

Evaluation of HER 2-overexpression Status in Breast Cancer Patients: Results From a Breast Cancer Registry

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Research

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Abstract

Background: The expression level of HER2 gene is low in normal breast tissue, but levels of these receptors are higher in half of cases of breast cancer. Different expression levels of HER2 gene in normal and malignant cells have made this gene an ideal biomarker for therapeutic purposes. In this study, the extent of HER2 overexpression and its relationship with the age and the occurrence of metastasis were evaluated in breast cancer patients.

Methods: In this cross-sectional study, 62 patients with breast cancer were evaluated at oncology clinics in Ilam province. Clinical examination for metastasis, examination of tissue samples for HER2 gene expression, and information related to variables were recorded in a breast cancer registry. The obtained data were analyzed using SPSS 20 statistical software by appropriate statistical tests.

Results: The mean age of the participants was 48.37 ± 10.98 , and 98.4% were women. The prevalence of increased HER2 gene expression was 37.1% in patients. There was an inverse relationship between patients' age and HER2 positivity (P value = 0.02). The chance of metastasis was 9 times higher (OR = 9.82) in cancer patients who had the HER2 gene expression

Conclusion: In Ilam province, the prevalence of HER2 positivity in breast cancer patients is almost similar to other parts of the country and is associated with the occurrence of metastasis and low age of breast cancer patients.

Background

Breast cancer is one of the most common types of malignancy in the age group of 45–55 years and the second leading cause of cancer death after lung cancer (1). Annually, more than 1,100,000 women are affected by breast cancer in the world (2–4). Many factors, such as proliferative breast lesions, radiation history, menstrual status, and pregnancy, have been suggested as risk factors for breast cancer. The status of some biomarkers (Ki67 HER2, PR, and ER) is effective in the prognosis and treatment of breast cancer (5).

One of the most important biomarkers is HER2 oncogene, which is a part of the message path (Signal Transduction Pathway). This protein is involved in the cell growth and plays a key role in the shift towards malignancy (6, 7). Different expression levels of HER2 gene in normal and malignant cells have made HER2 to act as an ideal biomarker for therapeutic purposes (3, 8). There are different methods to evaluate the expression of HER2 gene, such as measuring IHC of HER2 receptor, finding duplication of HER2 gene using FISH or PCR methods, and examining the extracellular amount of HER2 released into the blood by ELISA (9). Among these, the IHC method is superior to the other ones due to the ease of operation and low price.

An increased focus on quality indicators and the use of clinical registries for breast cancer in real world studies have shown higher compliance to recommend the therapy and better survival.

The HER2 gene is important in the prognosis and treatment of patients with breast cancer, which is highly prevalent in Iran and the world. Therefore, because no study has been done on the overexpression of HER2 gene in Ilam province, this study aims to determine the rate of HER2 overexpression in breast cancer patients and the relationship between the expression of this gene and the rate of metastatic patients with breast cancer.

Materials And Methods

This analytical-descriptive study was performed with focus on the use of clinical registries for breast cancer in 2020.

In order to carry out this research, the necessary permission was obtained from the Vice Chancellor for Research of Ilam University of Medical Sciences. (Code ethical: IR.MEDILAM.REC.1398.194)

Inclusion criteria were patient satisfaction, confirmed breast cancer in the pathology report, access to tissue samples, and absence of malignancy in other organs of the body. Exclusion criteria were patient dissatisfaction at each stage of the study and destroyed tissue samples. Tumor grade was statistically analyzed based on the age, histopathological diagnosis, tumor size, and lymph node involvement. Data collected from patients and those of examined tissue samples were analyzed by SPSS software version 20 at a significance level of $P < 0.05$. It should be noted that all ethical standards were observed in this study based on the Helsinki statement. Besides, patient information was maintained in a confidential manner, and the results and final information were published in the groups.

Results

The mean age of participants was 48.37 ± 10.98 . Overall, 98.4% of patients were women, and 18 (3.6%), 51 (10.3%), 61 (12.3%), 54 (9.10%), and 311 (68.2%) were in the age groups of under 20, 21-30, 40-31, 41-50, and 50 years and older, respectively (Table 1).

According to Table 1, most of the studied breast cancer patients had undergraduate and postgraduate education (33.9%), the majority were married (93.5%), and were mostly housewives (82.3%).

