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Original Research Article

# Expression of Braca1 and its Association with ER, PR and Her2 Neu in Breast Carcinoma

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**Abstract:**

**Background and Objectives:** Breast cancer is the most commonly diagnosed cancer with an estimated 2.3 million new cases and the leading cause of cancer death in females worldwide. Study of Breast Carcinoma 1(BRCA1) protein expression and its correlation with Estrogen receptor(ER), Progesterone receptor(PR), Human epidermal growth factor receptor2 (HER2 neu) may play a crucial role in predicting the prevalence of hereditary associated breast carcinoma to predict prognosis and as a predictive marker of response to different types of chemotherapeutic agents.

**Material and Methods:** In the present study, breast cancer tissues from a total of 70 breast carcinoma patients were subjected for histopathological examination, BRCA1, ER, PR, HER2neuimmunohistochemical (IHC) staining and the findings were evaluated. Data entry and analysis was done using SPSS Version 21.0 (IBM. Inc. Armonk. NY, USA)

**Results:** Out of 70 breast carcinoma cases, 60 cases were of Invasive Ductal Carcinoma, No Special type (NST) constituting 85.7%, forming the majority of the cases, followed by 4 cases of Invasive ductal carcinoma with medullary features (5.7%), 3 cases of Invasive Lobular Carcinoma (4.3%), 2 cases were Mixed Invasive Carcinoma (2.9%) and 1 case of Mucinous Carcinoma pure type (1.4%). Most of the tumors (35 cases) were of histological Grade II comprising of 50% followed by grade III (23 cases) constituting 32.9%. Equal percentage i.e. 50% (35 cases) each of the breast carcinoma cases were ER positive and ER negative. 25.70% (18 cases) of the breast carcinoma were PR positive and 74.3% (52 cases) were PR negative. 41.4% (29 cases) of the breast carcinoma are HER2 neu positive and 58.6% (41 cases) are HER2neu negative. Of the total 70 breast carcinoma cases, positive BRCA1 expression was found in 40% (28 cases) while negative BRCA1 expression was found in 60% (42 cases). Negative BRAC1 expression is seen in 85.7% of the total ER positive and 34.3% of the total ER negative cases and found to be statistically significant with p-value of 0.00. Negative BRCA1 expression is seen in 88.9% of the total PR positive cases and 50% of the total PR negative cases which was statistically significant (p-value= 0.004). While BRCA1 negativity was seen in 69% of the total HER2 positive cases and 53.7% of the total HER2 negative cases which was found to be statistically insignificant with p-value of 0.198. Of the 22 Triple negative breast carcinoma cases 18 cases showed BRCA1 positivity (18/22) constituting of 81.81% while 4 cases showed BRCA1 negativity comprising of 18.18% which was statistically significant with p-value of 0.00.

**Conclusion:** BRCA1 expression is significantly associated with estrogen receptor (ER) and progesterone receptor (PR) in breast carcinoma. No statistically significant association was found between BRCA1 expression and human epidermal growth factor receptor2 (HER2) in breast carcinoma. A higher number of cases with negative BRCA1 expression showed positive ER, positive PR and positive HER2 expression. BRCA1 positivity is high among triple negative breast carcinoma which signify a worst prognosis.

**Keywords:** BRCA1, ER, PR, HER2, immunochemistry, breast carcinoma.

## Introduction

Breast cancer is the most commonly diagnosed cancer (11.7% of the total cases), with an estimated 2.3 million new cases and the leading cause of cancer death in females worldwide.[1]According to GLOBOCAN 2020,females breast cancer in India accounts for 13.5% of all cancer cases and 10.6% of all deaths.[2]In Manipur, breast cancer comprises 15.4% of cancer in females, with age adjusted rate (AAR) as high as 10.0 per 100,000 woman.[3]

The breast cancer development is associated with several genetic and non-genetic factors.[4] The non-genetic factors include prolonged exposure to estrogen due to early age of menarche, late menopause, use of oral contraceptives, high fat diet, and sedentary lifestyle. BRCA1 gene is strongly implicated in the pathogenesis of breast among many other gene.[4]

BRCA1(Breast cancer susceptibility 1 gene) is a tumour suppressor gene located on chromosome 17q21.[5]The BRCA1 is a multi-functional protein and interacts with different protein in various cellular compartments and play essential roles in diverse cellular pathways such as DNA damage repair, cell-cycle arrest, apoptosis, genetic instability, transcriptional activation, and in tumorigenesis.[6-8] As observed in cancer patients, mutations in BRCA1 frequently occurs in 3 domains- N-terminal RING domain encoded by exons 2-7, coding regions of exons 11-13, and BRCA1 C –terminus encoded by exons 16-24 or BRCT domain.[9] Women with BRCA1/BRCA2 mutation have very high lifetime risk of developing breast and ovarian cancer.[10] The discovery of BRCA1 has enabled in identification of carriers, targeting the reduction of risk of breast cancers in carriers and to develop a new generation of targeted therapies (PARP inhibitors).[11]

The Estrogen Receptor(ER) and Progesterone Receptor(PR) are dimeric, gene-regulatory proteins and are endocrine steroid regulators modulating multiple aspects in the pathology of mammary gland.[12]They act through their nuclear receptors to modulate transcription of target genes.[12-13] ER (Estrogen Receptor) overexpression is a well-established prognostic factor in breast cancer patients.[14] Generally, ER positive breast cancersare associated with slow tumour growth, lower histopathological grade, DNA diploidy and thus a better overall prognosis. [14] An inverse relation exist between HER2 (Human Epidermal Growth Factor Receptor2) and the hormone receptor (ER and PR) expression.[15]

HER2 (Human Epidermal Growth Factor Receptor2) is a proto-oncogene encoding a 185-kDa tyrosine kinase glycoprotein belonging to the EGFR family, involved in signal transduction pathways that regulate cell growth and proliferation.[16] HER2 expression is associated with poor prognosis in breast carcinoma while ER (Estrogen Receptor) and PR (Progesterone Receptor) expression are indicators of response to hormonal therapy and better prognosis.[17]. High grade breast carcinoma is often positive for HER2 and tends to be negative for ER, PR with a high proliferation rate; conversely, low grade breast carcinoma is typically negative for HER2, is positive for ER, PR and has a low proliferation rate.[18]

Triple negative breast cancer (TNBC) lack the expression of ER, PR, and HER2 and accounts for 12-24% of all breast cancers and is also associated with hereditary breast cancers.[19-21] Triple-negative breast cancers are associated with a poorer survival and more aggressive pathology.[22] A number of studies reported triple-negative breast cancer as the predominant subtype among women carrying a deleterious germ-line mutation in BRCA1.[23]

