

Ethnic differences in the receptors status of estrogen, progesterone and Her2/Neu among breast cancer women: A single institution experience

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Abstract

Objective: To evaluate the Ethnic Differences in Estrogen (ER), Progesterone (PR) and Her 2/neu receptors among Women with Breast Cancer at JPMC, the largest public sector tertiary care hospital in Karachi.

Methods: The study was conducted at the oncology ward, JPMC Karachi from 1st July 2017 to 31st December 2018. During this period, more than 500 women with breast cancer of different ethnicities visited the oncology ward, however 450 patients were included in the study, as only they had the complete reports on the receptors status and tumour histology. The data collected included tumour histology, grade, receptors status, age and ethnicity. Data was analyzed with SPSS version 20 using the Chi-Square Test to observe statistical differences in the receptors status of different ethnicities.

Results: Analysis of receptors status as per ethnicity showed that ER was proportionately more positive in Pushtoon patients at the rate of 28 (75.7%) as compared to Urdu Speaking 116 (60.4%), Punjabis 48 (60%), Sindhis 38 (38.7%) and Balochis 26 (61.1%). Similarly, PR and Her-2/neu receptor were also higher in Pushtoons at the rate of 24 (64.9%) and 15 (40.5%) respectively. The behaviour of Triple Positivity was also more prominent in Pushtoons at the rate of 9 (24.3%) and the Pushtoons were also proportionately less likely to be Triple Negative at the rate 05 (13.5%) as compared to other ethnicities. All the results were statistically non significant (p values > 0.05).

Conclusion: In this study we observed a relatively higher expression of ER, PR and Her 2/neu Receptors in Pushtoons as compared to other ethnicities. Understanding the factors underlying these differences may provide further insight into the breast cancer aetiology in different populations.

Keywords: Breast Carcinoma; Breast CA; ER, PR and Her 2/neu Receptors; Ethnicity

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Introduction

Breast cancer is one of the prime causes of death in females globally as reported by the United States' Centers for Disease Control (CDC).¹ It is roughly calculated that breast cancer is diagnosed in more than one million women every year and more than four hundred thousand mortalities result from the disease making 14% of the total female deaths due to breast cancer.²⁻⁴ As claimed by the CDC, breast cancer in women, studied by prevalence and mortality is substantial and ever increasing.⁵

In Pakistan, the most common cancer affecting women is breast cancer representing more than 14% of all cancers reported.⁶ In Karachi's female population it is responsible for roughly, one third of the cancers.⁷ Early diagnosis, timely appropriate treatment and genetic susceptibility are linked to breast cancer survival. Prognosis is related to a variety of pathologic, molecular and clinical features comprising of histologic type, grade, tumour size and metastases of

lymph nodes. The management of this malignancy is influenced by the hormonal receptors namely progesterone and estrogen receptors (PR, ER) and the recently established HER-2/neu, all having a major impact.⁸ To predict the prognosis or a patient's response to endocrine therapy, the biologic characteristics such as Estrogen receptor (ER) and progesterone receptor (PR) status i.e. positive (+) or negative (-), for breast tumours are commonly evaluated.^{9,10} Some studies suggest that in comparison to using ER and PR statuses separately the predictive power is enhanced when both of them are combined.⁹⁻¹¹

Racial, genetic and cultural differences, as well as environmental conditions that alter throughout the world contribute to the geographic variations in breast cancer incidence.^{12,13} It has been established by multiple international studies that hormonal receptor status is influenced by the differences in racial and ethnic groups.¹³ Since, almost all of these studies were done in the western world; the relationship between hormonal receptor status and ethnicities within Pakistan (Sindhi, Punjabi, Balochi, Pushtoons, Urdu Speaking and others) was unknown. Considering the importance, this study was performed at Jinnah Postgraduate Medical Center (JPMC), Karachi to

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explore ethnic differences in hormonal receptor status (ER, PR & Her2/Neu) among breast cancer in women.

Patients and Methods.

