Original Article

BRCA 1 and 2 Mutations in Carcinoma Breast: An Indian Study

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Abstract

Background: Breast cancer is the most common cancer affecting women all over the world. In India, it is the second most common solid-organ malignancy after carcinoma cervix. Worldwide, approximately 5%–10% of the cases have been associated with various germline mutations. However, in India, studies correlating germline BRCA mutation with various clinicopathological variables are rare. In this study, we have tried to find out the difference in BRCA-mutated and BRCA-nonmutated patients. **Materials and Methods:** From May 2015 to May 2017, 50 patients with carcinoma breast were subjected to BRCA mutational studies by next-generation sequencing and further subdivided into BRCA-mutated and BRCA-nonmutated subgroups. Their clinical, pathological, characteristics were recorded and compared between two subgroups. They were followed up for a minimum of 9 months, and response to treatment was also recorded. **Results:** Out of 50 patients with carcinoma of the breast, only six patients were detected to be mutated and pathological mutations were detected in two (4%) patients only. All the BRCA-positive patients were female only. The most common age of presentation was >50 years while BRCA-positive patients presented earlier. Triple-negative breast cancer (TNBC) was the most common presentation and most patients presented in Stage III. **Conclusion:** Germline mutations in carcinoma breast can account for around 5%–10% of total breast cancers all over the world, but in our study, we have reported that 4% of the patients had BRCA mutations. BRCA-mutated carcinoma breast presents at younger age and more frequently with bilateral presentation as compared to BRCA-negative disease. BRCA-mutated carcinoma breast presents with more advanced disease and usually has a significant family history of either first- or second-degree relatives being affected. Overall TNBC status was more commonly found in both subsets of the patients. Overall BRCA-positive disease had more aggressive course of the illness as compared to BRCA-negative patients.

Keywords: *BRCA 1 and 2 mutations, carcinoma breast, germline mutations*

Introduction

In India, an average of 80,000 women are diagnosed with carcinoma of the breast, and 40,000 women die of this disease every year, and it is the second most common cancer among Indian women (19%) after cervical cancer (30%).[1]

Most women with breast or ovarian cancer have a sporadic rather than inherited cancer. About 10%–20% of women with breast cancer have one or more first-degree relatives who are also affected by breast cancer.[2,3] While only 5%–10% of unselected women with breast cancer have a hereditary form, up to 20% of women with a family history of breast cancer have a mutation in a major gene, most often in the breast cancer susceptibility genes 1 or 2 (BRCA1 or BRCA2; hereafter, BRCA).[3]

Most hereditary breast and ovarian cancers are due to highly penetrant germline BRCA mutations, which are inherited in an autosomal dominant fashion. In these patients, there are frequently several generations of women affected with breast cancer (often premenopausal) and in some families ovarian cancer as well. In addition, other BRCA-associated malignancies such as prostate, male breast, and pancreatic cancer may also be observed.

The clinical characteristics of women with breast cancer and germline BRCA mutations are illustrated by the Prospective Outcomes in Sporadic versus Hereditary Breast Cancer Study. That study analyzed 2733 women in the United Kingdom aged 40 years or less who were diagnosed with breast cancer from 2000 to 2008. Overall, 12.4% had a germline BRCA mutation, including 7.4% with a BRCA1 mutation and 5.4% with a BRCA2 mutation. There was no significant difference in overall survival at 2, 5,

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and 10 years when women with a BRCA mutation were compared with those who were BRCA mutation negative.[4]

Women with a germline BRCA1 mutation were more likely to have TNBC (TNBC) than those with a BRCA2 mutation or those who were BRCA mutation negative (61 versus 10 and 18%, respectively). Overall survival in women with TNBC and a germline BRCA mutation was slightly better than those without a BRCA mutation at 2 years, but there was no difference at 5 or 10 years. TNBCs were more likely in women with a germline BRCA1 mutation than those who had a BRCA2 mutation or were BRCA mutation negative.[5] The prevalence of germline BRCA mutations is markedly increased in women of Ashkenazi Jewish ethnicity, where the risk is estimated to be 30%–35%.[6]