AlteredBRCA1 protein expression is seen in ER, PR and HER2 negative tumours and shows the importance of BRCA1 expression as a screening test in sporadic breast carcinoma.[24]In some studies, Triple negative breast carcinoma are associated with poor prognostic factors and are more likely to be BRCA1 positive and so BRCA1 identification is important in management of patient for risk of contralateral breast cancer and also in blood relative of patients.[25]

Although breast cancer is still the second most common cause of cancer related deaths, breast cancer mortality has been declining because of advances in the use of adjuvant therapies.[26]Study of BRCA1 protein expression and its correlation with ER, PR, HER2 may play a crucial role in predicting the prevalence of hereditary associated breast carcinoma, to predict prognosis, and as a predictive marker of response to different types of chemotherapeutic agents.[5]

Since there is limited information available for the expression of BRCA1 and its relation with ER, PR, HER2 status in breast carcinoma in Manipur, this study was done to see the role of BRCA1 expression in carcinoma of breast as well as to verify the possible relationship ER between BRCA1 and, PR, HER2 expression in carcinoma of breast in a tertiary care hospital.

## Objectives

To determine the expression of BRCA1 protein in breast carcinoma.

To assess the association of BRCA1 protein expression with ER, PR, HER2 in breast carcinoma.

## Materials and Methods

### Target

A total of 70 cases of histologically confirmed cases of breast carcinoma were randomly screened to participate in a cross-sectional study conducted in Regional Institute of Medical Sciences (RIMS), a tertiary care hospital in Imphal, Manipur, India from January 2021 to October 2022.Grossing of resected specimen was performed as per the standard protocol.[27]Representative sections was taken from the tumour proper and adjoining areas (non-tumour area). All the tumour margins were examined and all lymph nodes was dissected and examined. The post-operative pathological specimens of all patients were fixed with 10% formalin, blocks were processed through increasing concentration of alcohol, cleared by xylene, embedded in paraffin wax, sections were cut at 3- 4 micron thickness on a rotary microtome and stained with haematoxylin and Eosin (H&E), Immunohistochemical staining for BRACA1, ER, PR and Her2 Neu were performed and scoring performed using specific scoring systems for each marker Data were collected, recorded, analysed using SPSS Version 21.0 (IBM. Inc. Armonk. NY, USA). Descriptive and inferential analysis was carried out in the study. Age in years is expressed as mean +/- standard deviation. Results on categorical data of marital status, parity, menopausal status, tumor size, stage, grade and lymph node invasion was presented in percentage. Chi-square test was used to find the association of BRCA1 expression with ER, PR, HER2 status. Significance was assessed at the level of 5% (p value =/< 0.05 is considered significant) with 95% confidence interval. Ethical approval was obtained from the Research Ethics Board (REB), RIMS, Imphal with Ref. No. A/206/REB-Comm (SP)/RIMS/2015/723//65/2020 dated 8th February 2021. Written informed consent was considered for the study before recruitment.

### Inclusion Criteria:

Histologically confirmed cases of breast carcinoma.

Age > 18 years.

### Exclusion Criteria:

Already treated cases with chemotherapy and or radiotherapy.

Patients receiving neo – adjuvant systemic therapy prior to mastectomy.

Inadequate tissue specimen.

### Immunohistochemistry:

Immunohistochemical staining for BRACA1,ER, PR and Her2Neu were performed using a Mini-kit detection system-HRP based polymer.

Anti ER antibody: Source-Rabbit Monoclonal, (BIOCARE MEDICAL) Clone- SP1.

Anti-PR antibody: Source-Mouse Monoclonal (DAKO), Clone- PgR 636.

Anti HER2 antibody: Source-Rabbit Monoclonal (Thermoscientific), Clone- SP3.

Anti-BRCA1 Antibody: Source-Rabbit Monoclonal (Merck Sigma Aldrich), Clone- MS 110.

Sections of 3-5µm thickness made in Poly-L-Lysine coated glass slides is kept overnight at 30-35 ºC or bake it at 60 ºC for 1 hour. Standard two-step immunohistochemistry was performed (in brief: A. dewaxing using xylene and hydration in decreasing concentration of ethanol. B. Antigen retrieval with phosphate buffer solution (PBS; pH 7.2-7.6) 3 times with 1 minute interval and then cleaning of the slides C. Blocking endogenous peroxidase. D. addition of primary antibody. E. Adding HRP labelled Polymer secondary antibody F. Colour development G. Contrast staining H. Dehydration , transparency and sealing.)

### Operational definition:

The breast tumours is classified according to "WHO Classification of tumours of the breast, 2019".[28] The histological examination was done according to the CAP (College of American Pathologists) Protocol, 2021. [29]

Scarff-Bloom-Richardson system (Nottingham grading system) is used for assessing histologic grade in breast carcinoma.[18]

Immuno-histochemical Evaluation: The cases is interpreted as BRCA1 positive if >20% of the cells show nuclear staining (score 2 and 3).[30] It is also interpreted as ER, PR positive if their total score is 3 or more, HER2 positive if complete circumferential membranous staining in >10%(score 3+).[31]

In the breast, BRCA1 staining is observed as brown nuclear staining with no cytoplasmic or membranous staining. Scoring system given by Yoshikawa et al [32] will be followed for scoring BRCA1 staining.

Allred scoring system is used for evaluation of Estrogen and Progesterone Receptor.[18] It is based on assessment of proportion and intensity of nuclear staining. The scores are summed to give a maximum of 8.

HER2 staining is observed as brown, membranous staining and graded[30].

## Result

A total of 70 breast carcinoma patients were included in the study. The age range was from 29-87 years(Mean 49.90years ±12). Tumor size range from 0.5 cm to 12.0 cm in greatest dimension with mean size of 2±0.637.Tumor with greatest dimension measuring 2-5 cm were found to be maximum in number comprising of 60%, followed by 20% each of tumor size <2 cm and>5 cmas shown in table 1.

