Frequency of HER-2 (c-erbB-2)Receptors in Breast Cancer Patients and its Association with other Etiological Factors

BUSHRA NISAR[1], MUHAMMAD AFZAL SAQIB[2], ASGHAR ALI[3]

ABSTRACT

Aim: To determine the frequency of HER-2 receptors in patients with breast cancer.
Methods: Thisstudy wasconducted at Department of Surgery, Sheikh Zayed Medical College/Hospital Rahim Yar Khan from November2014 to May 2015.
Total 120 consecutive females with cancer of breast were recruited in present study. A tissue biopsy was sent forIHC(immuneohistochemical) studies (c-erbB-2 receptors and PR/ER receptors) and completehistopathological analysis including histological grade and subtype oftumor.
Results: All 120 female patients of breast cancer diagnosed on histopathology of tissue sample were selected for this study. Average age of the selected females was43.3±12.5 years. The c-erbB-2 receptor, ER, PR receptor were found positive in 50(42%), 94(78.33%) and 81(67.5%) of patients respectively. Majority our patients 108(90%) tumor type was invasive ductal carcinoma on histopathology. In our study insignificant (P=0.446) association was seen betweenc-erbB-2 receptor status and obesity but significant (P=0.006) association between c-erbB-2 receptor status and age of the females was seen.
Conclusion: There is high rates of positive expression ofc-erbB-2 receptor in breast cancer patients and significantassociation was found between c-erbB-2 receptor and age of the patients. c-erbB-2receptor status should be checked in all patients with cancer of breast along with estrogen and progesterone receptor especially in young female.
Keywords: HER-2/neu, breast carcinoma, ER/PR, over-expression, co-expression

INTRODUCTION

In females, the most common canceris the cancer of breastand it is said that about 1 million women suffer from breast cancer every year.In middle aged women, it is the most common cause of death. There is a 10-fold variation inthe prevalence of breast cancer among the different countries.Among the multi-cultural populations, variations in prevalence of cancer of breast suggests that etiological factors vary in biological expression and their effect on the disease outcome. Breast cancer is commonly prevalent in Pakistani women[1].As this caner is increasing day by day sot there is need to develop different strategies for its prevention. Etiological is multifactorial like hormonal, genetic and environmental factros[2].

In Pakistan 1 in every 9 women suffering with this cancer and it is the highest rate in Asia. In Pakistan fifty out of one lac women are having cancer of breast while the women with almost same socio-economical conditions in India have decreased ratio

----

[1]Assistant Professor, Department of Histopathology, Sheikh Zayed Medical College/Hospital, Rahim Yar Khan
[2]Medical Superintenden, Sheikh Zayed Medical Collage/Hospital, Rahim Yar Khan
[3]Assistant Professor, Department of Surgery, Sahiwal Medical College, Sahiwal
Correspondence to Dr. BushraNisar, Email: bushranisar1234@yahoo.com

(19/100000). Exact cause is still not clear[3].In cancer of breast, hormone receptor status is very important parameter[4,5].HER-2/Neu (c-erbB-2) receptor is belonged to tyrosine kinase family of proteins and it is a trans-membrane growth factor receptor.Due to its role as an activator of signaling pathways, c-erbB-2plays animportant role in many cellular processes, including motility, resistance to apoptosis and proliferation.

Due to over-expression of c-erbB-2 receptor, this effect can be enhanced in cells of cancer, leading to increased cell proliferation and decreased cell death, as well as changes in cell motility. It is expressed in 10%-34% of carcinomas of breast. Over-expression of c-erbB-2 receptoris associated with poor response to hormone receptor modulators. These patients are resistant to conventional treatment. They can opt for herceptintreatment which is highly efficient for these patients[10].

The purpose of our study is to determine the prevalence of c-erbB-2 receptor in Breast cancer females. On literature search it has been observed that very limited data is available on this topic and no study available in our population especially in Southern Punjab. So a study is planned to know the prevalence of c-erbB-2 receptor status in women withcancer of breast. It may help us to adopt

strategies regarding prevention and treatment modification.

MATERIAL AND METHODS

It was a cross sectional study and conducted at Department of Surgery, Sheikh Zayed Medical College/Hospital Rahim Yar Khan from November 2014 to May 2015**.** Total 120 female patients having breast lump diagnosed as cancer on histopathology after tissue biopsy and having only lobular carcinoma / ductal carcinoma age range from 20-65 years were selected for study. Patients having recurrent breast cancer and patients who were not willing for immunohistopathology were excluded from the study. An approval was taken from institution review committee and written informed consent was taken from every patient.

C-erbB-2 receptors positive patients were those who were confirmed after immunohistochemical (IHC) staining of tissue biopsy. A Hercep test score of 3+ was considered as positive and a score less than this (0+,1+,2+) was taken as negative for c-erbB-2 receptor.

