ORIGINAL ARTICLE

FREQUENCY OF HORMONE RECEPTORS AND HER-2/NEU RECEPTOR POSITIVITY IN DIFFERENT HISTOLOGY IN BREAST CANCER PATIENTS

Ramchandani Ravi, Ghulam Haider, Khalil Ahmed, Saima Zahoor, Abdus Sami, Ramchandani Lata*

Department of Medical Oncology, Jinnah Postgraduate Medical Centre Karachi, Sindh-Pakistan

Background: This study was conducted to see the frequency of hormone receptors and Her-2/Neu positivity in different histology in breast cancer patients. **Methods:** It was a cross-sectional study conducted at the Department of Medical Oncology, Jinnah Postgraduate Medical Centre from June 2018-March 2019. Total 373 patients of age 22–81 years of which 360 female and 13 males, with histopathological proven diagnosis of breast cancer were included in the study using non-probability consecutive sampling technique. The immunohistochemistry (IHC) was performed on biopsy sample for the status of PR, ER and HER-2/Neu and the confirmation of Her-2/Neu was done by Fluorescent In situ Hybridization (FISH) technique if HER-2/Neu was equivocal by IHC testing. Information regarding demographics, family history, histology, grade, stage, metastatic site and other histopathological parameters were noted on predesigned proforma by the researcher. SPSS-23 was used to analyse data. **Results:** Total of 373 patients were included in the study. The mean patient age was 45.34±12.28 years. ER, PR, Her 2 Neu (IHC) & Her 2 Neu (FISH) were found positive in 206 (55.2%), 182 (48.8%), 121 (32.4%) & 23 (6.2%) patients, respectively. The histology with PR receptor & grade of tumour with ER & PR receptor showed statistical significance ($p<0.05$). **Conclusion:** ER, PR &HER-2/NEU expressions in breast cancer vary among different population and it is very important to find out the frequency among different histopathological types as it is of predictive and prognostic value. So, it is recommended to look for these markers and treat them accordingly.

Keywords: Breast cancer; progesterone receptor; Oestrogen receptor; HER-2/NEU receptor

Citation: Ravi R, Haider G, Ahmed K, Zahoor S, Sami A, Lata R. Frequency of hormone receptors and her-2/neu receptor positivity in different histology in breast cancer patients. J Ayub Med Coll Abbottabad 2020;32(3):323–6.

INTRODUCTION

Breast cancer is one of the frequent causes of death in females. Almost 8–10% of females are exposed to risk of having breast cancer during her lifetime.[1] In Western countries breast cancer is more common in older females (after 60 years) where as in Pakistan it is prevalent among younger females.[2] The breast malignancies are highly diverse with an extensive range of predictive and prognostic factors.[3] In the absence of systematic treatment, these prognostic factors are used to evaluate the disease prognosis & outcome whereas predictive factors used to identify response to therapy. The predictive factors such as hormone receptors & HER-2/NEU status have a huge impact on clinical outcomes.[4,5]

The progesterone receptor "PR" and oestrogen receptor "ER" statuses are the crucial factors for the progression and proliferation of breast cancer.[3] They are intracellular steroid receptor used as therapeutic and prognostic tools for the management of breast malignancy along with human epidermal growth factor receptor type 2 (HER-2/NEU).[4,6,] In breast cancer patients the measurable quantity of ER & PR are reported as 50–85%. The levels & positivity of ER & PR rise with age and highest levels are reported in postmenopausal females[7]The positivity of hormone receptors gives option for additional adjuvant or palliative hormonal therapy such as selective oestrogen receptor modulator (e.g. tamoxifen) or aromatase inhibitor (e.g. letrozole and anastrozole). The over expression of HER-2/NEU has been seen in high grade tumours and showed lower response rate to hormone receptor modulators when tumour is concomitantly ER or PR positive. HER-2/NEU is the marker for decreased disease-free survival in lymph node positive breast tumors.[6] It has been seen that larger tumour size, tumour grade, aggressive histopathological type and higher degree of lymph node involvement is associated with PR, ER negativity & HER-2/NEU positivity. Her2/neu positivity gives options for targeted therapy in setting of adjuvant, neoadjuvant or palliative treatment. In Pakistani population above 60% of the breast cancer patients presented with the advanced stage of the disease unlike America and Europe, due to lack of health awareness, lack of facilities, poor socioeconomic status,delay diagnosis and expense of treatment.[4] So, this study was carried out to note the frequency of hormone receptors and Her-2/Neu positivity in different histology in breast cancer patients.

