The New Ropanasuri Journal of Surgery

Volume 4 | Number 2 Article 3

12-31-2019

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New Ropanasuri Journal of Surgery 2019 Volume 4 No.2:9-14.

The New Ropanasuri Journal of Surgery

OPEN ACCESS

Published by Department of Surgery
Faculty of Medicine, Universitas Indonesia

Association Between Obesity and Hormone Receptor Characteristics Of Primary Breast Cancer At dr. Cipto Mangunkusumo General Hospital, Jakarta, In 2017

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Email: hardian312@gmail.com Received: 17/Dec/2019 Accepted: 20/Dec/2019 Published: 31/Dec/2019
Website: https://scholarhub.ui.ac.id/nrjs/ DOI:10.7454/nrjs.v4i2.1060

Abstract

Introduction. Obesity is an independent risk factor and prognostic factor of primary breast cancer. Abundant adipose tissue would lead to increment of blood estrogen level; thus, promoting proliferation of cancer cell, especially those with positive estrogen receptor (ER) and progesterone receptor (PR). No study reported the association between obesity and hormone receptor characteristics of primary breast cancer in Indonesia.

Method. We collected cases of primary breast cancer which is diagnosed and undergone immunohistochemistry examination at Cipto Mangunkusumo General Hospital in 2017. The subjects divided into obese group and non-obese group. The ER and PR characteristics of both groups were compared

Results. We collected 202 cases of primary breast cancer, with 89 cases (44%) in obese group and 113 cases (56%) in non-obese group. The mean body mass index (BMI) of the subjects was 24.45±4.3. Both groups were similar in terms of age, menopausal status, stage, histopathological morphology and grade. No significant association was found between obesity and ER or PR. We analyzed correlation between BMI and the percentage of expressed hormone receptor, but no correlation was found. This finding did not conform with other Western studies. Difference in characteristics of the subjects and other hormonal factors might contribute to the outcome.

Conclusion. There is no association between obesity and hormone receptor characteristics of primary breast cancer at Cipto Mangunkusumo General Hospital in 2017.

Keywords: obesity, hormone receptor, estrogen, progesterone, primary breast cancer

Introduction

Breast cancer is the most common cancer in females in the world. It has the highest rate of mortality due to cancer in Indonesia, accounted for 22% of all cancer mortality.[1] The estimated prevalence of breast cancer in Indonesia was 36,2 in every 100.000 persons, with mortality around 18.6 cases in every 100.000.2 Compared to developed countries, the mortality rate in Indonesia was higher due to more advanced stage at the time of diagnosis.[2,3]

Breast cancer and obesity are two related conditions. Obesity referred to an independent risk factor for breast cancer.[4] Gaining 5 kg/m^2 of body mass index (BMI) increases the risk by 2%.[5] Evidence showed that 50% of patients with breast cancer were overweight or obese at the diagnosis insitututed.[6] Majority of patients have a weight gain during and after completion of therapy. Changes in the body metabolism, physical activity, dietary habits, and changes in menstrual status contribute to weight gain in breast cancer.[7] Thus, the increment of weight after diagnosis become a predictor for higher mortality and worsen the prognosis.[8] Studies showed that there was significant weight gains in younger age, postmenopausal breast cancer, positive hormone receptor breast cancer, advance stage, pre-diagnostic underweight, and smokers.[8] Obesity has also become an independent prognostic factor for mortality and metastatic disease in breast cancer.[9] Obese patients have correlation to a higher stage when the diagnosis instituted, with larger tumor size, higher lymph node ratio, more and aggressive tumors.[10,11] Obese females also related with higher rates of recurrent disease, second primary cancer, more inferior quality of life, higher risk of lymphedema and other comorbidities in breast cancer, e.g., diabetes, hypertension, and another cardiovascular disease.[6]