The prevalence of BRCA mutations varies based on a number of factors, including type of cancer and age at diagnosis. For individuals whose ethnicity is associated with higher mutation frequency, particularly Ashkenazi Jews, any personal or family history of breast cancer is sufficient to warrant consideration of BRCA testing. Several founder mutations (i.e., particular BRCA mutations occurring among defined ethnic groups or individuals from a specific geographic area) have been observed. Aside from Ashkenazi Jews, founder mutations have also been reported worldwide in populations from the Netherlands, Sweden, Hungary, Iceland, Italy, France, South Africa, Pakistan, and Asia and among French Canadians, Hispanics, and African-Americans.[7,8]

Ashkenazi Jewish ancestry

In an unselected non-Jewish population in the United States, the chance of having any deleterious BRCA mutation is about 1 in 400. By comparison, in Ashkenazi Jews unselected for personal/family cancer history (from Central or Eastern Europe), roughly 1 in 40 individuals has one of three founder mutations: 185delAG (also known as 187delAG or c. 68_69delAG in BRCA1), 5382insC (also known as 5385insc or c. 5266dupC in BRCA1), or 6174delT (also known as c. 5946delT in BRCA2). These three mutations account for about 90% of mutations identified in this ethnic group. These particular BRCA mutations are not found exclusively in the Ashkenazi population; they have also been reported in individuals of non-Ashkenazi descent in Israel, Spain, Poland, and other countries in Central and Eastern Europe.[9-11]

Icelandic

A founder mutation in BRCA2, 999del5, is present in approximately 8% of female breast cancer cases, 40% of male breast cancer cases, and 6% of ovarian cancer cases in Iceland. It is present in 0.6% of the general Icelandic population. Another founder mutation in BRCA1, G5193A, has also been identified, but the prevalence of this mutation is very low.[12,13]

US Hispanic

Nine mutations account for 53% of the BRCA mutations identified in the Hispanic population in the United States, with the Ashkenazi Jewish founder mutation, 185delAG (187delAG), being the most common.[14]

Black American

Historically, the frequency of deleterious BRCA mutations in patients of African-American ancestry was reported to be low.[15]

BRCA1-related tumors typically occur in younger women and have more aggressive features, with high histological grade, high proliferative rate, aneuploidy, and absence of estrogen and progesterone receptors (ER and PR) and human epidermal growth factor receptor 2 (Her2Neu). This "triple-negative" phenotype of BRCA 1-related breast cancers is further characterized by a "basal-like" gene expression profile of cytokeratins 5/6, 14, and 17, epidermal growth factor, and p-cadherin.

Although BRCA 1 and 2 mutation-related carcinoma breast has been extensively studied in various populations, the frequency of BRCA 1 and 2 mutations in Indian scenario has not been extensively studied, and there is a paucity of data regarding this mutations. In this study, we tried to analyze the clinical association and frequency of BRCA 1 and 2 mutations in Indian patients.

Aim and objectives

Aim

To study the incidence and clinical profile of patients with BRCA 1 and 2 mutations in carcinoma breast and its comparison with patients without mutation.

Objectives

To study:

a. Patient profile
b. Response to treatment in patients with and without BRCA mutation
c. Progression-free survival.

Inclusion criteria

Patient meeting one or more of the following criteria were included in the study:

1. Known mutation in cancer susceptibility gene within the family
2. Any patient with male breast cancer
3. Personal history of breast cancer with one or more of following
   a. If diagnosed at <45 years of age
   b. If diagnosed at <50 years of age with
      - Additional breast cancer primary
      - One or more any degree of blood relative with breast cancer at any age

- One or more relative with prostate cancer (Gleason score >7)
- One or more close relative with pancreatic cancer
- Unknown or limited family history

c. If diagnosed at <60 years of age with TNBC

d. Diagnosed at any age with:

- One or more close blood relative with breast cancer diagnosed at <50 years
- Two or more close blood relative with breast cancer at any age
- One or more close blood relative with invasive ovarian cancer
- Close male blood relative breast cancer.