**Table 1: Distribution of tumor according to size. (N=70)**

| Tumor size (cm) | Frequency(n) | Percentage (%) |
|---|---|---|
| <2 | 14 | 20 |
| 2-5 | 42 | 60 |
| s>5 | 14 | 20 |
| Total | 70 | 100 |

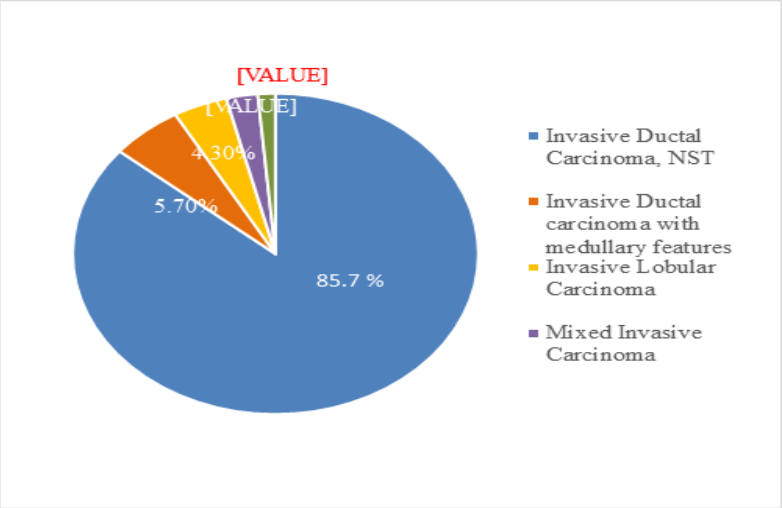


**Figure 1: Distribution of Tumors according to histological types(N=70**

Out of 70 breast carcinoma cases, 60 cases were of Invasive Ductal Carcinoma, NST (Fig 8) constituting 85.7%, forming the majority of the cases, followed by 4 cases of Invasive ductal carcinoma with medullary features (5.7%), 3 cases of Invasive Lobular Carcinoma (4.3%), 2 cases were Mixed Invasive Carcinoma (2.9%) and 1 case of Mucinous Carcinoma pure type (1.4%) as illustrated in Fig 1.

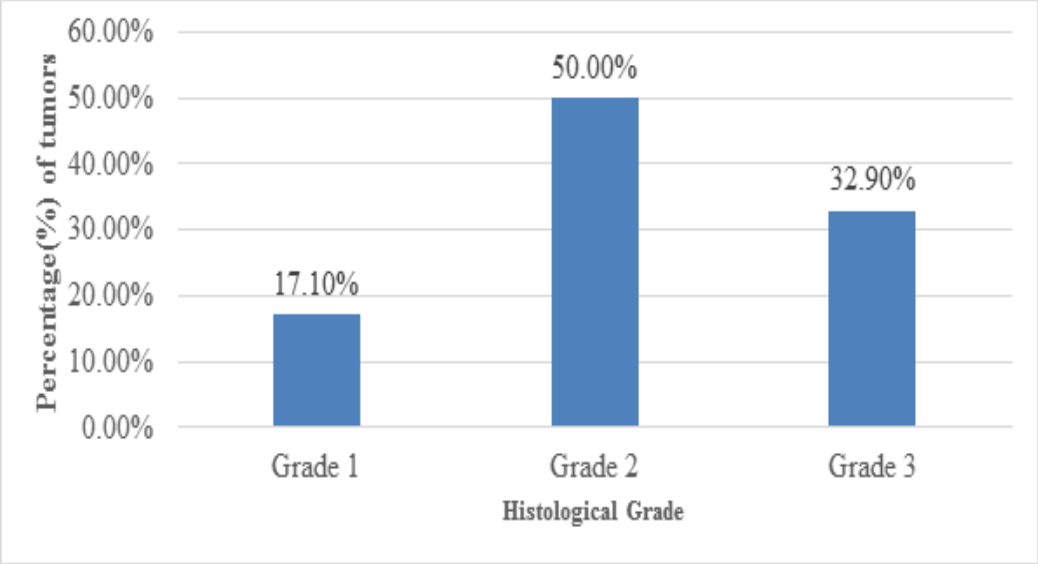


**Figure 2: Distribution of tumors according to Histological grade (N=70)**

Most of the tumors (35 cases) were of histological grade II comprising of 50% followed by grade III (23 cases) constituting 32.9%. Grade I tumors were found to be the least common with 17.1% (12 cases) as observed in Fig 2.

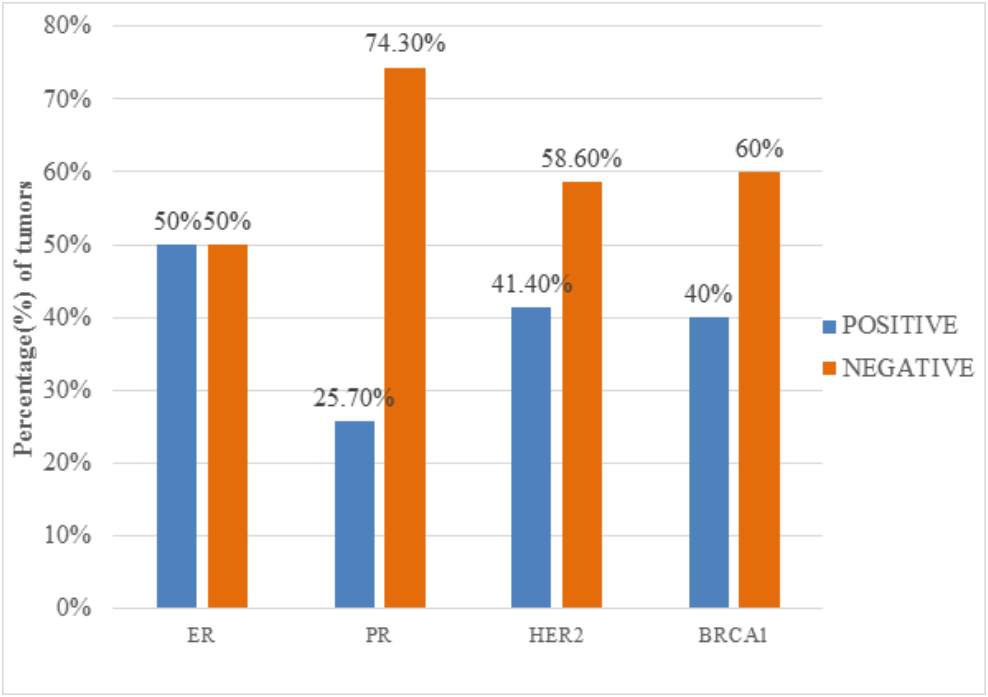


**Figure 3: Distribution of cases according to ER, PR, HER2, BRCA1 expression(N=70)**

Equal percentage i.e. 50% (35 cases) each of the breast carcinoma cases were ER positive and ER negative. 25.70% (18 cases) of the breast carcinoma were PR positive (Fig 10) and 74.3% (52 cases) were PR negative. 41.4% (29 cases) of the breast carcinoma are HER2 positive and 58.6% (41 cases) are HER2 negative. Of the total 70 breast carcinoma cases, positive BRCA1expression was found in 40% (28 cases) while negative BRCA1 expression was found in 60% (42 cases). This percentage of IHC expression is shown in Fig 3.

