

ORIGINAL ARTICLE

Analysis of Breast Cancer Receptors Status and Molecular Subtypes Among Female PopulationSAMEENA NAZ¹, MASHALL SIDDIQUI², AMIR IQBAL MEMON³, AISHA MASROOR BHATTI¹, ZOIYA INAYAT HUSSAIN¹, IQRA¹¹Department of Surgery, L.U.M.H.S, Jamshoro.²Consultant at Bahria Town International Hospital, Karachi.³Professor & Head of Dept. of Surgery (Unit II), L.U.M.H.S, Jamshoro.Corresponding author: Sameena Naz, Email: drsaminamansoor@gmail.com**ABSTRACT**

One of the leading cause of deaths in women is breast cancer. The incidence and prevalence of cancer is increasing day by day. The aim of this research was to analyse the relationship between HRS (hormonal receptor status) and age in females suffering from breast cancer. It was a cross-sectional study conducted at surgical department, LUMHS, Jamshoro, Sindh, Pakistan. The 200 females diagnosed with breast cancer were included in research. The mean age of the study sample was observed to be 48.68 ± 9.54 years. Out of 200 females, 79 (39.5%) females had positive expression of "ER (estrogen receptor)" while 80, (40%) had positive "PR (progesterone receptor)" expression and 41(20.5%) females were associated with "positive expression of HER2/neu (human epidermal growth factor receptor 2)". The age group of 41-50 years showed (30.4%) highest ratio of positive ER followed by (24%) PR and (17.5%) "HER/2 neu expression" respectively. A statistically significant correlation was found between ER expression and age and ($p=0.013$), PR expression and age and ($p=0.002$) while HER/2 neu expression showed insignificant correlation ($p=0.231$). The research also found that most of the females in their 40s were suffering from breast cancer also the older women had positive were "estrogen receptor (ER), progesterone receptor (PR), and HER2/neu expression" as compared to younger females but there are high chances of survival if breast cancer is diagnosed and managed timely. To do so awareness regarding self-care and self-analysis for women is important to prevent the prognosis of breast cancer.

Keywords: Breast Cancer, hormonal receptor status, estrogen, progesterone**INTRODUCTION**

One of the most common type of cancers in females is the breast cancer effecting every eighth women across the globe (Akram et al., 2017). Breast cancer is responsible for more than 16% of all malignancies and 25% of all invasive cancers in women (Aliyu & Musa, 2020). According to the WHO (World Health Organization) approximately more than 2.5 million women were diagnosed with breast cancer and it accounts for more than 685,000 mortalities in 2020-2021. Breast cancer is prevalent in females of every country including developed countries. After puberty breast cancer can be develop at any age and the risks of its development increases with the increase in age (Biro et al., 2021). In different regions of United States and Western Europe, 62 years of age is the mean age for the presentation of breast cancer, however, in Middle East and Asian countries (Youn & Han, 2020), the mean age for the diagnosis of breast cancer is relatively lower, like the mean age for breast cancer development in Pakistan is 47.5 years (Khan et al., 2021), in Saudi Arabia it is 48.8 years (Almutlaq et al., 2017) and in India mean age is 51.92 years (AlZaman et al., 2016).

According to Fredholm et al the prognosis of breast cancer in younger females is more aggressive and is advance in comparison to older females (Fredholm et al., 2009). It is evident that females in their younger age are prone to antagonistic spread of breast cancer as the low age is highly associated with fluctuation in hormones, intense hormonal changes and activation of cancer due to hormone receptor along with higher grades tumours, which are mostly poorly differentiated. Moreover, age is one of the important variable responsible for overexpression of various hormones and factors especially "HER2/neu (human epidermal growth factor receptor 2)" which is involved in worse prognosis of breast cancer (Fredholm et al., 2009; Pourzand et al., 2011). However, breast cancer is treatable if managed effectively but the treatment strategies of breast cancer are highly dependent on various physiological and anatomical factors, such as "age of patient", "stage of cancer", "size of tumour", "menopausal status", expression of, "HER2/neu", "hormone receptor status" and "status of axillary nodes" (Ruder et al., 1989). There is not much research conducted on association of hormonal status, age and prevalence of breast cancer among the females of Pakistan. The ethnic groups are also related with status of hormone receptor. However, it is still unclear how age effects the hormone receptor status. Therefore, this present research was designed to analyse the

correlation of hormone receptor status and age of females suffering from breast cancer.

