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Original Research Article

An observational study on the incidence of HER-2/neu receptor over-expression and comparison of clinical presentation between HER-2/neu positive and HER-2/neu negative breast cancer

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ABSTRACT

Background: Tumours that over express HER2/neu are less responsive to chemotherapy and patients with these tumours have a reduced survival compared with patients with normal levels of HER2/neu. The aim was to determine the frequency of HER-2/neu receptor over-expression in Breast cancer patients and its comparison to Her-2/neu negative breast cancer in respect to clinical presentation, risk factors, clinical staging, pathological staging.
Methods: 50 patients who presented with Invasive ductal carcinoma of breast, meeting inclusion and exclusion criteria were included in the study. They were divided into two groups; according to Her-2/neu receptor over-expression (Yes/No).Incidence of Her-2-neu receptor over-expression was determined among the sample population. Both groups were compared on the basis of various parameters.
Results: Young age at presentation, negative hormone receptor status (ER/PR), high grade of tumour, large sized tumour and increased axillary lymph nodes are more common in Her-2/neu over-expression patients. These parameters are statistically significant.
Conclusions: Her-2/neu overexpressing breast cancers have increased invasive and metastatic capability and are less responsive to chemotherapy. They have increased risk of recurrence and patients with these tumours have a reduced survival compared with patients with normal levels of HER2/neu.

Keywords: Breast cancer, Chemotherapy, HER-2/neu receptor

INTRODUCTION

Breast cancer originates most commonly from the inner lining of milk ducts or the lobules that supply the ducts.[1] Cancers originating from ducts are known as ductal carcinomas, while those originating from lobules are known as lobular carcinomas. Carcinoma breast is the commonest malignancy of females all over the world and second leading cause of death due to cancer among females. Worldwide, breast cancer accounts for 22.9% of all cancers (excluding non-melanoma skin cancers) in women.[2] Prognosis and survival rates for breast cancer vary greatly depending on the cancer type, stage, treatment, and geographical location of the patient.

The proto-oncogene HER-2/neu (C-erbB-2) has been localized to chromosome 17q and encodes a transmembrane tyrosine kinase growth factor receptor. The name for the HER-2 protein is derived from human epidermal growth factor receptor, as it features

substantial homology with the epidermal growth factor receptor (EGFR).[3,4]

HER-2/neu protein is a component of a four-member family of closely related growth factor receptors, including EGFR or HER-1 (erb-B1); HER-2 (erb-B2); HER-3 (erb-B3) and HER-4 (erb-B4)5. Amplification of the HER-2 gene or over-expression of its protein product is present in 25% to 30% of breast cancers.[6,7]

This study plans to co-relate Her- 2/ neu receptor positive breast carcinoma with the history of presentation of the disease, clinical staging, histopathological staging and aggressiveness of the disease in context to eastern Indian population.

The aim of the study was to determine the incidence of Her-2 /neu over-expression (defined as Her-2-positive +++ on IHC), to compare risk factors between Her-2 positive and negative breast cancer patients, to compare clinical stage (TNM) between Her-2 positive and negative breast cancer patients, to compare pathological stage (for M0) and grade between her-2 positive and negative breast cancer, to compare the response to neo-adjuvant chemotherapy between Her2/neu positive and negative patients in locally advanced breast cancer.

METHODS

Study was done at tertiary medical college and hospitals, Kolkata, India. Patients presenting with cytological/histological evidence (FNAC/core needle) of breast cancer seeking treatment in the Department of General surgery from 1st February 2013 to 30th September 2014. 50 Patients were taken for the study.

Inclusion criteria

- Female patients with cytological/histopathological evidence of malignant breast lump - infiltrating duct carcinoma
- Patients who are willing to give consent for the study
- Patients who can afford/ willing to undergo Her-2/neu immunohistochemistry study

Exclusion criteria

- Patients with breast malignancy other than ductal carcinoma
- Patients with any other secondary malignancy
- Patient who received any form of prior anti-cancer therapy
- Patients with history of prior breast surgery - lumpectomy/BCS/Mastectomy
- Patients refusing IHC for Her-2/neu
- Male breast cancer patients

Observational prospective study, non-randomized study was designed. Consecutive patients presenting with breast lump requiring investigation and treatment were recruited from outpatient department of N.R.S Medical College.

