Research Article

Non-Alcoholic Fatty Liver as a Risk Factor for Breast Cancer among Indonesian Pre-Menopausal Women: A Case-Control Study

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Abstract

Non-alcoholic fatty liver was commonly found in breast cancer patients. However, the role of fatty liver as risk factor for breast cancer development has not been established in Indonesian population. We designed a case-control study to evaluate the effect of obesity and/or fatty liver on breast cancer occurrence in Indonesian women. Subjects were breast cancer patients between July and December 2018 in Dharmais National Cancer Centre Hospital. Control group was female hospital staff. Characteristics of subjects included age, body mass index, and presence of fatty liver by abdominal ultrasound. Independent risk factor was identified using logistic regression analysis and expressed as adjusted OR with its 95% confidence interval (CI). A total of 218 patients and 218 controls were enrolled. Both of subject and control group had equal mean of age. Among breast cancer patients, tumor was predominated by estrogen-receptor positive (69.7%) and luminal A subtype (57.8%). Mean of body mass index was significantly higher in subject group compared to control (26.8 kg/m^2 vs 25.7 kg/m^2; p=0.007). Fatty liver (49.5% vs 35.8%; p=0.004) was significantly more common in subject groups than controls. In multivariate analysis, fatty liver was confirmed as risk factor for breast cancer in subjects (OR$_{adj}$: 1.56; 95%CI: 1.04–2.33; p=0.032). Obesity and fatty liver are common in breast cancer patients. Fatty liver is an independent risk factor for sporadic breast cancer. These findings warrant further studies to evaluate the mechanism of breast cancer in younger women that associated with non-alcoholic fatty liver pathogenesis.
Keywords: breast cancer, non-alcoholic fatty liver, obesity, risk factor.

Perlemakan Hati Non-Alkoholik sebagai Faktor Risiko Kanker Payudara pada Perempuan Pre-Menopause Indonesia: Studi Kasus-Kontrol

Abstrak

Perlemakan hati non-alkoholik sering ditemukan pada pasien kanker payudara namun studi terkait peran perlemakan hati sebagai faktor risiko kanker payudara, hingga saat ini belum ada di Indonesia. Studi kasus-kontrol ini dilakukan untuk mengevaluasi efek obesitas dan atau perlemakan hati terhadap kejadian kanker payudara pada perempuan Indonesian. Subjek adalah pasien kanker payudara antara bulan Juli hingga Desember 2018 di RS Pusat Kanker Nasional Dharmais. Kelompok kontrol adalah staf perempuan rumah sakit. Karakteristik subjek yang diteliti adalah usia, indeks massa tubuh, perlemakan hati yang didiagnosis dari pemeriksaan ultrasonografi abdomen. Faktor risiko independen dinilai menggunakan analisis regresi logistik dan ditampilkan sebagai adjusted OR dengan interval kepercayaan 95%. Sebanyak 218 pasien dan 218 kontrol diikutsertakan dalam studi. Kedua kelompok memiliki nilai mean usia yang sama. Pada kelompok pasien kanker payudara, jenis kanker didominasi oleh tipe estrogen-receptor positive (69,7%) dan subtype luminal A (57,8%). Mean dari indeks massa tubuh lebih tinggi bermakna dibandingkan kelompok kontrol (26,8 kg/m^2 vs 25,7 kg/m^2; p=0,007). Perlemakan hati (49,5% vs 35,8%; p=0,004) secara bermakna lebih sering ditemukan pada kelompok subjek dibandingkan kelompok kontrol. Pada analisis multivariat, perlemakan hati terbukti bermakna sebagai faktor risiko kanker payudara (OR$_{adj}$: 1,56; 95%CI: 1,04–2,33; p=0,032). Disimpulkan obesitas dan perlemakan hati sering ditemukan pada pasien kanker payudara. Perlemakan hati merupakan faktor risiko independen kasus kanker payudara yang sporadik. Temuan ini dapat menjadi landasan penelitian berikutnya untuk meneliti patogenesis perlemakan hati menyebabkan kanker payudara pada perempuan usia muda.
Kata kunci: kanker payudara, perlemakan hati non-alkoholik, obesitas, faktor risiko.

Introduction

Breast cancer is the most prevalent malignancy in women worldwide.[1] In Indonesia, breast cancer ranked the second after uterine cervical cancer with a prevalence of 0.5‰ based on 2013 national data.[2] The early release of 2018 national report indicated an increased of cancer prevalence and increased obesity in adults from 14.8% in 2013 to 21.8% in 2018.[3] These data showed that cancer and obesity is now a major health problem in Indonesia.