The difference in cancer subtype became a contributing factor to prognosis in the obese patient. Obesity is associated with a higher risk of positive hormone receptor (estrogen or progesterone receptor) breast cancer.[11-14] An increase in circulating estrogen levels and its bioavailability might play a role. Increase adiposity reflecting obesity leads to an increase in aromatase in adipose tissue. Thus, increasing circulating estrogen levels.[15] Sex hormone-binding globulin (SHBG), a glycoprotein produced by the liver that restricts estrogen biological activity, will decrease in obese; thus reduction on its level would lead to a higher risk of positive hormone receptor breast cancer.[15-18] Obesity would also increase insulin-like growth factor (IGF-1): a local factor promoting breast cell proliferation and differentiation, enhancing tumor growth.[19] Increase in leptin and adiponectin in an obese patient would also initiate proinflammatory cascade, leading to tumor progression.[20,21]

To date, there is no single study that reported the association between obesity and hormone receptor characteristics of breast cancer in Indonesia. Most of the evidence is based on Western

reviews, while ethnicity might play a role in subtypes of breast cancer.[22] Thus we conducted a study aimed to find out the association between obesity and hormone receptor characteristics of primary breast cancer in our center, which is Indonesian specific characteristics.

Method

This was a cross-sectional analytic study that compared the We conducted a cross-sectional study using secondary data from the medical reports. Data on those diagnosed with primary breast cancer and managed at dr. Cipto Mangunkusumo General Hospital during 2017. Those included in the study were: adult females, diagnosis of breast cancer confirmed with the histopathological examination, and immunohistochemistry for hormone receptor status. Breast metastasis with another origin, and recurrent diseases excluded. Age, body weight, height, menstrual status, tumor stage, histopathological morphology, the grading of tumor, ER status, and PR status and BMI calculated with body weight (kg) / height $(m)^2$ were variables of the study. The subjects classified into two categories based on the Asian classification of obesity: obese group if the BMI >25 and non-obese group if the BMI ≤25.[23] The characteristics of both groups were compared. The association between obesity and hormone receptor characteristic of primary breast cancer subjected to analysis. The proportion of positive hormone receptors of each group and the correlation between BMI and hormone receptor expression analyzed.

The study approved by independent reviewer board of Faculty of Medicine, Universitas Indonesia. 341/UN2.F1/ETIK/2018.

Results

Those were 202 subjects diagnosed with breast cancer during 2017 and met the criteria. The mean BMI of the subjects was 24.45 ± 4.3. The characteristics of the subjects presented in table 1. Obese group comprise of 89 subjects (44%), and non-obese group of 113 subjects (56%).

Table 1. Comparison between hormone receptor characteristic in obese group and non-obese

	Overall	Obese group	Non-Obese group	P value
Age	49.94 (SD ± 10.92)	51.12 (SD ± 11.26)	49 (SD ± 10.61)	p = 0.171
Menopausal Status				
– Pre-menopause	129 (63.9%)	55 (61.8%)	74 (65.5%)	p = 0.588
– Post-menopause	73 (36.1%)	34 (38.2%)	39 (34.5%)	
Stage (TNM)				
T				
– Tis	4 (2%)	2 (2.2%)	2 (1.8%)	
– T0	1 (0.5%)	0 (0)	1 (0.9%)	
– T1	4 (2.0%)	0 (0)	4 (3.5%)	
– T2	64 (31.7%)	30 (33.7%)	34 (30.1%)	
– T3	67 (33.2%)	30 (33.7%)	37 (32.7%)	
– T4	62 (30.7%)	27 (30.3%)	35 (31%)	
N				
– N0	81 (40.1%)	33 (37.1%)	48 (42.5%)	
– N1	78 (38.6%)	39 (43.8%)	39 (34.5%)	
– N2	32 (15.8%)	13 (14.6%)	19 (16.8%)	
– N3	11 (5.4%)	4 (4.5%)	7 (6.2%)	
M				
– M0	166 (82.2%)	73 (82%)	93 (82.3%)	
– M1	36 (17.8%)	16 (18%)	20 (17.7%)	
Category				
– Early breast cancer	41 (20.3%)	17 (19.1%)	24 (21.2%)	p = 0.903
– Locally advanced breast cancer	126 (62.4%)	57 (64%)	69 (61.1%)	
– Metastatic breast cancer	35 (17.3%)	15 (16.9%)	20 (17.7%)	
Histopathological morphology				
– Ductal invasive	162 (80.2%)	71 (79.8%)	91 (80.5%)	
– Lobular invasive	19 (9.4%)	9 (10.1%)	10 (8.8%)	
– DCIS	4 (2%)	2 (2.1%)	2 (1.8%)	
– Others	17 (8.4%)	7 (8%)	10 (8.9%)	
Grade				
– I	41 (20.3%)	21 (23.6%)	20 (17.7%)	p = 0.142
– II	104 (51.5%)	49 (55.1%)	55 (48.7%)	
– III	57 (28.2%)	19 (21.3%)	38 (33.6%)	

