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Monograph

Body composition and endometrial cancer outcomes

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Background: Obesity is a known risk factor for developing endometrial cancer. However, the association of obesity with endometrial cancer (EC) outcomes has not been clearly established. This study examined how outcomes in women with early stage EC vary with body composition measured via computed tomography (CT).

Methods: In this retrospective study, patients diagnosed with EC international Federation of Gynecology and Obstetrics stages I-III and available CT scans were included. Automatica software was used to assess the areas of visceral adipose tissue, subcutaneous adipose tissue (SAT), and intermuscular adipose tissue (IMAT) and skeletal muscle area.

Results: Of 293 patient charts assessed, 199 met eligibility criteria. Median body mass index (BMI) was 32.8 kg/m^2 (interquartile range [IQ] = 26.8-38.9); 61.8% had histologic subtype endometrioid carcinoma. Adjusted for age, international Federation of Gynecology and Obstetrics stage, and histologic subtype, a BMI of at least 30 vs less than 30 kg/m^2 was associated with lower endometrial cancer–specific survival (ECSS) (hazard ratio [HR] = 2.32, 95% confidence interval [CI] = 1.27 to 4.25) and overall survival (OS) (HR = 2.7, 95% CI = 1.35 to 5.39). Higher IMAT 75th vs 25th percentile and SAT of at least 225.6 vs less than 225.6 cm^2 were associated with lower ECSS (HR = 1.53, 95% CI = 1.1 to 2.13, and HR = 2.57, 95% CI = 1.13 to 5.88) and OS (HR = 1.50, 95% CI = 1.11 to 2.02, and HR = 2.46, 95% CI = 1.2 to 5.01), respectively. The association of visceral adipose tissue (75th vs 25th percentile) with ECSS and OS was not statistically significant (HR = 1.42, 95% CI = 0.91 to 2.22, and HR = 1.24, 95% CI = 0.81 to 1.89).

Conclusion: Higher BMI, IMAT, and SAT were associated with higher mortality from EC and lower OS. A better understanding of the mechanisms underlying these relationships could inform strategies to improve patient outcomes.

Endometrial cancer (EC) incidence and mortality are increasing (1,2). Obesity has a key role in endometrial cancer incidence, with half of cases attributed to being obese or overweight (3-6).

The association between obesity and EC outcomes is not fully understood. Studies examining the association between obesity and endometrial cancer mortality have revealed conflicting results. One potential reason for this is the use of body mass index (BMI) to measure bode size. BMI fails to distinguish body composition (ie, percentage visceral and subcutaneous fat and muscle mass) that is associated with metabolic health and cancer outcomes. Therefore, screening by BMI alone could misclassify mortality risk among endometrial cancer patients. Indeed, the metabolic dysfunction commonly observed among individuals with obesity has been associated with obesity-related cancers, independent of BMI (7-11). Moreover, studies have included populations predominantly Caucasian with varied distribution of EC subtypes, leading to inconsistent results, because BMI has a greater association with type I than type II tumors (9).

Despite the paradoxical association between obesity and EC outcomes, there is an established positive association between high BMI and mortality in other cancer types, such as higher mortality in obese breast cancer patients (12).

Distinguishing between body compartments such as visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) is important as these compartments may have different metabolic profiles. VAT is metabollically active, increasing the production of estrogen and secreting adipokines and cytokines that may result in inflammation, insulin resistance, angiogenesis, and immune system disregulation (5,13-15). SAT produces adiponectin, an adipokine associated with increased insulin sensitivity and decreased inflammation, confering the cell antiangiogenic, anti-inflammatory, and inhibitory properties (14,16,17). Different metabolic profiles have been used, for instance, in the recognition of sarcopenia and higher risk of death in other cancer sites, such as nonmetastatic breast cancer but, to our knowledge, those different metabolic profiles have not been studied in early stage EC (18).

Computed tomography (CT) and magnetic resonance imaging are the current standards for quantifying visceral adiposity and muscle mass (19,20). In EC populations, one study used CT in

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patients with advanced or recurrent EC (21), and another used magnetic resonance imaging for characterization of body composition in patients with early stage EC (22). These studies suggest that visceral adiposity may be an important prognostic factor in EC (21,22). However, the association of other measured body composition components, namely, SAT, intermuscular adipose tissue (IMAT), and skeletal muscle area (SMA), with outcomes is not well understood. The purpose of this study was to investigate the association between body composition, BMI, and outcomes in patients with nonmetastatic EC. The main hypothesis was that higher VAT would be associated with shorter EC-specific survival (ECSS) and that higher levels of adipose tissue would be related to worse outcomes.

Methods

This retrospective cohort study analyzed data from patients recently diagnosed with early stage EC (stage I-III) at the London Regional Cancer Program, London Health Sciences Center, in London, Ontario, Canada, from January 2010 to December 2020. Inclusion criteria included adults (aged 18 years or older), histologically confirmed EC, and an abdominal and pelvic CT scan available for determination of body composition (within 90 days prior or after surgery). Of 293 patient charts assessed, 199 patients met the eligibility criteria.

The original protocol and all amendments were approved by the Western University Health Science research ethics board in 2020. The study was conducted in accordance with the protocol. No written informed consent was needed as all data were de-identified and retrospective. All de-identified data were collected by investigators and associated site personnel, analyzed by the statistician, and interpreted by the authors. All authors participated in reviewing and editing the manuscript, approved the submitted draft, and attested that the study was conducted in accordance with the protocol.

