarian cancer and that diabetes may confer a modest increased risk [8,9]. Many studies do not evaluate associations with metabolic syndrome components across histotypes of ovarian cancer—a considerable information gap, given our general understanding that cancer etiology is heterogeneous by subtype.

We estimated associations between metabolic syndrome, its components, and risk of ovarian or fallopian tube cancer within the U.S.-based Surveillance, Epidemiology and End Results–Medicare linked database, which links insurance claims data to state cancer registry data. Using this large data resource, we examined prospectively documented exposure information in the claims data (i.e., before diagnosis) and evaluated associations by both histotype and grade.

2. Materials and methods

2.1. Study population

We created a case-control study within the Surveillance, Epidemiology and End Results (SEER)–Medicare linked database. This database links Medicare claims data to SEER registry data for patients with cancer and includes a 5% sample of Medicare enrollees without cancer living in the SEER registry areas; data are then deidentified for research [10]. Medicare is the main health insurer for persons aged 65 years and older in the U.S.; 95% of individuals 65 and older within the SEER registry can be matched to the Medicare enrollment files [11]. The Health Care Financing Administration collects information on claims for inpatient hospitalizations, outpatient hospital services, and physician services for persons with fee for service coverage; International Classification of Diseases revision 9 (ICD-9) diagnostic codes and ICD-9 procedure codes for all billed claims are available. All files contain dates of services. SEER-Medicare data are publicly available (<https://healthcaredelivery.cancer.gov/seermedicare/>); the National Institutes of Health Office of Human Subjects Research consider analyses of SEER-Medicare data to be exempt [12].

We used data from 17 SEER registries in these analyses. Cases were women diagnosed with first primary epithelial ovarian (ICD-O-3 site C569) or fallopian tube cancer (ICD-O-3 site C570) between ages 68 to 89 from 1994 through 2013. Except where explicitly contrasted, we make collective reference to these cancers as “ovarian cancer.” For each cancer case, the SEER data include month and year of diagnosis, cancer site, histology, and sociodemographic information. From the 5% random sample of Medicare enrollees, we selected female controls who did not have ovarian or fallopian tube cancer and who resided in a SEER registry area.

Details on our exclusion criteria are provided in Supplemental Fig. 1. We required cases and controls to be enrolled in Medicare parts A and B, but not be enrolled in a health maintenance organization (HMO), for at least one year continuously, during the period two to three years before an index date: the date of diagnosis for cases, a randomly selected date for controls. Women were also excluded if they were <68 or ≥90 years old at this date and if they enrolled in Medicare for a reason other than age. Among cases, we made exclusions based on: unknown month of diagnosis, unknown diagnostic confirmation or confirmation only by death certificate, and histology (e.g., non-epithelial, non-carcinoma). The most common histologic classification for ovarian cancers was papillary serous cystadenocarcinoma (24.0%) and for fallopian tube cancers, serous tubal intraepithelial carcinoma (37.1%, not tabulated). The histotype classifications/histology codes used in this analysis are described in Supplemental Table 1. We additionally excluded controls if their index date occurred before they lived in a SEER registry area or if they had a bilateral oophorectomy documented in

Medicare claims (ICD-9 procedure codes beginning with 65.5 or 65.6). Our final analytic population comprised 16,850 cases (16,170 women with ovarian cancer and 680 with fallopian tube cancer) and 281,878 controls.

2.2. Metabolic syndrome and its components

We collected prospective information on our exposures from the Medicare data. The Medicare claims codes for the signs and diagnoses that we used to define metabolic syndrome (i.e., components) are provided in Supplemental Table 2. To avoid potential exposure detection bias due to increased physician encounters preceding a cancer diagnosis, we did not use claims codes from the two years immediately preceding the diagnosis/index dates for either cases or controls. Instead, we identified codes that were documented between two to five years before these dates. We required that women be continuously enrolled in Medicare between two and three years before the diagnosis/index dates, but most women were continuously enrolled during the entire three-year period in which we searched for claims and therefore, had three years of data available (cases $n = 13,391$, controls $n = 178,780$; Supplemental Fig. 1). We also evaluated data from women who were enrolled continuously in Medicare for only one or two years and created a variable to represent length of enrollment: only the required one-year period two-to-three years before the diagnosis/index dates; the two-year period two-to-four years before these dates; or the entire three-year period in which we searched for claims (Supplemental Fig. 1). In our statistical modeling, we then adjusted for length of enrollment.