MATERIAL AND METHOD

It was a cross-sectional study conducted at the department of Medical Oncology, Jinnah Postgraduate Medical

Centre from June 2018 to March 2019. The sample size was estimated using Open Epi sample size by taking statistics of positive Her-2/Neu expression as 38.9%[4], margin of error as 5% & 95% confidence interval. The calculated sample sizeu came out as 366 cases however we have included 373 cases in our study. Newly diagnosed female and male patients of age 22-81 years treatment naïve with histopathological proven diagnosis of common breast cancer histology of either insitu or invasive carcinoma were included in the study using non-probability consecutive sampling technique. The patients with other histology of breast cancer (excluding insitu or invasive carcinoma like lymphoma, phyllodes, sarcoma of breast), pregnant or who had history of therapeutic intervention were excluded from the study.

The approval from ethical review committee was taken before conduct of the study. After taking informed consent from the patients' data was collected. The immunohistochemistry was performed for the status of PR, ER and HER-2/Neu on biopsy sample and the confirmation of Her-2/Neu was done by Fluorescent In situ Hybridization (FISH) technique if HER-2/Neu was equivocal, i.e., 2+ on by IHC testing. If HER-2/Neu was negative, i.e., 1+ or positive, i.e., 3+ on IHC then no need of confirmation by FISH testing. Information regarding demographics, family history, histology, grade, stage, metastatic site and other histopathological parameters were noted on predesigned proforma by the researcher.

SPSS-23 was used to analyse data. Frequencies and percentages were reported for qualitative variables whereas mean and standard deviation were calculated for quantitative variables. Chi-square was applied to the difference of outcome variable with respect to histology, grade and stage of tumour. *p*-value <0.05 was taken as statistically significant.

RESULTS

Total of 373 patients were included in the study. The mean patient age was 45.34±12.28 years. Majority of the patients were females (96.5%) as compared to males (3.5%). About 49.3% patients were married, 27 (7.2%) patients had family history of breast cancer in first- or second-degree relatives, 47 (12.6%) patient had history of other solid malignancy other than breast cancer and 299 patients showed no family history of malignancy. The most common histology of breast tumour was invasive ductal (80.7%). Majority of the patients had grade 3 of tumour (49.9%). About 68.1% cases had lymphatic invasion, 43.4% had vascular invasion & only 30% had neural invasion. Unilateral breast cancer was present in 91.4% of the cases. Most of the patients had stage 3 (42.1%) & 2 (31.4%) of carcinoma. The most frequent site of distant metastases were lungs (15%) followed by bone (6.4%), liver (2.4%) and brain (0.8%). (Table-2)

The frequency distribution of hormone receptors & Her-2/Neu are shown in Table-1. ER, PR, Her 2 Neu (by IHC) & Her 2 Neu (by FISH) were found positive in 206 (55.2%), 182 (48.8%), 121 (32.4%) & 23 (6.2%) patients, respectively. (Table-3)

The difference of ER, PR, and Her-2/ Neu receptors with respect to histology, grade and stage of tumour is shown in table-3. The histology with PR receptor, grade of tumour with ER & PR receptor showed statistical significance ($p<0.05$).