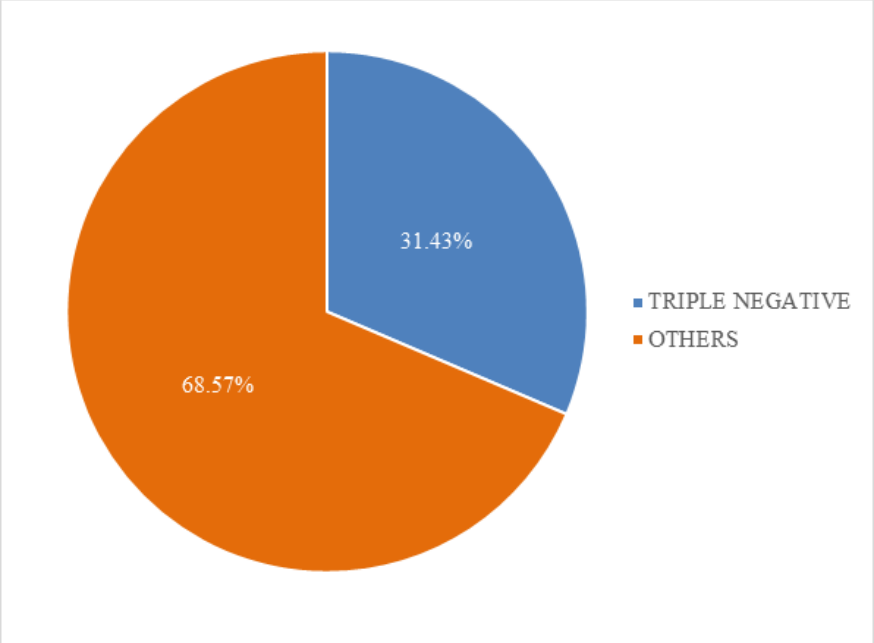


**Figure 4: Distribution of cases showing Triple negativity (N=70)**

Triple negative cases were found in 22 cases of breast carcinomas constituting 31.43% while other non-triple negative consist of the rest 48 cases consisting of 68.57% (Fig 4).

**Table 2: Association of BRCA1 expression with histopathological parameters (N=70).**

| Histopathological parameters | | BRCA1 expression | | P-value |
|---|---|---|---|---|
| | | Positive n(%) | Negative n(%) | |
| Tumor size (cm) | <2 | 8 (57.1%) | 6 (42.9%) | 0.281* |
| | 2-5 | 16 (38.1%) | 26 (61.9%) | |
| | >5 | 4 (28.6%) | 10 (71.4%) | |
| Histological type | Invasive ductal carcinoma, NST | 24 (40%) | 36 (60%) | 0.309* |
| | Invasive lobular carcinoma | 0 (0%) | 3 (100%) | |
| | Invasive ductal carcinoma with medullary features | 3 (75%) | 1 (25%) | |
| | Mucinous carcinoma pure type | 0 | 1 (100%) | |
| | Mixed invasive carcinoma | 1 (50%) | 1 (50%) | |
| Histological grade | Grade 1 | 4 (33.3%) | 8 (66.7%) | 0.142* |
| | Grade 2 | 11 (31.4%) | 24 (68.6%) | |
| | Grade3 | 13 (56.5%) | 10 (43.5%) | |
| In-situ compo-nent | Present | 16 (41%) | 23 (59%) | 0.844* |
| | Absent | 12 (38.7%) | 19 (61.3%) | |
| Lymphovascular invasion (LVI) | Present | 16 (42.1%) | 22 (57.9%) | 0.695* |
| | Absent | 12 (37.5%) | 20 (62.5%) | |

*- Chi-square test is applied

The association of BRCA1 with tumor size, histological type, histological grade, in-situ component and lymphovascular invasion (LVI) was assessed using Chi-square test . No statistically significant association was found between BRCA1 expression and tumor size (p-value=0.281), between BRCA1 expression and histological type (p-value=0.309) and between BRCA1 expression and histological grade (p-value=0.142). Similarly, no statistically significant association was found with BRCA1 expression and in-situ component (p-value=0.844) and between BRCA1 expression and lymphovascular invasion (p-value=0.695) (Table 2)

**Table 3: Association of BRCA1 with ER, PR and HER2 (N=70)**

| Variable | | BRCA1 | | P value |
|---|---|---|---|---|
| | | Positive n(%) | Negative n(%) | |
| ER | Positive | 5 (14.3) | *30 (85.7)* | 0.000* |
| | Negative | 23 (65.7) | 12 (34.3) | |
| PR | Positive | 2 (11.1) | *16 (88.9)* | 0.004* |
| | Negative | 26 (50.0) | 26 (50.0) | |
| HER2 | Positive | 9 (31.0) | *20 (69.0)* | 0.198* |
| | Negative | 19 (46.3) | 22 (53.7) | |

*- Chi-square test is applied

Negative BRAC1 expression is seen in 85.7% of the total ER positive and 34.3% of the total ER negative cases and found to be statistically significant with p-value of 0.00. Negative BRCA1 expression is seen in 88.9% of the total PR positive cases and 50% of the total PR negative cases which was statistically significant (p-value= 0.004).While BRCA1 negativity was seen in 69% of the total HER2 positive cases and 53.7% of the total HER2 negative cases which was found to be statistically insignificant with p-value of 0.198 (Table 3 ).

**Table 4: Association of BRCA1 with triple negative cases (N=70)**

| Variable | BRCA1 | | P-value |
|---|---|---|---|
| | Positive n (%) | Negative n (%) | |
| Triple negative | *18(81.81)* | 4(18.18) | 0.00* |
| Others | 10(20.83) | 38(79.16) | |

*- Chi-square test is applied

Of the 22 Triple negative breast carcinoma cases 18 cases showed BRCA1 positivity (18/22) constituting of 81.81% while 4 cases showed BRCA1 negativity comprising of 18.18% which was statistically significant with p-value of 0.00 (Table 4 ).

