ORIGINAL RESEARCH

Correlation between hormonal status of estrogen receptor and malignancy degree of invasive ductal breast cancer

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ABSTRACT

Background: Globocan data in 2018 shows the cancer incidence in Indonesia. The highest case in women is breast cancer. The chance of survival for patients with high malignancy (Grade III) is only 11.86%, while for patients with low malignancy (Grade I) can reach 71.69%. Estrogen exposure is a risk factor for breast cancer. The hormone causes its effect through the estrogen receptor which is a core protein. Patients with positive receptor have 5 and 10 years survival rate which is better than patients with negative estrogen receptor. **Objective:** To identify correlation between hormonal status of estrogen receptor and malignancy degree of invasive ductal breast cancer. **Materials and Methods:** This research was an observational analytic study. The sample used was patients' medical record data in 2015-2017 in Anatomic Pathology Unit, Central Laboratory Installation, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. **Results:** The data used were 694 patients medical record in 2015-2017. Approximately 56 patients (86%) had hormonal status of positive estrogen receptor with grade I cancer, 180 patients (70%) were in grade II, and 217 patients (45%) were in grade III. Approximately 9 patients (14%) had hormonal status of negative estrogen receptor with grade I cancer, 71 patients (28%) were in grade II, and 161 patients (34%) were in grade III. The result using Chi-Square test found Chi-Square value of 27.413 with a significance of 0.000 ($p < 0.01$). **Conclusion:** There was a positive correlation between the hormonal status of estrogen receptor and malignancy degree of invasive ductal breast cancer.

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BACKGROUND

Cancer is a condition characterized by uncontrolled cell growth, so that it can attack the surrounding tissue, and can spread to other parts of the body (Pecorino, 2012). Cancer is the second leading cause of death in the world and accounted for 8.8 million deaths in 2015. Meanwhile breast, colorectal, lung and ovarian cancer are often found among women (WHO, 2017).

According to data obtained from the Ministry of Health, Republic of Indonesia (2019), the prevalence of cancer in Indonesia reached 1.79 per 1000 populations, and in 2013 it showed an increase of 1.4 per

1000 populations. In a study about the data, the highest prevalence was found in D.I. Yogyakarta Province as much as 4.86 per 1000 population. Meanwhile, according to other data, the Globocan in 2018, it was known that the incidence of cancer in Indonesia was 136.2 per 100,000 populations. This figure puts Indonesia at number eight with the highest number of cases in Southeast Asia, and ranks 23 in the Asian region. The highest case in women was breast cancer which was 42.1 per 100,000 populations with mortality rate of 17 per 100,000 (Kementrian Kesehatan Republik Indonesia, 2019).

Breast cancer is caused by a proliferation of malignancies in the epithelial cells that limit the ducts or lobes of the breast. At first, cancer is cell hyperplasia with atypical cell develop-ment. Then, these cells continue to develop into *Ductal Carsinoma in Situ* (DCIS) and attack the stroma (Eroles, et al., 2012). Cancer takes 7 years to grow from one cell to a mass large enough to finally be palpable (approx. 1 cm in diameter). At this size, it is known that 25% of breast cancers have metastasized. The most common types of breast cancer are invasive and infiltrative (Price, et al., 2012). As many as 70-80% of breast cancer diagnoses are invasive ductal breast cancer types (National Breast Cancer Foundation, 2016).

Estrogen exposure is a risk factor for breast cancer. This hormone has an effect via the estrogen receptor which is a core protein. Consists of 2 subtypes, namely (ER)–α and (ER)–B. Both are transcription factors that mediate the action of estrogen (Pasaribu, et al., 2018; Payne, et al., 2008). Apart from the hormone estrogen, there is also the hormone progesterone which can affect breast development (Yue, et al., 2013). There are also receptors for progesterone (PR) in the breast.

The proliferation and malignancy of cancer cells, which are a reflection of the progressive state of cancer cells along with other factors, can be manifested by the classification of the degree of malignancy, namely I, II and III. The degree of malignancy is assessed based on tubular shape, nuclear pleomorphism and the number of mitosis. For patients with high malignancy (grade III), the chances of survival are only 11.86%, while the survival rate for patients with low malignancy (grade I) can reach 71.69%. Patients who are estrogen receptor positive have better survival rates of 5 years and 10 years than those with negative estrogen receptor tumors, because patients who have these receptors will respond to hormonal therapy (Safitriana, et al., 2017).