This is a prospective observational study conducted at Jinnah Postgraduate Medical Center, the largest public sector tertiary care hospital in Karachi. The patients referred to oncology ward of Jinnah Postgraduate Medical Center, Karachi, Pakistan between July 1, 2017 to December 31, 2018 for the management of breast cancer were included in the study. Ethical approval was obtained from the Institutional Review Board (IRB) JPMC Research Department. The study included clinically diagnosed and histologically verified breast cancer cases having complete details of the receptors status. All surgical specimens were immune histochemically analyzed to determine the estrogen and progesterone receptors status. Her2/neu was confirmed on FISH analysis whenever required i.e. IHC +2. Variables recorded were the name, age, ethnicity, address, histology, ER, PR and Her2/neu status and grading of the tumour. OPENEPI software was used to calculate the sample size, by keeping prevalence of breast cancer in Pakistan according to previously published literature, a Confidence Interval of 98%, and a margin of error to be of 5%, the obtained sample size was 450.¹⁴ More than 500 patients presented at oncology ward during the 18 months period. However, many patients were either lost to follow up, or their hormone receptor status information and other variables were incomplete. Many patients did not fulfill the inclusion criteria. Therefore, only 450 patients were included as this was the required sample size.

The receptors status of these 450 patients was arranged as i) ER+, ii) PR+, iii) Her-2/neu+, iv) ER+PR+, v) ER-PR- vi) Triple Positive, and vii) Triple Negative. The data was computerized using the software SPSS version 20. This software can perform validity of the entered data and detect duplicate registrations. The Chi-Square test was performed to observe statistical significance.

Results

The mean age of the patients was 46.72 ± 10.82 . years Table 1 shows the overall demographic details of the patients. Urdu speaking 192 (42.7%) outnumbered other ethnicities including Punjabi 80 (17.8%), Sindhi 67 (14.9%), Pushtoons 37 (8.2%) and Balochi 36 (8%). Table 2 shows break up of 450 cases of breast cancer by histology revealing that Infiltrating Ductal Carcinoma (IDC) was the most common histology in 430 cases (95.6%).

The results of the individual receptors status as per ethnicity as shown in Table 3 are as follows:

Table-1: Overall Demographic of patients (n=450)

Mean Age (years)	46.72 ± 10.82
18-35	73(16.2%)
36-50	233 (51.8%)
51 and above	144 (32%)
Ethnicity	
Urdu Speaking	192 (42.7%)
Punjabi	80 (17.8%)
Sindhi	67 (14.9%)
Pushtoons	37 (8.2%)
Balochi	36 (8.0%)
Others	38 (8.4%)

Table-2: Histological break up of 450 cases

BreastTumor Histology	n (%)
Infiltrating Ductal Carcinoma (IDC)	430 (95.6)
Infiltrating Lobular Carcinoma (ILC)	10 (2.2)
Metaplastic Carcinoma	5 (1.1)
Infiltrating Mixed ductal and lobular Carcinoma	1 (0.2)
Invasive Micropapillary carcinoma	1 (0.2)
Invasive Musinous Carcinoma	3 (0.7)

Table-3: Association of Individual Hormone Receptor status with Patients' Ethnicities (n=450).

Ethnicity	ER Positive n (%)	PR Positive n (%)	Her2/neu Positive n (%)
Urdu Speaking (n=192)	116(60.4)	101(52.6)	70(36.5)
Sindhi (n=67)	38(56.7)	33(49.3)	20(29.9)
Punjabi (n=80)	48 (60.0)	41(51.2)	26(32.5)
Pushto (n=37)	28(75.7)	24(64.9)	15(40.5)
Balochi (n=36)	26(61.1)	19(52.8)	08(22.2)
Others (n=38)	24 (63.2)	22(57.9)	10(26.3)
<i>p</i> -value	0.550	0.711	0.422

- ER was proportionately more positive but statistically insignificant ($p=0.550$) in Pushtoons 28 (75.7%) as compared to Urdu Speaking 116 (60.4%), Punjabis 48 (60%), Sindhis 38 (56.7%), Balochis 22 (61.1%) and others 24 (63.2%).
- PR was proportionately more positive but statistically insignificant ($p=0.711$) in Pushtoons 24 (64.9%) as compared to Balochi 19 (52.8%), Urdu Speaking 101 (52.6%), Punjabi 41 (51.2%), Sindhi 33 (49.3%) and others 22 (57.9%).
- Her2 was proportionately more positive but statistically insignificant ($p=0.422$) in Pushtoons 15 (40.5%) and Urdu Speaking 70 (36.5%) as compared to Punjabis 26 (32.5%), Sindhis 20 (29.9%), Balochis 8 (22.2%) and others 10 (26.3%).