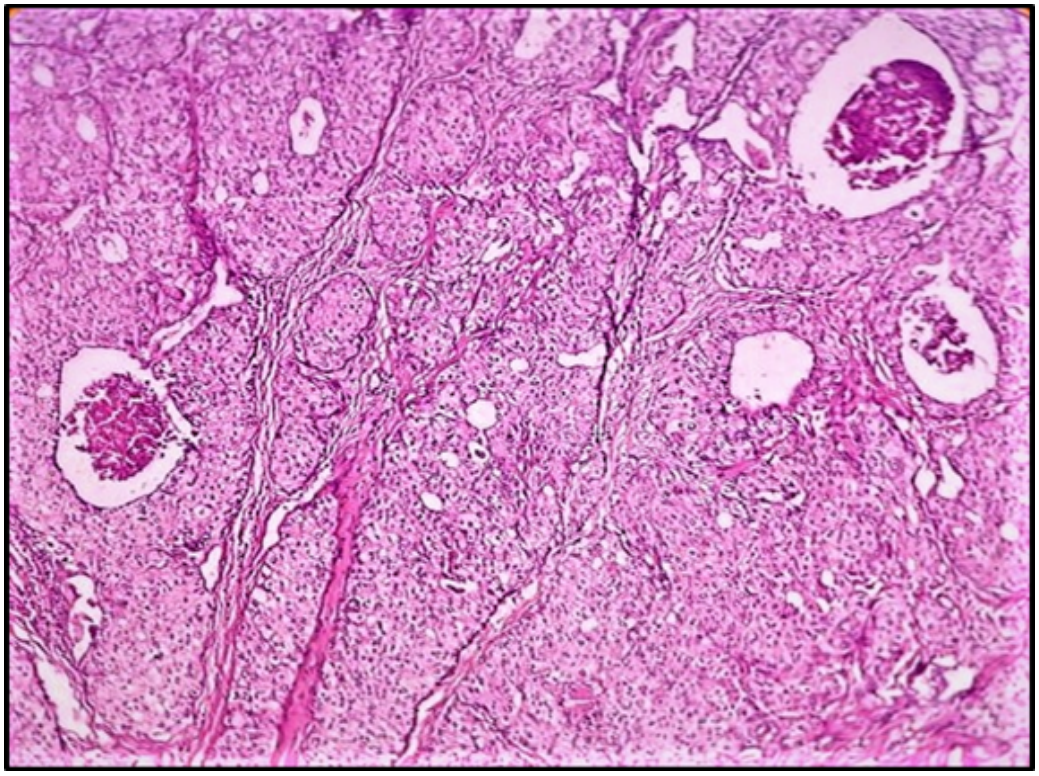

**Figure 5: Photomicrograph of Invasive ductal carcinoma, NST of breast, showing sheets of pleomorphic tumor cells separated by fibro collagenous septa along with comedo necrosis. (H&E stain,10X)**

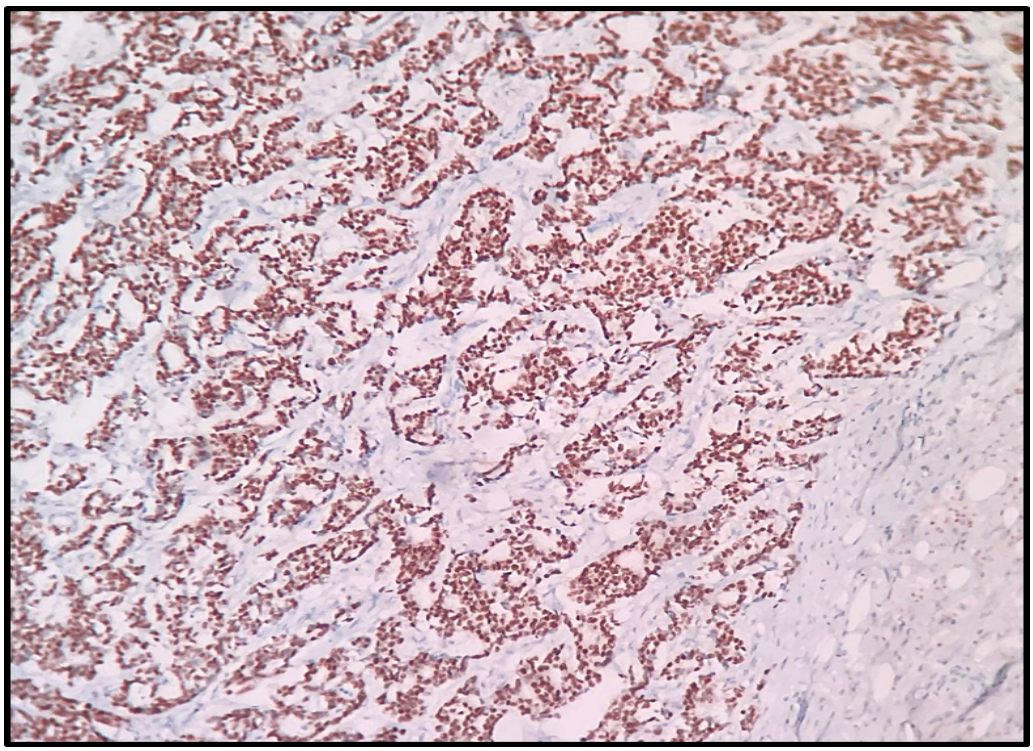

**Figure 6: Photomicrograph showing Invasive carcinoma of breast, NST, with positive nuclear staining for ER (ER IHC stain, Clone-SP1, 10X)**

