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Association of visceral and subcutaneous adiposity with tumor and histologic grade in breast cancer

İrfan Atik[1], Enes Gül[1], Nisa Bozbıyık[1], Tülay Koç[2]

[1]*Department of Radiology, Faculty of Medicine, Sivas Cumhuriyet University, Sivas, Turkiye*
[2]*Department of Medical Pathology, Faculty of Medicine, Sivas Cumhuriyet University, Sivas, Turkiye*

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ABSTRACT

Aims: Obesity is a risk factor for breast cancer. This study aims to evaluate the relationship between abdominal fat tissue and the risk of breast cancer and the histological degree of cancer with the help of computed tomography (CT).

Methods: This study is a retrospective, cross-sectional study. It consists of patients diagnosed with breast cancer and a control group. Abdominal fat tissue measurements were taken from the navel or 4th lumbar vertebra level using an abdominal CT workstation. Visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), fat ratio (FR), and waist circumference measurements were made. The relationship between the obtained measurements and breast cancer, histological grade, and hormone status was analyzed.

Results: Forty-one breast cancer patients and forty-two individuals without known diseases were examined. VAT and SAT were found to be higher in patients with breast cancer and it was statistically significant ($p<0.05$). Estrogen and/or progesterone receptor-negative patients tended to have a higher VAT rate. An increase in VAT and FR in breast cancer patients was found to have a more significant effect in patients with negative hormone receptors than in positive ones (estrogen receptor r: 0.585 $p<0.05$, progesterone receptor r: 0.579, $p<0.05$).

Conclusion: The relationship between breast cancer and abdominal adipose tissue has been demonstrated. In addition, a correlation was found between high VAT and FR and histological grade in patients with hormone receptor-negative.

Keywords: Breast cancer, abdominal visceral fat, abdominal subcutaneous fat, histological type of neoplasm

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer in women.[1] Obesity affects the incidence and progression of many cancer types and is thought to be associated with 20% of cancer deaths. It is estimated that this relationship is due to metabolism in adipose tissue, and the mechanism has not been fully elucidated.[2]

Some studies used body-mass index (BMI) to examine the relationship between obesity and breast cancer. Mortality was found to be low in those with high BMI.[3] Similarly, there are studies claiming that breast cancer survivors have a higher-than-ideal weight.[4] These inconsistencies cannot differentiate between adipose tissue and other tissues in BMI. For this reason, adipose tissue stores such as visceral and subcutaneous adipose tissue are not adequately represented.[5]

Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) indicate central obesity. Some studies have stated that SAT stored especially around the hips and thighs better reflects the metabolic profile.[6] In classical measurements of central obesity, VAT and SAT distinction cannot be made. Instead of classical measurements such as WC and BMI measurements of abdominal obesity, the determination of the amount of adipose tissue and accumulation sites with computed tomography (CT) gives more accurate results.[7]

VAT is a source of estrogen and cytokines that cause inflammation.[5] VAT is associated with hyperinsulinemia and may shorten the proliferation of tumor cells and the patient's life span.[8] In addition, high fasting insulin levels pose a risk for breast cancer and have been associated with poor prognosis and advanced disease.[9]

This study aims to investigate the relationship of specific adipose tissue depots such as VAT and SAT with breast cancer. It is also to evaluate the relationship between histological grade and adipose tissue.

Corresponding Author: İrfan Atik, irfanatik_91@hotmail.com

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METHODS

Study Population

This study is a retrospective, cross-sectional study. Before starting this study, approval was obtained from the Sivas Cumhuriyet University Faculty of Medicine Clinical Researches Ethics Committee (Date: 21.09.2023, Decision no: 2023-09/08). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Between January 2018 and June 2023, all female patients who were older than 18 years of age, had no previous cancer diagnosis, were diagnosed with breast cancer after biopsy, and had abdominopelvic CT imaging within 3 months before treatment were included. Among the patients with pathology results, the study did not include those with missing estrogen receptor (ER), progesterone receptor (PR), or Ki-67 index. In addition, patients with moving CT images were excluded. As a result, the study group consists of 41 patients who meet the inclusion and exclusion criteria for a diagnosis of breast cancer. As a control group, 42 healthy individuals over the age of 18, with no known diseases (e.g., diabetes, Cushing's syndrome, cancer) and who underwent abdominopelvic CT due to a traffic accident, were randomly selected and included in the study.

Pathological Evaluation

In this study, patients diagnosed with invasive breast cancer in the pathology department of this institution were evaluated. Histological grade, ER, PR, and Ki-67 index information of the cases were evaluated in this study.

Histological grade, modified Nottingham combined histological grading system was used. Histological grade was determined by evaluating three parameters: glandular/acinar/tubular differentiation, nuclear pleomorphism, and mitotic count. They were divided into grade 1, grade 2, and grade 3. Immunohistochemical evaluation: Nuclear staining of 1% or more was considered positive for ER and PR.[10]

Body Composition Analysis

In this study, images were performed using a 128-slice multi-detector CT (Aquilion, Toshiba Medical Systems, Tokyo, Japan) device using an abdominopelvic CT protocol. The technical parameters of this device are listed in Table 1.

