

Frequency of HER-2 receptors in patients with breast cancer

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Abstract

Objective: To determine the frequency of HER-2 receptors in patients with breast cancer.

Methods: This study was conducted at Department of Surgery, Bahawal Victoria Hospital and BINO Cancer Hospital Bahawalpur from 22-08- 2014 to 21-02-2015. This was a cross sectional study. A total of 126 consecutive cases of breast cancer were included in study. A tissue biopsy was sent for immunohistochemical (IHC) studies (HER-2/neu receptors and ER/PR receptors and detailed histopathological analysis including tumour subtype, histological grade. Patients having only ductal and lobular histopathologic type were included in the study. Name, age, weight, height and age at first live birth noted. Statistical Analysis was done with SPSS 16.

Results: 126 patients of breast cancer included in the study were diagnosed on histopathology of tissue sample. All patients were female. Age distribution ranged from 20- 73 years with a Mean±SD of age 44.1±11.2 years. 73 (57.9 %) patients were >41 years. The HER-2/neu receptor, ER, PR receptor were found positive in 41.3%, 61.9%, 53.2% of patients respectively. Majority of patients 113 (89.7 %) were found with invasive ductal carcinoma. 45 (35.7 %) patients were obese. In our study HER-2 Receptor status was not significantly associated with age at first live birth of respondents (n=126) and obesity but it was significantly associated with younger age groups (p<0.05)

Conclusion: There is a significant correlation between HER-2 receptor and younger age group. HER-2/neu receptor status should be checked in all breast cancer along with estrogen and progesterone receptor especially in young people.

Key words: Breast carcinoma, HER-2/neu, Estrogen receptor /Progesterone receptor

Introduction

The incidence of breast cancer is increasing worldwide. Invasive breast cancer is still the most common female malignancy worldwide and more than 1 million women are diagnosed with breast cancer each year. It is the most common cancer related cause of death in middle-aged women all over the world. There is a 10-fold variation in breast cancer incidence among different countries worldwide. Variations in incidence of breast cancer among multicultural populations suggest that etiological factors vary in biological expression and their impact on disease outcome. It is the most common cancer among women in many areas of Pakistan.¹ Ap-

proximately one in every nine Pakistani women is likely to suffer from breast cancer. This is one of the highest incidence rates in Asia. Amazingly Pakistani women show an incidence of 50/100,000 and in the neighboring country India with similar socio-cultural background the incidence is 19/100,000.³ The gradual increase in incidence of breast cancer has created an urgent need to develop strategies for prevention. Breast cancer appears to have a complex etiology, possibly with interplay of many causal factors including hormonal, genetic and environmental factors operating over a long period.² Increased exposure to estrogen is associated with an increased risk for developing breast cancer,

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whereas reducing exposure is thought to be protective.² Correspondingly, factors that increase the number of menstrual cycles, such as early menarche, nulliparity, and late menopause, are associated with increased risk. Moderate levels of exercise and a longer lactation period, factors that decrease the total number of menstrual cycles, are protective. The terminal differentiation of breast epithelium associated with a full-term pregnancy is also protective, so older age at first live birth is associated with an increased risk of breast cancer. Finally, there is an association between obesity and increased breast cancer risk. Because the major source of estrogen in postmenopausal women is the conversion of androstenedione to estrone by adipose tissue.

Hormone receptor status is a key parameter in molecular classification of breast cancer, which serves as a marker of hormone-dependent growth and predictor of responsiveness to hormonal treatments.^{4,5} A recent literature review found evidence that nulliparity, late age at first birth and postmenopausal obesity are associated with increased risk for estrogen receptor- α (ER- α)-positive cancers and that early menarche was more strongly linked to tumors coexpressing ER- α and progesterone receptor (PR).⁶ Subsequently, a meta-analysis updating this review affirmed the heterogeneous associations for nulliparity and late age at first birth, but not for age at menarche.^{7,8,9}

HER-2/Neu receptor is a trans-membrane growth factor receptor belonging to type I receptor tyrosine kinase family of proteins. Because of its function as an activator of signaling pathways, HER-2 plays a central role in a number of cellular processes, including proliferation, motility, and resistance to apoptosis. This effect may be enhanced by the over expression of HER-2 in cancer cells, leading to increased cell proliferation and decreased cell death, as well as changes in cell motility. It is expressed in 10 – 34% of breast carcinomas. In a study HER-2/Neu receptors expression was seen only in 16.35% cases.^{10,11} Similar findings were noted by Mud-duwa¹² (19.1%), while Dutta et al¹² reported a

high prevalence of HER-2/ Neu receptors over expression, in 64.16% of cases. HER-2/Neu receptors over expression are associated with poor response to hormone receptor modulators. These patients are resistant to conventional therapy. They can opt for herceptin therapy which is highly efficient for this patients.¹³ over expression of the HER-2 receptor is associated with poor prognosis in patients with breast cancer, as well as with aggressive tumor growth, high tumour grade, positive lymph node and distant metastases.¹⁰ Determination of HER-2 status in breast cancer has become important to identify potential candidates for anti-HER-2 therapy.

