pISSN: 2088-8686
eISSN: 2686-0864

SCRIPTA SCORE Scientific Medical Journal
Research

Profile of Breast Cancer Patients on Estrogen Receptor Expression in RSUD. Dr. Pirngadi Medan 2018-2019

Naomi Laksita Laras[1], Pimpin Utama Pohan[1]

[1]*Department of Surgery, Faculty of Medicine, Universitas Sumatera Utara, Medan*

**Correspondence: naomilaksitalrs@gmail.com*

ABSTRACT

Background: Breast cancer is a type of cancer with the highest incidence and become the leading cause of death in the world. The incidence rate continues to increase due to various risk factors such as endogenous and exogenous. Immunohistochemical examinations is useful to determine therapy and patient's prognosis. **Objectives**: This study aims to determine how the profile of breast cancer patients on the expression of estrogen receptor in RSUD. Dr. Pirngadi Medan 2018-2019. **Methods**: This is descriptive cross-sectional research using random-sampling technique. Data were obtained secondary from medical records of breast cancer patients in hospitals. Dr. Pirngadi Medan 2018-2019. **Results**: From 250 cases, 71 samples were taken in this study. Of the 71 samples, most of the patients were in the 46-55 year old group with negative ER with 18 people (58.1%), 13 people (56.5%) patients had tumor size T4 with positive ER, most of the patients did not have nodular metastases, distant metastases, family history and use of hormones with negative ER with 26 people (63.4%), 39 people (66.1%), 36 people (60%) and 42 people (62.7%), respectively (66.7%) patients had obese with negative ER, invasive ductal histopathology type with negative ER was mostly found in 41 people (63.1%) and the most histopathological grading was in grade 2 with negative ER with 26 people (57.8%). **Conclusion**: Almost all patients based on the characteristics of the majority of breast cancer have negative ER, except patients with T4 tumor size have positive ER.

Keywords: breast cancer, estrogen receptor, histopathology type, immunohistochemistry, metastases

ABSTRAK

Latar Belakang: *Kanker payudara merupakan jenis kanker dengan angka kejadian tertinggi dan menjadi penyebab utama kematian di dunia. Angka kejadian tersebut terus meningkat disebabkan oleh berbagai faktor risiko seperti faktor endogen maupun eksogen. Pemeriksaan imunohistokimia seperti reseptor estrogen berguna untuk menentukan terapi dan prognosis pasien.* ***Tujuan****: Penelitian ini bertujuan untuk mengetahui bagaimana profil pasien kanker payudara terhadap ekspresi protein reseptor estrogen di RSUD. Dr. Pirngadi Medan Tahun 2018-2019.* ***Metode:*** *Penelitian yang dilakukan adalah penelitian deskriptif observasional menggunakan desain cross sectional dengan teknik pengambilan sampel random sampling. Data diperoleh secara sekunder dari rekam medis pasien kanker payudara di RSUD. Dr. Pirngadi Medan Tahun 2018-2019.* ***Hasil:*** *Dari 250 kasus kanker payudara periode 2018-2019, diambil sampel sebanyak 71 buah rekam medis. Dari 71 sampel, sebagian besar pasien terjadi pada kelompok usia 46-55 tahun dengan ER negatif sebanyak 18 orang (58.1%), sebanyak 13 orang (56.5%) pasien memiliki ukuran tumor T4 dengan ER positif, sebagian besar pasien tidak mengalami metastasis pembuluh limfe, metastasis jauh, tidak memiliki riwayat keluarga dan penggunaan hormon dengan ER negatif dengan masing-masing sebanyak 26 orang (63.4%), 39 orang (66.1%), 36 orang (60%) dan 42 orang (62.7%), sebanyak 20 orang (66.7%) pasien memiliki IMT obesitas dengan ER negatif, tipe histopatologi duktal invasif dengan ER negatif paling banyak ditemukan sebanyak 41 orang (63.1%) dan derajat histopatologi terbanyak pada derajat 2 dengan ER negatif sebanyak 26 orang (57.8%).* ***Kesimpulan:*** *Hampir keseluruhan pasien berdasarkan karakteristik kanker payudara mayoritas memiliki ER negatif, kecuali pasien ukuran tumor T4 memiliki ER positif.*