The results of the combined receptors status with patients' ethnicities as shown in Table 4 are as follows:

- Both ER & PR were more likely to be positive in Pushtoons

Table-4: Association of Combined Hormone Receptors Status with Patients' Ethnicities (n=450).

Ethnicity	ER+ & PR+	ER- & PR-	Triple Positive	Triple Negative
Urdu Speaking (n=192)	94(49.0%)	69(35.9%)	28(14.6%)	35(18.2%)
Sindhi (n=67)	31(46.3%)	27(40.3%)	8(11.9%)	18(26.9%)
Punjabi (n=80)	41(51.2%)	22(40.0%)	10(12.5%)	18(22.5%)
Pushtoon(n=37)	24(64.9%)	9(24.3%)	9(24.3%)	05(13.5%)
Balochi (n=36)	17(47.2%)	12(33.3%)	4(11.1%)	10(27.8%)
Others (n=38)	21(55.3%)	13(34.2%)	5(13.2%)	08(21.1%)
p-value	0.517	0.632	0.561	0.460

24 (64.9%) but statistically insignificant ($p=0.517$) as compared to other ethnicities ranging from 46.3% to 55.3% in other ethnicities.

- Both Receptors were less likely to be negative in Pushtoons 9 (24.3%) but statistically insignificant ($p=0.632$) as compared to other ethnicities ranging from 33.3% to 40.3% in other ethnicities.
- The Pushtoons were proportionately more likely to be Triple Positive 9 (24.3%) as compared to other ethnicities ranging from 11.1% to 14.6%.
- The Pushtoons were proportionally less likely but statistically insignificant ($p=0.460$) to be Triple Negative 5 (13.5%) as compared to Urdu speaking 35 (18.2%), Punjabis 18 (22.5%), Sindhis 18 (26.9%), Balochi 10 (27.8%) and others 8 (21.1%).
- For the purpose of comparing histological variants of breast cancer with the receptors status, the 450 cases were divided into two groups as: IDC group as it was the dominant histology (430 cases representing 95.6% of the population) and the remaining histologies (20 cases) were collectively grouped as OTHERS. The results show that Her2 positivity was mainly seen in IDC histology as compared to other histological variants ($P\text{-value} < 0.05$). Similarly, a trend toward significant p-value was seen for triple positive (TP) as shown in Table 5.

Table-5: Association of Tumour Histology with Hormone Receptors Status.

Tumor Histology	ER+	PR+	Her2+	ER+PR+	ER-PR-	TP	TN
IDC(430) [n (%)]	262 (60.9)	229 (53.3)	148 (34.4)	217 (50.5)	156 (36.3)	64 (14.9)	89 (20.7)
Others(20) [n (%)]	14 (70)	11 (55)	01 (5)	11 (55)	6 (30)	0 (0)	5 (25)
p-value	0.411	0.879	0.006	0.692	0.567	0.093	0.583

Table-6: Association of Patients' Age with Hormone Receptors Status

Age Group (n= 450)	Receptors Status						
	ER+	PR+	Her2+	ER+PR+	ER-PR-	TP	TN
18-35 (73) [n (%)]	44 (60.3)	10 (54.8)	30 (41.1%)	37 (50.7%)	26 (35.6%)	16 (21.9%)	15 (20.5%)
36-50 (233) [n (%)]	134 (57.5)	119 (51.1)	76 (32.6%)	112 (48.1)	92 (39.5%)	33 (14.2%)	59 (25.3%)
>50 (144) [n (%)]	98 (68.1%)	81 (56.2%)	43 (29.9%)	79 (54.9%)	44 (30.6%)	15 (10.4%)	20 (13.9%)
p value	0.122	0.597	0.245	0.440	0.214	0.072	0.030

- When patients' age was compared to receptors status, only the triple negative (TN) breast cancer showed statistically significant p-value as shown in Table 6.

