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BRCA1 promoter methylation & its immunohistochemical correlation in sporadic breast cancer

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***Background & objectives*: Studies have shown that apart from hereditary breast carcinomas, breast cancer susceptibility gene 1 (*BRCA1*) mutations conferring to its loss are seen in sporadic breast carcinomas (SBC) as well. The aim of the present study was to assess *BRCA1* methylation in females presenting at King George's Medical University, Lucknow, with SBC by both immunohistochemistry (IHC) and methylation PCR with respect to hormonal profile and various morphological prognostic parameters. The primary objective was to look for the association between BRCA1 protein expression and DNA promoter methylation.**

***Methods*: 81 mastectomy specimens from SBC of invasive breast carcinoma (no special type) were included in this study. After a detailed morphological assessment, formalin fixed paraffin embedded tissue from a representative tumour area was selected for BRCA1 IHC by heat-mediated antigen retrieval under high pH and DNA extraction and further bisulphate treatment. *BRCA1* was studied for methylation by methylated and unmethylated PCR-specific primers.**

***Results*: *BRCA1* promoter methylation was present in 42/81 (51.9%) participants, with significant BRCA1 protein loss (72.7%; *P*=0.002). A significant association between BRCA1 loss and hormonal profile was found (*P*=0.001); maximum in triple negative breast carcinoma (TNBC) (72%; 18/25). Most of the TNBC also harboured methylation (68%). Although not significant grade II and III tumours, lymph vascular invasion, ductal carcinoma *in situ,* and nodal metastasis (≥3) were seen in a higher percentage in methylated tumours. Mortality in SBC was significantly associated with *BRCA1* loss (30.3%; *P*=0.024).**

***Interpretation & conclusions*: Study results highlight the concept of "BRCAness" in SBC as well. Hence, we can confer that identification of *BRCA1* loss in SBC can make it a perfect candidate for poly ADP-ribose polymerase inhibitors or cisplatin-based therapy like hereditary ones.**

Key words *BRCA1* - Breast cancer susceptibility gene 1 - immunohistochemistry - promoter methylation - sporadic breast carcinoma - triple negative breast cancer

Breast carcinoma accounts for 24.2 per cent of female carcinomas worldwide resulting in the highest mortality rate of about 16 per cent according to the Global Statistics for 2020 and 2040[1]. The Cancer

Genome Atlas (TCGA) Network breast carcinoma categorized it into four main subtypes according to various treatment modalities as Luminal A and B [oestrogen receptor/progesterone receptor (ER/PR) positive], Her2 (human epidermal growth factor receptor 2) positive with or without ER or PR expression (Her2neu enriched) and ER, PR, Her2 negative [triple-negative breast carcinoma (TNBC)][2].

Breast cancer susceptibility gene 1 (*BRCA1*) is a classic tumour suppressor gene located on chromosome 17 and is usually found in hereditary breast and ovarian carcinoma and associated with homologous recombination, DNA repair, and in transcription. *BRCA1* mutation has been related to familial breast carcinoma only. Few literature from the Western world as well as from India have demonstrated the role of *BRCA1* in sporadic breast carcinoma also[3-5].

Familial breast carcinoma is quite rare compared to sporadic breast tumours. The demonstration of BRCA1 protein loss and BRCA1 promoter methylation in malignant cells compared to normal mammary epithelial cells provide a substantial role of BRCA1 in sporadic tumours as well. Mostly, there is a loss of BRCA1 nuclear protein, in around 19 per cent of sporadic breast carcinomas (SBC), which have both nuclear and cytoplasmic BRCA1 protein loss[6].

The aberrant, *BRCA1* promoter hypermethylation, cytosine phosphate guanine (CpG) islands in promoter regions at 5' end of *BRCA1* induces downregulation expression of the BRCA1 protein expression. It can be detected in sporadic breast carcinoma, particularly in TNBCs[7].