Parameters studied

Incidence of HER-2/ neu Over-expression (HER-2-positive +++ on IHC)

Risk factors[14]

- Age at presentation
- Menstrual status
- Age at menarche
- Age at menopause
- Number of full term pregnancy
- Age at first full term pregnancy
- Nulliparity
- History of breastfeeding
- Family history of ovarian/ breast Ca among first degree relatives
- Hormone receptor status - ER/PR
- History of contraception - oral contraceptive pills
- Site of lump - left/right/bilateral
- Other 1. ER/ positive /

Compare clinical stage (TNM)

Number of early breast cancer/ locally advanced breast cancer/metastatic breast cancer in two groups at presentation.[15]

Compare pathological stage (for M0) and grade

- Tumour (T)
- Lymph node (N)

Other receptors

- T size
- Degree of differentiation or grade-well/moderately/poorly differentiated
- Lymphovascular invasion
- Skin - nipple areola involvement (T stage)
- Lymphocytic infiltration
- Number 1.ER/PR : positive/negative

Response to neo-adjuvant chemotherapy

The response to neoadjuvant chemotherapy for down staging locally advanced tumours will be recorded in terms of reduction in T-size and N-status.

Study technique

- 50 patients presenting with malignant breast lump meeting inclusion and exclusion criteria were included in the study

- Patients' risk factors and presenting symptoms as per protocol were documented
- General clinical examination and examination of breasts and axillae were performed on all patients and findings recorded
- Examination of abdomen and other systems were also performed
- Investigations and metastatic work-up was done as per standard guideline
- Patients who were staged as Locally advanced or metastatic breast cancer was subjected to core biopsy from the tumour mass and 17 histopathological examination, Her-2-neu expression study (IHC) before neoadjuvant or palliative chemotherapy
- Patients with early or resectable breast cancer were subjected to appropriate surgical management followed by histopathological examination and HER-2/neu expression (IHC) study
- Patients receiving neoadjuvant chemotherapy were assessed periodically for operability and operated when feasible, which was followed by pathological staging of the tumour
- Following collection of all the required data, total numbers of patients were divided into two arms according to HER-2/neu overexpression status (Yes/No). Incidence of HER-2-neu over-expression was determined among the sample population. The documented risk factors, clinical staging and pathological staging (For M0 - EBC and post NACT separately), pathological risk factors, hormone receptor status was compared between the two groups and any apparent difference was confirmed by statistical test of significance.

The data and outcome was analysed and compared using statistical software - MEDCALC SOFTWARE VERSION 16.4.2.0.

RESULTS

Incidence of HER-2/neu over-expression (HER – 2 - positive +++ on IHC)

In this study, it was found that 15 (30 %) out of 50 cases were HER- 2/neu positive and 35 (70%) cases were Her-2/neu negative, although there is a wide variation (15-35%) in HER-2/neu over-expression and amplification.

Table 1: Distribution of study population according to age group at presentation and HER- 2/neu status (n = 50).

Age group	Her2-neu +ve	Her2-neu -ve	P-value
<40	8	7	0.0434
>40	7	28	

Age distribution

In my study of 50 patients of breast cancer, Her-2/neu overexpression is present in 8 cases of <40 years of age group and in 7 cases of >40 years of age group (Table 1). Here, the p-value is 0.0434 (< 0.05), which is statistically significant.

Distribution of study population according to menstrual status

HER-2/neu receptor over-expression was present in 8 out of 16 Premenopausal women and 7 out of 34 post-menopausal women.

Distribution of study population according to HER- 2/neu status and age at menarche

HER-2/neu receptor over-expression was present in 9 out of 25 patients in whom menarche occurred below the age of 12 years of age and 6 out of 25 patients in whom menarche occurred above or equal to the age of 12 years. The p-value is 0.5371 (>0.05), which is statistically insignificant.

