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Hormone Receptor Status in Breast Cancer and its Relation to Age and Other Prognostic Factors at Tertiary Care Hospital at Central India

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Abstract

Introduction: Breast cancer is a major concern in modern India. The growing population of the patients and the increased death toll require immediate attention from the scientific and medical community.

Material and Methods: In this study, we have conducted a rigorous survey between 2012 and 2014 and investigated all possible contexts in relevance to the disease. Detail Analyzis was done for 112 patients. The focus was made on vital information n such as parity, age during first live birth, complaint details, location and exact clinical features of the problem, association of axillary lymph node, hormone receptor Analyzis, histopathological grading, and TNM staging.

Results: Our study showed that the age of menarche, the presence of lump in a specific quadrant was quite specific and supported the recently reported data. We have found that the mean age of the patient has declined as discussed in some of the recent studies. Only 8% of the participant patients were found to be nulliparous. Very less number of patients (11.60%) were found to link with the disease hereditarily. We observed that presence of positive nodes were almost triple than the patients with negative lymph nodes, thus, chances of survival in those patients were comparatively lower. Statistical co-relation was found between ER status, PR status, lymph nodes and age of the patients.

Conclusion: We expect this study will increase the present understanding of breast cancer in India. Detail Analyzis with larger population may yield confirmation to our Analyzis.

Keywords: Hormone receptor; ER status; PR status.

Introduction

A growing number of cases every year for almost all types of cancers is the cause of concern for the present medical system. The rising death toll irrespective of age, sex and geographical locations and lack of a cure, made the situation alarming and warrant immediate action from the global scientific and medical communities. For women, breast cancer is observed in almost all age groups irrespective of the geographical location and race a person belong to. The WHO based Globocan cancer monitoring and survey Analyzis suggested that in 2018 alone, 2,088,849 (11.6%)newcases have been reported in all age groups for men and women together.[1] In the same year, the number of the death toll due to breast cancer was reported as 6,26,679, i.e., 6.6% of the total death (9,555,027) caused by cancer.

Among Indian women, breast cancer turned out to be the most lethal form of cancer with an average age-adjusted rate of 25.8/100,000 women and calculated mortality of 12.7/100,000 women.[2] Detail

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inspection of the data suggested that the higher age-adjusted cases were observed in Delhi (41), Chennai (37.9) and Bangalore (34.4) followed by Thiruvananthapuram District (33.7).[2] Estimations suggested that the number of cases is higher in the urban and metropolitan regions of India whereas reports are less in the rural areas. Surprisingly, the mortality-to-incidence ratio has shown an opposite outcome with 66 in rural and 8 in the urban region. Age,[3,4] genetic makeup and genes,[5] economic condition,[6] lifestyle,[7] food habits, cultural beliefs, awareness, frequency of medical check up are vital in relation to the disease onset and progression. Griffith et al. recently reported the prognostic effect of somatic mutation in ER-positive breast cancers and emphasizedon the TP53, NF1, PIK3CA, and PIK3R1 genesas the prognostic driver sir respective of the clinical variables accounted for a particular case.[8] Thus, understanding the relationship of breast cancer with hormone receptor status and relevant prognostic factors is of immense importance. With this objective, we have attempted to focus on the correlation of these factors in women less than 45 years of age with respect to hormone receptor status (ER/PR). In this study, correlation of hormone receptor status (ER/PR) with lymph node status and histopathological grading and staging of breast cancer was investigated for the patients under 45 years of age.

Materials and Methods

The present study on the hormone receptor status and its relation with age and important prognostic factors was carried out in the Department of Surgery in central India at tertiary rural hospital, during the period of May 2012 to June 2014.

All the subjects those who were part of the study underwent detail physical and clinical examination and relevant information about them was collected and tabulated from hospital information system. Under diagnostic investigation, stage of the disease was detected using the standard TNM staging process, FNAC report, histopathology report, tumor grade, axillary lymph node status was considered. Inaddition, ER/PR status, primary treatment condition, adjuvant therapy related information, presence of any further complications due to surgery or chemotherapeutic treatment, and histopathological reports were also keenly observed and documented for this Analyzis.

