

DIFFERENCE OF BREAST CANCER ESTROGEN RECEPTOR (ER) BETWEEN OBESE PRE-MENOPAUSE WOMEN AND OBESE POST-MENOPAUSE WOMEN

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<https://doi.org/10.33508/jwmj.v5i3.4853>

ABSTRACT

Background: One of the risk of breast cancer is Obesity (BMI > 23Kg/m²) related to estrogen production between pre-menopause and post-menopause.

Aim: To investigate the difference of breast cancer estrogen receptor (ER) in obese women based on menopausal status.

Methods: This study was retrospective cross-sectional from secondary data (Medical Records) from Poliklinik Onkologi Satu Atap (POSA) RSUD Dr. Soetomo (ICD-10 C50) from 2013-2017 with inclusion criteria was BMI >23Kg/m². Data were analyzed using Chi-Square.

Results: There were 138 patient medical records collected which is 63 were obese pre-menopause and 75 were obese post-menopause. There were statistically a significant difference (p<0,05) based on Chi square test of breast cancer estrogen receptor for obese post-menopause women (66,7%) to obese pre-menopause (39,7%). Obese post-menopause women have 1,68 times greater risk factor to become estrogen receptor positive (ER+) compared to obese pre-menopause women. (PR = 1,68; 95% CI = 1,191-2,370)

Conclusion : There is a significant difference of breast cancer estrogen receptor in obese post-menopause women more frequent than obese pre-menopause women.

Keywords : Breast Cancer, Estrogen Receptors, Obese, Menopausal Status.

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INTRODUCTION

Breast cancer is the most common cancer in women with an incidence of 1.7 million new cases diagnosed in 2012 worldwide and accounting for 25% of all cancer cases. However, with the development of technology, mortality rates have decreased thanks to early diagnosis and advances in therapeutic management.¹

In 2012 there were 639,824 cases of breast cancer recorded in Asia and Indonesia was ranked fourth among countries with the highest incidence of breast cancer cases in Asia. The order of countries is as follows; China (187,213 cases), India (144,998 cases), Japan (55,710 cases), and India (49,998 cases).²

In this modern era, the lifestyle of today's society is different from the lifestyle of people in the past. Overweight and overweight (obesity) has become an epidemic phenomenon. According to international data from WHO, 31.2% of women in Indonesia are overweight. Increased body weight and body mass index will increase the risk of developing breast, colon, prostate and endometrial, kidney and gallbladder cancers. Simultaneously, the morbidity rate also increases with increasing body weight.³

The link between obesity and breast cancer is contained in hormonal factors, especially in the hormone estrogen. Recognition that there are three forms of the hormone estrogen found in the body, namely estrone (E1), estradiol (E2), and estriol (E3). Estradiol is the main estrogen because it has a stronger level of activity compared to estrone and estriol. When estradiol circulates in the plasma, it binds strongly to sex hormone-binding globulin (SHGB). Increased accumulation of SHGB can increase estradiol bioactivity against target cells. As a result of high endogenous estradiol/SHGB, there is an increase in aromatase and inflammation which can lead to breast cancer with positive estrogen receptor hormones.^{4,5}

Biglia et al. in their research at the hospital "Mauriziano Umberto I", Italy involving 2,148 breast cancer patients: 592 patients were pre-menopausal and 1,556 patients who were menopausal / post-menopausal. In their research it was found that women who are in the post-menopausal period are more likely to get positive breast cancer estrogen receptor status profile results compared to women who are in the pre-menopausal period.⁶ Crispo et al., 2016 also stated in their research that there is a relationship positive

BMI status and Luminal results (ER, PR, and HER2 hormonal receptors) in post-menopausal breast cancer patients.⁷

Yanai et al in their journal also conducted a study on BMI status on breast cancer hormone expression. Research conducted at the Tokushima Breast Cancer Clinic by selecting 525 breast cancer patients with Invasive Ductal Carcinoma (IDC) and Invasive Lobular Carcinoma (ILC) found that pre-menopausal women have a low BMI and post-menopausal women have a high average BMI. The journal stated that the immunohistopathological examination of post-menopausal patients has a tendency to have a positive estrogen receptor (ER+) status profile compared to pre-menopausal women.⁸ In breast cancer cells with positive estrogen hormone receptors (ER+) can provide a good prognosis because it is known has the least aggressive nature and can respond well to hormonal therapy (anti-estrogen). The journal said that there were no differences in the profile of estrogen receptor hormonal status in breast cancer estrogen receptor positive (ER+) or negative (ER-) in pre-menopausal obese or thin women.⁸ The prognosis in pre-menopausal women who are obese tends to be poor because they have tendency to acquire aggressive tumor properties (frequency of lymphatic tissue

metastases, larger tumor sizes, and high grades).⁸

Another study was conducted by Suleyman Sahin et al. in Turkey involving 3,767 breast cancer patients, it was found that there was a significant association in pre-menopausal obese (BMI>30Kg/m²) women with the incidence of Triple-negative breast cancer subtype (ER-,PR-,HER2-) compared to women who had BMI <30Kg/m² with p=0.007.⁹

One of the risk factors for breast cancer is obesity. The link between obesity and breast cancer is currently under further research. Therefore, researchers are interested in conducting research on differences in estrogen hormone receptor (ER) status in breast cancer between premenopausal and postmenopausal obese women.

