ORIGINAL RESEARCH

BRCA1 expression in breast carcinoma and it's association with family history

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INTRODUCTION

Breast cancer is the second most common cancer overall and the most frequent cancer among women in the world. It is estimated that about 1.6 million new cases were diagnosed in 2012 and it constitutes 25% of all the cancers.[1] The incidental rates may vary in different region of the world ranging from 27 per 100,000 in middle Africa and Eastern Asia to 92 per 100,000 in northern America.[1] Breast cancer has ranked number one among Indian females with 25.8 per 100,000 women and stand mortality rate of 12.7 per 100,000 women. Breast carcinoma is more prevalent in cities than in the rural areas but the mortality rate is the reverse i.e. more among rural women[2]. Annual incidence is approximately 1,44,00 new cases of breast cancer in India and it is on rise at present.[3] According to National cancer institute, estimated new cases of breast cancer in 2017 are 2,52,710 which constitute 15% of all the cancers. Various new and innovative technologies are being incorporated for improving early detection and diagnosis of breast cancer, despite the advancement in technologies, the casual mechanism underlying the disease have yet to be fully elucidated; 85% of breast cancer cases occurs sporadically without any known genetic mechanism. So secondary prevention through screening offers an alternative that has been widely accepted.[4]

BRCA1 is one of the biomarker which has received many attention in breast cancer carcinogenesis. BRCA1 is located in chromosome 17q21.[5] It encodes a nuclear protein of 1863 amino acids[5] that regulates transcriptional activation, DNA repair, apoptosis, cell-cycle checkpoint control and chromosomal remodelling.[6] BRCA1 is a classical tumour suppressor gene.[7] The presence of inherited mutation of BRCA1 continues to be one of the best defined overall risk factors for the development of breast cancer, however, these familial mutations, together with familial BRCA2 mutations, occur in less than 10% of all diagnosed cases of breast cancer.[8,9.]

Several investigators have reported that BRCA1 protein expression is reduced or absent in familial and sporadic breast cancer by immunehistochemical analysis.[10,11] Mechanisms other than direct mutation of *BRCA1* gene, such as allelic loss or methylations of the BRCA1 promoter region[12] may be involved in its altered protein expression. Studies also suggest that reduced expression of BRCA1 and BRCA2 protein may play an important role in breast carcinogenesis in sporadic cases and the mechanisms other than mutation may be involved in the reduced expression of BRCA1 protein. Therefore, the present study has been designed to analyse BRCA1 protein expression in sporadic and familial breast cancer cases and correlate the expression of these proteins with family history.

MATERIAL AND METHODS

A observational Cross-Sectional study was conducted in department of Pathology and department of Surgery, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi with the approval of institutional ethical committee from September 2017 to march 2019. All the cases of breast carcinoma diagnosed clinically in department of surgery and confirmed on histopathology were included in the study. Benign tumour of breast, malignancies other than breast carcinoma (breast sarcoma/lymphoma) and metastatic tumour to the breast were excluded. Convenient sampling was used and the sample size of 50 cases was achieved. Relevant clinical details & investigations were taken as per proforma. The breast cancer specimens sent for routine histopathological diagnosis were evaluated for size of the tumor (in case of mastectomy or lumpectomy), histological typing of the tumor, histological grading of the tumor using Nottingham Modification of Bloom and Richardson grading system, BRCA1, Ki67, ER, PR, and Her2/neu by immunohistochemistry, immunohistochemical surrogate for molecular subtype of tumor (using immunohistochemical evaluation of ER, PR, Her2/neu and Ki-67). Data was analysed using the SPSS version 20 software. The statistical correlation among BRCA1, Ki67, ER, PR, and Her2/neu was determined by Chi-square test. P value ≤ 0.05 was considered statistically significant. Data were analysed using SPSS (Statistical Package for the Social Sciences) software version 21 (or latest version).

RESULTS

Figure1: Age distribution of the cases.