BRCA1 deletion is usually associated with increased sensitivity to drugs that induce cross-links (platinum chemotherapy) and single- and double-stranded breaks (etoposide) in DNA[7]. The breaks in DNA are usually repaired by the repair pathway that involves base excision in which poly ADP-ribose polymerase 1 (PARP1) is one of the major components[8]. PARP inhibitors can be used as targeted therapy in BRCA1 loss cases.

Hence with the above knowledge, it is apparent that sporadic cancer may harbour BRCA1 loss, especially triple-negative cancers which have limited therapy options. BRCA1 loss will make such individuals candidates for platinum, etoposide-based therapy as well as PARP inhibitors[8]. Multiple research studies are being undertaken to clarify the role of BRCA1 expression in sporadic breast tumours, but there are many contradictory results among the various studies.

BRCA1 has been studied in sporadic breast cancers; both in the Western and Indian population[7,9-11]. The methodology used includes either molecular, mainly PCR or immunohistochemistry (IHC). Only a few studies have utilized both of these. *BRCA1* genetic testing is time-consuming and expensive. In developing countries such as India, where molecular diagnostics are less accessible to many, this study intended to study *BRCA1* using both molecular technique (methylation PCR) as well as IHC (protein expression) in formalin-fixed paraffin-embedded (FFPE) tissue samples to ascertain the association of *BRCA1* alteration through both techniques. Moreover, studying expression by both techniques on the same tissue can clarify regarding the exact difference that molecular alteration can make at the protein level. Hence, the present work was undertaken to study the *BRCA1* status in females presenting with sporadic breast cancer in a tertiary care centre in northern India by both IHC as well as molecular techniques.

The primary objective of this study was to assess the protein expression of *BRCA1* in invasive ductal carcinoma of the breast – no special type (IDC-NST) by IHC in females with no familial history of breast cancer in first- and second-degree relatives. Furthermore, the *BRCA1* status by both IHC and methylation PCR with respect to the hormonal profile of breast cancer, various morphological prognostic parameters, Nottingham grade and clinical outcome was assessed. The association of *BRCA1* protein expression (IHC) and DNA promoter methylation was also assessed.

Material & Methods

The present study was conducted in the department of Pathology, King George's Medical University, Lucknow, from June 2019 to September 2020 after approval from the Institutes Ethics Committee (ESR/262/Inst/UP/2013/RR-16). A written informed consent was obtained from all the study participants.

Inclusion & exclusion criteria: Cases of sporadic breast cancer (*i.e*. females with no history of breast cancer in first- and/or second degree relatives), in which mastectomy specimens were received and the histology diagnosis was IDC-NST were included in this study. These cases also had an adequate tumour mass and a written informed consent was obtained from the individual. Cases having an inadequate tumour sample, other subtypes of invasive breast

carcinoma, but unwilling to participate were excluded from the study.

A total of 81 masectomy cases of IDC-NST were included in the study. An FFPE tissue block from the representative tumour area on gross examination of mastectomy specimens was selected for further IHC and methylation study. 3-4 µm thick sections on silane-coated slide from this block was used for IHC. All the paraffin blocks were stored at room temperature and when the molecular test was performed, ten sections (7-8 µm) were collected in Eppendorf vials for DNA extraction and methylation study.

Unremarkable breast parenchyma on gross examination which was 5 cm away from the primary tumour site and harbouring unremarkable terminal ductal units with no evidence of hyperplasia either typical or atypical on microscopy was taken as internal control for each case. Excised breast tissue received (n=5) on account of cosmetic breast reduction surgeries with unremarkable morphology and with fibroadenoma (n=5) were used for standardization and as external control (as mentioned in the data sheet of the primary antibody used).

Morphological examination: FFPE blocks were processed for routine haematoxylin and eosin staining. The histological types, ductal carcinoma *in situ* (DCIS), tumour size, lymphovascular invasion, necrosis, nodal status and margins were assessed.