Kata Kunci: derajat keganasan, gambaran histopatologi, imunohistokimia, kanker payudara, reseptor estrogen
Received [18 Des 2022] | Revised [28 Feb 2023] | Accepted [28 Feb 2023]

INTRODUCTION

Breast cancer is a malignancy originating from gland cells, gland ducts and breast supporting tissues, but does not include breast skin.[1] According to World Health Organization, the breast cancer mortality rate reached 685,000 deaths in 2020 in the world. According to the World Cancer Prevention Organization and the World Health Organization, it is estimated that there will be an increase in the incidence of cancer in the world by 300 percent in 2030, and the majority occur in developing countries inculing Indonesia. One of the risk factors that can increase the incidence of breast cancer is obesity. In obese patients, estrogen synthesis occurs in fat deposits which affects the increase in breast tissue proliferation.[2] One of the factors that can increase the risk of recurrence is ER/PR expression negative.[3] Recently, expression of estrogen receptor (ER), progesterone receptor (PR) and overexpression and/or amplification of human epidermal growth factor receptor 2 (HER2) has been included to improve the classification predicting prognosis as well as potential response to endocrine treatment and monoclonal antibody (trastuzumab).[4]

Immunohistochemical technique is the technique of choice for determining these biologic markers because it is relatively easy, inexpensive and is used as a routine examination for every breast cancer patient. According to research at Sanglah Hospital Denpasar, the results of double positive hormonal receptor detection showed the second highest frequency, namely 45 patients (30.6%).[5] Research on this examination has not been done by many medical students. Therefore, researchers are interested in conducting research on how the actual clinicopathological profile of patients with estrogen receptor expression in breast cancer patients in RSUD. Dr. Pirngadi Medan 2018-2019.

METHODS

This study is an observational descriptive study with a cross sectional study. The location of this research is RSUD. Dr. Pirngadi Medan. The population in this study were all breast cancer patients listed in the 2018-2019 medical record data.

Based on the formula Slovin obtained 71 samples in this study. The inclusion criteria of this study included patients diagnosed with breast cancer for the 2018-2019 period, positive/negative estrogen receptor diagnostic results on immunohistochemistry examination, history examination results including age, family history and history of hormone use, tumor size results, lymph node metastases. and distant metastases at the patient's TNM stage, the results of the examination of weight and height as well as the results of the type of carcinoma and the grading diagnosis on histopathological examination.

The exclusion criteria for this study were incomplete medical record data on anamnesis, physical, histopathological examination, determination of the patient's TNM staging and immunohistochemical examination. This research has obtained ethical feasibility with the number: 693/KEP/USU/2021.

Table 1. Frequency Distribution

Characteristics	Amount n=71 (%)
Age	
• ≤25 years old	0
• 26-45 years old	21 (29,6)
• 46-55 years old	31 (43,7)
• ≥56 years old	19 (26,8)
Tumor Size	
• T1	19 (26,8)
• T2	21 (29,6)
• T3	8 (11,3)
• T4	23 (32,4)
Nodular metastases	
• N0	41 (57,7)
• Nx	22 (31)
• N1	3 (4,2)
• N2	4 (5,6)
• N3	1 (1,4)
Distant Metastases	
• M0	59 (83,1)
• M1	12 (16,9)
Family History	
• No	60 (84,5)
• Yes	11 (15,5)
Hormone	
• No	67 (94,4)
• Yes <8 years	2 (2,8)
• Yes ≥8 years	2 (2,8)
BMI	
• <18,5	2 (2,8)
• 18,5-22,9	22 (31)
• 23-24,9	17 (23,9)
• ≥25	30 (42,3)
Histopathological Classification	
• Ductal Invasif	65 (91,5)
• Ductal in Situ	1 (1,4)
• Lobular Invasif	4 (5,6)
• Lobular in Situ	0
• Other Types	1 (1,4)
Grading of Histopathologic	
• Grade 1	12 (16,9)
• Grade 2	45 (63,4)
• Grade 3	14 (19,7)
Estrogen Receptor	
• Positive	28 (39,4)
• Negative	43 (60,6)

