Association Between Abdominal Adipose Tissue Distribution and Risk of Endometrial Cancer: A Case-Control Study

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ABSTRACT

BACKGROUND: Obesity contributes to endometrial cancer (EC). However, it is not clear whether the distribution of adipose tissue affects the occurrence of endometrial carcinoma. This study aimed to evaluate the relationship between abdominal adipose tissue distribution and EC.

METHODS: We designed a case-control study with 115 women with EC and a control group. The total abdominal adipose tissue, visceral adipose tissue, and subcutaneous adipose tissue were measured by single slice computerized tomography at the level of umbilicus. Univariate and multivariate logistic regression models were used to calculate odds ratios (ORs) for the risk of EC associated with adipose tissue distribution. Furthermore, we analyzed the correlation between adipose tissue distribution and clinicopathologic features of endometrial carcinoma.

RESULTS: Multivariate analysis showed that a larger visceral adipose tissue ratio was associated with an increased risk of EC after adjusting for body mass index (BMI) and diabetes (OR = 1.046, 95% confidence interval = [1.008-1.079]). The ratio of International Federation of Obstetrics and Gynecology (FIGO) stage I and type I EC was higher in EC patients with larger visceral adipose tissue (84.5% vs 63.2%, P = .009; 91.4% vs 75.4%, P = .021). There was a higher positive ratio of progesterone receptor in EC patients with a larger subcutaneous adipose tissue area (91.2% vs 77.6%; P = .044).

CONCLUSIONS: Higher visceral adipose tissue ratio, independent of BMI, was associated with an increased risk of EC. Therefore, this study demonstrated that women with normal BMI, but abnormal abdominal adipose tissue distribution, have an increased risk for EC.

KEYWORDS: Endometrial cancer, abdominal adipose tissue, subcutaneous adipose tissue, computerized tomography, body mass index

Introduction

As 1 of the 3 major female genital organ malignancies, the incidence rates of endometrial cancer (EC) are increasing rapidly due to various metabolic diseases.[1] Furthermore, epidemiologic data show that obesity is most associated with EC. The development of 57% of ECs is attributed to obesity.[2] The underlying mechanism that explains how obesity promotes EC is complex, including alterations in adipocyte-derived estrogen signaling, insulin resistance, inflammatory responses, and adipokines.[3] Endometrial cancer has been classified into 2 subtypes according to pathologic and hormonal characteristics: type I (low-grade, estrogen-dependent) and type II (high-grade and estrogen-independent).[4] Evidence proves that the occurrence of type I EC is significantly related to the level of estrogen and progesterone in women. Obesity is a high estrogen state because

adipose tissue makes adrenal androgens aromatize estrogen. Moreover, estrogen stimulates endometrial hyperplasia, whereas periodic progesterone and periodic menstrual shedding maintain endometrial health during the reproductive period. In postmenopausal women, natural progesterone deficiency leads to obesity-driven nonantagonistic estrogen excess, which is the main theory behind endometrial carcinogenesis.[5]

Body mass index (BMI) and waist circumstance (WC) are commonly used to define obesity. Research shows that every 5-unit increase in BMI increases the risk of EC by 50%,[6] and every 10 cm increase in WC increases this risk by 27%.[7] However, it is still unclear whether weight gain or adipose distribution in women is more important than BMI to determine the association between EC risk and obesity. Recent studies have shown that the measurement of adipose tissue distribution based on computerized tomography (CT) scans have comparable or better predictive value for cancer than BMI measurements.[8,9]

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In CT examinations, total adipose tissue (TAT) is classified into subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT).[10] Research shows greater TAT, VAT, and SAT areas in patients with pancreatic ductal adeno cancer than the control group. Furthermore, there is strong evidence that visceral obesity increases the risk of colorectal, pancreatic, and gastroesophageal cancer.[11] Two recent studies also found that VAT scores are an independent predictor of breast cancer in postmenopausal women.[12,13] Renehan et al[14] showed that individuals with high quantities of VAT carry an increased risk of cardiovascular disease, type 2 diabetes, and developing breast, colorectal, and esophageal cancer compared with individuals with less VAT. Mounting evidence suggests that the distribution of abdominal adipose tissue may be related to the effect of therapeutic interventions on and prognosis of several types of cancers, including malignant melanomas,[15] colorectal,[16] and esophageal cancers.[17]

Within the context of EC, VAT has been associated with several of its risk factors, including hypertension,[18] diabetes mellitus,[19] and polycystic ovarian syndrome.[20] A prospective epidemiologic risk factor study found that central obesity was associated with increased risk of female genital organ cancers in postmenopausal women, independent of their BMI.[21] In addition, the studies by Ye et al[22] and Nattenmüller et al[23] demonstrated that higher VAT was associated with aggressive clinical features in EC, such as lymph node metastasis, extrauterine diseases, and poor prognosis.