All women of all age groups with breast cancer and who have undergone aunilateral mastectomy were included in the study. Patients who received neo-adjuvant chemotherapy were not considered in this study. The patients who did not undergo mastectomy or had undergone a bilateral mastectomy and received neo-adjuvant as part of their chemotherapy were excluded from the study. Statistical Analyzis was conducted using the SPSS 26 environment. Continuous variables were represented as mean ± SD and the categorical variables were presented as n (%). Chi-squaretest and Pearson's correlation Analyzis was used to find the association between different parameters. Pearson's correlation Analyzis was conducted between the ER statuses, PR status, Lymphnodeisolated, Lymph node histological parameter, and the histopathological outcome. *P*-values less than 0.05 was considered to be significant.

Results

The observation of the incoming patients suggests that 11,18,615 patients visited the hospital for treatment during the study phase of May 2012 to June 2014. The surgery outpatient department was attended by 1,03,916 patients. A large number of patients (73,811) took admission for one or the other treatment requirement and 13,812 patients received treatment from the Department of surgeryasan inpatient.

The number of malignant patients was 4927 and out of this 2139 patients had surgical malignancy. The observed malignant patient in Breast was 193 (9.02% of the 2139 malignant patients). Incidence of breast cancer was 9.02% of all the surgical malignancies.

Different relevant descriptive statistics were noted and analyzed in relation to breast cancer.

Detail information on the patients' age, age at menarche, parity status of breast cancer, age of the patient at the first child birth, breast feeding habit by the patient, the status of the menopause, family history was collected and analyzed.

Discussion

Identifying the prognostic factors and implementing them as essential disease markers and indicators may allow timely diagnosis, treatment and plausible cure for breast cancer. Several prognostic factors such as micro RNA (mir-24–3p) in metastasis process of breast cancer[9] and expression of androgen receptors in triple-negative breast Cancer[10] are being explored recently.

In Indian peninsular region, breast cancer was observed in the patients over 40 years of age, especially between 45–65 years of age[11] Reports suggest that till menopause, the risk of having breast cancer doubles every 10 years for women.[12] We have observed in this study that 48.21% of patients were present in the age Group 25–45 yrs. The youngest patient was 27 years and the eldest patient was of 72 years.

Early menarche is associated with an increased risk of breast cancer in females.[13] Our study suggested that 38 (33.92%) patients achieved menarche at the age of 13 years and 30 (26.78%) at the age of 14 years. Only 4 (3.57%) patients reported menarche at the age of 17 years. The mean age of the patients to have menarche was 14.03 years.

We have found 9 (8.03%) patients were nulliparous and majority of the patients (82%)had less than two children. Only, 5% of the total patients had more than 4 children, whereas 16%of patients were a mother to 3–4 children. In addition, 21 out of 112 patients had delivered more than 2 children. Nulliparity is associated with the breast cancer risk factor.[14] Therefore, 8% of our observation is under the increased risk compared to others. Our reports were found in accordance with the earlier reports by Lodha et al.[15]

Analyzis of the literature suggests that those mothers breastfeed the child is having almost 33%of lower risk of breast cancer compared to those women who do not breastfeed at all.[16] Our data suggested that out of 103 patients 97 (94.17%) performed breast feeding whereas only 6 patients (5.82%) did not breastfeed the child. Analyzis of the menopausal status suggested that 54 patients (48.21%) were having premenopausal and 58 (51.78%) patients reported postmenopausal. The ratio of pre and postmenopausal was 1:0.93. Further, our inspectionon the presence of family history revealed that 13 patients (11.60%) were having a family history of the disease whereas 99 (88.39%) were not having any such history.