Weight and height of all the patients was measured to calculate BMI. Age at first live birth was also noted. Tissue of tumor was send to laboratory for estrogen and progesterone status, grade of tumor, histological type, histopathological grade and c-erbB-2 Receptor status. All the laboratory findings were recorded along with demographic profile of the patients on pre-designed proforma. All the data were entered in SPSS version 17 and analyzed. Mean and SD was calculated for numerical variables and frequencies and percentages were calculated for categorical variable. Chi-square test was used to see the association between different study variables. P value ≤ 5% was considered as statistically significant.

RESULTS

Total 120 patients of breast cancer reporting to the Department of Surgery, Sheikh Zayed Medical College/Hospital Rahim Yar Khan were enrolled in the study. Diagnosis in all the patients was made on histopathology of tissue sample. Mean age of the patients was 43.3±12.5 years.

In our study 50(42%) patients found with 50(42%) c-erbB-2 receptor status and 70(58%) found with negative c-erbB-2 receptor status. (Fig. 1)

Twenty three (19%) patients found with Grade-I tumor followed by 36(30%) Grade-II and 61(51%) had Grade-III tumor (Fig. 2).

Out of 120 patients with breast cancer, ductal carcinoma was present in 108(90%) patients and lobular carcinoma was present in 12(10%) patients (Fig. 3).

Stratification in relation to age was done and two age groups were made, age group 20-45 years and 46-70 years. In age group 20-45 years, out of 44(36.67%) patients c-erbB-2 receptor was found positive in 11(25%) patients and out of 76(63.33%) patients of age group 46-70 years,c-erbB-2 receptor was found positive in 39(51.32%) patients. C-erbB-2 receptor status significantly (P=0.006) associated with age of the patients. (Table 1)

Among the 43(35.83%) obese patients, c-erbB-2 receptor was found positive in 20(46.51%) patients. In 77(64.17%) non-obese patients, c-erbB-2 receptor was found positive in 30(38.96%) patients. Insignificant (P=0.446) association of c-erbB-2 receptor with obesity was seen. (Table 2)

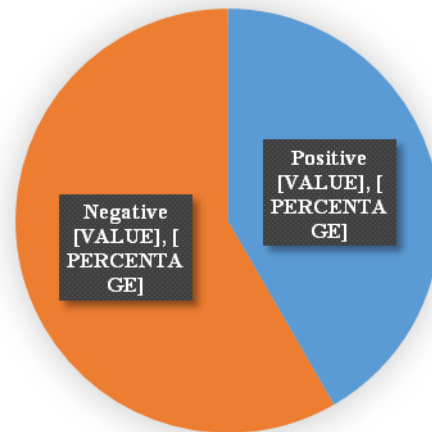Fig. 1: Frequency of HER-2/Neu receptor status

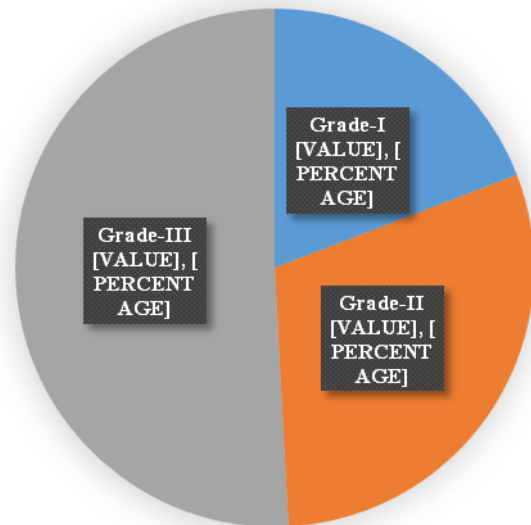Fig. 2: Histopathological Grades of tumor in respondents

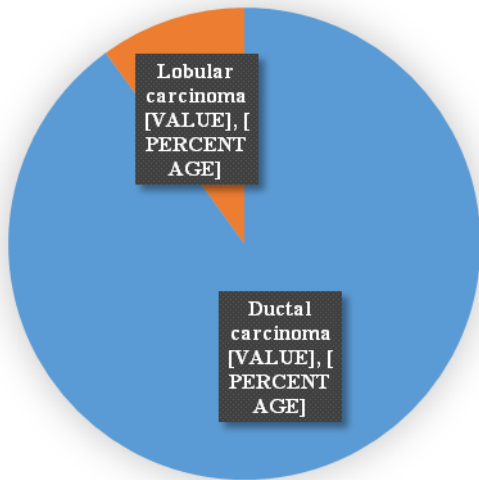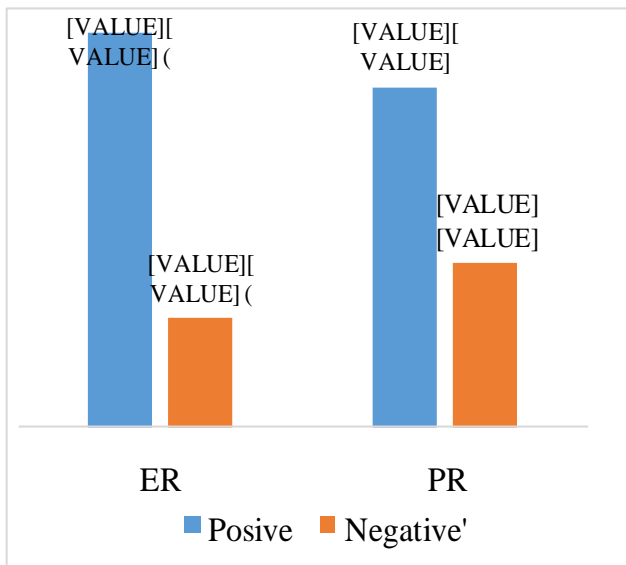Fig. 3: Histopathological type in Breast cancer Patients