Immunohistochemistry (IHC): A section showing normal ductal glands and the tumour was selected for IHC as described earlier[9] using ER [Oestrogen receptor; Flex polyclonal rabbit -a Hu ER alpha, Clone EP1, ready to use (RTU); DAKO AS/AS+], PR (Progesterone; Flex Monoclonal Mo a Hu PR, Clone PgR636, RTU; DAKO AS/AS+), Her2neu (polyclonal rabbit a Hu c-erb2 oncoprotein, RTU ; DAKO AS/AS+) and BRCA1 [polyclonal rabbit, RTU (AR345-5R); BioGenex Laboratories, Fremont, USA].

Breast cancer susceptibility gene 1 (*BRCA1) immunostaining and interpretation*: The sections were deparaffinized using xylene and then rehydration was done through graded alcohol and distilled water. For antigen retrieval, sections were treated with citrate buffer in pressure cooker for 15 min at 120°C followed by cooling at room temperature. Peroxidase blocking was done using H_2O_2 (3%) for 10 min along with protein blocking for 10 min. Overnight incubation of slides with BRCA1 primary antibody at 4°C in moist chamber was done followed by thrice washing with TRIS [Tris (hydroxymethyl) aminomethane] buffer at *p*H 7.6. Slides were incubated with polymer for next 30 min and further incubated with secondary antibody for 30 min. Diaminobenzidine was used as chromogen.

For IHC interpretation, the stained sections were examined under ×400, and the expression of BRCA1 (both cytoplasmic and nuclear) was interpreted. No immunoexpression was considered negative or complete loss of BRCA1. Immunoreactivity scores of BRCA1 staining were calculated by adding the number representing the percentage of immunoreactive cells and the number representing staining intensity. Both nuclear and cytoplasmic expression was recorded separately and average of both scores was used as total. The total score of 0-3 was taken as loss of BRCA1 and 4-8 was considered expression[12].

BRCA1 methylation: Genomic DNA extraction was done from FFPE tissue using commercially available DNA extraction kit (Purelink™ Genomic DNA Kit, Invitrogen, Thermo Fisher Scientific, USA). The extracted DNA was first put to bisulphate treatment. *BRCA1* promoter methylation was studied using methylated and unmethylated PCR-specific primers. The primers were adapted from Esteller *et al*[13], and Butcher and Rodenhiser[14], and were synthesized by Integrated DNA Technology, USA. The primers annealed in the promoter region and flanked the transcription site of *BRCA1*.

The PCR mixture contained 10 pmol of each primer, 2.5 µl of 10X PCR buffer, 0.8 µl of 10 mM deoxynucleoside triphosphates (dNTPs) mix, 1U of Taq polymerase, 5 µl treated DNA, and nuclease-free water to adjust total volume of 25 µl. The amplifications were carried out with the following conditions: 95°C for 10 min; 35 cycles at 95°C for 15 sec 58°C for 45 sec; and 72°C for 45 sec. The product was run on electrophoresis and visualized on agarose gel after staining with ethidium bromide (Fig. 1).

Statistical analysis: Statistical Package for the Social Sciences for windows (SPSS version 21.0 Software; IBM Corp., Chicago, IL, USA) was used for statistical analysis.

Results

Clinicopathological parameters: The details of demographic and histomorphology variables studied are summarized in Table I. A total of 81 cases were

