Correlation between Risk Factors and Protein Expression of ER, PR, and HER-2 in Breast Cancer Patients: A Population-Based Study in Makassar Indonesia

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ABSTRACT

Background: Breast cancer is a condition characterized by abnormal and uncontrollable growth of cells in breast tissue. According to Global Cancer Statistics 2020, it ranks as the leading cause of female cancer mortality. The disease has four subtypes defined by protein expression, namely Luminal A (ER/PR (+), HER2 (-)), Luminal B (ER/PR (+), HER2 (+)), triple-negative/basal-like (ER, PR, HER2 (-)), and HER2-enriched (ER (-), PR (+), HER2 (+)), each with distinct characteristics influenced by various risk factors. Therefore, this study aimed to explore the correlation between breast cancer risk factors and protein expression of ER, PR, and HER2.

Methods: The cross-sectional analytical study was conducted in Makassar, Indonesia, using secondary data from 259 breast cancer patients. Information on ER, PR, HER2 expression, and patient risk factors such as age, history of hormonal contraceptive use, and family history of breast cancer were extracted from medical records and subjected to statistical analysis using the Chi-square test, with significance set at $p < 0.05$.

Results: The results showed that there was a significant correlation between age $\geq 40$ years and the expression of ER, PR, and HER2 ($p < 0.005$). However, no significant correlations were observed between family history and hormonal contraceptive use with ER, PR, and HER2 expression.

Conclusions: This study established a meaningful correlation between risk factors of age and breast cancer subtypes based on ER, PR, and HER2 expression.

INTRODUCTION

Breast cancer is the new global cancer cases recorded in 2020, constituting a total of 16.6%, thereby becoming the most prevalent cancer for both sexes combined. It served as the primary cause of female cancer-related fatalities on a global scale, contributing to 15.5% of mortality. Meanwhile, in Indonesia, the figure is stated to increase to about 20.7% [1]. According to the estimates from the American Cancer Society in 2017, approximately 252,710 women and 2,470 men in the United States were anticipated to be diagnosed with invasive breast cancer. Additionally, 63,410 cases of in situ breast cancer were projected for women [2].

Since the early 2000s, breast cancer has been categorized into at least four subtypes based on protein expression. These subtypes include Luminal A (Estrogen Receptor (ER)/Progesterone Receptor (PR) positive, human epidermal growth factor receptor 2 (HER2) negative), Luminal B (ER/PR positive HER2 positive), triple-negative/basal-like (ER/PR and HER2 negative) and HER2-enriched (ER/PR negative, HER2 positive). In addition, the four subtypes are susceptible to several risk factors and have different characteristics in terms of onset and prognosis [3].
Various factors contribute to the development of different breast cancer subtypes. Modifiable risk factors comprise weight gain after 18 years of age, being overweight or obese, postmenopausal hormone use, physical activity, and alcohol consumption. Non-modifiable risk factors include older age, familial or personal history of breast cancer, history of benign breast tumors, and type 2 diabetes. Reproductive factors such as oral contraceptive use, nulliparity, and delayed first childbirth also exert influence. Protective factors consist of breastfeeding for at least one year, regular physical activity, and weight maintenance [3,4].

Based on the above-referenced studies, there was no analysis conducted on the correlation between age, history of hormonal contraceptive use, family history of breast cancer, and the expression profiles of ER, PR, and HER2 in patients. This prompted an investigation into understanding the correlations between risk factors and the expression of ER, PR, and HER2.

METHODS

This study conducted a cross-sectional analytic examination using secondary data extracted from patient medical records at Wahidin Sudirohusodo and Hasanuddin University Hospital in Makassar from January 2016 to September 2017. Breast cancer patients included those who had been diagnosed with breast cancer through histopathological findings, confirmed by immunohistochemical examinations of ER, PR, and HER2. Risk factors, denoting characteristics statistically associated with increased disease incidence, were explored. Age was defined as an individual lifespan from birth, while a family history of breast cancer incorporated instances of family members who had or were currently suffering from the condition. Hormonal contraception use was described as actions taken to prevent pregnancy, achieved through injections, pills, or implants. Inclusion criteria covered all available data on age, family history of breast cancer, hormonal contraception use, histopathological findings of breast cancer, and immunohistochemistry results of ER, PR, and HER2 in the medical records of patients. Data collection commenced after obtaining permission from the Medical Record Installation, consistent with ethical recommendation number 788/UN4.6.4.5.31/PP36/2022. Subsequently, patient data in the designated period were collected, observed, and processed. The chi-square test of SPSS 19.0 was used to analyze data, producing significant results if p<0.05.

