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The Correlation between Premenopausal Estrogen and Estrogen Receptors in Breast Cancer

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Abstract

Introduction. The correlation between the premenopausal estrogen hormone and estrogen receptors is unknown. The hormone estrogen has a risk factor for causing breast cancer. Meanwhile, the estrogen receptor plays a role in determining further treatment plans in breast cancer patients. Patients with high estrogen receptors have a better prognosis. If the premenopausal estrogen hormone can affect the estrogen-receptor, then the estrogen hormone can be modified to have a better prognosis.
Method. A cross-sectional study enrolled 32 subjects with complete data and was statistically analyzed to find the correlation between premenopausal estrogen hormone and estrogen-receptors.
Results. The estradiol ranged from 15.3 − 89.8 pg/mL, and estrogen receptors showed a range of 10–90%. The Spearman correlation test between the estradiol and the estrogen receptor showed a p-value = 0.864 and a negative correlation coefficient of 0.032.
Conclusion. Estrogen hormone is not statistically associated with estrogen receptors in premenopausal breast cancer patients, thus illustrating that the prognosis of breast cancer is not associated with the estrogen hormone.

Keywords: breast cancer; estradiol; estrogens; estrogen-receptors; premenopausal hormones

Introduction

Hormonal factors rolled as a risk factor in breast cancer, in addition to other carcinogenic factors such as chemicals, irradiation, viruses, genetics, and chronic irritation, as well as behavioral/lifestyle factors such as smoking, unhealthy eating patterns, alcohol consumption, and lack of physical activity.[1-3] Of the hormonal factor, estrogen is the crucial one. Estrogen is divided into endogenous and exogenous estrogens. The endogenous is found in three potential forms: estradiol, estrone, and estriol. Both exogenous and endogenous estrogen is referred to as the risk factors for breast cancer.[3]

Estrogen receptors showed a clinically important, that is, planning further treatment. High estrogen receptors reflect a good response to hormone therapy. In addition, high estrogen receptors have a better prognosis than those with low or no receptors. The correlation between estrogen and the estrogen receptor has been studied previously and showed contradictory findings. Some studies showed a significant correlation between estrogen and the estrogen–receptor, [4,5] particularly in the luteal phase and the positive estrogen receptor. However, another study showed that estrogen in premenopausal women was not significantly correlated with estrogen receptors.

Breast cancer in Indonesia showed a specific characteristic; it tends to be found in a younger population than in other countries, with a median age of 48 years compared to 68 years in European countries. Cancer at a younger age is associated with a poorer prognosis and is more progressive. A higher mitotic rate is poorly differentiated, tends to be negative estrogen receptors, and is more likely to recur and metastasize. The poor prognosis is further aggravated by the minimal awareness of the Indonesian population for early detection. Thus, those who were treated mostly were those with advanced stage.[10]
The differences in some studies' findings and different characteristics of the Indonesian population have driven the study to run. If the premenopausal estrogen hormone can affect the estrogen-receptor, then the estrogen hormone can be manipulated to get a better prognosis.

Method

The cross-sectional study proceeded in the Department of Surgery, FMUI – CMGH enrolling patients treated from December 2021 to May 2022. The inclusion criteria were those who remain in premenopausal age, i.e., stay to have menstruation regardless of age and patients who underwent immunohistochemical examination of estrogen receptors. Those who proceeded with hysterectomy, salpingo-oophorectomy, a history of hormonal therapy, and chemotherapy were excluded. Those who met the eligibility criteria were subjected to the study: some data were recorded, i.e., history of menstrual periods and proceeded blood estradiol test; the specimen was taken to the laboratory at CMGH. The blood specimen is taken during the mid-cycle phase or ovulation phase between the twelfth to the fourteenth day of each menstrual cycle. In the study, estradiol is referred to as the variable of interest since estradiol is the most active and predominant form of estrogen represents estrogen in premenopausal breast cancer. Finally, the estrogen–receptor is obtained through biopsy and/or surgical resection. The specimen was subjected to immunohistochemical examination in the anatomical pathology laboratory of CMGH. Data were subjected to statistical analysis to find the correlation, and a p-value < 0.05 was considered statistically significant. The committee of ethics, Faculty of Medicine, Universitas Indonesia, approved the study.