Measurements such as VAT, SAT, fat ratio (FR=VAT/VAT+SAT), and waist circumference (WC) were made at the level of the navel or 4th lumbar vertebra, which is a valid method.[11] Measurements were made using the oil analysis program (Aquarius iNtuition Edition ver 4.4.6, Califonia, USA) available at the station (Figure). The measurement of individuals in the study and control groups was made by two expert radiologists using the double-blind randomization method.

Statistical Analysis

SPSS 22.0 (SPSS Inc., Chicago, IL, USA) program was used to evaluate the characteristics of individuals in the study and control groups. The normality of the variables was analyzed using analytical methods (Kolmogorov Smirnov/Shapiro Wilk tests). Descriptive statistics of the data were given as standard deviation. In quantitative data, all means were analyzed using a t test. Spearman's correlation test was used to measure the correlation between variables. Type 1 error level was taken as 0.05.

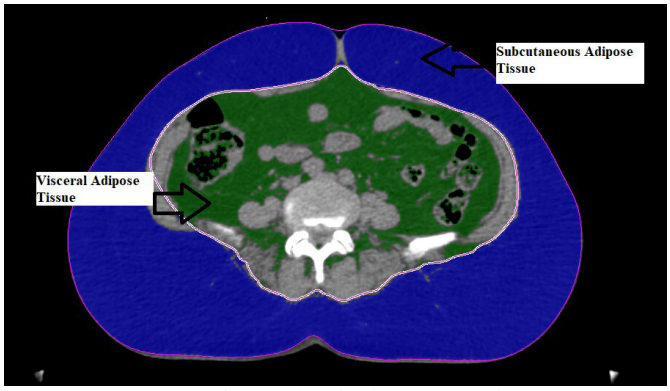

Figure. Measurement of visceral and subcutaneous adipose tissue at the level of the navel or 4th lumbar vertebra with computed tomography

RESULTS

There were 41 patients between the ages of 41 and 83 in the study group, and the mean age was 60.75. There are 42 individuals in the control group between the ages of 40 and 82, and the average age is 56.78 years. There was no statistically significant difference between the groups (p>0.05). In the study group, the mean VAT was 137.64 cm^2, SAT was 330.44 cm^2, and WC was 101.56 cm on average. In the control group, the mean VAT was 75.88 cm^2, SAT was 168.87 cm^2, and WC was 82.95 cm on average. There was a significant difference between the groups in terms of VAT, SAT, and WC (p<0.05). The fat ratio was 29.97 in the study group and 31.15 in the control group, and no statistically significant difference was found (p>0.05) (Table 2).

Table 2. Abdominal fat distribution and waist circumference of the groups

	Groups	n	Mean	SD	p
Age (years)	Case	41	60.75	10.72	p=0.101
	Control	42	56.78	11.07	
Visceral adipose tissue (VAT) (cm^2)	Case	41	137.64	65.66	p=0.0001*
	Control	42	75.88	33.94	
Subcutaneous adipose tissue (SAT) (cm^2)	Case	41	330.44	146.21	p=0.0001*
	Control	42	168.87	69.58	
Fat ratio	Case	41	29.97	11.09	p=0.586
	Control	42	31.15	8.28	
Waist circumference (cm)	Case	41	101.56	16.22	p=0.0001*
	Control	42	82.95	14.82	

Fat ratio: VAT/VAT+SAT, SD: Standard deviation, VAT: Visceral adipose tissue, SAT: Subcutaneous adipose tissue, p<0.05*: Statistically significant

Fifteen (36%) of the patients in the study group were found to be grade 1, 22 (53%) grade 2, and 4 (11%) grade 3 histological subtypes. The ER was positive in 29 (70%) patients, and the ER was negative in 12 (30%) patients. The PR was positive in

Table 1. Technical parameters of CT used in the study

CT scanner	Tube voltage (kV)	Total tube current (mA)	Slice thickness (mm)	Acquisition FOV (mm)	Rotation time (sn)	Pitch factor
128-slice multi-detector CT	120	100-400	3	400	0.5	1.58

CT: Computed tomography, FOV: Field of view

27 (65%) patients and negative in 14 (35%) patients. The Ki-67 index is in the range of 5-70, with a median value of 20. A correlation test was performed to investigate the relationship between ER, PR, Ki-67 index, histological grade, VAT, SAT, and FR. No statistically significant finding was detected (p>0.05).

Correlation analysis was performed to investigate the relationship between histological grade and VAT, SAT, FR, and Ki-67 index according to estrogen and progesterone receptor-negative status. In patients with negative estrogen receptors and/or progesterone receptors, the correlation between VAT and FR and histological grade was statistically significant (p<0.05). There is a correlation between SAT and Ki-67 index, but it is not statistically significant (p>0.05) (Table 3).