Data collection included age, height, weight, stage of EC (using the American Joint Committee tumor-node-metastasis staging and the international Federation of Gynecology and Obstetrics [FIGO] systems), tumor grade, histologic subtypes, date of recurrence and death, cause of death, and treatment type (chemotherapy, radiation, and/or surgery). BMI was calculated from height and weight measured objectively by clinic staff at diagnosis. Baseline CT scans were used to measure SAT, VAT, SMA, and IMAT. Measurements were taken from a single abdominal cross-sectional slide at the third lumbar area, which is correlated to body size (23), and images were analyzed using a validated automatic software called Automatica (17). SAT, VAT, IMAT, and SMA were quantified as surface area in squared centimeters as illustrated in Figure 1.

The primary endpoint was EC-specific survival (defined as time from EC diagnosis to death from EC). Secondary endpoints included endometrial distant recurrence–free survival (EDRFS; defined as the length of time from initial diagnosis to distant recurrence), and overall survival (OS; defined as time from the date of diagnosis to death from any cause).

The SAT area makes up the outer part of the CT image, and in some cases, the SAT area on the image was partially truncated. The degree of truncation was classified as clinically significant (n = 39), slightly significant (n = 78), or no significant (n = 82) by visual inspection of the images by 2 observers. Truncation was not random but tended to happen in larger women (mean BMI in the 3 groups were 43, 34, and 29 kg/m^2). All cases with significant truncation had a truncated SAT area measured at 225.6 cm^2 or larger. Because their untruncated areas would be even larger, their SAT areas could be accommodated in a categorical variable with high (≥225.6 cm^2) vs low (<225.6 cm^2) categories. Overall, approximately 75% of observations were assigned to the high SAT group (39 significantly truncated, 64 slightly truncated, and 44 untruncated cases).

Correlations among age, body composition variables, FIGO, and histologic subtype were calculated as follows: among the continuous variables age, BMI, VAT, IMAT, and SMA, Pearson correlations; between continuous and binary variables, point biserial correlations; among binary variables, phi coefficients. Kaplan–Meier survival plots were constructed for ECSS, OS, and EDRFS. Multivariable Cox proportional hazards models were used to examine the association of BMI, VAT, SAT, IMAT, and SMA with the survival outcomes, adjusted for the prognostic factors age, FIGO stage with categories I vs II and III, and histologic subtype with categories low risk (endometrioid) vs high risk (other). Hazard ratios (HRs) and 95% confidence intervals (CIs) for the continuous variables VAT, IMAT, and SMA were calculated at the 75th vs the 25th percentile (P_{75} vs P_{25}) of each variable's distribution, namely VAT 220 vs 94 cm^2, IMAT 25 vs 10 cm^2, and SMA 135 vs 103 cm^2. BMI was entered categorically into the regression model as obese (BMI ≥ 30 kg/m^2) vs nonobese (BMI < 30 kg/m^2) as was SAT with categories high (≥225.6 cm^2) vs low (<225.6 cm^2). In secondary analyses, we tested for effect modification by each of age, FIGO stage, and histologic subtype. These effect medication tests were performed by fitting survival models that include an interaction term for the body composition variable by the effect modifier. The Wald-type *P* value corresponding to the interaction term was reported.

The main hypothesis and outcome of the study were prespecified. Confidence intervals were provided, and effect sizes taken into account, and *P* values of at least .05 were taken as a guide to statistical significance, and no adjustment were made for multiple comparisons. Analyses were performed in S-PLUS 6.2.

Results

A total of 293 patient charts were assessed. Of these, 199 patients met the eligibility criteria (Figure 2). The median age was 65 years (interquartile range [IQR] = 58-71 years). By the FIGO staging system, 121 (60.8%) patients had stage I disease, 28 (14.1%) had stage II disease, and 50 (25.1%) had stage III disease. The median BMI was 32.8 kg/m^2 (IQR = 26.8-38.9) with 58.8% classified as obese. The most common histologic subtype was endometrioid carcinoma with 123 (61.8%) patients, followed by serous adenocarcinoma with 43 (21.6%) and carcinosarcoma with 19 (9.5%) (see Table 1).

The distributions of VAT, IMAT, and SMA area were fairly symmetric (Table 2). The mean values of VAT area, IMAT area, and SMA area were 158 (90.1) cm^2, 19.2 (12.4) cm^2, and 121.3 (22.9) cm^2, respectively. Low (<225.6 cm^2) SAT area and high (≥225.6 cm^2) SAT area were present in 52 (26.1%) and 147 (73.9%) cases.

