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International Journal of Radiology and Imaging. 01 (02). 30 Desember 2022: 38-47
e-ISSN 2830-506X
p-ISSN 2830-6007

THE RELATIONSHIP BETWEEN BREAST VOLUME AND BREAST MALIGNANCY IN MAMMOGRAPHY

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Abstract

Breast cancer is a major global public health problem and the most common type of cancer. The incidence of cases in Indonesia are about 42.1 per 100.000 population in 2019. There are multiple risk factors that underlie breast cancer malignancy. However, breast volume has not been yet included as a risk factor for breast cancer. The aim of this study is to analyze the association between breast volume and breast malignancy. This study is a cross-sectional study obtaining breast volume and BI-RADS score by performing mammography assessment at dr. Saiful Anwar General Hospital, Malang.

The inclusion criteria were women aged > 40 years and excluded those who have mammography contraindications such as pregnancy and breast-feeding. The parameters for calculating breast volume were the width, height, and compression thickness, and the BI-RADS category (0 – 6) was used to determine the malignancy.

There is no significant association using the non-parametric analytic test Kruskal Wallis analytic test ($p = 0.273$, $p < 0.05$) and a very weak negative correlation based on the correlation test Spearmanis correlation test (-0.127). There is no association between breast volume and the risk of malignancy based on BI-RADS mammography.

Keywords: *Breast Volume, Breast Cancer, Mammography*

INTRODUCTION

Breast cancer remains a serious global problem. According to data by WHO 2020, the number of new cases of cancer in the world is 19,292,789 and the mortality was 9,958,133. Breast cancer is a type of cancer that has the greatest incidence among other types of cancer worldwide. In 2020, the number of new cases of breast cancer was recorded at 2,261,419 (11.7% of other types of cancer) and became the biggest cause of death after lung, liver, and stomach cancer[1]. Indonesia ranks 8th in Southeast Asia and 23rd in Asia, with a cancer incidence rate of 136.2 per 100,000 population. The incidence of breast cancer in Indonesia, especially in women, is 42.1 per 100,000 population, with mortality averaging 17 per 100,000 population[2].

Breast cancer is more common in women than in men. According to the *Surveillance, Epidemiology, and End Results Program* (SEER) data for 2015, the incidence of invasive breast cancer in men is 1.1:100,000, while that in women is 126.5:100,000[3]. Studies show that age at menarche, age at first pregnancy, method of breastfeeding, family history of breast cancer, age, body mass index, history of alcohol consumption, history of smoking, oral contraceptives, history of abortion, breast density, history of hyperthyroidism, working hours, exercise, and diet were related to breast cancer development. Breast volume is still not classified as a risk factor for breast cancer[4].

The breast consists of dense tissues—epithelium and stroma and non-dense tissue—fatty tissue. These two types of tissue can differ in proportion to each woman. Women with dense tissue ≥75% have a 4—6 times greater risk of breast cancer than women with dense tissue ≤ 25%. Meanwhile, women with a larger breast volume have more epithelial cells (dense tissue). Women with larger breast volumes also tend to have higher concentrations of the hormone estrogen than those with smaller breast volumes. High levels of the hormone estrogen in circulation pose a higher risk of breast cancer[5].

Breast volume and breast cancer risk are also associated with genetic factors. A genome association study proved that there is a link between breast volume (breast size) and breast cancer risk, namely two SNP (single nucleotide polymorphisms) genomes, rs12173570 (adjacent to ESR1) and rs12371778 (adjacent to PTHLH). It has been shown that rs7089814 is significantly associated with breast volume[6].

Larger breast volume tends to have higher levels of IGF-1. IGF-1 levels are associated with more aggressive tumor characteristics. In breast cancer patients with type 2 diabetes and who are ER-negative, the risk of distant metastases is 2-fold. Larger breast volume affects tumor survival rate. Studies show that patients with a breast volume ≥ 850 mL have a shorter disease-free and metastasis-free survival[7].

Body Mass Index (BMI) also affects breast volume. In obese patients, breast volume tends to be larger than that in non-obese patients[8]. BMI ≥35 relatively has a higher level of malignancy compared to those who have a lower BMI[9]. Based on a study on a population of breast cancer patients in Denmark, women in the normal-obese group had an overall mortality rate 76% higher than women with normal weight. ER-negative and obese female breast cancer patients have poor survival rate[10].