Risk factors for breast cancer vary from genetics, diet, hormone, and metabolic factors (obesity). A recent meta-analysis among women in Southeast Asian countries shows that several modifiable risk factors were associated with breast cancer, i.e. nulliparous woman, overweight, and oral contraceptives use.[4] Obesity, as reflected by a high body mass index (BMI), has been associated with increased risk of many cancers, including breast.[5]

Non-alcoholic fatty liver disease (NAFLD) is a growing public health problem in Asia-Pacific region.[6] The new definition of NAFLD by the Asia-Pacific Working Party pointed out that this form of fatty liver disease is attributable to over-nutrition and its complication, including central obesity.[7] A recent hospital-based study in Jakarta showed that 51% of healthy adults underwent medical check-up had fatty liver, which was highly associated with metabolic syndrome.[8] Fatty liver is significantly associated with obesity and is regarded as a hepatic manifestation of metabolic syndrome.[9] Furthermore, a high prevalence of fatty liver (63%) has been reported among new breast cancer patients.[10]

Our previous study in Jakarta found that among 72 patients with breast cancer, 68 (94.4%) patients showed positive fatty liver by abdominal ultrasound.[11] However, this study was cross-sectional and could not confirm fatty liver as a risk factor for breast cancer. Therefore, we designed a case-control study to evaluate the effect of obesity and or fatty liver on breast cancer occurrence in Indonesian women.

Methods
Study Subject and Design

This was a case control study done on July to December 2018 in Dharmais National Cancer Centre Hospital. This study was approved by Dharmais Hospital Ethical Committee number 066/KEPK/V/2018. Subjects were breast cancer patients as cases, while female hospital staff without breast cancer served as controls. Patients with history of chronic liver disease and evidence of liver metastasis were excluded from analysis. Clinical data of breast cancer patients were obtained from their medical records, which included age at diagnosis, body mass index (BMI), disease stage, and tumor biology profile. 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 was grouped into normal or less (BMI $\leq$23 kg/m^2), overweight (BMI >23 and <25 kg/m^2), and obese (BMI$\geq$25 kg/m^2).[12]

Fatty Liver Assessment

Fatty liver assessment was done in both subject and control group using high-end ultrasound equipment. Transabdominal ultrasound is an imaging modality of choice to detect fatty liver since it is not expensive, non-invasive, and is readily available in many medical facilities. It has high accuracy and reliability for fatty liver diagnosis.[13] Diagnostic criteria for fatty liver include 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.[14,15]

Diagnosis of NAFLD was established if fatty liver on abdominal ultrasound was supported by lack of alcohol consumption (<20 g/day), negative hepatitis B or C, no evidence of autoimmune hepatitis and other known liver disease.

Statistical Analysis

Clinical characteristics of breast cancer patients and healthy control were presented descriptively. The association between clinical risk factors and breast cancer was tested using chi-square test; a p value of <0.05 was considered significant. Risk was indicated by the odd ratio (OR) and its corresponding 95% confidence interval (CI). Multivariate analysis was done to confirm independent risk factor for breast cancer.

Results
Characteristics of Subjects

A total of 218 breast cancer patients and 218 controls were enrolled in this study. Cases and controls were comparable by age (Table 1). Most of subjects in breast cancer group (52.3%) were $\leq$50 years. Tumor was predominated by estrogen-receptor (ER) positive (69.7%) and luminal A subtype (57.8%).

Table 1. Characteristics of the Study Subjects

Characteristics	Cases (n = 218)	Controls (n = 218)	p
Age (years), mean (SD)	50 (10)	50 (10)	0.791^1
≤50 years	114 (52.3)	118 (54.1)	0.701^2
>50 years	104 (47.7)	100 (45.9)	
BMI (kg/m2), mean (SD)	26.8 (4.38)	25.7 (4.21)	0.007^1
Underweight/normal	42 (19.3)	60 (27.5)	0.125^2
Overweight	39 (17.9)	36 (16.5)	
Obese	137 (62.8)	122 (56.0)	
Fatty liver	108 (49.5)	78 (35.8)	0.004^2

^{1}Student t-test; ^{2}chi square test

Obesity and Fatty Liver Assessment

Obesity and fatty liver were more commonly found in cancer groups than healthy controls (Table 1). Mean of BMI was significantly higher in breast cancer group than control group (26.8 kg/m^2 vs 25.7 kg/m^2; p=0.007). Univariate logistic regression showed that BMI and fatty liver were risk factors for breast cancer. However, after multivariate logistic regression was performed, it was showed that fatty liver is associated with breast cancer and this association is independent of BMI. On the other hand, in the multivariate analysis, BMI is not significantly associated with breast cancer risk (Table 2).