Age was moderately correlated with increased IMAT ($r = 0.4$) and decreased SMA ($r = -0.4$) (Table 2). BMI correlated strongly with markers of adiposity ($r = 0.7$ for VAT, $r = 0.6$ for SAT, and $r = 0.5$ for IMAT) and with SMA ($r = 0.6$). SAT and VAT correlated strongly with each other ($r = 0.6$), and each of SAT and VAT correlated moderately with IMAT ($r = 0.4$ for both). SMA also correlated strongly with VAT ($r = 0.5$) and moderately with SAT ($r = 0.3$). FIGO stage and histologic subtype risk level were weakly but

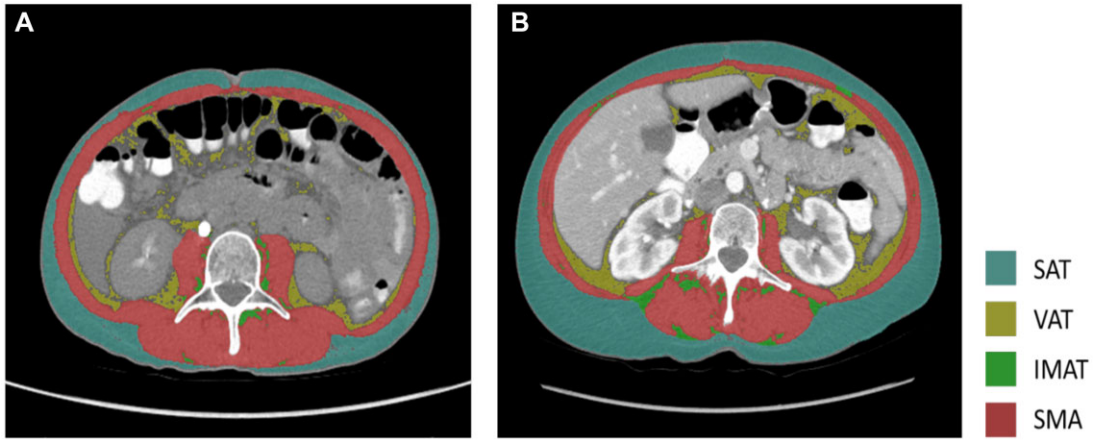

Figure 1. Women with similar BMI and ages but different body compositions. BMI for each is 22 kg/m^2. Compared with **(A)**, **(B)** has more SAT (**blue**), VAT (**yellow**), and IMAT (**green**) and less SMA (**red**). Patient ages are 59 and 58 years, respectively. Body measurements in cm^2 are SAT 54 vs 124, VAT 19 vs 24, IMAT 3 vs 7, and SMA 110 vs 92, respectively. BMI = body mass index measured in kg/m^2; IMAT = intermuscular adipose tissue; SAT = subcutaneous adipose tissue; SMA = skeletal muscle area; VAT = visceral adipose tissue.

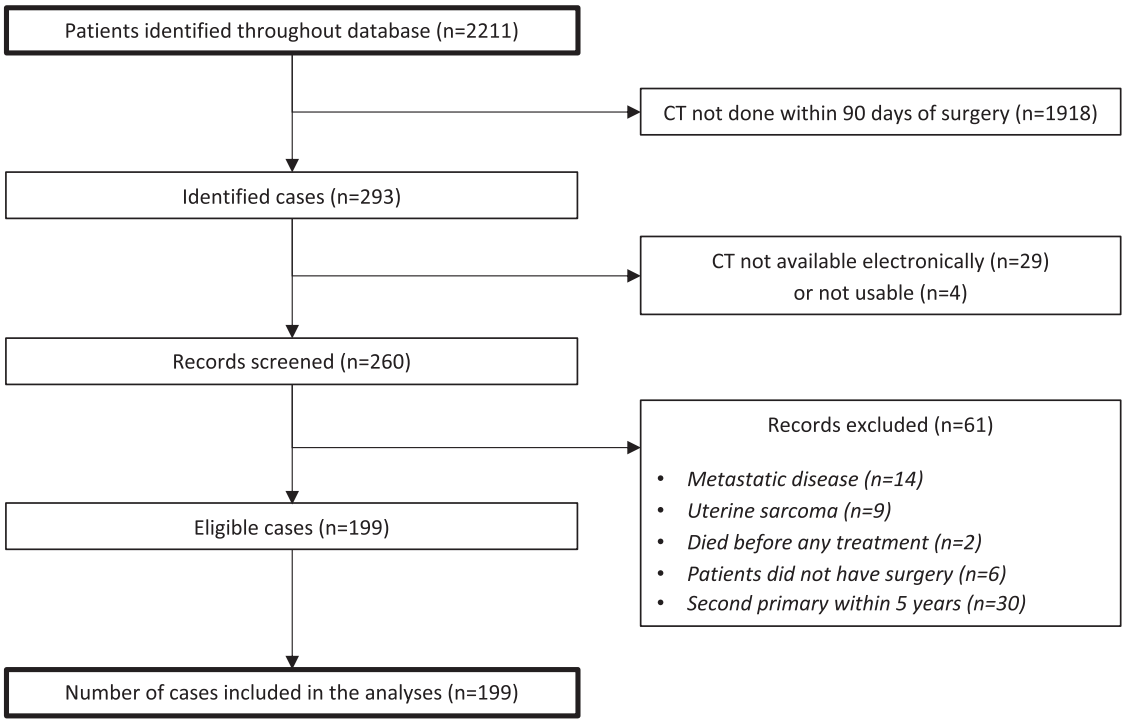

Figure 2. Patient flow. CT = computed tomography.

negatively correlated with BMI, VAT, and SMA ($-0.2 < r < -0.1$) and were uncorrelated with age and IMAT ($0 < r < 0.07$). In particular, 64% of FIGO stage I patients were obese vs 50% of FIGO stage II and III patients.

