CLINICAL STUDY OF CORRELATION BETWEEN ESTROGEN RECEPTOR (ER) AND PROGESTERONE RECEPTOR (PR) STATUS AND PATIENT CHARACTERISTICS IN CARCINOMA BREAST

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ABSTRACT

BACKGROUND AND INTRODUCTION

Breast carcinoma is the first among women of all races and Hispanic origin populations; most common carcinoma in women and account for 25% of all female cancers, which is more than twice the prevalence of cancer in women at any other site. Recent information suggests globally breast carcinoma is the second leading cause of cancer related death and is the most common cancer among women excluding the non-melanoma skin cancer. Estrogen and Progesterone play a central role in regulating growth kinetics of a variety of epithelial lining like in breast and endometrium and are powerful predictive markers in carcinoma of breast.

AIMS AND OBJECTIVES

To study the correlation between ER and PR status and patient characteristics like age of patient, menarche, menopause, parity, tumour size, lymph node status and tumour grade in carcinoma breast patient.

MATERIALS AND METHODS

Forty patients were included in this study who were admitted with breast carcinoma, the patient characteristics are correlated with ER and PR status studied by immunohistochemistry. This study was done over the period from October 2013 to September 2015.

RESULTS

Patients with both ER/PR positive are better differentiated, low grade, small sized tumours and with less chance of lymph node metastasis. Progesterone receptor negative status is associated with lymph node metastasis independent of other patient characteristics. Grade 3 and 4 tumours showed lower level of Estrogen and Progesterone receptors irrespective of age.

CONCLUSION

ER/PR positive group were better differentiated, showed better prognosis with hormonal therapy. They were less aggressive, low lymph node metastasis when compared with patients with either of the receptors negative or both the receptors negative. Hence immunohistochemistry is a must as it provides valuable prognostic, predictive and therapeutic information.

KEYWORDS

Estrogen receptor, Progesterone receptor, Carcinoma Breast, Immunohistochemistry, Tumour size, Tumour grade, Lymph node number.

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INTRODUCTION: Breast carcinoma is the first among women of all races and Hispanic origin populations; most common carcinoma in women and account for 25% of all female cancers, which is more than twice the prevalence of cancer in women at any other site.(1) Recent information suggests that globally after lung cancer, the carcinoma of the breast is the second leading cause of cancer related death and is the most common cancer among women excluding the non-melanoma skin cancer.(2) India accounts for nearly six percent of deaths due to breast cancer in the world and also that one out of every 22 women in India are diagnosed with breast cancer every year.(1)(2)

Contrary to the West where it is more common in the elderly, it is more common at a younger age in the Indian women, who present themselves in advanced stage with poor prognostic feature and have worse outcome when compared to their counterparts in the western countries.(3)

Estrogen plays a central role in regulating growth kinetics of a variety of epithelial linings, most importantly in the breast and endometrium. Breast cancer patients whose lesions contain both estrogen receptor [ER] and

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progesterone receptor [PR] have the best probability of remission following hormonal therapy (approaching 70%) than the group of patients whose lesions contain either receptor alone (approximately 30%), or very low levels of both receptors (approximately 10%).[4] It has been shown that tumours expressing ER and PR tend to be better differentiated and low-grade tumours. ER negative status has been shown to be predictive of recurrence of low stage tumours, independent of tumour grade, while negative PR status is associated with a significant risk of lymph node metastasis independent of other clinic pathological factors.[4]

It has been reported that the less differentiated Grade III and IV tumours showed significantly lower levels of estrogen and progesterone receptors in infiltrating ductal and lobular carcinoma irrespective of age. Patients younger than 53 years of age with Grade II and III infiltrating ductal carcinoma also had significantly lower levels of estrogen receptors, but not of progesterone receptors, when compared with those patients older than 53 years of age. The oestrogen receptor is probably the most powerful predictive marker, due to the genomic instability, molecular heterogeneity and clonal evolution. The treatment of breast cancer can be difficult as each case is different from the other.[5]

In breast cancer, to date relatively few markers have been reported to have established predictive power and of relevance. They are the well-known markers, the estrogen receptor (ER) and the progesterone receptor (PR) for selecting endocrine-sensitive breast cancers and human epidermal growth receptor HER-2 for identifying breast cancer patients with metastatic disease who may benefit from transtuzumab.[5] The estrogen receptor is probably the most powerful predictive marker in breast cancer management, both in determining prognosis and in predicting response to hormone therapies. Progesterone receptor is also a widely used marker, although its value is less well established. ER/PR is now recommended as mandatory in invasive breast cancer.

AIM: The aim of this study is to study the correlation between ER and PR status and patient characteristics like age of patient, menarche, menopause, parity, tumour size, lymph node status and tumour grade in carcinoma breast patients from October 2013 to September 2015 in our Hospital.

On reviewing the literature in the 19th century Beatson found that the estrogen receptors were important in breast carcinoma. Since the 1970s, considerable progress has been made in the integration of surgery, radiation therapy and chemotherapy to control local-regional disease, enhance survival, and increase the possibility of breast conservation by the identification of estrogen and progesterone receptors in the breast carcinoma specimen.

Steroid Hormone Receptor: There are two main steroid receptors, estrogen (ER) and progesterone (PR) receptors. These hormones, estrogen and progesterone play a major role in breast cancer especially the estrogen, its metabolites and progesterone enable in the development and progression of breast cancer. The risk for breast cancer is due to the duration of exposure to estrogen. In case of postmenopausal women, it is the duration of exposure to oestrogen and progesterone in the hormone replacement therapy which increases the chance for cancer by 26%.[6,7]

There are two main steroid receptors, estrogen (ER) and progesterone (PR) receptors. The estrogen and progesterone sensitive receptors are cytosolic, glycoprotein present in breast and certain tumour tissue. This is an important prognostic indicator.