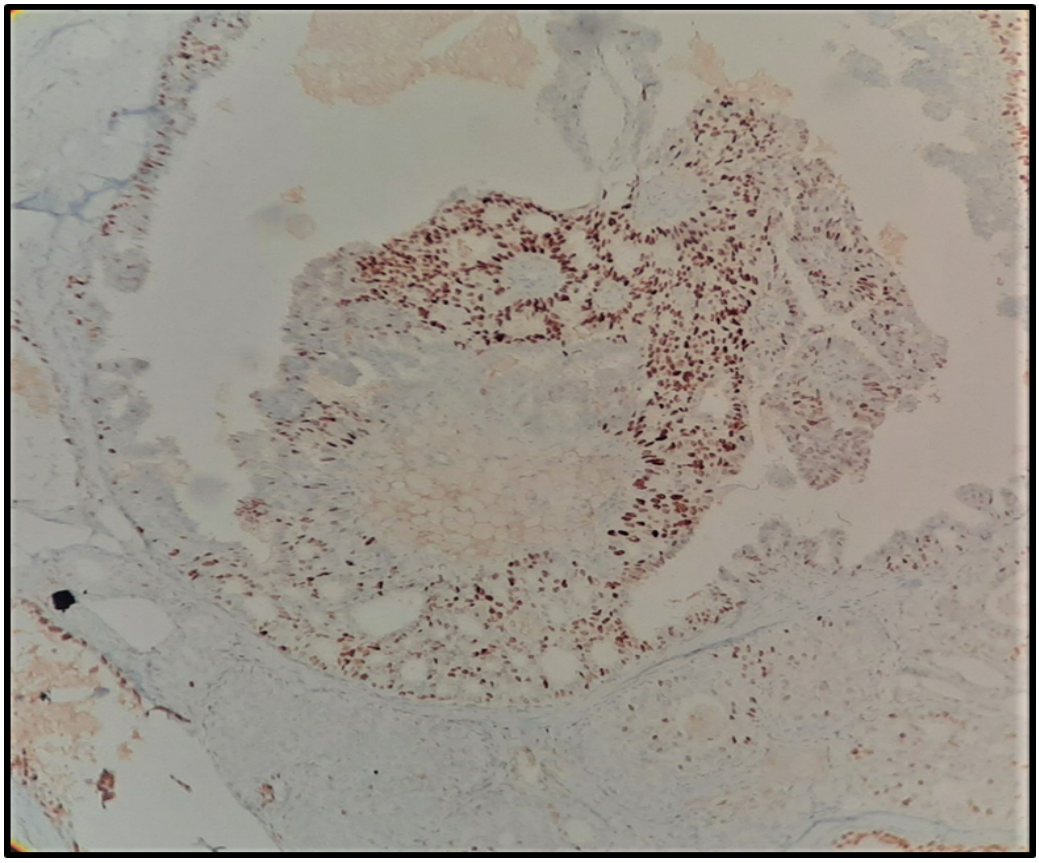

**Figure 7: Photomicrograph showing Invasive carcinoma of breast, NST, with positive nuclear staining for PR (PR IHC stain, Clone-PgR 636, 10X)**

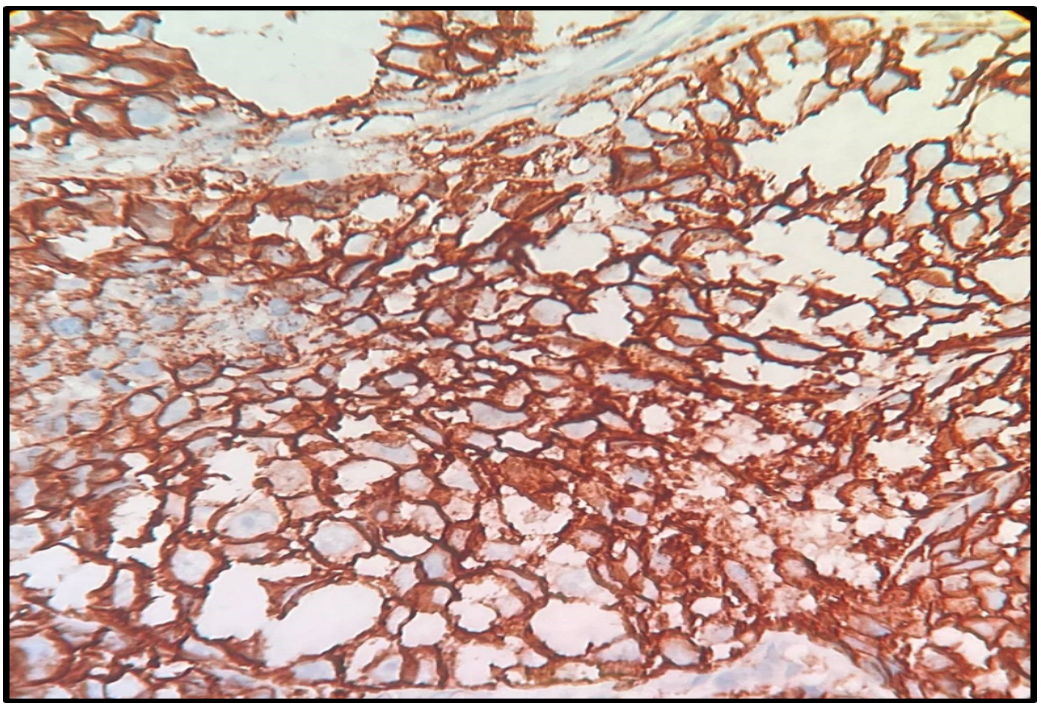

**Figure 8: Photomicrograph showing Invasive carcinoma of breast, NST, with Positive HER2 membrane staining (HER2 IHC stain, Clone-SP3, 40X)**

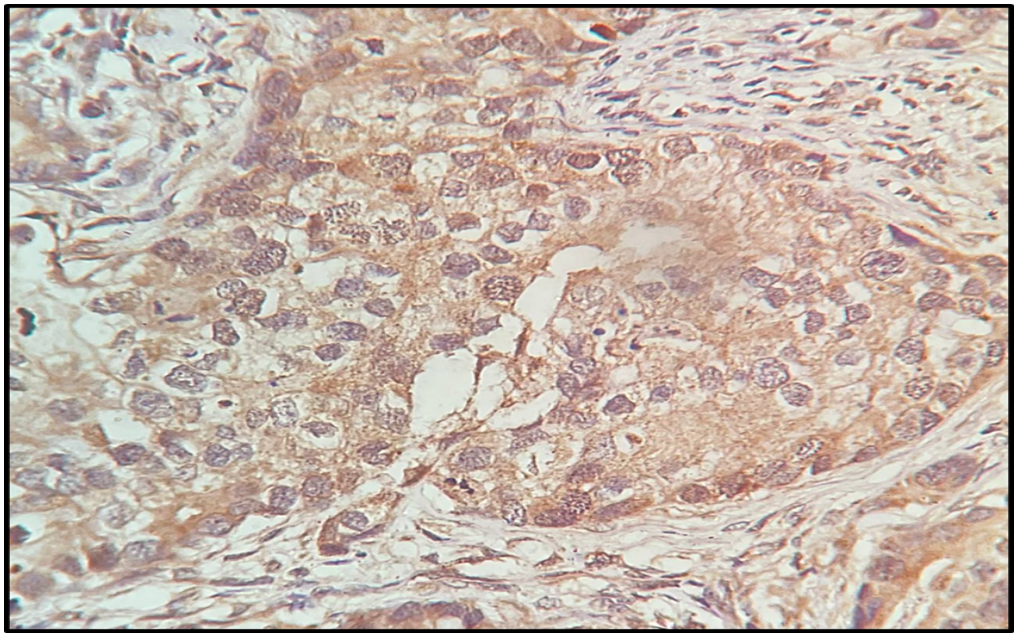

**Figure 9: Photomicrograph showing Invasive carcinoma of breast, NST, with positive BRCA1 staining (BRCA1 IHC stain, Clone-MS 110, 40X)**

## Discussion

In the present study, maximum number of the breast carcinoma cases presented in the age group of 41-50 years (34.3%). No statistically significant association of BRCA1 expression was found with age, which was consistent with study by Hussein et al[31], Amirrad et al.[33] However Juneja et al.[24] found that majority of the breast carcinoma cases were in the age group of 40-49 years (32%) and statistically significant association was found between altered BRCA1 expression and age.

