Prospective cohort study of metabolic syndrome and endometrial cancer survival

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Abstract:

Objective: Comorbidities are known to increase endometrial cancer risk, but the separate and combined impact of these risk factors on endometrial cancer survival remains unclear. This study aimed to determine the associations between metabolic syndrome and its components with disease-free survival, overall survival, endometrial cancer-specific survival and recurrence among endometrial cancer survivors. **Methods:** Cases from a population-based case-control study who were diagnosed with primary endometrial cancer between 2002 and 2006 in Alberta, Canada were followed until death or March 20, 2019. Baseline in-person interviews, direct anthropometric measurements and fasting blood samples were used to assess metabolic syndrome (presence of ≥3 of the following: waist circumference ≥ 88 cm, fasting blood glucose ≥100 mg/dL, triglycerides ≥150 mg/dL, high-density lipoprotein cholesterol <50 mg/dL and self-reported hypertension). Cox proportional hazards regression and Fine and Gray competing risk models were used to estimate multivariate-adjusted hazard ratios (95% CI) for these associations. **Results:** Among 540 endometrial cancer survivors, 325 had metabolic syndrome at diagnosis and 132 had a recurrence and/or died during the median 14.2 years of follow-up (range: 0.3–16.5 years). In multivariable analyses, being diagnosed with metabolic syndrome (HR = 1.98, 95% CI = 1.07–3.67) and having an elevated waist circumference (≥88 cm; HR = 2.12, 95% CI = 1.18–3.80; $HR_{per\ 5\ cm}$ = 1.21, 95% CI = 1.07–1.36) were associated with worse overall survival. Additionally, increasing waist circumference (per 5 cm) was also associated worse with disease-free survival ($HR_{per\ 5\ cm}$ = 1.11, 95% CI = 1.00–1.24). **Conclusion:** The metabolic syndrome, in particular central adiposity, were associated with worse overall and disease-free survival in endometrial cancer survivors.

Keywords: Endometrial Cancer | Survival | Metabolic syndrome | Co-morbidities

Article:

1. Introduction

Endometrial cancer is the sixth most frequently diagnosed cancer among women worldwide [1]. In 2018, the International Agency for Research on Cancer (IARC) estimated that 382,069 new cases of endometrial cancer and 89,929 endometrial cancer-specific deaths occurred globally [1] with the highest rates occurring in North America and Central and Eastern Europe [1,2]. Between 2005 and 2015, uterine cancer mortality rates increased 2.0% annually in Canada and 1.9% annually between 2011 and 2015 in the USA, making endometrial cancer one of the few cancer types with both increasing incidence and mortality rates [3,4].

Obesity and diabetes have been previously identified as major risk factors for endometrial cancer, whereas physical activity is thought to reduce endometrial cancer risk [2,5,6]. These risk factors may also be associated with endometrial cancer recurrence and mortality [7,8,9]. Specifically, obesity is an established risk factor for endometrial cancer survival, with convincing biological plausibility through metabolic disruptions, hormonal and growth factor imbalances, unopposed estrogens released by adipose tissue [10] and chronic inflammation that prompts tumor growth [2,10,11,12]. Furthermore, among cancer survivors, obesity has been associated with reduced responses to standard treatments, higher rates of metastatic disease and poorer prognoses compared to normal weight individuals [12]. Diabetes and hypertension may also increase cancer-specific mortality and all-cause mortality in this population [8,9,13,14,15]. However, the combined impact of these comorbidities on endometrial cancer survival outcomes remains unclear.

Metabolic syndrome is defined as the clustering of cardiovascular and metabolic disease risk factors including central adiposity, hypertension, hyperglycemia, elevated triglycerides and low high-density lipoprotein (HDL) cholesterol [16]. Women with metabolic syndrome are estimated to have a roughly two-fold elevation in endometrial cancer risk [5,17,18,19,20,21] compared to those without. Despite biological plausibility that metabolic syndrome may also be associated with endometrial cancer recurrence and survival [10,22], limited information on survival outcomes currently exists. Therefore, the objective of the current study was to determine the associations between metabolic syndrome and its components, defined by harmonized criteria [16] with disease-free survival, overall survival, endometrial cancer-specific survival and recurrence among endometrial cancer survivors.

