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REVIEW ARTICLE

ASSOCIATION BETWEEN BRCA1 POLYMORPHISMS AND BREAST CANCER IN SAARC COUNTRIES

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ABSTRACT

BRCA1 gene is highly contributed gene developing the breast cancer especially in female. Breast cancer is most prevalent cancer in South Asian Association for Regional Cooperation (SAARC) countries and risk of developing the breast cancer is now increasing rapidly. It was observed that in these countries breast cancer often develops at younger age of 30-45 years. The prevalence and the contribution of BRCA1 variations are totally different among these countries and studies. Due to the difference in genetics and epidemiology, risk factors result from ethnic differences in breast cancer. Variations of BRCA1 gene account for small study samples but the higher contributor variation of BRCA1 gene accounts with strong family history. Three BRCA1 variations (185delAG, 4184del4 and 3889delAG) are well considered in Pakistan and India. The objective of present study was to reveal the contribution of BRCA1 gene among breast cancer patients in SAARC countries. In this review, the data was collected from 8 participating SAARC countries (Pakistan, India, Sri Lanka, Bangladesh, Nepal, Maldives, Bhutan and Afghanistan). Totally 25 articles were selected from these countries. Additionally review articles were also studied for better assessment. The study presents the review on different studies of BRCA1 gene association with breast cancer.

KEY WORDS: BRCA1 Gene; Breast Cancer; Female; Risk; Genetics; Epidemiology; Pakistan; India; Afghanistan; Bangladesh.

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INTRODUCTION

Breast cancer is the most prevalent and leading cause of death in women worldwide.[10,17] Breast cancer accounts for about 23% of all malignant tumors in female. Each year, 400,000 women die from breast cancer.[31] Main cause of breast cancer is related to personal or family history of the disease and it is also caused by inherited mutation of BRCA1 gene (MIM # 113705). About 5-10% is hereditary breast cancer, in which 15-25% is caused by BRCA1 mutations.[16,32]

BRCA1 gene plays the significant role in repairing the damaged or destroyed DNA. So, any deficiencies in BRCA1 may lead to genetic instability and tumor genesis.[18,30,31] BRCA1 gene is located on chromosome at 17q21 covering more than 80kb distributed in 22 exons and encoded for a protein of 1,863 amino acids that was mapped and cloned in 1994.[14,31]

Among the Asian countries, Pakistan has the highest rate of breast cancer as well as ovarian cancer.[4] The mean age of female affected from breast cancer in Pakistan was less than 49 years whereas the mean age of western female was 54 years.[26] In Indian population, the average age at diagnosis for breast cancer risk was between 50-53 years.[24] Breast cancer is about 23% of all cancers in Sri Lankan females. Only one study indicated that the mean age of onset for familial and sporadic breast cancer patients was 47 years.[27] National Institute of Cancer Research and Hospital of Bangladesh reported that the average age among breast cancer patients was 41.8.[8] In Nepalian study, the mean age of onset breast cancer was 42.59.[5]

Figure1 shows the average age determined from selected studies of Pakistan, India, Sri Lanka, Bangladesh and Nepal.

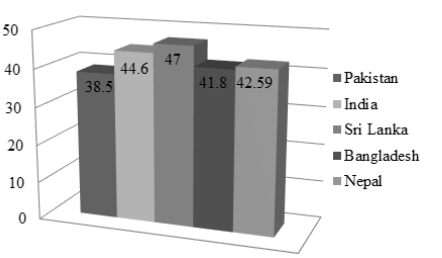

Figure1: The average age of patients with breast cancer from different SAARC countries

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The prevalence of BRCA1 gene was investigated in different studies of Pakistani familial breast cancer patients showing different frequency of 6.7% to 17.0%. Further 0.67% of Pakistani sporadic cancer patients had mutation in BRCA1. In Asian population, the prevalence of BRCA1 had been reported 8.0-31.8% in familial and 2.8-21.4% in early onset breast cancer patient.[14] The prevalence of BRCA1 gene among Indian population had unexplored due to smallest range of studies and different ethnicity of populations.[11] Beside this, most studies revealed familial breast cancer rather than sporadic breast cancer. Only one study from Sri Lanka found that the prevalence of BRCA1 mutations was 6.25% among familial breast cancer patients.[27] Due to limited research on breast cancer in Bangladesh and Nepal, the prevalence of BRCA 1 gene was not reported.[5,20]

