Original Article

Expression of BRCA1 by immunohistochemistry and its association with ER, PR, Her2neu status in infiltrative ductal carcinoma of breast

ABSTRACT

Background: Breast cancer is a heterogeneous disease, which differs in its clinical behaviors and responses to treatment and outcome. The prognosis of breast cancer depends on histopathological parameters and molecular subtypes. Among more than 300 genes, which are involved in the pathogenesis of breast cancer tumor suppressor gene such as *BRCA1* is known to play a significant role in hereditary cancers. However, its role in sporadic cases of infiltrating ductal carcinoma is yet to be established.

Aims and Objectives: To evaluate the expression of BRCA1 in infiltrative ductal carcinoma and to analyze the association of BRCA1 with histopathological parameters and estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor2 (Her2) neu expression.

Materials and Methods: This was a laboratory-based exploratory study in which 56 patients with infiltrative ductal carcinoma who underwent radical mastectomy from October 2019 to July 2021 were included. Patients with chemotherapy and radiotherapy, trucut biopsies, and incomplete patient details were excluded. Immunostaining for BRCA1 was performed. Individual clinicopathological parameters were compared with the *BRCA1* mutation. Statistical analysis was done using SPSS 22. A *P* value of < 0.05 was considered statistically significant.

Results: Among 56 cases of IDC, 18 cases (32.1%) showed *BRCA1* mutation. *BRCA1* mutation was associated with postmenopausal age, larger tumor size, lower tumor grade, and higher tumor staging. When we analyzed the biomarkers with *BRCA1* mutation, it showed a negative association with ER, PR, and Her2 neu and a high Ki67 proliferation index. No family history of breast carcinoma was seen in 34/56 patients where history was available.

Conclusion: Our study showed *BRCA1* mutation in 32.1% and associated with postmenopausal age group, larger tumor size, and higher staging and negative hormonal status of breast carcinoma.

KEY WORDS: BRCA1, infiltrating ductal carcinoma, Nottingham prognostic index

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INTRODUCTION

Breast carcinoma is the most commonly diagnosed cancer and the leading cause of cancer death among females worldwide constituting 27.5% of all cancers in our population.[1,2] Etiopathogenesis of breast carcinoma includes both non-genetic and genetic causes. Among non-genetic causes, numerous risk factors such as age, obesity, exposure to radiation, race/ethnicity, late parity, breastfeeding, early menarche and late menopause, hormone replacement therapy, alcohol, and smoking have been implicated.[3]

Among the genetic causes, the role of breast carcinoma genes (*BRCA*) and *p53* mutations remains undisputed. *BRCA* a tumor suppressor gene, is associated with family history or germline mutations and accounts for 5–10% of all breast carcinomas. This gene is located on chromosome 17p21 and is generally inherited as an autosomal dominant trait.[3] Germline mutations of *BRCA1* carry a lifetime risk of 50–85% for breast cancer and 15–60% for ovarian cancer.[4] Decreased levels of BRCA1 mRNA and protein expression and

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methylation of the BRCA1 promoter region have been seen in some sporadic breast carcinoma, indicating the involvement of BRCA1 even in the sporadic form.[5] Detection of these mutations is usually done using investigations such as DNA sequencing, microarray, reverse transcriptase, polymerized chain reaction, and immunohistochemistry. Some of the studies have shown that BRCA immunohistochemistry has 100% specificity and 80% sensitivity for detecting germline, somatic, or epigenetic mechanisms of *BRCA1* loss.[6]

About 30% of infiltrative ductal carcinoma shows down-regulation of BRCA1 mRNA and protein expression.[7] Reduced expression of BRCA1 protein may play an important role in mammary carcinogenesis in the Indian population and mechanisms other than mutations such as methylation that may be involved in reduced expression of the BRCA1 protein.[8] Hypermethylation of promoter gene CpG-rich areas results in the silencing of tumor suppressor genes.[9] Studies also show that the secondary effect of change in upstream regulatory pathways will result in a decreased expression of *BRCA1* in the cells.[10]

Because BRCA1 protein plays an important role in the development and progression of breast carcinomas, it can be used as a promising biomarker to select targeted and effective chemotherapeutic regimes in patients with breast carcinoma.[11] In view of the paucity of data on the expression of *BRCA* mutations in breast carcinomas using immunohistochemistry and its expression in patients without any family history of carcinoma breast, this study was conducted.