2. Methods

2.1. Study design

The Alberta Endometrial Cancer Cohort Study is a follow-up of women diagnosed with histologically confirmed, invasive, primary endometrial cancer between 2002 and 2006 who participated in a population-based case-control study in Alberta, Canada [23]. Full details of the case-control study have been previously reported [20,23]. Briefly, 549 (61.0%) of cases identified through the Alberta Cancer Registry who were residents of Alberta, English speaking, between 30 and 80 years of age, able to complete an interview and diet history questionnaire, and had no prior history of cancer except non-melanoma skin cancer, were included. Nine participants were excluded from this analysis due to unsatisfactory baseline interviews (n = 7), cancer misclassification (n = 1) and being diagnosed with an ineligible endometrial cancer sub-type (*neuroendocrine* endometrial cancer; n = 1). The remaining 540 participants (60.0%) were

included in this study. Ethical approval for the study was obtained from the Alberta Cancer Board, the Conjoint Health Research Ethics Board (University of Calgary) and the Health Research Ethics Board (University of Alberta). All participants provided informed, written consent.

2.2. Data collection

Participant's demographic information, menstrual and reproductive history, hormone use history, medical history, medication use information, family history of cancer, and lifetime smoking habits were collected via an interviewer-administered questionnaire following endometrial cancer diagnosis (mean 22 ± 11.5 weeks) [23]. Lifetime alcohol consumption and lifetime physical activity participation were measured with the Canadian Diet Health Questionnaire-I and the Lifetime Total Physical Activity Questionnaire (LTPAQ), respectively [24,25]. At the time of the interviews, standardized anthropometric measurements including the participant's height, weight and waist circumferences were taken in triplicate and the average was recorded as the final measurement [23]. Participants fasted for at least eight hours before blood samples were collected either pre-hysterectomy or four-six weeks post-hysterectomy if blood could not be drawn pre-surgery (pre-surgical $n = 235$; post-surgical $n = 286$). Blood samples were processed into blood fractions (serum, plasma, red blood cells, and buffy coat), frozen at −80 °C within 24 h of collection and stored in biorepository at the Tom Baker Cancer Centre, Calgary, Alberta [26].

2.3. Follow-up and outcome ascertainment

Clinical information including date of diagnosis, cancer histology and stage, primary and adjuvant treatment(s) received, cancer recurrence and occurrence of a new primary cancer diagnosis were abstracted from medical charts by the Alberta Cancer Registry trained Health Record Technicians. Overall stage (tumor, lymph node, metastasis (TNM)) was coded according to the American Joint Committee on Cancer guidelines [27]. Women with incomplete overall cancer TNM stage ($n = 8$) were coded based on available lymph node inclusion and metastatic information. Cancer grade (International Federation of Gynecology and Obstetrics) and tumor histology (endometrioid, mixed cell, serous, clear cell, mucinous adenocarcinoma, carcinosarcoma, adenosarcoma and other) were additionally available via tissue samples, as previously described [26]. Vital status and underlying cause of death data were provided by Vital Statistics Alberta and Statistics Canada, respectively. Vital status information from participants who died in provinces other than Alberta were obtained from data linkages between provincial cancer registries.

For the purpose of this analysis, cancer recurrence was considered as any primary site recurrence or progression, lymph node recurrence or metastasis of the primary cancer noted in the medical record. Deaths that were attributable to endometrial or uterine (NOS) cancer were categorized as endometrial cancer-specific deaths. Survival time was calculated as the time from the initial diagnosis of endometrial cancer until death or March 20, 2019, whichever occurred first. Disease-free survival was defined as the time from diagnosis to the first recurrence or death from any cause, while overall survival was the time from diagnosis until the time of death from any cause.

2.4. Statistical analysis

Metabolic syndrome was categorized with the harmonized definition using country- and sex-specific waist circumference criteria [16]. Participants with three or more of the following risk factors were classified as having metabolic syndrome: waist circumference ≥ 88 cm, fasting blood glucose levels ≥100 mg/dL, blood triglycerides ≥150 mg/dL, HDL cholesterol <50 mg/dL, or self-reported hypertension and/or hypertension medication use within one year of endometrial cancer diagnosis. The alternate hypertension criterion was used as direct blood pressure measurements were not available from the original case-control study [16,20]. Twenty-seven participants were missing one or more metabolic syndrome components (missing: waist circumference $n = 4$; fasting blood glucose levels $n = 20$; blood triglycerides $n = 23$; HDL cholesterol n = 20). Participants with partial missing metabolic syndrome data who still met three or more metabolic syndrome components criteria were classified as having metabolic syndrome ($n = 7$).