Table 2: Distribution of study population according to Her-2/Neu status and menstrual status and age at menarche and menopause (n = 50).

Menstrual status	HER 2-neu +ve	HER 2-neu -ve	p-value
Pre-menopausal	8	8	0.0741
Post-menopausal	7	27	
Age at menarche	**HER 2 -neu +ve**	**HER 2-neu -ve**	
<12	9	16	0.5371
≥12	6	19	
Age at menopause	**Her2-neu +ve**	**Her2-neu -ve**	
<45	4	12	0.8611
≥45	3	15	

Distribution of study population according to HER- 2/neu status and age at menopause

HER-2/neu receptor over-expression was present in 4 out of 16 patients in whom menopause occurred below the age of 45 years and 3 out 18 patients in whom menopause occurred above or equal to the age of 45 years Table 3.

Distribution of study population according to HER- 2/neu status and number of full term pregnancy

HER-2/neu receptor over-expression was present in 7 cases bearing two or less children & in 3 cases bearing more than two children. Here, the p-value is 0.5142(>0.05), which is statistically insignificant.

Distribution of study population according to HER- 2/neu status and age at first full term pregnancy

Out of 8 women of age at first full term pregnancy at >25 years of age 3 had HER-2/neu receptor over-expression and Out of 33 women of age at first full term pregnancy at ≤ 25 years of age 7 had HER-2/neu receptor over-expression. Here, the p-value is 0.6145 (> 0.05), which is statistically insignificant.

Table 3: Distribution of study population according to HER- 2/Neu status and number of full term pregnancy and age at first full term pregnancy (n = 50).

Number of full term pregnancy	Her2-neu +ve	Her2-neu -ve	P-value
≤2	7	16	0.5142
>2	3	15	
Age at 1st term pregnancy	**+ve**	**-ve**	
>25	3	5	0.6145
<=25	7	26	

Table 4: Distribution of study population according to HER-2/Neu status and parity and use of contraceptives (n = 50).

Parity	Her2-neu +ve	Her2-neu -ve	P-value
Nulliparity	5	4	0.1482
Multiparity	10	31	
H/o OCP used	**Her-2/Neu+ve**	**Her-2/Neu-ve**	**P-value**
Used	8	18	0.8530
Not used	7	17	

Distribution of study population according to HER- 2/neu status and parity

HER-2/neu receptor over-expression was present in 5 out of 9 nulliparous patients and 10 out of 41 multiparous patients. HERe, the p-value is 0.1482(>0.05), which is statistically insignificant.

Distribution of study population according to HER- 2/neu status and history of oral contraceptive pills use

HER-2/neu receptor over-expression was present in 8 out of 26 patients who used OCP and in 7 out of 24 patients who did not use OCP (Table 4). *Distribution of study population according to HER- 2/neu status and history of breast feeding*

Out of 15 HER-2/neu receptor over-expression patients 9 had H/O breast feeding and out of 35 HER-2/neu negative patients 26 had H/O breast feeding (Table 5). Here, the p-value is 0.5007 (>0.05), which is statistically insignificant.

Table 5: Distribution of patients according to h/o breast feeding nd Her/2 neu status

h/o breast feeding	Her2-neu +ve	Her2-neu -ve	P-value
Yes	9	26	0.5007
No	6	9	

Table 6:Distribution of study population according to HER-2 /Neu Status and family history of ovarian and breast carcinoma among 1st degree relatives.

F/H/O ovarian and breast carcinoma	Her2-neu +ve	Her2-neu -ve	p-value
Yes	3	6	0.8724
No	12	29	

Distribution of study population according to HER-2/NEU status and family history of ovarian and breast carcinoma among 1st degree relatives

HER-2/neu receptor over-expression was present in 3 out of 9 cases with family history of ovarian and breast cancer and 12 out of 41 cases without family history of ovarian and breast cancer. Here, the p-value is 0.8724 (>0.05), which is statistically insignificant (Table 6).

