

Human Epidermal Growth Factor Receptor-2 Expression in Ductal Invasive Carcinoma Mammariae In Correlation With Patients' Age and Tumor Differentiation

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ABSTRACT

Introduction: Breast cancer (BC) is a category of disorders in which the breast cells alter and develop uncontrolled. While most breast cancer risk factors are under our control, cancer cells can spread to other body parts when they reach the blood or lymphatic system. Activation of the human epidermal growth factor receptor 2 (HER2), activation of hormone receptors, and BRCA mutations are all molecular features of breast cancer.

Purpose: This study intended to evaluate the association of patient profiles to HER2 expression and the role of HER2 in predicting the degree of differentiation of breast cancer.

Method: The study was a descriptive-analytic study that enrolled 178 patients with invasive ductal breast cancer in Makassar. Data collection contains anamnesis of the patient's demographic information, clinical history, any supportive investigations performed, and the findings of immunohistochemistry testing, then analyzed using the Fisher exact test.

Results: There was a significant association between tumour differentiation and HER2 expression in breast cancer patients as evaluated by immunohistochemistry ($p=0.011$).

Additionally, no association was identified between age and HER2 expression ($p=0.057$).

Conclusion: These results suggest that the more advanced the tumours, the more biomarkers are generated. On the other hand, age does not affect the development of cancer.

Keywords: Breast cancer, HER2 expression, patient's profile

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INTRODUCTION

Breast cancer is a class of diseases in which the breast cells proliferate and change improperly, resulting in a lump or tumour. Breast cells multiply and alter abnormally, resulting in a lump or tumour. Breast cancers can develop in the lobules and ducts of the breast.¹ Breast cancer is the most frequent in women worldwide, and it is curable in 70% to 80% of cases. According to the current updates, advanced breast cancer spread to other body parts is considered a malignant tumour.²

Certain significant breast cancer risk factors are uncontrollable. Age is second only to gender in predicting

breast cancer risk. According to several researches, most breast cancers occur in women over 55. Men and women who have had their chests irradiated for another kind of cancer, heavy alcohol use, hormone replacement therapy (HRT), extreme overweight or obesity are other risks that cause the breast tumour.³

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Breast cancer spreads to other body regions via the circulatory or lymphatic systems. Lymph veins drain the breast of lymph fluid. Breast cancer cells can enter lymph veins and increase lymph nodes. If cancer cells reach your lymph nodes, they are more likely to spread to other body regions via the lymph system (metastasized). However, not all women with lymph node cancer develop metastases.⁴

Breast cancer is a complex disease involving molecular indicators such as HER2 activation, hormone receptor activation (oestrogen and progesterone receptors), and BRCA mutations.² Furthermore, the biological features of breast cancer change in terms of histologic type between younger and older women, but not in terms of hormone receptor expression.⁵

Around 30% of breast cancer patients have a palpable mass, dimpling, orange-peel look, redness colour, variable nipple discharge, swelling, blisters, excoriations, and nipple retraction. Diastasis ducti stellata (DCIS) is a collection of non-invasive, non-infiltrating tumours that the most frequent kind of breast cancer is IDC. 70% of IDC women have positive hormone receptors but negative HER-2. DCIS is further subclassified based on appearance, location, and cytological characteristics.⁶

Breast cancer is often identified mainly based on its histopathological appearance, emanating from the ducts' inner lining epithelium or the lobules that feed the ducts with milk.⁷ A typical histopathology slide comprises around 15x15 mm² of tissue. Segmentation of nuclei in histopathology pictures of breast cancer might be regarded as a fundamental functional block in various applications. Numerous research has already mentioned quantifying IHC nuclear staining. The degree of structural differentiation of the tissue, along with nuclear pleomorphism, is one of the early prognostic indications for breast cancer patients recognized by pathologists. The assessment of tumour development is almost definitely the most important and prognostically significant.⁸

