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Original Article

Carcinoma Breast and Correlation with Estrogen and Progesterone Receptor Status in Rajendra Institute of Medical Sciences, Ranchi

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Abstract

Introduction: Breast carcinoma is the second most common carcinoma in women and account for 22% of all female cancer, which is more than twice the prevalence of cancer in women at any other site. Its incidence has increased globally over the last several decades; the greatest increase has been in Asian countries. India accounts for nearly 6% of deaths and also that one in every 22 women in India are diagnosed with breast carcinoma every year. More than 80% of Indian patients are younger than 60 years of age. Hormones play an important role in the development and progression of breast cancer. Patients with hormone receptor positive tumors survive 2-3 times longer after a diagnosis of metastatic disease than do patients with hormone receptor-negative tumors.

Purpose: To correlate the expression of prognostic factors such as age of patient, menarche, menopause, parity, tumor size, number of lymph nodes and histological grading with estrogen, and progesterone receptor (ER/PR) status.

Methods: This study was carried out on a total of 75 patients with carcinoma breast admitted in the Department of General Surgery in Rajendra Institute of Medical Sciences, Ranchi from September 2012 to September 2014.

Results: According to the data of this study, a statistically significant correlation of ER/PR was found with menopausal status, parity, tumor size, number of lymph nodes, and tumor grade, whereas age of menarche had a significant correlation with only PR.

Conclusion: ER and PR status are highly important predictors in cases of carcinoma breast which necessitates routine evaluation of the hormonal receptor status for better management of the disease.

Key words: Carcinoma breast, Hormone receptor status, Menopausal status, Lymph node involvement, Parity, Tumor grade and size

INTRODUCTION

Breast carcinoma is the second most common carcinoma in women and account for 22% of all female cancer, which is more than twice the prevalence of cancer in women at any other site.[1] It is the most common site-specific cancer in women and is the leading cause of death from cancer for women aged 20-59 years.[2] It accounts for 26% of all newly diagnosed cancers in females and is responsible for 15% of the cancer-related deaths in women.[3] The incidence of breast cancer has increased globally over the last several decades; the greatest increase has been in Asian countries.[4] In Asia, breast cancer incidence peaks among women in their forties, whereas in the United States and Europe, it peaks among women in their sixties.[5] India accounts for nearly 6% of deaths and also that one in every 22 women

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in India are diagnosed with breast carcinoma every year with premenopausal patients constituting about 50% of all patients.[6,7] Over 100,000 new breast cancer patients are estimated to be diagnosed annually in India. Breast cancer cases are expected to increase by 26% by 2020, and most of these will be seen in developing countries.[8] Routine use of screening mammography in women >50 years of age reduces mortality from breast cancer by 33%.[2]

Data from the International Agency for Research on Cancer (IARC) registry suggest that 45% of newly diagnosed cases of breast cancer and 55% of breast cancer-related mortality currently occur in low- and middle-income countries. IARC trends also show a 20-30% increase in the incidence of breast cancer in developing countries during the past decade.[9]

More than 80% of Indian patients are younger than 60 years of age. A significant proportion of Indian breast cancer patients is younger than 35 years of age. Young age has been associated with larger tumor size, higher number of metastatic lymph nodes, poorer tumor grade, low rates of hormone receptor-positive status, earlier and more frequent locoregional recurrences, and poorer overall survival. There is a significant difference in the survival rates in developed and developing countries mainly because of a lack of early detection programs and inadequate resources for treatment.[10,11] Coleman reported >80% survival from breast cancer in North America and Europe compared with 60% in middle-income countries and 40% in low-income countries.[12]