Our primary definition for metabolic syndrome was based on the U.S. National Cholesterol Education Program Adult Treatment Panel III (NCEP-III) recommendation and required documentation of at least three of the following: central adiposity/elevated waist circumference, high blood pressure, high triglycerides, low HDL cholesterol, and/or impaired fasting glucose [4]. Any woman meeting this criterion or having a diagnosis of “dysmetabolic syndrome” (a code available after 2001), was considered to have metabolic syndrome (cases $n = 3751$; controls $n = 65,041$). We made comparisons to a reference group of women not meeting this definition (i.e., both women without any metabolic syndrome components and those with only one or two). There were 528 women classified as having metabolic syndrome because they had “dysmetabolic syndrome” documented, but not three or more metabolic syndrome components. Our results were consistent with those reported when limiting the metabolic syndrome definition to include only those meeting the NCEP-III criteria. Lastly, we also evaluated associations with the number of components documented (0/none [reference group], 1, 2, 3+).

We used codes for overweight, obesity, or morbid obesity as a proxy for central adiposity, because a code for central adiposity was unavailable before 2001; this code was additionally used to define metabolic syndrome after 2001. Low HDL cholesterol was infrequently recorded in the Medicare data; we used this information when defining metabolic syndrome but did not evaluate it as an independent risk factor for ovarian cancer. Diagnoses for hypertensive diseases served as a proxy for high blood pressure and type II diabetes diagnoses were included in our classification for impaired fasting glucose. There were 62 women who had a record of high fasting glucose, but not diabetes (not tabulated).

2.3. Statistical analysis

We used logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI) for the associations between metabolic syndrome, its components, and ovarian cancer. We used separate models for each exposure and adjusted for index/diagnosis date, age, race/ethnicity, geographic location, state buy-in status, history

of smoking/tobacco use, and length of continuous enrollment. Adjustment variables were categorized as shown in Supplemental Table 2; enrollment was categorized as described above and in Supplemental Fig. 1. History of smoking/tobacco use was determined by the presence/absence of the following ICD-9 diagnosis codes: V15.82, 305.1, 989.84 (personal history of smoking, tobacco use disorder, and toxic effect of tobacco, respectively). To assess effect modification by race, we ran separate models for each race group and then obtained p values from likelihood ratio tests comparing nested models with and without an interaction term between race and each metabolic syndrome exposure.

We additionally used logistic regression to evaluate associations with specific histotypes of cancer: serous, endometrioid, clear cell, mucinous, and other epithelial (with controls as the reference group). For cancers classified as serous, endometrioid, or other epithelial, we used logistic regression to further examine associations by tumor grade: high or low, compared with controls. We were interested in identifying potential etiologic risk factors for high grade tumors and therefore classified grades 3 and 4 as “high grade” across histotype. Only 618 (25%) of the 2491 low grade cancers were grade 1.

To comment on effect heterogeneity across histotype and grade and to examine the importance of metabolic syndrome and its components in predicting histotype, we also ran case-only models to obtain type III/Wald Chi-square test p values for each exposure. First, we used non-ordinal multinomial logistic regression models with histology as the outcome (reference group = serous cancers) and obtained p values to explore heterogeneity by histotype. To estimate differences by grade within the serous, endometrioid, and other epithelial histotypes, we used logistic regression comparing women with low grade tumors to those with high grade tumors (reference group). Lastly, to contrast effects by histotype among high grade cancers, we similarly used non-ordinal multinomial logistic regression, but compared women with high grade endometrioid tumors and high grade other epithelial tumors to those with high grade serous tumors (reference group).

All statistical tests were two-sided with an alpha of 0.05. We used SAS 9.4 (SAS Institute, Cary, North Carolina) for statistical analyses.

3. Results

We observed a similar mean age at cancer diagnosis/index date for cases and controls (Supplemental Table 3). In both groups, most women were White (cases: 88.5%, controls: 84.5%) and few were documented smokers/tobacco users (cases: 6.3%, controls: 7.2%). Approximately 22–23% of the cases and controls had metabolic syndrome. Hypertension, high triglycerides, and impaired fasting glucose were the most commonly documented metabolic syndrome components, with women who developed ovarian cancer being slightly more likely to have hypertension (cases: 72.2%, controls: 68.1%) and high triglycerides (cases: 53.2%, controls: 48.0%).