The tissue for receptor study is sent at low temperature in ice flask. It is assessed by quantitative analysis (frozen -70˚). If value is more than 10 units (Vmols) per n gram of tissue it is called estrogen receptor positive status. 60% of the postmenopausal cases are usually estrogen receptor positive and premenopausal cases are 30% positive. The determination of estrogen and progesterone receptor status used to require biochemical evaluation of fresh tumour tissue, using immunohistochemical techniques, hormone receptor status also can be measured in specimens obtained with fine-needle aspiration biopsy or core-needle biopsy.[6,7,8]

Tumour positive for hormonal receptors, hormonal therapy including tamoxifen is more beneficial. Tumours positive for both receptors have a response rate of >50%, tumours negative for both receptors have a response rate of <10%, and tumours positive for one receptor but not the other have an intermediate response rate of 33%. This can help guide treatment planning, hence testing for estrogen and progesterone receptors should be performed on all primary invasive breast cancer specimens.[8]

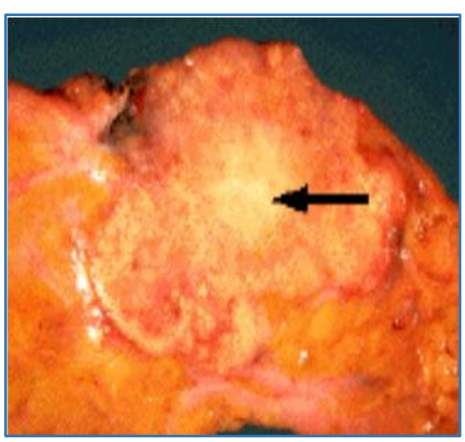


Fig. 1: Specimen of Breast

The arrow shows the invasive tumour in the specimen of breast taken after surgery, and this is sent to the pathologist for immunohistochemistry.

Recent Studies: Association of Hormone-Related Characteristics and Breast Cancer Risk by Estrogen Receptor/Progesterone Receptor Status in the Shanghai Breast Cancer Study.[9]

A study done by Ping-Ping Bao et al[9] in Vanderbilt University Medical Center in 2011 is a large, population

based case-control study of 3,443 cases and 3,474 controls being conducted in Shanghai, China Breast cancer risks associated with age at menarche, age at menopause, breastfeeding, age at first live birth, waist-to-hip ratio, and oral contraceptive use did not differ by hormone receptor status. Among postmenopausal women, higher parity was associated with reduced risk and higher body mass index with increased risk. These findings indicate that BMI, parity, hormone replacement therapy, and alcohol consumption may play different roles in subtypes of breast cancer.

Estrogen receptor and progesterone receptor status in breast cancer in relation to age, histological grade, size of lesion and lymph node involvement.[10]

A study done by Sofi GN et al[10] in 2012 in Srinagar is a prospective observational study done on 132 postsurgery mastectomy specimens compared ER and PR with age, histological grade, size of lesion and lymph node involvement concluded that ER and PR expression in breast cancers in the current study was found to be higher than studies done in India/Asia, but lower than studies conducted in the West, even on Indian/Asian immigrants. Markedly lower receptor expression in Indian/Asian studies is likely due to preanalytic variables, thresholds for positivity, and interpretation criteria.

Correlation of Hormone Receptor Expression with Histologic Parameters in Benign and Malignant Breast Tumours.[11]

A study done by Deepthi Gupta et al in Dept. of Pathology, University of Health Sciences, Rohtak, Haryana, 2015 is a study conducted in 75 patients showed, it was inversely correlated with grade of tumour, NPI, HER-2/neu status, tumour necrosis, lymphomononuclear infiltrate and elastosis. We found no relationship with tumour size, lymph node status or age.

MATERIALS AND METHODS:

Source of Data: This study was carried out on patients coming to the OPD of Department of General Surgery in our Hospital from October 2013 to September 2015. Around 40 patients with breast carcinoma not treated by chemotherapy, radiotherapy, hormonal therapy were included.

Method of Collection of Data: The clinical information like age of the patient, age of menarche, age of menopause, parity of the patient, tumour size and number of lymph nodes were collected. The histological grading was done according to the modified Scarff-Bloom-Richardson histological grading. The estrogen receptor and progesterone receptor immunohistochemical staining were done on the specimen and it was evaluated based on this factor to reach a prognostic conclusion.

Inclusion Criteria: Female patients with carcinoma of breast that have been sent for histological grading and ER, PR including core needle biopsy and postsurgical specimen.

Exclusion Criteria:

- Male patient.
- Those who have undergone any chemo reduction or radiation therapy as a treatment for carcinoma of breast in past.

METHOD: History: Each patient's detailed history was taken specially concerning their age, age of menarche, age of menopause, parity.

Examination: The patient is examined in detail, both the breasts are examined, especially the tumour size and lymph nodes are noted.

Histopathology: The surgical specimen or the biopsy specimen is sent for grading as per modified Scarff-Bloom-Richardson and immunohistochemistry for estrogen and progesterone receptors.

Protocol for Immunohistochemistry of Estrogen and Progesterone Receptors:

1. Slides are dried before actual usage.
2. Negative and positive controls are marked.
3. Sections are taken on to slides and kept in 37 degrees oven overnight.
4. Deparaffin the section, keep the slide in slide warmer at 60 degrees for 15 minutes.
5. Put in Xylene I for 5 minutes.
6. Put in Xylene II for 5 minutes.
7. Place in absolute alcohol for 2 minutes.
8. Keep slide in distilled water.
9. Endogenous peroxidase in tissue section is blocked using 0.5% hydrogen peroxide in methanol for 10 minutes.
10. Phosphate buffer wash given for 5 minutes.
11. Antigen retrieval is done using trisodium citrate 2.94 g, 5m1 HC1 and 1000m1 distilled water and heated in a pressure cooker for 2 minutes., then left for cooling.
12. Washed in distilled water.
13. Washed with phosphate buffer for 5 minutes.
14. Power block for 10 minutes.
15. Phosphate buffer wash up done for 2-5 minutes.
16. Primary antibody for estrogen and progesterone receptor is applied for 60 minutes.
17. Phosphate buffer is used for 5 minutes.
18. PP Block (enhancer) post primary for 30 minutes.
19. Phosphate buffer wash given for 2-5 minutes.
20. S.S Polymer is applied for 30 minutes.
21. Phosphate buffer wash is given for 5 minutes.
22. Mix of 3, 3 diaminobenzidine tetrahydrochloride (DAB) and buffer is applied for 5 minutes.
23. Washed with distilled water for 2 minutes.
24. The sections are stained with Harris's Haematoxylin for 30 sec.
25. Wash in water till blue.
26. Dehydrate, clear and mount the slide with DPX.
27. Slide is ready for reading.

