Fatty Liver and Its Associated Factors among Breast Cancer Patients in Dharmais Cancer Hospital, Jakarta

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ABSTRACT

Background: *Fatty liver is frequently found during ultrasound (US) examination of breast cancer patients. It is not known how the association between breast cancer and fatty liver. This study was aimed to obtaine the prevalence of fatty liver in breast cancer patients and its association with clinical characteristics of the patients.*

Method: *This was a cross-sectional study in Dharmais Cancer Hospital, Jakarta. Study subjects were breast cancer patients who came between January 2011 and December 2013. Fatty liver was assessed by using abdominal US and were grouped into mild, moderate, and severe. Clinical characteristics of the patients included age, body mass index (BMI), menopausal status, breast tissue density using breast imaging reporting and data system (BI-RADS), and immunohistochemical estrogen receptor (ER) status.*

Results: *A total of 72 patients were enrolled during the study period with the mean age of 47.5 years. Fatty liver was found in 68 (94.4%) patients. Sixty (83.3%) patients had moderate-to-severe fatty liver. Patients with moderate-to-severe fatty liver had significantly higher BMI (26.9 ± 5.39 vs. 23.6 ± 4.05 kg/m^2; $p = 0.005$). Fatty liver was not associated with the patient's age, menopausal status, and breast tissue density.*

Conclusion: *This study showed that the prevalence of fatty liver in breast cancer patients is very high. Fatty liver shows significant association with obesity but is not associated with breast tissue density or estrogen receptor status.*

Keywords: *breast cancer, breast cancer density, fatty liver, estrogen receptor*

ABSTRAK

Latar belakang: *Perlemakan hati sering didapatkan pada pemeriksaan ultrasonografi (US) pasien kanker payudara. Belum diketahui jelas hubungan antara kanker payudara dan perlemakan hati. Penelitian ini bertujuan untuk mengetahui prevalensi perlemakan hati pada pasien kanker payudara dan hubungannya karakteristik klinis pasien.*

Metode: *Penelitian ini merupakan studi potong lintang di rumah sakit (RS) Kanker Dharmais, Jakarta. Subjek penelitian adalah pasien kanker payudara yang datang sejak bulan Januari 2011 hingga Desember 2013. Perlemakan hati diperiksa dengan US abdomen dan dibagi menjadi ringan, sedang dan berat. Karakteristik klinis yang dinilai adalah usia, indeks massa tubuh (IMT), status menopause, kepadatan jaringan payudara dengan breast imaging reporting and data system (BI-RADS), dan status reseptor estrogen (RE) tumor secara imunohistokimia.*

Hasil: *Terdapat 72 orang pasien dalam periode penelitian dengan rerata usia 47,5 tahun. Perlemakan hati didapatkan pada 68 (94,4%) pasien. Sebanyak 60 (83,3%) pasien menunjukkan perlemakan sedang-berat. Pasien*

dengan perlemakan hati beratsecara bermakna memiliki indeks massa tubuh (IMT) yang lebih tinggi (26,9 ± 5,39 vs. 23,6 ± 4,05 kg/m^2; p = 0,005). Perlemakan hati tidak berhubungan dengan usia, status menopause, kepadatan jaringan payudara, dan RE status.

Simpulan: *Hasil penelitian ini menunjukkan bahwa prevalensi perlemakan hati pada kanker payudara sangat tinggi. Perlemakan hati menunjukkan hubungan bermakna dengan obesitas dan tidak berhubungan dengan kepadatan jaringan payudara dan status reseptor estrogen.*

Kata kunci*: kanker payudara, kepadatan jaringan payudara, perlemakan hati, estrogen reseptor*

INTRODUCTION

Breast cancer is the most prevalent malignancy in women. Breast cancer ranked the fifth as cause of death of all women.[1] Data from Indonesian shows the number of breast cancer patients in Indonesia is 40.58 of 100,000 populations which make it the biggest contributor of all malignancies in women.[2]

Fatty liver occurs when lipid droplets accumulate within hepatocytes and characterized by microvesicular and/or macrovesicular steatosis.[3] It is asymptomatic and often found incidentally during abdominal imaging for other reason. Indeed, fatty liver in breast cancer patients was first observed when assessing liver metastasis.[4] It is not known whether fatty liver is a coincidental finding or have related pathogenesis with breast carcinogenesis.

Transabdominal ultrasound is an imaging modality most often used for early diagnosis and evaluation of fatty liver because it is not expensive, non-invasive, and are readily available in many medical facilities. It has high accuracy and reliability for fatty liver diagnosis.[5] This study was aimed to know the prevalence of fatty liver among breast cancer patients and its associated clinical factors.