Exclusion criteria

All those patients not fulfilling the inclusion criteria will not be a part of the study.

Materials and Methods

Fifty patients of breast cancer were included in our study as per inclusion criteria. All were followed up for 24 months duration at 3, 6, 9, months after treatment and were assessed as per the RECIST criteria (ver 1.1).

A detailed history in terms of onset, age of presentation, age of menarche and menopause, symptomatology, oral contraceptive pill use, number of childbirth, and relevant clinical examination was done for each patient.

They were subjected to BRCA 1 and 2 mutational analysis by next-generation sequence analysis (whole exome sequencing) of the peripheral blood after due genetic counseling and after due informed consent of the patient.

Patients were divided into two groups, i.e., patient having BRCA 1 and 2 mutation and patients without mutation. For both the groups, they were provided treatment as per the existent guidelines and were followed up as per the interval mentioned above.

Institutional review board has cleared this study, and also, this study was cleared by the Institutional Ethical Committee.

Results

Out of total 50 patients, 46 (92%) were female and 4 (8%) were male. BRCA-mutational studies were done in all the patients, and it was detected in 6 (12%) patients. Of these six patients, pathological mutations were detected in two (4%) patients only. All the BRCA-positive patients were female only. BRCA1 mutations were more common as compared to BRCA2 mutations, and both the pathological mutations noted were of BRCA1: c. 140G>A type [Table 1].

The most common age of presentation was >50 years (28 out of 46, i.e., 60.8%), while 6.5% (3 out of 46) were in the young age group, and the rest were in the age range of 30–50 years. Among the male patients, all were in the age group of >50 years [Figure 1].

Four patients had bilateral breast involvement (8%). None of the male patients had bilateral disease. Three out of all BRCA-positive (50%) patients had bilateral disease, while rest of the 50% of the patients had unilateral disease. Both the patients with pathological mutations had bilateral disease [Table 2].

All patients with bilateral disease were in the age range of 30–50 years. All were nonmetastatic. Two of the patients were TNBC; rest were hormonal receptor positive. None was Her2Neu positive. All of these patients were presented in nonmetastatic stage (Stage I – nil, Stage II – 1, Stage III – 3, and Stage IV – nil). Out of all, only three had BRCA1 mutations detected with two of them being pathological mutation.

Most of the patients presented in Stage III (19 out of 50; 38%), while the second most common presentation was in Stage II (32%). In our study, only four out of 50 (8%) patients were detected in Stage I. Rest of the patients presented with upfront metastatic disease (11 out of 50 patients; 22%).

For males, the most common stage of presentation was Stage II (75%) while the rest (25%) presented in Stage III. None of the male patients presented with Stage I or Stage IV. Comparatively, for females, 18 out of 46 (39.1%) patients presented in Stage III while the second most common was Stage II (13 out of 46: 28.2%). Ten out of 46 (21.7%) females also presented with upfront metastatic disease. Hence, male patients comparatively presented at earlier stage and none had presented with metastatic disease.

Fifty percent of the BRCA-positive patients presented in Stage III were most common similar to BRCA negative.

Table 1: Types of BRCA mutations of carcinoma breast

Mutations detected	Pathogenic or benign	Number of patients
BRCA1: c.140G>A	Pathogenic	2
BRCA1: c.3548A>G	Benign	2
BRCA1:c.2612C>T	Benign	1
BRCA2: c.2971A>G	Benign	1