Despite the plethora of research on the association of TAT, SAT, and VAT with cancer, only a few studies have quantitatively explored the relationship between adipose tissue distribution and the risk and pathologic features of patients with EC.[21–23] This study aimed to further evaluate the relationship between abdominal adipose tissue distribution and EC.

Methods

Study population and data collection

We searched the electronic medical record database of Peking University People's Hospital, China, from 2010 to 2019 to identify all discharged patients with EC. This study was approved by the Ethics Committee of Peking University People's Hospital. The eligibility criteria for EC patients were as follows: underwent primary surgery treatment (total abdominal hysterectomy and bilateral salpingo-oophorectomy with or without pelvic and/or para-aortic lymphadenectomy); diagnosis of EC confirmed by pathology (mainly the 2009 International Federation of Obstetrics and Gynecology [FIGO] stage I to IV, Grade 1 to 3, type I endometrioid adenocarcinoma, and type II nonendometrioid adenocarcinoma); and availability of pre-operative abdominal CT images. The exclusion criteria were as follows: having undergone radiotherapy, chemotherapy, or fertility-preserving treatment prior to surgery.

Control subjects were selected among women who underwent routine examination in the hospital. Inclusion criteria of
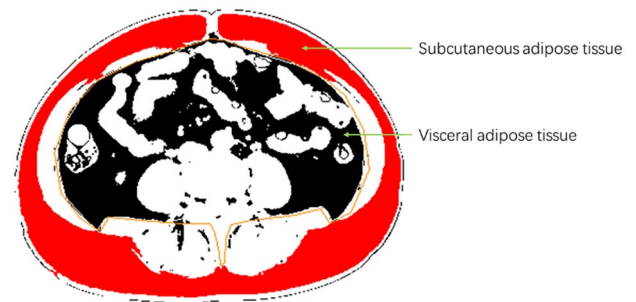

Figure 1. Cross-sectional abdominal computerized tomography (CT) image of subcutaneous adipose tissue (red) and visceral adipose tissue (black) for measurements of abdominal adipose tissue distribution in endometrial cancer patients.
Arrows indicate the visceral adipose tissue and subcutaneous adipose tissue.

the control group were as follows: (1) menstrual regularity in premenopausal patients, and no abnormal vaginal bleeding in postmenopausal patients and (2) imaging examination (gynecologic ultrasound or CT, magnetic resonance imaging [MRI]) or pathologic examination did not indicate endometrial lesions. Exclusion criteria were as follows: (1) history of EC or other malignant tumors, (2) have a long history of oral corticosteroids, and (3) there was a history of abdominal surgery within 1 year before abdominal CT examination. None of them had a history of cancer or corticosteroids use, and all of them were age-matched to the EC patients. A total of 115 patients with EC and 115 control patients were included in this study. Information on obesity, diabetes, hypertension, and family history of cancer were collected from the medical records of each participant.

Image analyses

The International Diabetes Federation recommended CT and MRI for the measurement of abdominal SAT and VAT in 2006. Two other studies show that VAT area (as extracted from a single scan obtained at the level of umbilicus, ie, approximately the level of L4-L5) was highly correlated with total VAT volume.[18,19]

Hence, we measured abdominal adipose tissue distribution (VAT and SAT) using a single cross-sectional CT image of a 5-mm thick slice at the level of umbilicus (Figure 1). We retrieved abdominal CT scans from the radiology department. ImageJ software (http://www.rsb.info.nih.gov/ij/download.html) was used for the semi-automatic analysis of abdominal CT images. Measurement thresholds with a lower attenuation limit of –190 HU and an upper attenuation limit of –30 HU were chosen to selectively measure adipose tissue. First, TAT area at the level of umbilicus was measured. Next, region of interest (ROI) was drawn along the inner edge of the abdominal muscles and the spine as the intraperitoneal area. Adipose tissue area within ROI was defined as abdominal VAT area. By subtracting VAT from TAT, the SAT area was calculated. The abdominal VAT proportion (VAT/TAT%) was calculated as VAT/TAT $\times$ 100.