OBJECTIVE

This study aimed to identify the correlation between the hormonal status of estrogen receptors and the degree of malignancy of invasive ductal breast cancer.

MATERIALS AND METHODS

The method used in this study was an observational analytic cross-sectional approach which aimed to determine the correlation of the hormonal status of estrogen receptors with the degree of malignancy of invasive ductal breast cancer in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

The study population used in this study included all medical record data of patients with invasive ductal breast cancer in 2015-2017 in the Anatomic Pathology Unit, Central Laboratory Installation of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

The sample data used were 694 patients with inclusion criteria, that all patients with invasive ductal breast cancer for which data were available regarding the hormonal status of estrogen receptor and the degree of breast cancer malignancy. Characteristics of respondents in this study included age, gender, location of breast cancer, estrogen receptor hormonal status, and the degree of malignancy of invasive ductal breast cancer.

The independent variable which was examined in this study was the hormonal status of estrogen receptor observed with immuno-histochemistry with the criteria as follows: it was categorized (-) if <1% of a cell nucleus is brown in immunohistochemistry, and it was categorized (+) if ≥ 1% of a cell nucleus was brown on immunohistochemistry (Lakhani & Ellis, 2012). Meanwhile, the dependent variable, the degree of malignancy of invasive ductal breast cancer with grade I criteria, occurred if the total score of *tubule formation, nuclear grade*, and *mitotic rate* = 3-5, then it was classified as degree II if the total score of *tubule formation, nuclear grade*, and *mitotic rate* = 6-7. Then, it was classified as degree III if the total score of *tubule formation, nuclear grade*, and *mitotic rate* = 8-9 (Atanda, et al., 2021).

This research was an analytical study which proved whether there was correlation between research variables in the form of nominal and ordinal data. The data analysis used was *Chi-Square* test (χ^2) to

determine the difference in the distribution of hormonal status of estrogen receptor between the degree of malignancy of breast cancer with the degree of confidence α = 99%. The significance value of *Chi-Square* (χ^2) was calculated using SPSS 23.

RESULTS

Characteristics of respondents

Based on the characteristics of age, the youngest age of patients was 22 years, and the oldest age was 84 years with an average age of the patient is 50 years.

Table 1. Characteristics of the respondents by age

	Min	Max	Median	Modus	Mean
Age	22.00	84.00	49.50	49.00	50.02

Table 2. Characteristics of respondents by gender, location of cancer, hormonal status of estrogen receptor and degree of malignancy

Characteristics	Group	Frequency	Percentage
Gender	Male	6	9%
	Female	688	99.1%
Location of Cancer	Mammae Sinistra	361	52%
	Mammae Dextra	330	47.6%
	Mammae Bilateral	3	0.4%
Estrogen Receptors	Positive	453	65.3%
	Negative	241	34.7%
Degrees of Malignancy	Degree I	65	9-4
	Degree II	251	36.2%
	Degree III	378	54.5%

Table 3. Chi-Square test on correlation between hormonal status and degrees of invasive ductal breast cancer

		Hormonal Status ER/AW		Chi-Square Score	P
		Positive	Negative		
Degrees of malignancy	Degree I	56	9	27.413	0.000
		86	14		
	Degree II	180	71		
		70	28		
	Degree III	217	161		
		45	34		

The majority of patients who were sampled in this study were female, they were 688 patients (99.1%), while 6 patients were male (0.9%). Based on the location of the cancer, most patients experienced breast cancer in mammae sinistra which are 361 (52%), mammae dextra consists of 330 patients (47.6%), while on bilateral mammae only consists of 3 patients (0.4%).

Regarding the hormonal status of estrogen receptor, 453 patients showed positive (+) estrogen receptor hormonal status, whereas the other 241 patients showed negative (-) estrogen receptor hormonal status. Then, in the degree of malignancy of invasive ductal breast cancer, 65 patients were at grade I, 251 patients were at grade II, and 378 patients were at grade III.