METHOD

This was a cross-sectional study conducted at Dharmais Cancer Hospital (DCH), Jakarta. Subjects were breast cancer patients hospitalized between January 2011 and December 2013. Cases were selected from medical record data and included if they had abdominal US recordings, mammogram and breast tissue specimens with immunehistochemistry assessment. Patients were included consecutively if they met research criteria until the minimum sample size required was achieved. Patients with history of chronic liver disease and evidence of liver metastasis were excluded from analysis. The minimum sample size at 5% confidence level, 10% absolute precision and 20% anticipated proportion was 62 patients. Clinical data were obtained from medical record, which included age at diagnosis, menopausal status and age at menopause, body mass index (BMI), and estrogen receptor (ER) results. BMI was calculated as body weight in kilograms divided by body height in meter square (kg/m^2). Based on BMI criteria for Asian population, nutritional status were grouped into normal or less (BMI $\leq$ 23 kg/m^2), overweight (BMI > 23 and $\leq$ 25 kg/m^2), and obese (BMI > 25 kg/m^2).[6]

Fatty liver was diagnosed by using high-end ultrasound equipment. Diagnostic criteria for fatty liver includes increasing echogenicity of the liver parenchyma, disappearance of portal vein wall echogenicity, excessive difference of echogenicity between liver and kidney parenchyma and ultrasound attenuation of the liver parenchyma. Fatty liver was negative when the echogenicity of right kidney and liver parenchyma was similar. The degree of fatty infiltration into the liver was further graded as mild (Grade 1) if there is mild increase of diffuse liver echogenicity with normal contour of intrahepatic blood vessels and diaphragm; moderate (Grade 2) if there is moderate increase of liver echogenicity and blurring of diaphragm and intrahepatic blood vessels; and severe (Grade 3) if there is evident increase of echogenicity. Posterior segment of the right lobes is difficult to see. The structures of intrahepatic blood vessels and diaphragm contour is hazy or invisible.[7,8]

Breast tissue density was assessed by using mammography taken craniocaudally and oblique mediolaterally. The result was classified according to the breast imaging reporting and data system (BI-RADS) as BI-RADS 1 to 4. BI-RADS 1 was defined when the breast was almost entirely fat or had less than 25% fibroglandular tissue; BI-RADS 2 was assigned if there were scattered fibroglandular tissue (25% to 50%); BI-RADS 3 was a heterogenously dense breast tissue (51% to 75% was fibroglandular); and BI-RADS 4 was extremely dense breast tissue (> 75% was fibroglandular tissue). Woman with BI-RADS 3 or 4 density should be informed about their dense breasts.[9,10]

Characteristics of the study subjects were analyzed descriptively and presented as tables. Continuous data were expressed as median and range due to skewed

data. Categorical data were expressed as percentage. Associations between categorical variables were tested using Chi-square or Fisher's exact tests. A *p* value of less than 0.05 was considered significant. Statistical analysis was done by using the SPSS 17.

RESULTS

There were 72 patients enrolled in this study; the median age was 47.5 (range: 29-79) years old. More than half of the patients were post-menopausal. Almost 70% of these patients were overweight or obese. Mammographic imaging showed that the majority of patients (76.4%) had BIRADS 3-4 which is consistent with breast cancer diagnosis. ER-negative was found in 39 (54.2%) patients (Table 1).

Table 1. Characteristics of the study subjects (n = 72)

Variable	Median (Range)	n (%)
Age	47.5 (29.0-79.0)	
Age group (years)		
< 40		16 (22.2)
50-50		30 (41.7)
> 50		26 (36.1)
Body mass index	25.4 (16.6-42.8)	
Nutritional status		
Normal or less (≤ 23 kg/m^2)		24 (33.3)
Overweight (> 23-25 kg/m^2)		15 (20.8)
Obesity (> 25 kg/m^2)		33 (45.8)
Age at menarche (years)		
≤ 12		1 (1.4)
> 12		71 (98.6)
Menopausal status		
No		41 (56.9)
Yes, at ≤ 50 years		24 (34.7)
Yes, at > 50 years		6 (8.3)
Estrogen receptor status		
Positive		33 (45.8)
Negative		39 (54.2)
Breast tissue density		
BI-RADS 1		2 (2.8)
BI-RADS 2		15 (20.8)
BI-RADS 3		22 (30.6)
BI-RADS 4		33 (45.8)
Fatty liver		
None		4 (5.6)
Mild		8 (11.1)
Moderate		20 (27.8)
Severe		40 (55.6)

BI-RADS: breast imaging reporting and data system

Fatty liver was found in 68 (94.4%) of patients; only 4 patients did not show fatty liver appearance. Sixty (83.3%) patients had moderate-to-severe fatty liver. To analyze factors associated with fatty liver, patients were grouped into none-to-moderate (n = 32) and severe (n = 40) patients. Severe fatty liver was significantly associated with higher BMI. There was no association between fatty liver and breast tissue density or ER status of the tumor (Table 2).