RESULTS

This research has been conducted in the Medical Record Instalation of RSUD. Dr. Pirngadi Medan to breast cancer patients for the period 2018-2019. A total of 71 samples that met the inclusion criteria were obtained from August to September 2021 at the RSUD. Dr. Pirngadi Medan using secondary data totaling 71 cases, with characteristics as shown in Table 1.

Based on the sample frequency distribution in Table 1, it is known that from 71 cases, most of the patients were in the 46-55 year age group, namely 31 people (43.7%), followed by the 26-45 year age group as many as 21 people (29.6%), the age group 56 years as many as 19 people (26.8%) and no patients were found in the age group 25 years.

Based on tumor size, the most common patients found were tumors of any size with extension to the chest wall/skin ulceration, namely 23 people (32.4%), followed by tumor size of 2-5 cm, which was 21 people (29.6%), tumor size < 2 cm in 19 people (26.8%) and tumor size > 5 cm in 8 people (11.3%).

Patient in hospital. Dr. Pirngadi Medan were mostly found not to have metastases to the lymph nodes as many as 41 people (57.7%), followed by metastases to the mobile ipsilateral axillary lymph nodes as many as 22 people (31%), metastases to the lymph nodes ipsilateral/supraclavicular infraclavicular lymph nodes with or without lymph node metastases as many as 4 people (5.6%), there were fixed and conglomerated ipsilateral axillary lymph node metastases in 3 people (4.2%) and in the last order found lymph node metastases that could not be assessed in 1 person (1.4%).

Based on the presence or absence of distant metastases, family history, history of hormone use, most of the patients were found not to have distant metastases, there was no family history and no history of

hormone use, each of which were 59 people (83.1%), 60 people. (84.5%) and 67 people (94.4%)

Based on the characteristics of body mass index, it was found that patients with a body mass index 25 were the most commonly found, namely 30 people (42.3%), followed by patients with a body mass index of 18.5-22.9 as many as 22 people (31%), patients with a mass index 23-24.9 as many as 17 people (23.9%) and patients with a body mass index <18.5 with the smallest incidence in 2 people (2.8%).

The most common histopathological type of breast cancer found in this study was ductal invasive which was 65 people (91.5%), followed by invasive lobular type as many as 4 people (5.6%), ductal type in situ and other types as many as 1 person each (1.4 %). Meanwhile, the type of lobular in situ histopathology was not found. In addition, most of the patients had a histopathological grade grade 2, namely as many as 45 people (63.4%).

Of the 71 cases of breast cancer in hospitals. Dr. Pirngadi Medan in 2018-2019, the majority of patients had negative estrogen receptor status, as many as 43 people (60.6%) and followed by positive estrogen receptor status as many as 28 people (39.4%).

Data on the profile of breast cancer patients on the expression of estrogen receptor protein based on their characteristics can be seen in Table 2. Table 2 shows that based on their characteristics, almost all breast cancer patients have negative estrogen receptors, except for patients with any tumor size with extension to the chest wall or skin ulcerations majority have positive estrogen receptor protein expression.

Table 2. Estrogen Receptor Expression Profile Based on Characteristics.