Due to high prognostic significance and frequency in Pakistani females with breast cancer, HER-2/neu receptor should be checked in all patients with breast cancer so that the positive cases should have specific anti HER-2 therapy which can improve survival in these patients. The result of our study will provide a current magnitude of HER-2/neu Receptor in Breast Cancer patients. Variations in incidence of breast cancer among multicultural populations suggest that etiological factors vary in biological expression. If the result of this study shows high prevalence of HER-2/neu Receptors in breast cancer it will indicate poor prognosis of our breast cancer patients. It will also help us to adopt strategies regarding prevention and treatment modification.

The purpose of this study is to determine the frequency of HER-2 receptors in patients with breast cancer.

Operational Definitions:

Breast Cancer: Patients having breast lump diagnosed as cancer on histopathology after tissue biopsy.

HER-2/neu Receptors: Positive patients will be those who are confirmed after immunohistochemical (IHC) staining of tissue biopsy. A HER-2 receptor test score of 3+ will be considered as positive and a score less than this (0+,

1+,2+) will be taken as negative for HER-2/neu receptor.

Body Mass Index (BMI): $BMI = \text{weight (kg)} / \text{height (m}^2\text{)}$

Material and Methods:

Study Design: This was cross sectional study carried out in Department of Surgery, Bahawal Victoria Hospital, Bahawalpur and BINO Cancer Hospital Bahawalpur.

Study Duration: Six months from 20-08-2014 to 20-02 2015.

Sample Size:

Anticipated proportion = 20¹¹, Confidence Interval = 95%, Precision required (d) = 0.07, Sample size (n) = 126. So a total 126 patients were included in the study.

Sampling Technique: Non probability consecutive sampling technique.

Sample Selection:

Inclusion criteria: Female patients with age between 20-75 years and diagnosed as a case of cancer of breast. Patients having only lobular carcinoma / ductal carcinoma.

Exclusion criteria: Patients having recurrent breast cancer. Patients who were not willing for immunohistopathology.

Data Collection:

All the patients presenting to Surgical Out-Patient Department of Bahawal Victoria Hospital and BINO Hospital Bahawalpur fulfilling the inclusion criteria were included in the study after taking informed written consent. Study was approved for institutional review board.

Weight and height of all the patients was measured to calculate BMI. Age at first live birth was noted. Tissue of tumor was send to laboratory for estrogen and progesterone status, grade of tumor, histological type, histopathological grade and HER-2/neu Receptors status. All the

data was recorded along with demographic profile of the patients on pre-designed proforma.

Data Analysis:

The data was analyzed by computer software SPSS Version 16. Mean and standard deviation was be calculated for numerical data i.e. age of the patient, Age at first live birth in years and BMI. The qualitative data like HER-2/NEU receptor status (Positive or Negative), type of cancer (ductal / lobular) and hormone receptor status was be labeled as frequency distribution table. Stratification will be done for age of the patient, Age at first live birth in years and obesity. Post stratification chi-square test will be applied to see the association of these with outcome variable i.e. HER-2/NEU receptor status (positive or negative). P value ≤ 0.05 was considered to be considered as significant.

Results:

A total of 126 patients of breast cancer reporting to the Department of Surgery Bahawal Victoria Hospital (B.V.H) and Bahawalpur Institute of Nuclear Medicine & Oncology (BINO) were enrolled in the study. Diagnosis in all the patients was made on histopathology of tissue sample. All patients were female. Age ranged from 18 to 73 years with a Mean \pm SD of age 44.1 \pm 11.2 years. Seventy three patients (57.9 %) were >41 years, while fifty three (42.1%) were \leq 41 years of age as shown in figure 1.

Invasive ductal carcinoma was the tumor type in 113 (89.7 %) while 13 (10.3 %) cases were with lobular carcinoma as shown in figure 2. The Her-2/neu receptor status was found positive in 52 patients (41.3%) and negative in 74 patients (58.7 %) of the total 126 cases as shown in figure 3.