Hormones play an important role in the development and progression of breast cancer. In postmenopausal women, hormone replacement therapy consisting of estrogen plus progesterone increases the risk of breast cancer by 26% compared to placebo. Tamoxifen, a selective estrogen receptor (ER) modulator, was the first drug shown to reduce the incidence of breast cancer in healthy women.[2] The best indicators of likely prognosis in breast cancer remain tumor size and lymph node status histological grade of the tumor, hormone receptor status, measures of tumor proliferation such as S-phase fraction, growth factor analysis, and oncogene or oncogene product measurements. Prognostic indices (such as the Nottingham prognostic index) have combined these factors to allow subdivision of patients into discrete prognostic groups. More recently, a computer-aided program has been developed, which incorporates the putative benefits of treatment allowing oncologist and patient to visualize the benefits of therapy.[13]

The patients with hormone receptor positive tumors survive two to three times longer after a diagnosis of metastatic disease than do patients with hormone receptor-negative tumors. Patients with tumors negative for both ERs and progesterone receptors (PRs) are not considered candidates for hormonal therapy. Tumors positive for ER or PRs has a higher response rate to endocrine therapy than tumors that do not express ER or PRs. Tumors positive for both receptors has a response rate of >50%, tumors negative for both receptors have a response rate of <10%, and tumors positive for one receptor but not the other have an intermediate response rate of 33%. The determination of ER and PR status requires biochemical evaluation of fresh tumor tissue.[2]

Today, however, ER and PR status can be measured in archived tissue using immunohistochemical techniques. Hormone receptor status also can be measured in specimens obtained with fine-needle aspiration biopsy or core-needle biopsy, and this can help guide treatment planning. Testing for ER and PRs should be performed on all primary invasive breast cancer specimens.[2]

Rajendra Institution of Medical Sciences (RIMS), Ranchi gets a good number of patients with carcinoma breast and this study on carcinoma breast and correlation of prognostic factors with ER and PR status is of high clinical significance paving the path for better management of patients suffering from the dreaded disease of carcinoma breast.

MATERIALS AND METHODS

This hospital-based study was conducted on patients with carcinoma breast admitted in the Department of General Surgery in RIMS, Ranchi from September 2012 to September 2014. A total of 75 patients with breast carcinoma were included in the study. The information such as name, registration number, age of the patient, age of menarche, age of menopause, parity of the patient, tumor size, and number of lymph nodes was collected. The specimens were sent for HPE and ER/PR status post modified radical mastectomy.

Inclusion Criteria

All female patients with proven cases of infiltrating carcinoma of breast that were sent for histological grading and ER, PR status following surgical treatment were included in the study.

Exclusion Criteria

Male patients:

- Patients of carcinoma breast who did not undergo surgical treatment.

RESULTS

The mean age of the carcinoma breast patients in this study was 48.84 years with standard deviation of ±13.35 years (Table 1).

Here, the hormone receptor positivity/negativity was compared with the age of patients. A definitive positive correlation could not be made as a number of patients as a whole was more in the age group of 35-44 years, still in the above-considered patients receptor positivity increased as the age increased. The mean age in ER+ group was 49.36 ± 1.94 and 47.8 ± 2.55 years in ER− group. The *P* value was 0.6364 which is statistically insignificant. In the case of the PRs, the negativity was seen maximum in age group of 35-44 years. The mean age in PR+ group was 48.78 ± 1.95 and 48.96 ± 2.54 years in PR− group. The p value was 0.9547 which makes the analysis insignificant (Table 2).

The mean age of menarche in ER+ group was 12.26 ± 0.13 and 12.12 ± 0.18 years in ER− group. The *P* value was 0.5443 which is insignificant. The mean age of menarche in PR+ group was 12.39 ± 0.136 and 11.88 ± 0.16 years in PR− group. The *P* value was 0.0254 which is significant. Hence, early menarche is associated with PR negative status (Table 3).

A total of 45 cases were premenopausal out of which ER+ as well as PR+ cases were 62.22%, whereas 30 were postmenopausal out of which ER+ was in 73.33% and PR+ was in 70% of cases. Hence, it was seen that postmenopausal cases had more ER as well as PR positivity (Table 4).