Based on the description of the background explained, the authors were interested in conducting a study titled “The Relationship between Breast Volume and Breast Malignancy in Mammography”. The results of this study are expected to contribute to a firther understanding that can benefit the public in identifying risk factors and prognosis for breast cancer.

METHODS

Research Design

This is an analytic observational study using a cross-sectional design. This study was conducted without providing intervention or treatment of the variables and aimed to analyze the relationship between breast volume and the risk of malignancy from mammography examination. The research data were obtained from breast examination screening at Dharma Wanita group of Universitas Brawijaya and the Association of Indonesian Radiographers (PARI) of Greater Malang Area at dr. Saiful Anwar General Hospital, Malang. Data collection was carried out from October to November 2021. The inclusion criteria were women aged at least 40 years, while the exclusion criteria in this study were pregnant women, lactating women, and participants who had contraindications for mammography. This study was approved by the Health Research Ethics Commission of dr. Saiful Anwar General Hospital, Malang.

The independent variable is breast volume (mL), while the dependent variable is the level of breast malignancy based on the BI-RADS category. Breast volume was calculated for each right and left breast using a formula reported in previous research by Kalbhen *et al*[11,12]. Breast Volume = $(\pi/4) \times H \times W \times C$ (Figure 1).

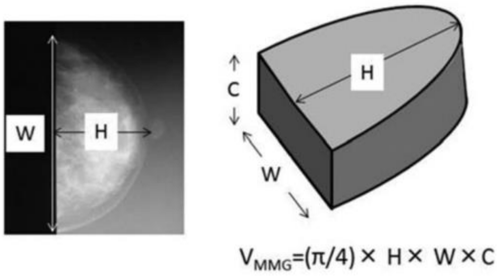

Figure 1 Breast volume formula

H = breast height (cm), W = breast width (cm), C = compression thickness (cm).

Study Subjects and Population

The population in this study was thw members of the Dharma Wanita group of Universitas Brawijaya and the Association of Indonesian Radiographers (PARI) of Greater Malang Area; meanwhile the samples in this study were those in the Dharma Wanita group of Universitas Brawijaya and the Association of Indonesian Radiographers (PARI) Malang Raya who fulfilled the inclusion criteria. The inclusion criteria were women aged at least 40 years, while the exclusion criteria in this study were participants who had contraindications for mammography such as pregnant and lactating women. Sampling in this study the probability sampling cluster random sampling with the samples involving members of the Dharma Wanita group and the Association of Indonesian Radiographers (PARI) in the Malang area. The minimum number of subjects required is 27 samples.

Data analysis

Statistical data analysis in this study used the Kruskal-Wallis test to assess the significance of the relationship between variables. The Kruskal-Wallis test was carried out because the data distribution was not normal on the BI-RADS score ordinal categorical variables. Furthermore, the Spearman's test was used to determine the direction of the relationship between variables. The two analytical tests in this study were carried out using the Software Statistical Product and Service Solution (SPSS) application.

RESULTS

The results of the study were obtained from primary data, which were measured directly through mammography examinations, physical examinations, and filling out questionnaires. A total of 32 points of data were obtained after the exclusion of the other 37.

Characteristics of Research Subjects

The description of the characteristics of the samples in this study is presented in Table 1. All research subjects were women, a total of 32 people (100%) and the majority were above 45 years old (87.5%). In addition, the authors collected data on the history of childbirth, age at first pregnancy, age at menarche, family history of cancer, and body mass index (BMI) as another risk factor for breast malignancy.

As many as 14 people (43.8%) had a history of giving birth twice; the most common age of the first pregnancy was in the range of 23—28 years, comprising 16 people (50%); the age of menarche was mostly at the age of 13 years, accounting for 8 people (25%). Another characteristic is a family history of cancer, where the majority of subjects did not have a family history of cancer, a total of 19 people (59.4%). The highest body mass index, ≥ 30, is demonstrated by 11 people (34.4%).

Table 1 Characteristics of Research Subjects

Characteristics	Frequency	Percentage (%)
Gender		
Female	32	(100%)
Age		
< 45	4	(12.5%)

≥ 45	28	(87.5%)
Childbirth history		
1	2	(6.3%)
2	14	(43.8%)
3	9	(28.1%)
4	3	(9.4%)
5	1	(3.1%)
6	2	(6.3%)
7	1	(3.1%)
Age at First Pregnancy		
17 – 22	4	(12.5%)
23 – 28	16	(50%)
29 – 32	12	(37.5%)
Age at Menarche		
11	2	(6.3%)
12	7	(21.9%)
13	8	(25%)
14	6	(18.8%)
15	7	(21.9%)
16	1	(3.1%)
17	1	(3 .1%)
Family History of Cancer		
No	19	(59.4%)
Yes	13	(40.6%)
Body Mass Index		
<18.5	1	3.1%
18.5 – 22.9	3	9.4%
23 – 24.9	7	21.9%
25 – 29.9	10	31.3%
≥ 30	11	34.4%