The independent board reviewer, i.e., the Committee of Ethics, Faculty of Medicine, Universitas Indonesia, approved the study (KET-137/UN2.F1/ETIK/PPM.00.02/2022 and protocol number 22-01-0096).

Results

Thirty-two subjects met the eligibility criteria. The subject was 22–51 years and grouped by age according to the study by Kurnia et al., as described in Table 1,[11] and the value of estradiol and estrogen (in median) as shown in Table 2.

Table 1 Subjects characteristics

Characteristics	n = 32
Age, n (%)	
20–29	3 (9.4)
30–39	8 (25)
40–49	17 (53.1)
50	4 (12.5)

Table 2. Estradiol and estrogen–receptor (n = 32)

Estradiol (pmol/L)	39.3 (15.3–89.8)
Estrogen receptor (%)	45 (10–90)

The following shows some research data with maximum and minimum values of age, estradiol, and estrogen that may have clinical significance, as seen in Table 3.

Table 3. Research data with a range of minimum and maximum values for age, estradiol values, and estrogen receptor values

Subjects	Age (year)	Estradiol (pmol/L)	Estrogen–receptor (%)
1	22	55.3	20
2	28	17.2	10
3	28	74.6	45
4	39	15.3	70
5	42	15.5	50
6	50	26.6	30
7	50	25.3	90
8	51	89.8	50

The age distribution and estrogen–receptors data were not normal. Thus, the Kruskal-Wallis test was used to analyze. The correlation between age and estrogen receptors showed a p-value of 0.785. Mann-Whitney test analysis was carried out to see the correlation of each group using the 40-49 age group as a reference, and the results were as shown in Table 4.

Table 4. Kruskal Wallis test between age and estrogen receptor

Age (year)	n	Estrogen receptor (%)	Overall p-value	p-value between groups
20–29	3	20 (10–45)	0.785*	0.631**
30–39	8	47.5 (10–70)		0.483**
40–49	17	45 (10–80)		Reference
50	4	70 (30–90)		0.417**

*Kruskal Wallis test, **Mann Whitney test

With this distribution, the Spearman correlation test between estradiol and estrogen receptors showed a p-value of 0.864 and a negative correlation coefficient of 0.032.

Table 5 Spearman correlation test between estradiol and estrogen receptor

Spearman Correlation		Estrogen receptor (%)
Value of estradiol (pg/mL)	Correlation coefficient	-0.032
	Sig (2-tail)	0.864
	n	32

Discussion

In this study, the 32 subjects enrolled are referred to as the minimum of a calculated sample using a correlation coefficient of 0.5. The age of subjects ranged from 22 to 51 years, with the highest frequency of 40–49 years (n = 17, 53.1%). A previous study showed that the incidence of breast cancer per 100,000 increases with age. For example, the incidence of breast cancer in patients aged 20–24 years is 1.4 per 100,000, aged 25-29 years is about 8.1 per 100,000, aged 30–39 is about 58.4 per 100,000, and aged 40–49 is about 198.5. per 100,000. This can be explained by hormonal factors, such as prolonged exposure to the hormone estrogen will increase the risk of breast cancer.