Characteristics	ER (+) n=71 (%)	ER (-) n=71 (%)
Age		
• 26-45 years old	8 (38,1)	13 (61,9)
• 46-55 years old	13 (41,9)	18 (58,1)
• ≥56 years old	7 (36,8)	12 (63,2)
Tumor Size		
• T1	7 (36,8)	12 (63,2)
• T2	5 (23,8)	16 (76,2)
• T3	3 (37,5)	5 (62,5)
• T4	13 (56,5)	10 (43,5)
Nodular Metastases		
• N0	15 (36,6)	26 (63,4)
• Nx	0	1 (100)
• N1	10 (45,5)	12 (54,5)
• N2	2 (66,7)	1 (33,3)
• N3	1 (25)	3 (75)
Distant Metastases		
• M0	20 (33,9)	39 (66,1)
• M1	8 (66,7)	4 (33,3)
Family History		
• No	24 (40)	36 (60)
• Yes	4 (36,4))	7 (63,6)
Hormone		
• No	25 (37,3)	42 (62,7)
• Yes <8 years	2 (100)	0
• Yes ≥8 years	1 (50)	1 (50)
BMI		
• <18,5	1 (50)	1 (50)
• 18,5-22,9	12 (54,5)	10 (45,5)
• 23-24,9	5 (29,4)	12 (70,6)
• ≥25	10 (39,4)	20 (66,7)
Histopathological Classification		
• Ductal Invasif	24 (36,9)	41 (63,1)
• Ductal in Situ	0	1 (100)
• Lobular Invasif	3 (75)	1 (25)
• Other Types	1 (100)	0 (43)
Grading of Histopathology		
• Grade 1	4 (33,3)	8 (66,7)
• Grade 2	19 (42,2)	26 (57,8)
• Grade 3	5 (35,7)	9 (64,3)

DISCUSSION

The estrogen receptor is the most important biological marker in breast cancer and as a transcription factor acting on the nucleus to regulate estrogen activity. Estrogen receptor expression can be a predictive response to hormonal therapy, thereby improving the prognosis for breast cancer. Tumors with negative estrogen receptors indicate that there is a

more aggressive tumor growth and proliferation and a high recurrence rate.[6] The principle of the biological activity of estrogen is that it affects the growth, differentiation and physiological function of several reproductive organs such as the breast, uterus and ovaries.[7] Therefore, the accuracy of the assessment of estrogen receptor protein expression is very important in the management of breast cancer patients.

Based on the results of the study of 71 cases, it was found that most of the patients were in the age group of 46-55 years, as many as 31 people (43.7%) and no patients were found in the age group 25 years. Along with the age of the patient, the physiological risk of suffering from breast cancer is greater because the body's immune system is already weak and has decreased so that it is susceptible to cancer. In addition, it may be caused by hormonal exposure for a long time, especially estrogen hormone and also degeneration of organ function or body cells as well as the influence of other risk factors that take time to induce cancer and can affect hormonal receptor status.[8]

Based on age, the results of this study are in accordance with research conducted at RSUD dr. Soegiri, Lamongan Regency, who stated that more than some respondents were aged 41-55 years, namely 29 people (58%) and none of the respondents aged 10-18 years were found (Sulistiyowati, 2012). The results of this study are also in line with research conducted by Prastyo and Nafiah, that negative estrogen receptor hormonal status was more commonly found in menopausal and postmenopausal women.[9] The increase in cases starting at the age of 40 years was caused by routine mammography examinations carried out by patients.[10]

Based on tumor size, it was found that the most common breast tumor size were tumors of any size with extension to the chest wall/skin ulceration as many as 23 people (32.4%) and with positive estrogen receptors as many as 13 people (56.5%). The results of this study are in accordance with research conducted at the RSUP. H. Adam Malik Medan period 2017-2018 which showed that the majority of breast cancer patients were any tumor size with extension to the chest wall/skin ulceration as many as 49 people (59.8%).[11]

The data of this study are also in accordance with the research conducted by Shaikh et.al which showed that from 118 cases of breast cancer, the majority of breast cancer patients with any tumor size and extension to the chest wall/skin ulceration tended to have positive estrogen receptor protein expression.[12] However, the data of this study is slightly different from the research conducted by Erić et.al which found that the majority of tumor sizes in breast cancer patients were 2-5 cm, followed by < 2 cm and followed by tumor size > 5 cm and tumors of any size with extension to the chest wall/skin ulceration.[13] This is probably caused by differences in the number of populations and the characteristics of each individual.