As the parity has increased, the ER as well as PR positivity has increased. The mean parity in the ER+ group was 3.3 ± 0.17 whereas it was 2.2 ± 0.3 in the ER− group. The *P* value is 0.0012 and it was significant. The mean parity of PR+ group was 3.4 ± 0.17, whereas it was 2.038 ± 0.28 in the PR− group. The *P* value was <0.0001 and it was highly significant (Table 5).

In this study, the most tumors were of size 2-3 cm and as the size of the tumor increased, the hormone receptors negativity has increased. The mean tumor size in ER+ group was 2.61 ± 0.13 and 4.34 ± 0.26 cm in ER− group. The *P* value was <0.0001 which makes the result highly significant. The mean tumor size in PR+ group was 2.6 ± 0.13 and 4.115 ± 0.28 cm in PR− group. The *P* value was <0.0001 which is highly significant (Table 6).

In most of the cases, the lymph nodes number was between 0 and 2, and they were mostly hormone receptor positive. The mean number of lymph nodes was 0.82 ± 0.12 in the ER+ group while it was 4.24 ± 0.59 in the ER− group. The *P* value was <0.0001 which is highly significant. The mean number of lymph nodes was 0.857 ± 0.146 in the PR+ group and was 4.038 ± 0.577 in

Table 1: Age distribution of carcinoma breast patients

Age (in years)	Number of patients
25-34	5
35-44	27
45-54	16
55-64	17
65-74	6
75-84	4

Table 2: Age and hormone receptor status is compared

Age (in years)	ER+	ER−	PR+	PR−
25-34	4	1	4	1
35-44	17	10	17	10
45-54	9	7	9	7
55-64	12	5	12	5
65-74	6	0	5	1
75-84	2	2	4	1

ER: Estrogen receptor, PR: Progesterone receptor

Table 3: Age of menarche and hormone receptor status

Age of menarche	ER+	ER−	PR+	PR−
11	11	6	8	9
12	21	13	22	12
13	12	3	11	4
14	6	3	8	1

ER: Estrogen receptor, PR: Progesterone receptor

Table 4: Menopausal status and hormone receptor status

Menopausal status	ER+	ER−	PR+	PR−
Pre-menopausal	28	17	28	17
Post-menopausal	22	8	21	9

ER: Estrogen receptor, PR: Progesterone receptor

Table 5: Parity and hormone receptor status

Parity	ER+	ER−	PR+	PR−
0	1	4	1	4
1	1	5	1	5
2	11	5	7	9
3	15	6	17	4
4	16	3	17	2
5	3	2	3	2
6	3	0	3	0

ER: Estrogen receptor, PR: Progesterone receptor

Table 6: Tumor size and hormone receptor status

Tumor size	ER+	ER−	PR+	PR−
<2	6	0	6	0
2-3	37	7	34	10
>3-5	6	10	8	8
>5	1	8	1	8

ER: Estrogen receptor, PR: Progesterone receptor the PR− group. The *P* value was <0.0001 which is highly significant (Table 7).

In this study, most of the cases were of Grade I and they showed hormone receptor positivity, and the negativity was found to increase with an increase in grade of the tumor. In Grade I, II and III tumors the ER positive cases were 84.21%, 78.26% and 0%, respectively. The p value is <0.0001 which makes the association between grade and ER highly significant. The Grade I, II and III tumors showed PR positivity of 89.47%, 60.87% and 7.14%, respectively. The *P* value is <0.0001 which is highly significant too (Table 8).

DISCUSSION

Carcinoma breast has known risk factors each of which was correlated separately with ER and PR status.