The age, menopausal status, cancer stage, histopathological morphology, and grade of the tumor were similar between the two groups. The association between obesity and hormone receptor (ER and PR) characteristic analyzed with the Chi-Square test, presented in Tables 2 and 3, we found no significant association this study. Further analysis proceeded to find out the correlation between BMI and expression of the hormone receptor. Pearson correlation test showed no significant correlation between BMI and neither estrogen receptor expression (p = 0.588) nor progesterone receptor expression (p = 0.236).

Table 2 Association between obesity and ER characteristic of primary breast cancer

	ER (+)	ER (-)	
Obese group	56 (62.9%)	33 (37.1%)	89
Non-obese group	72 (63.7%)	41 (36.3%)	113
	128	74	p = 0.907*)

*) Chi–Square

Table 3 Association between obesity and PR characteristic of primary breast cancer

	PR (+)	PR (-)	
Obese group	49 (55.1%)	49 (44.9%)	89
Non-obese group	59 (52.2%)	54 (47.8%)	113
	108	94	p = 0.776*)

*) Chi–Square

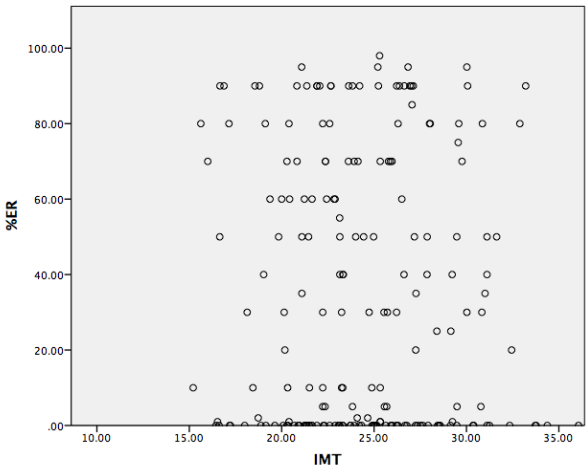

Figure 1. Correlation between BMI and ER expression (%ER) in primary breast cancer

Table 4 Statistical analysis between obesity and ER characteristic in pre-menopause primary breast cancer

	ER (+)	ER (-)	
Obese group	34 (61.8%)	21 (38.2%)	55
Non-obese group	45 (60.8%)	29 (39.2%)	74
	79	50	p = 0.908*)

*) Chi Square

Table 5Statistical analysis between obesity and PR characteristic in pre-menopause primary breast cancer

	PR (+)	PR (-)	
Obese group	31 (56.4%)	24 (43.6%)	55
Non-obese group	36 (48.6%)	38 (51.4%)	74
	67	62	p = 0.386*)

*) Chi Square

Table 6. Statistical analysis between obesity and ER characteristic in post-menopause primary breast cancer