The expected ratio of 4.4-11.1% has been varying in different local populations of Pakistan with BRCA germ line mutation in breast cancer cases.[17] Among the Indian population, 5-10% patients of breast cancer are directly contributed to BRCA1 and BRCA 2 gene.[11] The study on BRCA1 and breast cancer was not found in three South Asian countries (Maldives, Bhutan and Afghanistan) in our search range.

SAARC consists of 3% of world area and 21% of world's population. The present study was designed to determine the association of BRCA1 gene among the female breast cancer patients from populations of SAARC countries. For SAARC populations, the data available on BRCA1 was derived from family based, population based and hospital based studies [Table1, 2 and 3]. This review is focused on hereditary and sporadic breast cancer with the variations of BRCA1 gene. Twenty two articles were searched from 'PubMed' about BRCA1 polymorphisms and breast cancer. These studies estimated the variations of BRCA1 in SAARC population with breast cancer and fewer with ovarian cancer.

The studies summarized in Table 1, 2 and 3 include only those studies based on large populations covering maximum variations. The specific methods used for the detection of variations by each study group are also described in detail. Novel and reported variations studied in SAARC countries are presented in Table 4, consisting candidate founder variations. Table 4 summarized genetic studies of breast cancer conducted from SAARC countries.

Table 1: Studies regarding association between BRCA1 polymorphisms and breast cancer from Pakistan

Reference	Cancer organ	Cancer type	Study cohort	Subject	Case	Control	Ethnicity	Method
Liede, et al. 2002	Breast Ovarian	Invasive Epithelial	Case-Control	HB	341	200	Sindhi & Punjabi	PTT
Rashid, et al. 2006	Breast Ovarian	Bilateral	Familial	HB	176	-	Punjabi	SSCP, PTT, DHPLC
Malik, et al. 2008	Breast	Unilateral	Sporadic with negative family history	PB	150	100	Mixed	SSCP, PCR
Moatter, et al. 2011	Breast	Bilateral	Patients with moderate family history	HB	53	-	Sindhi	SSCP, PTT, PCR
Aziz, et al. 2016	Breast	Unilateral Bilateral	Case-Control	HB	80	40	Punjabi	Allele specific PCR
Rashid, et al. 2016	Breast	TNBC	Familial	HB	523	-	Mixed	SSCP, DHPLC
Samin, et al. 2018	Breast	-	Case-Control	HB	32	14	Punjabi	PCR
Abbas, et al. 2018	Breast	-	Case-Control	HB	100	100	Punjabi	PCR
Shabana, et al. 2019	Breast	-	Case-Control	PB	80	80	Mixed	PCR, RFLP
Ahmed, et al. 2019	Breast	-	Case-Control	PB	300	300	Pashtun	T-ARMS-PCR
Yousafzai, et al. 2019	Breast	-	Case-Control	HB	50	50	Baloch	PCR
Majeed, et al. 2020	Breast Ovarian	-	-	All	302	-	Mixed	PCR

Abbreviations: DHPLC, Denaturing High Performance Liquid Chromatography; HB, Hospital based; PB, Population based; PCR, Polymorphism chain reaction; PTT, Protein truncation test; RFLP, Restriction Fragment Length Polymorphism; SSCP, Single strand chain polymorphism; TNBC, Triple negative breast cancer.

