

**A COMPARATIVE STUDY OF HORMONE RECEPTOR EXPRESSION IN BREAST  
CARCINOMA PATIENTS****Dr. Supriya<sup>1</sup> and Dr. Vijay Verma<sup>2\*</sup>**<sup>1</sup>Department of General Surgery, Dr. RPGMC Tanda, Kangra, H.P, India.<sup>2</sup>Department of General Surgery, IGM, Shimla, H.P, India.**\*Corresponding Author: Dr. Vijay Verma**

Department of General Surgery, IGM, Shimla, H.P, India.

Article Received on 13/02/2021

Article Revised on 05/03/2021

Article Accepted on 25/03/2021

**ABSTRACT**

**Background:** Cancer of breast is the most common cancer affecting women worldwide, and is the second most common cause of cancer death next to lung cancer. Breast cancer is the most common malignancy in women and is the leading cause of cancer mortality worldwide. It is responsible for more than 500,000 deaths annually. In urban Indian population breast carcinoma is the most common cancer among women. The incidence of carcinoma breast patients has increased over a period of few years, reason being either increased awareness or early diagnosis. Hormone receptor status of a given breast cancer (ER, PR) provides information about the particular genetic type of cells which have become malignant and an indication of how the breast carcinoma will likely respond to chemotherapy and endocrine therapy (hormone related therapy) if required. Her2neu is a tumour biomarker associated with disease progression and metastatic potential. Ki67 is a proliferation marker which shows how fast the tumour is growing, whether or not there is evidence of cell damage and death. The tumors that are estrogen receptor (ER) positive and/or progesterone receptor (PR) positive have lower risks of mortality after their diagnosis compared to women with ER and/or PR-negative disease. **Material and methods:** Hormone receptor expression (ER, PR, HER2NEU and KI67) was studied in fifty patients of carcinoma breast, and also compared with similar studies in various parts of the world. **Results:** The result of our study reveals that the carcinoma breast patients of this region have more ER, PR and HER2NEU negativity which is different from that of other parts of the world. Also, KI positivity below 10% is predominant in our study which correlates with the worse prognosis of this disease. **Conclusion:** Carcinoma breast patients of this part of the subhimalayan region vary in hormone receptor expression, tumour subtype and age of diagnosis from that of other parts of the world.

**KEYWORDS-** triple negative breast cancer, estrogen receptor, progesterone receptor, HER2NEU receptor.**INTRODUCTION**

Cancer of breast is the most common cancer affecting women worldwide, and is the second most common cause of cancer death next to lung cancer.<sup>[1]</sup> Breast cancer is the most common malignancy in women and is the leading cause of cancer mortality worldwide. It is responsible for more than 500,000 deaths annually.<sup>[2]</sup> In urban Indian population breast carcinoma is the most common cancer among women. It is second to cancer of cervix in the rural population, based on national cancer registry data (2006).<sup>[3]</sup> The incidence of breast cancer is steadily rising in India. As per the ICMR-PBCR data, breast cancer is the commonest cancer among women in urban registries of Delhi, Mumbai, Ahmedabad, Calcutta, and Trivandrum constituting more than 30 percent of all cancers in females.<sup>[3]</sup>

Over 100,000 new breast cancer patients are diagnosed annually in India. The incidence is higher in urban areas being 1 in 22 in a lifetime compared to rural areas, where this risk is relatively lower being 1 in 60.<sup>[4]</sup> In India, 50-

70% of breast cancer patients present at an advanced stage.<sup>[5]</sup> Breast carcinoma is a disease of diversity and it can be categorized into subtypes with distinct biological features. The main motive behind the evaluation of such a newly detected palpable lump is basically to rule out malignancy. Evaluation of a breast lump involves the rational use of a detailed history, clinical breast examination, imaging modalities and tissue diagnosis.<sup>[6]</sup> It is sometimes difficult to determine whether a suspicious lump is benign or malignant simply from clinical assessment. A confident diagnosis can be made in 95% of cases through a combination of clinical examination, imaging and fine needle aspiration cytology (FNAC).<sup>[7]</sup>

