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Original Research

Value of computed tomography-defined visceral fat area as a risk factor for endometrial cancer

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Objective: Obesity is a risk factor for endometrial cancer. Recently, visceral fat is strongly associated with obesity-related carcinogenesis, more than subcutaneous fat. In this study, we hypothesized that the visceral fat measured by computed tomography (CT) contributes to the occurrence of endometrial cancer. *Methods*: A retrospective chart review of patients undergoing primary surgery for endometrial cancer was conducted. The volume of visceral fat was measured by CT scans performed at the fourth lumbar level for all participants. Body fat distributions assessed by a direct method in 52 endometrial cancer cases were compared with those of age- and BMI-matched healthy community controls. *Results*: Case group showed significantly higher mean visceral fat area (VFA; 76.2 $\pm$ 25.0 vs. 62.2 $\pm$ 13.9 cm^2, $P = 0.007$). The mean total fat area (TFA; 270.3 $\pm$ 99.9 vs. 238.9 $\pm$ 53.8 cm^2, $P = 0.137$) and subcutaneous fat area (SFA; 194.2 $\pm$ 86.5 vs. 176.7 $\pm$ 45.8 cm^2, $P = 0.315$), however, presents no significant differences. VFA showed lower correlation with BMI ($r^2 = 0.299$, $P < 0.001$) than to SFA ($r^2 = 0.528$, $P < 0.001$) or TFA ($r^2 = 0.584$, $P < 0.001$). In receiver operator characteristic (ROC) curve, at a VFA value of 70.8 cm^2, sensitivity and specificity of the case group was 55.8% and 75%, respectively. *Conclusion*: Increased abdominal visceral fat is associated with endometrial cancer risk and can be predicted by measuring CT scans. Furthermore, as the most independent factor of BMI, VFA may provide additional information for representative risks of endometrial cancer.

Keywords

Intra-abdominal fat; Computed tomography; Body fat distribution; Endometrial neoplasms

1. Introduction

The World Health Organization defines overweight and obesity as abnormal or excessive fat accumulation that may lead to health impairments [1]. Obesity is a serious and on the rise health problem and it has more than doubled worldwide since 1980. Obesity has been associated with metabolic syndrome, diabetes, cardiovascular diseases (heart disease, stroke, and hypertension), other chronic diseases, and psychological problems; obesity is the second most common cause of death that can be prevented [2]. Recent studies have shown that obesity is correlated to increased risks of several cancer types, including the esophagus, thyroid, postmenopausal breast, pancreas, gall bladder, colon, rectum, endometrium, kidney, and hematological malignancy [3, 4]. In the Occident, endometrial cancer is the most common gynecologic malignancy and the incidence of endometrial cancer has increased since the mid-2000s [5]. In recent years, the number of patients with endometrial cancer has increased due to an increase in the obesity population in South Korea [6]. Endometrial cancer is a representative cancer associated with obesity, and one large cohort study reported that for every 10 units of body mass index (BMI) increase, the relative risk of endometrial cancer increased by 2.89 times [7].

Histologically, endometrial cancer can be classified into two types. Type 1 makes up the majority of endometrial cancer and is mainly associated with the endocrine system, including nutritional factors and obesity. In type 1 endometrial cancer, the mechanism that incites tumors through the hormonal change related to obesity is referred to as 'unopposed estrogen hypotheses'. Among women with chronic anovulation in the premenopausal period, progesterone insufficiency means that there is no function to counteract the estrogen. In postmenopausal women, it is hypothesized that excess weight leads to the aromatization of estrogen in the adipose tissue which in turn causes the exposure to highly concentrated estrogen. Potischman, *et al.* [8] reported that high levels of androstenedione and testosterone increase the risks of endometrial cancer, and the rise of estrone and estradiol levels also contributes to its risk.

When visceral adipose tissue is excessive, adipokines, including leptin and interleukin, are secreted, causing chronic inflammation and insulin resistance. Recent studies have found excessive visceral adipose tissue plays an important role in carcinogenesis [9]. However, while most studies analyzing the relationship between obesity and endometrial cancer have used BMI as a parameter of obesity, few studies have focused on the role of visceral fat. In decades of obesity research, BMI has been an important indicator because of its accessibility and familiarity. Nevertheless, BMI alone is not enough to support the recent notion that obesity means ex-

Table 1. Characteristics of endometrial cancer and control cases.

