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BRCA1 Expression Profile in Breast Cancer Patients in West Nusa Tenggara

Rizka Vidya Lestari*[1], Novrita Padauleng[1], Fathul Djannah[2], Lale Maulin Prihatina[2], Bq. Ratna Kumaladewi[3], Rashieka Salma Aulia[4], Rommy Healthy Mikaila[4], Muhammad Fikri Adidaifa[4], Bq. Nurhandini Wulandari[4]

[1]Department of Histology, Medical Faculty of Mataram University, West Nusa Tenggara, Indonesia.
[2]Department of Pathology Anatomy, Medical Faculty of Mataram University, West Nusa Tenggara, Indonesia.
[3]Department of Pathology Anatomy, Provincial General Hospital, West Nusa Tenggara, Indonesia
[4]Medical student of Faculty of Medicine and Health Science Mataram University, West Nusa Tenggara, Indonesia.

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Abstract: Breast cancer is still the highest case in Indonesia. The mortality ratio: incidence of breast cancer in various countries can be influenced by differences in the clinical and biological profiles of tumors like BRCA1 expression status. In addition, several parameters that can be reviewed based on breast cancer incidence such as age and domicile can also be associated with BRCA1 expression. BRCA1 is tumor suppressor gene. This protein works as a cell cycle regulator. Germline mutations of BRCA1 are the main cause of inherited breast cancer. Breast cancer with BRCA1 mutations only contributes 20-40% to breast cancer incidence, but this condition have adverse tumor characteristics with poor prognosis. The aim of this study is to determine the BRCA1 expression profile in breast cancer patients in West Nusa Tenggara based on age and domicile status. A retrospective cross-sectional study of 50 breast cancer paraffin blocks obtained from Pathology Anatomy Laboratory collection in NTB Provincial Hospital and medical records. The expression of BRCA1 status were examined using immunohistochemistry techniques. BRCA1 expression profile in breast cancer patients will be analyzed descriptively using the frequency distribution of BRCA1 expression based on age and domicile. The negative BRCA1 expression is high at age <40 (59.1%) in Central Lombok and East Lombok districts (40%). Negative BRCA1 expression was found at age <40 years, found in two districts in NTB. Breast cancer with high negative BRCA1 expression was found at younger age. Patients with negative BRCA1 expression are mostly found in Central Lombok and East Lombok districts. there was no relationship was found between BRCA1 expression and age and domicile of breast cancer patients in NTB

Keywords: BRCA1, Breast Cancer

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Introduction

Breast cancer is a malignancy that characterized by abnormal cell growth, invading surrounding tissue and even spread to other tissues. According to GLOBOCAN (Global Cancer Observatory) 2020 data, breast cancer is one of the most commonly diagnosed cancers and causes 2.3 million new deaths worldwide (Sung, et al., 2021). Breast cancer has high biological complexity with different prognoses and therapeutic responses. Tumors with similar clinicopathological features have different biological behaviors. This is due to molecular differences based on their molecular subtypes, like luminal A luminal B, HER2+ and triple negative/ TNBC (Magklara, et al., 2015). Around 20%-40% of breast cancer patients are carriers of germline BRCA 1/2 mutation. Mutation in the BRCA1 gene is the main cause

Email: rizkavidyari92@unram.ac.id

of inherited breast cancer, but can also be involved in the process of cancer formation due to somatic mutations. BRCA1 (breast cancer gene)is a tumor suppressor gene that can maintain DNA integrity when mutation occur by repairing DNA damage and involved in regulating cellular activity (Sonnenblick, et al., 2014). Patients with BRCA1 mutations have a 45% to 85% chance of developing breast cancer. Although it only accounts for 20%-40%, breast cancer with BRCA1 mutation is known to have poor tumor characteristics, 80% of tumors are invasive ductal cancers that do not have a specific type so that they are similar to noncarriers (Ferlay, J. et al., 2019). Most of BRCA1 breast cancers are high-grade histological tumors (Wen & Chee-Onn, 2019). In addition, this mutation is found in every cell and can be inherited from one generation to another. Breast cancer with BRCA1 mutation is more common at young age with high proliferation index and can develops faster than the older age (Eun-Kyu Kim, 2020). In an effort to assess and evaluate the BRCA1 expression profile in breast cancer patients, this study aims to analyze the frequency of BRCA1 expression distribution based on the age and domicile of the patient.