Cox proportional hazards regression models were used to estimate multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for the associations between metabolic syndrome (yes, no), the number of metabolic syndrome components (0–1, 2–3, 4–5) and individual metabolic syndrome components with disease-free survival, overall survival and recurrence outcomes. Fine and Gray competing risk models were used for the endometrial cancer-specific survival outcome. The individual metabolic syndrome components tested were: waist circumference (≥88 cm, per 5 cm), fasting blood glucose levels (≥100 mg/dL, per 5 mg/dL), blood triglycerides (≥150 mg/dL, per 5 mg/dL), HDL cholesterol (<50 mg/dL, per 5 mg/dL), and self-reported hypertension (yes, no). Continuous exposures were centred at dichotomous cut-points. All models were hierarchically well-formulated and adjusted for endometrial cancer stage (I, II, III/IV), grade (I/II, III, unknown/non-applicable), primary cancer treatment(s) (hysterectomy, hysterectomy/chemotherapy, hysterectomy/radiation, hysterectomy/chemotherapy/radiation and/or hormone therapy, missing treatment), baseline age (years) and non-linear age (age^2) based on a priori biological plausibility. Additionally, disease-free survival models were adjusted for the time to first new primary cancer, overall survival models were adjusted for the time to first recurrence/new primary cancer, and endometrial cancer-specific survival models were adjusted for the time to first recurrence. Moreover, all metabolic syndrome component models were mutually adjusted for the other metabolic syndrome risk factors.

Additional confounding variables were identified via backwards elimination. Continuous BMI (kg/m^2) was included in all multivariable-adjusted models while there was only evidence that the number of major comorbidities (0, 1, ≥2 of any of the following: angina pectoris, pulmonary embolism, myocardial infarction, stroke, thrombosis) confounded the association between metabolic syndrome with disease-free and overall survival. There was insufficient evidence that lifetime alcohol consumption (grams/year), marital status (married/common law, other), hormone replacement treatment status (ever, never), parity (null,1–2, ≥2) menopausal status (pre or peri-menopausal, post-menopausal), smoking pack years defined as: (number of cigarettes smoked daily)*(duration of smoking in years)/ 20, highest education attained (≤high school, non-university certificate, university degree), residency (rural, urban) or first degree family history of uterine (NOS) or colorectal cancer (yes, no/missing) confounded the associations of interest. Nor

was there evidence that fasting blood insulin levels (pM/ml) confound associations in fasting blood glucose models.

Potential modification of the association between metabolic syndrome and its components with overall and disease-free survival by BMI (kg/m^2) and lifetime recreational physical activity (metabolic-equivalent task [MET]-hours/week/year) were assessed with Wald-tests. Associations with statistically significant effect modification are presented by median groups.

The proportional hazards assumption was evaluated with visual and statistical assessments of Schoenfeld residuals and Wald-tests for the interaction of the exposure variable and time in the Cox models and Fine and Gray models, respectively. Results are not presented for the analyses that did not satisfy the proportional hazards assumption. Sample size for this analysis was predetermined by the number of available cases; hence, the final analytical sample included participants with complete metabolic syndrome data (n = 520) and complete metabolic syndrome component data (n = 513; Fig. 1). All analyses were performed using Stata software version 15.1 (StataCorp LLC. College Station, TX).