A technique for classifying breast biopsy pictures stained with haematoxylin and eosin is proposed using Convolutional Neural Networks (CNNs).⁹ The images are divided into four categories: normal tissue, benign lesion, in situ carcinoma, and invasive carcinoma, as well as two subcategories: carcinoma and non-carcinoma. Computer-aided diagnosis solutions add to the process's cost reduction

and efficiency enhancement.¹⁰

The accumulation of knowledge about the pathophysiologic processes behind breast cancer has resulted in a dramatic increase in the number of biomolecular markers. Furthermore, because breast cancer is the most common kind of tumour globally, it remains a global public health concern. Breast cancer detection and screening have been assisted by breast cancer awareness, public awareness, and breakthroughs in breast imaging.¹¹

This study aimed to determine the relationship between patient characteristics and HER2 expression and the significance of HER2 in predicting breast cancer differentiation. The findings of this study are expected to become a source of information for the public in breast cancer prevention initiatives.

MATERIAL AND METHOD

It was cross-sectional descriptive-analytic research. The study involved 178 patients in Makassar who met the following criteria: invasive ductal breast cancer, full medical record, and no concomitant condition. Data collection includes patient demographics, clinical history, a history of any supporting investigations, and immunohistochemistry results. In addition, tables and narratives were used to show the relationships between the qualities studied.

RESULTS

Table 1. Sample characteristic

Characteristic	N	%
HER2 expression		
• Negative (0 dan +1)	74	41.6
• Positive (+2 dan +3)	104	58.4
Cancer differentiation		
• <i>Well Differentiated</i>	24	13.5
• <i>Moderately Differentiated</i>	87	48.9
• <i>Poorly Differentiated</i>	67	37.6
Age		
• 26-35 years	24	13.5
• 36-59 years	118	66.3
• >60years	36	20.2

According to Table 1, 74 samples (41.6 %) of patients were HER2 negative, whereas 104 samples were HER2 false positive (58.4%). Breast cancer was most prevalent in the moderately differentiated group (48.9%) and in women with 36-59 years old aged (66.3%).

The statistical analysis of data generated showed a strong

Table 2. Correlation between HER2 expression with age and degree of breast cancer.

Characteristic		HER2 expression		p-value*
		Negative	Positive	
Cancer differentiation	<i>Well Differentiated</i>	17 (70.8%)	7 (29.2%)	0.011
	<i>Moderately Differentiated</i>	38 (43.7%)	49 (56.3%)	
	<i>Poorly Differentiated</i>	19 (28.4%)	48 (71.6%)	
Age	21-35 years	15 (62.5%)	9 (37.5%)	0.057
	36-59 years	43 (36.4%)	75 (63.6%)	
	> 60 years	16 (44.4%)	20 (55.6%)	

*Uji Fisher-exact, sig<0.05

correlation between the degree of cancer differentiation and the expression of HER2 in breast cancer patients as determined by immunohistochemistry. This suggests that the more advanced the tumours, the more biomarkers are generated. On the other hand, there was no correlation between age and HER2 expression. This suggests that age does not affect the development of cancer.

DISCUSSION

Relationship between degrees of breast cancer differentiation and HER2 expression.

Breast cancer is not a single disease, but a collection of distinct tumours and increased HER2 expression is associated with a very aggressive subtype. Clinical outcomes of individuals with identical clinical and pathological features treated similarly may exhibit significant variances. This fact shows that the prognostic and predictive criteria that have been utilized to guide therapy selection in previous years should be personalized.¹²

In this study, we found that the high level of HER2 expression is directly associated with the degree of differentiation of breast cancer; the higher HER2 level will worsen cancer differentiation ($p=0.011$), which is also shown in figure 1.