Hormone receptor status of a given breast cancer (ER, PR) provides information about the particular genetic type of cells which have become malignant and an indication of how the breast carcinoma will likely respond to chemotherapy and endocrine therapy (hormone related therapy), if required. Her2neu is a

tumour biomarker associated with disease progression and metastatic potential. Ki67 is a proliferation marker which shows how fast the tumour is growing, whether or not there is evidence of cell damage and death. The determination of estrogen receptor (ER) and progesterone receptor (PR) activity in breast cancer is a standard medical practice nowadays. It is an important predictor of response to hormonal therapy and overall prognosis of the patient. The tumours that are estrogen receptor (ER) positive and/or progesterone receptor (PR) positive have lower risks of mortality after their diagnosis compared to women with ER and/or PR-negative disease. Clinical trials have also shown that the survival advantage for women with hormone receptor-positive tumours is enhanced by treatment with adjuvant hormonal and/or chemotherapeutic regimens.<sup>[5]</sup>

In breast cancer the average incidence of estrogen receptor and progesterone receptor positivity is 77% and 55% respectively as shown in the studies. However, lower rates of positive estrogen and progesterone receptor breast cancers are found in Indian population from the western literature. The frequency of negative estrogen receptor and progesterone receptor is much more common in India (46.5%) than in the West (10%). Breast cancer patients of Indian origin tend to be younger, tumours are often large when first diagnosed, and of a high grade as compared to western series.<sup>[8]</sup>

Estrogen and progesterone have an important role in the promotion and progression of hormone receptor-positive breast cancer so endocrine therapy is the primary component in the treatment of hormone-sensitive breast cancer in the adjuvant and metastatic settings. Exposure to estrogen for prolonged period is an important risk factor for breast cancer. Progesterone receptor (PR) expression in normal breast epithelium is regulated by ER. Hormone receptor status is considered to be important prognostic factors.<sup>[9]</sup> ER and PR status is routinely done nowadays to determine the need of hormonal therapy. There is evidence to suggest that hormonal factors may be associated with a stronger increased risk for ER+ PR+ than for ER- PR- breast cancer risk. Thus, associations reported in the many studies that treated breast cancer as a single entity may be modest, inconsistent, and attenuated because of the varying underlying ERPR distributions.<sup>[10]</sup>

The human epidermal receptor protein-2 (Her2neu) oncogene is a trans-membrane glycoprotein belonging to epidermal growth factor receptor family. It is expressed at low levels in a variety of normal epithelia, including breast duct epithelium. Amplification of the Her2neu gene and concomitant protein over expression is present in 10–20% of primary breast cancers.<sup>[11]</sup> The association between Her2neu gene (C-erbB2) amplification and poor prognosis was first determined in 1987 by Slamon et al, who showed that amplification of the Her2neu gene was strongly correlated with relapse and overall survival.<sup>[12]</sup>

Her2neu is an independent prognostic marker of clinical outcome in node positive patients. It is a marker of aggressive disease with propensity for recurrence and a target for treatment using humanized monoclonal anti Her2neu antibody trastuzumab (Herceptin). It gives substantial clinical benefit in patients with metastatic breast cancer so the determination of Her2neu status in breast cancer is of great interest<sup>[13]</sup>. Herceptin treatment has shown marked improvement in the patient's outcome.

Better understanding of molecular basis is required for effective development of treatment. The receptor status also varies with the histological type of breast carcinoma. 50-60% of IDC are ER/PR positive and 20-30% Her2neu positive.<sup>[14]</sup>

Gene expression profiling has identified five subtypes of breast cancer (luminal A, luminal B, normal breast-like, Her2neu over expression, and basal-like), each having different prognosis. Normal breast like subtype is said to be an artefact rather than a genuine type of breast cancer, resulting from lack or paucity of tumour in the tissue sample used for the microarray analysis. The basal-like and Her2neu positive subtypes have shorter relapse-free and overall survival than the luminal tumors.<sup>[13]</sup>

Immunohistochemical demonstration of hormone receptors in breast cancer is cost effective, can be done on paraffin processed tissue and the receptors are assessed within the actual tumour.

#### CLASSIFICATION OF BREAST CANCER ACCORDING TO MOLECULAR MARKERS

Based on ER, PR and Her2neu status, breast cancers can be divided into 4 major categories.

1. **Luminal A** – This includes cases with ER+ve/PR+ve, ER+ve/PR-ve, ER-ve/PR+ve and Her2neu –ve status.
2. **Luminal B** – This includes cases with ER+ve/PR+ve, ER+ve/PR-ve, ER-ve/PR+ve and Her2neu +ve.
3. **Her2neu positive** – This includes the cases which were ER-ve/PR-ve and Her2neu is +ve.
4. **Triple negative** – This includes cases which are negative for all the receptors, ER-ve, PR-ve and Her2neu -ve.