Table-1: Frequency of hormone receptors and her-2/neu receptor positivity

	Negative (%)	Weak (%)	Positive (%)
ER	32.2	12.6	55.2
PR	39.4	11.8	48.8
HER-2/Neu receptor (IHC)	50.9	16.6	32.4
HER-2/Neu (FISH)	10.5	No Need	6.2

Table-2: Baseline characteristics of study sample

Variable	n (%)	Variable	n (%)
Age Groups		Grade of Tumour	
≤40 years	153 (41)	Grade 1	9 (2.4)
>40 years	220 (59)	Grade 2	178 (47.7)
Mean±SD	45.34±12.28	Grade 3	186 (49.9)
Gender		Lymphatic Invasion	
Male	13 (3.5)	Yes	254 (68.1)
Female	360 (96.5)	No	119 (31.9)
Marital Status		Vascular Invasion	
Married	184 (49.3)	Yes	162 (43.4)
Unmarried	182 (48.8)	No	211 (56.6)
Divorced	7 (1.9)	Neural Invasion	
Family history of malignancy		Yes	112 (30)
Breast tumour	27 (7.2)	No	261 (70)
Other Malignancy	47 (12.6)	Breast involvement	
None	299 (80.2)	Unilateral	341 (91.4)
Histology		Bilateral	32 (8.6)
Invasive ductal	301 (80.7)	Stage	
Invasive lobular	23 (6.2)	I	5 (1.3)
Invasive lobular+ductal	3 (0.8)	II	117 (31.4)
Tubular	1 (0.3)	III	157 (42.1)
Mucinous	7 (1.9)	IV	94 (25.2)
Medullary	4 (1.1)	Metastatic site	
Metaplastic	12 (3.2)	Lungs	56 (15)
Inflammatory	2 (0.5)	Liver	9 (2.4)
Undifferentiated	1 (0.3)	Bone	24 (6.4)
Ductal carcinoma in situ	11 (2.9)	Brain	3 (0.8)
Lobular carcinoma in situ	3 (0.8)	Other	1 (0.3)
invasive NOS	1 (0.3)	None	280 (75.1)
Squamous carcinoma	2 (0.5)		
Papillary carcinoma	2 (0.5)		

Table-3: Stratification of hormone receptors and her-2/neu receptor positivity with respect to histological subtypes

VARIABLES	ER				PR				HEU-2/neu Receptor (IHC)				HEU-2/neu (FISH)			
	Negative	weak	positive	*p*-value	negative	weak	positive	*p*-value	negative	weak	positive	*P*-value	negative	positive	no need	*p*-value
HISTOLOGY																
Invasive ductal	101	40	160		123	31	147	0.01	142	54	105		32	22	247	0.99
Invasive lobular	5	0	18		5	2	16		17	2	4		1	1	21	
Invasive lobular+ ductal	1	0	2		1	0	2		2	1	0		1	0	2	
Invasive tubular	0	1	0		0	1	0		0	0	1		0	0	1	
Invasive mucinous	0	0	7		1	0	6		5	0	2		0	0	7	
Invasive medullary	2	0	2		1	0	3		1	1	2		1	0	3	
Metaplastic	5	4	3	0.06	7	4	1		9	1	2		1	0	11	
Inflammatory	1	0	1		1	0	1		2	0	0		0	0	2	
Undifferentiated	0	0	1		0	1	0		1	0	0	0.55	0	0	1	
Ductal carcinoma in situ	3	1	7		7	1	3		5	2	4		2	0	9	
Lobular carcinoma in situ	1	0	2		0	2	1		2	0	1		0	0	3	
Invasive NOS	0	1	0		0	1	0		1	0	0		0	0	1	
Squamous carcinoma	1	0	1		1	1	0		1	1	0		1	0	1	
Papillary carcinoma	0	0	2		0	0	2		2	0	0		0	0	2	
GRADE																
G1	2	0	7	0.01	2	0	7	0.01	5	0	4	0.64	0	0	9	0.45
G2	45	15	118		58	18	102		93	31	54		17	14	147	
G3	73	32	81		87	26	73		92	31	63		22	9	155	
STAGE																
I	0	0	5	0.24	0	1	4	0.59	5	0	0	0.08	0	0	5	0.27
II	42	10	65		47	15	55		59	25	33		12	13	92	
III	51	23	83		66	18	73		83	25	49		18	7	132	
IV	27	14	53		34	10	50		43	12	39		9	3	82	