Table 1. Clinicopathologic characteristics of the case group and control group.

VARIABLE	CASES (N = 115)	CONTROLS (N = 115)	*P* VALUE
Age at reference (years)	55 ± 9	57 ± 8	.133
Menopausal status			1.000
Pre-/peri-menopausal	32 (27.8%)	32 (27.8%)	
Postmenopausal	83 (72.7%)	83 (72.7%)	
Body mass index (kg/m²)			.011*
Normal/underweight (<25)	51 (44.3%)	69 (60.0%)	
Overweight (25-30)	48 (41.7%)	41 (35.7%)	
Obese (>30)	16 (14.0%)	5 (4.3%)	
Waist-to-hip ratio			.175
>0.8	49 (42.6%)	39 (33.9%)	
≤0.8	66 (57.4%)	76 (66.1%)	
Type II diabetes			.003*
Yes	31 (27.0%)	13 (11.3%)	
No	84 (73.0%)	102 (88.7%)	
Hypertension			.175
Yes	49 (42.6%)	39 (33.9%)	
No	66 (57.4%)	76 (66.1%)	

*$P < 0.05$.

Statistical analysis

In this study, SPSS 20.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. The quantitative data of normal distribution were described by mean value ± SD, and *t*-test was used for comparison between groups. The quantitative data of abnormal distribution were described by median (range), and the Mann-Whitney *U* test was used for comparison between groups. Qualitative data were described by n (n/N%), and the chi-square test was used for comparison between groups. Univariate analysis was used to calculate odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) for the risk of EC associated with adipose tissue distribution. Multivariate stepwise logistic regression models were used for adjusting the BMI and diabetes variables as confounding factors to further clarify the independent risk role of VAT and EC. All *P* values reported were 2-sided, and the level of statistical significance was set at $P < .05$.

Results
Patients

The clinicopathological characteristics of participants in the case (n = 115) and control groups (n = 115) are summarized in Table 1. At baseline, the 2 groups were matched by age and menopausal status. The average age of participants in the case and control groups was 55 ± 9 and 57 ± 8, respectively ($P > .05$). In both groups, the proportion of premenopausal and postmenopausal women was the same, ie, 27.8% and 72.2%, respectively. However, case group participants had a higher BMI than control group participants (25.8 ± 3.8 vs 24.5 ± 3.0 kg/m², respectively; $P < .05$), and they were more likely to have type II diabetes (27% vs 11.3%, respectively; $P < .05$).

Associations between abdominal adipose tissue distribution and patients with EC

We examined the associations between abdominal adipose tissue distribution and patients with EC (Table 2). The data showed that VAT and VAT/TAT% were significantly higher in the case than the control group ($P < .05$). However, the distribution of TAT and SAT did not differ significantly by group.

Risk of EC based on abdominal adipose tissue distribution

In the univariate logistic regression model, increase in both VAT and VAT/TAT% was statistically significantly and positively associated with EC prevalence (VAT, OR = 1.010; 95% CI = [1.003-1.017]; VAT/TAT%, OR = 1.035; 95% CI = [1.001-1.069]).

Table 2. Characteristics of abdominal adipose tissue distribution of the patient with endometrial cancer.

	EC (N = 115)	CONTROL (N = 115)	P VALUE[A]
TAT (cm²)	367.06 (156.23, 754.65)	354.16 (182.95, 648.95)	.098
VAT (cm²)	134.71 (64.50, 282.75)	118.15 (42.42, 254.40)	.005*
SAT (cm²)	238.48 (64.84, 550.22)	227.81 (97.54, 479.91)	.350
VAT/TAT (%)	36 (24, 71)	34 (16, 55)	.047*

Abbreviations: SAT, subcutaneous adipose tissue area; TAT, total adipose tissue; VAT, visceral adipose tissue; VAT/TAT%, abdominal visceral adipose tissue proportion.
Data depicted are in the format of: median (range).
[a]P values were derived using the Mann-Whitney *U* test.
*$P < 0.05$.

Table 3. Multivariate analysis of risk factors for endometrial cancer.

