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A Retrospective Analysis of Hormone Receptor Profile in Breast Cancer Patients from a Tertiary Cancer Center in Western Part of India and Study their Relationship with Her 2 Neu (IHC +FISH), Age and Menopausal States

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Abstract

Purpose: Estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptors (HER) are well-characterized and widely studied breast cancer predictive and prognostic markers that provide important and critical information. The objectives of the current study were to (1) evaluate the trends of ER, PR, and HER tumor markers in breast cancer patients, (2) demonstrate the relationship of ER, PR, and HER status with the age, menopausal status and the site of tumor, (3) evaluate the percentage of HER2 positive patients detected with the Fluorescent in situ hybridization (FISH) technique, and (4) stratify cases according to different molecular subtype classification of breast cancers (ER+ PR+ HER-, ER+ PR- HER1+, ER+ PR+ HER2+, ER+ PR+ HER3+, ER- PR+ HER1+, ER- PR+ HER1+, ER- PR+ HER2+, and ER- PR+ HER3+).

Methods: The breast cancer subtypes were based on standard Gallen consensus recommendation (2011). Association between various categorical data was analyzed using Chi-square test followed by Fischer's exact test. Differences between continuous data were analyzed using student-t test.

Results: A p value ≤ 0.05 was considered statistically significant. Our study suggests that the incidences of breast cancer were less in the age groups ≤ 40 years (20.6%) and >60 years (18.1%) compared to age groups 41-60 years (56.8%) (p<0.001). We found that younger age group (<40 years and 40-60 years) are more likely to develop breast cancer in India compared to 60-70 years and >70 years in western population reported in the literature. While number of ER+ patients in our patient population was 50.0%, number of triple positive patients was15.3%. A high (6.7%) pure PR cases was observed.

Conclusion: In summary, regardless of the hormone status whether it's single hormone receptor or triple marker, only age is a variable factor and demonstrates significant difference between HER positive (all the HER2+ cases which are confirmed positive by FISH and HER3+ cases) and negative population. The other two variable factors (menopause and lymph node positivity) are independent of the hormone status.

Keywords: Breast Cancer Subtypes; Menopause; Lymph Node; Overall Survival; Hormone Receptors

Introduction

Among all female cancer types, breast cancer is prevailing worldwide and represents at least 25% of all cancer types [1]. Considering different causal factors of the breast cancer, age contributes more to that of other factors. Although age-standardized incidence rates in India are lower than in the United Kingdom (UK) (25.8 versus 95 per 100,000), mortality rates are nearly as high (12.7 versus 17.1 per 100,000, respectively) as those of the UK [2]. Worldwide, the mortality rates have exponentially decreased in women since 1990 [3]. Since the incidence of breast cancer is stable (at least from 2004 until 2008), and the treatment plans and diagnosis methods have improved considerably with time, we believe that it has significantly impacted in lowering mortality rate over time. The TNM coding system of staging for breast cancer was initially conceived in 1959 by the American Joint Committee for cancer (AJCC). The evidence in the literature then available could not support the addition of biomarkers to the TNM staging classification (Seventh edition). Thus the TNM staging system was modified (Eighth edition) for a better understanding of biologic markers, such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), and their respective impact on prognosis, selection of therapy, and response [4]. Testing for ER, PR and HER considered a standard investigation in breast cancer patients as all these surrogate markers have demonstrated a significant prognostic and predictive role [5-9]. Apart from being a gold standard in the breast cancer cases, these markers are essential in reviewing the newly screened drugs in the market and also in the validation of available clinical data [10]. Amongst various subtypes of breast cancer, ER negative PR positive and HER Negative/HER 1+ (*i.e* ER– PR+ HER–, ER– PR+ HER1+, ER – PR+ HER2+, and ER– PR+ HER3+) is considered pure PR type. But the triple negative subtype (ER- PR- HER-) is considered to be the worst compared to other subtypes, especially among young women [11-19]. The primary cause of different and contrasting prognosis displayed by triple negative carcinoma subtypes is the socioeconomic influences especially in developing countries like India [20]. Different socioeconomic factors like poverty, improper and deregulated diet plan, frequency of postmenopausal hormone replacement or even the usage of oral contraceptives are more prevailing in India than other developing nations [13,15,16,21,22].