Variable	Endometrial cancer cases (n = 52)	Control (Before matched, n = 854)	Control (After matched, n = 52)	*P* * (Case vs. matched control)
Age (yr)	55.7 ± 1.7	55.2 ± 9.3	52.7 ± 1.1	0.147
BMI (kg/m^2)	24.4 ± 0.6	23.3 ± 3.4	23.6 ± 0.4	0.218
VF area (cm^2)	76.2 ± 25.0	.	62.2 ± 13.9	0.007
SF area (cm^2)	194.2 ± 86.5	.	176.7 ± 45.8	0.315
TF area (cm^2)	270.3 ± 99.9	.	238.9 ± 53.8	0.137
V/S ratio	0.55 ± 0.61	.	0.37 ± 0.09	0.086

Data are mean ± SD. BMI, body mass index; VF, visceral fat; SF, subcutaneous fat; TF, total fat; V/S, visceral fat/subcutaneous fat. * < 0.05, Mann-Whitney test.

cessive accumulation and metabolism of fat tissue. Therefore, this retrospective study was performed to predict the effect of subcutaneous and visceral fat on endometrial cancer using computed tomography (CT) scan measurements.

2. Materials and methods

2.1 Patient recruitment

We searched our medical records database to identify all endometrial cancer patients. From 2010 to 2014, a total of 124 patients were diagnosed with endometrial cancer with biopsy and a total of 52 final case groups were selected. Fig. 1 shows the flow chart of the patient enrollment process throughout the study. Patient data, including age, BMI, histological subtype, was collected from a retrospective database. The control group included 854 patients who did not have evidence of endometrial cancer with CT scan, at the same institution's health promotion center for the same period. To eliminate deviations in the surgical results, all patients were limited to those who underwent total laparoscopic hysterectomy [10, 11]. To balance case and control groups, the propensity score (PS) method was performed by using Matching packages (R version 3.1.2) [12]. PSs were calculated using a logistic regression model and the following covariates: age and BMI. Using PSs, the control subject was individually matched to endometrial cancer patients. Finally, there were a total of 104 subjects for this study, 52 for the control group and 52 for the case group.

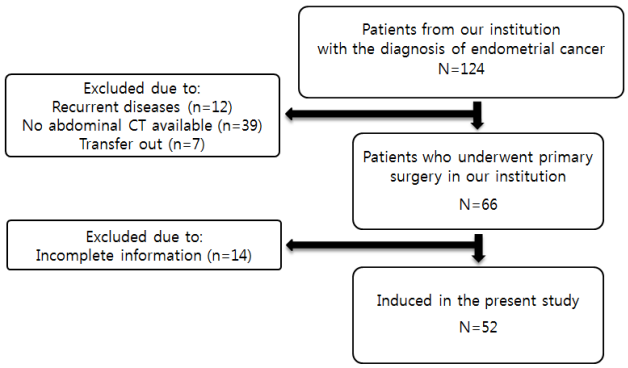

Fig. 1. Flow Chart of Patient Enrollment. Of a total of 124 patients, 52 patients were finally enrolled.

2.2 Adiposity measurement

The volume of subcutaneous adipose tissue and visceral adipose tissue was quantified by computed tomography scans (Sensation 64, Siemens Medical Solutions, Forchheim, Germany) with a 16 mm × 0.75 mm collimation, a 420 m/s rotation time, and a tube voltage at 120 kV. All CT scans were performed in a supine position (Fig. 2). Ten slices (1 cm thick) of the abdomen between the fourth and fifth lumbar vertebrae (L4-L5) were obtained from each patient. Two contours, the body perimeter and the inner margin of the abdominal muscles were identified using a dedicated workstation (Aquarius 3D Workstation, TeraRecon, San Mateo, CA).

2.3 Statistical analysis

Quantitative variables were compared using the Mann-Whitney test, but the results are presented as mean ± SD.