Metabolic syndrome was associated with reduced risk for ovarian cancer when compared to women who did not meet the diagnostic criteria (odds ratio [OR] 0.86, 95% confidence interval [CI] 0.82–0.89; Table 1). Having three or more metabolic syndrome components was not associated with risk when compared to a referent group of women without any components (OR 1.02, CI 0.96–1.07). Having one or two components modestly increased risks for ovarian cancer (one: OR 1.24, CI 1.18–1.30; two: OR 1.23, CI 1.17–1.29). Directions of effects varied when we examined the specific components of metabolic syndrome. Overweight/obesity and impaired fasting glucose were associated with cancer risk reductions (OR 0.84, CI 0.79–0.89 and OR 0.90, CI 0.87–0.93, respectively), while hypertension and high triglycerides were associated with modest increased risks (OR 1.08, CI 1.04–1.12 and OR 1.05, CI 1.01–1.08, respectively).

Table 1

Associations between metabolic syndrome, its components, and ovarian or fallopian tube cancer, SEER-Medicare linked data (1994–2013).

| | Cases | | Controls | | OR ^b | 95% CI |
|------------------------------------------------|------------|------|-------------|------|-----------------|-----------|
| | n = 16,850 | | n = 281,878 | | | |
| | n | % | n | % | | |
| Metabolic syndrome ^a (≥3 vs. <3) | 3751 | 22.3 | 65,041 | 23.1 | 0.86 | 0.82–0.89 |
| Number of metabolic syndrome components | | | | | | |
| 0 | 3085 | 18.3 | 65,943 | 23.4 | – | Reference |
| 1 | 4517 | 26.8 | 72,573 | 25.7 | 1.24 | 1.18–1.30 |
| 2 | 5524 | 32.8 | 78,822 | 28.0 | 1.23 | 1.17–1.29 |
| ≥3 | 3724 | 22.1 | 64,540 | 22.9 | 1.02 | 0.96–1.07 |
| Components of metabolic syndrome | | | | | | |
| Overweight/obesity | 1328 | 7.9 | 24,997 | 8.9 | 0.84 | 0.79–0.89 |
| Impaired fasting glucose | 4770 | 28.3 | 82,922 | 29.4 | 0.90 | 0.87–0.93 |
| Hypertension | 12,168 | 72.2 | 191,822 | 68.1 | 1.08 | 1.04–1.12 |
| High triglycerides | 8958 | 53.2 | 135,329 | 48.0 | 1.05 | 1.01–1.08 |
| Low HDL cholesterol | 104 | 0.6 | 1870 | 0.7 | – | – |

n = number, OR = odds ratio, CI = confidence interval.

^a Metabolic syndrome was defined as diagnoses for 3 or more components of metabolic syndrome (central adiposity or overweight/obesity, impaired fasting glucose [including type II diabetes], hypertension, high triglycerides, low HDL cholesterol) and/or a diagnosis of ‘dysmetabolic syndrome.’ Women meeting this definition were compared to a referent group of those not meeting it (i.e., including those with diagnoses for only one or two of the components). When comparing the number of metabolic syndrome components with which women were diagnosed, those without diagnoses for any of the components are the reference group (‘dysmetabolic syndrome’ not considered in this categorization).

^b Logistic regression models were run separately for each exposure. Models were adjusted for diagnosis date, age, race, geographic location, state Medicare buy-in, history of smoking or tobacco use, and length of Medicare enrollment.

We observed modification by race/ethnicity, particularly when comparing associations for the number of metabolic syndrome components and hypertension (Supplemental Table 4). Non-Hispanic black women had the greatest ovarian cancer risks associated with both hypertension (OR 1.34, CI 1.11–1.60, p for modification 0.12) and an increasing number of metabolic syndrome components (ORs of 1.68, 1.57, and 1.32 for having 1, 2, or 3 or more components, respectively; p for modification 0.16). The overall reduced risks noted with high fasting glucose and the increased risks with high triglycerides were largely explained by associations among non-Hispanic white women, while effect estimates were imprecise across other race groups.