MATERIALS & METHODS

It was a cross-sectional study was conducted at surgical department, LUMHS Jamshoro, Sindh, Pakistan, involving 200 female patients diagnosed with breast cancer, with age ranges from more than 18 years to 75 years from September 2021 to October 2022. The non-probability convenient sampling was used. The data was collected after getting the approval from hospital ethical committee and informed consent from the female patients. Females who with hysterectomy and pregnant women were excluded from the research. Data variables used were socio-demographics like age, hormonal replacement, menopausal status, family history of cancer/ breast cancer, and characteristics of tumour. Status of hormonal receptors was evaluated after performing IHC (Immunohistochemistry) determining the "status of lymph node, tumour stage and its location, type of cancer, laterality, as well as HRS (hormone receptor status) (progesterone, estrogen, HER2/neu)". The breast cancer was divided into "molecular subtypes such as luminal A and B, basal-like or triple-negative, and HER2/neu". All the cases of breast cancer reflecting "hormone-receptor positivity (estrogen-receptor and/or progesterone-receptor positive)", "HER2/neu negative", and have "low ki-67 protein ratio" were labelled as "luminal A subtype." The cases which were "hormone-receptor-positive with HER2/neu negativity or positivity and high levels of ki-67" were assigned as "luminal B subtype". "Triple-negative breast cancer contain both negative hormone-receptor status and HER2/neu". On the other hand, the cases where "hormone-receptor status was negative but "HER2/neu positive" were labelled as "HER/neu subtype".

The collected data was analysed using IBM SPSS 28. The variables were presented as frequency, percentages, mean and standard deviation. The correlation of age with HRS and molecular subtype was analysed using the chi-square and Pearson correlation test. A p-value of less than 0.05 was considered as statistical significant.

RESULTS

The mean age of the females included in the study with breast cancer was observed to be 48.68 ± 9.54 years. Most of the females belong to the rural areas, 86.5% of the females were

married, and 13.5% of the study population was unmarried. 89.5% of the female population had the history of breastfeeding, while 10.5% females did not have the breastfeeding history. 54.5% females were Premenopausal, while 45.5% were postmenopausal, 9% of the sample population had the family history of breast cancer, while 91% had the negative breast cancer history. Of 200 females, 6.5% were taking hormonal replacement therapy, and 93.5% of females were not taking any hormonal therapy (Table 1).

Almost 4.5% of the females had tumour size of 2-5 cm, 71.5% had moderately differentiated tumours and 9% had the tumour size of more than 5 cm, and 78% had positive and negative 22% lymph node status. Out of 200 females, majority of them 58.5% had to infiltrate ductal carcinoma, 66.3% possessed right-sided, the 60% females had tumours developed at the upper side of outer quadrant. Positive ER expression was observed in 39.5% females, followed by 40% had positive PR expression and positive HER2/neu expression accounts for 20.5% (Table 1).

Table 1: Basic and Clinical characteristics of research sample (n=200)

General Characteristics			
Research Variables	Response	N	%age
Marital status	Unmarried	27	13.5%
	Married	173	86.5%
Breastfeeding History	Yes	179	89.5%
	No	21	10.5%
Menopausal status	Premenopausal	109	54.5%
	Postmenopausal	91	45.5%
Family history of breast cancer	Yes	18	9%
	No	182	91%
Hormonal replacement	Yes	13	6.5%
	No	187	93.5%
Characteristics of Tumour			
Size of tumour	0-2 cm	09	4.5%
	2-5 cm	143	71.5%
	> 5cm	48	24%
Location of tumour	Upper inner quadrant	18	9%
	Lower inner quadrant	22	11%

	Central	02	1%
	Upper outer quadrant	120	60%
	Lower outer quadrant	38	19%
Grade of tumour	Poorly differentiated	51	25.5%
	Well differentiated	18	9%
	Moderately differentiated	131	65.5%
Status of lymph node	Positive	156	78%
	Negative	44	22%
Type of breast cancer	Infiltrating lobular carcinoma	24	12%
	Medullary carcinoma	59	29.5%
	Infiltrating ductal carcinoma	117	58.5%
Laterality	Bilateral	06	3%
	Right	133	66.5%
	Left	61	30.5%
Status of Hormone receptor	Positive Estrogen (ER)	79	39.5%
	Positive Progesterone (PR)	80	40%
	Positive HER2/neu	41	20.5%

The "luminal A" ratio and "luminal B" was observed in the age range of 41-50 years, accounting for 12.5% and 15.5% respectively. However, the "HER2/neu type" was more prevalent in age 30-40 years with 14.5% and 8% of "subtype triple-negative breast cancer" accounts for 8% was also observed in the same age group. There was observed in significant correlation between "molecular subtype" and age of the females suffering from breast cancer (p=0.279).

Additionally, the hormonal status analysis showed that "positive ER" was presented by the age group of 41-50 years comprising of 30.5 % while, "PR positive" presented 24%, as well as the "HER2/neu expressions" was observed to be 17.5%. Statistically significant correlation was found between "age group" and "ER expression" (p=0.013) and age and "PR expression" (p=0.002) conversely insignificant relation (p=0.231) was found between expression of HER2/neu and age (Table 2).