Spearman Correlation Analysis was used to identify the relationship between BMI and 3 other variables (visceral fat area, subcutaneous fat area, and total fat area). To evaluate the accuracy of the 3 measures, Receiver Operating Characteristics (ROC) analysis was performed. The area under the curve (AUC) was computed and Youden's index is used to detect the optimal cutoff point. The *P*-values < 0.05 were considered to be statistically significant. All statistical analyses were performed using SPSS version 14.0 (SPSS Inc., Chicago, IL) and R (version 3.1.2).

3. Results

3.1 Patient characteristics

Of the 124 patients who were pathologically diagnosed with endometrial cancer, 66 patients underwent primary surgery. On the other hand, a total of 58 out of 124 patients were excluded; 12 patients were treated with the recurrent disease diagnosed in other hospitals, 39 patients with unavailable CT images, and 7 patients transferred to other hospitals. We also ruled out 14 patients because of incomplete medical records. As a result, a total of 52 patients were enrolled to participate in this study.

The characteristics of endometrial cancer and a matched group of healthy individuals are shown in Table 1. Because the groups were matched by age, and BMI, there were no significant differences in basic characteristics between them.

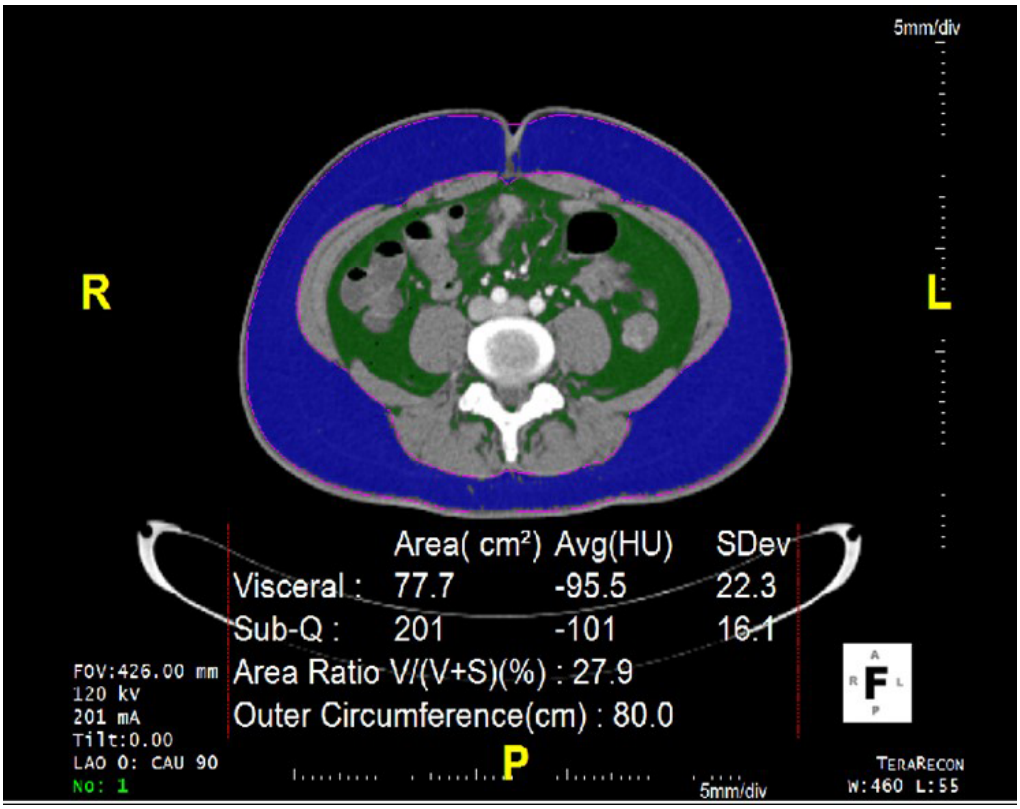

Fig. 2. CT image. Abdominal CT was used to measure the size of the subcutaneous fat area (SFA), total fat area (TFA) and visceral fat area (VFA).

Table 2. Multinomial logistic regression analysis between Fat area defined by CT and BMI.