Risk reductions associated with metabolic syndrome for both serous (OR 0.80, CI 0.76–0.85) and other epithelial cancers (OR 0.91, CI 0.85–0.96) likely explained the overall ovarian cancer risk reduction that we noted (Table 2). Metabolic syndrome was not associated with the other histotypes. The data suggested increases in risk for endometrioid tumors (OR 1.20, CI 0.98–1.47) and other epithelial tumors (OR 1.08, CI 0.99–1.17) among women with three or more metabolic syndrome components compared to none. Across most subtypes, we again observed stronger increased risks among women with only one or two components. For serous cancers, high triglycerides were associated with increased risk (OR 1.10, CI 1.05–1.16), while overweight/obesity (OR 0.77, CI 0.70–0.84) and impaired fasting glucose (OR 0.84, CI 0.80–0.89) were associated with reduced risks. Both hypertension and high triglycerides increased risk for endometrioid ovarian cancers (OR 1.33, CI 1.16–1.53 and OR 1.16, CI 1.02–1.32, respectively). Increased risks with hypertension were suggested for other epithelial tumors (OR 1.13, CI 1.07–1.20) and possibly, clear cell tumors (OR 1.16, CI 0.92–1.46).

Metabolic syndrome was associated with reduced risks for both high- and low-grade serous tumors (ORs of 0.73, and 0.85, respectively; Table 3). Having one or two metabolic syndrome components generally increased risks for serous, endometrioid,

Table 2

Associations between metabolic syndrome, its components, and major subtypes of ovarian and fallopian tube cancer, SEER-Medicare linked data (1994–2013).

| | Serous | | Endometrioid | | Clear cell | | Mucinous | | Other epithelial | | P ^c |
|------------------------------------------------|-----------------|-----------|-----------------|-----------|-----------------|-----------|-----------------|-----------|------------------|-----------|----------------|
| | n = 7543 | | n = 1114 | | n = 797 | | n = 386 | | n = 7010 | | |
| | OR ^b | 95% CI | OR ^b | 95% CI | |
| Metabolic syndrome ^a (≥3 vs. <3) | 0.80 | 0.76–0.85 | 0.91 | 0.78–1.06 | 0.89 | 0.69–1.14 | 0.97 | 0.81–1.17 | 0.91 | 0.85–0.96 | 0.02 |
| Number of metabolic syndrome components | | | | | | | | | | | 0.02 |
| 0 | – | Reference | – | Reference | – | Reference | – | Reference | – | Reference | |
| 1 | 1.24 | 1.15–1.33 | 1.43 | 1.20–1.71 | 1.27 | 0.94–1.72 | 0.98 | 0.80–1.20 | 1.25 | 1.16–1.34 | |
| 2 | 1.23 | 1.15–1.32 | 1.45 | 1.21–1.73 | 1.25 | 0.92–1.69 | 1.04 | 0.85–1.27 | 1.22 | 1.13–1.31 | |
| ≥3 | 0.95 | 0.88–1.03 | 1.20 | 0.98–1.47 | 1.08 | 0.77–1.51 | 0.99 | 0.79–1.25 | 1.08 | 0.99–1.17 | |
| Components of metabolic syndrome | | | | | | | | | | | |
| Overweight/obesity | 0.77 | 0.70–0.84 | 0.76 | 0.60–0.96 | 0.87 | 0.60–1.27 | 0.85 | 0.64–1.13 | 0.93 | 0.86–1.02 | 0.01 |
| Impaired fasting glucose | 0.84 | 0.80–0.89 | 0.86 | 0.75–1.00 | 0.82 | 0.65–1.04 | 1.03 | 0.88–1.21 | 0.97 | 0.92–1.02 | 0.002 |
| Hypertension | 1.01 | 0.96–1.06 | 1.33 | 1.16–1.53 | 1.16 | 0.92–1.46 | 1.01 | 0.86–1.18 | 1.13 | 1.07–1.20 | 0.008 |
| High triglycerides | 1.10 | 1.05–1.16 | 1.16 | 1.02–1.32 | 1.12 | 0.89–1.39 | 1.05 | 0.90–1.22 | 0.97 | 0.92–1.03 | 0.01 |

n = number, OR = odds ratio, CI = confidence interval.

^a Metabolic syndrome was defined as diagnoses for 3 or more components of metabolic syndrome (central adiposity or overweight/obesity, impaired fasting glucose [including type II diabetes], hypertension, high triglycerides, low HDL cholesterol) and/or a diagnosis of 'dysmetabolic syndrome.' Women meeting this definition were compared to a referent group of those not meeting it (i.e., including those with diagnoses for only one or two of the components). When comparing the number of metabolic syndrome components with which women were diagnosed, those without diagnoses for any of the components are the reference group ('dysmetabolic syndrome' not considered in this categorization).