The median follow-up times for ECSS, OS, and EDRFS were 4.2 years, 4.5 years, and 3.3 years, respectively. Of 199 patients, 49 (24.6%) died from any cause, and 39 (79.6%) died from EC. EC recurred in 47 (23.6%) patients; 39 of 47 patients had distant recurrences. ECSS, OS, and EDRFS at 5 years were 76%, 72%, and 70%, respectively (Figure 3).

Cox proportional hazards models were used to model the relationship between body composition and the survival outcomes (Table 3). When adjusted for age, FIGO stage and histologic subtype, the hazard ratio of VAT (P_{75} vs P_{25}) for EC death was 1.42 (95% CI = 0.91 to 2.22), which at a P value equal to .12 was not statistically significant. However, obesity, SAT (high vs low), and IMAT (P_{75} vs P_{25}) were associated with lower ECSS (HR = 1.73, 95% CI = 1.16 to 2.57; $P = .0067$; HR = 2.57, 95% CI = 1.13 to 5.88; $P = .025$; and HR = 1.53, 95% CI = 1.1 to 2.13; $P = .012$, respectively). Similar results were obtained for OS as for ECSS. None of the body composition relationships with EDRFS was statistically significant.

When effect modification models were fitted for the body composition variables with each of FIGO, histologic subtype, and age, it was found that higher IMAT was strongly associated with reduced survival for FIGO stage I but not for higher FIGO stages. For FIGO stage I, the IMAT hazard ratio related to ECSS was 3.60 (95% CI = 1.9 to 6.83; $P = .0001$; vs HR = 1.18, 95% CI = 0.78 to 1.79;

$P = .44$ for FIGO stage II and III; $P_{interaction} = .0033$). A similar pattern with slightly lower hazard ratios was seen for OS and EDRFS (Table 4).

Discussion

In this hospital-based retrospective cohort study among females recently diagnosed with early stage EC (stage I-III) in Canada, we found that higher IMAT and higher SAT were associated with lower ECSS and OS, and BMI was associated with lower OS and ECSS when adjusted by age, FIGO stage, and histology. In contrast to our hypothesis, we did not find an association between VAT and survival as shown by Celik et al. (22). In this study, we could not demonstrate a positive association among higher BMI, SAT, IMAT, or SMA and higher relapse rates. This could possibly be explained by lack of power because of the somewhat shorter follow-up for distant recurrences.

Potential explanations for the relationship between body composition and cancer outcomes are the effect of body composition on estrogen levels, inflammation, and oxidative stress (24,25). Obese individuals tend to have higher levels of estrogen and a decrease in sex hormone–binding globulin, a protein that binds to and inactivates estrogen. This increase in estrogen may stimulate the growth of EC cells and contribute to the higher risk and poorer outcomes seen in obese individuals with the disease (26). Furthermore, obesity is associated with an increase in chronic low-grade inflammation, which has been linked to an increased risk of cancer. It is thought that the pro-inflammatory cytokines and adipokines released by fat cells may stimulate the growth and spread of cancer cells. Finally, obesity may also increase oxidative stress, which can damage DNA and contribute to the development and progression of cancer (27,28).

This study found that markers of adiposity (SAT, VAT, and IMAT) correlated with each other, with BMI, and with SMA, corroborating findings by de Paula and Chaves. (29). Furthermore, aligning with previous longitudinal research showing that skeletal muscle mass and strength tends to decline with age (30), this study found that age correlated positively with IMAT and negatively with SMA and BMI highlighting the importance of age as a prognostic parameter in patients with EC (31).

In this study, higher BMI was associated with higher mortality from EC and lower OS. The findings of this study are supported by data shown by Calle et al. (8) in a prospective study in which women with EC and a BMI of at least 40 kg/m^2 had a relative risk of death of 6.25. Additionally, Kokts-Porietis et al. (9) showed in a recent meta-analysis that in patients with EC and a BMI of at least 30 kg/m^2 (compared with BMI < 30 kg/m^2), there was an association with increased all-cause mortality (HR = 1.34, 95% CI = 1.12 to 1.59) and recurrence (HR = 1.28, 95% CI = 1.06 to 1.56).

Muscle quality, measured not only as skeletal muscle loss (sarcopenia) but also with muscle fat deposition, has gained relevance for investigation purposes in cancer patients (32). However, to our knowledge, this has not been studied yet in EC populations. Our study is the first to find a statistically significant association between IMAT and poorer ECSS and OS in patients with early stage EC. Furthermore, an effect modification model using FIGO stage indicated that higher IMAT is statistically significant for lower ECSS and OS, specifically when FIGO stage is I. This should be studied in a larger cohort.

Table 1. Patient characteristics[a]

Patient characteristics (n = 199)	
Age median (IQR), y	65 (58-71)
BMI, median (IQR), kg/m^2	32.8 (26.8-38.9)
<30	82 (41.2%)
≥30	117 (58.8%)
AJCC stage, No. (%)	
I	122 (61.3)
II	26 (13.1)
III	51 (25.6)
FIGO stage, No. (%)	
I	121 (60.8)
II	28 (14.1)
III	50 (25.1)
Histologic subtype, No. (%)	
Endometrioid	123 (61.8)
Carcinosarcoma	19 (9.5)
Clear cell carcinoma	10 (5)
Serous carcinoma	43 (21.6)
Undifferentiated or dedifferentiated carcinoma	4 (2.0)
Received adjuvant chemotherapy, No. (%)	
No	149 (74.9)
Yes (carboplatin and paclitaxel, n = 49; cisplatin and ifosfamide, n = 1)	50 (25.1)
Received adjuvant radiation, No. (%)	
No	61 (30.7)
Yes	133 (66.8)
Unknown	5 (2.5)

[a] AJCC = American Joint Committee tumor-node-metastasis staging; BMI = body mass index; FIGO = International Federation of Gynecology and Obstetrics systems; IQR = interquartile range.