Table 3. Correlation analysis between abdominal fat distribution and grade in hormone receptor-negative patients

		Visceral adipose tissue	Subcutaneous adipose tissue	Fat ratio	Ki-67
ER (-) patients histological grade	Correlation coefficient	0.585	0.084	0.585	0.140
	Sig (2-tailed)	0.046*	0.796	0.046*	0.665
	n	12	12	12	12
PR (-) patients histological grade	Correlation coefficient	0.579	0.138	0.707	0.374
	Sig (2-tailed)	0.048*	0.637	0.005*	0.188
	n	14	14	14	14

ER (-): Estrogen receptor-negative, PR (-): Progesterone receptor-negative, p<0.05*: Statistically significant

DISCUSSION

In this study, the relationship between abdominal fat tissue parameters and breast cancer was evaluated with analyses performed at the workstation from abdominal CT, and a significant difference was detected. Additionally, a relationship was found between VAT and FR values in the hormone receptor-negative patient group. No relationship existed between histological grade and VAT, SAT, FR, and WC.

Obesity is a risk factor for breast cancer.[12] In a recent study by Smith et al.,[13] it was stated that the risk of breast cancer increases with an increase in BMI index. Many studies have examined the relationship between obesity and breast cancer with less specific data such as BMI or WC. In this study, only fat tissue measurement was made, excluding areas other than adipose tissue, such as other organs and muscle tissue. Thus, the relationship between breast cancer and fat tissue was intended to be revealed more accurately. The amount of VAT and SAT was found to be higher in breast cancer patients, and it is estimated that abdominal fat tissue is associated with cancer. Similar to this study, a study evaluating fat tissue with CT also stated that the risk of breast cancer increased 1.5 times.[7]

Abdominal adipose tissue comprises VAT around the internal organs and SAT under the skin. VAT has a higher hormonal effect than SAT. Insulin resistance, increased insulin level, increased fatty acid amount, and increased estradiol bioavailability are known important effects. These hormonal changes increase the risk of breast cancer.[14] Obesity may pose a risk for the formation and progression of breast cancer in several ways. Among the molecular mechanisms between obesity and tumor formation are aromatase enzyme and estrogen increase in adipose tissue, circulating insulin and insulin-like growth factor (IGF-1), adipokine amount, and signaling pathways that cause chronic inflammation.[15]

Generally, similar age, gender, and body fat percentages in BMI are close to each other. However, unlike VAT, BMI, and WC, it differs according to age, gender, and race.[7] Fat distribution seems to be very important not only for metabolic disorders but also for susceptibility to cancer.[14] Showing the body fat distribution by taking cross-sectional images with CT is an accurate method since it is easy to distinguish from other tissues. In terms of breast cancer risk, CT provides the most accurate information by dividing the abdominal adipose tissue into sections.[16] In this study, the areas where fat is stored in the abdominal region were specifically measured and it was shown that it may cause breast cancer due to many of the above hormonal mechanisms and metabolites.

Hormone receptor status is very important in breast cancer and is a prognostic indicator. Hormone receptor negativity is an indicator of rapid growth and is a poor prognostic factor.[17] In this study, parameters such as histological grade, ER, PR, Ki-67 index, and VAT, SAT, and FR relationships were evaluated in patients with breast cancer. A negative correlation was found with VAT and FR in both ER-negative patients and PR-negative patients, which was statistically significant (p<0.05). This shows that the increase in VAT affects the histological grade in patients with hormone receptor-positive rather than negative ones. In the study conducted by Lee et al.,[18] high VAT and mortality rates were found in patients with negative progesterone receptors. In another study, similar to these results, it was shown that increased intra-abdominal fat tissue and breast cancer risk were more associated with estrogen and/or progesterone-negative patients.[7] In general, breast cancer patients with positive estrogen and progesterone receptors live longer than those with negative estrogen and progesterone receptors.[19] In addition, these receptors must be positive for hormone therapy. Intra-abdominal adipose tissue increases the risk of breast cancer and negatively affects the prognosis.[20] In addition, it is thought that the relationship between intra-abdominal fat tissue and histological grade varies according to the hormone receptor, as seen in previous studies.

The strong points of the study include the ability to perform quantitative measurements with CT, as well as the capability to differentiate fat tissue from other soft tissues and organs. Additionally, comparing the results with pathology findings is another strong aspect.

Limitations

There are some limitations of this study. First of all, since it is a retrospective study, the data are based on medical records. In addition, although there are many risk factors for breast cancer, it was only associated with intra-abdominal adipose tissue in this study. It is recommended that the relevant study be conducted prospectively in large populations.

CONCLUSION

It was concluded that there is a relationship between VAT and SAT and breast cancer. In addition, it is thought that the relationship between high VAT and FR and hormone receptor negativity is related to the inability to apply hormone therapy and poor prognosis.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Sivas Cumhuriyet University Faculty of Medicine Clinical Researches Ethics Committee (Date: 21.09.2023, Decision no:

2023-09/08).

Informed Consent
Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Financial Disclosure
The authors declared that this study has received no financial support.

Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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