Correlation between hormonal status and degrees of invasive ductal breast cancer

Patients who had positive estrogen receptor (+) hormonal status with grade I malignancy were 56 patients (86%), 180 patients (70%) had grade II, and 217 patients (45%) had grade III. Nine patients (14%) had negative estrogen receptor hormonal status with grade I malignancy, 71 patients (28%) had grade II, and 161 patients (34%) had grade III.

The result of the analysis using Chi-Square test earned Chi-Square value which was 27.413 with a significance value of 0.000 ($p < 0.01$). This showed that with a study error rate of 1%, it could be concluded that there was a significant correlation between the hormonal status of estrogen receptor and the degree of malignancy of invasive ductal breast cancer in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia in 2015-2017.

DISCUSSION

Characteristics of respondents

The sample data used were 694 patients. Characteristics of respondents in this study can be identified based on age, gender, location of breast cancer, estrogen receptor hormonal status, and the degree of malignancy of cancer. Based on the characteristics of age, patient had the youngest age that was 22 years, and the oldest age was 84 years with an average age of the patients was 50 years.

The majority of the patients were female, as many as 688 patients (99.1%), while 6 patients were male (0.9%). Based on the location of the cancer, most patients experienced breast cancer on mammae sinistra which was 361 (52%), 330 patients (47.6%) experienced on mammae dextra, while only 3 patients (0.4%) experienced on bilateral mammae.

Regarding the hormonal status, 453 patients showed positive estrogen receptor hormonal status (+), ≥ 1% positive staining tumor cells on immunohistochemistry. Whereas, the other 241 patients showed negative estrogen receptor hormonal status (-), it was found that <1% positive staining tumor cells were immuno-histochemical. Then, in the degree of malignancy of invasive ductal breast cancer, 65 patients were at grade I, 251 patients were at grade II, and 378 patients were at grade III.

Correlation between hormonal status and degrees of invasive ductal breast cancer

The correlation between hormonal status of estrogen receptor and degrees of malignancy of invasive ductal breast cancer in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, which was done with Chi-Square and earns Chi-Square value in the amount of 27,413 with a significance value of 0,000 ($p < 0.01$). This showed that the error rate of the study was 1%, which can be concluded that there was a significant correlation between hormonal status of the estrogen receptor and degrees of malignancy of invasive ductal breast cancer in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

The results of this study were consistent with research conducted by Zanellia (2012) regarding the correlation between estrogen receptor hormone status and the severity of invasive ductal breast cancer in the Department of Anatomic Pathology (Faculty of Medicine, Universitas Airlangga - Dr. Soetomo General Academic Hospital, Surabaya, Indonesia) for the period of 2009-2011 in 295 patients. The results showed that patients with negative hormone status had the highest grade III, while those with positive hormone status had the most severity grade, grade II. The test results using Chi-Square test indicated that Chi- Square value which was calculated was greater than Chi-Square table and the significance value was smaller than 95% confidence level. Thus, it can be concluded that there was a difference in the distribution of estrogen hormone status between the rates of invasive ductal breast cancer and possible association between estrogen receptor hormone status and the severity of invasive ductal breast cancer.

The degree of malignancy is an important determinant in determining cancer outcome. The degree is also associated with patterns of survival, high-grade breast cancer tends to recur and experience early metastasis (Agustina, 2015). Since the expression of hormonal receptor is associated with histopathological assessment, the expression status can be considered in determining the prognosis of the disease (Yang, et al., 2020).

Data on Chi-Square value and the characteristics of respondents were also in accordance with the research of Pasaribu, et al. (2018) which states that estrogen receptor (ER) is the most important predictive factor examined in breast carcinoma. About two-thirds of women <50 years with breast carcinoma have positive ER expression, while about 80% of tumors in women >50 years are ER positive. This has significant therapeutic implications (Pasaribu, et al., 2018; Payne, et al., 2008).

The results of the discussion of this study provide conclusions in accordance with Bauer's study, women with cancer who have negative ER status have worse prognosis or disease progression. Meanwhile, women with positive ER have lower chance of getting degree. These results occur because there is strong correlation between estrogen receptor as a factor that stimulates the proliferation of breast cells to continue growing (Gity, et al., 2018; Bauer, et al., 2007).