Interestingly, most of the patients reported the presence of the painless lump (76.78%) whereas only 5.35% complaint about having a painful lump. The obtained report of pain less lump further indicates the lack of awareness in women about the symptoms of breast cancer and seeking immediate medical attention in the earlier stage of the disease. Burgess et al., stated a similar reason for delaying initial reporting earlier.[17]

Probably due to the late reporting of the disease or lack of awareness in the patients, most of the patients of this study population were found to have a tumor size of >5.1 cm (56.25%). Following next was the patients who had tumor size between 2.1 cm – 5 cm (37.50%) Only 6.25% of the total patients had a lump of less than 2 cm in size with lymph node involvement as we did not include early breast cancer in ourstudy.

Histopathological grading Analyzis revealed that out of a total 112 patients, 78 (69.64%) were in Grade III and 34 (30.35%) were in Grade II. None of the patients in Grade I was considered for the study. The obtained data suggested that majority of the patients (65 in number, 58.03%) under consideration were in Stage III (a + b + c), followed by Stage II (42 in number, 37.50%). Patients found in Stage I and Stage IV were only 2 (01.78%) and 3 (2.67%) respectively. The detail of the various Staging and sub staging information is providedin (Table 1). Most numbers of patients were found in Stage IIIa (37, 33.03%) followed by Stage IIIb (16, 14.28%) and Stage IIIc (12, 10.71%) respectively. TNM staging may not bedirectly impacting the decision making and treatment direction determination[18,19] but it helps a lot in grouping and subgrouping the patient population and categorizing them as per the clinical relevance.

Table 1: Observation outcome of the TNM staging for the study population.

TNM Stage	No. of patients (%)
Stage I	2 (1.78)
Stage II	42 (37.5)
Stage IIIa (T_{1-2} N_{1-2} M_0)	37 (33.03)
Stage IIIb (T_4 N_{0-2} M_0)	16 (14.28)
Stage IIIc (T_{any} N_3 M_0)	12 (10.71)
Stage IV (T_{any} N_{any} M_1)	3 (2.67)
Total	112 (100)

Clinical inspection of the lymph nodes was conducted and 88 patients (78.57%) were foundtohave palpable lymph node whereas 24 patients (21.42%) were having non-palpable lymphnodes. Axillary lymph nodes frequency and the patterns of lymphnode involvement have been rigorously studied earlier.[20,21] The observed involvement of the axillary lymph nodes suggests that 48.21% (54 patients) of the total patients were having 6–9 axillary lymph nodes followed by more than 10 nodes were found in 40 patients (35.71%). Presence of positive and negative nodes was found to be 73.21% and 26.78% respectively. An excellent study has established that higher the number of negative lymph node, better the survival chance for the patient after invasive surgical treatment.[22] The lymph node ratio (LNR) also proved to be a better predictor of survivalin breast cancer patients compared to the pN classification technique.[23]

Hormonal prognostics factors are important and reliable to understand the disease condition and progression. Up and down-regulation of Estrogen and Progesterone hormones and inter activity of their respective receptors, i.e., Estrogen receptor (ER) and Progesterone receptor (PR) are related and have a deep influence in breast cancer formation and progression. Table 2 represents the outcome of the Analyzis pertaining to the status of ER and PR observed. The maximum number of patients (56 patients, 50%) were found in ER+ group for the patient category of ≥46 years and similar category of the PR counter part was having 46 patients (41.07%). The estimated Chi-square values were found to be significant. Thus, most of the patients (72 patients, 64.28%) were found under the ER+/PR+ group in this study, followed by ER+/PR-(17.83%), ER-/PR-(12.5%) and ER-/PR+(5.35%).

Table 2: Observed Estrogen receptor(ER) and Progesterone receptors (PR) status of the patients andstatistical estimation.