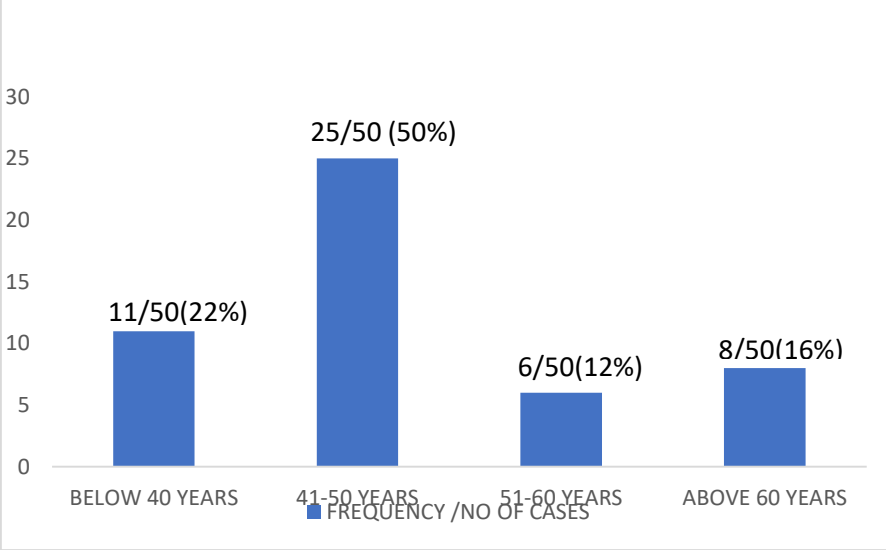

Figure1 shows age distribution of the cases. Majority of the participants were in the age group of 41-50 years (50%), followed by below 40 years (22%).

Figure 2: Showing frequency of cases according to modified BR scoring system.

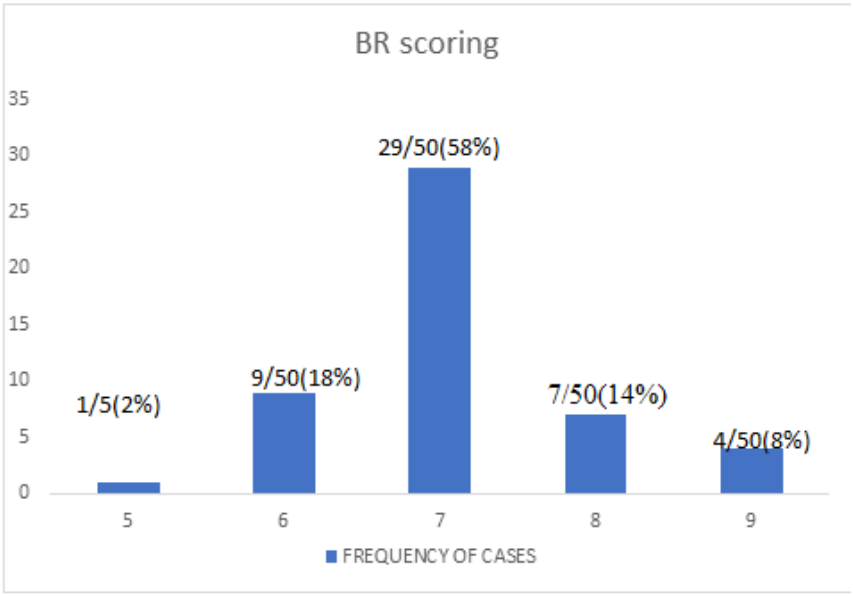

Figure 2 shows frequency of cases according to modified BR scoring system. Results showed that 29/50 that is 50% were falling in BR scoring 7, followed by 18% in Br scoring 6.

Figure 3: Showing frequency of patients with oestrogen receptor and progesterone receptor status.