	OR	95% CI	*P*
VF area	0.045	0.022–0.068	0
SF area	0.03	0.023–0.038	0

CI, confidence interval; other abbreviations as in Table 1.

Represent how much a factor VFA, SFA influences BMI.

Although there was no significant difference in subcutaneous fat area (SFA), total fat area (TFA) and visceral fat area (VFA) were noticeably elevated in those with endometrial cancer than in healthy controls (Table 1).

3.2 Correlation analyses among BMI and Fat area

To evaluate the correlation power among BMI and Fat area, BMI showed a positive correlation with visceral fat (VF, $r^2 = 0.299$, $P < 0.001$), subcutaneous fat (SF, $r^2 = 0.528$, $P < 0.001$), and total fat (TF, $r^2 = 0.584$, $P < 0.001$). VFA has the lowest r^2 which means that visceral fat is the most independent factor from BMI (Fig. 3). This is reflected in the equation, BMI = 15.219 + 0.045 × VF + 0.30 × SF. As TF and SF have a close relationship and multicollinearity between them, they were automatically removed during the statistical analysis (Table 2).

3.3 Cutoff values of the visceral fat area for discriminating the subjects with endometrial cancer

A ROC curve for the VFA, SFA, and V/S ratio (visceral fat/subcutaneous fat ratio) which were used to identify subjects with endometrial cancer was created. The AUC reached 0.654 for VFA ($P = 0.007$), 0.557 for SFA ($P = 0.315$), and 0.594 for V/S ratio ($P = 0.097$) (Fig. 4). With the help of the ROC curve analysis, we managed to establish the cutoff point for the VFA value. At the value of 70.8 cm^2, sensitivity and specificity in the success group reached 55.8% and 75%, respectively.

4. Discussion

Many studies are analyzing the impact of BMI on the risk and prognosis of endometrial cancer. Several papers evaluated the correlation between body fat distribution and endometrial cancer using waist circumference and waist: hip ratio, many have concluded that upper-body fat deposition increases the risk of endometrial cancer [13–15].

However, anthropometric data including BMI cannot accurately determine fat distribution. In this study, it is noteworthy that this study used an optimal technique to estimate fat areas by CT scan rather than body fat measurement [16]. The study also confirmed that, unlike subcutaneous fat, visceral fat is more directly related to the development of endometrial cancer. Furthermore, this is the first study that suggests a VFA cutoff point as a parameter for determining the risk of endometrial cancer.