Enhancement of tumor size affects to increased risk of lymphatic metastases.[14] According to the researcher's assumptions, patients from RSUD. Dr. Pirngadi Medan mostly did not experience lymph node metastases due to the presence of estrogen receptors which tended to lead to the degree of malignancy of the disease, not the occurrence of metastases, so that patients also tended to have negative estrogen receptors because the histopathological degrees were found to be mostly moderate to poorly differentiated.

Metastases describes a complex interaction involving tumor intravasation, circulation, extravasation, proliferation and angiogenesis. Although patients with estrogen receptor negative are in a

minority of patients with distant metastases, patients have a much worse prognosis than those with estrogen receptor positive. This can be caused by the high risk of increasing the spread of cancer to other organs.[15] The data of this study are also in accordance with the research conducted at the hospital Peruvian who explained that from 1198 cases of breast cancer, as many as 1142 people (95.3%) did not experience distant metastases (M0).[16] The results of this study are also in line with research conducted by Hoefnagel et.al which showed that breast cancer patients who did not experience distant metastases were more often found to have negative estrogen receptor expression and those who experienced distant metastases tend to have positive estrogen receptors.[17]

Family history is one of the most important factors because cancer can be influenced by genetic disorders. Some families have a higher risk of developing breast cancer than others. Like a woman's risk for breast cancer increases 1.5-3 times if her mother or sister has breast cancer.[18] From genetic factors, five to ten percent of breast cancer is the effect of gene mutations, such as breast cancer susceptibility gene 1 (BRCA1) and breast cancer susceptibility gene 2 (BRCA2).[19]

The majority of this study did not have a family history and with negative estrogen receptors as many as 36 people (60%). These results are slightly different from the research conducted at RSUD Dr. Wahidin Sudirohusodo who showed that breast cancer patients, either without or with family history risk factors, both had more positive estrogen receptor hormonal status.[20] According to the researcher's assumption, the difference in the results of this study was caused by the patients in the RSUD. Dr. Pirngadi Medan experienced breast cancer not because of differences in the characteristics of samples with different lifestyles and other histories, so that the incidence of breast cancer may be caused by other factors such as chronic exposure to estrogen so that receptors experience downregulation so that it also affects the status of the estrogen receptor tend to be found to be negative.

Long-term use of contraception can increase the risk of breast cancer.[1] The presence of exposure/exposure to the hormone estrogen will increase the risk of breast cancer, while reducing this exposure can reduce the occurrence of breast cancer.[6] Prolonged use of hormones can disrupt the balance of the hormone estrogen in the body, resulting in normal cell changes to become abnormal.[21]

The results of this study are slightly different from the study in the city of Padang which stated that patients with a history of hormonal contraception were more commonly found in the incidence of breast cancer as many as 78 people (60.5%) compared to patients who did not have a history of hormonal contraception and the majority had positive estrogen receptors.[6] This difference can be caused by other factors such as differences in the characteristics of patients who have different lifestyles or are more dominant in using non-hormonal contraception.

Body mass index is associated with insulin resistance and changes in cytokine production by adipose tissue which act as major contributors to the aggressive nature of developing breast cancer through its influence on angiogenesis and stimulation of the invasiveness of cancer cells.[6] The mechanism linking excess body fat and increased risk of breast cancer is thought to be related to insulin and insulin-like growth factors (IGF) which is known as an antiapoptotic protein. Furthermore, chronic hyperinsulinemia has been found to decrease blood concentrations of sex hormone binding globulin leading to an increase in circulating estrogen.[22]