METHODS

This study is a comparative analytic study with a cross-sectional study design to study the profile of estrogen hormone receptor (ER) status in breast cancer between obese and postmenopausal women. The study was conducted retrospectively using medical records of breast cancer patients at the One-Stop Oncology Polyclinic (POSA) Dr. Soetomo Surabaya in 2013-2017.

The inclusion criteria were medical records with body mass index (BMI) data, patients with BMI > 23 kg/m², estrogen hormone receptor (ER) examination data, menopausal status data, if there was no menopausal status, the researcher determined the age of menopause based on the patient's age. The exclusion criteria of this study were the initial diagnosis more than one year from the writing of medical records, patients using hormonal contraception and hormonal replacement at the time of diagnosis, and patients with relapse or metastases.

The independent variable of this study was the menopausal status of obese women with breast cancer. The dependent variable is the results of examination of the hormone estrogen (ER) for breast cancer.

The data obtained will be analyzed with the Pearson chi-square test with a 2x2 table. The data will be displayed in tabular form. The significance limit (α) used in this study was 5% ($p=0.05$) and power (β) was 80%.

RESULTS

Of the 138 samples that met the inclusion criteria, there were 63 obese women who were not yet menopausal and 75 obese women who were menopausal. Positive estrogen receptor test results were found in 60.3% of obese women who were

not yet menopausal and 66.7% of obese women who were menopausal.

Table 1. Distribution of Hormonal Status in Obese Breast Cancer Patients Against Estrogen Receptors (ER)

Hormone Status	Hormonal Receptor				Total n		p
	ER ⁺ ^b		ER ⁻ ^b		(%)		
	n	%	n	%	n	%	
Post-Menopause ^a	50	66.7	25	33.3	75	100	0.003
Pre-Menopause ^a	25	39.7	38	60.3	63	100	

Estrogen receptor (ER) analysis for breast cancer in obese women before menopause and postmenopausal women with the Chi Square analysis test obtained $p = 0.003$ (0.05). This shows that there is a significant difference in the status of the hormone estrogen receptor (ER) in breast cancer in obese women who have not gone through menopause and have gone through menopause. Based on the calculation of the prevalence ratio (PR) it obtained a value of 1.68 (95% CI = 1.191-2.370). This shows that postmenopausal obese women are at risk of having positive breast cancer estrogen receptor hormone status (ER⁺) by 1.68 times compared to obese women who have not yet reached menopause.

DISCUSSION

Based on the theory, in postmenopausal obese women, the formation of estrogen comes from peripheral fat tissue, while in premenopausal obese women the

formation of estrogen is still regulated by the work of the ovaries.¹¹ The higher the peripheral fat tissue, the higher the concentration of estrogen (estradiol). Fat induces the production of pro-inflammatory cytokines (TNF α), interleukin (IL)-6, IL-8, IL-1 β , and cyclooxygenase-2 (COX-2). The increase in COX-2 causes an increase in prostaglandins, where prostaglandins have a role in increasing the aromatase process.¹³⁻¹⁵ An increase in pro-inflammatory cytokines can activate macrophage immune cells to form CLS-B. This process can lead to the formation of excessive adipose-stromal cells (ASCs). On the other hand, the main ingredient for the formation of estrogen is cholesterol, an increase in cholesterol originating from fat tissue can increase the aromatase process so that the hormone estrogen will increase.¹⁴ Each hormone has its own receptors located throughout the body. Estrogen has two receptors namely ER α and ER β receptors. ER α receptors are found in the mammary glands, uterus, ovum, bones, and the male reproductive organs (testes). ER α plays a role in breast cancer mRNA levels. Exposure of ER α to estradiol can cause overexpression of ER α so that the estrogen hormone test for breast cancer becomes positive (ER+).¹⁵

Based on the theory, research results published in the journal *Gynecological Endocrinology* by Nicole Biglia et al. in 2013, there were significant results on the incidence of postmenopausal obese women and the incidence of positive ER/PR (p=0.017).⁶ An epidemiological cohort study conducted by China J. Nattenmüller et al. in Europe stated that there was an association of women with above average BMI (obese) to have less aggressive breast cancer estrogen hormone receptors (ER+, PR+, HER2-) with a value of p=0.009.¹⁶ It was explained in the journal that obese women had menopause activity high aromatase which turns androstenedione into estrogen in fat tissue.⁶ In a study conducted by Elisa V. Bandera et al reported in the journal *Breast Cancer Research and Treatment*, there was a relationship in newly obese women at menopause with the incidence of positive estrogen receptor breast cancer (ER+) (OR 1.31; 95% CI = 1, 02-1.67).¹⁷ In obese women who are not yet menopausal, the frequency of breast cancer with positive estrogen receptors (ER+) is less common because estrogen levels in obese women who are not yet menopausal are regulated by more frequent menstrual cycles so that free estrogen levels in the body can be reduced.¹⁷ Related to the menstrual cycle, research

conducted by Mostafa Rad. et al. regarding the association of menstrual disorders to obesity in premenopausal women reported that menstruation still affects free estrogen. can cause an increase in estrogen as a result of the aromatase process in peripheral fat tissue.¹⁷

Suleyman, et. al who stated that obese women have not yet menopause significantly associated with triple-negative subtypes (ER-, PR-, HER2-).⁹

CONCLUSION

In this study, which was conducted on 138 obese women at POSA from 2013-2017, there was a significant difference between positive estrogen receptors in premenopausal and postmenopausal women.

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