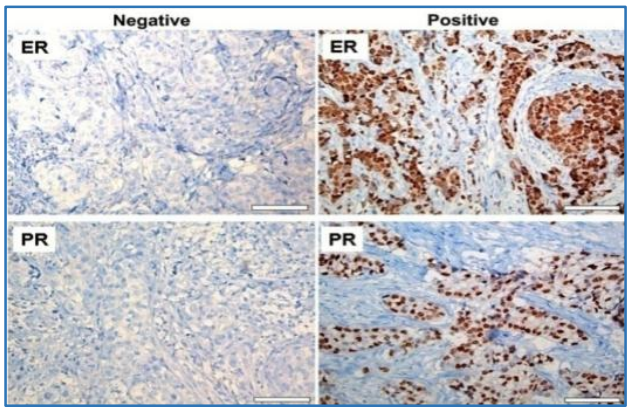
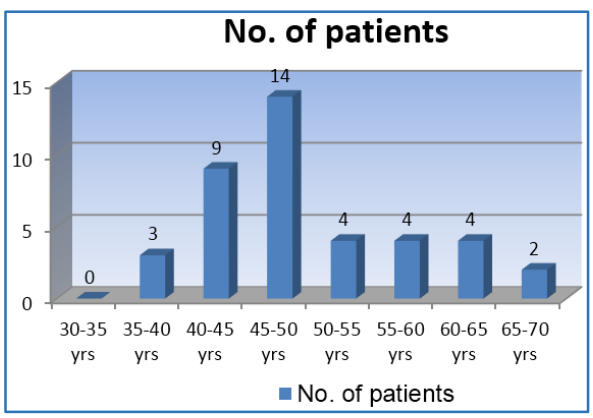


Fig. 2: Immunohistochemistry of receptors

OBSERVATIONS AND RESULTS: This study was carried out on patients coming to the Outpatient Department of Surgery and in our hospital from October 2013 to September 2015. Around 40 patients with breast carcinoma not treated by chemotherapy, radiotherapy, hormonal therapy were included.

Age	No. of patients
30-35 yrs.	0
35-40 yrs.	3
40-45 yrs.	9
45-50 yrs.	14
50-55 yrs.	4
55-60 yrs.	4
60-65 yrs.	4
65-70 yrs.	2

Table 1: Age distribution among the carcinoma breast patients



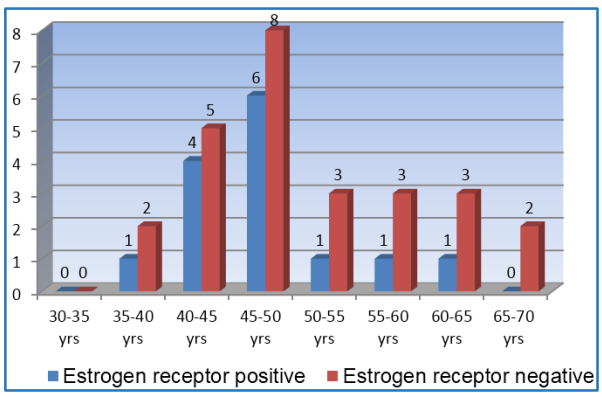
Graph 1: Patients' age distribution

Here, the patients who took part in the study were from 35 to 70 yrs of age, maximum people were in the age group of 45-50 yrs. The specimen from these women were sent for estrogen and progesterone receptor status analysis. The mean age of the patients in the study is 48 yrs and standard deviation is ±3.6.

Age of patients	Estrogen receptor positive	Estrogen receptor negative
30-35 yrs.	0	0
35-40 yrs.	1	2
40-45 yrs.	4	5
45-50 yrs.	6	8
50-55 yrs.	1	3
55-60 yrs.	1	3
60-65 yrs.	1	3
65-70 yrs.	0	2

Table 2: Age and Estrogen Receptor status

P=0.462.



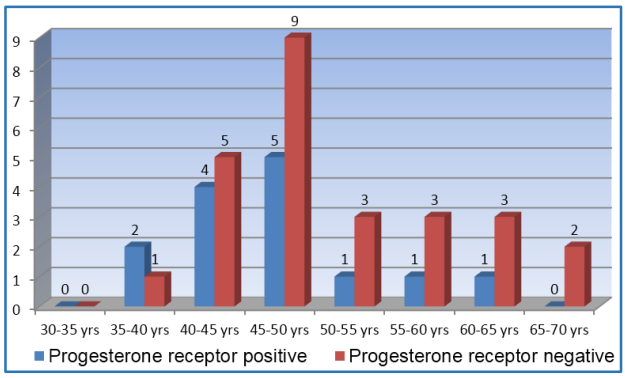
Graph 2: Age and Estrogen Receptor

Here the estrogen receptor positivity/negativity is compared with age of patient. A definitive positive correlation cannot be made as number of patient as a whole is more in the age group of 45-50 yrs., still in the above considered patients, receptor positivity is persisting as the age increases. The statistical analysis is done using Fischer exact test according to which the p value is 0.462 which is not significant.

Age of patients	Progesterone receptor positive	Progesterone receptor negative
30-35 yrs.	0	0
35-40 yrs.	2	1
40-45 yrs.	4	5
45-50 yrs.	5	9
50-55 yrs.	1	3
55-60 yrs.	1	3
60-65 yrs.	1	3
65-70 yrs.	0	2

Table 3: Age and the Progesterone Receptor status

P=0.402.



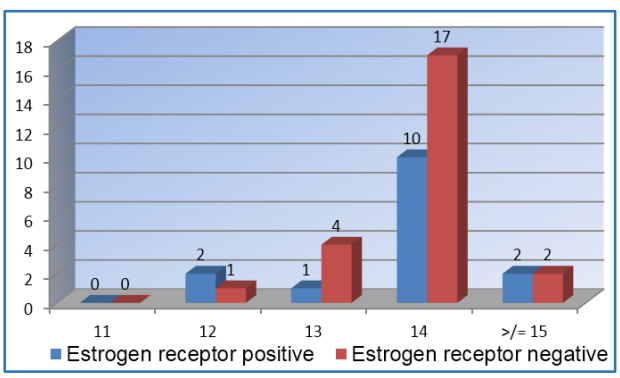
Graph 3: Age and Progesterone Receptor

In case of the progesterone receptor the negativity is seen maximum seen in 45-50 yrs, the study is done using the Fischer exact test and the p value is 0.402 which makes the analysis insignificant.