Table 2. Summary statistics and correlations for age and body composition variables including correlations with FIGO stage and histologic subtype[a]

			Age		BMI		VAT		SAT		IMAT		SMA	
Variable	**Mean (SD)**	**Median (IQR)**	***r***	***p***	***r***	***p***	***r***	***p***	***r***	***p***	***r***	***p***	***r***	***p***
Age	65.2 (9.8)	65 (58-71)			-0.1	0.081	0.0	0.86	0.0	0.64	0.4	<.0001	-0.4	<.0001
BMI	33.6 (9)	32.8 (26.8-38.9)	-0.1	0.081			0.7	<.0001	0.6	<.0001	0.5	<.0001	0.6	<.0001
VAT	158 (90.1)	154 (94-220)	0.0	0.86	0.7	<.0001			0.6	<.0001	0.5	<.0001	0.6	<.0001
SAT	Low: 52 (26.1%)	High: 147 (73.9%)	0.0	0.64	0.6	<.0001	0.6	<.0001			0.4	<.0001	0.3	<.0001
IMAT	19.2 (12.4)	15.9 (10.1-24.6)	0.4	<.0001	0.5	<.0001	0.4	<.0001	0.4	<.0001			0.1	0.41
SMA	121.3 (22.9)	119 (103-135)	-0.4	<.0001	0.6	<.0001	0.5	<.0001	0.3	<.0001	0.1	0.41		
FIGO stage I, II and III			0.04	0.6	-0.14	0.044	-0.13	0.059	-0.16	0.29	0.01	.85	0.04	.6
Histologic subtype levels low risk, high risk			0.07	0.32	-0.16	0.024	-0.17	0.014	-0.19	.0067	-0.005	0.49	0.07	0.32

[a] r = Pearson correlation, $p = P$ value for null hypothesis that $r = 0$, BMI = body mass index; FIGO = International Federation of Gynecology and Obstetrics systems; IMAT = intermuscular adipose tissue; IQR = interquartile range; SAT = subcutaneous adipose tissue; SMA = skeletal muscle area; VAT = visceral adipose tissue.

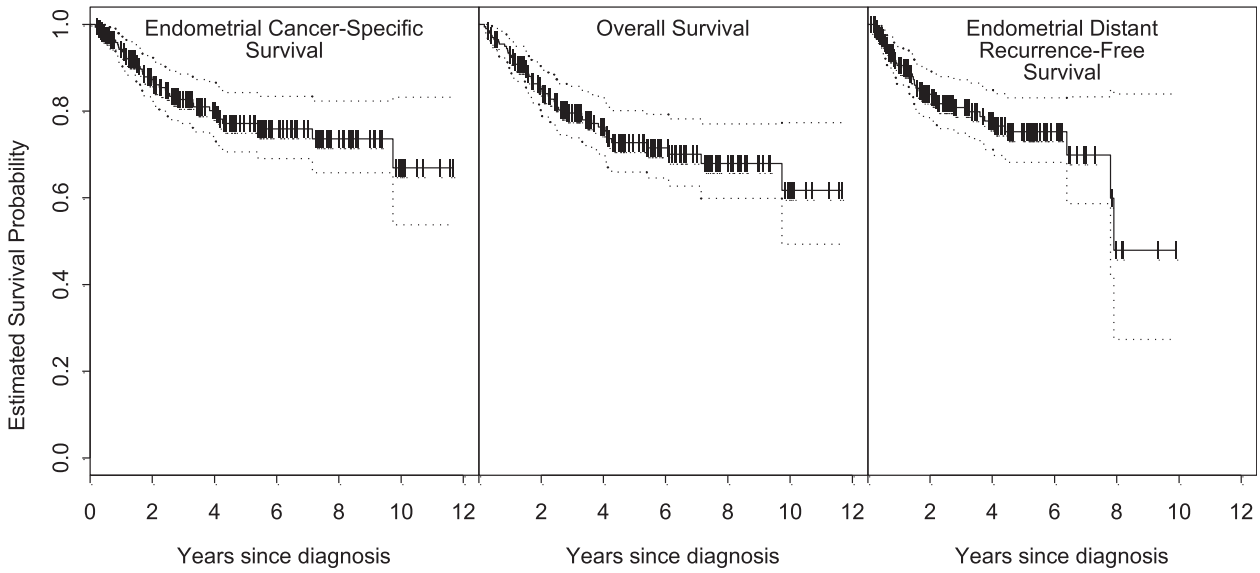

Figure 3. Kaplan–Meier estimates of ECSS, OS, and EDRFS. ECSS = endometrial cancer–specific; EDRFS = endometrial distant recurrence-free survival; OS = overall survival.