The results of this study are in accordance with research conducted at

RSUP. H. Adam Malik period 2018 which shows that the majority of patients with breast cancer have an obese body mass index, which is 42 people (40.8%).[23] In addition, it is also in line with the research conducted by Sari et.al which shows that obese breast cancer sufferers in Padang tend to have negative estrogen receptor protein expression so that they have a worse prognosis. In addition, based on research analysis conducted in Ken Saras Hospital, explained that consumption of fatty foods was 1,105 times more likely to develop breast cancer.[24]

Histopathological types of breast cancer can be categorized into invasive invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC) and non-invasive ductal carcinoma in situ (DCIS), lobular carcinoma in situ (LCIS), and other types of carcinoma. Invasive ductal carcinoma (IDC) is the most common type of breast cancer. About 80% of all breast cancers are invasive ductal carcinomas. Until now, prognostic factors have not been able to provide strong information on risks and accurate therapy.[25] Invasive breast cancer patients with negative estrogen receptor expression have a variety of histopathologies and some of them show that they are poorly differentiated and less effective with endocrine therapy treatment.[26]

This research is in line with that conducted by Susilo at RSUD Dr. Soetomo Surabaya showed that breast cancer patients with negative estrogen receptors were more often found in the invasive ductal type, namely 108 people (53.7%) and only 93 people (46.3%).[27] According to the researcher's assumption, the invasive ductal type has complex risk factors and closely related to chronic estrogen hormone exposure which can be influenced by the age of early menarche so that the estrogen receptor is downregulated when it binds to the nucleus and causes the patient to tend to have a negative estrogen receptor.

The histopathological degree of the sample in this study, using the standard measurement of 'Nottingham Modification of Bloom-Richardson System', by looking at the picture of tubular formation, nuclear pleomorphicity and mitotic activity of tumor cells.[28] Grade 1 is also called a well-differentiated cell. Grade 1 has slow development and little cell division. Grade 2 is called moderately differentiated. Grade 2 have cells that are not like normal cells and cell growth occurs somewhat faster than normal cells. Grade 3 are poorly differentiated cells. Grade 3 consists of cells that are very different from normal cells, their growth is fast and disorganized, irregular and many divisions occur new cell.[29] The duration of exposure to estradiol affects gradinghistopathology in cancer breast.[30]

This study is in accordance with research conducted at the hospital. Cipto Mangunkusumo who showed that based on the histopathological grade, patients with moderate grade (grade 2) were found more often, namely 1053 cases (40%) compared to patients with low and high malignancy degrees.[31] The results of this study are also in line with research conducted at RSUD Dr. Moewardi Surakarta which shows that of the threegrading histopathology, each of them had negative estrogen receptor expression which was mostly found compared to positive estrogen receptor expression.[30] According to the researcher's assumptions, patients in RSUD. Dr. Pirngadi Medan is more commonly found with moderate to poor histopathological degrees because the symptoms of the disease are not felt so that most patients come already at an advanced stage with negative estrogen receptors, which indicates that the patient is predicted to have a poor prognosis.

CONCLUSION

Based on the results of the analysis and discussion that have been described, it can be concluded that most of the patients based on the characteristics of age, lymph vessel metastases, distant metastases, family history, history of hormone use, body mass index, histopathological classification and histopathological degree were found to have the most expression of receptor proteins. estrogen negative, unless patients with tumor size T4 (any size with extension to the chest wall/skin ulceration) have estrogen receptor positive. The limitation of this study is the incomplete medical record data according to the inclusion criteria, especially on histopathological and immunohistochemical examinations.

REFERENCES

[1] Ministry of Health. Pocket book for cervical cancer and breast cancer prevention. Ijb. 2009;p. 24.Available at: http://dx.doi.org/10.12692/ijb/14.4.492-496%0A.

[2] Balasubramaniam, SM, Rotti, SB, & Vivekanandam, S. Risk factors of female breast carcinoma: A case control study at Puducherry. Indian J Cancer. 2013;50(1):65-70.