Thirty eight Patients (30.2%) were with age at fist live birth less than 31 year and 13 patients (10.3%) were with more the 40 years. Remaining patients 75 (59.5%) had their first live birth in between these two age groups as shown in figure 4.

Estrogen receptors were found positive in 78

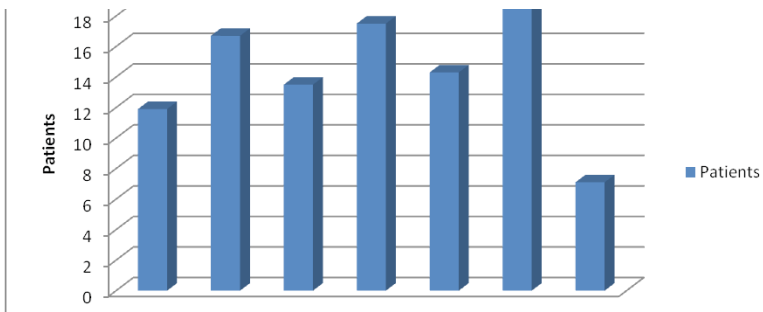


Fig. 1: Age distribution in breast cancer patients in years (n=126)

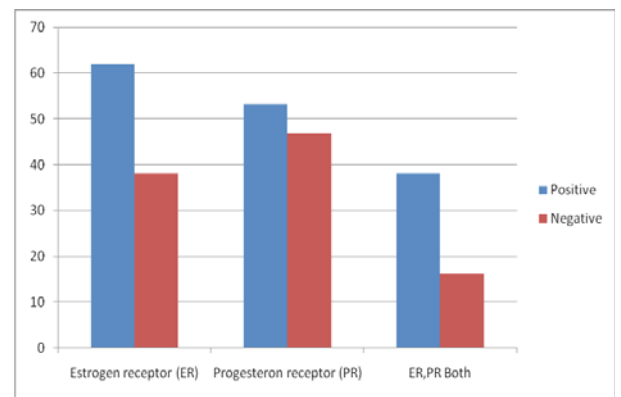


Fig. 5: Frequency of Estrogen and progesterone receptor in respondents (n=126)

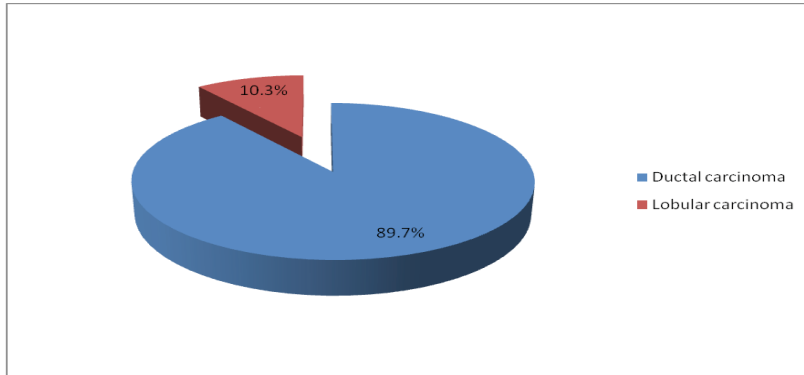


Fig. 2: Histopathological type in breast cancer patients (n=126)

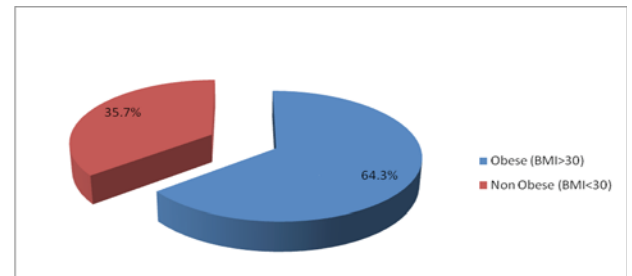


Fig. 6: Obesity among breast cancer patients (n=126)



Fig. 3: Frequency of HER-2 receptors in Breast cancer patients (n=126)

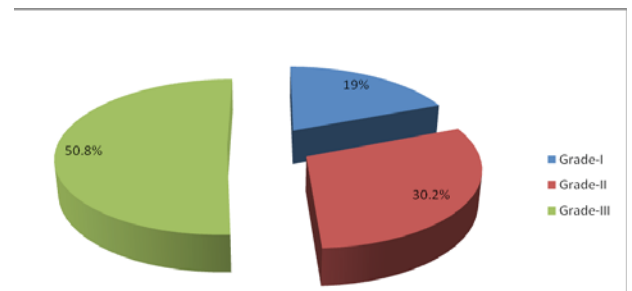


Fig. 7: Histopathological grades of tumor in respondents (n=126)