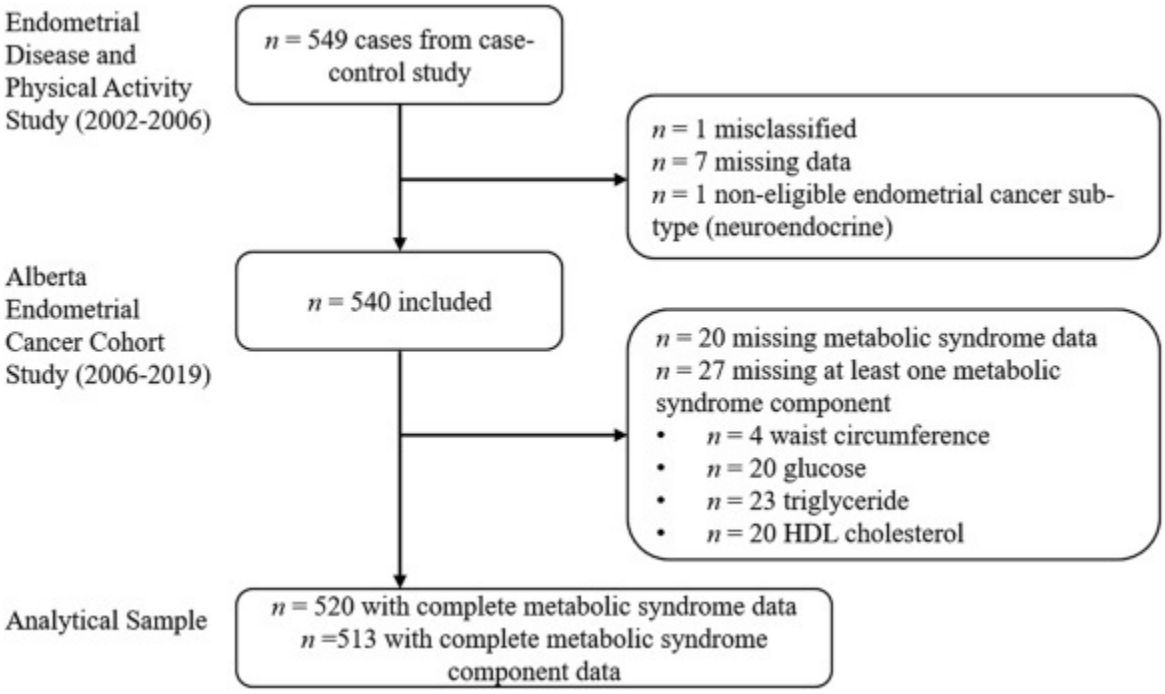

Fig. 1. Participant Flowchart for the Alberta Endometrial Cancer Cohort, Alberta, Canada.

3. Results

Among the 540 endometrial cancer survivors, 325 (60.2%) had metabolic syndrome at the time of endometrial cancer diagnosis and 132 had a recurrence and/or died during the median 14.2 years of follow-up (range: 0.3–16.5 years). Specifically, there were 73 recurrences, 50 endometrial cancer-specific deaths and 111 overall deaths during follow-up. Most participants were diagnosed with endometroid histology (81.5%), low stage and grade endometrial cancer (Stage I: 77.8%; Grade I: 53.3%), had hysterectomy as part of primary treatment (97.6%) and a mean age of 59.1 (SD 9.3) years (Table 1).

Table 1. Participant Characteristics of the Alberta Endometrial Cancer Cohort by Vital Status, Alberta, Canada ($N = 540$).