ER status				PR status				Total patients
<45 years		≥46 years		<45 years		≥46 years		
+	–	+	–	+	–	+	–	112
36	18	56	2	32	22	46	12	
32.14	16.07	50	1.79	28.57	19.64	41.07	10.71	Percentage
10.7				4.58				2-value
0.0001				0.032				*p*-value

Additional Analyzis of the hormone receptor categories in the patients with relation tolymphnode status is presented in Table 3. The outcome depicted that the presence of ER and PR simultaneously also coexisted with lymph nodes in 92.85% of the patients. Surprisingly, the absence of both ER and PR showed the presence of lymph nodes in the considered patients (Table 3).

Research reports have outlined that ER influences the expression of PR genes[24] ER and PR expression are higher and lower in premalignant and malignant lesionsin comparison to the neighboring healthy tissues[25] Therefore, ER and PR levels are used as a prognostic indicator for the clinical purpose to understand the course of the disease and assess the adjuvant hormonal therapy response. Further, the clinical and molecular investigation revealed that ER+/PR+ patients survive long and respond to hormonal therapy than ER-/PR- patients. Individually, ER or PR is not sufficient to act as an excellent prognostic factor, thus, a combination of both are used to solve the purpose. In breast cancer, ER+/PR+ was found to be associated with parity, age at menarche, age at first childbirth, BMI, and waist-hip ratio. We have reported that Estrogen receptor, tumor staging axillary node metastasis and histopathological grading are related to each other in many aspects. An earlier study also supported such an outcome.[26]

Table 3: Hormone receptor status and its relation with lymph node status formetastasis.

Hormone receptor status	Total cases	LN +VE	LN –VE
ER+/PR+	28	26 (92.85%)	02 (7.14%)
ER+/PR–	8	06 (75%)	02 (25%)
ER–/PR+	4	03 (75%)	01 (25%)
ER– /ER–	14	14 (100%)	00 (00%)

Table 4 reflects the distribution of hormone receptors and the observed TNM staging in this study. No patient's data was under the Stage I, Stage IV and Grade1.

The probable correlation was investigated for ER and PR with age of the patient, lymphnode status and histopathological grading. Estimation of the correlation was done by Pearson Correlation and its significance was conducted through a two-tailed test. To improve and confirm the obtained outcome, bootstrap was set to 1000 along with a 95% confidence interval. Following the study objective, correlation Analyzis was done between the ER status, PR status and two important age related variable, ie., actual age of the patient and age of the patient at menarche. Patient's age was found to be negatively correlated with the ER and PR status. Age at menarche of the patients also displayed the similar trend for the PR status. However, the relation between ER status and PR status was found to be strongly correlated. The other Analyzis was conducted between receptor status (ER and PR), age and lymphnode status which further confirmed the probable relation between the ER and PR. Patient age was also found to be associated with the lymphnode status. Correlation Analyzis of the ER, PR status and the staging did not show any statistically significant relation al information, even though the outcome hinted towards probable positive correlation. Rest of the parameters did not show any correlation. Study with a larger patient population may provide a better outcome.

Table 4: Relation of hormone receptor status and staging of breast cancer and histopathologicalgrading

Hormone Receptor status	Total	Stage I	Stage II	Stage III	Grade 2	Grade 3
ER+/PR+	28	0	12 (42.85%)	16 (57.1%)	11 (39.28%)	17 (60.71%)
ER+/PR–	8	0	03 (37.5%)	05 (62.5%)	04 (50%)	04 (50%)
ER–/PR+	4	0	01 (25%)	03 (75%)	01 (25%)	03 (75%)
ER–/ER–	14	0	0	14 (100%)	02 (14.28)	12 (85.71%)

Conclusion

Most of the participant patients in this study were having early menarche by 14 years of age (63.92%), and mother of two or more children. Several patients were found to have young age (48%) and were within the age group of 25–45 years. Out of all, 8% of the patients were found nulliparous, thus, having increased disease risk. Interestingly, most of the participant patients were not having any hereditary link to the disease. An attempt was made to investigate the probable relationship between the clinical and social features considered herein. We believe this study will help future breast cancer related epidemiological studies in India and will serve as a knowledge resource.

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