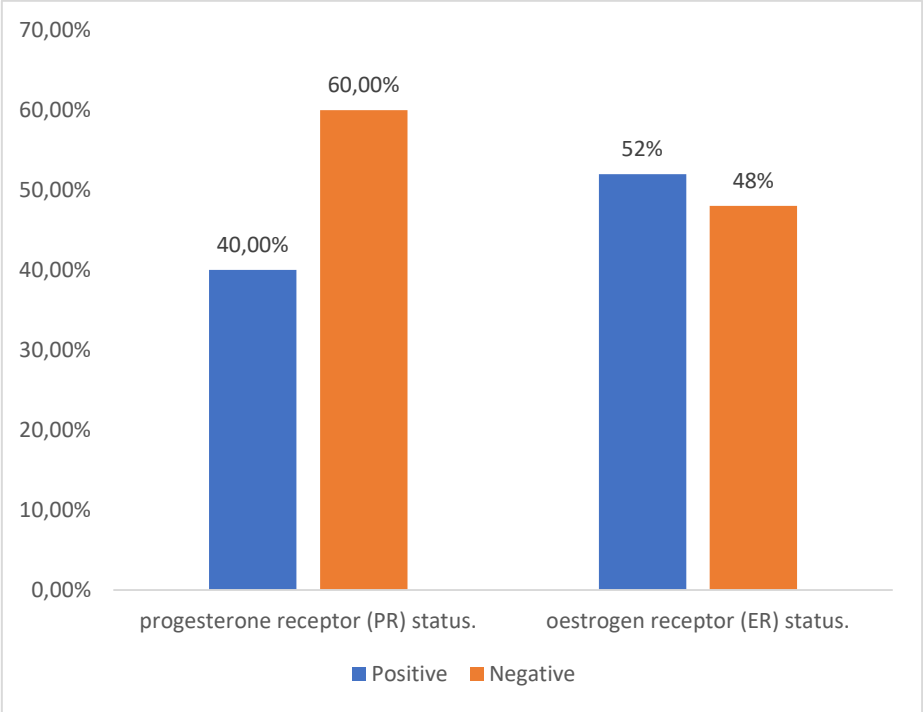

Figure 3 shows frequency of patients with oestrogen receptor and progesterone receptor status. 40% of the participants were positive for progesterone receptor status and 52% of the participants were positive for estrogen receptor status.

Figure 4: Frequency of cases with HER2neu status and Ki 67 status

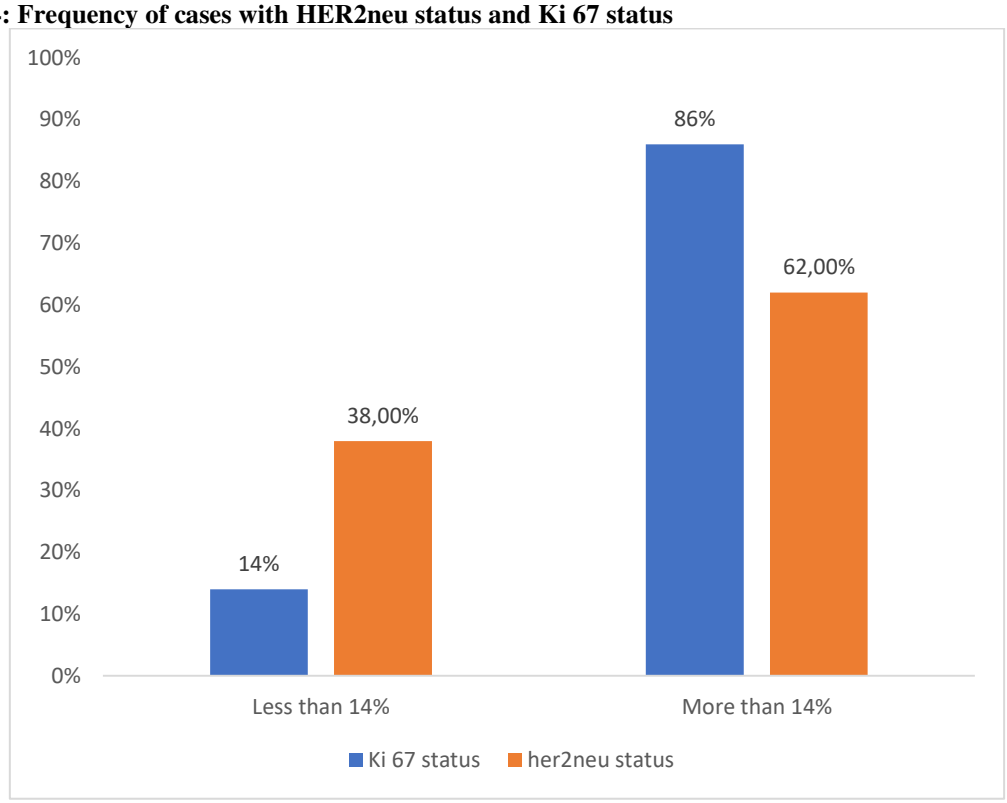

Figure 4 shows frequency of cases with HER2neu status and Ki 67 status. Results showed that 86% of the participants had more than 14% in Ki 67 status and 62% of the participants had more than 14% in HER2neu status.