	UNIVARIATE		MULTIVARIATE	
	OR [95% CI]	P VALUE	OR [95% CI]	P VALUE
BMI (kg/m²)	1.115 [1.030-1.207]	.007*	1.120 [1.031-1.215]	.007*
Type II diabetes	2.896 [1.425-5.884]	.003*	2.698 [1.301-5.597]	.008*
Hypertension	1.447 [0.848-2.469]	.176		
SAT	1.000 [1.000-1.000]	.306		
VAT/TAT (%)	1.035 [1.001-1.069]	.041*	1.046 [1.008-1.079]	.017*

Abbreviations: BMI, body mass index; TAT, total adipose tissue; VAT, visceral adipose tissue; VAT/TAT%, abdominal visceral adipose tissue proportion.
*$P < 0.05$.

Table 3 shows the OR of the prevalence of EC based on abdominal adipose tissue distribution after adjustments for BMI and diabetes. After these adjustments, the multivariate-adjusted ORs [95% CI] for the VAT/TAT% was 1.046 [1.008-1.079].

Abdominal adipose tissue distribution and clinicopathologic features in patients with EC

We dichotomized all patients with EC into 2 groups based on the median value of VAT (Table 4). The proportion of FIGO stage I and type I EC was higher in EC patients with a larger VAT area (84.5 % vs 63.2%, *P* = .009; 91.4% vs 75.4%, *P* = .021).

Thereafter, we dichotomized all patients with EC into 2 groups based on the median value of SAT (Table 5). There was a higher positive ratio of progesterone receptors (PRs) in EC patients with a larger SAT area (91.2 % vs 77.6%; *P* = .044).

Discussion

This study revealed a positive relationship between abdominal VAT ratio and EC in Chinese women. Compared with the control group, the area and the proportion of abdominal VAT in the case group significantly increased. Furthermore, this association between EC and abdominal VAT ratio persisted after adjusting for BMI and diabetes. These results are consistent with prior research, which showed that central obesity was a risk factor for female genital organ cancers in postmenopausal women, independent of their BMI.[21] However, this cited study focuses on the impact of overall adipose tissue distribution on the risk of EC based on measurements using whole-body dual-energy X-ray absorptiometry scanners. Meanwhile, this study explored the impact of abdominal adipose tissue distribution related to central obesity on the risk of EC using abdominal CT images.

Our findings also hint for some potential mechanism that explains the relationship between VAT and EC. Insulin resistance is an important factor that supports the association between visceral obesity and EC,[24] and the correlation between VAT and insulin resistance is well established in the literature.[25,26] In addition, adipose tissue is an important endocrine organ, meaning that it can secrete adipokines, including adiponectin, leptin, resistin, and visfatin. Adiponectin is a protective factor of EC and is mainly secreted by SAT,[27] although the increase in VAT ratios leads to a decrease in serum adiponectin levels.[28] Another study found that plasma levels of interleukin-8 are strongly associated with VAT in patients with EC.[29] Interleukin-8 can promote angiogenesis and mitogenesis by binding to the chemokine receptors CXCR1 and CXCR2. However, researchers have yet to identify acceptable levels of VAT, as well as the thresholds above which VAT begins to detrimentally affect metabolic and inflammatory processes, ultimately inducing tumor progression.

Recently, some studies have found that the relationship between estrogen and VAT is controversial. One study showed that VAT contributed more to estradiol production than SAT.[30] Another research demonstrated that total TAT, VAT, and SAT

Table 4. Visceral adipose tissue and clinicopathologic features in endometrial cancer patients.

	VAT ⩽ 134.71 (N = 57)	VAT > 134.71 (N = 58)	P VALUE
FIGO stage			.009*
I (%)	36 (63.2)	49 (84.5)	
II and above (%)	21 (36.8)	9 (15.5)	
Histology			.021*
Endometrioid (%)	43 (75.4)	53 (91.4)	
Nonendometrioid (%)	14 (24.6)	5 (8.6)	
Histologic grade			.079
Grade 1 (%)	22 (38.6)	25 (43.1)	
Grade 2 (%)	14 (24.6)	22 (37.1)	
Grade 3 (%)	21 (36.8)	11 (19.0)	
Deep myometrial invasion (⩾50%)			.788
<1/2	42 (73.7)	44 (75.9)	
⩾1/2	15 (26.3)	14 (24.1)	
LN metastasis (n = 106)			.120
Negative	43 (82.7)	50 (92.6)	
Positive	9 (17.3)	4 (7.4)	
Lymphovascular invasion (n = 111)			.235
Negative	40 (72.7)	46 (82.1)	
Positive	15 (27.3)	10 (17.9)	
ER			.521
Negative	7 (12.3)	5 (8.6)	
Positive	50 (87.7)	53 (91.4)	
PR			.286
Negative	11 (19.3)	7 (12.1)	
Positive	46 (80.7)	51 (87.9)	
Ki-67	0.40 ± 0.24	0.40 ± 0.20	.925