^b Logistic regression models were run separately for each exposure and each case group (comparing to controls as the reference). Models were adjusted for diagnosis date, age, race, geographic location, state Medicare buy-in, medical history of smoking or tobacco use, and length of Medicare enrollment.

^c Chi square test P values to assess heterogeneity by histotype. We used case-only non-ordinal multinomial logistic regression models with histology as the outcome (reference group = serous cancers) to obtain effect estimate p values for metabolic syndrome and each of its components.

and other epithelial tumors, regardless of grade. Three or more metabolic syndrome signs was only clearly associated with increased risk for the other epithelial cancers (high-grade: OR 1.20, CI 1.03–1.40; low-grade: OR 1.44, CI 1.03–2.00). Risk reductions associated with overweight/obesity and impaired fasting glucose were indicated across most subtypes/grades. Hypertension was associated with a risk reduction of borderline statistical significance for high-grade serous tumors (OR 0.93, CI 0.87–1.00) and risk increases for low-grade serous and low-grade endometrioid tumors, as well as with all other epithelial cancers. P values for

heterogeneity were statistically significant across grade within the serous and endometrioid histotypes. High triglycerides were the most consistent risk factor for ovarian cancer, with associations noted for all but the low-grade endometrioid cancers. High triglycerides was the only factor that increased risk for all high-grade cancers (ORs ranging from 1.10 for high-grade serous to 1.37 for high-grade endometrioid). However, we did not observe statistical heterogeneity of the high triglyceride effects across grade within the histotypes.

Table 3

Associations between metabolic syndrome, its components, and tumor grade for selected histotypes of ovarian and fallopian tube cancer, SEER-Medicare linked data (1994–2013).

| | Serous High grade | | Serous Low grade | | P ^c | Endometrioid High grade | | Endometrioid Low grade | | P ^c | Other epithelial High grade | | Other epithelial Low grade | | P ^d | |
|------------------------------------------------|-------------------|-----------|------------------|-----------|----------------|-------------------------|-----------|------------------------|-----------|----------------|-----------------------------|-----------|----------------------------|-----------|----------------|------|
| | n = 4622 | | n = 1119 | | | n = 472 | | n = 532 | | | n = 1978 | | n = 420 | | | |
| | OR ^b | 95% CI | OR ^b | 95% CI | | OR ^b | 95% CI | OR ^b | 95% CI | | OR ^b | 95% CI | OR ^b | 95% CI | | |
| Metabolic syndrome ^a (≥3 vs. <3) | 0.73 | 0.68–0.79 | 0.85 | 0.72–1.00 | 0.31 | 1.03 | 0.81–1.30 | 0.83 | 0.66–1.04 | 0.24 | 0.91 | 0.81–1.03 | 1.05 | 0.82–1.36 | 0.50 | 0.01 |
| Number of metabolic syndrome components | | | | | 0.63 | | | | | 0.12 | | | | | 0.86 | 0.09 |
| 0 | – | Ref | – | Ref | | – | Ref | – | Ref | | – | Ref | – | Ref | | |
| 1 | 1.22 | 1.12–1.33 | 1.30 | 1.10–1.54 | | 1.27 | 0.98–1.66 | 1.53 | 1.17–1.98 | | 1.41 | 1.24–1.61 | 1.50 | 1.13–2.00 | | |
| 2 | 1.19 | 1.09–1.30 | 1.41 | 1.19–1.67 | | 1.26 | 0.96–1.64 | 1.67 | 1.29–2.16 | | 1.41 | 1.24–1.62 | 1.43 | 1.06–1.91 | | |
| ≥3 | 0.85 | 0.77–0.94 | 1.08 | 0.88–1.33 | | 1.23 | 0.91–1.67 | 1.18 | 0.87–1.60 | | 1.20 | 1.03–1.40 | 1.44 | 1.03–2.00 | | |
| Components of metabolic syndrome | | | | | | | | | | | | | | | | |
| Overweight/obesity | 0.71 | 0.63–0.80 | 0.83 | 0.65–1.05 | 0.38 | 0.78 | 0.54–1.14 | 0.69 | 0.49–0.99 | 0.52 | 0.85 | 0.71–1.01 | 1.13 | 0.80–1.59 | 0.17 | 0.53 |
| Impaired fasting glucose | 0.79 | 0.74–0.85 | 0.80 | 0.69–0.92 | 0.68 | 0.91 | 0.73–1.13 | 0.80 | 0.65–0.98 | 0.55 | 0.91 | 0.82–1.02 | 0.98 | 0.78–1.24 | 0.70 | 0.14 |
| Hypertension | 0.93 | 0.87–1.00 | 1.17 | 1.02–1.33 | 0.09 | 1.08 | 0.88–1.33 | 1.64 | 1.33–2.02 | 0.001 | 1.22 | 1.10–1.35 | 1.29 | 1.03–1.61 | 0.98 | 0.01 |
| High triglycerides | 1.10 | 1.03–1.17 | 1.29 | 1.13–1.47 | 0.43 | 1.37 | 1.12–1.68 | 1.07 | 0.89–1.29 | 0.22 | 1.16 | 1.05–1.28 | 1.30 | 1.05–1.61 | 0.47 | 0.34 |

