Review Article

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BRCA MUTATIONS LEADING BREAST CANCER IN INDIAN WOMEN

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ABSTRACT

Breast cancer is the most threatening cancer all over the world as well as in India. One of the major risk factors of breast cancer development is BRCA mutation, which prevalence is more in India in comparison to worldwide. BRCA gene mutation is mainly responsible for familial breast cancer cases. BRCA mutation could be caused by the deleted mutation missense mutation, frameshift mutation, which in result leads to stop codon and truncated protein synthesis, these alterations could be with exon or intron of gene or both. Because of alteration in BRCA gene, BRCA proteins lose their function which ultimately leads to breast cancer. In this review, we discussed the effect of BRCA gene mutation in breast cancer with different regions of the Indian population.

KEYWORDS: BRCA mutations, breast cancer, Familial breast cancer, BRCA proteins, Indian women breast cancer.

INTRODUCTION

According to International Agency for Research on Cancer Globocon 2018 report breast cancer is the second most threatening cancer with an average cumulative risk of 5.03, which is the highest cumulative risk of incidence than any other cancer worldwide. On the global breast cancer incidence were 2,088,849 (11.6%) and mortality number 626,679 (6.6%). With mortality cumulative risk of 1.41, it is the second most deaths occurring cancer after lung cancer (1). In the scenario of India, breast cancer is leading cancer with the highest incidence and mortality cumulative risk, respectively, 2.70 and, 1.52. The total mortality number was 87090 against the total incidence number 162468 (2). Now taking consideration of the above-mentioned data, we can understandably say that breast cancer is the most vulnerable and dangerous cancer worldwide as well as India.

In the induction and progression of cancer, genetic and environmental factor play a very important role, as especially in the case of breast cancer family genetic history became the most major risk factor. The risk depends on the number of relatives afflicted by breast or ovarian cancer, the degree of connection to these relatives, and their age at disease diagnosis (3). In general breast cancer normally occurred as sporadic, but 10-20% breast cancer cases reported in women with a familial breast cancer history. In most cases of the family history breast cancer mutations were mainly reported in *BRCA1* (breast cancer susceptibility gene 1) and *BRCA2* (breast cancer susceptibility gene 2) (4). The proteins BRCA1 and BRCA2 play an important role in maintaining genetic integrity through concise and consistent DNA repair through homologous recombination. The functional loss of BRCA proteins leads to the genomic instability that consequently converts the normal cell into tumorous cells (5).

BRCA Mutation in Indian population-

North India-In India first BRCA1 and BRCA2 gene mutations were identified by Saxena et al. 2002, this study included 20 samples from Indian breast cancer, clinical trials referred to as the Department of Cancer Surgery in 1997–1998 at Safdarjang Hospital, New Delhi. In this study 6 gene modifications of BRCA1 or BRCA2 mutations were found in 5 familial breast cancer women out of which, two novel splice variants were recognized in BRCA1 (331 + 1G>T; 4476 + 2T > C). In the BRCA2 gene, more than one person was identified with the missense mutation, which showed the particular-population polymorphisms (6). A similar study with BRCA1 was followed in the same year at the Institute of Rotary Cancer Hospital affiliated to the All-India Institute of Medical Sciences, New Delhi. In that research 90 cases were registered for the analysis of BRCA1 gene mutations, in which 30 were the family breast cancer history and 10 sporadic breast cancers with 50 normal control cases. Eight-point variation in nucleotide was recognized by PCR mediated mutagenesis and SSCP analysis. On exon 11(E1250X)and 20(E1754X), two deleterious mutations were found which lead to the protein truncation and non-sense mutation and 6 newly amino acid modification (F1734S, D1739Y, V1741G, Q1747H, P1749A, R1753K) identified.