Materials and Methods

This is a descriptive observational with cross sectional study design. A total of 50 FFPE (Formalin Fixation and Paraffin Embedding) of breast cancer tissue were examined for BRCA1 status using immunohistochemistry techniques. Samples were obtained from the medical records of the Anatomical Pathology Laboratory of the NTB Provincial Hospital. The results of BRCA1 status and its distribution by age and domicile in this study are categorical data that will be analyzed descriptively in the form of frequency and proportion. The relationship between BRCA1 expression with age and domicile will be analyzed using chi-square. All data are processed using the SPSS statistical analysis program with a 95% confidence interval and a significance limit (p values) <0.05.

Result and Discussion

Examination of BRCA1 expression with Immunohistochemistry method

BRCA1 expression examination was performed using the immunohistochemistry (IHC) method. Based on the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines (2013), BRCA1 expression is considered positive if there are >20% brown-stained tumor cells in the nucleus. While BRCA1 expression is considered negative if <20% brown-stained tumor cells are found in the nucleus. (**Figure 1).**

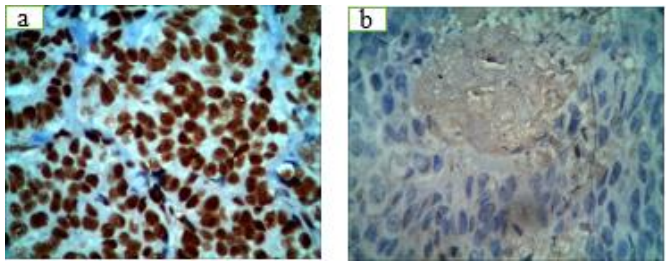

Figure 1. Immunohistochemical staining with anti-BRCA1 antibody in breast cancer tissue at 400x magnification. a) Positive expression of BRCA1 expression, b) Negative expression of BRCA1 expression.

Positive BRCA1 expression indicates cells still have BRCA1 protein that is able to work and regulate a number of important cellular mechanisms (Park, M. et al., 2022). Generally, positive BRCA1 expression is found in patients who are likely to get breast cancer at a young age. BRCA1 can regulate the process of breast cell proliferation by interacting with estrogen receptors, this is closely related to patient survival rates not only in hereditary breast cancer but also in sporadic breast cancer (Chang et al., 2022). Conversely, decreased BRCA1 expression, either due to germline mutations in hereditary breast cancer or hypermethylation in sporadic breast cancer, can increase the risk of breast cancer in women at younger age. Several previous studies have shown that lower levels of BRCA1 expression as a tumor suppressor gene are associated with poor prognosis (Darbeheshti et al., 2018). On the other hand, the presence of somatic mutations or hypermethylation in the BRCA1 gene promoter can cause decreased BRCA1 expression in sporadic breast cancer cells with histological features similar to hereditary breast cancer.

Distribution of BRCA1 Expression, Age, and Domicile in Breast Cancer Patients

This following table is the frequency distribution of BRCA1 expression, age, and domicile in breast cancer patients in West Nusa Tenggara.

Table 1. Frequency Distribution of BRCA1 Expression, Age, and Domicile in Breast Cancer Patients

Parameters	Number	%
BRCA1 Expression	**n= 50**	
Positive	25	50%
Negative	25	50%
Age	**n= 50**	
<40 y.o	22	44%
≥40 y.o	28	56%
Domicile	**n=50**	
Mataram	6	12%
Lombok barat	7	14%

Lombok Tengah	6	12%
Lombok Timur	15	30%
Sumbawa	6	12%
Bima	5	10%
Dompu	5	10%

Based on table 1, it is known that the number of breast cancer patients with negative and positive BRCA1 expression is 50% each. Breast cancer patients at age ≥40 years are 28 (56%) and breast cancer patients at age <40 years are 22 (44%). Mataram has 6 (12%) cases of breast cancer, West Lombok has 7 (14%) cases, Central Lombok has 6 (12%) cases, East Lombok has 15 (30%) cases. Sumbawa has 6 (12%) cases, Bima and Dompu have 5 (10%) cases. Data from the NTB Provincial Health Office in 2021 and 2022 shows that East Lombok is the area with the highest breast cancer cases compared to other areas in West Nusa Tenggara.