n = number, OR = odds ratio, CI = confidence interval.

^a Metabolic syndrome was defined as diagnoses for 3 or more components of metabolic syndrome (central adiposity or overweight/obesity, impaired fasting glucose [including type II diabetes], hypertension, high triglycerides, low HDL cholesterol) and/or a diagnosis of 'dysmetabolic syndrome.' Women meeting this definition were compared to a referent group of those not meeting it (i.e., including those with diagnoses for only one or two of the components). When comparing the number of metabolic syndrome components with which women were diagnosed, those without diagnoses for any of the components are the reference group ('dysmetabolic syndrome' not considered in this categorization).

^b Logistic regression models were run separately for each exposure and each case group (comparing to controls as the reference). Models were adjusted for diagnosis date, age, race, geographic location, state Medicare buy-in, medical history of smoking or tobacco use, and length of Medicare enrollment.

^c Chi-square test P values to assess heterogeneity by grade within histotypes. For each histotype, we used case-only logistic regression models comparing women with low grade tumors to women with high grade tumors (reference group) to obtain effect estimate p values for metabolic syndrome and each of its components.

^d Chi square test P values to assess heterogeneity by histotype among high grade cancers. We used case-only non-ordinal multinomial logistic models comparing women with high grade endometrioid tumors and high grade other epithelial tumors to those with high grade serous tumors (reference) and obtained effect estimate p values for metabolic syndrome and each of its components.

4. Discussion

To our knowledge this is the largest study on metabolic syndrome and ovarian cancer, with respect to the number of women with cancer included. This allowed us to examine risks across histotype. Although we identified reduced risks associated with metabolic syndrome, especially for serous cancers, this was driven by associations with specific syndrome components. We did not identify associations with having three or more components when we compared to women with none. However, for most histotypes, having one or two specific components increased risk. Interestingly, we identified increased risks for endometrioid tumors with hypertension and found high triglycerides to be a consistent risk factor for all high-grade tumors.

Many researchers have examined metabolic syndrome components and ovarian cancer risk, but we found only three evaluating a composite “metabolic syndrome” exposure. Most comparable with ours is the Metabolic Syndrome and Cancer Project (Me-Can), a prospective cohort of ~290,000 women recruited in Europe ($n = 644$ cases); researchers using this data did not identify associations between ovarian cancer and metabolic syndrome among women living to age 50 years or older, using a standardized sum of z-scores for the syndrome components within their population [5]. A prospective and nationally representative study from Korea found no association between ovarian cancer ($n = 82$ cases) and a “high-risk metabolic profile”—a categorization similar to the NCEP-III definition, but which used information on serum cholesterol versus triglycerides [7]. Lastly, a recent case-control study from China ($n = 573$ cases) assessed exposures at or after cancer treatment and found metabolic syndrome was associated with a three-fold increased risk (using several definitions for the syndrome) [6].