The estradiol of 32 subjects in the study showed a normal value, with the lowest of 15.3 pg/mL at the age of 39 years and the highest of 89.8 pg/mL at the age of 51. However, the data were not distributed normally, with a median value of 39.3 pg/mL. This wide range remains normal, considering that the reference value of estradiol in premenopausal women in the mid-cycle phase is also wide, namely 38–649 pg/mL. There is no categorical distribution for estradiol. Premenopausal women's mid-cycle estradiol in research subjects was still in the normal range. Theoretically, hormonal factors are risk factors for breast cancer. The higher the endogenous estrogen hormone (estradiol), the higher the risk of breast cancer. Estrogen would decrease at menopause, but it is no data for a younger age, the higher the estrogen.[17] There is also no pattern of estradiol based on age. Estrogen receptors in these 32 subjects showed a wide range between 10–90% with an abnormal distribution (median 45%). From this range, it was found that all subjects showed a positive estrogen receptor type. Thus, the study is referred to as a study that analyzed positive estrogen receptor subjects. Furthermore, in all subjects, there is a tendency for lower estrogen receptorsat a younger age; for example, the youngest subject, age 22 years, has a 20% estrogen receptor, and at 28 years, it has a 20% estrogen receptor. Likewise, the oldest subject was 51 years with a 50% estrogen receptor, and the 50-year-old had a 90% estrogen receptor.

The correlation between age and estrogen receptors was then analyzed to exclude this factor as a confounding factor. The analysis shows no significant correlation (p = 0.785) both overall and between groups with the age group 40–49 as a reference (with p values for each age group 20–29, 30–39, and 50, namely 0.631; 0.483; and 0.471, respectively). Thus, it is concluded that age is not a confounding factor that may lead to bias in the analysis of the correlation between estrogen and the estrogen receptor. However, data showed that younger people tend to have low estrogen receptor values. In addition, a previous study also showed that breast cancer at a young age (premenopausal) is more aggressive and tends to have negative estrogen receptors.[10,18-21] Although not statistically significant, we can conclude that there is a clinical significance that the younger the age, the lower the estrogen receptor. Therefore, surgeons can consider this to check estradiol in young breast cancer patients to predict the treatment and prognosis of premenopausal breast cancer patients. Hormonal factors include estrogen and progesterone, while this study only focused on examining estradiol but no other hormones. More prolonged hormone exposure increases the risk of breast cancer. However, this study focused on the duration of hormonal exposure of the subjects, such as the length of menstruation, the first time of menstruation, history of pregnancy, and history of breastfeeding.

The Spearman correlation test showed no statistically significant correlation between estrogen and the estrogen receptor in premenopausal breast cancer patients (p = 0.864). Although the correlation coefficient has a minus value (r = -0.032), which means there is an inverse correlation between the two variables. However, the correlation is too weak that may be ignored. This can be caused by the large range value of estradiol and estrogen receptors. The larger the numerical range of the variables, the larger the subject is needed to obtain significant and representative analysis findings. No reference explains the correlation between estrogen levels and the estrogen receptor with certainty. Theoretically, the higher the estrogen, the greater the risk of a person may have breast cancer. The role of estrogen is to occupy the estrogen receptor in breast cancer tissue, stimulating cell proliferation and supporting cell mutations so that cancer is formed.[22] Estradiol plays a role in carcinogenesis by interacting with estrogen receptors, which raises the question of whether the initial value of estradiol plays a role in the estrogen receptor in breast cancer that causes cancer, especially at a young age or premenopausal because it has more active and aggressive cell dividing. From the theoretical explanation above, it can be hypothesized that the higher the value of estrogen, the more aggressive the cell proliferation in the breast, and the more progressive it will lead to a worse prognosis, which was shown as the lower the value of the estrogen-receptor. Thus, it can be said that estrogen and the estrogen receptor have a negative correlation.