Frequency Distribution of BRCA1 Expression by Age

Based on Table 2, it is known that the number of breast cancer patients with positive BRCA1 expression was found at the age of <40 years (40.9%) and ≥40 years (57.1%). While breast cancer patients with negative BRCA1 expression were found at the age of <40 years (59.1%) and ≥40 years (42.9%). BRCA1 mutation can increase the risk of breast cancer at young age (<40 years: 59.1%). Research data conducted by Kara et al, 2015 showed that as many as 10-20% of women with breast cancer (diagnosed before the age of 40) have mutations in the BRCA1/2 gene. This mutation can worsen the condition of breast cancer patients because there is progressive growth of cancer cells which can increase the risk of metastasis. Patients diagnosed with invasive breast cancer aged 18–40 years are mostly BRCA1/2 mutation carriers, have a poor prognosis and high mortality rate (Copson et al., 2018).

Table 2. Frequency Distribution of BRCA1 Expression by Age

Parameters	**BRCA1 Ekspression Status**		**Number (%)**
Age	**Positive**	**Negative**	
<40 y.o	9 (40,9%)	13 (59,1%)	22 (100%)
≥40 y.o	16 (57,1%)	12 (42,9%)	28 (100%)

Frequency Distribution of BRCA1 Expression by Domicile

Based on Table 3, it is known that the highest positive and negative BRCA1 expression was found in East Lombok district. Negative BRCA1 expression was found in all patients from Central Lombok district. The results of medical records of all patients with negative BRCA1 expression in both areas were aged <45 years. This strengthens the theoretical basis that BRCA1 mutation breast cancer tends to be found at young age (Chen, Y. et al., 2021). The incidence of breast cancer with BRCA1 mutations in a region is known to be closely related to the incidence of breast cancer in the family history, consequently this gene can be inherited. East Lombok is known to be the area with the highest incidence of breast cancer in NTB followed by Central Lombok. Although changes in the nature of the BRCA1 gene are only 0.2%-0.3% or around 1:400 of a population. However, in certain populations with geographical and cultural conditions, changes in the BRCA1 gene and the incidence of mutations can be higher (National Comprehensive Cancer Network/NCCN, 2024).

Table 3. Frequency Distribution of BRCA1 Expression by Domicile

Parameters	**Status Ekspresi BRCA1**		**Total (%)**
Domisili	**Positif**	Negatif	
Mataram	4 (66,7%)	2 (33,3%)	6 (100%)
Lombok barat	4 (57,1%)	3 (42,9%)	7 (100%)
Lombok Tengah	0(0%)	6 (100%)	6 (100%)
Lombok Timur	9 (60,0%)	6 (40,0%)	15 (100%)
Sumbawa	5 (83,3%)	1 16,7%)	6 (100%)
Bima	1 (20,0%)	4 (80,0%)	5 (100%)
Dompu	2 ((40,0%)	3 ((60,0%)	5 ((100%)

Further examination is needed regarding whether the breast cancer is inherited or sporadic to determine whether the disruption of BRCA1 expression occurs due to mutation/hypermethylation or disruption of other gene functions involving BRCA1.

Conclusion

Breast cancer with high negative BRCA1 expression was found at age <40. Patients with negative BRCA1 expression are mostly found in Central Lombok and East Lombok districts. Early detection of BRCA1 mutations needs to be done especially in young women with early onset breast cancer to facilitate the selection of relevant treatment or prevention for women at risk of breast cancer.

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