Such complex gene changes occur only in breast cancer families' history cases, but not in the female of control populations. Only three splice-site alterations and two intronic mutations were observed (7). Valarmathi et al. did a study with 20 sporadic breast cancer patients with 69 normal females as control. There were 21 sequence variations, including 15-point mutations. In exon 2 (c.187 188delAG); exon 11 (c.3672G > T) [p. Glu1185X] 5 deleterious pathogenic, protein-truncating frameshift and non-sense mutations were discovered of BRCA1 and in BRCA2 exon 11 (c.5227dupT, c.5242dupT, c.6180dupA) 4 newly putative mutation recognized with fourteen amino acid substitutions (8). A report published by Hedau et.al. 2004, in 124 untreated breast cancer women in which 100 sporadic and 24 familial cases were registered. In the 100 cases for sporadic breast cancer studied, in SSCP activity were shown variations only exon 2 of BRCA1 as well as BRCA2 in 6 patients, 2 (2%) in BRCA1 and 4 (4%) in BRCA2, and only exon 5 of p53 gene in 3 cases. Out of 24 familial breast cancer patients, 6 were reported for the variation in the BRCA1 gene with four protein truncation and at exon 7 two missense amino acid substitution found. Whereas BRCA2 and p53 have no variation in gene with familial breast cancer cases (9). In a cohort study done by Saxena et al. 2006 on 204 breast cancer north Indian women with 140 age match control to investigate the role of *BRCA1* and *BRCA2* germline mutations and polymorphism in familial heredity. BRCA1 and BRCA2 genes analyzed by direct sequencing of detecting variants with heteroduplex analysis for the germline mutation and polymorphism.Changes in the BRCA1/2 sequence were identified in 14.2% early-onset patients with no breast cancer family history and 11.7% in genealogy breast cancer cases (10). The study was conducted to explore sequence alterations in the BRCA2 gene in the ethnically pure Kashmiri population in a case-control fashion by utilizing PCR. BRCA2 sequence mutational analysis discovered five sequence variations, four in exon 11 and only on exon 2 UTR. The somatic mutation leads to the missense mutation at codon 991 and silent mutation at 1131, no polymorphism was found, whereas at codon 846 and 868 represent to had heterozygous polymorphism (11). In a study conducted on 381 individuals, diagnosed with breast cancer to discover the role of BRCA1 Gene's mutation of Exon 11. BRCA1 mutations were observed in 4.7% (18/381) cases and 12 sequence alterations identified with 11 novels mutation in exon 11 of the BRCA1 gene. Mutations of BRCA1 genes were often considerably linked to family history and was strongly connected to the metastatic presentation, younger age, and negatively to the ER / PR / HER2 (12). Between May 2015 and May 2017, 50 breast cancer patients are subdivided into sub-groups of BRCA-mutated and BRCA-non-mutated sequences by next-generation sequencing. Just 6 individuals were diagnosed in 50 patients with breast carcinoma mutation and two (4%) patients had pathological alteration observed. The most common age at which BRCA-positive patients had been identified was > 50 years. The most common and most cases diagnosed in phase III were triple-negative breast cancer (TNBC). Germline breast mutations can constitute about 5%–10% of total worldwide breast cancers but in this research, only 4% of patients with BRCA mutations were identified (13). A total of 206 breast and ovarian cancer patients were screened for BRCA1/2 germline mutation in north India with the National Comprehensive Cancer Network (NCCN) guidelines for genetic testing. Out of 206 patients, 45 had BRCA1 mutation and 17 BRCA2 mutations, whereas 1 had both mutations. 5 newly identified mutation with BRCA gene were c.541G>T, c.1681delT, c.2295delG, c.4915C>T and exon 23 deletion and 7 mutations (c.2214 2215insT, c.2295delG, c.3607C > T, c.4158 4162delCTCC, c.4571C > A, splice-site 3 (C > T) and exon 21–23 duplication) observed multiple times, whereas 16 different BRCA2 mutations were identified -9 were lethal (6 frame-shifts, 2 nonsense and 1 significant deletion) and 7 VUS.A single pathogenic BRCA2 (c.932 933insT) mutation was described. Two mutations have been identified (c.9976A > T and c.10089A > G) twice; no major hormone receptor variation was found in the status of BRCA1, BRCA2, and non-carrier transporters (14). The number of cases with pathogenic variants in the genes of BRCA1 and BRCA2 was 20.4% of the 49 cases tested in the cohort study of 51 cancer-predisposing genes. The number of cases with only BRCA1 models was 12.2%, whereas the case with only BRCA2 mutation was 8.2% and with BRCA1/2 8.2%, unknown significance (VUS) was also observed. The frequency of cases without pathogenic variations of BRCA1/2 has been detected at 51%. In these cases, the sensitivity to the spontaneous occurrence of other cancers can still be ruled out of the possibility of hereditary breast and ovarian cancer syndrome (15). To evaluate the level of BRCA1 and BRCA2 protein in sporadic breast cancer 40 patients by immunohistochemistry (IHC) were studied. Most patients have shown only reduced or undetectable amount of BRCA1 protein expression in breast cancer tissue in stage 3 with comparison to control had more pronounce expression of BRCA1. While in BRCA2 protein had no difference in breast

cancer tissue as well as in control tissue. But BRCA2 shown an increasing amount of protein level in those patients which had very low BRCA1 expression and it is more common in postmenopausal patients (16).