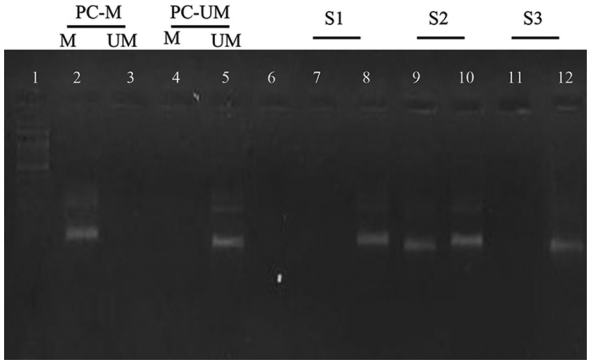

Fig. 1. Analysis by MSP PCR of the promoter region of BRCA1. Lane 1 indicates 100 bp ladder, Lane 2: positive control for methylated DNA; Lane 5: shows positive control for unmethylated DNA, Lane 6: negative control; Lane 7-8, 9-10 and 11-12 shows clinical samples with results for methylated and unmethylated PCR, respectively. The presence of a visible PCR product in those lanes marked UM indicates the presence of unmethylated genes of *BRCA1*; the presence of a product in those lanes marked M indicates the presence of methylated genes. MSP PCR, methylation-specific PCR; *BRCA1*, breast cancer susceptibility gene 1

categorized into four main hormonal subtypes *i.e.* luminal A (ER/PR+ Her2neu−; Ki67 <14%), luminal B (ER/PR+ Her2neu+; Ki67 >14%), Her2neu enriched (ER/PR–, Her2neu+) and TNBC (ER/PR/Her2neu all negative). Tumour with either one or more of the following morphological parameters were considered aggressive cancers:gross tumour size of >5 cm, tumour necrosis, presence of lymph, vascular invasion, presence of DCIS component, positive resection margins and involvement of ≥3 lymph nodes. Grade II tumours with tumour size between 2 and 5 cm and nodal metastasis were frequent in our study group.

BRCA1 protein expression: The expression of BRCA1 in both internal and external controls was recorded. Staining in breast carcinoma cells was both nuclear and cytoplasmic and the intensity ranged from strong to absent (Fig. 2). BRCA1 was seen to be diffusely and strongly expressed by ducts of adjacent unremarkable breast parenchyma (Fig. 2A). BRCA1 protein expression was evaluated in all 81 cases, out of which complete loss of BRCA1 expression was seen in 33 (40.7%) cases and protein expression was present in 48 (59.3%) cases (Table II).

Comparison of BRCA1 protein expression and hormonal profile: The association between BRCA1 protein loss with hormonal profile was found to be significant (*P*=0.001). Least BRCA1 loss was seen in luminal A category 4/22 (18.2%) followed by Her2 enriched 7/24 (29.2%), luminal B 4/10 (40%). The maximum loss of protein expression was found in TNBC (72%; 18/25) (Table III). Both nuclear and cytoplasmic BRCA1 loss were seen in tumour cells. ER-negative tumours were found to be more frequent in BRCA1 protein loss category (62%).

BRCA1 protein expression and DNA promoter methylation: In our study, loss of BRCA1 protein was present in 33/81 cases, these 72.7%, (24/33) cases showed *BRCA1* promoter methylation (Table IV). The association between DNA promoter methylation and BRCA1 protein loss was found to be significant (*P*=0.002) (Table IV).

Correlation of BRCA1 promoter methylation with various prognostic parameters: Although no significant correlation was found between *BRCA1* promoter methylation and various prognostic parameters including as necrosis, LVI, DCIS, tumour size >5 cm, and LN ≥3 positivity, LVI (26.2%), DCIS (47.6%) and LN ≥3 positivity (61.9%) were present in higher percentage in methylation cases compared to unmethylated tumours. High grade tumours (grade II and III) (54.7%) had promoter methylation, but this association was not found to be significant (*P*=0.322). When *BRCA1* promoter methylation was studied with respect to hormonal profile, cancers in luminal A and luminal B categories showed methylation in eleven cases each. Three cases of Her2 were enriched and 17 cases of TNBC were methylated, respectively. There was a significant association (*P*=0.043) between *BRCA1* promoter methylation and TNBC, most of the TNBC cases had methylation compared to non-TNBCs (68 *vs*. 32%) (Table V).

Association between BRCA1 protein expression and promoter methylation: Mortality in breast carcinoma cases was significantly associated (*P*=0.024) with BRCA1 protein loss (30.3%) compared to protein expression (10.4%). Promoter methylation showed more patients succumbed to disease compared to unmethylated cases (23.8 *vs.* 12.8%), however, this association was not found to be significant (*P*=0.203).