The present study did not find any significant correlation between tumor size and BRCA1 nuclear expression (p-value-0.281). However, Rakha et al.[34] found a positive correlation between large tumor size and BRCA1 nuclear expression.

In the present study, Invasive Ductal Carcinoma, NST is found to be commonest type (85.7%) followed by Invasive ductal carcinoma with medullary features (5.7%). No statistically significant association was found with BRCA1 expression and histological type of breast carcinoma. Similar results have been reported by Amirrad et al.[33], Hedau et al.[35]

Most of the cases presented in histological grade 2 constituting 50% followed by grade 3 with 32.9%. Our study observed no association of negative BRCA1 expression with histological grade of tumour. This was concordant with results of Yoshikawa et al.[32], Juneja et al.[24]. However, Verma et al.[30] observed that among Grade 3 breast carcinomas 63.6% showed reduced and absent BRCA1 expression. Significant association between BRCA1 expression and histological grade of breast cancer were also observed by Rakha et al.[34], Hedauet al.[35], Sharma et al.[25], Hussein et al.[31], Amirrad et al.[33]

In the present study, lymphovascular invasion was present in 38 cases (54.3%) and absent in 32 cases (45.7%). In-situ component was found in 39 cases (55.7%) and was absent in 31 cases (44.3%). No statistically significant association was found between BRCA1 expression and lymphovascular invasion (LVI) (p-value-0.695), between BRCA1 expression and in-situ component (p-value-0.844). Agarwal et al.[36] found a much lower percentage with LVI and DCIS constituting 20.2% and 26.1% of breast cancers respectively.

In the present study positive BRCA1 was found in 40% cases, whereas Sharma et al.[25]]reported 36%, Verma et al.[30] reported 55.6%, Juneja et al.[24] found 74%, Hussein et al.[31] reported 20.5% BRCA1 positivity. Rakha et al.[34] reported complete loss of nuclear BRCA1 expression in 15% breast carcinomas and reduced nuclear expression in 39% of the cases. Hedau et al.[35] evaluated the level of BRCA1 protein expression in 40 sporadic breast cancer cases out of which, 12 cases (30.0%) showed a decreased BRCA1 protein expression. Agarwal et al.[36] found loss of BRCA1 protein expression in 48.2% cases (146/303) and statistically significant correlation was found between BRCA1 protein expression and hormonal profile.

Our study found ER positivity in 50% of breast cancers, while PR positivity was found in 25.70% of breast cancers. Negative BRCA1 expression is seen more with ER-positive (p-value-0.00) and PR-positive cases (p-value-0.004). However, Amirrad et al.[33], found ER positivity in 51% and PR

positivity in 49% of breast cancers. Negative BRCA1 expression is seen with ER negative and PR negative breast cancers, although no statistically significant association was obtained in their study.

In the present study HER2 positivity was found in 41.40% of breast cancers. A much higher percentage (87%) was found in a study by Amirrad et al.[33] Our study also observed that negative BRCA1 expression is seen more in HER2 positive cases (p-value-0.198). Concordant result has been observed ina study done by Amirrad et al.[33], Yoshikawa et al.[32], where they found that most of the breast cancers with negative BRCA1 expression also showed HER2 positivity, although this association was not statistically significant. In contrast to the present study, Juneja et al.[24], Hussein et al.[31], found negative BRCA1 expression more in HER2 negative cases.

Our study found BRCA1 positivity in 81.81% of the triple negative cases and found to be statistically significant (p-value-0.00). These results are in concordance with results of Sharma et al.[25] where they found that BRCA1 positivity is higher in triple negative primary tumours (60.5%) as compared to other groups (p-value-0.009). However, results are discordant with Agarwal et al.[36]where they found BRCA1 protein loss (negativity) more frequent in triple negative breast carcinomas (TNBC) (61.5%) of total TNBC cases (p-value-0.003).

## Conclusion

BRCA1 expression is significantly associated with estrogen receptor (ER) and progesterone receptor (PR) in breast carcinoma. No statistically significant association was found between BRCA1 expression and human epidermal growth factor receptor2(HER2) in breast carcinoma. A higher number of cases with negative BRCA1 expression showed positive ER, positive PR and positive HER2 expression. BRCA1 positivity is high among triple negative breast carcinoma which signify a worst prognosis. No statistically significant association of BRCA1 was found with age, paritytumor size, histological type, histological grade, in-situ component and lymphovascular invasion (LVI).. Further studies with larger sample size and follow up may be neededto establish BRCA1 to be used as a potential predictive and prognostic marker in breast carcinoma.

## References


1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021; 71(3):209-249.
2. International Agency for Research on Cancer.IndiaSource:Globocan 2020. [cited 11 June 2021]. Available from:http://gco.iarc.fr/today/data/factsheets/populations/356-india-fact-shee ts.pdf.
3. National Centre for Disease Informatics and Research, National Cancer Registry Programme, ICMR. Report of National Cancer Registry Programme 2012-2016. Bangalore, India: NCDIR-NCRP(ICMR);2020.
4. Ported PL. Global trends in breast cancer incidence and mortality. SaludPublica Mex 2009;51Suppl 2:s141-6.
5. James CR, Quinn JE, Mullan PB, Johnston PG, Harkin DP. BRCA1, aPotential Predictive Biomarker in the Treatment of Breast Cancer.Oncologist. 2007;12(2):142-50.
6. Deng CX, Scott F. Role of the tumor suppressor gene Brca1 in genetic stability and mammary gland tumor formation. Oncogene. 2000; 19(8):1059-64.
7. Deng CX, Brodie SG. Roles of BRCA1 and its interacting proteins. Bioessays. 2000; 22(8):728-37.
8. Bhattacharyya A, Ear US, Koller BH, Weichselbaum RR, Bishop DK. The breast cancer susceptibility gene BRCA1 is required for subnuclear assembly of Rad51 and survival following treatment with DNA cross-linking agent cisplatin. J Biol Chem. 2000; 275(31):23899-903.
9. Clark SL, Rodriguez AM, Snyder RR, Hankins GD, Boehning D. Structure-Function ofThe-TumorSupressor BRCA1. ComputStructBiotechnol J.2012; 1(1).
10. Ford D, Easton DF, Stratton M, Narod S, Goldgar D, Devilee P et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. Am J Hum Genet. 1998; 62:676-89.
11. Rehman FL, Lord CJ, Ashworth A. Synthetic lethal approaches to breast cancer therapy. Nat Rev Clin Oncol.2010;7:718-724.
12. Ross JS, Hortobagyi GN. Molecular Oncology of Breast Cancer. Jones and Bartlett Publishers, Sudsbury, Massachusetts. 2005.
13. Jensen EV, Jordan VC. The estrogen receptor: a model for molecular medicine. Clin Cancer Res. 2003; 9:1980.
14. Taneja P, Maglic D, Kai F, Zhu S, Kendig RD, Fry EA et al. Classical and Novel Prognostic Markers for Breast Cancer and their Clinical Significance. Clin Med Insights Oncol.2010;4:15-34.
15. Bansal C, Sharma A, Pujani M, Pujani M, Sharma KL, Srivastava AN, et al. Correlation of Hormone Receptor and Human Epidermal Growth Factor Receptor-2/new Expression in Breast Cancer with Various Clinicopathologi-