Figure 5: Showing frequency of cases according to surrogate molecular classification.

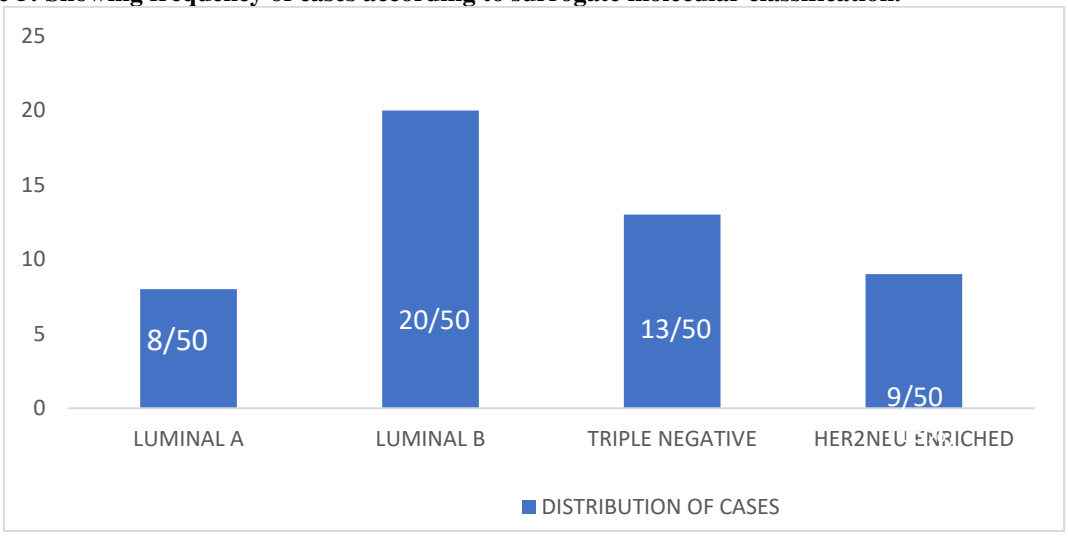

Figure 5 shows frequency of cases according to surrogate molecular classification. Results showed that majority of the participants (40%) had luminal B, followed by 26% had triple negative.

Figure 5: Showing distribution of cases according to BRCA1 status

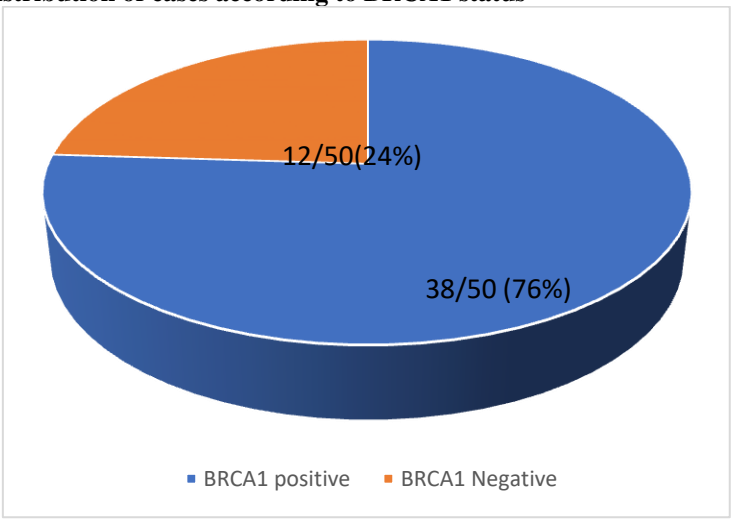

Figure 5 shows distribution of cases according to BRCA1 status. Result showed that 76% of the participants were BRCA 1 positive.

Table 1: Distribution of cases of BRCA1 status with modified BR grading.

	BRCA1 status	
	Negative	**Positive**
Grade I	1 (100.00%)	0 (0.00%)
II	5 (13.51%)	32 (86.49%)
III	6 (50.00%)	6 (50.00%)
Total	12 (24.00%)	38 (76.00%)

Table 1 shows distribution of cases of BRCA1 status with modified BR grading. Results showed that 86.49% of the participants had grade III, followed by 50% having grade III.

Table 2: Frequency of cases according to ER and BRCA1 status.