OBJECTIVES

1. To evaluate the expression of BRCA1 in infiltrative ductal carcinoma
2. To analyze the association of BRCA1 with histopathological parameters and estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor2 (Her2) neu expression.

MATERIALS AND METHODS

The sample size was estimated based on the down-regulation or absent expression of BRCA1 in tumor tissues. It was reported to be 30% in a study done by Hedau *et al.*[12] in 2015 with a 95% level of confidence and an absolute error of 12%. A total of 56 cases that included both prospective and retrospective cases were included in the study.

Our study was a laboratory-based exploratory study conducted in the Department of Pathology from Oct 2019 to July 2021. Females with invasive ductal carcinoma irrespective of age were included in the study. Infiltrating ductal carcinoma (IDC) cases subjected to neoadjuvant radiotherapy/chemotherapy before modified radical mastectomy and women who underwent chemotherapy for other cancers over the past 5 years were excluded from the study.

Institutional Ethical clearance was obtained before the start of the study. After anonymizing the retrospective cases, demographic details, histopathological details, slides, blocks were archived from the Dept of Pathology. For prospective cases, informed consent was taken from the patients' demographic details, histopathological details, slides, and blocks were collected. All slides were reviewed and data such as tumor size, grade of the tumor, lymph node metastasis, and biomarkers such as ER, PR, Her2 neu, Ki67 were reinterpreted and documented. Blocks were cut as per the standard operating procedure, stained with IHC marker BRCA1 (biogenex) and scoring was done. Immunohistochemistry was done following the principle of the horseradish peroxidase antiperoxidase method.

The grading systems and scoring systems used are as follows:

Tumor grading was done with modified Scarff–Bloom–Richardson grading.[13] Nottingham prognostic index were used to calculate the prognosis using the formula

$NPI = (0.2 \times S) + N + G$

S is the size of the index lesion in centimeters
N is the number of lymph nodes involved: 0 = 1,1-3=2,>3=3
G is the grade of tumor: Grade I=1, Grade II=2, Grade III=3 (Based on the modified Bloom- Richardson grading).

All IHC slides for ER and PR were scored using Allred scoring, Her2 neu was scored as per the ASCO guidelines 2018, and Ki67 was scored as per Kanyilmaz *et al*.[14-16]

Scoring of BRCA1 was done based on the scoring system given by Yoshikawa *et al.*[17] which is as follows. Score 0– 0% nuclear staining (absent staining), Score 1–< 20% nuclear staining (reduced staining), Score 2–20%–80% nuclear staining, Score 3–> 80% nuclear staining. (Primary antibody for BRCA1 polyclonal rabbit, Biogenex; control tissue Biogenex FB-345 P, Nucleus)

Statistical analysis

Data were entered in MS Excel and analysis was done using the SPSS22 version Armonk, NY: IBM Corp software. To assess the association between histopathological parameters and BRCA1 with the ER, PR, and Her2 neu status, Pearson's correlation test was used. A *P* value <0.01 was considered statistically significant.

RESULTS

The mean age of presentation was 52 years. The majority of the patient belonged to 50–59 years, which constituted 17 cases (30.1%) followed by 40–49 years constituting 12 cases (21.4%), 9 cases (16%) belonged to 31–39 years, 60–69, and >70 years each age group.

The present study shows BRCA1 expression in 18/56 cases. The figure shows the BRCA1 altered expression [Figures 1–3].

