

High BMI Leads to Increased Breast Cancer Risk in Postmenopausal Women

Tiffany Tantoso¹, Mega Sari Sitorus^{2}, Lita Feriyawati³, Dian Dwi Wahyuni⁴*

¹ Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

^{2,3} Department of Anatomy, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

⁴ Department of Microbiology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

Abstract. Obesity is a worldwide problem that has been steadily increasing even in developing countries. Obesity has been linked to various types of cancer, one of which is breast cancer. Breast cancer has been classified into various types based on gene and hormone receptor expressions, which offered new insights to therapies and prognoses. We conducted a case control study using 42 breast cancer patients and 43 healthy women, all of which are older than 55 years of age and have experienced menopause, and for case subjects, additional immunohistochemistry profiles have been provided. Data were collected by interviews and medical records. For data analysis, we used Pearson's Chi-Square test and Fisher's Exact test. Results showed that high BMI is significantly associated with breast cancer, and risk is elevated ($p < 0.05$, OR = 1.263, 95% CI = 1.007-1.583). No significant association with molecular subtypes was observed.

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1 Introduction

Obesity is a global phenomenon that has been steadily on the rise in recent years. Number of adult women with obesity increased from 69 million in 1975 to 390 million in 2016. An additional 213 million children and adolescents and 1.30 billion adults were in the overweight range.[1] In Indonesia, the proportion of obese adults increased from 14.8 to 21.8 in just about 5 years.[2] This alarming rate of increase is thought to be due to the rapid urbanization and increase in the sedentary lifestyle.[3]

Obesity has been linked to various cardiovascular and metabolic diseases, and has been associated as a risk for various cancers, such as colon and liver cancer (for men), and ovarian (for premenopausal women) and breast cancer (for postmenopausal women).[4] Engaging in moderate or strenuous physical activity, maintaining normal body weight, limiting intake of red meat and

*Corresponding author at: Department of Anatomy, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

E-mail address: ms_sitorus@yahoo.com

alcohol, and increasing plant-based consumption has been shown to reduce postmenopausal breast cancer risk.[5]

Breast cancer is a complex and heterogenous disease which are categorized into different subtypes. Vallejos *et al.*⁶ divided the subtypes into 4 categories: Luminal A, Luminal B, HER2 – overexpression, and basal type, which are based on hormone receptor status. These molecular subtypes have differentiating characteristics of their own and affects treatment plans and prognoses in recent years.[7]

2 Methodology

For this case control study, we used purposeful sampling to collect data. All subjects must meet the following criteria: female, has experienced menopause, older than 55 years old, and willing to participate in the study. Additional criteria for case subjects include having histopathological diagnosis of breast cancer and having immunohistochemistry profiles of Estrogen Receptor (ER), Progesterone Receptor (PR), and Human Epidermal Growth Factor Receptor (HER2/neu) on their medical records. Subject was excluded if subject has/had a malignancy originating from locations other than the breast (breast cancer as a result of metastases). Data were collected through interview with subjects and medical records. We grouped subjects with BMI of 23 kg/m² or above into a single category (high) and the anything below that cut-off point into another (normal/low). The cut-off point is decided by WHO's Asia-Pacific BMI classification. Immunohistochemistry profiles are collected and stratified into Luminal A (ER/PR+, HER2-), Luminal B (ER/PR+, HER2+), HER2 overexpression (ER/PR-, HER2-), and Basal type (ER-, PR-, HER2-). Figure 1 shows the immunohistochemical staining of breast cells for ER, PR and HER2 expressions with

DAB (3,3'-Diaminobenzidine), which when reactive, displays a brown color in cell membrane and nucleus.