Distribution of study population according to ER and HER- 2/neu status

In our study 54% (n = 27) patients, had ER positive status and 46% (n=23) patients had ER negative status. HER-2/neu receptor over-expression was present in 3 out of 27 ER positive cases and 12 out of 23 ER negative cases. Here, the p-value is 0.0044 (< 0.05), which is statistically significant.

Distribution of study population according to Pr and HER- 2/Neu status

In our study 52% (n = 26) patients had PR positive status and 48% (n = 24) patients had PR negative status.HER-2/neu receptor over-expression was present in 4 out of 26 PR positive cases and 11 out of 24 PR negative case. Here, the p-value is 0.0415 (<0.05), which is statistically significant (Table 7).

Distribution of study population according to HER-2/Neu status and laterality of breast carcinoma

HER-2/neu receptor over-expression was present in 8 out of 15 in right sided breast carcinoma patients, 5 out of 15 in Lt sided breast carcinoma patients and 2 out of 15 in Both sided breast carcinoma patients.

Distribution of study population according to HER-2/Neu status and clinical stage (Tnm) such as number of early breast cancer/ locally advanced breast cancer/metastatic breast cancer

Out of 11 early breast cancer patients HER-2/neu receptor over-expression was present in 1 case, out of 19 locally advanced breast cancer patients HER- 2/neu receptor over-expression was present in 6 cases and out of 20 metastatic breast cancer patients HER-2/neu receptor over-expression was present in 8cases (Table 8).

Distribution of study population according to HER- 2/neu status and T-size of breast carcinoma

Out of 19 women with tumour size ≤ 5 cm HER-2/neu overexpression was in 2 cases and Out of 31 women with tumour size >5 cm HER-2/neu over-expression was in 13 cases.

Table 7: Distribution of study population according to ER and PR status and HER 2-neu status.

ER status	HER 2-neu +ve	HER 2-neu -ve	p-value
+ve	3	24	0.0044
-ve	12	11	
PR status	**Her- 2/Neu +ve**	**Her- 2/Neu-ve**	
+ve	4	22	0.0415
-ve	11	13	

Table 8: Distribution of study population according to HER- 2/Neu status and laterality of breast carcinoma and clinical stage (TNM) (n=50).

Laterality	Her-2/Neu+ve	Her-2/ Neu -ve	P-value
Right	8	17	0.9039
Left	5	14	
Bilateral	2	4	
Clinical stage	**Her- 2/Neu +ve**	**HER- 2 /Neu-ve**	
Early breast cancer	1	10	0.1954
LABC	6	13	
Metastatic breast cancer	8	12	

Here, the p-value is 0.1954(>0.05), which is statistically insignificant.

Distribution of study population according to HER- 2/neu status and breast carcinoma grade

Association of HER-2/Neu receptor status with tumour grade HER-2/neu protein receptor over-expression was present in nil out of 9 in grade I tumour, 7 out of 24 in grade II tumours and 8 out of 17 in grade III tumours (Table 9).

Distribution of study population according to HER- 2/neu status and lymphovascular invasion of breast carcinoma

Lymphovascular invasion is present in 8 out of 15 HER-2/neu Positive cases and in 8 out of 35 HER-2/neu negative cases.

Table 9: Distribution of study population according to HER- 2/Neu Status and T-size and breast carcinoma grade (n = 50).

T size	HER- 2/ Neu+ve	HER- 2/ Neu-ve	P-value
≤5	2	17	0.0419
>5	13	18	
Grade	**Her- 2/Neu +ve**	**Her- 2/Neu-ve**	
I	0	9	0.0446
II	7	17	
III	8	19	

In both the cases p value is significant.

Table 10: Distribution of study population according to HER- 2/Neu status and lymphovascular invasion, skin-nipple areola involvement and lymphocytic infiltration (n = 50).

Lymphovascular invasion	HER-2/Neu+ve	HER-2/Neu-ve	P-value
Yes	8	8	0.0741
No	7	27	
Skin nipple areola involvement	**HER-2/Neu+ve**	**HER-2/Neu-ve**	
Yes	4	8	0.9424
No	11	27	
Lymphocytic infiltration	**Her-2/Neu+ve**	**Her-2/Neu-ve**	
Yes	3	6	0.8724
No	12	29	

Table 11: Distribution of study population according to HER- 2/Neu status and number of lymph node involved in breast carcinoma (n = 50).