Age and Hormone Receptor Status

Fisher *et al*., in 1980, studied 178 invasive breast cancer cases. Well-differentiated tumors were more frequently ER+ in older women.[14]

Mohammed *et al*., in 1986, reviewed 490 consecutive human breast biopsy and mastectomy specimens which were correlated with ER and PR content of the tissue. 63% of the patients with Grade IV infiltrating ductal carcinoma were younger than 53 years of age ($P < 0.001$). Patients younger than 53 years of age with Grade II and III infiltrating ductal carcinoma also had significantly lower levels of ERs, but not of PRs, than those patients older than 53 years of age ($P < 0.001$).[15]

Ruder *et al*., in 1989, reported a study over 171 Israeli women diagnosed with breast cancer and found that age tended to be associated positively with both ER+ and PR+.[16]

Table 7: Lymph node number and hormone receptor status

Lymph node number	ER+	ER−	PR+	PR−
<2	37	5	36	6
2-5	13	11	13	11
>5	0	9	0	9

ER: Estrogen receptor, PR: Progesterone receptor

Table 8: Histological grade and hormone receptor status

Histological grade	ER+	ER−	PR+	PR−
I	32	6	34	4
II	18	5	14	9
III	0	14	1	13

ER: Estrogen receptor, PR: Progesterone receptor

Amaral and Sergio, in 2001, studied 306 patients with infiltrating ductal carcinoma and found that both ER and PR were significantly associated ($P < 0.05$) with patient's age (<60 years vs. >60 years). When the association was studied between different levels of positivity for HR (+++ vs. ++ vs. + vs. negative) and patient's age (<60 years vs. >60 years), significant *P* value ($P < 0.01$), for both ER and PR was found.[17]

Britton *et al*., in 2002, studied 1556 women aged 20-44 years with carcinoma breast. As age increased, the proportion of women with ER+PR+ tumors increased, and this finding corresponded primarily with a decline in the proportion of women diagnosed as having ER− PR− tumors.[18]

Alvarez Goyanes *et al*., in 2008, examined 1509 tumors from Cuban women diagnosed with breast cancer. Analysis of age at the time of diagnosis showed that ER expression was greater in patients in the group aged >50 years ($P < 0.05$).[19]

Pourzand *et al*., in 2011, organized an analytic cross-sectional study of 105 women diagnosed with breast cancer and found a direct correlation between positive PR status and being younger than 40 (P < 0.05). Also, compared with older women, young women had tumors that were more likely to be large in size and have higher stages (P < 0.05).[20]

Ahmed *et al*., in 2011, studied 157 formalin-fixed, paraffin embedded tissue block samples from the breast lesions. Primary breast cancer cases had their ages ranging from 21 to 80 years with a mean age of 46 years.[21]

In this study (Tables 1-3), out of 75 cases of carcinoma breast, who were from 25 to 84 years of age (mean age 48.84 ± 13.35), ER+ and PR+ cases were 50 (66.66%) and 49 (65.33%), respectively. The mean age in ER+ group was 49.36 and 47.8 in ER− group. The *P* value was statistically insignificant. The mean age in PR+ group was 48.78 and 48.9 in PR− group. The *P* value was insignificant. Still, as the age increased, ER and PR positivity increased which is in accordance with the above studies.

Age of Menarche and Hormonal Receptors

Rosen found the association between ER− and early menarche statistically borderline ($P = 0.09$).[22]

Amaral and Sergio, in 2001, found a statistically significant association between PR− and early menarche (<11 years) ($P < 0.05$).[17]

In this study, the mean age of menarche in ER+ group was 12.26 and 12.12 years in ER-group ($P = 0.5443$, insignificant), whereas it was 12.39 years in PR+ group and

11.88 years in PR− group ($P = 0.0254$) which is significant. This finding is in accordance with the above findings.

Menopausal Status and Hormonal Receptors

Mohla *et al.*, in 1982, studied 146 black women with breast cancer and found that postmenopausal patients and primary tumors showed higher ER+ than premenopausal patients and metastatic sites, respectively.[23]

Ruder *et al.*, in 1989, found that being postmenopausal, older at menopause or at first birth, were correlated positively with ER and negatively with PR.[16]

Amaral and Sergio, in 2001, found a statistically significant positive association between ER and menopausal status (pre- vs. post-menopause, $P = 0.0008$). The association observed between PR and this same variable was small and not statistically significant ($P = 0.37$).[17]

In this study, postmenopausal cases had more ER and PR receptor positivity similar to the findings as that of Mohla and Eisenberg but, not as that of Ruder, who found a negative correlation of PR with menopausal status.