Age at menarche	Estrogen receptor positive	Estrogen receptor negative
11	0	0
12	2	1
13	1	4
14	10	17
>/=15	2	2

Table 4: Age of Menarche and Estrogen Receptor status

p=0.590.



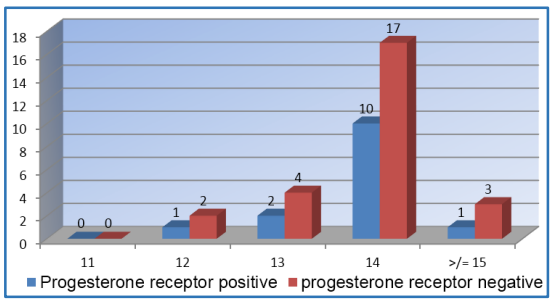
Graph 4: Age of menarche and Estrogen receptor

The study is done using the age at which the women have attained their menarche and their estrogen receptor status to find if there is any variation in the positivity/ negativity of estrogen receptor and age of menarche. The statistical analysis is done with Fischer exact test the p value is 0.590 which makes it insignificant.

Age at menarche	Progesterone receptor positive	Progesterone receptor negative
11	0	0
12	1	2
13	2	4
14	10	17
>/=15	1	3

Table 5: Age of menarche and Progesterone Receptor status

P=0.999.



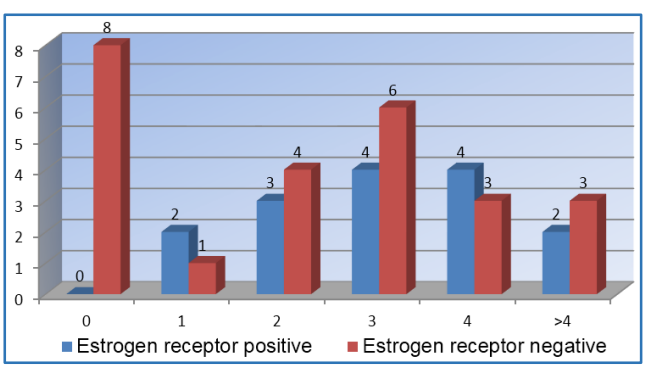
Graph 5: Age of Menarche and Progesterone Receptor

Here the patient's age of menarche is compared with the progesterone receptor status, most of the women attained their menarche at the age of 14, and most of them were progesterone negative they were 17 in number. The statistical analysis was made using Fischer exact test, the p value was found to be 0.999 hence it was insignificant.

Parity	Estrogen receptor positive	Estrogen receptor negative
0	0	8
1	2	1
2	3	4
3	4	6
4	4	3
>4	2	3

Table 6: Parity and Estrogen Receptor status

P=0.191.



Graph 6: Parity of patient and Estrogen Receptor

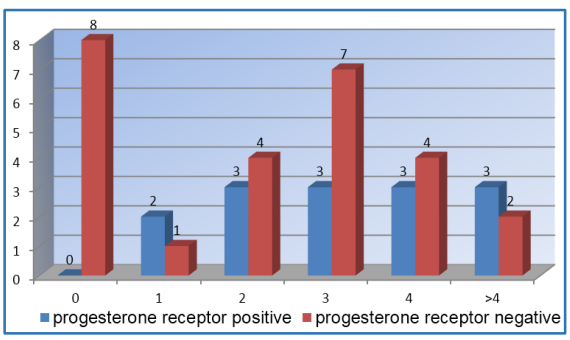
Here the study is done between the parity of the patient and the estrogen receptor, which shows that among 8 nulliparous women in the study they were all estrogen negative, as the parity has increased the estrogen positivity has increased. The study was done using Fischer exact test and the p value 0.191 and it was insignificant.

Parity of patient	Progesterone receptor positive	Progesterone receptor negative
0	0	8
1	2	1
2	3	4
3	3	7

4	3	4
>4	3	2

Table 7: Parity and Progesterone Receptor status

P=0.155.



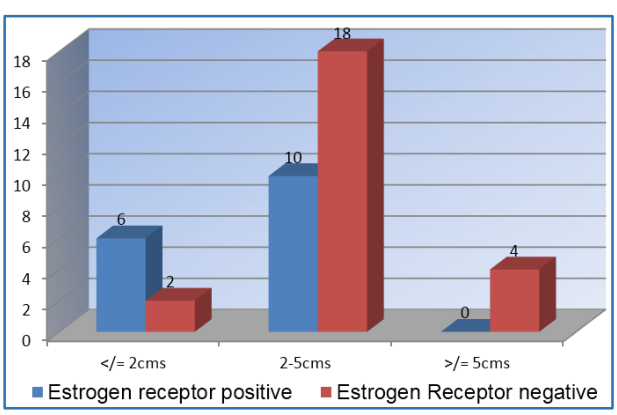
Graph 7: Parity of Patient and Progesterone Receptor

Here the study is done between the parity of the patients and the progesterone receptor, among the 8 nulliparous women they were all progesterone negative. The study is done using Fischer exact test the p value was 0.155 and it was to be insignificant.

Tumour size	Estrogen receptor positive	Estrogen receptor negative
<2 cm	6	2
2-5 cm	10	18
>5 cm	0	4

Table 8: Tumour Size and Estrogen Receptor Status

P=0.044.