Table 3. Multivariable Cox models for body composition variables and ECSS, OS, and EDRFS[a]

	ECSS		OS		EDRFS	
Variable	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
BMI (≥30 vs <30)	2.32 (1.27-4.25)	.0067	2.7 (1.35-5.39)	.005	1.17 (0.61-2.24)	.64
VAT (P_{75} vs P_{25})[c]	1.42 (0.91-2.22)	.12	1.24 (0.81-1.89)	.32	1.20 (0.75-1.91)	.46
SAT (high vs low)[b]	2.57 (1.13-5.88)	.025	2.46 (1.2-5.01)	.013	1.59 (0.75-3.35)	.23
IMAT (P_{75} vs P_{25})[c]	1.53 (1.1-2.13)	.012	1.50 (1.11-2.02)	.0078	1.31 (0.93-1.85)	.12
SMA (P_{75} vs P_{25})[c]	1.50 (0.94-2.41)	.091	1.33 (0.83-2.12)	.24	1.11 (0.66-1.87)	.69

[a] Each model was adjusted for age, FIGO, and histologic subtype. BMI = body mass index; CI = confidence interval; ECSS = endometrial cancer–specific survival; EDRFS = endometrial distant recurrence-free survival; FIGO = FIGO.International Federation of Gynecology and Obstetrics systems; HR = hazard ratio; IMAT = intermuscular adipose tissue; OS = overall survival; SAT = subcutaneous adipose tissue; SMA = skeletal muscle area; VAT = visceral adipose tissue.
[b] High SAT defined as SAT area ≥ 225.6 cm^2.
[c] P_{25}, P_{75} = 25th and 75th percentiles of the variable's distribution, respectively.

Table 4. Multivariable model for IMAT with interaction that lets IMAT differ by FIGO stage status[a]

	ECSS		OS		EDRFS	
Variable	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
$P_{interaction}$	.0033		.005		0.025	
IMAT (P_{75} vs P_{25}) when FIGO stage =I	3.60 (1.9-6.83)	.0001	2.80 (1.67-4.68)	.0001	2.65 (1.34-5.23)	.0049
IMAT (P_{75} vs P_{25}) when FIGO stage =II and III	1.18 (0.78-1.79)	.44	1.15 (0.78-1.70)	.48	1.10 (0.73-1.66)	.65

[a] Model was further adjusted for age and histologic subtype. CI = confidence interval; ECSS = endometrial cancer–specific survival; EDRFS = endometrial distant recurrence-free survival; HR = hazard ratio; IMAT = intermuscular adipose tissue; OS = overall survival.

Sarcopenic obesity is known to be a poor prognostic factor in cancer (33). However, there is considerable heterogeneity defining sarcopenic obesity in the literature. The association of IMAT with SMA and age and the poor outcomes found in this study makes IMAT a candidate to be used in the assessment of sarcopenic obesity. Increased IMAT is associated with inflammation, insulin resistance, and functional deficit in skeletal muscle. Moreover, IMAT levels are dependent on age and independent of BMI (34,35). IMAT may be associated with leptin and C-reactive protein expression (36); however, further studies are needed to characterize the specific secretory profile of IMAT and its use as an index for sarcopenic obesity.

Early identification of sarcopenia in cancer patients is needed. There is a relationship with low lean mass and poorer treatment tolerance, impaired quality of life, and reduced survival in cancer populations (37,38). Early intervention with multimodal and multidisciplinary approaches might counteract the multifactorial nature of cancer-related sarcopenia thus improving cancer outcomes. In addition, the role of metabolic changes in cancer pathogenesis and the contribution of obesity, insulin resistance, and adipocytokines in the increased risk of cancer recurrence and death have been demonstrated (15,39,40). In this study, we conducted anthropometric measurements at diagnosis but did not correlate them with metabolic markers. Thus, a limitation in this study is that it is unknown whether anthropometric measurements combined with metabolic factors (such as circulating levels of high-sensitivity C-reactive protein, tumor necrosis factor alpha, interleukin 6, plasminogen activator inhibitor 1,

adiponectin, C-peptide, insulin, and leptin) are better prognostic markers compared with body composition alone and how metabolic factors could have affected our observations.

Another limitation is that the SAT area on some images was partially truncated. By categorizing SAT, we retained all the cases in the study at the cost of reduced power and a somewhat arbitrary cut-point. However, excluding the truncated points would also reduce power and may introduce bias by preferentially excluding higher BMI patients. We also had a shorter follow-up (<5 years) and will continue to follow this cohort.

In conclusion, higher BMI, IMAT, and SAT were associated with higher mortality from EC and lower OS. This study did not show an association of anthropometric variables with EDRFS. The aim of the study was to explore biological factors that could point to mechanisms of action rather than change clinical practice. Future studies may consider assessing the association of anthropometric measurements and metabolic alterations in ECSS, OS, and EDRFS in early stage EC, as well as the association of body composition according to new molecular classifications in EC, which may provide additional insight in the field of obesity and cancer outcomes.

Data availability

Data will be made available upon reasonable request. Individual patient data are not published to maintain patient confidentiality.

Author contributions

Diana P Arteaga, MD (Conceptualization; Data curation; Investigation; Writing—original draft; Writing—review & editing), Corina DeKraker, MSc (Conceptualization; Data curation), Marguerite Ennis, PhD (Formal analysis; Methodology; Software), Nicole Dewey, MD (Data curation), Emily A. Goebel, MD (Conceptualization; Writing—review & editing), Stephen Welch, MD (Conceptualization), Isabel Pimentel, MD (Conceptualization; Writing—review & editing), Joseph E. Ippolito, MD, PhD (Writing—review & editing), and Ana Elisa Lohmann, MD, PhD (Conceptualization; Funding acquisition; Project administration; Resources; Supervision; Writing—review & editing).