In this retrospective study, we have evaluated expression of the tumor markers (prevalence) of different subtypes of breast cancer in Indian population as prognostic factors. Compared to western countries, the breast cancer patients of Indian origin have a tendency

to fall into younger age group and the tumors are often larger when they are first diagnosed [23]. This encouraged us to conduct a retrospective study keeping age, menopause and lymph node positivity as the primary clinic pathologic characteristics.

Materials and Methods

This is a 2-year retrospective cohort study on cases that were diagnosed between August 2015 and August 2017 at the Bhagwan Mahaveer Cancer Hospital and Research Center, Jaipur (Rajasthan), India. This study is based on retrospective collection of data of wide range of patient population during the study period. We searched for newly diagnosed invasive breast cancer cases in women. Data of 470 Indian women aged above 18 years and diagnosed with primary breast cancer was collected and analyzed.

This study did not require any ethical committee approval as it is a retrospective cohort study. Data on the following clinic-pathological characteristics were collected: age, menopausal status and lymph node positivity, and site of tumor. The inclusion criteria in this study were:

(1) the patient must be a woman and diagnosed with breast cancer, (2) the patient must be older than 18 years, (3) the patient must be a resident of India, (4) ER, PR Her 2 Neu tests for the patient must have been performed by IHC, (5) FISH results for the patient were available for HER2 neu 3+ cases by IHC. FISH test was performed only in IHC proven HER 2+ cases as FISH is not required for the other sub types (especially HER1+ and HER3+) patients. The exclusion criteria included: (1) the patient must be a man, (2) the patient's age must be less than 18 years, and (3) the patient whose biopsy did not reveal tumor.

Statistical analysis

All the collected data were analyzed statistically using SPSS version 21. Descriptive statistics, frequency and percentage were used to describe the data. Association between various categorical data was analyzed using Chi-square test followed by Fischer's exact test. Differences between continuous data were analyzed using student-t test. A p value ≤ 0.05 was considered statistically significant

Results

The results of association of age, menopause status, site of tumor and lymph node positivity with single hormone receptor status is presented in Table 1 and the association of age, menopause status, site of tumor and lymph node positivity with triple marker status is presented in Table 2. Out of the 470 new invasive breast cancer cases, irrespective of the status of other receptors, 235 (50%) were only ER +patients (i.e. ER+ PR- HER-), 222 (47.2%) were only PR+patients (i.e. ER- PR+ HER-), 233 (49.6%) were only HER+patients, 72 (15.3%) were triple positive patients, and 81 (17.2%) were only triple negative patients. Forty four out of 75 HER2+ patients (58.7%) were confirmed by FISH. It may be noted that although there were 47.2% PR+ patients, total pure PR cases (i.e., ER– PR+ HER–, ER– PR+ HER1+, ER– PR+ HER2+, and ER– PR+ HER3+) is 6.7% in our study compared to 3 to 4 % globally (Table 2). This is a remarkable observation that may provide motivation for further studies of breast cancer in Indian population.

According to a decade old surveys conducted by the Indian Council of Medical Research (ICMR), the incidence of breast cancer in India has increased to double and it has been increasing exponentially since then [20,23-25]. In those surveys, the data represent a strong relationship of age with the occurrence of breast cancer in Indian women. It was found that the Indian breast cancer patients were younger than breast cancer patients from western cohorts. However, when the patient population was compared with different age groups within India, we observed an interesting outcome. The number of cases of breast cancer were less in the age groups of ≤ 40 years and >60 years as compared to the age groups of 41-60 years in this study cohort (*$p<0.001$, Table 1 and Figure 1).

Our finding is in agreement with previous study reported in the literature [26], which suggested that the breast cancer peaks somewhere between 40 years and 50 years of age. Many of the patients in the reported study were HER2 positive and were negative for ER/PR, which is similar to our observation in the present study population (Table 1). Unlike the women from western countries, the United Kingdom in particular, Indian women has a tendency of developing the disease early at the age of about 40 years [26]. We also observed that onset of breast cancer at early age, or in fact at any age, are independent of the status of menopause (Tables 1 and 2).