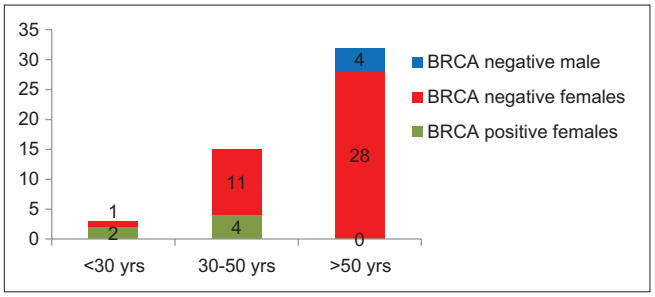

Figure 1: Age- and sex-wise distribution in carcinoma breast

Table 2: Various characteristics studied

Characteristics	BRCA-positive females	BRCA-negative females	BRCA-negative males	Total number of patients
Side of breast affected				
Left	2	19	1	22
Right	1	20	3	24
Bilateral	3	1	0	4
Family history				
First degree	2	5	1	8
Second degree	3	3	0	6
Stage				
Stage I (including IA and IB)	0	4	0	4
Stage II (including IIA and IIB)	2	11	3	16
Stage III (including IIIA-IIIC)	3	15	1	19
Stage IV	1	10	0	11

Table 3: Sites of metastasis in carcinoma breast

Sites of metastasis	Number of patients
Skeletal	7
Liver	5
Lung	4
Brain	5
Skin nodules	2
Others	3

Only one patient had presented with metastatic disease. Out of the two patients with pathological mutation, one presented in Stage III while the other in Stage IV [Table 3].

Eleven patients presented with metastatic disease out of total 50 patients (22%). In our study, we found that the most patients had multi-organ disease with seven patients having two or more than two organ system involvement. The most common site of metastasis was skeletal (7 out of 11 patients with metastatic disease; 63.6%) and the next common site of involvement was liver (5 out of 11 patients; 45.4%). Few rare sites of metastasis were also reported such as kidney, Krukenberg tumor, and adrenals. None of the male patient presented with Stage IV. Only one patient with pathological BRCA mutation had presented with multiple metastasis [Table 3].

BRCA-positive patients also presented with complaints of lump in the breast (100%), pain and discharge being the second most common presentation, which was similar to BRCA-negative patients. Patients with pathological mutation presented with metastatic disease had bony pain and hepatomegaly [Table 4].

Detailed history was taken from all the patients about their family history, and overall 13 patients gave a significant family history (26%). While there were few patients who could not give the exact details of their family tree, however, out of the 13 patients with positive family history, eight had history of first-degree relative being affected (61.5%) while six had history of second-degree relative being affected including one having both first- and second-degree relatives being affected.

Out of four male patients, one (25%) had a significant history of first-degree relative being affected, while in female patients, 12 (26%) gave positive family history.

Among BRCA-positive patients, five out of six (66.67%) patients gave positive family history. Both the patients with pathological mutations had positive family history of first-degree relative being affected. Comparatively, BRCA-positive patients had more chances of having significant family history [Table 3].

Out of the patients with positive family history, it was detected that among the first-degree relative, history of being affected by carcinoma of the breast was most common (4 out of 8; 50%). Other common afflictions were carcinoma of the ovary, stomach, and prostate.

Overall, the most common hormonal status detected was TNBC. Out of the 50 patients, 22 were detected to have TNBC status (44%). The second most common presentation was "triple positive" (ER+/PR+/Her2Neu3+) which was detected in 13 patients (26%), while the least common presentation was ER+/PR+/Her2Neu− (14%).

Out of all male patients, 100% were hormonal receptor positive (irrespective of Her2Neu status) as compared to females where the TNBC was the most common presentation (22 out of 46; 47.8%). Hormonal receptor-positive (irrespective of Her2Neu) status was detected in 16 out of 46 females (34.7%). Her2Neu3+ was seen in 25% of male patients as compared to 43.4% (20 out of 46) of female patients.

In both BRCApositive and negative patients triple negative breast cancer was the most common presentation (83.34% & 42.5% respectively). Only one patient was detected to be hormonal receptor positive (16.67%) as compared to 37.5% of BRCA-negative patients (15 out 40). None of the BRCA-positive patients were Her2Neu positive as compared to 43.4% of BRCA-negative patients [Figure 2].