Discussion

Breast Cancer is not only the most frequently diagnosed invasive malignancy but it is the second leading cause of death among females worldwide. The literature shows that most of the risk factors associated with breast malignancy are non-modifiable.¹⁵ Recent studies have reported that ethnicity/race has an influence on the prevalence and clinical characteristics of breast cancer, emphasizing the immense need for studies in all ethnic and racial patients globally.¹⁶ However, majority of the research on ethnicity/race and its association with breast cancer has been done in the West. Pakistan is a diverse country with multilingual, multiethnic and multiracial populations residing in it.¹⁷ In Pakistan, not much work has been done on exploring the correlation between the ethnicities and different clinical and histological characteristics of breast cancer. Therefore, the purpose of this study was to explore the correlation between the different distributions of hormonal receptor status (HRS) in different ethnic groups in Pakistan.

The major findings of this study are: 1) In Pushtoons, the Estrogen Receptor was proportionately more positive as compared to others but statistically insignificant. 2) Statistically insignificant but Progesterone Receptor also favoured Pushtoons in contrast to others. 3) Her2 was relatively more over expressed in Pushtoons and Urdu Speaking than other ethnicities. Naturally, Pushtoons were more likely to be triple positive (24.3%) as compared to other ethnicities ranging from 11.1% to 14.6%. It has been established in previous studies that ER and PR positive breast cancer patients have better prognosis than the patients with ER and PR negative tumours at the time of the diagnosis.^{18,19} The patients with hormone receptor positive status are shown to have better survival rates when treated with chemotherapy and adjuvant hormonal regimes as shown by clinical trials.^{20,21} The present study suggests that the ethnic group Pushtoons may have lower risks of mortality and are likely to respond better to adjuvant hormonal regimes because the breast cancer tumours are more likely to have positive hormonal receptor status than other ethnicities.

Numerous studies have demonstrated differences in certain biological breast cancer characteristics associated with survival, including hormone receptor status and histology, among women of different racial and ethnic groups. To the best of our

knowledge there are no local studies on the correlation of ethnicities of Pakistan and Hormonal Receptor Status for comparison. However, our findings are generally consistent with the internationally published studies in this area, a study done by CP Hunter et. al²² suggests that variations in breast cancer incidence in different cultures are because of etiologic factors differing in biologic expressions influencing disease outcome. This study also emphasizes on the impact of behavioural, socio demographic and cultural dynamics on the expression of biologic disease in different population subgroups. This difference of expression leads to the difference in mortality and survival rates and ultimately, treatment plans, outcomes and prognoses.²² This finding supports our study by demonstrating the difference in prevalence and biologic expressions due to variations in the racial and ethnic subgroups. Christopher Li in his famous SEER study in United States expressed that breast cancer tumour characteristics differ by race/ethnicity.²³ Both lifestyle and biological factors contribute to the difference in biological expression of the disease. In this study it was concluded that Relative to non-Hispanic whites, African Americans, Native Americans, Filipinos, Chinese, Koreans, Vietnamese, Indians/Pakistanis, Mexicans and South/Central Americans living in the United States had relatively elevated risks of presenting with Estrogen and Progesterone receptor-negative breast cancer.²⁴ Pegoraro et. al in their study showed that receptor status is not linked to the stage of the disease nor the degree of nodal involvement except very large ones but it is associated with differences in race.²⁵ This finding leads us to believe that the receptor status depends on the racial and ethnic variations and increases the importance of the study to correlate the receptor status and ethnic variations in Pakistan which would probably open the gates for more specific therapy and better chances of survival.

Pre-menopausal women having breast cancer tend to have more negative Hormonal Receptor Status as compared to postmenopausal women. One of the alternate explanations of higher triple positive count in Pushtoons is that they are more conservative and don't usually bring young females to hospitals lowering the possibility of ER-/PR- diagnoses.²⁶ One of the potential limitations of this study is small sample size (n=450), and the small proportion of Pushtoons (n=37, 8.2%) in the sample size. Another possible limitation is the mean age of the sample i.e. 46.7 years. 68.0% of the sample size of this study falls in the category of pre-menopausal women (16.2% in the category of 18- 35 years and 51.8% in the category of 36-50 years). The hormone receptor status is known to differ by menopausal status as pre-menopausal women mostly present as ER-/PR-.²⁷

Conclusion

In this study, we observed a relatively high expression of ER, PR and Her-2/neu receptors in Pushtoons as compared to other ethnicities. Further studies are needed with a better sample size to explore the correlation of Ethnicities with Receptors Status among women with breast cancer in Pakistan.

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