	BRCA1 status	
	Negative	**Positive**
ER Status Positive	3(11.54%)	23 (88.46%)

Negative	9 (37.50%)	15 (62.50%)
Total	12 (24.00%)	38 (76.00%)

Table 2 shows frequency of cases according to ER and BRCA1 status. Results showed that 88.46% of the participants were found to have both BRCA 1 status and ER status positive.

Table 3 shows distribution of cases according to PR status and BRCA1 status.

	BRCA1 status		Total	P value
	Negative	Positive		
PR Status				
Negative	10 (33.33%)	20 (66.67%)	30 (100.00%)	0.091
Positive	2 (10.00%)	18 (90.00%)	20 (100.00%)	
Total	12 (24.00%)	38 (76.00%)	50 (100.00%)	

Table 3 shows distribution of cases according to PR status and BRCA1 status .Results showed that there was no statistically significant association found across PR status and BRCA 1 status with p value =0.091.

Table 4: Distribution of cases according to HER2NEU and BRCA1 status.

	BRCA1 status	
	Negative	Positive
Her2neu Status		
Positive	8(42.11%)	11 (57.89%)
Negative	4(12.19%)	27 (87.10%)
Total	12 (24.00%)	38 (76.00%)

Table 4 shows distribution of cases according to HER2NEU and BRCA1 status. Results showed that 57.8% of the participants were positive for both HER2neu status and BRCA1 status.

DISCUSSION

There are variety of clinical and pathological factors which are routinely used to categorize patients with breast cancer in order to assess prognosis and determine the appropriate therapy including hormonal therapy. These include patient age, axillary lymph node status, tumour size, histological grade and lymphovascular invasion, hormone receptor status and HER2 status. Considering these factors in combination is of greater clinical value than viewing each in isolation, and the combined approach forms the basis of a number of schema used to group patients into various risk categories such as the St Gallen criteria, the NIH consensus criteria, the Nottingham Prognostic Index. Although these risk categories have been of great value for assessing prognosis in different groups of patients, their role in determining prognosis and evaluating risk in an individual patient with breast cancer is limited, as patients with similar combinations of features may have very different clinical outcomes. Better modalities, therefore are required to help assess prognosis and determine the most appropriate treatment for patients on an individual basis.

Recently many molecular techniques particularly gene expression profiling have been used for breast cancer classification and to redefined prognosis and response to various chemotherapy,

Radiotherapy and hormonal therapy. These new molecular diagnostic techniques have a major impact on the management of patients with breast cancer. This review focuses on the emerging role of molecular techniques in providing new insights into breast cancer classification and in assessing prognosis of patient with breast cancer.[13]

Luminal A subtype is the most common of all IHC subtypes and comprises mainly of low-grade carcinomas. Characterized by ER/PR positivity, it displays low proliferative index. It has the most favourable prognosis among all subtypes. Luminal B type shows high proliferative index (>14% as per St. Gallen's molecular classification)[14] which has been used to differentiate it from luminal A types. Prognosis is better than other subtypes but worse than luminal A. Basal-like cancers are called so because of the positivity for basal high molecular weight CKs and specific myoepithelial cells markers (CK5/6, CK17, Caveolin1, Calponin1, p63). They lack ER, PR, and Her2/neu expression (triple negative) while Ki-67 is high. They carry worst prognosis, being poorly differentiated and having higher chances of soft tissue and visceral relapse and central nervous system metastasis.[15] However, they are less likely to have lymphomatous spread. Her2/neu subtypes histologically corresponding to very aggressive high-grade ductal NOS carcinomas with poor prognosis but respond well to the humanized monoclonal antibodies against Her2/neu or Her2/neu tyrosine kinase inhibitors (trastuzumab). They are ER- and PR-negative tumours with a high Ki-67 positivity.[14]

Sathwara J et al. conducted a study on Indian population which shows a 5 years survival range of 42-48% among breast cancer patients, whereas a hospital based study across India shows a 5 years survival rates ranging from 40-45%.[14] A wide variety of factors are responsible for the low survival rates in breast cancer patients in India including patient factors such as Indian population present at a much higher stage of disease, tumour biology, and cancer treatment options, marital status and age at diagnosis including

lack of awareness of their disease, low education rates and because of their financial status.[14] Young patients have showed to have a better survival rates compared to older females (>35 years). It has been reported in various studies that low socioeconomic status and poor educational status are related to poor survival rates.[14] Indian population mostly present at a late stage (stage III and IV) compared to in developed countries like United States of America. Other factors like Axillary nodal status, age, tumour size, pathologic grade, and hormone receptor status have been established as prognostic factors in breast cancer.[15]