Table 2. The Association of Breast Cancer with BMI and Fatty Liver as Risk Factors

Risk Factors	Univariate		Multivariate	
	Crude OR (95% CI)	p	Adj OR (95% OR)	p
BMI (kg/m^2)	1.06 (1.01 - 1.11)	0.007	1.04 (1.00-1.09)	0.06
Fatty liver	1.76 (1.20 - 2.59)	0.004	1.56 (1.04-2.33)	0.032

Interaction effect and collinearity between BMI and fatty liver has been tested. It is showed that there were no significant interaction effect and collinearity between BMI and fatty liver.

Discussion

In this study we found that breast cancer was more common in younger age group (≤50 years old). Data from American Cancer Society 2017 shows, that most breast cancer cases were found in woman after 50 years old.[16] This data is different from our findings since breast cancer patient in this study tend to be younger. Different molecular features and gene expression may play role in young age breast cancer. Further study is needed to evaluate molecular and genetic factor in young age breast cancer in Indonesia.

We also found that obesity (based on BMI) and fatty liver were different variables for breast cancer development. The results showed that obesity was more common in breast cancer cases than the controls. The logistic regression analysis confirmed fatty liver as the independent risk factor for breast cancer patients.

There are many established risk factors for breast cancer in Indonesia, but the role of fatty liver is still not clearly known. Previous study showed that 94% of breast cancer patients had fatty liver and severe fatty liver was significantly associated with obesity, but not with age or menopausal status, suggesting the role of metabolic syndrome in the young, premenopausal patients.[11] It seems that BMI and fatty liver serve a different role as risk factor of breast cancer in younger women.

The association of obesity (by anthropometric measurement) and breast cancer in pre-menopausal women is inconsistent. Obesity is

generally not perceived as a risk factor for breast cancer in premenopausal women.[17] A study in Taiwan found an incremental increased risk of breast cancer in patients with BMI higher than 27 kg/m^2, 30 kg/m^2 and 35 kg/m^2 only in post-menopausal women[18], suggesting the increased role of adipose tissue-derived estrogen due to the excess of fat in obese women.[19] On the other hand, estrogen in pre-menopausal women is produced mainly by the ovaries and may not related to breast cancer risk.[20] Pre-menopausal Asian women are known to have higher risk of breast cancer with increased BMI whereas the Caucasian or African women showed inverse relationship of increased BMI and pre-menopausal breast cancer.[21,22] A recent meta-analysis concluded that central obesity, by waist circumference measurement, is associated with increased risk of pre- and postmenopausal breast cancer, independent of general obesity.[23]

Breast cancer is usually a disease of aging women with a prevalence of less than 7% of all breast cancer patients in developed countries[24] and up to 20% in less developed countries.[25] Our study showed that breast cancer patients aged 50 years or less were predominating. Young breast cancer has been associated with more aggressive behavior such as higher grade, more proportion of triple negative and HER2-positive tumors and more advanced stage at diagnosis.[26] The role of growth factors, rather than hormones, might be more important in young-onset breast cancer.[27] In this study, there were 8 patients with HER2-positive tumors; all of them also had fatty liver (data not shown). However, the exact mechanism of pre-menopausal, non-familial breast cancer is still unclear. This current result may challenge the proposed opinion that young onset breast cancer in Asia is a transient phenomenon that will be decrease over time since it is more likely associated with genetic rather than environmental factors.[17]

Our study showed that fatty liver has a stronger role as risk factor of breast cancer than the anthropometric BMI. It seems that although fatty liver is associated with increased BMI, the risk of getting breast cancer in might not related to general obesity. The logical explanation for this finding would be other factor(s) in the pathogenesis of fatty liver that also responsible for breast cancer development. Nutritional pattern among adolescence could be the next focus of research. Few studies tried to link increased carbohydrates intake (mainly sucrose or simple sugars) and higher breast density.[28,29] However, the association between carbohydrate intake and breast cancer is complex. A dose-response meta-analysis conclude that the potential influencing factors were menopausal and hormone receptor status, but not BMI.[30] On the other hand, carbohydrate intake is also strongly associated with fatty liver development. Carbohydrate serves as substrates for *de novo lipogenesis* and may contribute to liver fat accumulation when excessively consumed.[31] National data showed that 53.1% of Indonesian population aged $\geq$ 10 years consumed sugar above the World Health Organization limit of recommendation, i.e. 50 gram per day.[2] Therefore, excessive carbohydrate intake may potentially share contribution in the pathogenesis of both fatty liver and cancer.

Limitation of this study was the case-control design. Although we found the significant association between fatty liver and breast cancer, the exact pathogenesis is still unexplainable. Therefore, further studies are needed to know the exact mechanism of both fatty liver and obesity as a risk factor of breast cancer.

Conclusion

Obesity and fatty liver are commonly found in breast cancer patients. Fatty liver is an independent risk factor for sporadic breast cancer in Indonesia. These findings warrant further studies to evaluate the mechanism of breast cancer in women that associated with non-alcoholic fatty liver pathogenesis.

Acknowledgements

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