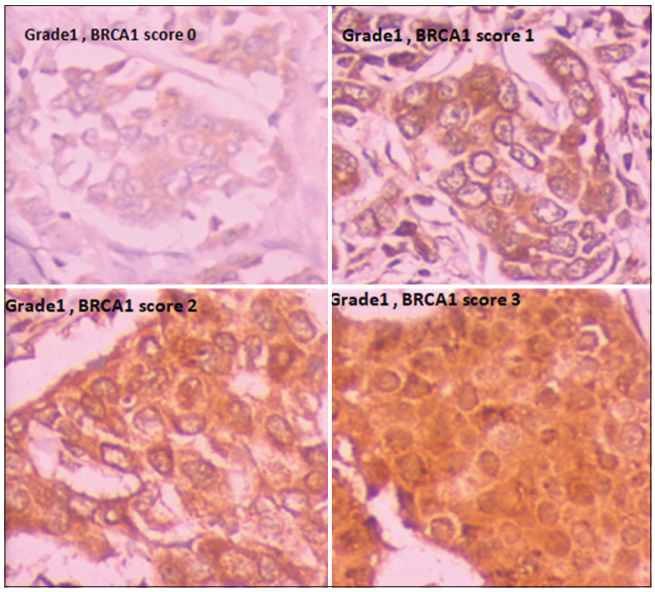

Figure 1: IDC Grade 1- BRCA1 IHC – 100x (Score 0, Score 1, Score2, Score 3)

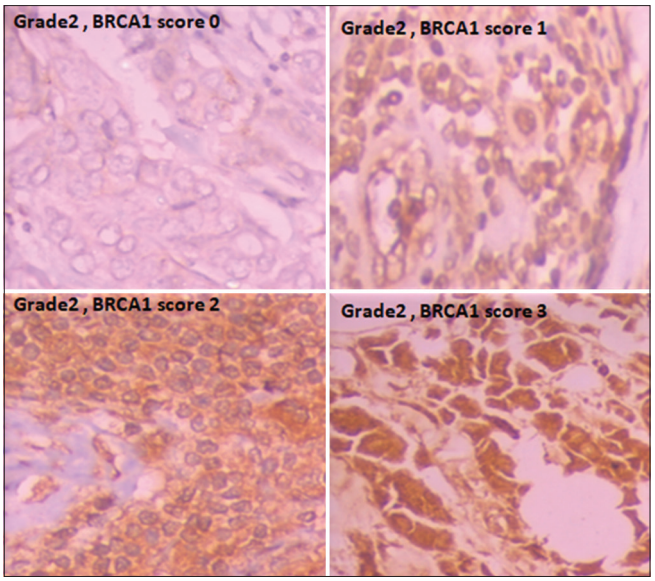

Figure 2: IDC Grade 2- BRCA1 IHC – 100x (Score 0, Score 1, Score2, Score 3)

BRCA1 mutation is associated with postmenopausal status in 72%. Among 56 cases, 36 patients responded to our query on family history of carcinoma of breast/ovary among first-degree relatives. No positive history was found in any of the cases. The other clinicopathological features are shown in Table 1.

We found that 57.1% had tumor sizes between 2 and 5 cm. *BRCA1* expression was significantly correlating with the size of tumor with $P < 0.01$ ($r = 0.714$). No correlation was found between lymph node status and *BRCA1* expression.

Tumor grade was negatively correlated with *BRCA1* expression with $P < 0.01$ ($r = -0.395$). The majority of cases were in Grade I tumor (46.4%). Also, we noted a statistically significant correlation between BRCA1 expression and higher tumor stage ($r = -0.513$). Out of 18 BRCA1 mutated cases, 83.3% belonged to higher staging.

Out of 56 cases, 13 cases were in the Nottingham prognostic index category II, among which 8 cases (44.2%) showed altered BRCA1 expression. Twenty-one cases were of NPI category III, out of which only 8 cases (44.2%) showed altered BRCA1 expression. The next 13 cases were of NPI category IV, out of which 2 cases (11.1%) showed altered BRCA1 expression. The altered BRCA1 expression and NPI category were statistically significant ($r = -0.801$).

Among 56 cases, we found a negative correlation with altered BRCA1 expression ER and PR with $P < 0.01$ ($r = -0.308$) and ($r = -0.395$), respectively.

With respect to the molecular subtyping in IDC breast carcinoma, 41.1% distribution was seen in luminal A type. Among the *BRCA1* mutated cases, 44.2% were in luminal A type. When we look into the triple-negative breast carcinoma cases, 3/15 (16.6%) showed *BRCA1* mutation.