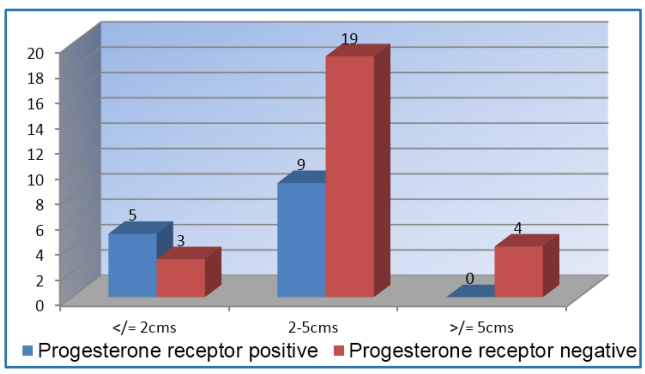
Graph 8: Tumour Size and Estrogen Receptor

Here the study is done between the tumour size and the estrogen receptor status. In this study, most of the women had tumour in the range of 2-5 cm and as the size of the tumour increased the estrogen receptor negativity has increased. The statistics analysis is done using Fischer exact test and the p value was found to be 0.044 hence the study was found to be significant.

Tumour size	Progesterone receptor positive	Progesterone receptor negative
<2 cm	5	3
2-5 cm	9	19
>5 cm	0	4

Table 9: Tumour Size and Progesterone Receptor Status

p=0.044.



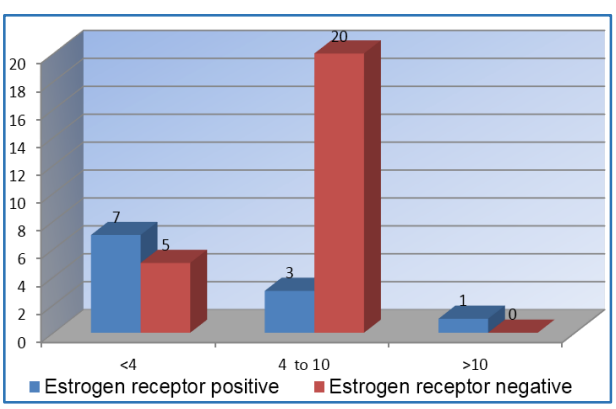
Graph 9: Tumour Size and Progesterone Receptor

Here the tumour size and the progesterone receptor status is compared most of the tumour are in the range of 2-5 cm and they are mostly progesterone negative, and as the size increases the receptors are negative. The study is done using the Fischer exact test and the p value is found to be 0.044 and it is found to be significant.

Lymph node number	Estrogen receptor positive	Estrogen receptor negative
<4	7	5
4-10	3	20
>10	1	0

Table 10: Lymph node number and Estrogen Receptor status

P=0.008.



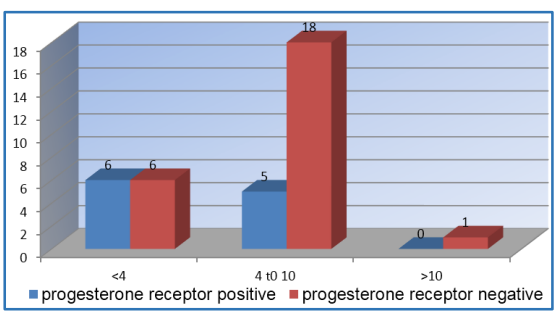
Graph 10: Lymph Node number and Estrogen Receptor

Here the lymph node number and the estrogen receptor status is compared, most of the cases the lymph node numbers were between 4 and 10, and they were mostly estrogen receptor negative. The study was done with Fischer exact test and p value was found to be 0.008 which is highly significant.

Lymph node number	Progesterone receptor positive	Progesterone receptor negative
<4	6	6
4-10	5	18
>10	0	1

Table 11: Lymph Node Number and Progesterone Receptor status

P=0.044.



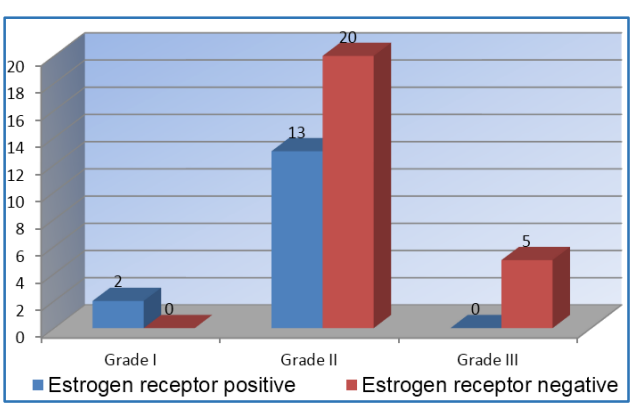
Graph 11: Lymph Node Number and Progesterone Receptor

Here the lymph node number and the progesterone receptor status is compared, most of the women had 4 to 10 lymph nodes and they were mostly progesterone negative. The study was made using Fischer exact test and the p value was found to be 0.044 and is significant.

Tumour grade	Estrogen receptor positive	Estrogen receptor negative
Grade I	2	0
Grade II	13	20
Grade III	0	5

Table 12: Tumour grade and Estrogen Receptor status

p=0.025.



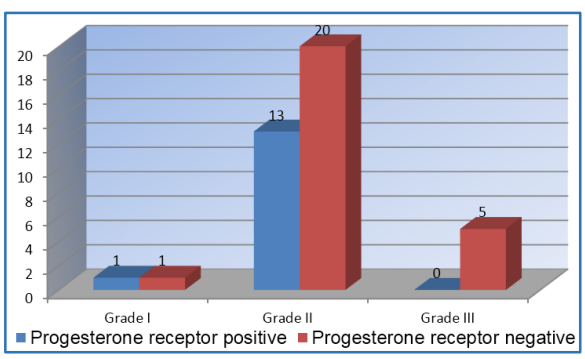
Graph 12: Tumour Grade and Estrogen Receptor

Here the grade of the tumour is compared with the estrogen receptor status, in this study most of the cases were grade 2 and they showed estrogen receptor negative, and the negativity is found to increase with increase in grade of the tumour. The statistical analysis is done using the Fischer exact test which shows p value is 0.025 which makes the association between grade and estrogen receptor significant.

Tumour grade	Progesterone receptor positive	Progesterone receptor negative
Grade I	1	1
Grade II	13	20
Grade III	0	5

Table 13: Tumour Grade and Progesterone Receptor status

P=0.025.