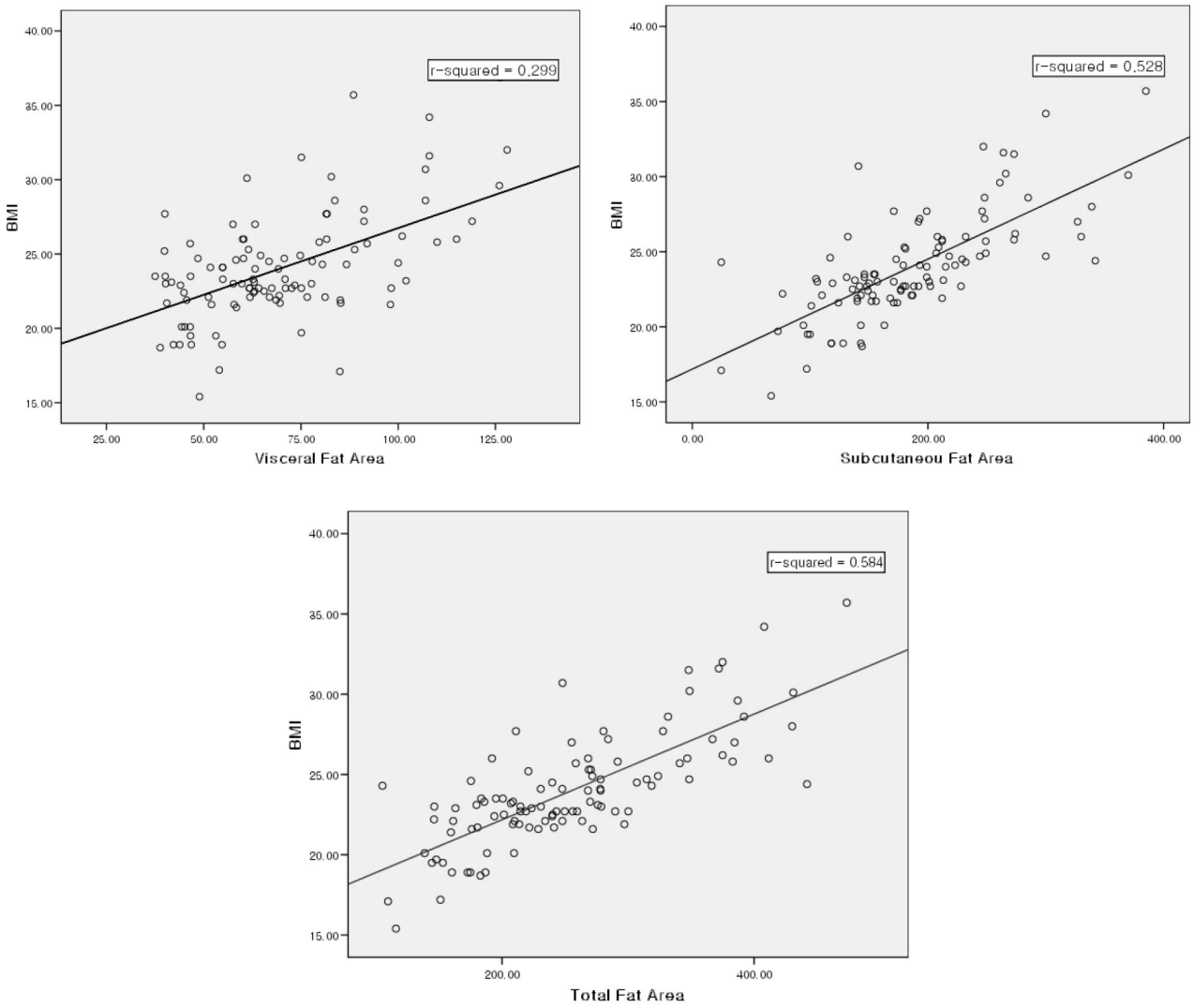

Fig. 3. Correlation analyzing BMI among and Fat area. Among the three fat areas, visceral fat area has the lowest r2, which is the most independent factor from BMI.

There are several limitations to our study. First of all, the size of the sample was limited due to a study by one gynecologic doctor. The risk factors for endometrial cancer are age, diverse hormonal factors such as hormone replacement therapy after menopause, history of oral contraceptives or tamoxifen usage, obesity, family history of cancer, and diabetes. Nevertheless, our study lacks a risk factor assessment due to insufficient clinical data. This bias can tend to overestimate the impact of VFA in patients with endometrial cancer. One other limitation of this study was that our analysis of this cross-sectional data could not provide causal explanations. Further studies are needed to prospectively relate the accumulation of visceral fat to the presence of risk factors.

Endometrial cancer patients had a significantly high VFA compared to the control group. On the other hand, there were no differences in SFA and TFA between the two groups. As a result, this means that among people of the same height and weight, those with high levels of visceral fat increase the risk of endometrial cancer. These results are supported by recent studies reporting a role of visceral fat in carcinogenesis [17].

Interestingly, our study found that TFA did not differ between endometrial cancer patients and controls. This may be due to the high absolute value of the SFA, which is primarily composed of TFAs. In the cancer group, SFA was 194.2 $\pm$ 86.5 cm^2, VFA level was 76.2 $\pm$ 25.0 cm^2.

The strength of the present study is cohort research of well-matched controls for age and BMI. Using BMI-matched controls, we found that visceral fat is not a bystander but independent of BMI. VFA showed better risk correlation with endometrial cancer than BMI, SFA, and TFA through correlation and multiple regression analyses. Therefore, patients with the same BMI could show higher risk of endometrial cancer if they show increased visceral fat.

