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Association Between Level of Expression of Human Epidermal Growth Factor Receptor 2 (Her-2 Neu) And Age Among Breast Cancer Patients

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ABSTRACT

Objective: To determine the association between human epidermal growth factor receptor 2 with age among patients presenting with breast cancer.

Study Design: Comparative cross-sectional study.

Place and Duration of Study: Medical Oncology Department, Jinnah Postgraduate Medical Centre, Karachi Pakistan, from Aug 2019-Jan 2020.

Methodology: Total 194 females of age 20-85 years with confirmed diagnosis of breast cancer were included in the study. The immunohistochemistry was done for the status of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 and the validation of human epidermal growth factor receptor 2 was done by Fluorescent In situ Hybridization technique in each female.

Results: The patient's age was from 24-82 years old with mean age of 46.57±11.45 year. Out of 194, 108 cases had positive progesterone receptor expression (55.7%), 114 had positive estrogen receptor expression (58.8%) and 67 had positive human epidermal growth factor receptor 2 expression (34.5%). The females of age greater 46 years were more likely to be human epidermal growth factor receptor 2 positive as compared to females of age less and equal to 46 years.

Conclusion: The results showed that females with age more than 40 years have significant association with human epidermal growth factor receptor 2, whereas age is an independent variable with regards to estrogen receptor and progesterone receptor status.

Keywords: Age, breast cancer, biomarkers, estrogen receptor (ER), human epidermal growth factor receptor 2 (HER 2 NEU), progesterone receptor (PR).

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INTRODUCTION

HER-2/NEU is abbreviated as human epidermal growth factor receptor 2 and is an erythroblastic cancerous gene. It is a part of epidermal growth receptor family. It is also known as c-erbB-2 oncogene.[1] The overexpression of this oncogene is found in different variety of cancers like ovaries, stomach, oral cavity, colon, pancreas and breast. Unfortunately, overexpression of HER-2/NEU gene in breast cancer leads to worst prognosis and lesser survival for the patient. However, the suppression of this gene results in suppressing malignant cells, ultimately increasing survival for the patients. Incongruities have been found among studies where HER-2/NEU genes are also found to be associated with chemo-resistance 2. Human epidermal growth factor receptor.[2] is sometimes amplified and localised with another oncogene gene GRB7 found in specially breast and testicular cells. It is amplified in up to 30% breast malignancies and has great predictive and prognostic applications. [3]

The overexpression and amplification of HER-2/NEU has been regarded as a biomarker of prognosis and eligibility to offer HER-2/NEU targeted therapy. It has become one of the most effect way to target its repression via chemotherapy.[4] HER-2/NEU and progesterone receptors are partially regulated by oestrogen hormones. oestrogen functions in way to upregulate progesterone but down regulate HER/2 NEU.[5] Consequently, ER positive breast cancers shows inverse relation with HER/2 NEU and progesterone receptors. Suggesting strong prediction for PR–ve status where +ve HER2/neu is found and ER positive breast cancer is confirmed.[6, 7]

According to the literature, breast carcinoma is more common in western populace as compare to Asian populace. Numerous evidences have shown that age is an imperative risk factor in developing breast carcinoma. In Asian populace, the most likely age of cancer is between 40 to 50 years.[8] However, in western population breast carcinoma develops at older ages

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between 60 to 70 years.[9] Evidence suggest that overexpression and amplification of HER-2/NEU leads to oncogenesis, shortens disease free survival, provides worst prognosis and worst outcomes.[3]

There is very little data available for the prevalence and incidence of breast cancer sub types. Literature have shown statistics with regards to breast carcinoma as a whole. Similarly, there is paucity of data in the context of age. There are reported age-related associations of breast cancer in one study conducted by Huang *et al*.[10]. Additionally, different ethnicities have been reported to show different results in breast cancer patients. It is stated that the features of breast carcinoma in Asian population is dissimilar as compare to other countries in terms of onset of tumour which shows a moderately younger middle age at the time of diagnosis. There is dearth of data regarding reproductive status and HER-2/NEU. Therefore, it is significantly crucial to find out association between level of expression of her-2 neu and age among breast cancer patients.

METHODOLOGY

The comparative cross-sectional study was carried out at Medical oncology department of, Jinnah Postgraduate Medical Centre Karachi from Aug 2019-Jan 2020. The sample size of 194 was estimated using WHO sample size calculator by taking statistics of HER-2/neu positive as 11.5%.[11] margin of error as 4.5% and 95% confidence level.

Inclusion Criteria: Female patients of age 20-85 years with confirmed diagnosis of breast cancer were included.

Exclusion Criteria: The patients with pleural effusion, bilateral breast cancer, metastatic disease, as-cites or pregnant ladies were excluded from the study.