Many studies of individual metabolic syndrome components and ovarian cancer risk are prospective and enroll women younger than those in our study; therefore, these studies have less power to detect the modest, but informative, associations we identified. Meta-analyses indicate that findings vary substantially with study design, age of the population, histotype, and timing and type of exposure assessment (e.g., body mass index [BMI] versus waist circumference). This is evident in analyses for obesity and type II diabetes, which may increase risk for ovarian cancer, but the associations are weak to modest and heterogeneous [8,9,13]. For example, a meta-analysis by Liu and colleagues did not support an association between overweight/obesity and ovarian cancer among postmenopausal women ($n = 6$ studies; risk ratio 0.93, CI 0.61, 1.42; $I^2 = 77.6\%$), but work from the Ovarian Cancer Cohort Consortium, whose member studies are predominately composed of postmenopausal women, indicate that BMI may modestly increase risk for endometrioid ovarian cancers [8,14]. Lee and colleagues found diabetes increased risk for ovarian cancer in their meta-analysis, but there was no discernable association when limiting to studies that used blood glucose measurement to determine diabetes status ($n = 4$ studies; risk ratio 1.06, CI 0.79, 1.42; $I^2 = 0\%$) [9]. In the Me-Can study, reduced ovarian cancer risk with high blood glucose was suggested, but statistically imprecise for women older than 50 years of age and women with serous tumors ($n = 327$) [5]. Ovarian cancer was not associated with glucose and insulin levels in Women's Health Initiative ($n = 130$ cases) [15]. Both studies used baseline measures of glucose, whereas our assessment window was shortly before cancer diagnosis.

The relationship between high triglycerides and ovarian cancer risk is inconsistent across large prospective studies [5,16–18]. Effect magnitudes from the Me-Can study for high triglycerides and risk of serous tumors were similar to ours, but not statistically significant [5]. Most studies of metabolic syndrome components and ovarian cancer do not present analyses stratified by tumor grade.

Similar to our findings, researchers for the Me-Can study observed that increasing baseline blood pressure increased risk for endometrioid tumors ($n = 66$), with statistical significance [5]. Interestingly, the Nurses' Health Studies I and II, which evaluated hypertension, found no such association—though their analyses suggest duration of and treatment for hypertension may increase risk for ovarian cancer. [19] They do not show effect estimates by histotype, but report lack of an association with endometrioid tumors ($n = 80$) [19]. In our analysis, risks for ovarian cancer associated with hypertension were predominantly explained by greater risks noted among non-Hispanic black women. We are unaware of other studies reporting a similar finding, but this clearly merits further investigation; the pathogenesis of ovarian cancer and hypertension may be unique for black women, as may be treatment needs and utilization [20,21]. In our study population, endometrioid tumors were equally prevalent among white (6.5%) and black women (6%), but black women were more likely to have clear cell (6.6 vs. 4.5%) and other epithelial cancers (50.0 vs. 41.1%; not tabulated). We also found that having 3 or more metabolic syndrome components (compared to having none) was associated with increased ovarian cancer risk among black women, while metabolic syndrome itself was not (compared to women with fewer than 3 components). In other words, the occurrence of 3 or more components, while associated with ovarian cancer, did not increase risk relative to having fewer components—because specific components of metabolic syndrome, rather than the syndrome itself, are driving the risk (e.g., hypertension).

Wu and colleagues theorize that energy oversupply within a tissue microenvironment facilitates carcinogenic clonal selection and expansion, and that this process underlies associations between cancer and a range of risk factors like obesity, chronic inflammation, and hyperglycemia [3]. Arguably, most of the signs for metabolic syndrome are potential manifestations of this mechanism in action. In addition to providing energy, high glucose influences cellular proliferation and survival through the insulin/insulin-like growth factor (IGF) axis, which also plays a role in regulating the ovarian cycle [22,23]. Many components of the IGF system are expressed in ovarian cancers, but associations between circulating markers and ovarian cancer risk are not straightforward (reviewed in [24,25]). Fatty acids derived from triglycerides can be used for energy and membrane synthesis in proliferating cells [26]. Availability of fatty acids in the tumor microenvironment (via omental adipocytes) has been proposed as mechanism by which ovarian cancer metastasizes [27].

Although “metabolic syndrome” is in theory, an ideal exposure to represent dysregulated energy balance, its utility as a marker for both underlying insulin resistance and future cardiovascular disease (CVD) risk was called into question in a joint statement from the American Diabetes Association and the European Association for the Study of Diabetes [28]. They note that use of term “metabolic syndrome” can create the impression that a diagnosis confers “a greater risk [for CVD] than its components, or that it is more serious than other CVD risk factors, or that the underlying pathophysiology is clear.” [28] Our study highlights these same concerns in the context of ovarian cancer research and the complexity in evaluating composite exposures like “metabolic syndrome,” which is problematic in several ways.