Characteristics (Mean (SD); N (%))	**All (n = 540)**	**Alive (*n* = 429)**	**Disease-Free Survival (*n* = 132)**	**Overall Deaths (*n* = 111)**	**Cancer-Specific Deaths (*n* = 50)**
Age at diagnosis (years)	59.1 (9.3)	57.6 (8.8)	63.5 (9.8)	64.9 (9.2)	62.7 (7.7)
Highest Education					
High school diploma	177 (32.8)	134 (31.2)	50 (37.9)	43 (38.7)	15 (30.0)
Non-university certificate	249 (46.1)	198 (46.2)	61 (46.2)	51 (46.0)	26 (52.0)
University degree	114 (21.1)	97 (22.6)	21 (15.9)	17 (15.3)	9 (18.0)
Married/common-law	372 (68.9)	300 (69.9)	84 (63.6)	72 (64.9)	30 (60.0)
White	507 (93.9)	401 (93.5)	123 (93.2)	106 (95.5)	46 (92.0)
Urban residence	363 (67.2)	300 (69.9)	77 (58.3)	63 (56.8)	32 (64.0)
Parity					
0	111 (20.6)	91 (21.2)	23 (18.70)	20 (18.0)	8 (16.0)
1–2	248 (45.9)	208 (48.5)	45 (36.59)	40 (36.0)	21 (42.0)
>2	181 (33.5)	130 (30.3)	55 (44.72)	51 (46.0)	21 (42.0)
Post-Menopausal	415 (76.9)	312 (72.7)	116 (87.9)	103 (92.8)	45 (90.0)
Histology					
Endometroid	440 (81.5)	366 (85.3)	91 (68.9)	74 (66.7)	28 (56.0)
Non-Endometroid	100 (18.5)	63 (14.7)	41 (31.1)	37 (33.3)	22 (44.0)
Overall AJCC stage					
I	428 (79.3)	362 (84.4)	78 (59.1)	66 (59.5)	17 (34.0)
II	69 (12.8)	49 (11.4)	25 (18.9)	20 (18.0)	11 (22.0)
III/IV	43 (8.0)	18 (4.2)	29 (22.0)	25 (22.5)	22 (44.0)
FIGO Grade					
I	288 (53.3)	250 (58.3)	47 (35.6)	38 (34.2)	10 (20.0)
II	125 (23.2)	102 (23.8)	27 (20.5)	23 (20.7)	11 (22.0)
III	73 (13.5)	41 (9.6)	36 (27.3)	32 (28.8)	18 (36.0)
Not Reported/Missing	54 (10.0)	36 (8.4)	22 (16.7)	18 (12.2)	11 (22.0)
Primary treatment					
Hysterectomy	527 (97.6)	422 (98.4)	120 (90.9)	105 (94.6)	46 (92.0)
Chemotherapy	45 (8.3)	26 (6.1)	20 (15.2)	19 (17.1)	17 (34.0)
Hormone therapy	6 (1.1)	6 (1.4)	2 (1.5)	0 (0)	0 (0)
Radiation therapy	168 (31.1)	124 (28.9)	52 (39.4)	44 (39.6)	21 (42.0)
Not Received	33 (6.1)	16 (3.7)	25 (18.9)	17 (15.3)	12 (24.0)
New Primary Cancer	92 (17.0)	63 (14.7)	33 (25.0)	29 (26.1)	2 (4.0)
Family History of Uterine or Colorectal Cancer	88 (16.3)	64 (14.9)	27 (20.5)	24 (21.6)	12 (24.0)
BMI (kg/m^2)	32.3 (7.9)	32.1 (17.1)	33.2 (17.6)	33.0 (9.1)	33.3 (17.6)
Smoker (Ever)	271 (50.2)	218 (50.8)	62 (47.0)	53 (47.8)	19 (38.0)
Lifetime recreational PA (Mets-hours/week/year)	12.1 (9.2)	12.5 (9.6)	11.2 (8.9)	10.5 (7.5)	10.6 (7.3)
Metabolic Syndrome	325 (60.2)	248 (57.8)	87 (65.9)	77 (69.4)	37 (74.0)
Metabolic Syndrome Components					
0–1	81 (15.0)	68 (15.9)	15 (11.4)	13 (11.7)	5 (10.0)
2	114 (21.1)	98 (22.8)	23 (17.4)	16 (14.4)	6 (12.0)
3	147 (27.2)	117 (27.3)	32 (24.2)	30 (27.0)	18 (36.0)
4	130 (24.1)	95 (22.1)	41 (31.1)	35 (31.5)	14 (28.0)
5	48 (8.9)	36 (8.4)	14 (10.6)	12 (10.8)	5 (10.0)

Characteristics (Mean (SD); N (%))	All (n = 540)	Alive (*n* = 429)	Disease-Free Survival (*n* = 132)	Overall Deaths (*n* = 111)	Cancer-Specific Deaths (*n* = 50)
Waist Circumference (cm)	98.0 (18.8)	97.4 (18.2)	100.6 (20.1)	100.5 (20.9)	99.1 (22.5)
Fasting Glucose (mg/dL)	122.6 (43.4)	123.2 (44.1)	120.1 (38.7)	120.4 (40.4)	118.3 (38.5)
Triglycerides (mg/dL)	146.8 (97.9)	143.8 (97.5)	161.6 (102.7)	158.2 (98.7)	154.6 (87.8)
HDL Cholesterol (mg/dL)	37.3 (12.7)	37.9 (12.4)	34.9 (13.7)	35.2 (13.8)	36.3 (13.9)
Hypertension (self-reported)	186 (34.4)	133 (31.0)	57 (43.2)	53 (47.8)	22 (44.0)

AJCC: American Joint Committee on Cancer, FIGO: International Federation of Gynecology and Obstetrics, BMI: body mass index (kg/m^2), PA: Physical Activity, HDL: High-Density Lipoprotein.
Women with incomplete TMN stage (n = 8) were categorized as Stage I.

In the multivariable-adjusted analyses, a statistically significant association between metabolic syndrome and worse overall survival (HR = 1.98, 95% CI = 1.07–3.67) was observed (Table 2). The association with metabolic syndrome and endometrial cancer-specific survival did not reach statistical significance (HR = 1.80, 95% CI = 0.75–4.33). Likewise, there was insufficient evidence of associations between metabolic syndrome with disease-free survival or endometrial cancer recurrence in these analyses (Table 2).

Table 2. Disease-Free Survival, Overall Survival, Endometrial Cancer-Specific Survival and Recurrence Outcomes for Endometrial Cancer Survivors in the Alberta Endometrial Cancer Cohort, Alberta, Canada (N = 520).