DISCUSSION

The carcinoma of breast is most fatal disease among females. It is major cause of death in females in Pakistan. The management of breast cancer is quite extensive and depends upon various histological markers. The clinical outcomes of breast cancer are related to HER-2/NEU marker and ER PR levels. Hence, the study is conducted to ascertain the frequency of these chemical markers among different histopathological types of breast cancer.

In the current study, the mean age of female participants is 45.34±12.28 years which is almost similar to the study conducted in Peshawar[2] whereas findings were bit different in another study where mean age was 53.8±11.6 years.[8] The present study had focused on females and only 13 males were part of the study however this is contradictory to one Indian study conducted by Syeda *et al*[9], and other African study[10] where males and females both were enrolled and different populations were studied respectively.

In this study, it was found that most common histology of breast tumour was invasive ductal (80.7%) and majority of the patients had grade 3 of tumour (49.9%). These findings are analogous with Korean study conducted by Lee JH PS *et al*[11] and Japanese study carried out by Ohta T TF *et al* in the year 2005[12] that shows higher prevalence of invasive lobular carcinoma.

Overall, in the light of study by Radojicic J *et al* it can be stated that breast cancers can exist with negative ER, PR and Her2/neu markers and there is no significant relation with survival or disease free patient.[13] Conversely, Van de Ven *et al* reported that there was good response to HER2 with FISH while there was negative HER2 response in 43% patients when treated.[14] In addition, the findings are similar to Naeem M *et al* study where 46% patients had positive HER-2/neu receptor status however HER-2/neu receptor status was not statistically significant with different histopathological type ($p > 0.05$) and similar results with ER/PR status ($p < 0.05$).[2]

Moreover, the findings can be equivalent with Khabaz MN *at el* study. He reported that around

20% Sulaimaniyah women were HER2 positive with negative ER and PR status. But as no significant differences in ER or HER2 status were found between Kurdish and Arabic patients.[15] The findings are also similar to Lund Mj Be *et al*., Carey LA PC *et al*., Porter PL LM *et al* and Huang HJ NP *et al*. They reported that positive HER2 status was present among Kurds and Arabs that showed high grades of cancer. The study reports that approximately 22% patients had stage 3 cancers with ER negative and positive HER2.[16–19] It is also reported that in USA population there was less occurrence of positive HER 2 status.[15]

CONCLUSION

HER-2/NEU marker and ER PR levels vary among different population and it is very important to find out the frequency among different histopathological types as it is of predictive and prognostic value. So, it is recommended to look for these markers and treat them accordingly.

AUTHORS' CONTRIBUTION

RR: Literature search, conceptualization of study, data collection, data analysis, data interpretation, write-up, proof reading. GH: Conceptualization of study design, write-up, proof reading. KA: Data collection, write-up, proof reading. SZ , SQ: Write-up, proof reading. RL: Data collection, proof reading.