RESULTS

During the study period, 352 breast cancer cases were identified, but only 259 met the inclusion criteria. Risk factors evident in the sample comprised age, history of hormonal contraceptive use, family history of breast cancer, and the expression of ER, PR, and HER2. While not all medical records provided complete data, each variable was separately analyzed.

The distribution of breast cancer patients, based on age from the 259 breast cancer samples, showed that 215 (83.0%) samples were aged ≥ 40 years, while 44 (17.0%) were under 40 years. When considering the history of hormonal contraceptive use in 259 samples, 129 samples contained data on this history, with 78 (60.5%) showing a history of hormonal contraceptive use. Examining family history, out of 259 samples, 151 had data on family history, and 35 (23.2%) samples had family history, while the remaining 116 (76.8%) samples did not have a family history of breast cancer. The distribution of patients based on the expression of ER, PR, and HER2 was observed in 91 samples. The highest occurrence was in Luminal B type (ER / PR (+) HER2 (+)), with 26 (28.6%) samples, followed by HER2-enriched type (ER(-) PR(-) HER2(+)), with 25 (27.5%), then Luminal A (ER/PR(+) HER2(-)), with 22 (24.2%), and finally, the Triple-negative/basal-like type (ER PR HER2 (-)), with 18 (19.8%), as shown in Table 1.

Out of the 259 samples with available age and ER, PR, and HER2 expression data, 91 samples were used for analysis. Among patients aged ≥ 40 years, 75 (82.4%) had family history, while the remaining 116 (76.8%) did not. For those aged < 40 years, 44 (17.0%) patients, with the majority falling into the Luminal B (ER / PR (+) HER2 (+)) category, comprising 26 (28.6%) patients. For those aged < 40 years, there were 16 (17.6%) patients, with the majority falling into HER2-enriched type (ER (-) PR (-) HER2 (+)), totaling 8 (8.8%). A significant (p=0.02) correlation between age and the expression of ER, PR, and HER2 was observed, as shown in Figure 1.

<table>
<thead>
<tr>
<th>Table 1. Characteristics of study samples</th>
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<tbody>
<tr>
<td>Risk Factors</td>
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<tr>
<td>Age (n = 259)</td>
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<tr>
<td>≥ 40 years</td>
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<tr>
<td>&lt; 40 years</td>
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<tr>
<td>History of Hormonal Contraceptive Use</td>
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<td>(n = 129)</td>
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<tr>
<td>Yes</td>
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<tr>
<td>No</td>
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<tr>
<td>Family History of Breast Cancer (n = 151)</td>
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<tr>
<td>Yes</td>
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<tr>
<td>No</td>
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<tr>
<td>Expression of ER, PR, HER2 (n = 91)</td>
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<tr>
<td>ER/PR(+) HER2(-) (Luminal A)</td>
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<tr>
<td>ER/PR(+) HER2(+) (Luminal B)</td>
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<tr>
<td>ER PR HER2 (-) (Triple-negative)</td>
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<td>ER(-) PR(-) HER2(+) (HER2-enriched)</td>
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ER: estrogen receptor, PR: progesterone receptor, HER2: human epidermal growth factor receptor 2
Figure 1. Association of age risk factor and protein expression of ER, PR, and HER2. Chi-square test, *Significant: $p < 0.05$.

Figure 2. Association between history of hormonal contraceptive use risk factors and ER, PR, HER2 Expression. Chi-square test, *Significant: $p < 0.05$.

Figure 3. Association between family history risk factors and ER, PR, HER2 expression. Chi-square test, *Significant: $p < 0.05$.
Among the 259 samples, 47 had data on the history of hormonal contraceptive use and ER, PR, and HER2 expression. Among patients with a history of hormonal contraceptive use, 33 (70.2%) were identified, with the majority falling into the Luminal A type (27.7%, 13 patients). For those without a history of hormonal contraceptive use, there were 14 (29.8%), with most falling into the HER2-enriched type (10.1%, 5 patients). No significant correlation \( (p > 0.05) \) was observed between the history of hormonal contraceptive use and the expression of ER, PR, and HER2, as shown in Figure 2.