CONCLUSION

There was significant correlation between hormonal status of estrogen receptor and degree of malignancy of invasive ductal breast cancer at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia in 2015-2017.

REFERENCES

Agustina, R. 2015. Peran derajat differensiasi histopatologik dan stadium klinis pada rekurensi kanker payudara [Role of histopathologival differentiation degree and clinical stage in breast cancer recurrence]. Majority. Downloaded 16 June 2021 from https://juke.kedokteran.unila.ac.id/ index.php/majority/article/ download/1461/1296.

Atanda, A., Imam, M., Umar, A., Yusuf, I., Bello, S., 2021. Audit of Nottingham system grades assigned to breast cancer cases in a Teaching Hospital. Atpjournal.org. Downloaded 16 June 2021 from https://www.atpjournal.org/article.asp?issn=22510060;year=2017;volume=8;issue=2;spage=104;epage=107;aulast=Atanda.

Eroles, P., Bosch, A., Pérez-Fidalgo, J.A., Lluch, A., 2012. Molecular biology in breast cancer: Intrinsic subtypes and signaling pathways. Cancer Treatment Reviews, 38(6): 698-707.

Gity, M., Borhani, A., Mokri, M., Shakiba, M., Atri, M., Batavani, N., 2018. Sonographic features of estrogen-negative breast cancers: A correlation study with human epidermal growth factor type II overexpression. Journal of Diagnostic Medical Sonography, 34(6): 484-88.

Lakhani, S., Ellis, I., 2012. WHO Classification of Tumours of The Breast. Lyon: IARC.

Ministry of Health, Republic of Indonesia. 2019. Hari Kanker Sedunia 2019 [World Cancer Day 2019]. Jakarta. Downloaded 6 June 2019 from http://www.depkes.go.id/article/view/ 19020100003/hari-kanker-sedunia- 2019.html.

National Breast Cancer Foundation. 2016. Invasive Ductal Carcinoma. Downloaded 6 June 2017 from http://www.who.int/cancer/en/.

Pasaribu, E., Issakh, B., Maritska, Z., 2018. Trend kanker payudara di Semarang: Analisis tipe histologi dan molekuler [Breast cancer trend in Semarang: Analysis of histological and molecular type]. Jurnal Kedokteran dan Kesehatan: Publikasi Ilmiah Fakultas Kedokteran Universitas Sriwijaya, 5(3): 108-13.

Pecorino, L. 2012. Molecular Biology of Cancer. Oxford: Oxford University Press.

Price, S.A. Wilson, L.M. 2012. Patofisiologi: Konsep klinis proses-proses penyakit [Pathophysiology: Clinical concept of disease processes]. Jakarta: EGC

Safitriana, A., Yazid, N., Suprijono, A. Hubungan antara derajat diferensiasi dengan adanya reseptor estrogen pada penderita karsinoma payudara jenis duktus invasif [Correlation between differentiation degree and the presence of estrogen receptor in invasive ductal breast cancer patients]. Downloaded 7 June 2017 from Universitas Diponegoro. Available at http://eprints.undip.ac.id/22404/1/11_asli_-_hubungan_derajat_diferensiasi_-_noor_yazid_-_59-62.pdf.

WHO, 2017. Cancer. Downloaded 6 June 2017 from at http://www. who.int/cancer/en/ (Retrieved 6 June 2017).

Yang, Z., Li, N., Li, X., Lei, L., Wang, X., 2020. The prognostic impact of hormonal receptor and HER-2 expression discordance in metastatic breast cancer patients. OncoTargets and Therapy 13: 853-63.

Yue, W., Yager, J., Wang, J., Jupe, E., Santen, R. Estrogen receptor dependent and independent mechanisms of breast cancer carcinogenesis. Steroids, 78(2): 161-70.

Zanellia, Q.P. 2012. Hubungan status hormonal estrogen dengan derajat keganaan kanker payudara duktal invasif [Correlation between estrogen hormonal status and degree of malignancy of invasive ductal breast cancer]. Undergraduate Thesis. Surabaya: Universitas Airlangga.