Graph 13: Tumour Grade and Progesterone Receptor

Here the graph compares the grade of the tumour and the progesterone status of the tumours, most of the tumours were grade 2 and most of them were progesterone were negative, as the grade increases the negativity increase. The statistical analysis is done using Fischer exact test and the p value is 0.025 which makes it significant. Menopause is compared with the estrogen and progesterone status of the tumours, but this association was difficult as only 20 of the patients among 40 had attained menopause at the time of diagnosis.

DISCUSSION: Prognostic and predictive factors are universally utilised in the management of breast cancer and can be used to stratify patients into two groups; those who are expected to derive the most benefit from adjuvant systemic therapy and those for whom the risks and costs of adjuvant therapy outweigh the expected benefit. ER/PR status is both prognostic and predictive. Generally, ER and PR positivity is associated with better prognosis and vice versa.

Present study is a prospective observational study carried out on patients admitted in our hospital from October 2013 to September 2015. Around 40 patients were included in present study. The age group under study was from 30-70 yrs. among whom maximum were in the age group of 45-50 yrs., the mean age is 48 years and the standard deviation is ±3.6.

The present study was carried out on 40 patients and correlation of expression of ER, PR with age of patient, age of menarche, parity of patient, menopausal status and some clinical parameters like tumour size, lymph node number and pathological parameters like tumour grade were considered. The results obtained were found to be more or less similar to those reported in the international literature with some exceptions. Many previous studies have shown that menstrual and reproductive factors, including age at menarche, age at first live birth, and parity, are mainly associated with hormone receptor-positive tumours and not with hormone receptor-negative tumours, but present study shows no correlation with the above factors. Some investigators have also reported no significant differences in risk associated with delayed first live birth[12,13] or early menarche[12,13] for ER+/PR+ and ER-/PR- breast cancer. The associations of other reproductive factors did not appear to differ by the ER/PR status of the tumour.

A recent study by Grann and co-workers[14] that also used data collected from the SEER program reported that joint ER/PR status was an independent predictor of outcome in a large cohort of women with breast carcinoma.

In the present study, the statistical analysis was done by using Fischer exact test and found that number of patients with estrogen receptor positive are less than those with estrogen receptor negative and the progesterone receptor negative are more than those with progesterone receptor positive among study population of which majority are in the age group of 45-50 yrs.

In the present study, age of menarche and estrogen receptors or progesterone receptors does not show correlation which is similar to study done by Ping–Ping Bao et al[9] which is a large population based study done on 3,443 cases and 3,474 controls conducted in Shanghai, China. Present study does not show correlation between parity of the patient and estrogen receptor and progesterone which is indifferent to that of study done by Ping-Ping Bao et al[9] which concludes that high parity patients have both estrogen and progesterone receptor positive in postmenopausal women.

In present study, most of the patients have tumour size between 2-5 cm which accounts for 70% of cases of which 25.9% have both ER and PR positive and both ER and PR negative in 55 %, rest of 15% have either ER positive or PR positive. Tumour size </= 2 cm accounts for 20% of cases of which 50% of cases are both ER and PR positive and 12.5% of cases were both ER and PR negative and rest of cases were either ER positive or PR positive. Tumour size >/= 5 cm shows 100% of them are both ER and PR negative. From the above it can be said that as the tumour size increases both ER and PR negativity increases and on comparing with study done by Sofi GN et al[10] results appear to be similar as there was no difference with regard to ER/PR positive or ER/PR negative.

Tumour size and its distribution among patients was depicted in the following table as %.

Tumour size	**>/= 2 cm (No. of patients and %)**	**2-5 cm (No. of patients and %)**	**>/= 5 cm (No. of patients and %)**
Total no. of patients	8(20%)	28(70%)	4(10%)
ER+ve	6(75%)	10(35.7%)	0(0%)
ER–ve	2(25%)	18(64.3%)	4(100%)
PR+ve	5(62.5%)	9(32.1%)	0(0%)
PR–ve	3(37.5%)	19(67.8%)	4(100%)

Table 14

From the above table it is evident that most common size of tumour at presentation is 2-5 cm and as the size of tumour size increases ER and PR positivity decreases and as the size of tumour increases the ER and PR negativity increases which can be seen as appreciated as increase in percentage.

In the present study, majority of patients have lymph node number between 4-10 accounting to 57.5% of total number of patients. In patients with lymph node number <4 which accounts for 30% of total number of cases, which 41% are ER positive and 58.3% are ER negative and PR is in 50% of patients positive and 50% of patients negative. In patients with lymph node number between 4-10 accounting to 57.5 % which accounts to majority of cases of which 13% are ER positive and 86.9% are ER negative and PR is positive in 21% of patients and negative in 78.2% of patients. Patients with no lymph nodes account to 10% of cases of which all cases are ER positive that is 100% of cases and PR is positive in 75% of patients. Patients with lymph node number >10 are only 2.5%, that is only one case presented with lymph nodes greater than 10 which is having ER positive and PR negative, in this case positivity of ER is linked to less tumour size and probably leading to early metastasis involving large number of lymph nodes.

Lymph node involvement in present study is depicted as % in following table.

Lymph nodes involved	**No. lymph nodes No. of cases and %**	**<4 nodes No. of cases and %**	**4-10 nodes No. of cases and %**	**>10 nodes No. of cases and %**
Total no. of patients	4(10%)	12 (30%)	23 (57.5%)	1 (2.5%)
ER+ve	4 (100%)	5 (41.7%)	3 (13.1%)	1 (100%)
ER-ve	0(0%)	7 (58.3%)	20 (86.9%)	0(0%)
PR+ve	3(75%)	6(50%)	5 (21.8%)	0(0%)
PR-ve	1(25%)	6(50%)	18 (78.2%)	1 (100%)

Table 15

From the above table, it is evident that most common number of lymph nodes that are involved at presentation is between 4-10 lymph nodes. As the number of involved lymph nodes increases, the ER positivity and PR positivity decreases; and as the number of lymph nodes increases, ER negativity and PR negativity increases which is seen as increase in percentage.

In the present study, majority of patients are having tumour with Grade II pathologically as the grade of the tumour increases, ER /PR positivity decreases which is evident in below table in terms of percentages; and as the grade of tumour increases, ER/PR negativity increases. As the tumour grade increases, both the progesterone and estrogen receptor negativity increase, by which it can be said that grade of tumour and ER/PR status are dependent on each other and a significant correlation can be achieved.