Hormonal receptor and Her2Neu status were also assessed as per the stage of the disease. For Stage I,

the most common presentation was TNBC with almost 50% of the patients being TNBC (2 out of 4). In Stage II, the most common presentation was triple positive (7 out of 16; 43.7%) while the TNBC was second most common (31.2%). Out of the 19 patients who presented in Stage III, 10 were TNBC (52.6%) being the most common while ER−/PR−/Her2Neu3 + being the second most common. Most of the patients with metastatic disease were also triple negative (5 out of 11; 45.4%) [Table 5].

In our study, we had an overall mortality of three patients out of 50 (6%). All were females with the age of all being >50 years, initial stage of the patients were one in Stage III, and other two were upfront metastatic disease. Two of the patients were TNBC while the other was ER−/PR−/Her2Neu3+. Out of three patients, one was BRCA positive (Stage IV, TNBC) while rest of the two were BRCA negative.

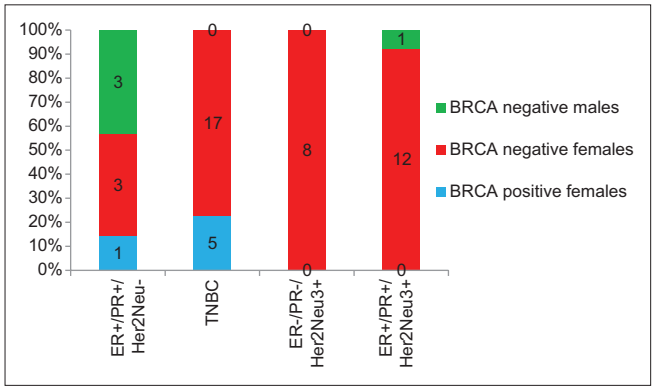

Figure 2: Hormonal receptor and human epidermal growth factor receptor 2 Neu status in carcinoma breast

Discussion

In this study, we have tried to detect the prevalence of germline BRCA 1 and 2 mutations and also analyze the differences between two subsets of Indian population, i.e., BRCA-positive and BRCA-negative patients.

This study is unique in Indian scenario in the sense that we have tried to correlate the differences in these two subsets of populations which as per the western and most of the world literature behaves very differently.

Almost a third of all breast cancer patients are believed to have familial disease pattern, and some 5% are believed to be hereditary, with the BRCA 1 and 2 gene mutations having been identified as the major genetic causes. In an Indian study on 226 breast cancer patients, 20.7% had a positive family history.[16]

Genetic screening/diagnosis is not routinely performed in most Indian center due to paucity of funds and facilities. As a result, there are scarce data on the genetic composition and BRCA 1/2 mutations in Indian patients. The available studies hint at a rather low incidence of BRCA mutations. In most populations, 6%–10% of patients with breast cancer have mutation in BRCA gene, irrespective of their family history. Although there are no robust figures, various Indian studies have reported BRCA mutations in 9%–25% of familial breast cancer cases.[17-21]

Table 4: Various clinical manifestations in carcinoma breast

Clinical manifestations	BRCA-positive females	BRCA-negative females	BRCA-negative males	Total
Lump in the breast	6	38	4	48
Pain	2	5	1	9
Skin ulceration	0	5	0	5
Bloody discharge	0	3	0	3
Nonbloody discharge	2	3	1	6
Bony pain	1	2	0	3
Axillary swelling	1	0	1	2
CNS manifestations (seizure, altered sensorium, etc.)	0	4	0	4
Hepatomegaly	1	2	0	3
Weight loss	0	1	1	2

CNS: Central nervous system

Table 5: Stage-wise distribution of hormonal receptor status in carcinoma breast

Stage	Total patients	ER+/PR+/Her2 Neu−	TNBC	ER−/PR−/Her2 Neu 3+	ER+/PR+/Her2 Neu 3+
Stage I (including IA and IB)	4	1	2	-	1
Stage II (including IIA and IIB)	16	1	5	3	7
Stage III (including IIIA, IIIB and IIIC)	19	3	10	4	2
Stage IV	11	2	5	1	3
Total	50	7	22	8	13

TNBC: Triple-negative breast cancer, ER: Estrogen receptor, PR: Progesterone receptor, Her2: Human epidermal growth factor receptor 2