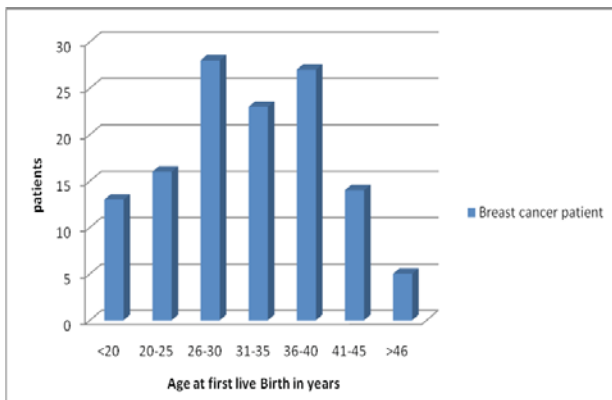


Fig. 4: Age at first live birth (years) of respondents (n=126)

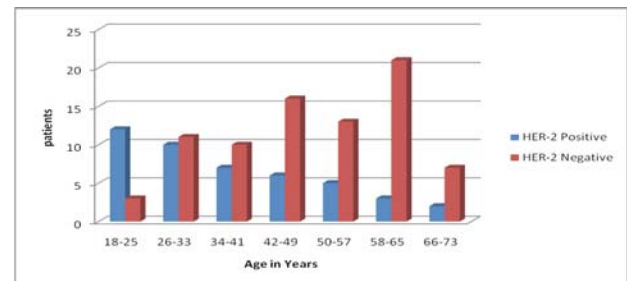


Fig. 8: Frequency of HER-2 receptors and age of respondents (n=126)

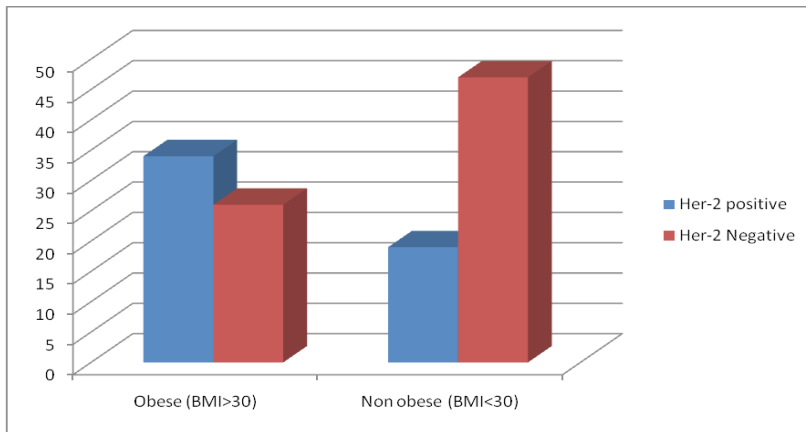


Fig. 9: Obesity and HER-2 receptors status in breast cancer patients(n=126)
 $\chi^2=5.893$ $p= 0.4352$

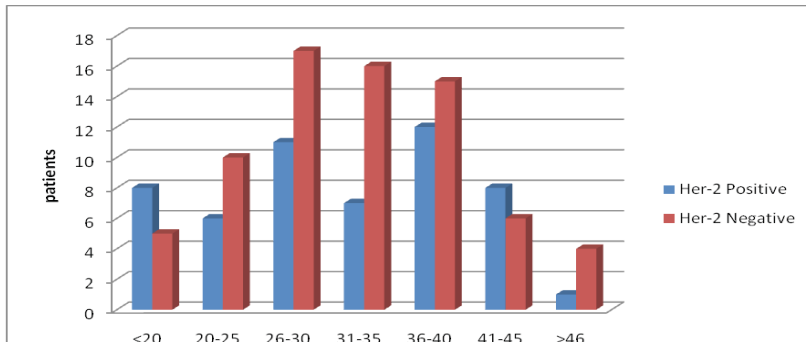


Fig. 10: Age at first live birth and HER-2 receptors in respondents patients (n=126)
 $\chi^2=5.893$ $p= 0.4352$

(61.9%) of patients while estrogen receptor negative patients were 48 (38.1%). Progesterone receptors were found positive in 67 (53.2%) of patients while progesterone receptor negative patients were 59 (46.8 %) as shown in table 5. Co-expression of estrogen and progesterone receptor was present in 32 (25.4%) patients as shown in figure 5.