Grade of tumour	Grade I	Grade II	Grade III
Total no. of patients with each grade and %	2(5%)	33(82.5%)	5(12.5%)
ER+ve	2(100%)	13(39.4%)	0(0%)
ER-ve	0(0%)	20(60.6%)	5(100%)
PR+ve	1(50%)	3(39.4%)	0(0%)
PR-ve	1(50%)	20(60.6%)	5 (100%)

Table 16

In the present study, majority of patients are in the age group of 40-50 years. Estrogen receptor and progesterone receptor either positive or negative does not follow increasing or decreasing trend with respect to all age groups. But on an average in all the age groups, ER negativity and PR negativity is more than ER/ PR positivity, from which any inference can be made out.

Parity	0	1	2	3	4	>4
Total no. of patients and in %	8(20%)	3(7.5%)	7(17.5%)	10(25%)	7(17.5%)	5(12.5%)
ER+ve	0(0%)	2 (67%)	3(43%)	4(40%)	4(57%)	2(40%)
ER–ve	8(100%)	1(33%)	4(57%)	6(60%)	3(43%)	3(60%)
PR+ve	0	2(67%)	3(43%)	3(30%)	3(43%)	3(60%)
PR–ve	8(100%)	1(33%)	4(57%)	7(70%)	4(57%)	2(40%)

Table 17: Age and ER/PR status

Age	30-35 yrs	35-40	40-45	45-50	50-55	55-60	60-65	65-70
Total no. of patients	0(0%)	3(7.5%)	9(22.5%)	14(35%)	4(10%)	4(10%)	4(10%)	2(5%)
ER+ve	0(0%)	1(33%)	4(44%)	6(43.8%)	1(25%)	1(25%)	1(25%)	0(0%)
ER–ve	0(0%)	2(67%)	5(56%)	8(57%)	3(75%)	3(75%)	3(75%)	2(100%
PR+ve	0(0%)	2(67%)	4(44%)	5(36%)	1(25%)	1(25%)	1(25%)	0(0%)
PR–ve	0(0%)	1(33%)	5(56%)	9(64%)	3(75%)	3(75%)	3(75%)	2(100%

Table 18

In present study, majority of patients have attained menarche by age of 14 years, and age of menarche and ER/PR positivity or negativity does not follow any particular trend of increasing or decreasing percentages.

Age of menarche and presence of ER or PR cannot be correlated as the percentages are continuously increasing and decreasing and it can be inferred that they do not follow any particular trend and no significant positive or negative relation can be made out between presence of estrogen receptor or progesterone receptor and age of Menarche.

Age of menarche	11 yrs.	12 yrs.	13 yrs.	14 yrs.	>/=15 yrs.
Total no. of patients and in %	0	3(7.5%)	6(15%)	27(67.5%)	4 (10%)
ER+ve	0	2(67%)	1(17%)	10(37%)	2(50%)
ER–ve	0	1(33%)	5(83%)	17(63%)	2(50%)
PR+ve	0	1(33%)	2(33%)	10(37%)	1(25%)
PR–ve	0	2(67%)	4(67%)	17(63%)	3(75%)

Table 19

In the present study majority of patients are having 2 or 3 or 4 children, and even here ER and PR cannot be correlated as they do not follow particular trend of either increasing or decreasing percentages which shows no significance. But the thing that is obvious is those who have nulliparous are 100% estrogen receptor and progesterone receptor negative.

- Comparing age and estrogen receptor status using the Fischer exact test the p value 0.402 no significant inference could be made.
- Comparing age and progesterone receptor status using Fischer exact test with p value 0.402 no significant inference could be made.
- Menarche and estrogen receptor status were studied in 40 women and it was analysed using Fischer exact test p value was 0.590 due to no significant inference could be made.
- Menarche and progesterone receptor status studied in 40 women showed most of them attained their menarche at the age of 14 as the age increased there has been increase in progesterone negativity, Fischer exact test 0.999 gives no significance.

- Parity and estrogen receptor done in 40 women showed 8 of the nulliparous women were estrogen negative, but the Fischer exact test done on the women showed p value 0.191 which doesn't give the study any significance.
- Parity and progesterone receptors studied among 40 women showed that nulliparous women were progesterone negative, using the Fischer exact test p value was 0.155 which made the comparison insignificant.
- Tumour size when compared with estrogen receptor status in 40 women, most of them in the study had tumour size between 2 and 5 cm most of them were estrogen receptor negative and as the size increased the negativity has increased. The Fischer exact study showed p value of 0.044 making the comparison significant.
- Tumour size and progesterone receptor status is compared and an increase in negativity is seen as the size of the tumour increases, the Fischer exact test gives a p value of 0.044 making the comparison significant.
- Lymph node size and estrogen receptors is compared and an increase in lymph node number showed increase in negativity of estrogen receptors, the statistical analysis was done using Fischer exact test and the p value is 0.008 and the comparison is significant.
- Lymph node number and progesterone receptor status shows that as the lymph node number increases the progesterone receptor becomes negative, and the analysis is done using Fischer exact test, the p value is 0.044 which makes this comparison significant.
- Tumour grading and estrogen receptor status, among the 40 women most of the cases were grade 2 and they were mostly estrogen negative, the analysis was done with Fischer exact test with p value 0.025, it shows the comparison is significant.
- Tumour grading and progesterone status showed that as the grade increased, the negativity of the progesterone receptor increased, the Fischer exact test had p value of 0.025 which made it significant.
- The menopause age could not be considered as among the 40 women taken less than 20 only attained menopause and it didn't show any relation to estrogen or progesterone receptor status.

From the above discussion, it can be said that ER and PR are more correlated with tumour size, lymph node number and grade of the tumour that is chance of ER and PR becoming positive is more in case of small size tumours, in cases where less number of lymph nodes are involved and in those with tumours of low grade. On comparing the present study with similar studies which uses similar variables, some variables show correlation in some studies, some of the variables are not considered and some of variables showing differences between studies. Here, different studies are compared with present study in chronological order from older ones to the most recent studies.