Breast cancer is a disease of old age with peak incidence in the fifth and sixth decades in the western countries, but in India the disease is seen a decade earlier, probably because of shorter life expectancy in Indian women (about 65.3 years as per Indian data in 2005).<sup>[7]</sup> The risk factors for breast cancer in western population include late age of childbirth, nulliparity, smaller duration of breast feeding, smoking etc. while in India early menarche and late menopause are the risk factors and longer duration of breastfeeding, early childbirth and multiparity are protective factors.<sup>[7]</sup>

### Aims and objectives

The purpose of this study is to assess the profile of carcinoma breast patients based on their hormone receptor status comparing it with that of patients from other parts of the world.

### MATERIAL AND METHODS

This was a hospital based study which was conducted over fifty patients of carcinoma breast over a period of one year after taking their informed consent. Patients who had already undergone surgery for breast carcinoma outside this hospital or who were admitted only for radio or chemotherapy were not included in this study.

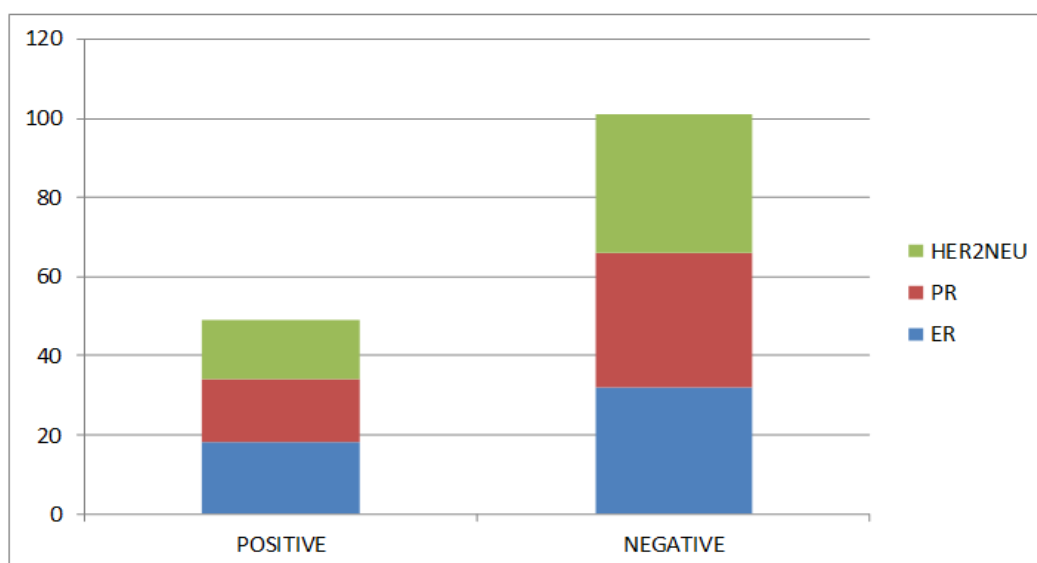
Detailed history of the patients were taken including their age, marital status, occupation and their chief complaints of having either lump or pain whether cyclical or noncyclical or ulcer or any discharge or retraction from nipple. Detailed personal history including menstrual history, parity, age at menarche, age at marriage, age at menopause, age at first child birth, duration of breastfeeding after each child birth, history of oral contraceptives, hormone replacement therapy, smoking and alcohol were taken. A complete medical, surgical as well as family history of the patient was taken. Any history of malignancy in family was enquired about. For biomarker profile patients were subjected to estrogen and progesterone receptor, Her2neu receptor and ki67 marker.

### OBSERVATIONS AND RESULTS

Fifty patients were included in this study. Age of patients ranged From 29-75years. Mean age of presentation was 51.2years.

### HORMONE RECEPTOR STATUS

	ER	PR	HER2NEU
POSITIVE	18	16	15
NEGATIVE	32	34	35
TOTAL	50	50	50



In our study, it was seen that 60% of the patients had lump on the left side and 40% had lump on right side with 62% patients having lump in upper –outer quadrant.