HER2 is classified as an epidermal growth factor (EGF) receptor, along with three other erb receptors: epidermal growth factor receptor 1 (HER1, erbB1), HER2 (erbB2), HER3 (erbB3), and HER4 (erbB4) (erbB4).¹³ This molecule regulates various physiological processes via epidermal growth factors, including cell proliferation, survival, and apoptosis.¹⁴

This gene produces a 185-kDa transmembrane protein growth factor receptor with cytoplasmic tyrosine kinase activity that conveys growth-regulating signals. Within

each tumour cell nucleus, the HER2 gene is amplified twofold to twentyfold relative to the chromosome 17 copy number. The HER2 gene increases protein expression. In addition, tumour cells have up to 2 million HER2 molecules per cell instead of the usual 20,000, which increases receptor activation, signalling, uncontrolled cell division and tumour formation.¹⁵

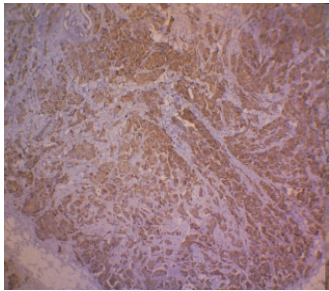
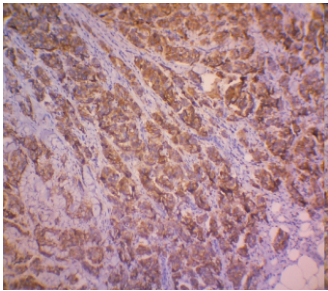
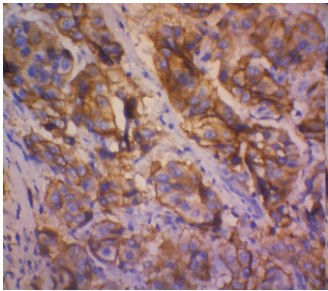
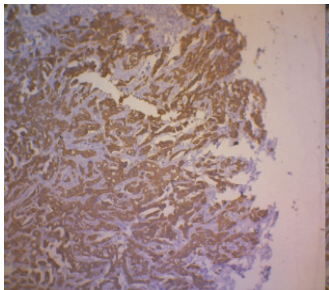
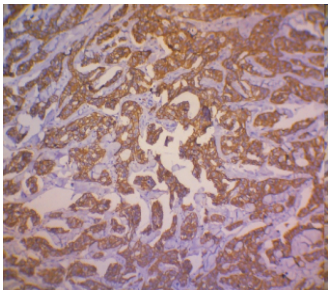
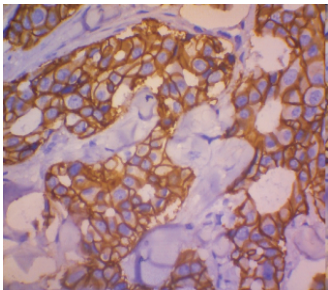
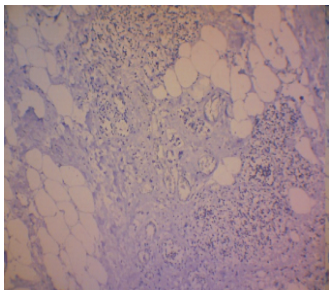
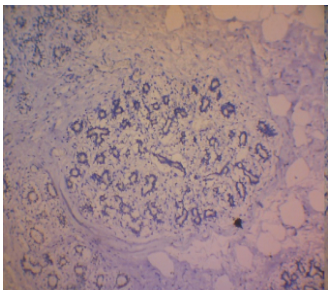
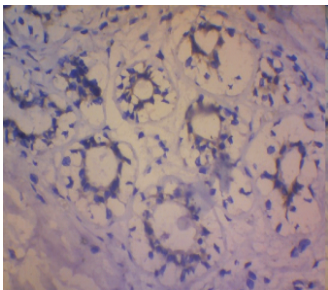
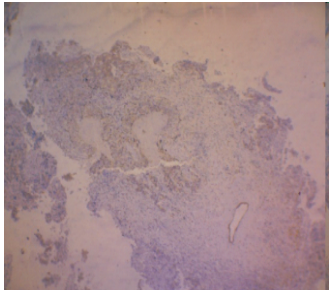
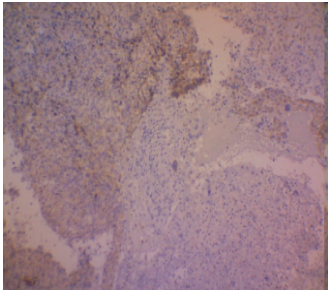
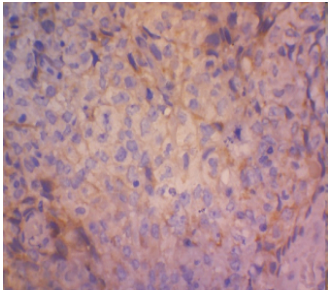
HER2 promotes the growth and survival of the primary tumour and distant lesions, which result in metastases upon complete transformation.¹⁶ Around 20%30% of breast cancer tumours overexpress HER2. It is associated with a more aggressive form of the illness, a greater likelihood of recurrence, and an increased risk of death. HER2 mutations act similarly to HER2 amplification as effective carcinogenic drivers. The activation of the human epidermal growth factor receptor 2 (HER2) functionally has been demonstrated to promote carcinogenesis significantly, prompting the research of HER2-directed therapies in malignancies with HER2 genetic mutations.¹⁷