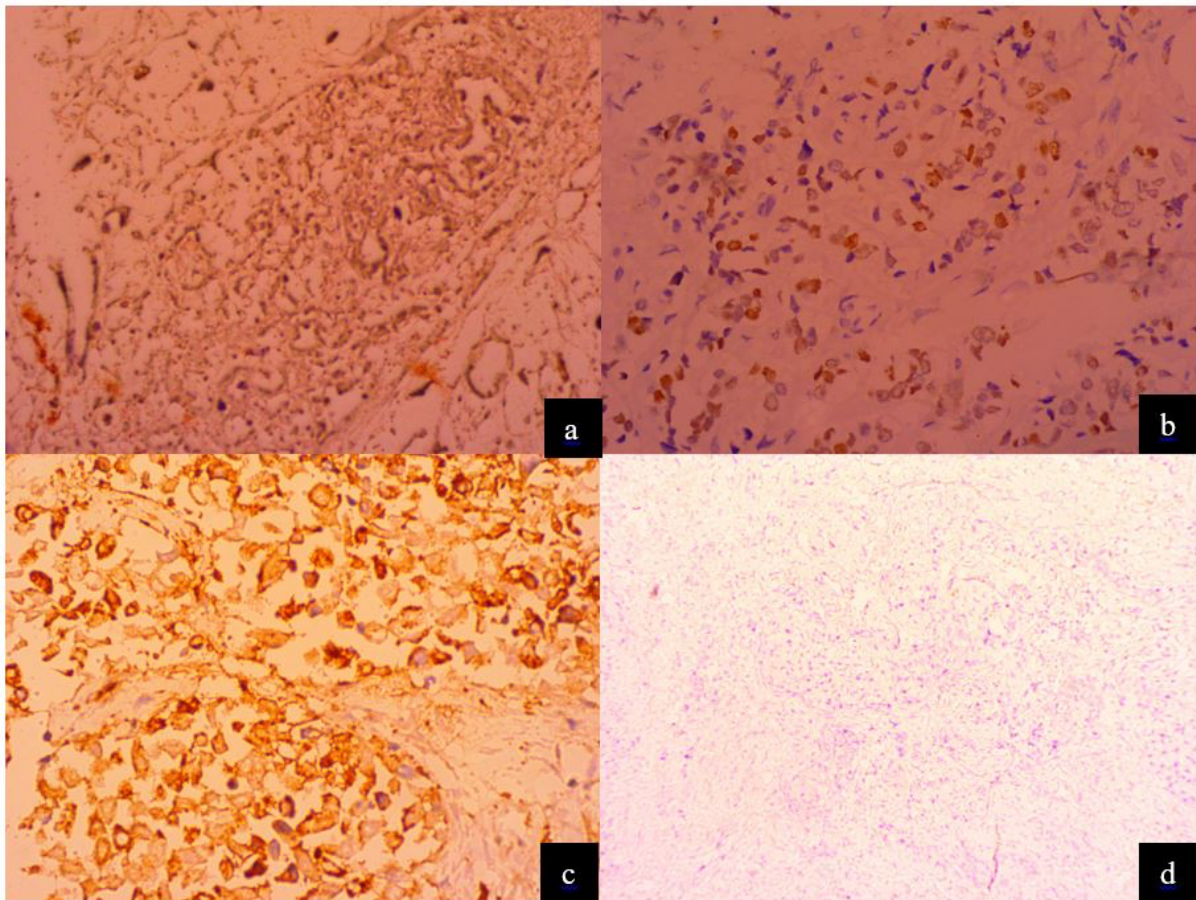


Figure 1 Immunohistochemistry, (a) ER positive (400x), (b) PR positive (400x), (c) HER2 positive (400x), and (d) HER2 negative (100x), stained with DAB (Original).

3 Results

3.1 Characteristics of cases and controls

Characteristics of subjects by age are presented in Table 1. Most subjects were 55 – 60 at age. Out of all subtypes, most patients suffer from luminal A cancer (71.4% at age range of 55 – 60, 19% at age range of 61 – 70, and 2.9% at age range of 71 – 80. Luminal B appears to be the rarest out of all subtypes (3 out of 42 subjects).

Table 1 Characteristics of cases and controls by age

Age range	Control (43/85)	Luminal A	Luminal B	HER2-overexpression	Basal Type
	n (%)	n (%)	n (%)	n (%)	n (%)
55 – 60	21 (48)	15 (71.4)	2 (66.7)	9 (69.2)	3 (60)
61 – 70	11 (25.6)	4 (19)	1 (33.3)	4 (30.8)	1 (20)
71 – 80	7 (16.3)	2 (9.5)	0 (0)	0 (0)	1 (20)
81 – 90	4 (9.3)	0 (0)	0 (0)	0 (0)	0

3.2 Associations between overweight, obesity and breast cancer risk

Table 2 presents the risk of breast cancer associated with BMI. Results show that postmenopausal women with high BMI are 3 times more likely to develop breast cancer than those that aren't (OR = 1.263, 95% CI = 1.007-1.583). Since the p-value is smaller than 0.05, we can safely assume that overweight and obesity are associated significantly with breast cancer

Table 2 Association between overweight, obesity and breast cancer risk in cases and controls

BMI	Control (43/85)	Case (42/85)		p-value
	n (%)	n (%)	OR (95% CI)	
High (≥ 23 kg/m ²)	30 (69.8)	37 (88.1)	1.263 (1.007-1.583)	0.039
Normal/low (<23 kg/m ²)	13 (30.2)	5 (11.9)	0.394 (0.154-1.008)	

OR = Odds ratio, CI = Confidence Interval

3.3 Associations between overweight, obesity and molecular subtypes

Table 3 shows the association between molecular subtypes of breast cancer and BMI. Analysis results show little association between the two ($p > 0.05$).