In our study, out of 50 females, 14(28%) patients were found to have early breast carcinoma. Locally advanced carcinoma was found in 36(72%) cases which show that LABC is more common in this region which is different from other parts of the world where early breast cancer is more prevalent.

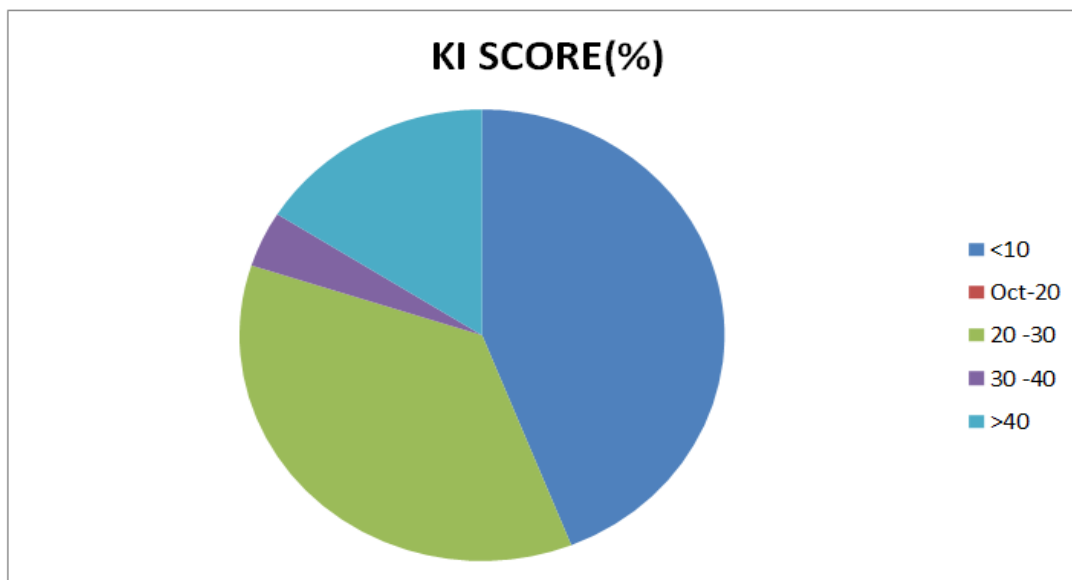
In our study, 50 (100%) patients had invasive ductal carcinoma not otherwise specified either on FNAC or core needle biopsy.

In our study, 36% patients were ER positive and 64% patients were ER negative. 32% of the total patients were PR positive and 68% patients were PR negative. HER2 positive patients were 30%. HER2 negative patients were 70%. 44% patients had less than 10% KI positivity whereas 36% patients had KI positivity between 20-30%. More than 40% KI positivity was found in 16% patients.

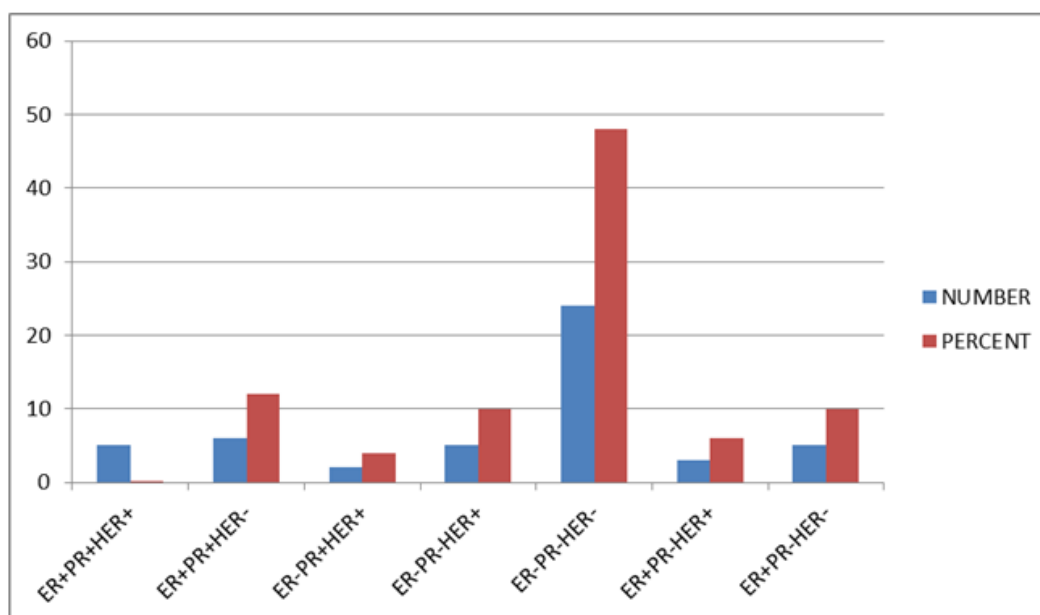
In our study, 48% patients were triple negative which was the most common molecular type of carcinoma breast. 11 out of 50 (22%) patients were in LUMINAL A group followed by LUMINAL B group, 10 out of 50(20%).