Table 2. Association between fatty liver clinical characteristics of breast cancer (n=72)

Breast tissue density	n	Fatty liver		*p*
		Severe (n = 40)	None-to-Moderate (n = 32)	
Mean age (years)		46.2 ± 9.48	49.2 ± 11.74	0.227*
Mean BMI (kg/m^2)		26.9 ± 5.39	23.6 ± 4.04	**0.005***
Postmenopausal status	31	16 (40.0%)	15 (46.9%)	0.558#
ER-negative	33	18 (45.0%)	15 (46.9%)	0.874#
BI-RADS 3-4	55	31 (77.5%)	24 (75.0%)	0.804#

*t-test, #Chi-square test; BMI: body mass index; ER: estrogen receptor; BI-RADS: breast imaging reporting and data system

However, among patients with BI-RADS 3-4, severe fatty liver tended to be more in ER-positive patients. Among patients with BI-RADS 1-2, none-to-moderate fatty liver was proportionally higher in ER-negative patients (Table 3).

DISCUSSION

Fatty liver is a growing public health problem in Indonesia especially among the urban people with modern lifestyle. A recent hospital-based study showed that 51% of healthy adults underwent medical check-up had fatty liver which was highly associated with metabolic syndrome.[11] In this study, fatty liver was found in almost all patients (94.4%) which was very high. Obesity correlates well with fatty liver and fatty liver has been regarded as hepatic manifestation of metabolic syndrome.[12] Consistent with that finding, our study also found higher BMI among subjects with severe fatty liver compare to subjects with none-to-

Table 3. Association between fatty liver and estrogen receptor status based on BI-RADS (n = 72)

Fatty liver	Estrogen Receptor		p	OR	95% CI
	Positive	Negative			
BI-RADS 1-2					
Severe	5 (55.6%)	4 (44.4%)	0.131^	8.750	0.737 - 103.824
None-to-moderate	1 (12.5%)	7 (87.5%)			
BI-RADS 3-4					
Severe	17 (54.8%)	14 (45.2%)	0.375*	0.607	0.201 - 1.833
None-to-moderate	16 (66.7%)	8 (33.3%)			

^Fisher's exact test; *Chi-square test; BI-RADS: breast imaging reporting and data system

moderate fatty liver. However, BMI was not correlated with age or menopausal status (data not shown).

Studies have linked obesity with various cancers, including breast cancer.[13] Patient's nutritional status was associated with the occurrence of breast cancer, especially among the postmenopausal women.[14,15,16] Obesity causes high aromatase production in the breast tissue and increases local estrogen predisposing it to hyperplasia and cancer. Theoretically, obesity increases breast cancer risk through the activation of adipokine and cytokine. Adipokine in fat cells may affect breast cancer development through the balance of leptin and adiponectine. Inflammation of visceral fat tissues in obese women can also activate inflammatory cytokines and induce the expression of pro-inflammation mediators such as tumor necrosis factor alpha (TNF-α), interleukin 1b (IL-1b) and cyclooxygenase 2 (COX2). All these changes could induce aromatase enzyme in estrogen synthesis. The synthesized estrogen will then contribute to high breast density which is a risk factor of breast cancer.[16]

Our results show no association between fatty liver and breast tissue density or ER status. Breast tissue density was strongly associated with breast cancer, either ER-positive or ER-negative.[17] However, our study included only patients with breast cancer who were supposed to have denser breast tissue.

The very high percentage of fatty liver among our patients and its association only with BMI suggests that obesity and metabolic syndrome could be an emerging risk. Study trying to prove fatty liver as a risk factor for breast cancer development is underway. Giving that 70% of our study subjects were overweight or obese, we could say that we are seeing younger and more premenopausal patients. This should raise our awareness since obesity is not a risk factor for breast cancer in premenopausal women.[18]

In post-menopausal women, the adipose tissues are the primary source of estrogen. The excess of fat strongly correlates with breast cancer which is shown by the increasing risk with increasing BMI.[19] On the other hand, circulating estrogen in pre-menopausal women is not always related to breast cancer risk.[20] Estrogen mainly comes from the ovaries and will be altered by any change of ovarian function. Evidence linking obesity and breast cancer in young women are lacking. Excess adiposity or obesity tend to cause irregular menses and reduced fertility suggesting some degree of ovarian insufficiency.[21] Therefore, this ovarian dysfunction in young, obese women will appear like a "protective" effect towards breast cancer development among premenopausal women.

This study has some limitations. First, it is designed as a cross-sectional study among breast cancer patients only. To establish fatty liver as a risk factor for breast cancer risk, the ideal design is a prospective cohort study. However, it is more expensive and takes very long time to have cases with breast cancer. Alternatively, a case-control study could be sufficiently done to confirm findings from this study. Secondly, fatty liver diagnosis was based on US imaging, not proven by liver biopsy. Although US has high accuracy, fatty liver can be seen on US when there is a significant fat content in the liver, which is estimated to be around 33%.[22] Thus, the true prevalence of fatty liver among breast cancer patients could be more than reported. However, liver biopsy is an invasive procedure and will not be recommended for routine use in cancer patients.

CONCLUSION

Fatty liver is a common finding among breast cancer patients with 94% prevalence in our study. Severe fatty liver has significant association with body mass index or obesity, but not with age or menopausal status, suggesting that metabolic syndrome could play important role in breast cancer development, especially among young, premenopausal women. There is no association between severe fatty liver and breast tissue density or estrogen receptor status.

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