Forty five patients (35.7%) were obese and eighty one (64.3%) patients were non-obese in my study as shown in figure 6.

50.8% patients were found to have grade III tumor while only 19.0% patients were found with grade I tumor histopathologically as shown in figure 7.

HER-2 Receptor status was not significantly associated with age at first live birth of respondents

(n=126) and obesity but it was significantly associated with younger age groups ($p < 0.05$) as shown in figure 8,9,10 respectively.

Discussion:

HER-2/Neu receptor is a trans-membrane growth factor receptor belonging to type I receptor tyrosine kinase family of proteins. HER-2/Neu receptor over expression is associated with poor response to hormone receptor modulators. These patients are resistant to conventional therapy. Over expression of the HER-2 receptor is associated with poor prognosis in patients with breast cancer, as well as with aggressive tumor growth and metastases. Our study comprised of 126 cases of invasive breast cancer with a mean age of 44.1 years. This is similar with the data from a study in northern area¹ and is also comparable with a study in Yamen where mean age of the breast cancer patient was 43.75 years.¹⁴ In Asian breast cancer mean age of patients is found to be lower (47years) when compared to the Western countries with an average difference of one decade.¹⁵

Our study showed that 78% of cases had positive Estrogen receptor expression while 67% expressed Progesterone. Expression of estrogen and progesterone in my study is high as compared to a study in Yamen with estrogen receptors expressed in 43.8% and progesterone receptors in 27% patients.^{6,8} This is similar when compared to some Western studies which have reported 73% ER positivity and 58% PR positivity. A recent study from Mumbai also showed that hormone receptor expression in India is lower compared to the West.¹⁶ similar result also found in a study in Bangladesh where Estrogen Receptor expression was positive in 69.0%, PR expression was positive in 72.3% of patients.¹⁷

In our study HER-2/neu was found positive in 42.1% patients and negative in 57.9%. Naem M, in 2008, has reported 46% of breast cancer patients positive for HER-2/neu receptor.¹ A study in December 2007 in Karachi, Pakistan has observed 31% positive overexpression for HER-2/neu receptor.¹⁸ A study conducted in

2011 showed 30.6% HER-2 receptor expression.¹⁴ Her-2 receptor expression was found 28.4% a study in Bangladesh.¹⁷

With respect to age 55 patients (43.6%) were ≤ 40 years of age and 71 patients (56.4%) were > 40 year of age and HER-2 receptor expression (54.7%) is more in younger age group. This is similar to what is reported in literature, that HER-2/neu over expression tends to decline with age.¹ Al-ahwal has reported 34.1% of his young patients (≤ 40 years) positive for HER-2/neu receptor and 65.9% of those above 40 years of age.¹⁹

Majority of our breast patients were found with invasive ductal carcinoma on histopathology This is similar as compared to other studies where more than ninety percent of breast cancers were invasive ductal carcinoma.¹ The commonest histological grade was III 50.8 % and followed by Grade II (30.2%), this in opposite to a study conducted in yamen in 2011 where majority of patient presented with grade II (55.2%) followed by grade I (25.3%).¹⁵ This late presentation might be due to more aggressive nature of tumour in our region and it may be due to unawareness about breast cancer.

Eighty one patient in my study were found obese with BMI > 30 and only 45 (35.7%) patient were with BMI < 30 . Her-2 receptor status was positive in 34 obese and 19 non obese patient out of total 126 breast cancer patient. This association with obesity was not significant ($p=0.9747$). this was different to a study where HER-2 receptor status was positively correlated with increasing BMI among post-menopausal women ($p=0.048$)²⁰ but this is similar to what found in literature.⁵ In our study age at first live birth of patients and HER-2 receptor positivity was not significantly related ($p=0.4352$). Literature review also show non significance association of HER-2 receptor with age at first live birth in breast cancer patients.²¹ But HER-2 receptor show significant association with younger age group.

Conclusion:

In conclusion, study of HER-2/neu receptor in breast cancer patients indicates that there are high rates of positive expression of these receptors. There is a significant correlation between HER-2 receptor and younger age group. HER-2/neu receptor status should be checked in all breast cancer along with estrogen and progesterone receptor especially in young people because it has a great impact on further management with herceptin and anthracycline based chemotherapeutic agents. There is also need to explore HER-2 receptor co-relation with other etiologi- cal factors especially in young people.

Hormone receptors and Her-2 receptors are the major determinant of breast cancer aggressiveness and predictive prognostic factors.

Conflict of Interest: None

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Role and contribution of authors:

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