Association of Hormone-Related Characteristics and Breast Cancer Risk by Estrogen Receptor/Progesterone Receptor Status in the Shanghai Breast Cancer Study.[9]

A study done by Ping-Ping Bao et al in Vanderbilt University Medical Center in 2011. It is a large, population based case-control study of 3,443 cases and 3,474 controls being conducted in Shanghai, China, breast cancer risks associated with age at menarche, age at menopause, breastfeeding, age at first live birth, waist-to-hip ratio, and oral contraceptive use did not differ by hormone receptor status. Among postmenopausal women, higher parity was associated with reduced risk and higher body mass index with increased risk. These findings indicate that BMI, parity, hormone replacement therapy, and alcohol consumption may play different roles in subtypes of breast cancer.[9]

Age, age of menarche, parity, in correlation with estrogen receptors and progesterone receptors was done in few studies. In present study, there is no correlation as no significant P values could be obtained by correlating with estrogen receptors and progesterone receptors and above factors where as a study done by Ping–ping Bao et al[9] which is a large population based case control study shows higher parity was associated with reduced risk and higher body mass index with increased risk in postmenopausal women.

Study	**Ping-Ping Bao et al[9]**	**Present study**
Type of study	Population based case control study	Prospective observational study
Age of menarche, age of menopause	No correlation with ER and PR	No correlation with ER and PR
Breast feeding	Considered and shows no correlation	Not considered
BMI	Considered and shows increased risk in postmenopausal women	Not considered
Parity	Shows high parity reduced risk	Considered but shows no correlation
Tumour size	Not considered	Considered and shows significant correlation
Tumour grade	Not considered	Considered and shows majority are grade II and shows significant P values with ER not with PR
Lymph node number	Not considered	Considered

Table 20

Estrogen receptor and progesterone receptor status in breast cancer in relation to age, histological grade, size of lesion and lymph node involvement.[10]

A study done by Sofi GN et al in 2012 in Srinagar is a prospective observational study done on 132 post surgery mastectomy specimens compared ER and PR with age, histological grade, size of lesion and lymph node involvement concluded that ER and PR expression in breast cancers in the current study was found to be higher than studies done in India/Asia but lower than studies conducted in the West, even on Indian/Asian immigrants. Markedly lower receptor expression in Indian/Asian studies is likely due to preanalytic variables, thresholds for positivity, and interpretation criteria.[10]

	Sofi GN et al[10]	**Present study**
Mean age	48.2 yrs.	48 yrs.
Mean duration of symptoms	Considered 6.32 months	Not considered
Age of menarche, parity and age of menopause	Not considered	considered
Tumour size	Most lesions between 2-5 cm (65.1%)	Most lesions between 2-5 cm (70)%
Most common tumour grade	Grade II	Grade II
Lymph node involvement	Seen in 65.2% of cases	Seen in 90% of cases

Table 21

Correlation of Hormone Receptor Expression with Histologic Parameters in Benign and Malignant Breast Tumours.[11]

A study done by Deepthi Gupta et al in Dept. of Pathology, University of Health Sciences, Rohtak, Haryana, 2015 is a study conducted in 75 patients showed the results that scoring of steroid receptors paralleled intensity of hyperplasia in benign breast diseases but in breast carcinoma, it was inversely correlated with grade of tumour, NPI, HER-2/neu status, tumour necrosis, lymphomononuclear infiltrate and elastosis. We found no relationship with tumour size, lymph node status or age.

Study	**Deepthi Gupta et al**[14]	**Present study**
Patient age	Majority are >40. No relationship is found	Most common in 40-50 years of age. No relationship is found
Age of menarche and Parity	Not considered	Considered. No correlation can be made
Menopause	ER/PR–ve in postmenopausal women	Could arrive at any conclusion as more 50% attained menopause
Tumour Size	No relationship	Significant relationship. Small size tumours are more ER/PR positive
Most common grade of tumour	Grade I	Grade II
Pathological parameters considered	Tumour necrosis, lymphatic vessel invasion, tumour grade, lymphomononuclear infiltrate, elastosis	Tumour grade
HER-2/neu	considered	Not considered

Table 22

SUMMARY: This is a prospective study in which 40 women with breast carcinoma were taken and their age, age of menarche, menopause, parity, tumour size, lymph node number and tumour histological grade is compared with the estrogen and progesterone status, this was done over a time period of October 2013 to September 2015. The statistical analysis was done using Fischer exact test.

Among 40 women, maximum patients were in the age group of 45 to 50 yrs. The Fischer exact test showed significance of 0.044 in case of tumour size and the estrogen receptor status. As the size increases, the estrogen receptor status was negative. The progesterone receptor status also showed that as the tumour size increased, the negativity increased and the p value was 0.044 which makes it significant.

The lymph node number was compared with the estrogen receptor status, it was found that as the number of lymph nodes increased, the estrogen receptors were negative and the Fischer exact test showed p value of 0.008 which makes it significant. The lymph node number is compared with the progesterone receptor status which becomes negative as the number of lymph nodes increases the p value is 0.044 which makes it significant.

The histological grade of the tumours were compared with the estrogen status it showed that the well differentiated grade 1 were more estrogen positive; and as it became moderately, poorly differentiated, the estrogen receptors became negative, the p value was 0.025 which made this result significant .The histological grading of the tumour was compared with the progesterone receptor and was found to be negative as the tumour becomes less differentiated and but the p value is 0.250, hence the study's significance cannot be told about. The other factors like age, menarche and menopause show no significant relationship in this study.

CONCLUSION: This was a prospective observational study and based on the study, the following conclusion can be arrived at,

The estrogen and progesterone receptor positive cases:

- Well differentiated.
- Less aggressive.
- Low lymph node metastasis.

The estrogen and progesterone both negative or one of them negative:

- Moderately to poorly differentiated.
- More chances of lymph node metastasis.
- More aggressive.

The presence or the absence of these estrogen or progesterone receptors will help people with breast cancer to decide on the type of treatment to be undertaken.

The women with estrogen and progesterone receptor positive status can opt for hormonal therapy which will be beneficial for them. In the women with estrogen and progesterone receptor negative status, hormonal therapy will be ineffective.

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