Research data

The research data consisted of the independent variable, namely breast volume and the dependent variable, the BI-RADS category score. Breast volume is the volume of each breast, which was measured based on the width, height, and *compression thickness* using mammography. The BI-RADS category score is based on ACR (American College of Radiology) BI-RADS fifth edition.

Table 2 Research Data

Variable	**Frequency**	**Percentage (%)**
Breast Volume		
100 – 500 mL	15	23.4%
501 – 1000 mL	30	46.9%
1001 – 1500 mL	11	17.2%
1500 – 2000 mL	5	7.8%
> 2000 mL	3	4.7%
BI-RADS		
BI-RADS 0	2	3.1%

BI-RADS 1	30	46.9%
BI-RADS 2	24	37.5%
BI-RADS 3	7	10.9%
BI-RADS 4	1	1.6%

Based on Table 2, the highest breast volume is in the range of 501—1000 mL, namely in 46.9% of the subjects, while the BI-RADS category scores in the subjects of this study were mostly in the BI-RADS 1 category which means a negative findings with a 0% probability of malignancy in the 30 samples of breast volume data (46.9%). The negative findings of mammae bilateral (BI-RADS 1) shows that there are no suspicious findings such as microcalcifications or masses (Figure 2).

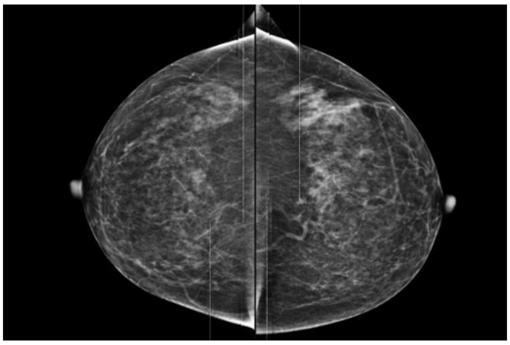

Figure 2 Negative findings of mammae bilateral

Another findings of BI-RADS data were BI-RADS 0, 2, 3, and 4b. The BI-RADS 0 shows that there are incomplete assessment of mammography. A further work-up need to be performed to obtain more information (Figure 3). The BI-RADS 2 might shows a round opacities, macrocalcifications of fibroadenoma or cyst, scattered macrocalcifications, or vascular calcifications. An isodense nodule with calcifications and irregular margin sized ±0,8 cm x 0,9 cm in the upper outer quadrant of the right breast can be found in this sample (Figure 4).

In 1 of 7 samples with BIRADS 3, an equal density mass with regular margin can be found in the upper outer of the left mammae. It sized ± 1,5 x 0,6cm and ± 3,3cm from the nipple viewed in left craniocaudal (LCC) projection and ± 2,8 cm in left mediolateral oblique (LMLO) projection (Figure 5). There is one sample indicating BI-RADS 4b with moderate suspicion of malignancy. This sample shows an equal density nodule, sized 22 mm x 17 mm, with irregular shape, microlobulated margin, and fine pleomorphic calcification in the upper inner quadrant. Moreover, a focal breast asymmetry and architectural distortion can also be found in the upper outer zone of the right mammae. (Figure 6).