	Disease-Free Survival (*n* = 125/520)		Overall Survival (*n* = 106/520)		Endometrial Cancer-Specific Survival (*n* = 48/520)		Recurrence (*n* = 69/520)	
	Events /Cases	Multivariable HR (95% CI)	Events /Cases	Multivariable HR (95% CI)	Events /Cases	Multivariable HR (95% CI)	Events /Cases	Multivariable HR (95% CI)
Metabolic Syndrome								
No	38/195	1.00	29/195	1.00	11/195	1.00	22/195	1.00
Yes	87/325	1.05 (0.68–1.63)	77/325	1.98 (1.07–3.67)	37/325	1.80 (0.75–4.33)	47/325	0.77 (0.43–1.38)
Waist Circumference (cm)								
<88	32/168	1.00	28/168	1.00	13/168	1.00	18/168	1.00
≥88	90/345	1.66 (0.98–2.79)	75/345	2.12 (1.18–3.80)	34/345	2.14 (0.73–6.31)	50/345	1.21 (0.58–2.52)
Per 5 cm increase		1.11 (1.00–1.24)		1.21 (1.07–1.36)		1.09 (0.91–1.31)		1.04 (0.90–1.21)
Fasting Glucose (mg/dL)								
<100	44/177	1.00	38/177	1.00	17/177	1.00	25/177	1.00
≥100	78/336	NR	65/336	NR	30/336	0.65 (0.33–1.31)	42/336	0.77 (0.46–1.30)
Per 5 mg/dL increase		0.98 (0.95–1.00)		0.98 (0.96–1.01)		NR		0.98 (0.95–1.01)
Triglycerides (mg/dL)								
<150	69/331	1.00	58/331	1.00	24/331	1.00	38/331	1.00
≥150	53/182	1.35 (0.90–2.02)	45/182	1.32 (0.83–2.10)	23/182	1.26 (0.56–2.86)	30/182	1.08 (0.61–1.89)
Per 5 mg/dL increase		1.01 (1.00–1.01)		1.00 (0.99–1.01)		1.00 (0.98–1.01)		1.00 (0.98–1.01)
HDL Cholesterol (mg/dL)								
≥50	16/73	1.00	14/73	1.00	7/73	1.00	9/73	1.00
<50	106/440	0.61 (0.34–1.08)	89/440	0.55 (0.29–1.03)	40/440	0.31 (0.12–0.82)	59/440	0.63 (0.29–1.34)
Per 5 mg/dL increase		0.94 (0.87–1.02)		0.96 (0.88–1.04)		1.01 (0.85–1.21)		0.95 (0.85–1.06)
Hypertension								
No	70/339	1.00	54/339	1.00	26/339	1.00	44/339	1.00
Yes	52/174	0.90 (0.60–1.34)	49/174	1.18 (0.77–1.81)	21/174	1.01 (0.85–1.21)	24/174	0.55 (0.31–1.00)

Hazard Ratios (HR), Confidence Interval (CI), Not Reported (NR), Components models (n = 513).

Multivariable models adjusted for stage (I/missing, II, III/IV), grade (I/II, III, missing), primary treatment(s) (hysterectomy, hysterectomy/chemotherapy, hysterectomy/radiation, hysterectomy/chemotherapy/ radiation and/or hormone therapy, missing treatment), baseline age (years), non-linear age (age^2) and continuous BMI (kg/m^2). Disease-free survival model additionally adjusted for time to first new primary cancer; Overall survival additionally adjusted for time to first new primary cancer/recurrence; Endometrial cancer-specific survival additionally adjusted for time to first recurrence.

All models for metabolic syndrome components were mutually adjusted for the other components.

Disease-free survival and overall survival metabolic syndrome multivariable models were additionally adjusted for number of major comorbidities (0, 1, ≥2).

For the individual components of metabolic syndrome, waist circumference (≥88 cm) was associated with statistically significantly worse overall survival (HR = 2.12, 95% CI = 1.18–3.80) but not disease-free survival (HR = 1.66, 95% CI = 0.98–2.79), endometrial cancer-specific survival (HR = 2.14, 95% CI = 0.73–6.31) or recurrence (HR = 1.21, 95% CI = 0.58–2.52). Positive linear dose-response relationships were observed per 5 cm increase in waist circumference with overall survival ($HR_{per\ 5\ cm}$ = 1.21, 95% CI = 1.07–1.36) and disease-free survival ($HR_{per\ 5\ cm}$ = 1.11, 95% CI = 1.00–1.24) in the multivariable-adjusted models.