Fig. 4: ER/PR Status

DISCUSSION

C-erbB-2 receptor belonged to tyrosine kinase family of proteins and it is a trans-membrane growth factor receptor.Its over expression is associated with poor response and poor prognosis in patients with cancer of breast[10].

Our study comprised of 120 cases of invasive breast cancer with average age of 43.3±12.5 years. Similar average age of the patients with cancer of breast was documented by Favret et al,[12] Naeem et al[13] and Sandhu et al.[14] In our study c-erbB-2 was positive in 42% patients and negative in 58%. Naeem et al,[13] found c-erbB-2 receptor positive in 45.8% patients of breast cancer which is in agreement with our study. On the other hand Naqvi et al[4] reported positive overesression of c-erbB-2 receptor in 31% patients. Alahwal MS[15] found 28.3% patients of breast positive for c-erbB-2 receptor. Ariga et al[16] reported in their study that 15% patients was found positive for c-erbB-2 receptor.

Naqvi et al,[17] in 2002 reported that positive over-expression of c-erbB-2 receptor was found in 33% patients of breast cancer. These studies are in contrast with our findings for c-erbB-2 receptor status.

Our study showed that 78.33% of cases had positive estrogen receptor expression while 67.5% expressed Progesterone. Expression of estrogen and progesterone in my study is high as compared to a study in Yemen with estrogen receptors expressed in 43.8% and progesterone receptors in 27% patients.[18] This is similar when compared to some Western studies which have reported 73% ER positivity and 58% PR positivity. Similar result also found in a study in Bangladesh where Estrogen Receptor expression was positive in 69%, PR expression was positive in 72.3% of patients[19].This variation may be because of different biological expression of breast cancer in different demographic profile.

In this study c-erbB-2 receptor found positive in 25% patients of age group 20-40 years and 51.32% in age group 41-60 years. Al-ahwal[15] has documented 34.1% of his young females (≤40 years) positive for c-erbB-2 receptor and 65.9% of those above 40 years of age. These findings are comparable with our findings.

Most of the females with cancer of breast were found with inavasive ductal carcinoma on histopathology which is comparable to other studies where more than 90% of breast cancers were invasive ductal carcinoma[13]. The most common histological grade was III 51% followed by Grade II 30% and Grade III was 19%. These findings are in contrast with a study conducted in Yemen in 2011

Table 1: Association of HER-2/neu receptor status with age

Age	HER-2/neu receptor status		Total
	Positive	Negative	
20-40	11(25%)	33(75%)	44(36.67%)
41-60	39(51.32%)	37(48.68%)	76(63.33%)
Total	50 (42%)	70 (58%)	120

P value: 0.006

Table 2: Relation of HER-2/neu receptor status with obesity

Obesity	HER-2/neu receptor status		Total
	Positive	Negative	
Obese	20(46.51%)	23(53.49%)	43(35.83%)
Non-obese	30(38.96%)	47(61.04%)	77(64.17%)
Total	50 (42%)	70 (58%)	120

P Value 0.446

where majority of patient presented with grade II (55.2%) followed by grade I (25.3%).[18] This is almost close to study conducted in India in 2011 where majority of histological grade was III (44%).[20]This difference in studies might be due to interplay of different etiological factor in different demographic profile.

In present study out of 43 obese patients, c-erbB-2 receptor was found positive in 46.51% patients and out of 77 non-obese patients, c-erbB-2 receptor was found positive in 38.96% patients. The association of c-erbB-2 receptor status with obesity was not statistically significant (P = 0.446). This was different to a study where c-erbB-2 receptor status was positively correlated with increasing BMI among post-menopausal women (p=0.048).[21]

CONCLUSION

In conclusion, study of c-erbB-2 receptor in breast cancer patients indicates that there are high rates of positive expression of these receptors. There is a significant correlation between c-erbB-2 receptor and younger age group. C-erbB-2 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 trastuzumab and anthracycline based chemotherapeutic agents. There is also need to explore c-erbB-2 receptor correlation with other etiological factors especially in young people.