In this study, one of the patients did not report smoking, alcohol, or drug use. The prevalence of increased HER2 gene expression was 37.1% in patients. There was a direct relationship between the occurrence of metastasis and HER2 positivity and age (P value = 0.04). There was an inverse relationship between patients and HER2 positivity (P value = 0.01). The prevalence rates of ER and PR receptors in patients were 64.5% and 58.1%, respectively.

Metastases were observed in 83% of patients that presented the expression of her2 gene (Table 2).

Only the HER2 variable was significant among the age, PR, ER, and HER2 variables included into the model.

The chance of metastasis in cancer patients who showed the expression of HER2 gene was 9 times higher (OR=9.82) than that in HER2-negative patients (Table 3).

Discussion

Due to the increasing prevalence of breast cancer and the need for a special attention, this study examined one of the proto-oncogenes associated with this disease.

Overall, 37.1% of the breast cancer patients in this study were positive for the HER2 gene expression, which is consistent with the results of a study conducted in Tehran by Kadivar et al. (10).

However, 23.3% (11) in Isfahan, 32% (12) in Gilan, 13.6% (13) in Arak, and 30.8% (14) were reported in other studies by different researchers. It seems that the reason for the difference in the prevalence obtained in our study and the above studies is due to three factors of genetic differences in different races, different living environments, and, consequently, different levels of exposure to carcinogens and mutants and differences in how. It is clear that any report of the severity of HER2 overexpression in tissue samples depends on the operator and this may explain some of the differences in the prevalence rates in different studies.

Furthermore, evidence such as 32.1% (15) in Turkey, 16.1% (16) in Palestine, 32.3% (17) in Saudi Arabia, 15.6% (18) in Ivory Coast, 34.2% (19) in Japan, 17.6% (20) in Kenya, 21% (21) in Hong Kong, 20.9% (22) in Puerto Rico, and 17.5% (23) in Jordan shows that different percentages of the HER2 gene positivity have been expressed in these patients.

The relationship between patients' ages was examined in the present study. Breast cancer was also treated with the HER2 gene overexpression. According to the results, the rate of HER2 overexpression was directly related to the ages of the patients, which is similar to that of a study by Martinez et al. They reported that increased expression of the HER2 gene in patients under 50 years of age was more than that of patients over 50 years of age. In a study by Mirzaei et al.(24) in Tehran, however, no significant relationships were found between the HER2 gene positivity and the ages of patients. This difference in the results can be due to the selection of patients in the mentioned studies, where only patients with Infiltrating Ductal Carcinoma were present, while our study consisted of patients with all types of breast cancer.

In the present study, the positive association of the HER2 gene with the occurrence of metastasis was evaluated in the patients. Our study showed that the chance of metastasis in cancer patients who showed the HER2 gene expression was 9 times higher (OR = 9.82) than that in HER2-negative patients.

According to findings of Khudabakhshi et al. (25), the HER2 gene overexpression was directly related to the occurrence of metastasis in patients with breast cancer. In a study by Najafi et al., the chance of metastasis or death in HER2-positive patients was 2.64 times higher than that in HER2-negative patients, and more metastasis was found in breast cancer patients who were HER2 positive.

Findings of Mirzaei et al. showed that HER2 positive patients were exposed to higher-grade tumors. Despite the above three studies that confirmed the results of the present study, Naini et al. observed no relationships between the HER2 gene hypermethylation, tumor size, and grade with the disease stage. This can be caused by a low sample size (20 patients) in the latter study and the evaluation of only one type of breast cancer (invasive ductal carcinoma). In the present study, 62 patients were evaluated in terms of all types of breast cancer.

In this study, the rates of PR and ER receptors were examined in patients, 64.5% and 58.1% of which were ER and PR positive, respectively. The reported prevalence of these receptors were respectively 68.8% and 63.8% (Mirzaei et al.), 72.4% and 64.8% (Semnani et al., (14), 46.6% and 43.8% (Moradi et al.), 70% and 72.6% (Kuzhan et al., (15), and 75% and 59.5% (Khabaz). Accordingly, the rates obtained in most studies are similar to those of the present study, and the differences may be due to genetic and environmental factors.

Due to the high prevalence of increased HER2 gene expression in patients with breast cancer, its association with the occurrence of metastasis, and its special importance, future studies are recommended to investigate the effectiveness of drugs affecting this receptor.

The diagnosis of the HER2 gene overexpression through tissue sample examination is invasive and costly, on the one hand, and the diagnosis of this disorder is of vital importance in breast cancer patients, on the other hand. It is, therefore, recommended to find alternative methods to study tissue samples, such as examining the serum level of HER2, and comparing the sensitivity and specificity of these methods with the current method (histological examination).