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Conflicts of interest

ME declared consulting fee from Mount Sinai Hospital, London Health Sciences Centre and Sunnybrook Health Sciences Centre. EAG declared honoraria from Merck Canada Inc. AEL declared research funding in kind from Epic Sciences and honorarium from La Roche Posay and Novartis. The other authors declared no potential conflicts of interest.

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The research ethics board approved this study prior to its initiation. The study was conducted according to the guidelines of the declaration of Helsinki and approved by the Western University Health Science Research Ethics Board (HSREB) (protocol waiver 117981, December 22, 2020).

Patient consent was waived considering the retrospective nature of this project and absence of impact the results would bring to patients' management and outcome.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-249. doi:10.3322/caac.21660.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global Cancer Statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries [published correction appears in *CA Cancer J Clin*. 2020;70(4):313]. *CA Cancer J Clin*. 2018;68(6):394-424. doi:10.3322/caac.21492.
3. Onstad MA, Schmandt RE, Lu KH. Addressing the role of obesity in endometrial cancer risk, prevention, and treatment. *J Clin Oncol*. 2016;34(35):4225-4230. doi:10.1200/J Clin Oncol.2016.69.4638.
4. Lauby-Secretan B, Scoccianti C, Loomis D, et al.; for the International Agency for Research on Cancer Handbook Working Group. Body fatness and cancer–viewpoint of the IARC working group. *N Engl J Med*. 2016;375(8):794-798. doi:10.1056/NEJMsr1606602.
5. Donohoe CL, Doyle SL, Reynolds JV. Visceral adiposity, insulin resistance and cancer risk. *Diabetol Metab Syndr*. 2011;3:12. doi:10.1186/1758-5996-3-12.
6. Ali AT. Risk factors for endometrial cancer. *Ceska Gynekol*. 2013;78(5):448-459.
7. Caan BJ, Cespedes Feliciano EM, Kroenke CH. The importance of body composition in explaining the overweight paradox in cancer-counterpoint. *Cancer Res*. 2018;78(8):1906-1912. doi:10.1158/0008-5472.CAN-17-3287.
8. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med*. 2003;348(17):1625-1638. doi:10.1056/NEJMoa021423.
9. Kokts-Porietis RL, Elmrayed S, Brenner DR, Friedenreich CM. Obesity and mortality among endometrial cancer survivors: a systematic review and meta-analysis. *Obes Rev*. 2021;22(12):e13337. doi:10.1111/obr.13337.
10. Merritt MA, Strickler HD, Hutson AD, et al. Sex hormones, insulin, and insulin-like growth factors in recurrence of high-stage endometrial cancer. *Cancer Epidemiol Biomarkers Prev*. 2021;30(4):719-726. doi:10.1158/1055-9965.EPI-20-1613.