Firstly, the prevalence of metabolic syndrome components varies between women meeting and not meeting the criteria for a diagnosis. In our population, women with metabolic syndrome or 3 or more syndrome components were much more likely to have impaired fasting glucose than women with only one or two components—among whom hypertension and high triglycerides were relatively, more prevalent (Supplemental Table 5). Therefore, any comparison between these groups is potentially evaluating very different pathogenic processes. Secondly, is the choice of reference

group: metabolic syndrome was associated with reduced ovarian cancer risk when we made comparisons to women who did not meet the diagnostic criteria (those without any components and those who had only one or two). We found no association when comparing women with three or more components to those without any, but women with one or two specific components had increased ovarian cancer risk. These results suggest that specific metabolic syndrome components are associated with ovarian cancer, that these associations can vary in direction, and that associations with metabolic syndrome itself are likely driven by the prevalence of these components in a study population. Therefore, combining these components into a composite variable is both biologically and statistically inappropriate in ovarian cancer studies.

The prevalence of both high triglycerides and hypertension in our study are comparable with estimates reported in the National Health and Nutrition Examination Surveys data for older female respondents during the timeframe in which our study occurred [29,30]. The number of women with obesity in our study is clearly underestimated. In the middle of our study period, 35–40% of U.S. women aged 65–74 years were obese in nationally representative data [30]. As such, our effect estimates for metabolic syndrome or having multiple syndrome components are not being driven by obesity to the same extent noted in other studies. The prevalence of impaired fasting glucose/type II diabetes is higher in our study than that reported among older women participating in large U.S. based national health surveys, which report estimates around 18% [31,32]. While diabetes is not strongly associated with ovarian cancer—if energy oversupply is a risk factor, our risk reductions with impaired fasting glucose are interesting, but require replication.

Women with diabetes documented in Medicare records may be unique. Landon and colleagues report that only a third of Medicare beneficiaries who were newly diagnosed with diabetes in 2007 and 2014 were not taking medication(s) for the condition, with metformin being the first drug used for most [33]. Increasingly, researchers are exploring medications used to treat components of metabolic syndrome in ovarian cancer research. In this analysis, we estimated the total effect of diabetes, hypertension, and high triglycerides on cancer risk; medications may be one mechanism through which these factors influence disease risks. Estimating the direct effect of these conditions independent of medication use would require mediation analyses to control for confounding by changes in obesity, HbA_{1c} levels, and medication use over time; data such as these are typically unavailable. Furthermore, adjusting for or stratifying on the use of a medication may unintentionally change the exposure being evaluated. For example, women not taking metformin could be very different than women who do; they may have diabetes that is well-managed through lifestyle changes or they may have comorbidities that contraindicate its use (e.g., renal dysfunction).

Use of SEER-Medicare linked data has some limitations. Claims information is largely unavailable for women enrolled in HMOs. Generally, Medicare beneficiaries enrolled in HMOs are younger and healthier [10]. We excluded women enrolled in HMOs due to the potential for differential exposure ascertainment among this group. Not all services are billed to Medicare; some beneficiaries have a primary insurance payor through an employer health plan. However, Medicare is a national program that enrolls most Americans over 65 and is therefore one of the most representative resources for data on this population. We would not have data on bilateral oophorectomy that occurred before the age of 65, but Medicare data also provide medical record-based diagnoses, which may be more accurate than self-reported information for some conditions. Importantly, we add analyses by cancer histotype and grade to the scientific literature and provide insight on factors that influence metabolic syndrome's utility as an exposure.

Our findings are in line with other studies indicating metabolic syndrome and its components are not strong ovarian cancer risk factors, though specific components may play a role in its development. The high prevalence of metabolic syndrome calls attention to the importance of improving and managing metabolic health among postmenopausal women. However, evaluating metabolic syndrome as a composite cancer risk factor could be misleading and etiologically uninformative.

Author's contributions

Conception and design: KAM and BT

Methodology: All authors

Acquisition of data, funding: KAM and BT

Data curation: TSM

Formal analysis: TSM

Interpretation of data: All authors

Writing, original draft: KAM

Writing, review, and revision of the manuscript: All authors

Study supervision: KAM and BT

Declaration of competing interest

The authors declare no conflicts of interest.

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This study used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The authors acknowledge the efforts of the National Cancer Institute; the Office of Research, Development and Information, CMS; Information Management Services (IMS), Inc.; and the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER-Medicare database.

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Role of the funding source

The sponsors had no role in the: study design; analysis and interpretation of data; writing of the report; or in the decision to submit the paper for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ygyno.2019.08.032>.

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