Original Article

Relationship of HER-2 Overexpression with Size and Stage of Tumor in Patients with Primary Breast Carcinoma

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Abstract

Background: *Receptor study for carcinoma breast is now a common practice before neoadjuvant therapy. Human Epidermal growth factor Receptor 2 (HER2) overexpression acts as a predictive marker of tumor aggressiveness.*

Objective: *To determine the association of HER-2 overexpression in relation to tumor size and stage of breast carcinoma.*

Materials and Methods: *A cross sectional study was carried out in SSMC & Mitford Hospital from July 2008 to June 2010. 52 patients with primary breast carcinoma were selected. Clinical features and histopathological findings were studied. Size, stage and overexpression to HER-2 receptor were the primary variables. Chi-square test, Mann Whitney test and Odds Ratio were performed for data analysis.*

Results: *Out of 52 patients, 38.5% were 41 – 50 years of age, and nearly 60% of the patients were in the premenopausal state. Over half (51.9%) of the patients had a history of contraceptive use and 21.1% of the patients had a family history of breast cancer. Overexpression of HER-2 (56.3%) was found to be significantly associated with lymph node positivity (p = 0.005). 52.6% of the advanced stage (stage IIIa – stage IV) tumors had overexpression of HER-2. 57.1% of tumor ≥5cm exhibited overexpression of HER-2 as opposed to only 16.7% of the tumor <5cm (p = 0.031). The risk of having HER-2 amplification was estimated to be 5-fold (95% CI = 1.3 – 18.6) higher in patients with larger tumors.*

Conclusion: *In primary breast carcinoma with larger tumor and in stage III-IV are more often associated with HER-2 overexpression. So, patients in these group will be benefited from immunotherapy.*

Keywords: *Primary Breast Carcinoma, Her-2 Overexpression, Tumor size.*

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Introduction

Carcinoma of the breast is the most common malignancy of females all over the world. It is the second leading cause of death due to cancer among females and the fifth most common cause of cancer death.[1] In Bangladesh breast cancer is the second most common malignancy among women and the estimated incidence of breast cancer 17% .[2] An annual report of 2005 from the National Institute of Cancer Research and Hospital has shown that the frequency of breast cancer is 10.3% in all cases of malignancy and 24.3% in spite affecting female.[3]

Risk factors associated with breast cancer are long reproductive period, delay in first pregnancy, nulliparity etc. However, there may be a genetic component to breast cancer risk, there is also strong evidence that environmental factors play an important role. There may be ecological factors that determine breast cancer risks. The standard initial treatment for breast cancer is surgical resection of the tumor and radiation given to the breast and adjacent lymph nodes. Adjuvant therapy with Tamoxifen improves survival of treated cases. There is strong evidence that radiation and Tamoxifen therapies lessen recurrence following surgery. Metastatic disease is treated with radiation and/or chemotherapy and hormonal therapy to reduce local symptoms and to induce remission. Apart from all these treatments, HER-2 overexpressed metastatic breast cancer can be treated effectively and safely with trastuzumab as a single agent in 1st line treatment.[4]

HER-2 overexpression, a predictive marker of tumor aggressiveness and responsiveness to therapy, occurs in 20-30% of

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breast cancer. Although breast cancer is a heterogeneous disease, HER-2 measurement is carried out in primary tumor. Human epidermal growth factor receptor 2 (HER-2) over-expressed breast cancer is one of the subtypes of breast cancer that is gaining major interest with the discovery of targeted therapy as an effective treatment modality. The HER-2 gene is located on chromosome 17q. The HER-2 gene encodes a 185 kDa transmembrane phospho-glycoprotein with tyrosine kinase activity. HER-2 gene amplification is found in 10-35% of invasive breast cancer. Cells transfected with HER-2 acquire a more malignant phenotype as they are correlated with poor prognostic tumor characteristics eg. higher histological grade, advanced stage, increased tumor size, lymph node involvement, lympho-vascular invasion and lower ER expression. Amplification of the HER-2 gene is a significant predictor of both overall survival and time to relapse in patients with lymph-node-positive breast cancer.[5]