The relationship between age and menopause and the possibility of developing breast cancer with earlier or prolonged menopause is well documented [27,28]. There is an increased risk of breast carcinoma if a woman menstruation cycle begins at early age (less than 12 years of age). Similarly, prolonged menstruation leads to longer exposure of hormones like estrogen and progesterone, and hence the woman is more likely to develop breast cancer [27,28].

Our patient population was divided into several different groups based on the distribution of the triple marker status as per the St. Gallen consensus recommendation [29]. When we established a correlation of the triple marker status to the different breast cancer prognostic markers, we observed only one factor, i.e. age that was correlated and statistically significant at different age groups (Table 3). Other markers were not associated and found to be independent of the hormone status of the patient. The overall clinicopathologic characteristic is listed in Table 3. It was interesting to observe that both the youngest and oldest patients were positive for all three hormones (mean value of ER- PR- HER+ in both ≤ 40 years and>60 years was 17.1). However, between the ages of 41-60 the levels of all three hormones show in their peak (65.8%). We observed no significant differences between pre and post menopause physiological changes over the level of hormones and it was true for the lymph node activity (Table 3). This observation is in contrary to those observed for western women in the literature (60-70 years and>70 years) [30], and hence, we speculate that the levels of prognostic markers for breast cancer in Indian women are regulated differently than the women of western origins. HER expression decreases significantly after 60 years of age. Expression of ER and PR was not age dependent. There is a trend towards decrease disease severity as node number positive is seen in postmenopause women. Alternatively, younger women tend to have more aggressive form of the disease. ER+ patients tend to have disease in left side whereas ER- negative cases have a tendency for disease towards right side. PR+ patients tend to have more number of positive lymph nodes than PR negative patients.

Discussion

In the present work, we studied the prognostic markers of breast cancer subtypes in Indian women where 100% of the patient populations were of Indian origin. The length of the study was 2 years. Data on all the 470 patients was collected and categorized according to

the level of different breast cancer tumor marker hormones. The classification was based on the gold standard St. Gallen consensus recommendation [29].

All the markers (ER+ PR+ HER-, ER+ PR+ HER+, ER- PR+ HER-, ER- PR+ HER+, ER+ PR- HER-, ER+ PR- HER+, ER- PR- HER-, ER- PR- HER+) were predominantly higher in the 40-60 years age group population. ER+ PR+ HER2+ was also predominant in the age group of 40-60 years, and the younger women were most likely surging ER+ PR+ HER3+ level. This observation is somewhat very similar to previously reported data, but surprisingly not in Indian population [14,15,21,30]. This suggests a possible genetic drift between the two population and the genes were inherited throughout the course of evolution. The triple negative (ER- PR- HER1-) breast cancer subtype was observed mostly with younger age population, a trend similar to one of the previous studies [15]. The most noteworthy finding of our study was the significantly high (6.7%) pure PR cases (i.e. ER–PR+ HER–, ER– PR+ HER1+, ER– PR+ HER2+, and ER– PR+ HER3+) compared to 3 to 4% worldwide reported so far.

The variation in onset of breast cancer in different group of patient population also depends upon various socioeconomic factors. One of the factors is household activity. There is a significant chance that the variation in the occurrence of breast cancer in different age group might be because of the different degree of household activities they are involved in. The degree of breast cancer risk is inversely proportional to the intensity of household work as reported previously [31]. Apart from household activities, heavy association with different tobacco products is also known to initiate breast cancer among women, especially in India [32-34]. In addition to the socioeconomic factors, environmental factors also play a significant role in Indian population of breast cancer patients as India is listed among world's top most polycyclic aromatic hydrocarbon (PAH) emitting country. PAH has direct impact on breast cancers as it is highly lipophilic in nature and is found predominantly in fat tissues. PAH frequently interacts with different cancer promoting hormonal receptors and is one of the unknown and less studied breast cancer inducer [35-37].

While the majority of breast cancer patients in western countries are postmenopausal and in the older age group of 60-70 years and >70 years, it is the younger generation (40-60 years) in India who are the victims [26]. According to previous report, it is the early onset of breast cancer that leads to more triple negative subtype cancers than the breast cancer occurring in late stage [38]. This triple negativity is definitely a poor prognostic factor and makes the routine screening more difficult [39]. It is noteworthy that Indian population demonstrates more triple negative breast cancer patients especially in younger age compared to the breast cancer population of western countries. This fact has been intensely studied and demonstrated by several different groups previously with convincing dataset [40-43].