Lifetime recreational physical activity prior to diagnosis (MET-hours/week/year) significantly modified (*p*-value<.05) the associations between metabolic syndrome, waist circumference (per 5 cm), HDL cholesterol (per 5 mg/dL) and hypertension with overall survival as well as the association between HDL cholesterol (per 5 mg/dL) and disease-free survival in the multivariable-adjusted models. Specifically, among endometrial cancer survivors with lower lifetime recreational physical activity (<9.7 MET-hours/week/year), those with metabolic syndrome had worse overall survival (HR = 2.45, 95% CI = 1.19–5.05) compared to participants without the syndrome. No association with metabolic syndrome and overall survival was observed among survivors with higher recreational physical activity (for ≥9.7 MET-hours/week/year, HR = 0.88, 95% CI = 0.46–1.69). Increasing waist circumference was associated with worse overall survival for women with lower ($HR_{per\ 5\ cm}$ = 1.30, 95% CI = 1.13–1.49), as well as higher ($HR_{per\ 5\ cm}$ = 1.16, 95% CI = 1.02–1.32) lifetime recreational physical activity. Improved overall survival ($HR_{per\ 5\ mg/dL}$ = 0.85, 95% CI = 0.76–0.96) and disease-free survival ($HR_{per\ 5\ mg/dL}$ = 0.85, 95% CI = 0.76–0.94) was observed for greater HDL cholesterol levels (per 5 mg/dL) among women with lower physical activity. Lastly, hypertension was associated with worse overall survival (HR = 1.80, 95% CI = 1.02–3.18) among endometrial cancer survivors with lower lifetime recreational physical activity.

Finally, the models assessing the number of metabolic syndrome components and fasting blood glucose did not satisfy the proportional hazard assumption and are therefore not reported.

4. Discussion

In the current study, endometrial cancer survivors with metabolic syndrome had approximately a two-fold decrease in overall survival compared to study participants who did not have this syndrome. Our findings also suggest that metabolic syndrome may be associated with worse endometrial cancer-specific survival although the association was not statistically significant in the multivariable-adjusted model. There was insufficient evidence of an association between metabolic syndrome and disease-free survival or endometrial cancer recurrence in the present study. Finally, of the individual metabolic syndrome components, only waist circumference was observed to be associated with survival outcomes.

To our knowledge, this investigation is the first study among endometrial cancer survivors to use a standardized definition of metabolic syndrome to test its association with survival outcomes as well as the first conducted in a North American context. Our findings are generally consistent with prior literature that observed worse overall and endometrial cancer-specific survival with metabolic syndrome among endometrial cancer survivors. Ni and colleagues [28] used a study-specific definition of metabolic syndrome (presence of ≥three of the following components: history of Type 2 diabetes, medically-treated hypertension, diagnosed or treated hyperlipidemia and either waist circumference ≥ 80 cm or BMI ≥28 kg/m^2) to assess the association with all-cause mortality among histologically confirmed endometrial cancer cases (n = 385; n = 64 deaths) in China. The authors noted that endometrial cancer survivors with the study-specific metabolic syndrome had 6.65 (95% CI = 1.93, 47.79) times the hazard of all-cause mortality compared to those without metabolic syndrome [28]. The same study-specific metabolic syndrome definition used by Ni et al. [28], was also associated with worse overall survival among 139 Chinese non-endometrioid uterine cancer patients [29]. Within the Metabolic Syndrome and Cancer Project (Me-Can), metabolic syndrome was associated with 1.56 (95% CI = 1.32, 1.84) times the hazard of uterine cancer-specific mortality per one-unit increment of composite metabolic syndrome Z-score [30].