South India- Rajkumar et al. 2003 for the first time with the use of Denaturing High-Performance Liquid Chromatography (DHPLC) for the mutational analysis of BRCA1, BRCA2, and CHEK2 (1100delC) in India. With the familial history of breast cancer, 22 patients were selected in the study out of which 3 detected for the deletion and nonsense mutation turns the result in to stop codon and lead to developing the truncated protein. two of these patients had BRCA1 and one get the BRCA2 gene mutation. In BRCA1 their one had a novel five base nucleotide deletion. No CHEK2 (1100delC) mutation was observed in this study (17). BRCA1 mutations were tested by conformation sensitive gel electrophoresis (CSGE) followed by sequencing in a sample of 23 Tamil Nadu (South India) patients with family history of breast cancer and ovarian cancer. A novel 1307delT mutation of BRCA1 in exon 11 in a 43-year-old Indian woman with breast-cancer is discovered. This mutation leads to a premature stop codon of amino acid residue 409 as well as a new DdeI restriction site. In an expanded study of the population, a similar mutation was also observed in the maternal uncle and son. The 1307delT is a novel mutation and it is not reported in any population or study (18). A similar study conducts with south Indian women by Vaidyanathan et. al. 2009, 61 patients of familial breast and ovarian cancer were selected for the analysis of germline mutation in *BRCA1* and *BRCA2* gene, reported the prevalence 24.60% and 3.28% respectively. On BRCA1 3 novel mutation (295delCA; 4213T→A; 5267T→G) were discovered and 3 previously known mutations were identified. While on the BRCA2 gene, one novel mutation (4866insT) discovered and one previous mutation reported (19). Study to assess 185delAG mutation BRCA1 on exon 2 in South Indian women with breast cancer carried with 200 total number of samples. The 185delAG deletion was identified in 1/200 patients with a rate of 0.5%. With family cases 1/29, it is 1/5 (20%) with traditional breast cancer history that multiple relatives are affected throughout the group (20).

East India-The BRCA1 protein had been truncated by the development of individual stop codon in the amino acid positions 39, 303, and 1265 these abnormalities reported by an examination of 185DelAG, 1014DelGT and 3889DelAG mutation of exons 2 and 11 in North-West India patients (21). To evaluate the possible incidence of 185delAG (BRCA1) and 6174delT (BRCA2) mutation in Eastern Indian breast cancer patients, 231 breast cancer women were selected by histologically. Out of 231 breast cancer patients, 130 had familial breast cancer history whereas 101 without any familial history of breast cancer. In the molecular analysis of BRCA1 and BRCA2, the mutations 185deIAG and 6174deIT respectively not detected in any patients (22). BRCA1 and 2 sequence analysis NGS were completed and 13/24 cases (54%) were detected in sequence variation, 69% (9/13 cases) in gene BRCA1, and 4/13 cases in gene BRCA2 were identified. In 7 patients, seven previously reported pathogenic mutations of BRCA1 were identified. Only one known pathogenic mutation was reported in exon 20 of BRCA2. Five variations of unknown significance (VUSs) were reported, two in the BRCA1 gene, and three in BRCA2 genes (23).

Northwest India-To examines the relationship Expression of vascular endothelial growth factor in BRCA1-related breast cancer, 50 cases of breast cancer samples were examined for histopathological examination with immunohistochemistry of BRCA1 and HIF1αVEGF. The immunohistochemical result shown that 27 cases have increased expression of BRCA1in 2, HIF1α in 39 patients, and VEGF rose in 21 cases. Out of 27 cases of BRCA1 25 cases had also increased the level of HIF-1α whereas VEGF shown with 16 cases. Their research indicated that BRCA1 correlated with the increased expression of HIF1α and VEGF (24).

Across the India-Over 1000 breast cancer were screened for the mutation multi-gene panel for breast cancer and ovarian cancer, including BRCA1 and BRCA2. Out of 1010 cases, 304 cases were identified with mutation and 56 new alterations in the gene were detected. A large number (84.9%) of genetic variations were reported in BRCA1/2 genes in comparison to non-BRCA genes (15.1%).In patients whose diagnosis age was lower than 40 and family members with breast and/or ovarian cancer had a high rate of mutation above 75%. These results have shown that genetic variations in the large-risk breast cancer genes BRCA1/2, TP53, and PALB2 in the Indian women become high (25).

Gene	Exon/Intron	Mutation	Reference
BRCA1	Exon 1	22 C>G	10
	Exon 2	c.187_188delAG, T131G, A128G, 185delAG, 185 delAG, 147 G>A, 186 G>A, c.68_69delAG	8,9,10,12,14,19,19,22