**KI 67 STATUS**

KI SCORE IN %	NO. OF PATIENTS	PERCENTAGE
<10	22	44
10-20	0	0
20-30	18	36
30-40	2	4
>40	8	16

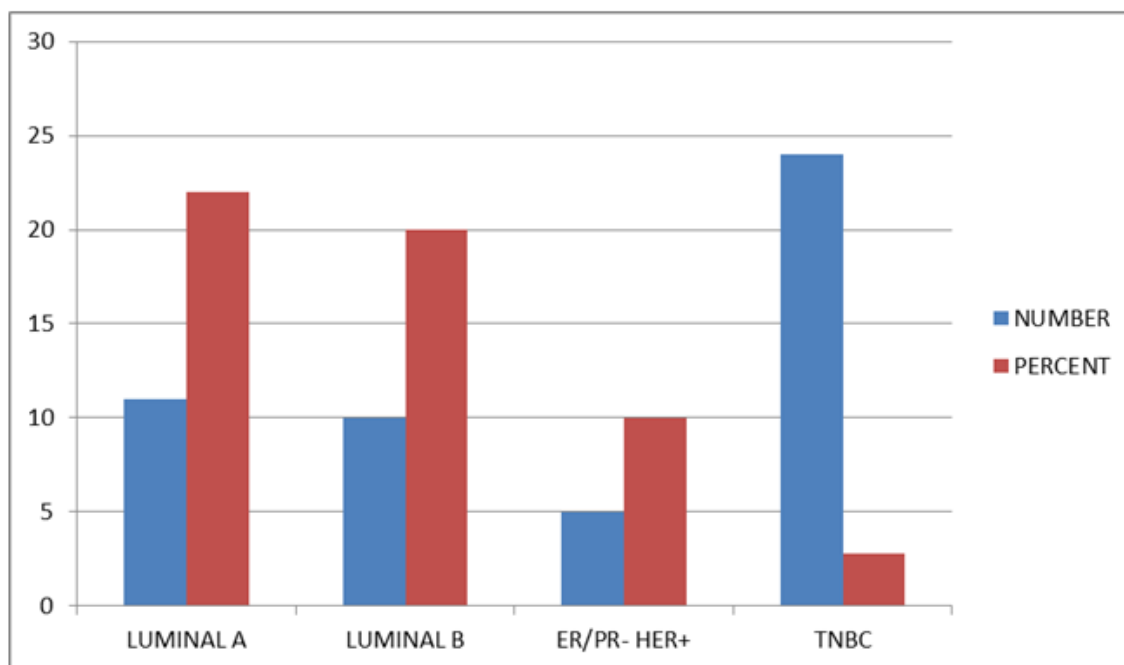
**IMMUNOHISTOCHEMICAL SUBTYPES**

IMMUNOHISTOCHEMICAL SUBTYPE	NO. OF PATIENTS	PERCENTAGE
ER+PR+HER+	5	10
ER+PR+HER-	6	12
ER-PR+HER+	2	4
ER-PR-HER+	5	10
ER-PR-HER-	24	48
ER+PR-HER+	3	6
ER+PR-HER-	5	10



**LUMINAL CLASSIFICATION**

LUMINAL TYPE	NO. OF CASES	PERCENTAGE
LUMINAL A	11	22
LUMINAL B	10	20
ER/PR-HER+	5	10
TRIPLE NEGATIVE	24	48
TOTAL	50	100

**DISCUSSION**

The findings of our study was compared with similar studies conducted in various parts of India as well as the world. Regarding ER positivity, Bhagat et al in their study conducted at Surat, Gujarat found out 48.27% of the cases to be positive for estrogen receptor.<sup>[15]</sup> In a study conducted at Jaipur by Jain et al on 203 patients, they found out 37.4% of the cases to be ER positive.<sup>[16]</sup> Nikhra et al, in their study done at Vadodara, Gujarat reported ER positivity in 39.5% of the cases.<sup>[17]</sup> The above three studies showed results of ER positivity which were comparable with our present study. Regarding PR positivity, Pathak et al found out PR positivity in 19% of the cases. This study was done in Nepal and the results were slightly lower than our present study.<sup>[18]</sup>