Abbreviations: ER, estrogen receptor; FIGO, International Federation of Obstetrics and Gynecology; LN, lymph node; PR, progesterone receptor; VAT: visceral adipose tissue.
*$P < 0.05$.

were all related to plasma levels of estrone and estradiol, but not with VAT ratios.[31] Among the 115 cases of EC in this study, the differences in clinicopathologic features between the patients with high SAT lied in increased PR expression. This is consistent with another research by Mauland et al[32]: by analyzing the distribution of abdominal adipose tissue in 170 patients with EC, these researchers found that an increase in abdominal SAT volume was related to positive PR expression.

However, this study has some limitations. As a retrospective case-control study, we selected noncancer women rather than completely healthy women as controls, because the data of physical examination for normal women in our clinical center are limited. In addition, we only monitored the weight and CT scanning results of these women during their hospitalization. However, the weight change and fat distribution of women before cancer were not monitored, which may affect the outcome, resulting in unavoidable offsets. Furthermore, as this study included only cases with CT scan results, the number of cases was limited, and this may have caused some selection bias. Moreover, we dichotomized the sample by the median VAT/ TAT% value. For that, the lack of an appropriate and scientifically validated threshold may have hindered our ability to

Table 5. Subcutaneous adipose tissue and clinicopathologic features in endometrial cancer patients.

	SAT ≤ 238.48 (N = 58)	SAT > 238.48 (N = 57)	*P* VALUE
FIGO stage			.427
I (%)	41 (70.1)	44 (77.2)	
II and above (%)	17 (29.3)	13 (22.8)	
Histology			.086
Endometrioid (%)	45 (77.6)	51 (89.5)	
Nonendometrioid (%)	13 (22.4)	6 (10.5)	
Histologic grade			.268
Grade 1 (%)	21 (36.2)	26 (45.6)	
Grade 2 (%)	17 (29.3)	19 (33.3)	
Grade 3 (%)	20 (34.5)	12 (21.1)	
Deep myometrial invasion (≥50%)			.872
<1/2	43 (74.1)	43 (75.4)	
≥1/2	15 (25.9)	14 (24.6)	
LN metastasis (n = 106)			.181
Negative	46 (83.6)	47 (92.2)	
Positive	9 (16.4)	4 (7.8)	
Lymphovascular invasion (n = 111)			.235
Negative	40 (72.7)	46 (82.1)	
Positive	15 (27.3)	10 (17.9)	
ER			.235
Negative	8 (13.8)	4 (7.0)	
Positive	50 (86.2)	53 (93.0)	
PR			.044*
Negative	13 (22.4)	5 (8.8)	
Positive	45 (77.6)	52 (91.2)	
Ki-67	0.43 ± 0.25	0.37 ± 0.18	.138

Abbreviations: ER, estrogen receptor; FIGO, International Federation of Obstetrics and Gynecology; LN, lymph node; PR, progesterone receptor; VAT: visceral adipose tissue.
*$P < 0.05$.

provide more useful correlations between VAT and markers of EC.

Implications

This study clinically demonstrated that women with normal BMI but abnormal abdominal adipose tissue distribution should be instructed on the greater risk of EC to which they may be exposed.

Conclusions

Our findings demonstrated that abdominal VAT ratio was independently associated with the risk of EC in Chinese women. Further prospective studies with larger sample sizes are required to understand the causal relationship between abdominal adipose tissue distribution and EC prevalence.

Author Contributions

YC completed data processing, article writing, proofreading, and revision. ZW completed data collection, data processing, and first draft writing. XJ mainly provided imaging data. RZ was mainly involved in article ideas and data guidance. JW was

mainly involved in article design, supervision, and revision of article. All authors read and approved the final.

Ethical Approval and Consent to Participate

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