11. Von Gruenigen VE, Tian C, Frasure H, Waggoner S, Keys H, Barakat RR. Treatment effects, disease recurrence, and survival in obese women with early endometrial carcinoma: a Gynecologic Oncology Group study. *Cancer*. 2006;107(12):2786-2791. doi:10.1002/cncr.22351.
12. Picon-Ruiz M, Morata-Tarifa C, Valle-Goffin JJ, Friedman ER, Slingerland JM. Obesity and adverse breast cancer risk and outcome: mechanistic insights and strategies for intervention. *CA Cancer J Clin*. 2017;67(5):378-397. doi:10.3322/caac.21405.
13. Stocks T, Borena W, Strohmaier S, et al. Cohort profile: the Metabolic syndrome and Cancer project (Me-Can). *Int J Epidemiol*. 2010;39(3):660-667. doi:10.1093/ije/dyp186.
14. Goodwin PJ, Stambolic V. Impact of the obesity epidemic on cancer. *Annu Rev Med*. 2015;66:281-296. doi:10.1146/annurev-med-051613-012328.
15. Avgerinos KI, Spyrou N, Mantzoros CS, Dalamaga M. Obesity and cancer risk: emerging biological mechanisms and perspectives. *Metabolism*. 2019;92:121-135. doi:10.1016/j.metabol.2018.11.001.
16. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. *J Clin Endocrinol Metab*. 2004;89(6):2548-2556. doi:10.1210/jc.2004-0395.
17. Cnop M, Havel PJ, Utzschneider KM, et al. Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. *Diabetologia*. 2003;46(4):459-469. doi:10.1007/s00125-003-1074-z.
18. Caan BJ, Cespedes Feliciano EM, Prado CM, et al. Association of muscle and adiposity measured by computed tomography with survival in patients with nonmetastatic breast cancer. *JAMA Oncol*. 2018;4(6):798-804. doi:10.1001/jamaoncol.2018.0137.
19. Paris MT, Tandon P, Heyland DK, et al. Automated body composition analysis of clinically acquired computed tomography scans using neural networks. *Clin Nutr*. 2020;39(10):3049-3055. doi:10.1016/j.clnu.2020.01.008.
20. Xiao J, Mazurak VC, Olobatuyi TA, Caan BJ, Prado CM. Visceral adiposity and cancer survival: a review of imaging studies. *Eur J Cancer Care (Engl)*. 2018;27(2):e12611. doi:10.1111/ecc.12611.
21. Gillen J, Mills KA, Dvorak J, et al. Imaging biomarkers of adiposity and sarcopenia as potential predictors for overall survival among patients with endometrial cancer treated with bevacizumab. *Gynecol Oncol Rep*. 2019;30:100502. doi:10.1016/j.gore.2019.100502.
22. Celik E, Kizildag Yirgin I, Goksever Celik H, et al. Does visceral adiposity have an effect on the survival outcomes of the patients with endometrial cancer? *J Obstet Gynaecol Res*. 2021;47(2):560-569. doi:10.1111/jog.14560.
23. Dabiri S, Popuri K, Cespedes Feliciano EM, Caan BJ, Baracos VE, Beg MF. Muscle segmentation in axial computed tomography (CT) images at the lumbar (L3) and thoracic (T4) levels for body composition analysis. *Comput Med Imaging Graph*. 2019;75:47-55. doi:10.1016/j.compmedimag.2019.04.007.
24. Engin A. Obesity-associated breast cancer: analysis of risk factors. *Adv Exp Med Biol*. 2017;960:571-606. doi:10.1007/978-3-319-48382-5_25.
25. Petrelli F, Cortellini A, Indini A, et al. Association of obesity with survival outcomes in patients with cancer: a systematic review and meta-analysis. *JAMA Netw Open*. 2021;4(3):e213520. doi:10.1001/jamanetworkopen.2021.3520.
26. Key TJ, Appleby PN, Reeves GK, et al.; for the Endogenous Hormones Breast Cancer Collaborative Group. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. *J Natl Cancer Inst*. 2003;95(16):1218-1226. doi:10.1093/jnci/djg022.
27. Renehan AG, Roberts DL, Dive C. Obesity and cancer: pathophysiological and biological mechanisms. *Arch Physiol Biochem*. 2008;114(1):71-83. doi:10.1080/13813450801954303.
28. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat Rev Cancer*. 2004;4(8):579-591. doi:10.1038/nrc1408.
29. de Paula NS, Chaves GV. Percentiles for body composition parameters based on computed tomography in patients with endometrial cancer. *Nutrition*. 2020;79-80:110873. doi:10.1016/j.nut.2020.110873.
30. Metter EJ, Conwit R, Tobin J, Fozard JL. Age-associated loss of power and strength in the upper extremities in women and men. *J Gerontol A Biol Sci Med Sci*. 1997;52(5):B267-B276. doi:10.1093/gerona/52a.5.b267.
31. Uharcek P. Prognostic factors in endometrial carcinoma. *J Obstet Gynaecol Res*. 2008;34(5):776-783. doi:10.1111/j.1447-0756.2008.00796.
32. Horii N, Sawda Y, Kumamoto T, et al. Impact of intramuscular adipose tissue content on short- and long-term outcomes of hepatectomy for colorectal liver metastasis: a retrospective analysis. *World J Surg Oncol*. 2020;18(1):68. doi:10.1186/s12957-020-01836-5
33. Xia L, Zhao R, Wan Q, et al. Sarcopenia and adverse health-related outcomes: an umbrella review of meta-analyses of observational studies. *Cancer Med*. 2020;9(21):7964-7978. doi:10.1002/cam4.3428.
34. Hamrick MW, McGee-Lawrence ME, Frechette DM. Fatty infiltration of skeletal muscle: mechanisms and comparisons with bone marrow adiposity. *Front Endocrinol (Lausanne)*. 2016;7:69. doi:10.3389/fendo.2016.00069.
35. Rivas DA, McDonald DJ, Rice NP, Haran PH, Dolnikowski GG, Fielding RA. Diminished anabolic signaling response to insulin induced by intramuscular lipid accumulation is associated with inflammation in aging but not obesity. *Am J Physiol Regul Integr Comp Physiol*. 2016;310(7):R561-R569. doi:10.1152/ajpregu.00198.2015.
36. Al Saedi A, Hassan E, Duque G. The diagnostic role of fat in osteosarcopenia. *J Lab Precis Med*. 2019;4:7. doi:10.21037/jlpm.2019.02.01.
37. Ryan AM, Prado CM, Sullivan ES, Power DG, Daly LE. Effects of weight loss and sarcopenia on response to chemotherapy, quality of life, and survival. *Nutrition*. 2019;67-68:110539. doi:10.1016/j.nut.2019.06.020.
38. Shachar SS, Deal AM, Weinberg M, et al. Skeletal muscle measures as predictors of toxicity, hospitalization, and survival in patients with metastatic breast cancer receiving taxane-based chemotherapy. *Clin Cancer Res*. 2017;23(3):658-665. doi:10.1158/1078-0432.CCR-16-0940.
39. Yang X, Li X, Dong Y, et al. Effects of metabolic syndrome and its components on the prognosis of endometrial cancer. *Front Endocrinol (Lausanne)*. 2021;12:780769. doi:10.3389/fendo.2021.780769.
40. Kliemann N, Ould Ammar R, Biessy C, et al. Metabolically defined body size phenotypes and risk of endometrial cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Cancer Epidemiol Biomarkers Prev*. 2022;31(7):1359-1367. doi:10.1158/1055-9965.EPI-22-0160.