Ahmed et al found PR positivity in 27% of the cases.<sup>[19]</sup> Bhagat et al reported PR positivity in 37.93% cases.<sup>[15]</sup> Nikhra et al in their study found out 41.8% cases to be PR positivity<sup>17</sup>. These studies conducted in India showed results comparable to our present study.

Regarding HER positivity, In the studies conducted by Rajesh NG and Ambroise et al, HER-2/neu positivity was seen in 27.9% and 27.1 0% cases respectively.<sup>[9,10]</sup> These results were lower than the present study, this could be due to the larger study population in the two

studies. Jain et al reported HER-2/neu positivity in 35% cases.<sup>[16]</sup>

Nikhra et al observed HER-2/neu positivity in 32.5% of the cases.<sup>[17]</sup> The results of both the studies were comparable with the present study. Sharma et al observed HER-2/neu positivity in 32.5% of the cases.<sup>[22]</sup> This result was comparable with the present study.

A significant number of cases in the present study comprised of TNBC cases. 48% cases belonged to this category. This observation was comparable to other studies conducted in India by Ghosh,<sup>[23]</sup> et al, Sharma et al, Nikhra et al where the incidence of TNBC was 29.8%, 31 .9% and 31 .7% respectively. Therefore, it may be inferred that TNBCs are the most common molecular group of breast cancer prevailing in India.

This KI67 interpretation of our study is comparable with the result of Inwald et al whose retrospective study also showed that 57% of the patients with KI67 positivity below 15% had better prognoses.<sup>[24]</sup>

**COMPARISON OF ER POSITIVITY.**

Serial no.	Author	Total no. of cases	No. of ER positive cases	Percentage(%)
1	Bhagat et al	58	28	48.27
2	Pathak et al	136	38	28
3	Ghosh et al	2001	1025	51.2
4	Jain et al	203	76	37.4
5	Nikhra et al	43	17	39.5
6	Park E H et al	9881	7326	74.1
7	Ahmed et al	137	60	43.8
8	Present study	50	18	36

**COMPARISON OF PR POSITIVITY.**

Serial no.	Author	Total no. of cases(n)	No. of PR positive cases	Percentage(%)
1	Bhagat et al	58	22	37.9
2	Pathak et al	136	26	19
3	Nikhra et al	42	18	41.8
4	Park E H et al	8669	5407	62.4
5	Ahmed et al	137	37	27
6	Present study	50	16	32

**COMPARISON OF HER2NEU POSITIVITY.**

Serial no.	Author	Total no. of cases(n)	No. of Her2neu positive cases	Percentage(%)
1	Ambroise et al	321	87	27
2	Jain et al	203	71	35
3	Sharma et al	662	215	32.5
4	Nikhra et al	43	14	32.5
5	Rajesh NG	704	194	27.9
6	Present study	50	15	30

**COMPARISON OF TNBC.**

Serial no.	Author	Total no. of cases (n)	Percentage of TNBC(%)
1	Ghosh et al	2001	29.8
2	Sharma et al	972	31.9
3	Nikhra et al	43	31.7
4	Present study	24	48

**KI SCORE INDEX COMPARISON.**

KI SCORE ( %)	NO. OF PATIENTS(n)	PERCENTAGE(%)
<10	22	44
10-20	0	0
20-30	18	36
30-40	2	4
>40	8	16

**CONCLUSION**

To conclude, this study shows that carcinoma breast is a disease with a gender bias, more commonly affecting females. This study shows that this part of subhimalayan region have their patients in their thirties or forties which is comparatively earlier in comparison to their western counterparts. Patients usually present as locally advanced type which is also different from western world. Triple negative breast cancers are more common in this region while in other parts of the world, Luminal A is the commoner subtype. Thus, the present study concludes that the carcinoma breast in this part of India has

different clinical and molecular presentation from that of other parts of the world.

**Conflicts of Interest**

None

**Source of funding**

None

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