Table 2: Relation of hormonal receptor status, molecular subtype and age in females with breast cancer (n=200)

Age group	Breast cancer Subtype								Status of Hormonal receptor											
	Luminal A		Luminal B		HER2/neu type		Triple-negative		Estrogen Receptor (ER)				Progesterone Receptor (PR)				HER2/neu			
	N	%	N	%	N	%	N	%	+ve		-ve		+ve		-ve		+ve		-ve	
19-29	1	0.5	9	4.5	5	2.5	2	1	05	2.5	03	1.5	12	6	11	5.5	04	2	11	5.5
30-40	10	5	16	8	29	14.5	16	8	50	25	45	22.5	62	31	48	24	23	11.5	54	27
41-50	25	12.5	31	15.5	30	15	5	2.5	61	30.5	20	10	24	12	31	15.5	34	17	38	19
50-60	17	8.5	2	1	23	11.5	6	3	10	5	09	4.5	03	1.5	09	4.5	16	8	37	18.5
>70	3	1.5	2	1	1	0.5	3	1.5	03	1.5	01	0.5	01	0.5	02	1	04	2	01	0.5
P value	0.279								0.013				0.002				0.231			

DISCUSSION

Various research studies have demonstrated that high levels and higher bioavailability of estrogen in circulating blood leads high risk of "breast cancer" (Kaaks et al., 2005; Tin Tin et al., 2021) however the incidence and prevalence of breast cancer in young females is low in comparison to elderly population (Al-Shamsi, 2020). Despite the low prevalence in young females the outcomes of breast cancer in younger population are severe. According to the study of Narod, the breast cancer developed in young age is observed to be poorly differentiated in comparison to the breast cancer established in older age (Narod, 2012). Therefore, the management as well as the prognosis of breast cancer depends on the age of patient (Sinaga et al., 2018). This research was designed to analyse the effect of age on hormone receptor status (HRS) as well as their correlation in females suffering from breast cancer. Additionally, it is noteworthy that the relationship among "obesity", "breast cancer" and total risk seems to be extremely reliant on the status of menopausal. Thus, in "postmenopausal" females, "obesity" is involved in increasing the threat of "breast cancer" (Shafiqa Mehmood et al., 2022).

The results of present research suggested the significant relationship between "ER status, PR status" and age demonstrating that the age group ranging from 40 years to 51 years is significantly related with "PR" as well as the "ER status" whereas "HER2/neu status" showed insignificant association. These results are not supported by the study which examined the effects of hormone receptors on females based on the age. The results of his study showed the insignificant association of "ER status and PR status" with age (Lee et al., 2015; Rossi et al., 2019). However, the study by (Pourzand et al., 2011) are in accordance with the results of present research exhibiting a significant differences in the hormonal status of younger female groups with ages ranging from 2 6 years to 40 years and older females with age over 40 years to 80 years. The research also showed that the women with the age of 28 years to 40 years had PR-positive breast cancer which supports the findings of present research. There is observed a little difference in age groups which may be due to sample size, ethnic variations, racial variation, etc. Furthermore, the present research also supported the fact that each tumour developed in different age group has differences in

biological characteristics and features thus the influence of age on the outcomes of HRS-specific treatment is important.

The research analysis also revealed that the size of most of the tumours were of 1.5cm to 4.5 cm, with "positive status of lymph node" and "moderately differentiated". These results were in accordance with the research study by (Parise et al., 2010) demonstrating that the females with breast cancer having "positive ER and PR" had the mean tumour size 2+ 1.5cm and also moderately differentiated. The mean age of our research population was observed to be 50+6 years showing that breast cancer is more prevalent in older women, these findings are supported by the studies showing the prevalence of breast cancer in females of 60 years in US and 46 years in the Iranian females suffering from breast cancer (Anderson et al., 2007; Finkeldey et al., 2021).

The present study also determined the relationship between "molecular subtype of cancer" and age of the patient as according to the research involving "molecular subtype" of the breast cancer also effects the rate of survival in the patients of breast cancer (Chang et al., 2019). The present research also found that the most common subtype of breast cancer is "luminal A" supported by the study of (Fahad Ullah & Progress, 2019) however there was found insignificant correlation between the subtypes of cancer subtypes and age of patients but the other study found the significant association between subtypes and increased age (Jenkins et al., 2014). The slight variations in the results of various studies is due to the demographic features, genetic variation, stage of tumour, age and racial discrimination, HRS.

CONCLUSIONS

After all the discussion it is concluded that most of the women diagnosed with breast cancer were in their late 40s. The older age females with breast cancer were "PR (progesterone receptor), ER (estrogen receptor), and HER2/neu positive" while the younger females were "HER2/neu, estrogen receptor progesterone receptor (PR) negative". Additionally, there was found insignificant relation of the hormonal status "HER2/neu" and age. So, it is evident that the female older than 40 years of age may have high survival rates. However, these results cannot be generalized to the whole population and multicentre, large-scale, and long-term research is necessary to fully understand the survival rates and prognosis.

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