The HER-2 oncogene was first described in 1985 as a cell receptor of the tyrosine kinase gene family, with a primary sequence similar to the human epidermal growth factor receptor.[6] Another study later demonstrated that amplification of the HER-2 was a significant predictor of both overall survival and time to relapse in patients with breast cancer.[5] The prognostic impact of HER-2 overexpression was strongest in node-positive patients. In most studies, there seems to be no significant difference in the incidence of HER-2 overexpression between different ethnic groups. The current methods of determining overexpression of HER-2 in breast cancer is, immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH). HER-2 overexpression has been associated with tumor type, higher grade and hormone receptor negativity.[7] Other studies also showed that HER-2 overexpression was associated with large tumors and lymphovascular invasion.[8] This present study was intended to find the association of HER-2 over-expression in relation to stage and size of the tumor in patients with primary breast cancer, which would help the clinician in decision making for better management of breast carcinoma.

Materials and Methods

This cross-sectional study was conducted in the Department of Surgery, Sir Salimullah Medical College & Mitford Hospital over a period of two years from July 2008 to June 2010. Patients of breast carcinoma attending to receive treatment/evaluation for their breast carcinoma were the study population. Females of both pre and post-menopausal age group having primary breast cancer were in inclusion criteria. Patients who had already received immunotherapy or radiotherapy and recurrent breast cancer patients were exclude from this study. The sample size was calculated as 896. But during the study period, no more than 52 subjects were feasible to be included in the study. The demographic variables included in the study were age, socioeconomic status and residence. Clinical features of breast cancer and histopathological findings were also studied. Size, stage and overexpression of primary breast cancer were the primary variables. Tumor measuring 5 or more than 5 cm was termed as large sized tumor. According to the grading of immunohisto-chemical staining for HER-2 /neu over expression, score 0 to score 2+ was designated as not overexpressed, while score 3+ was designated as overexpressed or strongly positive. Data were processed and analyzed using SPSS. The test statistics used to analyze the data were descriptive statistics, Chi-square Probability Test, Mann Whitney Test and Odds Ratio with 95% confidence interval for Odds Ratio. For all analytical tests, the level of significance was set at 0.05 and $p < 0.05$ was considered significant.

Results

The present study was aimed at finding the association of HER-2receptor with stage and size of breast carcinoma. A total of 52 patients of female breast carcinoma were included in the study. The findings of the study are presented below.

Table I: Age distribution of the patients (n = 52)

Age (yrs)	Frequency	Percentage
≤ 40	19	36.5
41 – 50	20	38.5
51 – 60	07	13.5
> 60	06	11.5

Mean age = (45.8 12.6) years; range = (22 – 75) years Out of 52 patients, 36.5% was 40 or < 40 years old, 38.5% 41 – 50 years, 13.5% 51 – 60 years and 11.5% > 60 years old. The mean age of the patients was 45.8 ± 12.6 years and the lowest and highest ages were 22 and 75 years respectively. (Table I)

Table II: Distribution of patients by other pertinent characteristics (n = 52)

Pertinent characteristics	Frequency	Percentage
Reproductive status		
Premenopausal	31	59.6
Postmenopausal	21	40.4
H/O contraceptive use		
Yes	27	51.9
No	25	48.1
Family H/O breast cancer		
Present	11	21.2
Absent	41	78.8

Nearly 60% of the patients were in premenopausal state and the rest (40.4%) in postmenopausal state. Over half (51.9%) of the patients had history of contraceptive use and 21.1% of the patients had family history of breast cancer. (Table II)

Table III: Distribution of patients by characteristics of the tumor (n = 52)