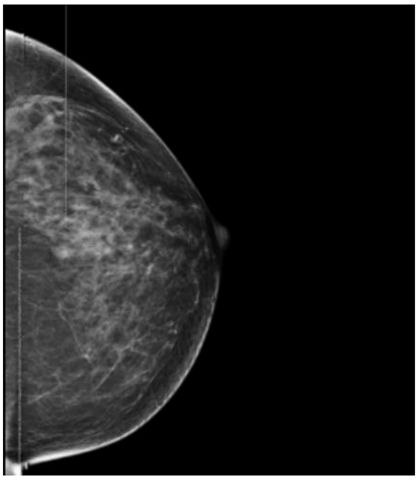

Figure 3 BI-RADS 0 findings of the left mammae

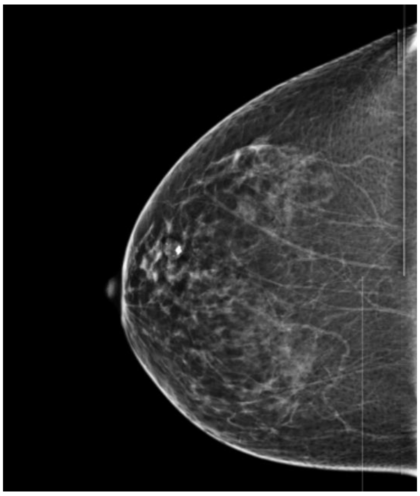

Figure 4 BI-RADS 2 findings of the right mammae

Nodule with calcifications in the upper outer quadrant

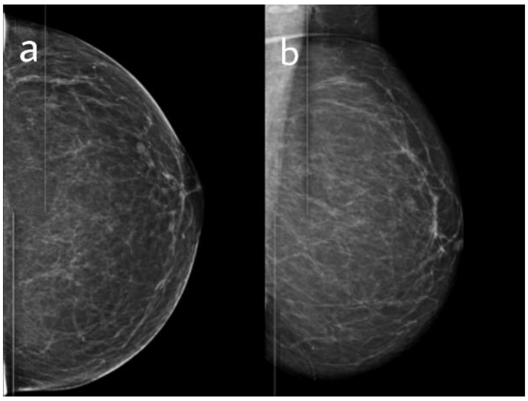

Figure 5 BI-RADS 3 findings of the left mammae

(a) left craniocaudal (LCC) projection ; (b) left mediolateral oblique (LMLO) projection.

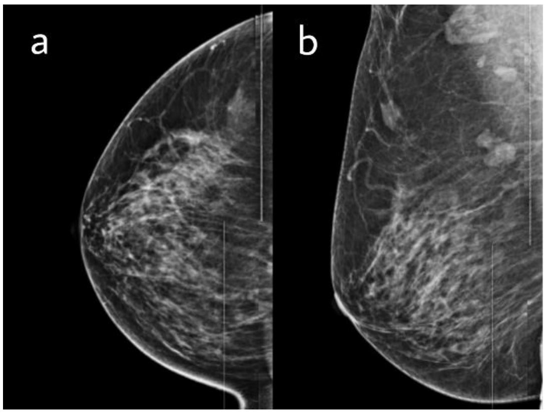

Figure 6 BI-RADS 4b findings of the right mammae with moderate suspicion of malignancy

(a) left craniocaudal (LCC) projection ; (b) left mediolateral oblique (LMLO) projection.

Statistical analysis

Statistical analysis was performed with the SPSS Statistics 23 software with the Kruskal-Wallis and Spearman's tests. Kruskal Wallis analysis was used to analyze the relationship between two variables. The Spearman's test was used to see the direction of the relationship between breast volume and malignancy based on the BI-RADS category score.

Based on Table 3, the results of the statistical analysis using the Kruskal-Wallis test showed that there is no relationship between breast volume and the level of malignancy based on the BI-RADS score is 0.273 ($p>0.05$). Meanwhile, based on Table 4, the significance value or Sig. (2-tailed) of 0.317 ($p>0.05$) indicates that there is no relationship between breast volume and the level of malignancy based on the BI-RADS score. The correlation coefficient is -0.127, suggesting that the strength of the correlation between breast volume and the BI-RADS score is weak. The correlation coefficient is negative, which can be concluded that breast volume has a negative correlation with the level of malignancy based on the BI-RADS score.

Table 3 The Relationship between Breast Volume and Malignancy Level Based on BI-RADS Category Scores Using the Kruskal-Wallis

	BI-RADS Score	**Frequ-ency**	**Asymp. Sig**
Breast Volume	0	2	
	BI-RADS 1	30	
	BI-RADS 2	24	0.273
	BI-RADS 3	7	
	BI-RADS 4	1	

Table 4 The Relationship between Breast Volume and Malignancy Level Based on the BI-RADS Category Score Using Spearman's Test

		Breast Volume	BI-RADS Score
Volume	Correlation Coefficient	1.000	-0.127
	Sig. (2-tailed)		0.317
	N	64	64
BI-RADS	Correlation Coefficient	-0.127	1.000
	Sig. (2-tailed)	0.317	
	N	64	64

DISCUSSION

The results of this study do not show a significant relationship between breast volume and the risk of malignancy. This is in line with previous research by Tavani *et al*[13] which stated that there is no direct relationship between breast volume and the risk of breast malignancy and it is not a major factor in the risk of breast malignancy.