In the current study, women with a waist circumference above 88 cm had approximately half the overall survival compared to women with a waist circumference below 88 cm. Furthermore, for every additional 5 cm increase in waist circumference above 88 cm, women were estimated to have a 21% decrease in overall survival and an 11% decrease in disease-free survival. Our findings also suggest that greater waist circumference may also be associated with worse disease-free survival, endometrial cancer-specific survival and recurrence although these associations were attenuated by BMI. Previous research has shown that both waist circumference and BMI are positively correlated with estrogen levels in endometrial cancer survivors, unopposed estrogens released by adipose tissue is a known risk factor of endometrial cancer tumor proliferation [10,31]. The underlying mechanism of pathogenesis via adipose tissue and elevated estrogen concentrations may partially explain why the associations between waist circumference with disease-free survival, endometrial cancer-specific survival and recurrence were attenuated by BMI. However, waist circumference is a strong indicator of central adiposity which has been positively associated with additional biological mechanisms related to hyperglycemia, dyslipidemia, hyperinsulinemia and systemic inflammation that may also drive tumor pathogenesis [10]. Previous findings from the Nurses' Health Study observed that women had a 34% (95% CI = 23%–39%) increase in all-cause mortality and a 18% (95% CI = 9%–28%) increase in obesity-related (colon cancer, breast cancer, pancreatic cancer, uterine, ovarian, and

kidney cancer) cancer mortality per ~10 cm increase in waist circumference in multivariable adjusted models including adjustments for BMI [32].

To our knowledge, the present study is the first to assess whether lifetime physical activity prior to diagnosis impacts the relationship between metabolic syndrome at diagnosis and its components with survival outcomes among endometrial cancer survivors. Our findings suggest that women with greater lifetime recreational physical activity participation do not experience the same harmful associations between metabolic syndrome, waist circumference, and hypertension with overall survival compared to those with lower amounts of lifetime physical activity participation. A protective association was also observed with increasing HDL cholesterol and survival outcomes among women with lower lifetime physical activity participation. These findings add to current literature that suggests cancer survivors with greater physical activity participation experience better survival, although specific estimates among endometrial cancer survivors are limited [33,34]. Arem and colleagues previously reported an association between pre-diagnosis recreational moderate-to-vigorous-intensity physical activity and lower overall 5-year mortality, but not 10-year mortality, endometrial cancer-specific mortality or all-cause mortality in the Women's Health Initiative [35] and the National Institutes of Health- American Association of Retired Persons (NIH–AARP) Diet and Health Study [36].

This study has several key strengths, including a substantial study follow-up time of nearly 17 years. Participants were representative of the larger endometrial cancer survivor population living in Alberta since cases were originally identified through the Alberta Cancer Registry which has a $\geq$ 95% case ascertainment rate [37] of histologically confirmed, endometrial cancer cases. Additionally, data linkage with national and provincial registries ensured that comprehensive vital status data were captured. Direct measurements of most of the metabolic syndrome components, particularly the anthropometric measures and blood assays, were assessed in multiple to provide valid and reliable data. Finally, covariates were extensively measured during the in-person interviews and interviewers were trained with cognitive interview methods.

Some limitations must be acknowledged in the current study. Primarily, the small sample size and limited number of events may have hindered the ability of the current study to observe statistically significant associations. Particularly the estimates of endometrial cancer-specific survival and recurrence should be interpreted with caution because of the small number of events in the dichotomized analyses. Larger studies are thus needed to confirm and contribute to our findings. Moreover, some results could not be presented because the proportional hazard assumptions were violated. The metabolic syndrome was only assessed at the time of cancer diagnosis and may not represent an individual's health status for the entire follow-up period. Consequently, the prevalence of metabolic syndrome may have been underestimated in this cohort. However, previous findings from the Atherosclerosis Risk in Communities Study suggest that, for the majority of individuals (76%), the severity of metabolic syndrome increases over time [38]. Moreover, medical treatment of individual risk factors failed to reduce the severity of metabolic syndrome during the follow-up period in the Atherosclerosis Risk in Communities Study [38]. Therefore, women in the current study likely did not have improved metabolic heath status during follow-up if they had metabolic syndrome or some of its components at baseline. Finally, given that the study participants represent a largely homogenous group of White

(93.9%), well educated (67.2% ≥ high school education), endometrial cancer survivors living in Alberta, the current findings may not be generalizable to all populations including racial-ethnic minority populations in Canada.

Given that endometrial cancer mortality rates are currently rising [3,4] and women living with endometrial cancer have greater amounts of diagnosed, undiagnosed or undertreated cardiometabolic risk factors compared to the general population [39], identifying opportunities to intervene is becoming increasingly important. In this study, the results suggest that the association between metabolic syndrome and endometrial cancer survival is largely explained by central adiposity. Moreover, endometrial cancer survivors with greater lifetime recreational physical activity had improved survival despite metabolic syndrome risk factors compared to those with lower lifetime physical activity. Additional research is needed to confirm these results and improve our understanding of the role of physical activity and other lifestyle factors in modifying the metabolic syndrome and survival associations among endometrial cancer survivors.

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Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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