When the HER2 gene is amplified, or HER2 expression is elevated, the HER family of receptors and their accompanying signalling pathways play a critical role in cell growth and survival.¹⁸ HER2 expression increased metastasis development, resulting in a decreased survival rate in mice with heterogeneous HER2 expression.¹⁹ To identify patients who may benefit from focused curative treatment, researchers can employ HER2 expression as a prognostic and predictive biomarker. (20)

Relationship of age and HER2 expression

In this study, the breast cancer progression with HER2 expression adjusted by the patient's age did not show a significant correlation based on the statistical result ($p=0.057$). However, most HER2-positive cases were in the 36 to 59-year age group. The findings are similar to some

FIGURE 1. HER2 EXPRESSION BASED ON AGE

HER2 EXPRESSION	GROUP	OBJECTIVE MAGNIFICATION		
		4X	10X	40X
POSITIVE (+)	YOUNG WOMAN			
	OLD WOMAN			
NEGATIVE (-)	YOUNG WOMAN			
	OLD WOMAN			

published data, which reported an increasing incidence of young breast cancer patients in recent years. More than two million women were diagnosed with BC in 2020, accounting for 11.7% of malignant neoplasms. In Indonesia, about 65,858 (16.6%) cancer patients are diagnosed with breast cancer, with 22,430 deaths.²¹

Recent research has revealed a surge in premenopausal women's occurrence. Aravind et al. (2021) revealed that the incidence of breast cancer in young Indian women is related to aggressive histology and loss of estrogen and progesterone receptor expression.²² According to Clarke et al. (2012), black women have a higher breast cancer incidence than white women until they reach the age of 40, while white women have a lower incidence after that (black-white crossover). The primary reasons for the black-white crossover are the high prevalence of triple-negative breast cancer in younger black women and the high rates of HR+/HER2 breast cancer in elderly white women.²³ It is also consistent with research conducted by Tagliabue (2021) on 8831 breast cancer patients, which revealed that the age range 50-69 years was the most prevalent (41.7%). In 5735 instances, the molecular subtype HER2/HR+ was the most prevalent (66.2%), while HER2+/HR- was the least prevalent (6.2%).²⁴

Even though HER2 expression was not linked to age in this investigation, numerous studies found that younger age was linked to a worse result in hormone receptor-positive subset treatment.²⁵ It could be concluded that age is a significant risk factor for breast cancer and has become an important issue to provide better care and survivorship of the patients.²⁶

CONCLUSION

Most patients in this study had breast cancer with HER2 positive, moderately differentiated histological degrees and were adults (32-59 years). It is also known that high HER2 expression correlates with breast cancer differentiation, whereas age has no association with HER2 expression.

Conflict of Interest: None

Funding: None

Written informed consent: Taken

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