In the case of family history, 59 out of 259 samples had data on breast cancer family history and ER, PR, and HER2 expression. Sixteen patients (27.1%) had a family history of breast cancer, predominantly in Triple-negative and Luminal A types (8.5% each, 5 patients each). For patients without a family history of breast cancer, there were 43 (72.9%), with the majority falling into Luminal A type (22.0%, 13 patients). No significant correlation \( (p > 0.05) \) was found between family history of breast cancer and the expression of ER, PR, and HER2, as seen in Figure 3.

**DISCUSSION**

The medical record data were collected for 259 breast cancer cases out of a total of 352 from January 2016 to September 2017. Some patient records did not have complete data, such as family history, history of hormonal contraceptive use, and expression of ER, PR, and HER2. This study showed a significant \( (p = 0.002) \) correlation between age and the expression of ER, PR, and HER2. The result was consistent with a study reporting a significant association between ER expression and older patient age [5]. However, this differed from other explorations indicating no significant correlation between age group and immunohistochemical subtype \( (p = 0.742) \) [6]. This disparity could be attributed to variations in breast cancer incidence distribution based on age groups across different hospitals. In this study, breast cancer was more prevalent in older age \( (\geq 40 \text{ years}) \) with 75 (82.4%) cases, compared to 16 cases (17.6%) in the age group < 40 years. Another investigation found a higher incidence in pre-menopausal age \(< 50 \text{ years}) \) with a total of 82 (71.9%) cases, showing variations in age-based incidence among different immunohistochemical subtypes.

The results showed a significant correlation between risk factors of age \( \geq 40 \text{ years} \) and Luminal A and Luminal B types, but no significant correlation was found for age as risk factors associated with triple-negative and HER2-enriched types (unpublished data). This result was consistent with a discovery indicating the prevalence of the Luminal A subtype in older individuals, while basal-like and HER-2 positive subtypes were more common in younger individuals [7]. Alzaman et al. [8] also reported that aggressive breast cancer subtypes were HER2-enriched and triple-negative types, and were more prevalent in younger women. A considerable proportion of younger breast cancer patients showed the triple-negative subtype, known for its high aggressiveness. Additionally, most younger patients with breast cancer tested negative for ER and PR, showing the more aggressive nature of cancer. This discovery contributed to the understanding of the increased aggressiveness of tumors in younger women.

This study also found that breast cancer patients who used hormonal contraception (60.5%) outnumbered those who did not (39.5%). The results were in line with an investigation that reported a 2.9 times greater risk of developing breast cancer among those using hormonal birth control compared to non-users, with a significance value of \( p = 0.001 \) [9]. The results were substantiated by the theoretical basis of hormonal imbalance including progesterone and estrogen, key components in hormonal birth control materials. Two theories explain the contribution of estrogen and progesterone to breast cancer. Firstly, an increased risk of cell mutation during division due to elevated estrogen and progesterone levels, and secondly, the stimulation of breast cancer stem cell growth [10,11]. However, no significant correlation \( (p = 0.322) \) was found between the use of hormonal contraceptives and the expression of ER, PR, and HER2. This result was consistent with Turkoz et al. [12], which also reported no significant difference between breast cancer subtypes (Luminal A, Luminal B, triple-negative, and HER2-enriched) and the use of oral contraceptives.

According to this study, there was no significant correlation \( (p = 0.613) \) found between family history and the expression of ER, PR, and HER2. These results were consistent with Redondo et al., which reported no correlation between family history and types of breast cancer [13].

The results provided data on the association between risk factors for breast cancer and cancer subtypes defined by ER, PR, and HER2 status. This information could contribute to specific risk factors by breast cancer subtype, aiding in the development of risk prediction models and risk reduction strategies. However, it should be acknowledged that this study had limitations, as the data was obtained from patient medical records collected by different health workers.

**CONCLUSIONS**

This study identified a significant correlation between risk factors of age \( \geq 40 \text{ years} \) and the expression of ER, PR, and HER2. However, no association was observed between family history of breast cancer and hormonal contraceptive use with ER, PR, and HER2 expression.
DECLARATIONS

Competing interest
The author(s) declare no competing interest in this study.

Ethics approval and consent to participate
Ethics approval from Komite Etik Penelitian Universitas Hasanuddin No. 788/UN4.6.4.5.31/PP36/2022.

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