The recent study in Indonesia by Putri *et al* showed that the left breast tend to have a higher risk of malignancy than the right breast. This is because the left breast size is slightly larger than the right breast due to hemodynamic asymmetry. However, this minimal increase in size does not influence the risk of breast malignancy. Therefore, parenchymal mass, or mammary gland cell mass, is more likely to be a predictor of breast cancer malignancy than breast size[14].

Based on the results of this study, a weak and non-significant negative correlation was found between breast volume and malignancy based on the BI-RADS score. That being said, in theory, reducing the number or volume of the breast would reduce the risk of breast malignancy. Smaller breast volume indicates a smaller number of cells in the breast, i.e., with fewer target cells, there is less tendency for cells to transform into malignancy. However, this may not occur in women with a strong genetic risk of developing malignancy, regardless of the target cell count[15]. Meanwhile, based on genetic research using the LDSC (linkage disequilibrium score) regression method that tested the relationship between SNP (single nucleotide polymorphisms) genes and BMI (body mass index), breast volume, and breast cancer risk by Ooi *et al*[16] it was found that, there was no clear genetic evidence to show an association between breast volume and the risk of developing breast cancer or malignancy.

The results of a study by Koch *et al*[17] using the bra size measurement method showed no differences in breast volume in breast cancer patients and in the general female population. The relationship between breast volume and the risk of malignancy is difficult to identify directly without taking into account mammographic density measurements which are strong and independent risk factors for malignancy. The total breast volume on mammography is a combination of dense and non-dense areas. Lower density is inversely related to the risk of malignancy[17].

An increased density of the breast increases the risk of cancer compared to a lower breast density. This is because breast density may obscure a mass and increase the risk of developing interval cancers, which occur between mammographic screenings[18]. Breast density indicates the amount of epithelial and breast stroma, whereas breast malignancy most often develops from epithelial cells. A greater amount of epithelial tissue increases the chance of developing breast cancer[19]. Mammographic density in pre-menopausal women is significantly associated with breast cancer mortality[8].

On the other hand a recent study by Lubián López *et al*[8] who used a cross-sectional study design in post-menopausal women with breast cancer in the Caucasian population also pointed out that there was no relationship between breast volume and tumor prognosis. In this study, a consistent relationship was found between breast volume and body mass index (BMI), but no consistent relationship was found between breast volume and central obesity, while central obesity was associated with a worse tumor or cancer prognosis. Breast volume is not related to tumor prognosis because of the low volume relationship with central adiposity[8,16]

Lubián López *et al*[8] also found that women with larger breast volumes had a prevalence of positive estrogen receptor (ER) tumors compared to women who had smaller breast volumes. Estrogen signaling is an important factor in the initiation and development of breast cancer, which is mediated by specific receptors, namely estrogen receptors (ER), through activating mechanisms or suppressing transcription in target organs. Estrogen signaling is involved in the proliferation and differentiation of mammary epithelial cells. Estrogen functions as a mitogen for cell promotion in the G1 phase and S phase. The presence of dysregulation of estrogen signaling increases cell proliferation and breast cancer development[20].

Another possible mechanism underlying the relationship between breast volume and cancer prognosis is an increase in IGF-1 (insulin-like growth factor 1) levels. Larger breast volume can be a marker of IGF-1 levels. High IGF-1 levels are associated with mammographic density in pre-menopausal women, while mammographic density has a significant relationship with breast cancer mortality[8]. Markkula *et al* (2012) stated that larger breast volume may be associated with higher IGF-1 levels in young nulliparous women who do not use oral contraceptives[7].

Hormonal factors, namely estrogen and IGF-1, may influence the relationship between variables in this study. Another limitation is that the sample is from a relatively healthy female population. From the mammography screening examination data at dr. Saiful Anwar General Hospital, Malang, the characteristics of breast malignancy as seen from the BI-RADS score in this sample are less varied, so a larger sample with more variations is needed.

CONCLUSION

There is no statistically significant relationship between breast volume and the risk of malignancy with a weak, negative correlation between breast volume and breast malignancy. This shows that if there is an increase in breast volume, it will be followed by a decrease in the BI-RADS score, albeit very weak.

Further research is needed to incorporate breast density into the research subjects to examine the relationship between breast volume and risk of malignancy. In addition, it is also necessary to carry out additional analyses related to other factors such as BMI, genetic factors, and hormonal factors on the risk of malignancy in breast volume. Subsequent studies need to be carried out with a larger and more varied sample to reduce the possibility of bias.

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