Lymph node no	HER-2/Neu+ve	HER-2/Neu-ve	P-value
Nil	2	10	0.0314
1-3	1	9	
4-9	5	12	
>9	7	14	

Distribution of study population according to HER- 2/neu status and skin-nipple areola involvement of breast carcinoma

Skin-nipple areola involvement is present in 4 out of 15 HER-2/neu Positive cases and in 8 out of 35 HER-2/neu negative cases (Table 10).

Table 12: Distribution of study population according to HER- 2/Neu status and response to neo-adjuvant chemotherapy of breast carcinoma (n = 50).

Neo-adjuvant chemotherapy	HER-2/Neu+ve	HER-2/Neu-ve	P-value
Respond	1	6	0.5936
Not respond	14	29	

Distribution of study population according to HER- 2/neu status and lymphocytic infiltration of breast carcinoma

Lymphocytic infiltration was present in 3 out of 15 HER-2/neu positive cases and in 6 out of 35 HER-2/neu negative cases.

Distribution of study population according to her- 2/neu status and number of lymph node involved in breast carcinoma

Out of 12 lymph node negative patients only 2 have HER-2/neu over-expression, out of 10 patients involving 1-3 lymph nodes only 1 has HER-2/neu overexpression, out of 17 patients involving 4-9 lymph nodes only 5 have HER- 2/neu over-expression and out of 11 patients involving >9 lymph nodes 7 have HER-2/neu over-expression (Table 11).

Distribution of study population according to HER- 2/neu status and response to neo-adjuvant chemotherapy of breast carcinoma

Out of 15 HER-2/neu receptor over-expression patients only 1 patient responded to neo-adjuvant chemotHERapy and out of 35 HER-2/neu Negative patients only 6 patients responded to neo-adjuvant chemotherapy Table 12.

DISCUSSION

Incidence of her-2/neu over-expression (Her-2/neu positive +++ on IHC)

In our study, we found that 15(30 %) out of 50 cases were HER-2/neu positive and 35 (70%) cases were HER-2/neu negative. This is in agreement with various studies where HER-2/neu or its protein P185 is over-expressed in 10-35% of breast cancer patients in the western population an over amplification of this gene in 25- 30%, have been reported.[8-10]

Age at presentation

In our study HER-2/neu overexpression was associated with younger age. This is in agreement with the study done by Rilke F et al, who found - HER-2/neu over-expression is associated with young age.[11]

Menstrual status

In our study HER-2/neu receptor over-expression was present in 8 out of 16 premenopausal women and 7 out of 34 post-menopausal women.

Khorshid et al and Al-moundhri et al in their respective studies reported no association between HER2/neu immunopositivity and menopausal state and thereby showed similar results to our study.[12,13]

Age at menarche, age at menopause

Our finding regarding the age at Menarche and Menopause is corroborative with a retrospective analysis of breast cancer cases conducted by Siddiqui T et al, who showed the age of menarche and the age of Menopause has no statistical significance between the HER-2/neu positive and the HER-2/neu negative Breast cancer in the population.[14]

Number of full term pregnancy, age at first full term pregnancy, parity, family history of ovarian/breast cancer among first degree relatives, site of lump (left /right/bilateral), skin-nipple areola involvement. All of these have insignificant association with Her-2/neu receptor over-expression.