[3] Ashariati, A.M.I. Comprehensive Breast Cancer Management. Surabaya. 2019

[4] Vuong, D., Simpson, PT, Green, B., Cummings, MC, Lakhani, S. R. Molecular classification of breast cancer. Virchows Archiv. 2014;pp. 1–14. doi: 10.1007/ s00428-014-1593-7

[5] Wiguna, N.I.P and Manuaba, I.T.W. Characteristics of Immunohistochemical Examination of Breast Cancer Patients at Sanglah Hospital Period 2003-2012. Udayana Medical Journal. 2012

[6] Sari, SE, Harahap, WA and Saputra, D. Effect of Risk Factors on Estrogen Receptor Expression in Breast Cancer Patients in Padang City. Andalas Health Journal. 2018;7(4),p. 461. doi:10.25077/jka.v7i4.902

[7] Rahman, A., D. Relationship of HER-2/neu expression and hormonal receptors with histopathological grading in young female breast cancer patients. Indonesian Journal of Cancer. 2012;p.6(3).

[8] Sihombing, M. and Sapardin, A.N. Breast Tumor Risk Factors in Women Age 25-65 Years in Five SubDistricts, Central Bogor District. Journal of Reproductive Health. 2014;p.5(3), pp. 175–184

[9] Prastyo Kurniati, Y. and Nafiah, I. Phenotype of Estrogen Receptors by Age and Occupation in Invasive Breast Cancer. University Research College. 2019; pp.709–715. Available at: http:// repository.urecol.org/index.php/proceeding/article/ view/711

[10] Johnson, RH, Anders, CK, Litton, JK, Ruddy, K. J., Bleyer, A. Breast cancer in adolescents and young adults. Pediatric Blood and Cancer. 2018;p.65(12), pp. 1– 9. doi:10.1002/pbc.27397

[11] Thomas, A.A. The relationship between the degree of histopathology with hormonal and non-hormonal immunohistochemical expression in patients with ductal invasive breast cancer at Haji Adam Malik General Hospital Medan[Thesis]. Medan: Faculty of Medicine, University of North Sumatra. 2019

[12] Shaikh, F., Jamal, Q., Baig, S., Hadi, NI, Majeed, N. Correlation of hormone receptor and HER-2/neu expression with clinicopathologic parameters in primary breast tumors.

Asian Pacific Journal of Cancer Prevention. 2016;p.17(7), pp. 3363–3367

[13] Erić, I.,Erić, AP, Kristek, J., Koprivčić, I., Babić, M. Breast cancer in young women: Pathologic and immunohistochemical features. Acta Clinica Croatica. 2018;p.57(3),pp.497–502.doi:10.20471/acc.2018.57.03.13

[14] Wetan, N.M.Y. Differences in Characteristics of Early Stage Breast Cancer Patients With and Without Axillary Lymph Node Metastases at Sanglah Hospital Denpasar.JBN (National Surgery Journal). 2019;3(1), p. 11. doi: 10.24843/jbn.v03.i01.p03

[15] Kennecke, H., Yerushalmi, R., Woods, R., Cheang, M. CU, Voduc, D., Speers, C. H. et al. Metastatic behavior of breast cancer subtypes. Journal of Clinical Oncology. 2010; p.28(20), pp. 3271–3277. doi:10.1200/JCO.2009.25.9820

[16] Vallejos, C., Gómez, H., Cruz, W., Pinto, J., Dyer, R., Velarde, R.. et al. Breast cancer classification according to immunohistochemistry markers: Subtypes and association with clinicopathologic variables in a peruvian hospital database. Clinical Breast Cancer. 2010;p.10(4), pp. 294–300. doi:10.3816/CBC.2010.n.038

[17] Hoefnagel, LDC, Van de Vijver, MJ, Van slooten, HJ, Wesseling, P., Wesseling, J., Westenend, P. J. et al. Receptor conversion in distant breast cancer metastases. Breast Cancer Research. 2010; p.12(5). doi:10.1186/bcr2645