Discussion

BRCA1 is an important tumour suppressor gene which helps in maintaining genomic instability by uplifting homologous recombination repair. It is a DNA repair mechanism and in particular for double-stranded breaks[13]. *BRCA1* is inherited in an autosomal dominant

Table I. Demographic, clinical, histology and immunohistochemistry variables of the studied population

Characteristics	Number of cases, n (%)
Age (yr)	
≤50	50 (61.7)
>50	31 (38.3)
Laterality	
Right	33 (40.7)
Left	48 (59.3)
Quadrant	
Upper outer	35 (43.2)
Upper inner	12 (14.8)
Lower outer	9 (11.1)
Lower inner	4 (4.9)
Central	21 (25.9)
Size of tumour (cm)	
<2	3 (3.7)
2-5	72 (88.9)
>5	6 (7.4)
Mean size of tumour (cm)	3.63±1.22 (1-8)
Mitotic score	
Score 1	31 (38.3)
Score 2	39 (48.1)
Score 3	11 (13.6)
Mean mitotic count±SD (range)	14.47±8.22 (2-40)
Nottingham grade	
Grade 1	17 (21)
Grade 2	50 (61.7)
Grade 3	14 (17.3)
Necrosis	
Absent	19 (23.5)
Present	62 (76.5)
Microcalcification	
Absent	65 (80.2)
Present	16 (19.8)
LVI	
Absent	60 (74.1)
Present	21 (25.9)
PNI	
Absent	73 (90.1)
Present	8 (9.9)
DCIS	
Absent	43 (53.1)
Present	38 (46.9)
Margins absent	81 (100)
Lymph nodes metastasis	
Absent	36 (44.4)
Present	45 (55.5)
Number of lymph nodes involved	
<3	19 (42.2)
≥3	26 (57.8)
Molecular subtyping (hormonal profile)	
ER/PR+ Her2neu−; (Luminal A)	22 (27.2)
ER/PR+ Her2neu+; (Luminal B)	10 (12.3)
ER/PR−, Her2neu+; (Her2neu enriched)	24 (29.6)
ER/PR/Her2neu−; (TNBC)	25 (30.9)
Outcome	
Succumbed to disease	15 (18.5)
Alive	66 (81.5)

SD, standard deviation; LVI, lymphovascular invasion; PNI, perineural invasion; DCIS, ductal carcinoma *in situ*; ER, estrogen receptors; PR, progesterone receptors; TNBC, triple negative breast cancer

fashion and activated by *p53* gene and other unknown mechanisms. Loss of heterozygosity of *BRCA1* in sporadic breast carcinoma shares genotype as well as phenotype features with familial breast carcinoma with defect in the DNA repair pathway[16].

Anomalous CpG hypermethylation in gene promoter region associated with loss of gene expression is an important mechanism for inactivation of tumour suppressor genes in malignant cells[17]. This is well reported in sporadic breast carcinoma, particularly in TNBC[17]. Women deficient in the *BRCA1* gene are frequently found to have TNBC. TNBC is generally seen in younger age group, diagnosed in advanced stage with increased risk of metastasis and poor prognosis. These are not responsive to conventional receptor-target therapies also[18].

Few SBC cases harbor *BRCA1* phenotype with similar molecular characteristics like *BRCA1/2* mutant breast carcinoma, known as "BRCAness" which makes it sensitive to PARP inhibitors as well as platinum-based therapy[19].