Conclusion

According to the results of this study, the rate of increase in the HER2 gene expression is 37.1% in patients with breast cancer in Ilam province. Besides, the positiveness of this gene is associated with breast cancer at a younger age and the occurrence of metastasis in these patients. It is a weakening factor in the prognosis in these patients.

Abbreviations

-HER2; Human Epidermal Growth Factor Receptor Type2, ER; Oestrogen Receptor, PR; The progesterone receptor

Declarations

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Contribution:

HN developed and designed the evaluation, collected the clinical data (NM) and drafted the manuscript. HN, ESh and MB participated in the study conception and design, supervised the study and revised the manuscript critically for important intellectual contents. ESh revised the manuscript critically for important intellectual contents. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed in the current study are attained from the corresponding author on reasonable request.

Ethics approval and consent to participate

In order to carry out this research, the necessary permission was obtained from the Vice Chancellor for Research of Ilam University of Medical Sciences. (Code ethical: IR.MEDILAM.REC.1398.194). All ethical principles were considered in this article. The participants were informed about the purpose of the research and its implementation stages; they were also assured about the confidentiality of their information.

Consent for publication; Not applicable.

Competing interests: The authors declared no conflict of interest.

References

1. Berrian JL, Liu Y, Lian M, Schmaltz CL, Colditz GA. Relationship between insurance status and outcomes for patients with breast cancer in Missouri. *Cancer*. 2020.
2. Kaufman CS. ASO Author Reflections: Is Survival Sufficient? There's More to Address for the Breast Cancer Surgeon. *Ann Surg Oncol*. 2020.
3. O'Shaughnessy J, Brezden-Masley C, Cazzaniga M, Dalvi T, Walker G, Bennett J, et al. Prevalence of germline BRCA mutations in HER2-negative metastatic breast cancer: global results from the real-world, observational BREAKOUT study. *Breast Cancer Res*. 2020;22(1):114.
4. Samuel Eziokwu A, Varella L, Lynn Kruse M, Jia X, Moore HCF, Thomas Budd G, et al. Real-world Outcomes of Cyclin-dependent Kinase Inhibitors Continued Beyond First Disease Progression in Hormone Receptor-positive Metastatic Breast Cancer. *Clin Breast Cancer*. 2020.
5. Berg T, Jensen MB, Jakobsen EH, Al-Rawi S, Kenholm J, Andersson M. Neoadjuvant chemotherapy and HER2 dual blockade including biosimilar trastuzumab (SB3) for HER2-positive early breast cancer: Population based real world data from the Danish Breast Cancer Group (DBCG). *Breast*. 2020;54:242-7.