[18] Priyatin, C., Ulfiana, E. and Sumarni, S. Risk Factors Affecting Breast Cancer Incidence in RSUP. Dr. Kariadi Semarang. 2013; p.5(october), pp. 9–19

[19] Gelgel, J.P.P and Christian, I.S. Characteristics of Women's Breast Cancer in Sanglah General Hospital Denpasar 2014-2015. Udayana medical journal. 2020;9(3), pp. 52–57. Available at: https:// ojs.unud.ac.id/index.php/eum/article/ view/ 60009/34745

[20] Meylani, I.T. Relationship of Risk Factors with Expression of ER, PR, HER2 in Breast Cancer Patients at RSUP DR. Wahidin Sudirohusodo[Thesis]. Makassar; Hasanuddin University Faculty of Medicine. 2017.

[21] Abidin, H. Syahrir and Richa. Risk Factors for Breast Cancer Incidence in Labuang Baji Hospital Makassar. Journal of Scientific Health Diagnosis. 2014; p.4(2), pp. 236–242

[22] Rojas, K. and Stuckey, A. Breast Cancer Epidemiology and Risk Factors. Clinical Obstetrics and Gynecology. 2016; p.59(4),pp.651–672.doi:10.1097/GRF.0000000000000239

[23] Mardiah, H. Relationship between Age and Body Mass Index (BMI) with Histopathological Features in Breast Cancer Patients at RSUP. Haji Adam Malik Medan[Thesis]. Medan; Faculty of Medicine, University of North Sumatra. 2019.

[24] Yulianti, I., S, HS and Sutiningsih, D. Breast Cancer Risk Factors (Case Study at Ken Saras Hospital Semarang. Journal of Public Health. 2016.

[25] Stendahl, M., Kronblad, A., Ryden, L., Emdin, S., Bengtsson, N.O, Landberg, G. Cyclin D1 overexpression is a negative predictive factor for tamoxifen response in postmenopausal breast cancer patients. British Journal of Cancer. 2004;p.90(10), pp. 1942–

1948. doi: 10.1038/sj.bjc.6601831
[26] Putti, T.C, Abd El-Rehim, D.M, Rakha, E.A, Paish, C.E, Lee, A.H.S, Pinder, S.E., Ellis I.O. Estrogen receptor negative breast carcinomas: A review of morphology and immunophenotypical analysis. Modern Pathology. 2005;Vol.18(1), pp. 26–35. doi:10.1038/modpathol.3800255
[27] Susilo, I. Expression of Er (Estrogen Receptor) Protein in Breast Cancer Degree of Malignancy Mild, Moderate, and Severe). Nurse Journal. 2012;Vol.7(1), pp. 88–93
[28] Lester, SC. The Breast in Robbins and Cotrans Pathology Basic of Disease, 8th ed. Pennsylvania: Elsevier Saunders. 2010.
[29] Suarfi, A.S, Anggraini, D. and Nurwiyeni, N. Histopathological Overview of Malignant Breast Tumors at the Anatomical Pathology Laboratory of M. Djamil Hospital Padang in 2017. Health & Medical Journal. 2019;Vol.1(1), pp. 7–14. doi:10.33854/heme.v1i1.213
[30] Warjianto, W., Soewoto, W., Alfianto, U., Wujoso, H. Relationship of Estrogen Receptors, Progesterone Receptors and Her-2/Neu Expression with Histopathological Grading in Breast Cancer Patients in RSUD dr. Moewardi Surakarta. Smart Medical Journal. 2020;Vol.3(2), p. 96. doi:10.13057/smj.v3i2.35228
[31] Rustamadji, P. and Marisca, S. Histopathological and Immunophenotypic Characteristics of Breast Cancer at Cipto Mangunkusumo Hospital Jakarta, Indonesia. Medicinus. 2017;Vol.6(3), pp. 1–7