Parity and Hormonal Receptors

Ruder *et al.* found that nulliparity was correlated positively with ER and negatively with PR.[16]

Britton *et al.* found that nulliparous women were at increased risk of all tumor types except ER− PR+. An inverse association was observed between months of lactation and each of the hormone receptor tumor subtypes, with the strongest risk reduction observed for ER+ PR− tumors.[18]

In this study, as the parity has increased, the ER and PR positivity has increased similar to above studies.

Tumor Size and Hormonal Receptors

Amaral and Sergio found statistically significant association between ER and PR+ tumors and tumor size <4.0 cm ($P < 0.005$).[17]

Alvarez Goyanes *et al.* found that ER expression was associated with low nuclear grade and histological grade, and with smaller tumor size ($P < 0.05$).[19]

Pourzand *et al.* found that younger women had tumors that were more likely to have higher stage, larger size, and PR+ ($P < 0.005$).[20]

In this study, as the size of the tumor increased, the ER and PR− has increased which was statistically significant ($P < 0.0001$) and is in accordance with the above studies.

Lymph Node Number and Hormonal Receptors

Stierer *et al.* and MacGrogan *et al.* showed that the presence of hormonal receptors (ER and PR) were not associated with nodal status.[24,25]

Amaral and Sergio did not find any association of nodal status with hormonal receptors.[17]

Alvarez Goyanes *et al.* found that ER expression tended to decrease as the number of metastatic axillary lymph nodes increased, although this association was not statistically significant.[19]

Ahmed *et al.* found a significant positive association between ER or PR expression with lymph node involvement ($P = 0.004$ and $P = 0.022$, respectively).[21]

Pourzand *et al.* found that 59.6% of ER+ patients had lymph node involvement; 60.4% of ER− patients had involved nodes, and the difference was not statistically significant ($P = 0.88$). Similarly, 57.1% of PR positive patients had lymph node involvement compared with 64.2% of PR negative patients and it was also not statistically significant ($P = 0.42$).[20]

In this study, a significant association of lymph node status and ER/PR receptors was found. This finding is in accordance with that of Ahmed *et al.*

Histological Grade and Hormone Receptor Status

Fisher *et al.* (1980) found positive ER to be significantly associated with high nuclear and low histologic grades.[14]

Mohla *et al.* also found a significant correlation between the ER+ and tumor grade.[23]

Mohammed *et al.* studied the ER and PRs in human breast cancer and correlation with histologic subtype and degree of differentiation. Of the four grades of differentiation, the less differentiated Grade III and IV tumors showed significantly lower levels of ER and PRs in infiltrating ductal and lobular carcinoma ($P < 0.001$). Patients younger than 53 years of age with Grade II and III infiltrating ductal carcinoma also had significantly lower levels of ERs, but not of PRs, than those patients older than 53 years of age ($P < 0.001$).[15]

Amaral and Sergio found statistically significant association between ER and PR+ tumor and low histological grade ($P = 0.01$).[17]

Alvarez Goyanes *et al.* also found significant association between ER and PR+ tumors and low histological grade ($P = 0.01$).[19]

Ahmed *et al.* found no statistically significant association between ER, PR and tumor grade.[21]

In this study, the Grade I, II and III tumors showed ER positivity of 84.21%, 78.26% and 0%, respectively, and PR+ of 89.47%, 60.87% and 7.14%, respectively, which is highly significant statistically ($P < 0.0001$) and is in accordance with the above studies.

CONCLUSION

This study conducted at RIMS, Ranchi evaluated the ER/PR status and correlation with other prognostic factors.

According to the data of this study, a statistically significant correlation of ER/PR was found with menopausal status, parity, tumor size, number of lymph nodes and tumor grade, whereas age of menarche had significant correlation with only PR.

To conclude, ER/PR status is highly important predictor in cases of carcinoma breast which necessitates routine evaluation of the hormonal receptor status for better management of the disease.

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