Characteristics of the tumor	Frequency	Percentage
Tumorlaterality		
Right	21	40.4
Left	31	59.6
Location		
UOQ	37	71.2
UIQ	04	7.7
LOQ	04	7.7
LIQ	03	5.8
Central	02	3.8
Diffuse	02	3.8
Size of thetumor		
< 5 cm	36	69.2
≥ 5 cm	16	30.8

Tumor characteristics show that in about 60% of the cases left breast was involved and in 71.2% cases the lesion was found in the upper-outer quadrant of the breast. About 70% of the tumors were < 5 cm and the rest was 5 or > 5 cm in size. (Table III)

Table IV: Distribution of patients by clinical staging (n = 52)

Clinical staging	Frequency	Percentage
Stage -I	00	0.0
Stage -II	33	63.5
Stage -IIIa	15	28.8
Stage -IIIb	03	5.8
Stage -IV	01	1.9

Clinical staging of breast carcinoma shows that 63.5% had stage-II, 28.8% stage-IIIa, 5.8% stage-IIIb and rest 1.9% stage-IV disease.

Definition of staging according to category is stated below:
Stage-I: A breast lump of <2 cm in size but no palpable axillary lymph nodes (i.e. T1, N0, M0).
Stage-II: A breast lump of 2-5 cm in size with palpable but mobile axillary lymph nodes (i.e. T2, N1, M0).
Stage-IIIa: A breast lump of >5 cm in size with palpable and fixed axillary lymph nodes (i.e. T3, N2, M0.).
Stage-IIIb: Any size of the breast lump that invade the skin or chest wall with or without palpable ipsilateral supraclavicular lymph nodes, (i.e. T4, N3, M0).
Stage-IV: Any size of the breast lump with distant metastasis with or without palpable axillary lymph nodes (i.e Any T, Any N and M1). (Table IV)

Table V: Distribution of patients by HER-2 receptor status (n = 52)

HER-2 receptor	Frequency	Percentage
0	23	44.2
1+	10	19.2
2+	05	9.7
3+	14	26.9

According to HER-2 receptor status, 44.2% patients were found negative, 19.2% patients had HER-2 receptor status 1+, 9.7% 2+ and 26.9% 3+. Based on criteria of HER-2 over-expression (HER-2 3+), 14(26.9%) out of 52 patients were over-expressed and the rest (73.1%) was not over-expressed.
According to grading of the Immunohistochemical staining the following categories are:
score 0 = no staining or membrane staining in less than 10% of cells.
Score 1+ = a faint / barely perceptible membrane staining in more than 10% of cells. Cells are only stained in part of the membrane.
Score 2+ = weak to moderate complete membrane staining in more than 10% cells.
Score 3+ = strong complete membrane staining in more than 10% of cells. (Table V)

Table VI: Distribution of patients by histopathological diagnosis (n = 52)

Histopathological diagnosis	Frequency	Percentage
Invasive ductal carcinoma	48	92.4
Lobular carcinoma	02	3.8
Papillary carcinoma	01	1.9
Medullary carcinoma	01	1.9

Histopathological diagnosis demonstrates that majority (92.4%) of the patients had invasive ductal carcinoma, 3.8% lobular carcinoma, 1.9% papillary carcinoma and another 1.9% medullary carcinoma. (Table VI)

Table VII: Distribution of patients by histopathological findings (n = 52)

Histopathological findings	Frequency	Percentage
Differentiation		
Poorly differentiated	19	36.6
Moderately differentiated	31	59.6
Well-differentiated	02	3.8
Lympho-vascular invasion		
Present	13	25.0
Absent	39	75.0

Histopathological examination revealed that 36.6% of patients had poorly differentiated, 59.6% moderately differentiated and 3.8% well-differentiated cell type. One-quarter (25%) of the cases exhibited lympho-vascular invasion. (Table VII)

Table VIII: Association between HER-2over-expression and lymph node status.