Table 3 Association between overweight, obesity and molecular subtypes

BMI	Case								p-value
	Luminal A		Luminal B		HER2-overexpression		Basal type		
	n	%	n	%	n	%	n	%	
High (≥ 23 kg/m ²)	18	85.7	3	100	11	84.6	5	100	1.000
Normal/low (<23 kg/m ²)	3	14.3	0	0	2	15.4	0	0	

4 Discussion

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Discussion

In this case control study, we found that high BMI is significantly associated with increased risk of developing breast cancer in postmenopausal women (OR = 1.263, 95% CI = 1.007-1.583, $P < 0.05$), while women with BMI below the cut-off point ($<23 \text{ kg/m}^2$) are at a decreased risk (OR = 0.394, CI = 0.154-1.008). This is in line with the results of a meta-analysis study in which elevated breast cancer risk was found in postmenopausal women with increased BMI.⁸ However, the results in the study weren't statistically significant. Another study conducted in Indonesia suggests that high BMI elevates the risk of breast cancer, but similarly, the results are not statistically significant.^[9]

We found no significant association between overweight and obesity with breast cancer molecular subtypes ($p > 0.05$). Associations between the two are still inconsistent to this day. A study showed increased risk of luminal cancer in postmenopausal women with overweight and obesity (OR = 1.48, 95% CI = 1.08 – 2.04, $P < 0.0001$),^[10] and increased risk of triple negative cancer in premenopausal women in another study.^[11] However, some studies have also shown that the correlation was statistically insignificant.^{[12],[13],[14]}

While the exact mechanisms are unknown, there are multiple theories regarding the association between obesity and breast cancer. One theory suggests the involvement of adipokines such as leptin and adiponectin, which are produced by adipocytes.^[18] Another theory suggests that increase in adipose tissue results in elevated circulating hormones such as estrogens, insulin and insulin-like growth factor (IGF) which act as mitogens.^[19]

Increase of proliferation activity by leptin is thought due to enhanced signaling pathways. One such pathway appears to be primarily mediated by the ER (estrogen receptor).^[19] This is supported by a study where a positive correlation between Ob-R (leptin receptor) and ER was found,^[20] and another study which discovered increased proliferation and invasion of breast cancer cells by leptin secreted from adipose stromal/stem cells from obese women.^[21]

Adiponectin has been documented to have anti-proliferation and anti-angiogenic properties. A study of adiponectin treatment on human breast cancer cells reveal reduced cell proliferation in MCF-7 cells and T47-D cells, significantly more in MCF-7 cells.¹⁹ Inhibition of angiogenesis by inhibition of VEGF (Vascular Endothelial Growth Factor)-induced PAE (Porcine Aortic Endothelial)/VEGFR (Vascular Endothelial Growth Factor Receptor)-2 cell migration was observed in another study.^[22]

Circulating estrogens and androgens are positively associated with BMI²³ and breast cancer risk.²⁴ As the ovaries no longer produce adequate levels of estrogens after menopause, the body

relies on adipose tissue to generate more by increasing the expression of aromatase, the enzyme needed for the last step of estrogen biosynthesis. This occurs in the undifferentiated preadipocytes / adipose stromal cells (ASCs). Since the expression of aromatase increase in response to tumor-derived factors, it can create a positive feedback loop between the tumor and and the adipose stroma²⁵.

There may be other factors unaccounted for which may confound our study results. Since we used the weight and height of the time of the diagnosis to calculate the BMI, the duration of exposure to the increased BMI are unknown. Numerous studies have shown that weight change was associated with breast cancer risk.[11],[15],[16] A prospective study conducted by Kawai et al. calculated the BMI gained from age 20 years, and women with a weight gain of 12 kg and more appeared to have a higher risk compared to women whose weight have been stable (lost or gained < 2 kg) or women who lost 5 kg and more. The study also discovered that weight loss was associated with a decreased risk.[17]

While there were past studies that observe the connection between BMI and breast cancer risk, few were conducted (or published) in Indonesia and made the distinction by menopausal status, and even fewer by molecular subtypes.

5 Conclusion

Overweight and obesity are significantly associated with increased risk of breast cancer, while correlation with breast cancer molecular subtypes is statistically insignificant.

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