6. de Paula BHR, Kumar S, Morosini FM, Calabria Cardoso DEM, de Sousa CAM, Crocamo S. Real-world assessment of the effect of impact of tumor size on pathological complete response rates in triple negative breast cancer after neoadjuvant chemotherapy. *Chin Clin Oncol*. 2020.
7. Gui X, Li H, Yan Y, Zhang R. Efficacy of lapatinib combined with capecitabine in patients with HER2-positive metastatic breast cancer in a real-world study. *Oncol Lett*. 2020;20(6):378.
8. Dawood S, Konstantinova M, Perazzo F, Kim SB, Villarreal-Garza C, Franco SX, et al. Optimizing the management of HER2-negative metastatic breast cancer in the era of PARP inhibitors-proceedings from breast cancer expert group meeting. *Chin Clin Oncol*. 2020;9(5):61.
9. de Boer R, Hui R, Lim E, Yeo B, Zdenkowski N. Optimizing care for younger women with hormone receptor-positive, HER2-negative metastatic breast cancer. *Asia Pac J Clin Oncol*. 2020;16 Suppl 5:3-14.
10. Joulaei A, Joulaei S, Kadivar M, Hajibabaei FJInr. Living with breast cancer: Iranian women's lived experiences. 2012;59(3):362-8.
11. Mokarian F, Hashemi F, Moatamedi N, Ramezani MA, Mohajeri MR, Abdeyazdan N, et al. Investigation of Prognostic Factors in Breast Cancer and their Relationship with Age and Cancer Stage. 2012;30(193).
12. Najafi B, Fakheri TJJoGUoMS. Relationship of HER-2 with other clinical-pathological diagnostic criteria in breast cancer patients. 2006;15(57):21-7.
13. Moshfeghi K, Almasi Hashiani A, Motezaker JJTIJoO, Gynecology, Infertility. The relationship between HER2-overexpressing and incidence of breast cancer recurrence. 2014;17(100):10-5.
14. Semnani V, Farhidzadeh E, Mirmohammadkhani M, Ghahremanfard FJK. Investigation of blood levels of vitamin D in women with breast cancer and its correlation with prognostic markers. 2017:735-41.
15. Kuzhan A, Adli M, Alkis HE, Caglayan DJO. Hormone receptor and HER2 status in patients with breast cancer by races in southeastern Turkey. 2006;2012.
16. Khaled H, Salem B, Omar A-s, Omar H, Fuad S, Jerusalem PJPAJoO. Prevalence of hormonal receptors ER, PR and HER-2 NEW in breast cancer cases in Palestine. 2009;2(3):28-31.
17. Khabaz MNJAPJCP. Immunohistochemistry subtypes (ER/PR/HER) of breast cancer: where do we stand in the West of Saudi Arabia. 2014;15(19):8395-400.
18. Effi AB, Kouli BS, Koffi KD, Traore ZC, Kouyate MJAPJoCP. Breast cancer molecular subtypes defined by ER/PR and HER2 status: Association with clinicopathologic parameters in ivoirian patients. 2016;17(4):1973-8.
19. Luangxay T, Virachith S, Hando K, Vilayvong S, Xaysomphet P, Arounlangsy P, et al. Subtypes of Breast Cancer in Lao PDR: A Study in a Limited-Resource Setting. 2019;20(2):589.
20. Sayed S, Moloo Z, Wasike R, Bird P, Oigara R, Govender D, et al. Is breast cancer from Sub Saharan Africa truly receptor poor? Prevalence of ER/PR/HER2 in breast cancer from Kenya. 2014;23(5):591-6.

21. Yau T, Sze H, Soong IS, Hioe F, Khoo U, Lee AWJHKMJ. HER2 overexpression of breast cancers in Hong Kong: prevalence and concordance between immunohistochemistry and in-situ hybridisation assays. 2008.
22. Ortiz AP, Frías O, González-Keelan C, Suárez E, Capó D, Pérez J, et al. Clinicopathological factors associated to HER-2 status in a hospital-based sample of breast Cancer patients in Puerto Rico. 2010;29(3):265.
23. Sughayer MA, Al-Khawaja MM, Massarweh S, Al-Masri MJP, Research O. Prevalence of hormone receptors and HER2/neu in breast cancer cases in Jordan. 2006;12(2):83-6.
24. Mirzaei H-R, Sabahat A, Nasrollahi F, Mohammadi-Yeganeh LJP. Correlation between ER, PR, HER2 receptors and prognostic factors in breast cancer. 2010;15(4).
25. Khodabakhshi R, Reza Gohari M, Moghadamifard Z, Foadzi H, Vahabi NJRJoMS. Disease-Free Survival of Breast Cancer Patients and Identification of Related Factors. 2011;18(89).

Tables

Table 1: Demographic characteristics of the participants in the study

Variable		N (%)
Gender	Female	1(1.6)
	Man	61(98.4)
(year) Age	≥ 20	2(3.2)
	30-40	16(25.8)
	41-50	19(30.6)
	50-60	19(30.6)
	60 ≥	6(9.7)
Education	Illiterate	17(27.4)
	Less than a diploma	19(30.6)
	Diploma	21(33.9)
	Associate degree	5.7(8.1)
Marital status	Single	4(6.3)
	Married	58(93.5)

Table 2: Distribution of PR and ER receptors in breast cancer patients in the study

variable		Metastasis		P-value
		No	Yes	
HER22	Negative	38(67.9%)	1(16.7%)	0.22
	Positive	18(32.1%)	5(83.3%)	
ER	Negative	21(37.5%)	1(16.7%)	0.29
	Positive	35(62.5%)	5(83.3%)	
PR	Negative	24(43.6%)	1(16.7%)	0.20
	Positive	31(56.4%)	5(83.3%)	

Table 3: Results of logistic regression model

Variables	B	S.E.	Wald	df	Sig.	Exp. (B)
HER22	2.285	1.206	3.588	1	.058	9.826
Constant	-3.762	2.931	1.648	1	.199	.023

a. Variable(s) entered on step 1: age, HER22, ER, and PR.