REFERENCES

1. Naeem M, Nasir A, Aman Z, Ahmad T, Samad A. Frequency of HER-2/neu receptor positivity and its association with other features of breast cancer. J Ayub Med Coll Abbottabad. 2008 Sep;20(3):23–6.
2. Dutta V, Chopra G, Sahai K, Nema S. Hormone receptors, Her-2/neu and chromosomal aberrations in breast cancer. Med J Armed Forces India. 2008 Jan;64(1):11–5.
3. Brunicardi FC. Schwartz's principles of surgery. 9th ed. USA. Mcgraw Hill; 2010
4. Naqvi SQH, Naqvi A, Anwar M, Khan MS, Akhund AA. Significance of HER-2/neuOncoprotein overexpression in invasive ductal breast cancer. Ann AbbasiShaheedHosp Karachi Med Dent Coll 2007;12:79–83.
5. Sherman ME, Rimm DL, Yang XR, Chatterjee N, Brinton LA, Lissowska J, et al. Variation in breast cancer hormone receptor and HER2 levels by etiologic factors: a population-based analysis. Int J Cancer. 2007 Sep 1;121(5):1079–85.
6. Eliassen AH, Colditz GA, Rosner B, Willett WC, Hankinson SE. Adult weight change and risk of postmenopausal breast cancer. JAMA 2006;296:193–201.
7. Panjwani P, Epari S, Karpate A, Shirsat H, Rajsekharan P, Basak R, et al. Assessment of HER-2/neu status in breast cancer using fluorescence in situ hybridization & immunohistochemistry: experience of a tertiary cancer referral centre in India. Indian J Med Res. 2010 Sep;132:287–94.
8. Payne SJ, Bowen RL, Jones JL, Wells CA. Predictive markers in breast cancer - the present. Histopathology 2008;52:82-90.
9. Walker RA. Use and assessment of diagnostic and predictive markers in breast pathology. Current Diagnostic Pathology. 2007 Apr;13(2):126–34.
10. Vaidyanathan K, Kumar P, Reddy CO, Deshmane V, Somasundaram K, Mukherjee G. ErbB-2 expression and its association with other biological parameters of breast cancer among Indian women. Indian J Cancer. 2010 Mar;47(1):8–15.
11. Arafah M: Hormone Receptors and Her 2/neu in Breast CancerCilt/Vol. 26, No. 3, 2010; Sayfa/Page 209-215.
12. Favret AM, et al: Locally advanced breast cancer: Is surgery necessary? Breast J 7:131, 2001. [PMID: 11328324]
13. Naeem M, Nasir A, Aman Z, Ahmad T, Samad A. Frequency of HER-2/neu receptor positivity and its association with other features of breast cancer. J Ayub Med Coll Abbottabad. 2008 Sep;20(3):23–6.
14. Sandhu DS, Sandhu S, Karwasra RK, Marwah S. Profile of breast cancer patients at a tertiary care hospital in north India. Indian J Cancer. 2010 Mar;47(1):16–22.
15. Alahwal MS. HER-2 positivity and correlations with other histopathologic features in Breast Cancer patients–hospital basd study. J Pak Med Assoc 2006;56: 65–8.
16. Ariga R, Zarif A, Korasick J, Reddy V, Siziopikou K, Gattuso P. correlation of HER-2/neu gene amplification with other prognostic and predictive factors in female breast carcinoma. Breast J 2005;11:278–80.
17. Naqvi SQH, Jamal Q, Mahmood RK, Zaidi SMH, Abbass F. Significance of HER-2/neuOncoprotein Overexpression on node positive invasive breast cancer. J CollPhysSurg Pak 2002;12:534–7.
18. Favret AM, Carlson RW, Goffinet DR, Jeffrey SS, Dirbas FM, Stockdale FE. Locally advanced breast cancer: is surgery necessary? Breast J. 2001 Apr;7(2):131–7.
19. Mostafa M, larsen M, and loveR.Estrogen Receptor, Progesterone Receptor, and Her-2/neu Oncogene Expression in Breast Cancers Among Bangladeshi Women. J Bangladesh CollPhys Surg. 2010; 28(3): 157–162.
20. Shet T, Agrawal A, Nadkarni M, et al (2009). Hormone receptors over the last 8 years in a cancer referral center in India: what was and what is? Indian J Pathol Microbiol,52,171-4.
21. Li J, Huang Y, Zhang B-N, Fan J-H, Huang R, Zhang P, et al. Body mass index and breast cancer defined by biological receptor status in pre-menopausal and post-menopausal women: a multicenter study in China. PLoS ONE. 2014;9(1):e87224.