Our finding is corroborative with a retrospective analysis of Breast Cancer cases conducted by Siddiqui T et al who showed similar results - that the number of full term pregnancy and the age of first full term pregnancy, parity, family history of ovarian and breast cancer, laterality, and skin-nipple-areola involvement had no statistical significance between HER-2/neu positive and negative breast cancer in the population.[12]

History of breast feeding

It has insignifican relationship with HER-2/neu receptor over-expression. Our finding corroborates with the study on breast cancer cases by Marilie D et al, in New Jersey State Department of Health and Senior Services, Applied cancer epidemiology program ;in 1990 - 1992 ,where a total of 371 Breast cancer tissue samples were tested for HER-2/neu gene presence and found that there was little or no heterogeneity of effect for lactation (ratio of the OR, 0.72 for ever versus never; 95% CI, 0.44–1.15).[10]

Comparision of clinical staging such as early/locally advanced/metastatic breast cancer

It has insignificant relationship with HER-2/neu receptor over-expression. Our finding is corroborative with the study on breast cancer cases by Marilie D et al, in New Jersey State Department of Health and Senior Services, Applied Cancer Epidemiology Program; 1990 - 1992, where a total of 371 breast cancer tissue samples were tested for HER-2/neu gene presence there was little or no

heterogeneity in relation to stage (in situ, local, regional/distant)[10]

Lymphovascular invasion, lymphocytic infiltration

It has insignificant relationship with Her-2/neu receptor over-expression. Our finding is corroborative with the study on Breast Cancer cases by Khorshid et al and Al-Moundhri et al, who reported that no association was found between HER2/neu immunopositivity and vascular and/or lymphatic invasion & also lymphocytic infiltration of the tumour.[12,13]

Hormone receptor status - ER/PR

It has significant relationship with It has insignificant relationship with HER-2/neu receptor over-expression. Our finding is corroborative with the several studies. Alahwal et al in his study has mentioned this inverse association between HER-2/neu and ER status.[15] In his study HER-2/neu was positive in only 19.5% of cases with positive ER status versus 80.5% of cases with negative ER status.

History of oral contraceptive

Her-2/neu receptor over-expression was present in 8 out of 26 patients who used OCP and 7 out of 24 patients who did not use OCP in our study. Though it is statistically insignificant, there is positive co-relation between HER-2/neu overexpression and use of oral contraceptive pill.

On the basis of case-case comparisons of 72 Swedish, premenopausal breast cancer patients, Olsson et al reported that breast cancer with HER-2/neu amplification (31% of all cases) was positively associated with early oral contraceptive use (20 years).[9]

Tumour size

Out of 19 women with tumour size ≤ 5 cm HER-2/neu overexpression was seen in 2 cases and Out of 31 women with tumour size >5 cm HER-2/neu over-expression was seen in 13 cases. HERe, the p-value is 0.0419 (<0.05), which is statistically significant. Our findings corroborate with the other similar studies. Nidam M et al found HER-2 neu positivity in 35% patients with tumour size >5cms.[16]

Degree of differentiation or grade

In our study higher-grade tumours were more likely to demonstrate HER-2/neu amplification than lower grade. Our finding is also corroborative with the study on Breast Cancer cases by Hoff et al, who reported higher-grade tumours were more likely to demonstrate Her-2/neu amplification than lower grade ductal carcinomas ($p < 0.001$).[17]

Lymph node: number

In our study it is found that there is Positive co-relation between HER-2/neu over-expression and increased number of lymph node involvement. Our finding is corroborative with several studies. Tokatli F in 2005 from Turkey has reported 20% of his patients positive for HER-2/neu and a significant association was observed between HER-2/neu and increasing number of involved axillary lymph nodes ($p = 0.014$).[18]

Response to neo-adjuvant chemotherapy

In the present study- out of 15 Her-2/neu receptor over-expression patients only 1 patient responded to neo-adjuvant chemotherapy and out of 35 HER-2/neu Negative patients only 6 patients responded to neo-adjuvant chemotherapy. Here, the p-value is 0.5936 (>0.05), which is statistically insignificant. Our finding is corroborative with other studies. HER2/ neu receptor over-expression has also been linked to CMF (cyclophosphamide, methotrexate, 5 - fluorouracil) resistance in clinical trials and taxol resistance in cell line.[19-21]

CONCLUSION

HER-2/neu overexpressing breast cancers have increased invasive and metastatic capability and are less responsive to chemotherapy. They have increased risk of recurrence and patients with these tumours have a reduced survival compared with patients with normal levels of HER2/neu.

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