The ethical approval was sought from Institutional Review Committee (NO.F.2-81-IRB/2019-GENL/32732/JPMC). Written informed consent was taken from eligible patients. The immunohistochemistry (IHC) was done for the status of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2/Neu) and the validation of Her-2/Neu was done by Fluorescent In situ Hybridization.[12] technique in each female. Data regarding age, stage of tumor, grade of tumor and histological type were noted on predesigned questionnaire. The data was processed using SPSS version 23. For qualitative variables, frequencies and percentages were reported, whereas for quantitative variables mean and standard deviation were measured. Chi-square was applied to see the relationship between variables. A p-value≤0.05 was taken as statistically significant.

RESULTS

Out of 194, 108 cases had positive PR expression (55.7%), 114 had positive ER expression (58.8%) and 67 had positive HER-2/neu expression (34.5%) (Figure).

The patient's age was from 24-82 years old with mean age of 46.57±11.45 year. We have classified patients into 9 age groups with a difference of five years on the basis of H.J. Huang's methodology,

Table-I: Relationship of Her-2/Neu with Estrogen Receptor (Er) and Progesterone Receptor (Pr) In Females By Age Difference of Five Years (n=194)

Age groups	Estrogen receptor	HER 2 NEU		*p*-value	Progesterone Receptor	HER 2 NEU		*p*-value
		+ve n(%)	-ve n(%)			+ve n(%)	-ve n(%)	
≤ 35 years	+ve	5(83.3)	1(16.7)	0.37	+ve	4(66.7)	2(33.3)	0.161
	-ve	17(56.7)	13(43.3)		-ve	9(30)	21(70)	
36-40 years	+ve	8(66.7)	4(33.3)	0.273	+ve	10(83.3)	2(16.7)	0.139
	-ve	8(40)	12(60)		-ve	11(55)	9(45)	
41-45 years	+ve	6(85.7)	1(14.3)	0.027	+ve	6(85.7)	1(14.3)	0.378
	-ve	8(32)	17(68)		-ve	16(64)	9(36)	
46-50 years	+ve	15(88.2)	2(11.8)	0.017	+ve	13(76.5)	4(23.5)	0.187
	-ve	11(47.8)	12(52.2)		-ve	12(52.2)	11(47.8)	
51-55 years	+ve	6(85.7)	1(14.3)	0.596	+ve	5(71.4)	2(28.6)	0.637
	-ve	7(63.6)	4(36.4)		-ve	6(54.5)	5(45.5)	
56-60 years	+ve	5(71.4)	2(28.6)	0.999	+ve	6(85.7)	1(14.3)	0.009
	-ve	6(66.7)	3(33.3)		-ve	1(11.1)	8(88.9)	
61-65 years	+ve	4(100)	0	0.167	+ve	0	4(100)	0.048
	-ve	2(40)	3(60)		-ve	4(80)	1(20)	
66-70 years	+ve	3(75)	1(25)	0.143	+ve	2(50)	2(50)	0.492
	-ve	0	3(100)		-ve	0	3(1000	
> 70 years	+ve	2(66.7)	1(33.3)	0.999	+ve	2(66.7)	1(33.3)	0.999
	-ve	1(100)	0		-ve	1(100)	0	

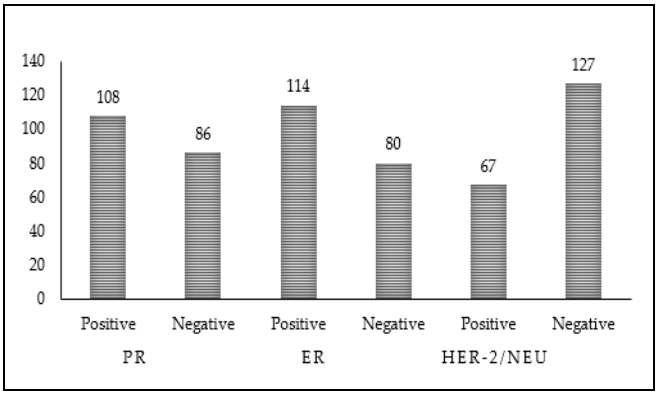

Figure: Frequency Distribution of Hormonal Receptors

starting at age less than and equal to 35 years and ending at age greater than 70 years.[10] The association between ER status and HER-2 Neu status were displayed in above mentioned Table-I. Positive association was found ER status and HER-2 Neu status in females of aged 41-45 years and 46-50 years (p<0.05). However no significant relationship was found in age less than 41 years and more than 50 years. There was a statistically significant relationship between PR status and HER-2/neu in females of aged 56-60 years and 61-65 years, but no relationship was found in other age groups.