The study findings showed no significant correlation between estrogen and estrogen receptors in breast cancer patients at premenopausal age. This is paralleled to the previous study.[6,9] One large-scale case-control study conducted in 10 European countries enrolling 801 breast cancer cases showed no correlation between estradiol and progesterone on estrogen receptors and the risk of breast cancer in premenopausal age. The study found that the value of testosterone significantly correlated with the estrogen receptor in postmenopausal-age patients.[7] In this study, the age of the study subjects was close to that of the subjects, with a median age of 45.6 years (26.7–56.9). However, the number of research subjects was much higher than in this study, and the characteristics of the population in Europe were also different from Indonesia, with a more heightened awareness of health examinations. In Indonesia, patients tend to come with a long history of illness. Another study, a case-control conducted in Malaysia with 207 breast cancer cases, examined the role of estrogen, progesterone, testosterone, and prolactin in pre and postmenopausal breast cancer patients. There were 73 cases of premenopausal breast cancer analyzed in the study. The finding showed that in the premenopausal group, there was no significant correlation between hormones and the risk of breast cancer. However, in postmenopausal age, estrogen and progesterone are risk factors with OR 1.48 – 4.23 and p values of 0.025 and 0.006. This study has a research subject that is more similar to Indonesia because both are developing countries in Southeast Asia.[9]

This study did not examine estradiol at various menstrual phases but the mid-cycle estradiol. This somehow made us unable to take the highest estrogen in subjects. This is evidenced by a study by NHS (Nurses' Health Study) II on 18521 subjects with 634 subjects of premenopausal breast cancer patients, which found that estradiol in the luteal phase had an OR of 1.7 times (CI 1.00 – 2.9 and p-value 0.02) for the occurrence of breast cancer with positive estrogen and progesterone receptors, while free estradiol has no association with estrogen-receptors.[8] In this NHS study, no mid-cycle estradiol was investigated. Theoretically, the higher the number of estrogen receptors, the better the prognosis for breast cancer. The results of this study can answer the prognostic aspects that are still controversial.[15,16] Several things that can be explained in this study are: 1) Estrogen receptors are not associated with menopausal status, and 2) The estrogen receptors are not constant, so it is unknown what influences this. 3) Estrogen receptors at a young age or premenopausal age vary but tend to be lower at a young age.

Conclusions

Estrogen is not statistically associated with estrogen receptors in premenopausal breast cancer patients, thus illustrating that the prognosis of breast cancer patients is not related to the estrogen produced by the body. Therefore, based on these results, modifying estrogen to get a better breast cancer prognosis is not a solution.

The risk of breast cancer increases with increasing age. The correlation between age and estrogen receptors does not show statistical significance, but there is a clinical meaning. The younger the period, the lower the estrogen receptor. Therefore, it can be applied in daily health practice for premenopausal breast cancer patients to predict treatment options and prognosis. Meanwhile, the estradiol in this study showed normal premenopausal estradiol in breast cancer patients.

Disclosure

The authors declare no conflict of interest.

Role of authors

Conceptualization 123, data curation 3, formal analysis123, funding acquisition 3, investigation 123, methodology 123, project administration 123, resources 123, software 3, supervision 12, validation 12, visualization 3, writing – original draft preparation 3, writing – review and editing 123.