With regard to menopause, although there seems to be a trend towards decrease disease severity as node number positive is seen in post-menopause women, we did not observe any significant difference in any subtype of breast cancer among pre and post menopause patients. The findings are similar to that of Surakasula et al. [44] who reported that the risk factors for both pre-and post-menopausal breast cancer were found similar other than late menopause in postmenopausal patients. Having dense breast tissue was a predominant risk factor among all women. Late presentation was the common phenomenon in almost all patients. Similarly, in our case also, the younger women could have denser breast tissue, which made them less amenable for diagnosis. Moreover, the environmental factors could also influence the onset of breast cancer. Therefore, developing countries like India needs urgent and fast actions on health plan to prioritize health care needs, especially in those areas where the cancer treatment and early diagnostic facilities are not available. As discussed above because of different socioeconomic and environmental issues, compared to other cancer types the breast cancer incidents especially in younger generation is most likely to increase exponentially in coming years: A recent report suggests that in India [45], breast cancer is definitely contributing significantly to the mortality rate especially in big metropolitan cities like New Delhi, where the pollution is in its peak level. To combat this major issue, it is required to have a multidisciplinary approach coordinating with different awareness programs (especially in rural areas), establishing breast cancer screening programs (especially in urban areas where the pollution rate is more) and inaugurating early breast cancer detection facilities across the country.

Conclusion

In summary, in this current retrospective database, we revisited and evaluated different tumor markers as prognostic factors of different breast cancer subtypes emphasizing age as one of the important factor. We showed that younger age group (40-60 years) are more likely to develop breast cancer than older population (>60 years) in India. No significant difference was found about breast cancer cases amongst pre-menopause and post-menopause women. Higher incidence of triple negative breast cancer was found in younger patients compared to older patients. A significantly high (6.7%) pure PR cases were found in our study compared to global data. Based on our study, we acknowledge that the prognosis of the hormonal status in young Indian breast cancer patients needs more intense investigation of Indian population in a larger dataset.

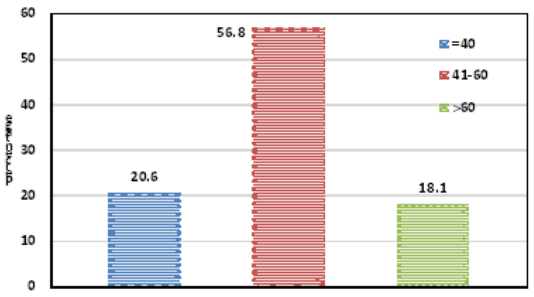

Figure 1: Age distribution of the study population. In the age groups ≤ 40 years and>60 years the incidences of breast cancer were less as compared to age groups 41-60 years in this study cohort (p<0.001).

Variables	ER	P value	PR	P value	HER	P value

	+	-		+		-		+	-
Mean Age	51.2 ± 11.6	50.7 ± 11.2	0.671	51.0 ± 11.4	50.8 ± 11.4	0.842	50.3 ± 10.3	51.5 ± 12.3	0.23
Age									
≤ 40	48.40%	51.60%	0.638	45.30%	54.70%	0.768	48.50%	52.50%	0.006
	-46	-49		-43	-52		-47	-50	
41-60	50.60%	49.40%		49.40%	50.60%		55.10%	44.90%	
	-132	-129		-129	-132		-147	-120	
>60	55.30%	44.70%		47.10%	52.90%		35.30%	64.70%	
	-47	-38		-40	-45		-30	-55	
Menopause									
Pre	51.30%	48.70%	0.84	47.30%	52.70%	0.92	44.70%	55.30%	0.086
	-77	-73		-71	-79		-68	-84	
Post	50%	50%		48.20%	51.80%		52.10%	48.90%	
	-142	-142		-137	-147		-151	-139	

Table 1: Distribution of patients age and menopause status according to single hormone receptor/HER status.