Our study showed that the mean age for Infiltrating ductal carcinoma case group was 47.82 years and the age range was from 28 to 70 years . A study conducted by Ambroise et al. in Indian population showed a mean age of 53.8 years (ranging from 24 to 99). We divided the age groups as the following: i) 20-29 ii) 30-39 iii) 40-49 iv) 50-59 and v) more 60 yrs and above. Most patients were in the 41 to 50 group. The most common surrogate molecular classification in our study group was luminal B (n=20) followed by triple negative (n=13), Her 2 neu (n=9) and luminal A (n=8). The majority of tumours were of grade II (74%) followed by grade III (24%) and only 1(2%) case in grade I which were comparative to a study conducted by Ambroise et al. in Indian population, where 57.3% patients were of grade II followed by grade III (33.3%).[16]

Morphologic classification, histologic grade, status of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2), along with tumor stage, are used to guide clinician for proper modern management including hormonal therapy. The routine immunohistochemical (IHC) analysis for ER, PR, and HER2 provides critical prognostic and predictive information. ER positive cases are eligible for antiestrogen therapy.[17] PR is largely regulated by estrogen, and PR negativity is associated with decreased response to tamoxifen therapy. About 12% to 20% of cases show HER2 gene amplification and/or protein overexpression, and are associated with poor prognosis and predictive of response to anti-HER2 targeted therapy.[18,19] Approximately 10% to 15% cases of breast cancer are ER, PR, and HER2 negative (triple-negative breast cancer), and these tumors currently lack any targeted therapy and they are likely to show poor prognosis.[20,21]

Perou and sorlie et al. used global gene expression profiling in early 2000s and identified 5 intrinsic subtypes of invasive breast cancers: luminal A, luminal B, normal breast-like, HER2-enriched, and basal-like subtypes. Each subtype is unique in incidence, survival, and response to therapy.[22]

In our study, we found negative expression of BRCA1(on IHC) showing significant correlation with family history of BRCA1 related cancers (breast cancer), (p value = 0.009). In our study population, family history of BRCA1 related cancers were present in 5 cases which constitutes 10% of all cases. All the cases had family history of BRCA1 related cancers (breast cancer)in one of their first degree relatives and it was statistically significant (p value = 0.009). Tazzite A et al. used a comparative cohort study on 570 women with diagnosed and treated cases of breast cancers to see relationship between family history of breast cancer and clinicopathological features in Moroccan patients and they found 18.4% of cases were showing family history of breast cancers in one of their first degree relatives.[117] Another population based study by Verkooijen HM et al. to see impact of familial risk factors on management and survival of early onset breast cancer: a population based study, where they studied 3709 women between 1990 to 2001. A total of 7% patients were reported with positive family history in one of their first degree relatives.[23]

In our study BRCA1 expression did not show statistical significant differences in age frequencies among the study populations (p value = 0.818). However the highest frequencies of the cases (40%) were in the age group of 40-50 years, result of which is similar to a study done by Ciernikova S et al. to show age and geographical distribution in families with BRCA1/BRCA2 Mutation in the Slovak Republic where the hereditary breast and ovarian cancer families were diagnosed within 5th decades of life.[24] Our study also did not show BRCA1 correlation with surrogate molecular classification(p=0.398), whoever it showed significant co-relation with modified bloom Richardson grading (p=0.007). In our study we could not correlate BRCA1 expression with histological type of breast carcinoma as all the cases included in the study were diagnosed with infiltrative duct carcinoma NOS.

The BRCA1 gene shows linkage disequilibrium, where all the breast cancers did not show negative/reduced expression on immunohistochemistry. This means that all the breast cancers did not show mutation in the BRCA1 gene. This particularly complicates the understanding of the role of BRCA1 genes, as the effects on tumorigenesis might be due to various other factors. As a whole, the mechanisms by which BRCA1 regulates the expression of tumor antigens are complex and requires more molecular studies on the subject for a better understanding of their role in tumorigenesis.

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