REFERENCES

1. Pietras RJ, Arboleda J, Reese DM, Wongvipat N, Pegram MD, Ramos L, *et al*. HER-2 tyrosine kinase pathway targets estrogen receptor and promotes hormone-independent growth in human breast cancer cells. Oncogene 1995;10(12):2435–46.
2. 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;20(3):23–6.
3. Sughayer MA, Al-Khawaja MM, Massarweh S, Al-Masri M. Prevalence of hormone receptors and HER2/neu in breast cancer cases in Jordan. Pathol Oncol Res 2006;12(2):83–6.
4. Faheem M, Mahmood H, Khurram M, Qasim U, Irfan J. Estrogen receptor, progesterone receptor, and Her 2 Neu positivity and its association with tumour characteristics and menopausal status in a breast cancer cohort from northern Pakistan. Ecancermedicalscience 2012;6:283.
5. DeVita VT, Lawrence TS, Rosenberg SA, editors. DeVita, Hellman, and Rosenberg's cancer: principles & practice of oncology. 9th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2011; p.2638.
6. Dutta V, Chopra GS, Sahai K, Nema SK. Hormone Receptors, Her-2/Neu and Chromosomal Aberrations in Breast Cancer. Med J Armed Forces India 2008;64(1):11–5.
7. Masood S. Assessment of prognostic factors in breast fine-needle aspirates. Am J Clin Pathol 2000;113(5 Suppl 1):S84–96.
8. Ambroise M, Ghosh M, Mallikarjuna VS, Kurian A. Immunohistochemical profile of breast cancer patients at a tertiary care hospital in South India. Asian Pac J Cancer Prev 2011;12(3):625–9.
9. Zubeda S, Kaipa PR, Shaik NA, Mohiuddin MK, Vaidya S, Pavani B, *et al*. Her-2/neu status: a neglected marker of prognostication and management of breast cancer patients in India. Asian Pac J Cancer Prev 2013;14(4):2231–5.
10. Stark A, Kleer CG, Martin I, Awuah B, Nsiah-Asare A, Takyi V, *et al*. African ancestry and higher prevalence of triple-negative breast cancer: findings from an international study. Cancer 2010;116(21):4926–32.
11. Lee JH PS, Park HS, Park BW. Clinicopathological features of infiltrating lobular carcinomas comparing with infiltrating ductal carcinomas: a case control study. World J Surg Oncol 2010;8(1):34–10.
12. Ohta T, Tusjimoto F, Nakajima Y, Fukuda M, Takag M. Ultrasonographic findings of invasive lobular carcinoma differentiation of invasive lobular carcinoma from invasive ductal carcinoma by ultrasonography. Breast Cancer 2005;12(4):8–10.
13. Radojicic J, Zaravinos A, Vrekoussis T, Kafousi M, Spandidos DA, Stathopoulos EN. MicroRNA expression analysis in triple-negative (ER, PR and Her2/neu) breast cancer. Cell Cycle 2011;10(3):507–17.
14. Van de Ven S, Smit VT, Dekker TJ, Nortier JW, Kroep JR. Discordances in ER, PR and HER2 receptors after neoadjuvant chemotherapy in breast cancer. Cancer Treat Rev 2011;37(6):422–30.
15. Khabaz MN. Immunohistochemistry subtypes (ER/PR/HER) of breast cancer: where do we stand in the West of Saudi Arabia. Asian Pac J Cancer Prev 2014;15(19):8395–400.
16. Lund MJ BE, Hair BY, Ward KC, Andrews JH, Oprea-Ilies G, Bayakly AR, *et al*. Age/race differences in HER2 testing and in incidence rates for breast cancer triple subtypes: a population-based study and first report. Cancer 2010;116(11):2549–59.
17. Carey LA PC, Livasy CA, Dressler LG, Cowan D, Conway K, Karaca G, *et al*. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA 2006;295(21):2492–502.
18. Porter PL, Lund MJ, Lin MG, Yuan X, Liff JM, Flagg EW, *et al*. Racial differences in the expression of cell cycle-regulatory proteins in breast carcinoma. Cancer 2004;100(12):2533–42.
19. Huang HJ, Neven P, Drijkoningen M, Paridaens R, Wildiers H, Van Limbergen E, *et al*. Hormone receptors do not predict the HER2/neu status in all age groups of women with an operable breast cancer. Ann Oncol 2005;16(11):1755–61.

Submitted: May 9, 2019	*Revised: September 27, 2019*	*Accepted: September 30, 2019*

Address for Correspondence:

Dr. Ramchandani Ravi, Department of Medical Oncology, Jinnah postgraduate medical Centre Karachi-Pakistan
Cell: +92 336 813 0612
Email: ramchandaniravi86@gmail.com