	ER (+)	ER (-)	
Obese group	22 (64.7%)	12 (35.3%)	34
Non-obese group	27 (69.2%)	12 (30.8%)	39
	49	24	p = 0.681*)

*) Chi Square

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Table 7 Statistical analysis between obesity and ER characteristic in pre-menopause primary breast cancer

	PR (+)	PR (-)	
Obese group	18 (52.9%)	16 (47.1%)	34
Non-obese group	23 (59%)	16 (41%)	39
	41	32	p = 0.604*)

*) Chi Square

Subgroup analysis performed to evaluate the association between the obese group and the non-obese group based on menopausal status — no significant association displayed in premenopausal subjects nor postmenopausal subjects

Discussion

The increasing prevalence of obesity become a significant problem in developed and developing countries, and it is related to the increasing incidence of breast cancer.[24] A thorough understanding of the relationship between obesity and breast cancer become essential to determine comprehensive management and its prognosis, especially in the obese population.10 The relationship between breast cancer and obesity was explained initially by Abe et al. in 1976, showed that a 20% increment of ideal body weight would lead to bigger tumor size, higher lymphatic invasion, and more reduced survival in females with breast cancer.[25] Obesity is known as an independent risk factor for breast cancer, especially in the postmenopausal period. Obesity would increase the risk of breast cancer by 12-15% post-menopause, while obesity and the risk for breast cancer in pre-menopause females is still controversial.[4,26]

Studies showed a strong correlation between obesity and breast cancer with positive hormone receptor (ER+/PR+), but not in other subtypes.[4] Our study shows the different results: there is no significant association between obesity and hormone receptor characteristics in primary breast cancer. The difference in population characteristics and other factors influencing hormone receptor expression in primary breast cancer could affect this outcome.

Our population characteristic is different from the population characteristic in Western studies. During the period from 2011 until 2014, the prevalence of obesity in premenopausal females aged 20 to 59 was 35% in the United States (US).[27] The number is much lower in the Asia region. In Singapore, the study showed that 35% of female aged 18-19 was overweight, and 14% classified as obese.[28] Data from Selangor, Malaysia, showed that the prevalence of obesity in Malaysian females aged 20-59 was 16,7%.[29] In Indonesia, the prevalence of overweight in adult females aged 20-75 was 26,4%, and the prevalence of obesity was 13.22% in 2007.[30] Difference in socioeconomic status, culture, and ethnicity could underlie this difference in the prevalence of obesity.[28]

There are also differences in age and stage of breast cancer during the time of diagnosis in our study and Western studies. The mean age of diagnosis in our study was 49.94 years (SD±10.92), while in the US, only 20% of breast cancer diagnosed under the age of 50.[27]. In 2010 until 2014, the median age of breast cancer diagnosis in the US was 62 years.[31] The stage of initial diagnosis also differs. Our study reveals that most cases diagnosed in locally advanced stage (62,4%), followed by an early stage (20,3%) and metastatic stage (17.3%). In the US, 63% of the cases diagnosed in early stage, 28% in the locally advanced stage, and 6% in metastatic stage.[32]

Estrogen and progesterone are the essential hormones in the etiology of breast cancer due to their proliferative effect.[33] The proliferative effect of these hormones mediated with each receptor and the receptor expression of each hormone in breast tissue reflect their responses to specific hormones. The estrogen

receptor is a nuclear receptor acting as a ligand-dependent transcription factor that regulates the gene that plays a role in proliferation, invasion, angiogenesis, and survival of breast cancer cells. This receptor will, directly and indirectly, increase tyrosine kinase of many growth factor receptors (e.g., HER1, HER2, and insulin-like growth factor-1 receptor) and signaling molecule such as membrane protein, signaling adaptor molecule, and cellular kinase.[34]

Progesterone receptor expression considered as a part of pathway mediated by estrogen; thus, PR expression considered to picture ER expression.[35,36] Around 96% cell expressing one of the receptor hormone (either ER or PR) will express the other.[36] PR expression does not reflect the response to hormonal therapy, but if combined with ER, they will give more prognostic value.[37]

Breast cancer with positive hormone receptors has different behavior. It shows the stronger clinical response to hormonal therapy, better differentiation in morphologic appearance, increasing incidence with age, and slowing down with menopause.[12] Risk factors for different subtypes of breast cancer were studied, but the result showed some controversies.