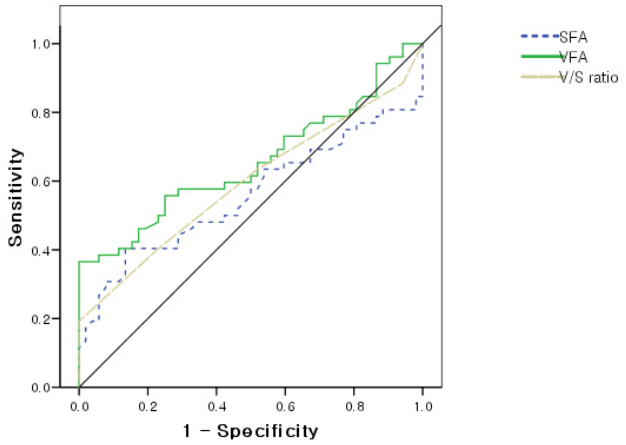

Fig. 4. Receiver operating characteristic curves for VFA, SFA, and V/S ratio to predict the presence of endometrial cancer. The AUC reached 0.654 for VFA ($P = 0.007$), 0.557 for SFA ($P = 0.315$), and 0.594 for V/S ratio ($P = 0.097$).

In breast cancer cases, a notable correlation has been reported between changes in adipocytokine levels and increased breast cancer risk in postmenopausal women [18–20]. As hormone-related cancer, endometrial cancer is thought to have an etiology similar to breast cancer. Likewise, in postmenopausal women, fat cells suppressed by endocrine organs, especially visceral fat cells, can be assumed to play an important role in endometrial carcinogenesis. (1) Premenopausal women produce estradiol (E2) in the ovary, but in menopaused women, androgen is produced in adipose tissue converted to estriol (E3) aromatization. (2) Although progesterone has an anti-cancer effect, postmenopausal women have reduced progesterone levels [21]. (3) Early postmenopausal is associated with a preferential visceral fat increase regardless of age or total adiposity [22]. These three theories can support our hypothesis.

Despite the aforementioned limitations, our research has advantages as follows. A study by a single researcher has an advantage in terms of reproducibility and uniformity of treatment results and harvesting tissue. In this study, we found that VFA was superior to SFA and in V/S ratio in identifying endometrial cancer, as indicated by VFA's larger AUC. Our study also showed that the cutoff points of 70.8 cm^2 VFA were optimal in yielding maximal sensitivity and specificity in the prediction of endometrial cancer, using the ROC curve. Similar to this study, the Japanese-American study by Hayashi *et al.* [23] set the VFA cutoff point to 75 cm^2, and in the Japanese study by Miyawaki *et al.* [24] set the cutoff point to 65 cm^2.

Our research set the cutoff point in between the cutoff points of these studies as it was deemed acceptable to set the cutoff point at a level that increases the risk of central obesity-related disease [25, 26]. There is a difference in the cutoff points of central obesity according to ethnicity. Since only Korean were analyzed in this study, large-scale research including other ethnicities is needed to produce a reliable cutoff point of central obesity. Furthermore, the addition of a large-scale study to derive a cutoff value that increases the risk of endometrial cancer will increase the awareness of the risk of endometrial cancer in obese women and may help to reduce the incidence.

In conclusion, this study shows that VFA can be an independent risk factor of endometrial cancer superior to BMI. These results demonstrate the limitations of determining obesity-related cancer risks only through BMI. Furthermore, this study shows the significant impact of visceral fat on the development of endometrial cancer. The study highlights the need for further research regarding the potential physiological and pathological pathways of visceral fat.

Abbreviations

AUC, area under the curve; BMI, body mass index; CT, computed tomography; PS, propensity score; ROC, receiver operator characteristic; SF, subcutaneous fat; SFA, subcutaneous fat area; TF, total fat; TFA, total fat area; V/S ratio, visceral fat/subcutaneous fat ratio; VF, visceral fat; VFA, visceral fat area.

Author contributions

JSK conceived and designed the experiments; SP analyzed the data; JC and WYK contributed reagents and materials; JC wrote the paper.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Soonchunhyang University Hospital. Subjects have given their written informed consent.

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Conflict of interest

The authors declare no conflict of interest.

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