Table 1: Demographic features and clinicopathological features of all causes

	Frequency	Percentage
Age		
31-39	9	16.0
40-49	12	21.4
50-59	17	30.1
60-69	9	16.0
>70	9	16.0
Tumor size		
T1 (<2 cm)	9	16.1
T2 (2-5 cm)	32	57.1
T 3 (>5 cm)	15	26.8
Grade		
1	26	46.4
2	21	37.5
3	9	16.1
7th AJCC TNM staging		
I	6	10.7
II	30	53.6
III	20	35.7
NPI prognostic index		
Excellent	9	16.1
Good	13	23.2
Moderate	21	37.5
Poor	13	23.2

DISCUSSION

Breast cancer is a leading cause of cancer mortality among women worldwide. Numerous studies have proved that these malignancies are multifactorial and lifestyle, genetic, and environmental factors play a major role in their development. Literature shows that several genes are associated with the pathogenesis of breast carcinoma and 15–20% of them are familial. Family history of breast carcinoma/ovarian carcinoma increases the risk of development of breast carcinoma in the younger age group. Widespread screening by mammography has increased the rate of early detection of breast carcinoma in high-risk groups. *BRCA1*, which is a tumor suppressor gene, displays an autosomal

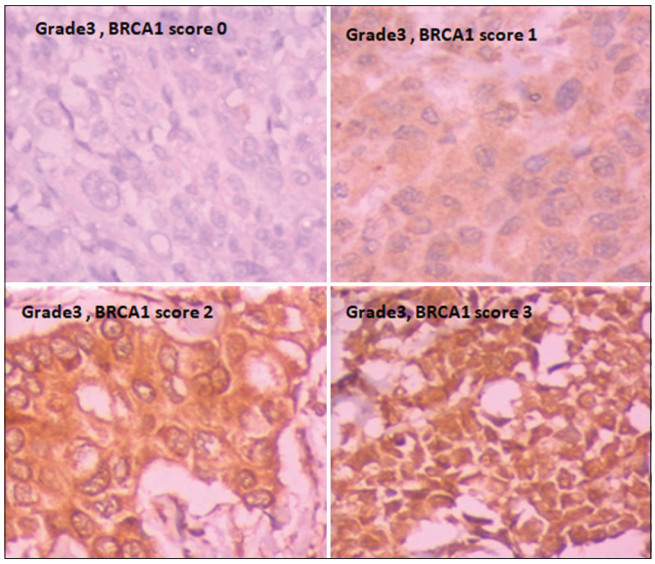

Figure 3: IDC Grade 3- BRCA1 IHC – 100x (Score 0, Score 1, Score 2, Score 3)

dominant pattern of inheritance with variable penetrance. Even though it is involved in familial cancer, it may be involved during the evolution of breast carcinoma even in sporadic cases.[18] In the present study, the age group ranged from 31 to 82 years with a mean age of 52 years, which is similar to the study done by Verma *et al.*,[11] with 26.7% cases in the premenopausal and 73.2% cases in the post-menopausal age group.

Among 18 cases, *BRCA1* mutation was associated with larger tumor size. In the present study, 11 (61.1%) *BRCA1* mutations were found to be with large tumor size (>2 cm), which is in concordance with the study done by Verma *et al.*[11] (64.8%), Rekha *et al.*[19] (38.7%) and Sharma *et al.*[20] (81.5%). It is discordance with the study done by Fang *et al.*[21] showed 60% in lower tumor size (<2 cm = 60%).

BRCA1 mutation associated with larger tumor size may be because of the aggressive behavior of the tumor.

Our study shows no significant association between lymph node involvement and *BRCA1* expression. Similar results were seen in the study done by Verma *et al.*[11] and Yoshikawa *et al*.[17] However, the study done by Rakha *et al*.[19] and Yang *et al.*[22] showed a negative association between lymph node involvement and *BRCA1* mutation.

In the present study, the frequency of altered *BRCA1* expression was observed in 42.3% of grade 1 cases, which correlated with the study done by Hussein *et al*.[23] It is contradicting with the study done by Sharma *et al.*[20] which showed no *BRCA1* mutation in grade 1. However, Verma *et al.*,[11] and Rakha *et al.*[19] found that *BRCA1* mutation was associated with a higher grade.

In our study, grade 1 tumors showed more BRCA1 positivity as compared to other studies. This may be due to the varied behavior of these genes in our geographic area.