HER-2	Lymph node status		χ^2	p-value
	Positive (n = 16)	Negative (n = 36)		
Overexpressed	9(56.3)	5(13.9)	8.065	0.005
Notoverexpressed	7(43.7)	31(86.1)		

Data were analyzed using Chi-square (x2).
Figures in the parentheses denote corresponding percentage.
Over 55% of the node positive breast carcinoma were overexpressed as opposed to 13.9% of the node negative disease. Over expression of HER-2was found to be significantly associated with lymph node positivity (p = 0.005) (Table VIII)

Table IX: HER-2overexpression and histopathological grading

Grading	HER-2		χ^2	p-value
	Overexpressed (n = 14)	Not overexpressed (n = 38)		
Poorly differentiated	7(50.0)	12(31.6)		
Moderately differentiated	7(50.0)	24(63.2)	1.984	0.371
Well- differentiated	0(0.0)	2(5.2)		

Data were analyzed using Chi-square (X^2).
Figures in the parentheses denote corresponding percentage.

HER-2 overexpression was not found to be associated with histopathological grading, although overexpression was considerably higher among poorly differentiated variety of tumor (p = 0.371). (Table IX)

Table X: Association between HER-2 overexpression and tumor size.

HER - 2	Size of tumor (cm)		p - value
	Median	Range	
Overexpressed	5.5	2.2–8.0	0.259
Not overexpressed	3.5	2.5–7.0	

Data were analyzed using **Mann Whitney Test** and were presented as **median (range)**
Comparison of size of tumor between patients of breast carcinoma with and without overexpression showed no significant difference between the groups (p = 0.259). (Table X)

Table XI: Risk of having over-expressed HER-2in patients with primary breast carcinoma with larger tumor size.

Tumor size(cm)	HER - 2		Odds Ratio (95% CI)	χ^2	p - value
	Overexpresse (n = 14)	Normal (n = 38)			
<5	6(16.7)	30(83.3)	5.0 (1.3–18.6)	4.676	0.031
≥ 5	8(57.1)	8(21.1)			

Data were analyzed using Chi-square (x2).
Figures in the parentheses denote corresponding percentage.

Fifty percent of the larger sized tumor (5 or > 5cm) exhibited over-expression of HER-2 as opposed to only 16.7% of the smaller sized tumor. The risk of having HER-2 over-expression was estimated to be 5 times (95% CI = 1.3 – 18.6) higher in patients with larger sized tumor than that in patients with smaller sized tumor.
Small sized tumor: Tumor measuring less than 5 cm was regarded as small sized tumor.
Large sized tumor: Tumor measuring 5 or more than 5 cm was termed as large sized tumor. (Table XI)

Table XII: Risk of having over-expressed HER-2 in patients of primary breast carcinoma with stage-IIIa to stage-IV

Stage	HER -2		Odds Ratio (95% CI)	χ^2	p-value
	Overexpressed (n = 14)	Not Overexpressed (n = 38)			
Stage I -II	4(12.1)	29(87.9)	8.0 (2.0 –32.0)	10.058	0.002
Stage III-IV	10(52.6)	9(47.4)			

Data were analyzed using Chi-square (x2).
Figures in the parentheses denote corresponding percentage.
More than 50% of the advanced stage (stage IIIa – stage IV) tumors had overexpression of HER-2 compared to 12.1% of the tumors of stage I – stage II. The risk of developing HER-2 over-expression was found to be 8 times (95% CI = 1.3 – 18.6) higher in patients with advanced stage tumor than that in patients with stage I-II (p = 0.002). (Table XII)