BRCA1 loss has been associated with DNA promoter methylation and BRCA1 mutated cells are

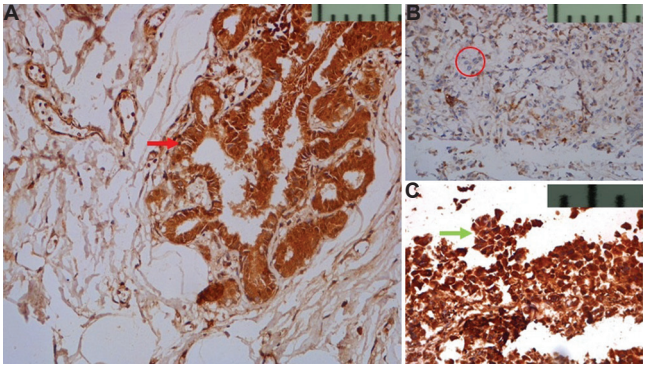

Fig. 2. (**A**) Nuclear and cytoplasmic expression of BRCA1 (red arrow) seen in normal TDLU (DAB, ×200). (**B**) Faint cytoplasmic expression in <25 per cent of tumour cells is seen, tumour cells are encircled as compared to normal TDLU in (**A**) (DAB, ×200). (**C**) Strong nuclear and cytoplasmic expression (green arrow) in >75 per cent of tumour cells as compared to normal TDLU in (**A**) (DAB, ×400) TDLU, terminal duct lobular unit

Table II. BRCA1 immunohistochemistry (IHC) results

	BRCA1 IHC	Total (n=81)
Nuclear expression	No expression	25
	Expressed	56
Cytoplasmic expression	No expression	62
	Expressed	19
Total *BRCA* expression	No expression	33
	Expressed	48

highly sensitized to inhibition of PARP enzyme[19]. PARP inhibitors cause replication fork stalling, leading to the formation of DNA substrates which further leads to the restart of replication by homologous recombination and are important for cell survival[20]. Hence, PARP inhibitors might be applicable in loss of *BRCA1* function due to hypermethylation in sporadic tumours.

In the present study, total *BRCA1* protein expression was assessed in 81 sporadic breast carcinoma cases and was found to be absent in 33 (40.7%) and expressed in 48 (59.2%). There is literature pertaining to nuclear, *BRCA1* protein expression as well as cytoplasmic in breast tumour cells[9]. In the present study, nuclear as well as cytoplasmic expression was found in cases (Table II) and controls and none of the cases had only nuclear expression as observed by Al-Mulla *et al*[21]. Moreover, the expression of *BRCA1* must always be interpreted with respect to adjoining unremarkable terminal ducts enclosed in any section from a tumour as is done for hormonal (ER/PR) markers, whenever possible.

Maximum *BRCA1* loss in TNBC in our study suggests that similar hereditary breast carcinoma with *BRCA1* mutation; sporadic cases may be frequently ER/PR/Her2neu negative too[22]. More ER-negative tumours harbored *BRCA1* loss[22] . This shows that loss of good prognostic markers such as ER also had *BRCA1* loss, hence conferring poor prognosis to *BRCA1* loss by its own virtue and its association with ER loss[23]. It has been suggested by Lee *et al*[24] that loss of expression of nuclear *BRCA1* (20.4%) positively correlated with a high histological grade while a complete loss of its nuclear expression correlated with other prognostic markers. Based on this the role of *BRCA1* nuclear expression in the pathogenesis and prognosis of sporadic breast carcinoma was highlighted. The above findings (IHC results) also designate that high-grade tumours undergo some alteration at the molecular level. Studies have shown that *BRCA1* loss in SBC could also be due to silencing due to promoter methylation[9,25].

BRCA1 promoter methylation was present in 42/81 (51.9%) cases. Although no significance was found while assessing promoter methylation and various prognostic parameters in the present study; but the poor prognostic variables were more frequent in *BRCA1* methylated tumours. Tian *et al*[26] studied the concept of BRCAness in breast cancer by both *BRCA1* germline mutations and methylation studies in TNBCs. They found that the BRCAness phenotype was largely associated with large tumour size (>2 cm), positive lymph node, tumour grade 3, high Ki67% levels (P=0.001), and basal like breast carcinoma. They concluded that BRCAness overall confers poor outcome to patients. Similar results were seen by Prajzendanc *et al*[25] . In contrast almost equal distribution of grade, tumour size, and tumour necrosis in breast cancers in the present study could be the reason for non-significant results in the said context. The reason behind this observation could be that women in India seek medical attention only when the disease is quite advanced[25,27]. Furthermore, all hormonal profiles of breast cancers, with multiple prognostic variables were included in this study. Hence our results could be more representative of *BRCA1* status and prognostic variables. Although multiple post-translational mechanisms also play a part in this, still some association of *BRCA1* methylation in prognosis stands.