We found a significant association between tumor staging and *BRCA1* expression. *BRCA1* mutation was seen more with a higher tumor stage. This finding is supported by the earlier study done by Ashraf *et al.*[24] and Bugrein *et al*.[25]

When we analyzed the NPI with the *BRCA1* mutation, 44.4% of cases were in Category I and II each. Our findings were in concordance with the study done by Rakha *et al*.[19]

We have done a follow-up via telecommunication, 8/56 died. When we looked into the survival rate, eight patients died and one among them died because of complications associated with angina. Among eight cases, only three (37.5%) cases showed *BRCA1* mutation and all were in the postmenopausal age group. It may be because of the uneven distribution of cases in the two age groups. However, due to the small size of sample number, no logical conclusions could be arrived at in understanding the survival status of these patients. A study done by Hussein *et al.*[23] showed a negative association of ER and PR with a *BRCA1* mutation, which was seen in 52.72%. Similar findings were also seen with Her2 neu negative (63.63%) with a *BRCA1* mutation. This is useful in molecular profiling and BRCA1 can be considered a useful prognostic marker in breast carcinoma patients. A study was done by Verma *et al.*[11] showed that ER negativity (62.5%) was associated with altered *BRCA1* expression. Similar findings were seen in the study done by Yang *et al.*,[22] Yoshikawa *et al.*[17] but there was no significant association. In addition, a study done by Rakha *et al.*[19] noticed a significant association between ER negativity and BRCA1 expression.

Sharma *et al.*[20] also supported our findings that the frequency of ER/PR-negative expression was seen with a *BRCA1* mutation.

Our findings correlate with the study of the Chinese population by Fang *et al.*[21] that showed that 77.8% of *BRCA1* mutated cases were ER/PR negative and 88.9% showed Her2 neu negative. It is also supported by the findings of Ye e*t al.*[26] and Kumar *et al*.[27]

Earlier studies proved that BRCA1 acts as the inhibitor of the E-ER signaling by interacting and inhibiting ER or inhibiting downstream effectors of ER. The functional interaction between E-ER and BRCA1 ensures the quality of replicated genome DNA when the cells experience proliferation under the mitogenic effect of E-ER. When BRCA1 is absent or insufficient, the balance is broken down and the cells start to accumulate genomic mutations, contributing to the oncogenic transformation of mammary epithelial cells. A study done by Foulkes *et al.*[28] showed that 70–80% of breast carcinoma cases were ER-negative. In addition, they found that ER positivity was associated with sporadic breast cancer. Another mechanism of inhibition of the transcriptional activity of ER is by BRCA1 protein.[29]

Ki67 proliferation index frequency is high (71%) in *BRCA1* mutated cases as found by Sharma *et al*.[20] Similar findings

were seen in a study done by Ye *et al.*[26] (79.37%). This may be due to the aggressive behavior of the tumor.

Patients with *BRCA1* mutations are known to be benefited by poly-ADP ribose polymerase (PARP) inhibitor therapy. Selection of patients for this treatment depending on the family history of *BRCA1* mutation would be futile in resource-deficit countries where the genetic analysis for *BRCA1* mutation takes a lot of time and money. More studies have to be done to look into the benefit of PARP therapy in BRCA1 breast carcinoma cases, irrespective of familial history. In addition, they may get a better outcome with anthracycline-taxane-containing regimens. Hence, targeted therapy may give a better prognosis in triple-negative cases even though they have high-grade BRCA1.[30] The role of BRCA1 in the routine breast carcinoma workup panel is debatable, further multicentric studies with a larger population are needed.

CONCLUSION

This study was done to look into the altered expression of *BRCA1* in infiltrating ductal carcinoma, 32.1% of cases showed mutated *BRCA1* expression. BRCA1 expression correlated with postmenopausal age, larger tumor size, higher tumor grade and stage, and negative hormonal status. Family history of breast cancer was not present in any of the patients where personal history was available. In view of the availability of PARP inhibitor therapy in *BRCA1* mutated patients, the feasibility of routine use of this immunohistochemistry marker in all cases of infiltrating ductal carcinoma, irrespective of family history, should be looked into.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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