The study of Oh (2017) showed in healthy breast tissue, advance age-related to higher ER expression, although it showed no relation with PR expression. Body height and BMI influenced PR expression but did not affect ER expression. The duration of breastfeeding affected ER expression, but other reproductive factors such as age of menarche, parity, age of first childbirth, number of childbirth, menopausal status, and age of menopause did not affect ER or PR expression in healthy breast tissue.[38] Alcohol consumption related to ER expression, but family history of breast cancer did not associate with hormone receptor expression.[38]

Factors affecting ER and PR expression in breast cancer tissue seem to differ. Althuis stated that factors related to breast cancer with positive hormone receptors are factors related to hormonal exposure, such as nulliparity, delayed in childbearing, age of menarche, and the use of exogenous hormonal therapy. Our study did not include these factors.

Menopausal status is an essential factor in the association of obesity and breast cancer. Adipose tissue would produce aromatase, an enzyme responsible for estrogen biosynthesis, which has more role in post-menopause.[39] Subgroup analysis performed to evaluate the association between obesity and receptor hormone characteristics in pre-menopause and post-menopause period, but no significant association found.

The study by Women's Health Initiative in 2015 showed that in postmenopausal females aged 50 to 79, obesity (especially with BMI more than 35 kg/m^2) had a higher risk of developing breast cancer.[39] Other studies showed a similar result.[4,6,40] This finding seems to be found only in positive hormone receptor breast cancer. In contrast, negative hormone receptor and triple-negative disease did not have any correlation with BMI.[38,39] Postmenopausal obesity-related to less aggressive tumor subtype, i.e. Positive ER and PR, negative HER2, low Ki67, positive Bcl-2, and negative p53, especially in patients did not receive hormonal therapy.[40]

In pre-menopause females, the relation between obesity and breast cancer is still controversial. Van de Brandt et al. stated that premenopausal obesity would lower the risk of breast cancer.[4] Kawai et al. showed that increasing BMI after age 18 would increase the risk of triple-negative breast cancer while decreasing the risk of positive hormone receptor breast cancer.[42] One of the hypotheses supporting this theory was the high level of estrogen synthesis from ovaries, and peripheral tissue would elicit a negative feedback mechanism in hypothalamus-pituitary axis, suppressing ovarian activity and decrease progesterone level as a promoter of breast proliferation.[38]

Ethnicity may play a role in hormone receptor expression in primary breast cancer. Munsul (2013) added racial factor as a contributing factor since the risk of breast cancer increase in obese Caucasian and Negroid females, but not in Hispanics.[13] A further question arises about the role of race in the association between obesity and positive hormone receptor breast cancer. There is no study about this in Asia yet. Thus, the role of the race could not be concluded.

This study has a limitation. The timing of measurement of BMI was not equal, whether the BMI was measured at the time of diagnosis, or while receiving and even completing any treatment. Changes in body weight during treatment are not taking into account. This study used secondary data from the medical report, so information bias and selection bias should be taken into account. No other factors related to increased estrogen exposure such as parity, delayed in childbearing, age of menarche and exogenous hormonal use analyzed in this study. Incomplete medical record data became our major limitation.

Conclusion

In this study, there is no significant association between obesity and hormone receptor characteristic of primary breast cancer in dr. Cipto Mangunkusumo General Hospital in 2017 in both premenopausal and postmenopausal periods.

Disclosure

The author(s) declare have no conflict of interest to disclose

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