Discussion

The incidence of breast cancer varies greatly around the world; it is lowest in less-developed countries and greatest in the more-developed countries. Breast cancer is strongly related to age with only 5% of all breast cancers occur in women under 40 years old. However, it can occur in younger women. In this study, the demographic characteristics of patients showed that the mean age of the patients was 45.8 years and the youngest and oldest patients were 22 and 75 years old respectively. Nearly 60% of the patients were in premenopausal state and about 52% had history of contraceptive use. Left breast involvement was frequently common (60%) with predominant site of lesion being upper and outer quadrant (71.2%). Over 30% of the tumors were larger (5 or > 5 cm) sized. More than one-third of the patients presented with stage-III and stage-IV disease with node positivity being > 30%. HER-2 overexpression was not found to be associated with patient's reproductive status or histopathological grading but it demonstrated its significant presence in patients with node positive disease.
As breast cancer management requires consideration of several tumor-related factors, their correlation with other prognostic factors is important for clinicians. It is agreed in general that tumor size, number of lymph nodes and tumor grade are the most powerful predictors of prognosis. During the recent years over expression of HER-2/neu has provided another target for treatment of breast cancer using monoclonal antibodies.[9]
In the present study, HER-2/neu over-expression was 26.9% which is nearly consistent with the findings of a Malayan study in which over-expression was found to be around 31%.[10] In Pakistan it is reported to be 31% .[11] However, a much lower figure (18.1%) was reported by Ayadi.[12] in Tunisian patients with breast carcinoma. Node positive breast carcinoma were frequently overexpressed (56.3%) than the node negative disease (13.9%) (p = 0.005). As over-expression of HER-2 was compared between the larger and smaller sized tumors, more than 57% of the patients with HER-2 over-expression had tumor size 5 or > 5 cm as opposed to 21% of the patients without over-expression. The risk of having HER-2 over-expression was estimated to be 5-fold (95% CI = 1.3 – 18.6) higher in patients with larger tumor than that in patients with smaller tumor (p = 0.031). Although a number of observational studies including the present one demonstrated significant association of HER-2 with tumor size and stage, none these studies had scope of studying a cause and effect relationship and hence it was not possible to conclude whether HER-2 overexpression is an effect of larger size and advanced stage of the tumor or vice-versa. Aberrant signaling through these receptors is believed to play a direct role in malignant transformation and/or progression. Evidence obtained in model systems supports that progression of HER-2 amplified breast cancers is driven by HER-2 gene activity. When the level of engineered HER-2 expression in tumor cell lines mimics the disease state, important phenotypic changes are observed, including increased growth in vitro, decreased anti-estrogen response, increased production of angiogenic factors, as well as increased tumorigenicity and metastatic potential in vivo.[13-15]
Patients with HER-2-positive tumors have worse outcomes than those with HER-2-negative tumors, particularly when the estrogen receptor is also negative.[16] Therefore, assessing HER-2 over-expression in patients with primary breast cancer offers a number of advantages like assessing tumor aggressiveness, management options and prognosis. Amplification of the HER-2 gene is detected in approximately 25% of human breast cancers and this genomic alteration is predictive of poor clinical outcome.[17,18]

In a recent study by Harriet T. Rothschild et al.[19] shows for tumor size, number of positive nodes, ER/PR status, and local therapy received, patients with HER2-positive status had worse DFS than those with HER2-negative tumors (HR 2.0, 95% CI 1.0–4.1, p = 0.05). They also found HER2 positivity was significantly associated with a higher rate of pleomorphic ILC (invasive lobar carcinoma) when compared to HER2- negative and HER2-low cases (33% versus 9.8% and 9.9% respectively, p > 0.001). Another recent study by Joyce O'Shaughnessy[20] found HER2 over-expression occurs in 15% to 20% of patients with early-stage breast cancers. Without HER2-targeted therapy, 30% to 50% of patients relapse within 10 years, many developing incurable metastatic disease. Among HER2 + patients, larger tumor size was found to be a negative prognostic factor. In compare to our study we found similar result in larger tumor with HER-2 positive patients.

Conclusion

From the findings of the present study, it can be concluded that the majority of the patients of primary breast carcinoma with larger tumor size are more often associated with HER-2 overexpression than those with smaller tumors and stage I-II disease. As HER-2 overexpression is commonly found in larger size and advanced stage of primary breast cancer, this group of carcinoma cases will benefit from immunotherapy.

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