cal Factors. Indian J Med Paediatr Oncol.2017;38(4):483-9.
16. Zhou BP, Hung MC. Dysregulation of cellular signalling by HER2/neu in breast cancer. Semin Oncol. 2003;30(Suppl 16):38-48.
17. Siadati S, Sharbatdaran M, Nikbakhsh N, Ghaemian N. Correlation of ER, PR and HER-2/Neu with other Prognostic Factors in Infiltrating Ductal Carcinoma of Breast. Iranian J Pathol.2015 Summer;10(3):221-226.Elliis IO, Lee AHS, Pinder SE, Rakha EA. Tumors of the Breast. In: Fletcher CDM, editor. Diagnostic Histopathology of Tumors, 4th ed. Philadelphia: Elsevier saunders;2013. p.1057-1145.
18. Elliis IO, Lee AHS, Pinder SE, Rakha EA. Tumors of the Breast. In: Fletcher CDM, editor. Diagnostic Histopathology of Tumors, 4th ed. Philadelphia: Elsevier saunders;2013. p.1057-1145.
19. Foulkes WP, Smith IE, Reis-Filho JS. Triple-negative breast cancer. N England J Med. 2010;363(20):1938-48.
20. Stevens KN, Vachon CM, Couch FJ. Genetic susceptibility to triple-negative breast cancer. Cancer Res. 2013;73(7):2025-30.
21. Metcalfe K, Lubinski J, Lynch HT, Ghadirian P, Foulkes B, Gronwald J et al. Family history of cancer and cancer risk in women with BRAC1 or BRCA2 mutations. J Natl Cancer Inst. 2010;102(24):1874-8.
22. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA. 2006; 295:2492-2502.
23. Phipps AI, Buist DSM, Malone KE. Family History of Breast Cancer in First-Degree Relatives and Triple-Negative Breast Cancer Risk. Breast Cancer Res Treat.2011 April; 126(3):671-678.
24. Juneja K, Varshney A, Kumar R, Singla M, Sharma P, Sharma VK. BRCA1 expression and its association with histological typing, grade, ER, PR, HER2 in carcinoma of breast. Indian J Pathol. 2019;6(3):376-80.
25. 25. Sharma M, Madan M, Manjari M, Madhukar M, Singh T, Gupta S. BRCA1 Positivity in Triple Negative Breast Cancers: A Prospective Study in Tertiary Care Cancer Hospital. Trop J Pathol Microbiol. 2020; 2(2):64-9.
26. 26.Tremont A, Lu J, Cole JT. Endocrine therapy for early breast cancer: Updated review. Ochsner J. 2017 Winter;17(4):405-11.
27. Suvarna SK, Layton C, Bancroft JD, editors. Bancroft's Theory and Practice of Histological Techniques. 8th ed. Philadelphia: Elsevier Saunders;2019
28. Lokuhetty D, White VA, Watanabe R, Cree IA, (Eds): WHO Classification of Tumours of the Breast.5th Edition. IARC: Lyon;2019.
29. Fitzgibbons PL, Bartley AN, Connolly JL. Template for Reporting Results of Biomarkers Testing of Specimens from Patients with Carcinoma of the Breast. Version: 4.5.0.1.CAP;2021.
30. Verma D, Agarwal K, Tudu SK. Expression of breast cancer type 1 and its relation with expression of estrogen receptors, progesterone receptors, and human epidermal growth factor receptor 2/neu in breast carcinoma on trucut biopsy specimens. Indian J Pathol Microbiol. 2018;61(1):31-38.
31. Hussein IA, Ahmed ST, Hameedi AD, Naji RZ, Alharbawi L, Alkhayatt M. Immunohistochemical Expression of BRCA1 Protein, ER, PR and HER in Breast Cancer: A Clinicopathological Study. Asian Pac J Cancer Prev. 2020; 21(4):1025-29.
32. Yoshikawa K, Honda K, Inamoto T, Shinohara H, Yamauchi A, Suga K et al. Reduction of BRCA1 protein expression in Japanese sporadic breast carcinoma and its frequent loss in BRCA1 associated cancer. Int J Cancer. 2000;88(1):28-36.
33. Amirrad M, Al-Mulla F, Varadharaj G, John B, Saji T, Anim JT. BRCA1 Gene Expression in Breast Cancer in Kuwait: Correlation with Prognostic Parameters. Med Princ Pract. 2005;14:67-72.
34. Amirrad M, Al-Mulla F, Varadharaj G, John B, Saji T, Anim JT. BRCA1 Gene Expression in Breast Cancer in Kuwait: Correlation with Prognostic Parameters. Med Princ Pract. 2005;14:67-72.
35. Rakha EA, El-Sheikh SE, Kandil MA, El-Sayed ME, Green AR, Ellis IO. Expression of BRCA1 protein in breast cancer and its prognostic significance. Hum Pathol. 2008; 39(6):857-65.
36. Hedau S, Batra M, Singh UR, Bharti AC, Ray A, Das BC. Expression of BRCA1 and BRCA2 proteins and their correlation with clinical staging in breast cancer. J Cancer Res Ther.2015;11:158-63.
37. sAgarwal P, Khan F, Gupta S, Bhalla S, Thomas A, Anand A et al. Co-Relation of Hormonal Profile and BRCA1 in Sporadic Breast carcinoma: A Single Institutional Experience of 303 patients. ClinPathol. 2022 Feb 14; 15:1-7.