References

1. Youlden DR, Cramb SM, Yip CH, Baade PD. Incidence and mortality of female breast cancer in the Asia-Pacific region. Cancer Biol Med. 2014;11(2):101–15.
2. Tjindarbumi D, Mangunkusumo R. Cancer in Indonesia, present and future. Jpn J Clin Oncol. 2002;32(Suppl):S17-21.
3. Yue W, Wang JP, Li Y, Fan P, Liu G, Zhang N, et al. Effects of estrogen on breast cancer development: role of estrogen-receptor-independent mechanisms. Int J Cancer. 2010;127(8):1748–57.
4. Fortner RT, Eliassen AH, Spiegelman D, Willett WC, Barbieri RL, Hankinson SE. Premenopausal endogenous steroid hormones and breast cancer risk: results from the nurses' health study II. 2013;1–11.
5. Key TJ, Appleby PN, Reeves GK, Travis RC, Alberg AJ, et al. Sex hormones and risk of breast cancer in premenopausal women: a collaborative reanalysis of individual participant data from seven prospective studies. Lancet Oncol. 2013;14(10):1009–19.
6. Kaaks R, Tikk K, Sookthai D, Schock H, Johnson T, Tjønneland A, et al. Premenopausal serum sex hormone levels in relation to breast cancer risk, overall and by hormone receptor status - results from the EPIC cohort. Int J Cancer. 2014;134(8):1947–57.
7. Sturgeon SR, Potischman N, Malone KE, Dorgan JF, Schairer C, Brinton LA, et al. Serum levels of sex hormones and breast cancer risk in premenopausal women: a case-control study (USA). Cancer Causes Control. 2004;15(1):45–53.
8. Sieri S, Krogh V, Bolelli G, Abagnato CA, Grioni S, Pala V, et al. Sex hormone levels, breast cancer risk, and cancer receptor status in postmenopausal women: the ORDET cohort. Cancer Epidemiol Biomarkers Prev. 2009;18(1):169–76.
9. Ho CC, Rohaizak M, Zulkifli SZ, Siti-Aishah MA, Nor-Aini U, Sharifah-Noor-Akmal SH. Serum sex hormone levels in pre-and postmenopausal breast cancer patients. Singapore Med J. 2009;50(5):513–8.
10. Anwar S, Raharjo C, Herviastuti R, Dwianingsih E, Setyoheriyanto D, Avanti W, et al. Pathological profiles and clinical management challenges of breast cancer emerging in young women in Indonesia: a hospital-based study. BMC Women's Health. 2019;19(1).
11. Kurnia A. Breast cancer at a young age. In: Ramli M, Albar ZA, Panigoro SS, Julian ED, Kartini D, Husein AM (ed). Restore breast youthfulness in benign and malignant tumors. Jakarta: FK UI Publishing Center; 2014. p. 105-115.
12. Rabaglio M, Castiglione M. Breast cancer in younger women. In: Jatoi I, Kaufmann M (ed). Management of breast disease. German: Springer; 2010. p. 509-540.
13. Goldhirsch A, Gelber RD. Breast cancer in young women. In: Harris JR, Lippman ME, Morrow M, Osborn CK (ed). Diseases of the breast. Philadelphia: Lippincott Williams & Wilkins; 2004. p. 1339-1350.
14. Sun YS, Zhao Z, Yang ZN, Xu F, Lu HJ, Zhu ZY, et al. Risk factors and prevention of breast cancer. Int J Biol Sci. 2017;13(11):1387–97.
15. Liu JY, Chen TJ, Hwang SJ. The risk of breast cancer in women using menopausal hormone replacement therapy in Taiwan. Int J Environ Res Public Health. 2016;13(5):482.
16. Narod SA. Hormone replacement therapy and the risk of breast cancer. Nat Rev Clin Oncol. 2011;8(11):669–76.
17. Wiknjosastro H. Physiology of menstruation. In: Obstetrics. Edition III. Jakarta: Bina Pustaka; 2002. p. 45–51.
18. Huang W, Newman B, Millikan R, Schell M, Hulka B, Moorman P. Hormone-related Factors and Risk of Breast Cancer in Relation to Estrogen receptorand Progesterone Receptor Status. Am J Epidemiol. 2000;151(7):703-714.
19. Yip C, Bhoo Pathy N, Uiterwaal C, Taib N, Tan G, Mun K et al. Factors affecting estrogen receptorstatus in a multiracial Asian country: An analysis of 3557 cases. Breasts. 2011;20:S60-S64.
20. Kiang D, Kennedy B. Factors affecting estrogen receptors in breast cancer. Cancer. 1977;40(4):1571-1576.
21. Narod SA. Breast cancer in young women: reviews. Nat Rev Clin Oncol. 2012;9:460-470.
22. Yue W, Yager J, Wang J, Jupe E, Santen R. Estrogen-receptor-dependent and independent mechanisms of breast cancer carcinogenesis. Steroids. 2013;78(2):161-170.
23. Siegel RL, Miller KD, Jemal A. Cancer statistics. CA Cancer J Clin. 2017;67(1):7–30.