Table 1: A list of BRCA Mutation in Indian Breast Cancer Patients

	Exon 5	295delCA	19
	Exon 7	A448C[a,c], T459C[a,c], 465 G>A, 448 A>C, 459 T>C, c.541G>T	9,10,14
	Exon 10	c.2214_2215insT, c.2269delG, c.2295delG, c.2362delG, c.3328-3330delAAG, c.3607C T, c.4041_4042delAG,c.2426A>G, c.1504_1508del	14,22
	Exon 11	3867G>T , c.3672G>T, 1027 delA, 3596 del4, 3667A>G, 3672 G>T, 3679 G>T, 3730 G>T, 3740 G>C, 3769C>A, 3867 G>T, 3797 C>G, 3846 A>G, 4184del4,c.4108delT, c.4158_4162delCTCTC, 1307delT, 2983C→A, 4213delT, 3450delCAAG	7,8,10,14,18,19
	Exon 11 A	1230 del C, 1238 del A, 1273 ins G, 1415 ins A, 1611 del C, 1614 ins C,	12
	Exon 11 B	2025 ins C, 2361 ins C, 1961 del G, 2354 A to C, 2354 A to C	12
	Exon 12	C4302T, 4302 C>T, c.4328G>A, 1386 delCTCTC, c.4224_4231del, c.4286A>G, c.1504_1508del	9,10,14,17,23
	Exon 13	T4427C, CGATGA	9,17
	Exon 15	c.4571C>A, Splicesite_3 (G>T)	14
	Exon 16	4956insG[a,b], 4956 A>G, 5075 G>A, 4956 insG,	9,10
	Exon 17	5119 A>G, 5154 C>T , Splicesite_3 (C>T)	10, 14
	Exon 18	5267T→G	19
	Exon 20	[5341T>G;5364C>G],[5341T>G;5379G>T],[5341T>G; 5379G>T],[5341T>G;5379G>T], 5319T>C,5339G>T, [5341T>G;5364C>G], 5360A>C, 5377G>A, 5341 T>G, 5364 C>G, 5379 G>T,	7, 10,
	Exon 21	c.5278-1 G>T	14
	Exon 21-23	Duplication (exons 21–23)	14
	Exon 23	Deletion (exon 23), c.5465G>A	14
	Exon 24	Deletion (exon 24)	14
	Intron 5	331+1G>T,	6
	Intron 7	561-34T>C	9
	Intron 13	4476+2T>C	6
	Intron 14	(g.50962G>A) (IVS14-1 G>A)	23
	Intron 16	c.5074+1G>A	23

Cont. Table 1: A list of BRCA Mutation in Indian Breast Cancer Patients

	Intron 18	5271+66G>A,	9
	IVS-5	331+1 G>T	10
	IVS-7	560+38 T>C, 561-34 C>T	10
	IVS-10	790-12 delG	10
	IVS-13	4476+2T>C	10
	IVS-18	18 5271+66A>G	10
BRCA2	Exon 2	G292C, C282G, G203A, 203 G>A, G:C>A:T	9, 10,11
	Exon 2 5' UTR	G203A	9
	Exon 10	1593A>G, c.932_933insT, c.950_951insA, c.1792A>G	10, 14,23
	Exon 11	5007A>C[b,e], c.5227dupT, c.5242dupT, c.6180dupA, 5639T>C, 5929G>A, 5624C>T,16515C>T, 6376 ins AA, A:T>G:C, c.2808_2811delACAA, c.5095G>A, c.6125A>C, 4866InsT, 6079delAGTT, c.5986G>A	6, 8, 10, 11, 14, 19, 23
	Exon 11O	1235 delCTTAA	17
	Exon 12	c.6886A>C	14
	Exon 14	7470A>G, c.7301A>C	10, 14
	Exon 15	c.7445C>T	23
	Exon 18	8345A>G[b,], 8345A>G	6, 10
	Exon 19	8576 insC	10
	Exon 20	c.8587dup	23
	Exon 22	9079 G>A	10
	Exon 27	c.9976A>T	14
	Exon 27B	9999delA	10
	IVS2	2 295+90 T>A	10
	IVS-3	3 545	10
	IVS-7	859+75A>T	10
	IVS-8	8 909+56C>T	10
	IVS-25	9729+58InsG	10

Cont. Table 1: A list of BRCA Mutation in Indian Breast Cancer Patients

CONCLUSION

As in our review, the research papers were mainly reported from North India, followed by South India, East India, and northwest India, now it is an urgent need to research in western India also to assess the BRCA mutation possibility and impact all over the Indian population. On the account of breast cancer initiation and development BRCA mutation is the most important gene alteration which is ranging 10-15% worldwide while in India, a study conducted by Vaidyanathan et al. 2009 estimated BRCA mutation 28%.

The careful assessment of BRCA gene mutations helps us to identify the particular candidates which are susceptible to breast cancer development. In breast cancer cases 5-9% of cases were reported based on family history of breast cancer. It was evaluated that approximately 80% of the family history of breast cancer is due to the combination of BRCA1 and BRCA2 gene mutation. In the Indian population BRCA mutation mainly show the deletion mutation, silent mutation frame-shift mutation, and missense mutation which can lead to stop codon, truncated protein synthesis, and change in amino acids and their position.

On account of current knowledge of BRCA mutation in India, we can clearly say that the BRCA gene most reliable target for detection of breast cancer in susceptible familial history candidates, as well as it can be used as a treatment target for breast cancer cure.

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