Variables	**Side**		**P value**	**Lymph node**		**P value**	**Node number**		**P value**
	Left	**Right**		**Positive**	**Negative**		**1**	**>1**	
Mean Age	51.6 ± 10.6	50.1 ± 11.3	0.224	50.9 ± 10.7	51.2 ± 10.4	0.85	52.6 ± 10.6	49.3 ± 10.6	0.07
Age									
≤ 40	41.4% (29)	58.6% (41)	0.257	58.3% (28)	41.7% (20)	0.704	40.7% (11)	59.3% (16)	0.424
41-60	51.8%(101)	48.2% (94)		55.0% (88)	45.0% (72)		52.9% (46)	47.1% (41)	
>60	54.1% (33)	45.9% (28)		61.9% (26)	38.1% (16)		57.7% (15)	42.3% (11)	
Menopause									
Pre-	47.4% (54)	52.6% (60)	0.562	58.5% (48)	41.5% (34)	0.786	42.6% (20)	57.4% (27)	0.094
Post-	51.2% (108)	48.8% (103)		56.0% (94)	44.0% (74)		57.4% (52)	42.6%(41)	
ER Status									
Positive	54.7% (88)	45.3% (73)	0.081	59.0% (72)	41.0% (50)	0.443	47.9% (34)	52.1% (37)	0.394
Negative	46.3% (74)	53.8% (86)		54.0% (67)	46.0% (57)		56.1% (37)	43.9% (29)	
PR Status									
Positive	49.7% (76)	50.3% (77)	0.824	59.2%(71)	40.8% (49)	0.442	45.7% (32)	54.3% (38)	0.098

Negative	51.2% (86)	48.8% (82)		54.0% (68)	46.0% (58)		58.2% (39)	41.8% (28)	
HER status									
Positive	48.2% (81)	51.8% (87)	0.58	59.1% (78)	40.9% (54)	0.446	48.7% (37)	51.3% (39)	0.502
Negative	51.9% (82)	48.1% (76)		54.2% (64)	45.8% (54)		54.7% (35)	45.3% (29)	

Table 2: Association of Age, Menopause status, and single hormone receptor/HER status with disease severity.

Variables	ER+ PR+ HER-	ER+ PR+ HER+	ER- PR+ HER-	ER- PR+ HER+	ER+ PR- HER-	ER+ PR- HER+	ER- PR- HER-	ER- PR- HER+	P value
Age									
≤ 40	14.9% (17)	29.4% (20)	10% (1)	25% (5)	28% (7)	11.1% (2)	32% (24)	17.1% (19)	0.020
41-60	57.9% (66)	61.8% (42)	80% (8)	65% (13)	44% (11)	72.2% (13)	46.7% (35)	65.8% (73)	
>60	27.2% (31)	8.8% (6)	10% (1)	10% (2)	28% (7)	16.7% (3)	21.3% (16)	17.1% (19)	
Menopause									
Pre-	32.7% (37)	40% (26)	20% (2)	30% (6)	37.5% (9)	29.4% (5)	46.7% (35)	27.3% (30)	0.196
Post-	67.3% (76)	60% (39)	80% (8)	70% (14)	62.5% (15)	70.6% (12)	53.3% (40)	72.7% (80)	
Side									
Left	51.2% (42)	53.8% (28)	37.5% (3)	27.3% (3)	73.3% (11)	58.3% (7)	50% (26)	47.2% (42)	0.431
Right	48.8% (40)	46.2% (24)	62.5% (5)	72.7% (8)	36.7% (4)	41.7% (5)	50% (26)	52.8% (47)	
Lymph Node									
Positive	57.4% (35)	60.5% (26)	60.0% (3)	63.6% (7)	70% (7)	50% (4)	45.2% (19)	57.6% (38)	0.882
Negative	42.6% (26)	39.5% (17)	40% (2)	36.4% (4)	30% (3)	50% (4)	54.8% (23)	43.4% (28)	
Node Number									
1	54.3% (19)	32% (8)	66.7% (2)	42.9% (3)	71.4% (5)	50% (2)	47.4% (9)	62.2% (23)	0.396
>1	45.7% (16)	68% (17)	33.3% (1)	57.1% (4)	39.6% (2)	50% (2)	52.6% (10)	37.8% (14)	

Table 3: Association of triple marker status with Age, menopause and disease severity.

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