Kumar *et al*. were the first one to study the germline BRCA1 mutation analysis in familial breast cancer in India. They examined the coding sequence of the BRCA1 gene in 14 breast cancer patients with a positive family history of breast and/or ovarian cancer. Their data from 14 different families suggest a lower prevalence of germline mutations in the BRCA1 gene among Indian women with family history of breast cancer.[18]

Singh *et al*. evaluated 381 women diagnosed with breast cancer and further categorized into three groups according to the family history. They detected that the mean age of onset for 381 women was 47.50 ± 10.407 years. Approximately 33.1% of cases were diagnosed under the age of 40 years. Out of the 381 cases, 33 (9%) belonged to first-degree relative and 18 (5%) were second-degree relative of breast cancer patient. They also screened for alterations in the coding sequences of BRCA 1 gene in 381 breast cancer patients. There were 18 (4.7%) patients having BRCA1 gene mutation. When they compared BRCA1 gene mutation with family history, BRCA1 showed a significant association. BRCA1 mutation was more frequently observed in tumor sample obtained from women who were ≤40 years of age. Mutations noted in patients <40 years and >40 years were 11.9% out of the 126 cases and 1.2% of the 255 cases respectively. Multivariate analysis suggested that there was a strong significant association of mutation and age at diagnosis, i.e., patients aged ≤40 years have more higher incidence than the patients aged >40 years (odds ratio [OR] = 11.244, 95% confidence interval [CI] = 1.227–103.062). BRCA1 mutation that was found most frequently with family history was to be found independently associated with metastatic presentation. The increased frequency of metastatic presentation persisted on multinomial logistic regression analysis, suggesting an independent association between BRCA1 mutation (OR = 6.567, 95% CI = 1.073–40.174). BRCA1 mutation was negatively correlated with ER, PR, and HER-2 with the significant level of $P = 0.051$, $P = 0.074$, $P = 0.028$, respectively. They concluded that self-risk information could assist in taking preventive measures and could also induce a high-risk woman to adopt breast screening that may promote early detection and improve chances of surviving breast cancer.[22]

Vaidyanathan *et al*. explored the contribution of BRCA 1 and 2 mutations in the development of hereditary breast cancer among 61 breast or ovarian cancer patients from South Indian women. Mutations were identified in 17 patients (28.0%); 15 (24.6%) had BRCA1 mutations and two (3.28%) had BRCA2 mutations. While no specific association between BRCA1 or BRCA2 mutations with cancer type was seen, mutations were more often seen in families with ovarian cancer. While 40% (4/10) and 30.8% (4/12) of families with ovarian or breast and ovarian cancer had mutations, only 23.1% (9/39) of families with breast cancer carried mutations in the BRCA 1 and 2 genes. In addition, while BRCA1 mutations were found in all age groups, BRCA2 mutations were found only in the age group of ≤40 years. Their study emphasized the importance of mutation screening in familial breast and/or ovarian cancers and the potential implications of these findings in genetic counseling and preventive therapy.[23]

Nonetheless, a United States study concluded that the prevalence of BRCA mutations was similar across diverse ethnicities after complete sequencing of BRCA genes among female patients of various ethnicities who were tested at Myriad Genetic Laboratories, Inc. (Myriad; Salt Lake City, USA). The study analyzed 1183 Asian females, which accounted for 2.6% of the study population. Among the Asian patients, 12.7% had BRCA 1/2 mutation. The mutation frequencies of BRCA 1/2 genes in Western European, Latin American, African, and Middle Eastern females were 12.1%, 14.8%, 15.6%, and 9.4%, respectively.[24-28]

Conclusion

Breast cancer is the second most common cancer in India, and world over, around 5%–10% of the cases are due to germline mutations, but for India, we do not know the exact figures due to heterogeneous population. BRCA-mutated carcinoma breast presents at younger age and more frequently with bilateral presentation as compared to BRCA-negative disease. They present with more advanced disease and usually have significant family history of either first or second degree relatives being affected. Overall TNBC status was more commonly found in both subsets of the patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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