The correlation between *BRCA1* protein loss and DNA promoter methylation was found to be significant (P=0.002; Table IV) similar to the findings of Bal *et al*[9] and Miyamoto *et al*[28]. Hence, it can be deduced that

Table III. Association of BRCA1 protein expression (IHC) and hormonal profile

BRCA1 (IHC)	Total (n=81)	Luminal A (n=22), n (%)	Luminal B (n=10), n (%)	Her2neu enriched (n=24), n (%)	TNBC (n=25), n (%)
Loss	33	4 (18.2)	4 (40)	7 (29.2)	18 (72)
Expression	48	18 (81.8)	6 (60)	17 (70.8)	7 (28)

χ^2=16.090 (df=3); *P*=0.001.

Table IV. *BRCA1* methylation results and association of molecular expression and BRCA1 protein expression (n=81)

BRCA1 methylation status		n (%)	
Unmethylated		39 (48.1)	
Methylated		42 (51.9)	
BRCA1 expression	Total (n=81)	Unmethylated (n=39), n (%)	Methylated (n=42), n (%)
No expression	33	9 (27.3)	24 (72.7)
Expressed	48	30 (62.5)	18 (37.5)

χ^2=9.720; *P*=0.002.

Table V. Association of *BRCA1* (methylation) expression and hormonal profile

BRCA1 methylation status	Total (n=81)	Luminal A (n=22), n (%)	Luminal B (n=10), n (%)	Her2 enriched (n=24), n (%)	TNBC (n=25), n (%)
Unmethylated	39	9 (40.9)	8 (80)	14 (58.3)	8 (32)
Methylated	42	13 (59.1)	2 (20)	10 (41.7)	17 (68)

χ^2=8.134 (df=3); *P*=0.043.

BRCA1 promoter methylation was associated with decreased protein expression and epigenetic silencing of *BRCA1* promoter regions.

We found significant correlation of molecular categories as compared to methylation results as seen when they were compared with protein expression (IHC). *BRCA1* promoter methylation was found to be maximum in TNBC (Table V) similar to previous reports[9].

However, the difference between the IHC and molecular results needs explanation. These may be explained by the following: First, molecular alterations could be either methylation silencing, deletion, point mutation, and others, and second, post-translation modifications.

Hence, reduced expression of *BRCA1* protein and mRNA expression along with DNA promoter methylation in SBC cells compared with normal mammary epithelial cells provides a promising role of the *BRCA1* gene in sporadic tumours. It is not only associated with a prognosis of these tumours but also provides evidence that patients harboring *BRCA1* loss may benefit from PARP inhibitors (Olaparib) and platinum based chemotherapy.

The limitation of the present study is that we performed only methylation PCR in our study group to study the molecular alteration in SBC. India is a geographically and genetically variable country needs a larger multicentric study for *BRCA1* evaluation in SBC to formulate its own *BRCA1* testing and therapeutic guidelines.

To conclude, this study highlights the role of the *BRCA1* gene in SBC among women in the Northern part of India. The loss of *BRCA1* protein expression may be due to DNA promoter methylation in sporadic breast tumours as well apart from hereditary breast carcinomas which show *BRCA1* mutations. TNBC tumours showed a significant loss of *BRCA1*, therefore highlighting the concept of BRCAness. These SBCs can therefore be benefited from PARP inhibitors and cisplatin based therapy as recommended in hereditary breast carcinomas. Hence, it is recommended that females with SBC, especially TNBC must be advised *BRCA1* IHC scoring to identify cases which may benefit from the above chemotherapy.

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***Conflicts of Interest*:** None.

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