On the basis of mean age of the females, we have divided the entire patients into two age groups (age ≤46 years and age>46 years) and these age groups were compared with clinic-pathological characteristics. The females of age greater 46 years were more likely to be HER-2 Neu positive as compared to females of age less and equal to 46 years (Table-II).

In Table-III Her-2/neu is compared with clinicopathological characteristics and Her-2/neu showed positive and significant association with ER and PR expressions (p<0.05).

DISCUSSION

The present study has determined association of age with HER-2neu status among breast cancer patients. In contrast to western countries, there is little information about any association between age and her-2neu expression level in this part of the world. Researches have shown discrepancies about the incidence and prevalence, treatment provided, patient compliance and screening among different population in patients having breast cancer.[13-17]. Wang *et al*. showed around 28% of positive HER-2/NEU expression.[11]

Table-II: Comparison of Age with Clinicopathological Characteristics (n=194)

Variables		Age Group ≤46 years (n=103)	Age Group >46 years (n=91)	*p*-value
Estrogen receptor				
Positive	n	55	59	0.106
	%	48.2	51.8	
Negative	n	48	32	
	%	60	40	
Progesterone receptor				
Positive	n	58	50	0.848
	%	53.7	46.3	
Negative	n	45	41	
	%	52.3	47.7	
Human epidermal growth factor receptor 2				
Positive	n	25	42	0.001*
	%	37.3	62.7	
Negative	n	78	49	
	%	61.4	38.6	
Stage				
I	n	6	4	0.607
	%	60	40	
II	n	26	19	
	%	57.8	42.2	
III	n	40	44	
	%	47.6	52.4	
IV	n	31	24	
	%	56.4	43.6	
Grade				
I	n	2	3	0.454
	%	40	60	
II	n	62	47	
	%	56.9	43.1	
III	n	39	41	
	%	48.8	51.3	
Histological subtype				
Infiltrating ductal carcinoma	n	92	85	0.315
	%	52	48	
Lobular cancer	n	11	6	
	%	64.7	35.3	

Table-III: Comparison of Her2/Neu Status with Clinicopathological Characteristics (n=194)

	Human Epidermal Growth Factor Receptor 2 +ve	Human Epidermal Growth Factor Receptor 2 -ve	*p*-value	OR(95% CL)
Estrogen receptor				
+ve	54	60	0.001	4.63 (2.30-9.32)
-ve	13	67		
Progesterone receptor				
+ve	48	60	0.001	2.82 (1.49-5.32)
-ve	19	67		
Stage				
I-II	20	35	0.736	1.19 (0.58-2.14)
III-IV	47	92		
Grade				
I-II	42	72	0.42	1.28 (0.69-2.35)
III	25	55		
Histological type				
IDC	61	116	0.945	0.96 (0.34-2.73)
ILC	6	11		

In Pakistan, around 43% of breast cancer patients were hormone receptor positive. About 58% of the breast cancer patients had third stage carcinoma and 8.7% had HER-2 positive with 51% positive hormone receptor.[18] Literature have also found that in pre-menopausal women there is no association between lesser response to anti-oestrogens and overexpression of HER2/NEU in ER positive breast cancer.[19] Similarly other study also claimed insignificant association between HER-2/NEU and menopausal status or any stage of tum-our.[20] Clavel-Chapelon *et al*. has found out that wide variety of inconsistencies with regards to breast cancer between pre and post-menopausal women have been established.[21] The present study findings are in con-currence with two studies,[10,11] conducted on this topic.

The current study results showed positive association between ER status and HER-2 Neu status and females of age between 41 to 45 years and 46 to 50 years (p<0.05). However, no significant relationship was found in age less than 41 years and more than 50 years. There was a statistically significant relationship between PR status and HER-2/neu in females of aged 56-60 years and 61-65 years, but no relationship was found in other age groups. Ma *et al*. determined the overexpression among young women between 35 to 44 years.[22] Li *et al*. suggested that overexpression of HER/NEU is not associated with either birth age or menopausal age.[23]

The univariate analysis in the current study results also showed that age is not an important factor in predicting ER or PR status or staging of the cancer. However, females of age greater 46 years were more likely to be HER-2 Neu positive as compared to females of age less and equal to 46 years. Similar analysis carried out in other studies showed that lymph node status, tumour size more than twenty millimetre and age less than 45 years are not predicted by positive HER2/NEU status.[20,24] Present results showed that clinicopathological characteristics of HER-2/NEU positive and significant association with ER and PR expressions (p<0.05).

CONCLUSION

The results showed that females with age more than 40 years have significant association with HER2/NEU receptor and age more than 40years are associated with increased expression of HER-2 NEU. The results should be considered as prognostic factor while treating the breast cancer patients.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MA: & GH: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

MA: & TA: Conception, study design, drafting the manuscript, approval of the final version to be published.

ASQ: & WHS**:** Critical review, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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