Table 2: Studies regarding association between BRCA1 polymorphisms and breast cancer from India

Reference	Cancer organ	Cancer type	Study cohort	Subject	Case	Control	Ethnicity	Method
Kumar, et al. 2002	Breast Ovarian	Hereditary	Familial	FB	14	-	North India	CSGE
Rajkumar,et al. 2003	Breast Ovarian	Hereditary Early onset	Familial	FB	19	-	South India	DHPLC
Saxena, et al. 2006	Breast	Early onset, late onset and bilateral	Case-Control with sporadic patients	HB	204	140	North India	HDX
Vaidyanathan, et al. 2009	Breast Ovarian	Hereditary	Familial	FB	39	-	South India	CSGE, PCR
Soumittra, et al. 2009	Breast Ovarian	Hereditary, early onset, unilateral and bilateral	Familial, genetic screening	FB	71	-	South India	PCR-DHPLC
Hansa, et al. 2012	Breast	-	Familial	HB	32	-	North East India	PCR
Chakraborty, et al. 2013	Breast	Hereditary	Familial	HB	103	-	Mixed	PCR , In silico analysis
Chakraborty, et al. 2015	Breast	Hereditary	Familial	HB	231	-	East India	Allele specific PCR
Kour, et al. 2019	Breast	-	Case-Control	HB	255	255	North India	PCR-RFLP

Abbreviations: CSGE, Conformation sensitive gel electrophoresis; DHPLC, Denaturing High Performance Liquid Chromatography FB, Family based; HB, Hospital based; HDX, Heteroduplex analysis; PCR, Polymorphism chain reaction; RFLP, Restriction fragment length polymorphism.

Table 3: Studies regarding association between BRCA1 polymorphisms and breast cancer from Sri Lanka, Nepal, Bangladesh, Maldives, Bhutan and Afghanistan.

Reference	Cancer organ	Cancer type	Study cohort	Subject	Case	Control	Country	Method
Silva, et al. 2008	Breast	Hereditary and Sporadic	Case-Control	FB	130	40	Sri Lanka	SSCP, PCR
Bhatta, et al. 2016	Breast	-	Case-Control	HB	50	20	Nepal	PCR
Nishat, et al. 2019	Breast	-	Patients with negative family history	HB	65	-	Bangladesh	PCR, Sanger sequencing
Chowdhury, et al. 2020	Breast	Unilateral	Cross sectional	HB	50	-	Bangladesh	PCR, Sanger sequencing

Abbreviations: FB, Family based; HB, Hospital based; PCR, polymorphism chain reaction.

Table 4: Studies regarding variation scale of BRCA1 gene and breast cancer from different SAARC countries

Country	Exons	Variations	Variations detected	No of BRCA1 variations		Reference
				Patient	Control	
Pakistan	2, 11 and 12	Not specified	185del AG, 1912TtoG, 161delAAAT, 2080insA, 3889delAG, 4184del4, 4284delAG, 1476delG, 2041insAandIVS14-1AtoG, 1127delA, 2266delG,2722CtoG	31	None	Liede, et al. 2002
	2, 7, 8, 11, 15, 17, 20 and 24	185delAG, 185insA, 550delA, 589delCT, Q491X, Q531, 2388delG, 3812inT, Q1395X, 5149delCTAA, 5376insA, IVS20-1GtoC, S1503X and R1835X	All	23	None	Rashid, et al. 2006
	2, 3 and 13	Not specified	1452delA	5	None	Malik, et al. 2008
	2, 5, 6, 11, 16, 20 and 22	Not specified	4837AtoG, 271TtoG, 5231delG, 1123TtoG	4	None	Moatter, et al. 2011
	2 and 15	185delAG and 4627CtoA	185delAG	1	None	Aziz, et al. 2016
	2	185delAG, 185insA	185delAG	1	None	Samin, et al. 2018
	-	rs80356932; 4491CtoT	T-T variant of rs80356932	-	-	Abbas, et al. 2018
	11, 16 and 20	1294del40, E1250X, 5382insC	E1250X	1	None	Shabana, et al. 2019
	-	miRNA binding site rs8176318GtoT	rs8176318	-	-	Ahmed, et al. 2019
India	2, 7, 11 and 12	Not specified	465 G to A, 1027 del A, 185 del AG	3	None	Kumar, et al. 2002
	2, 11, 16 and 17	Not specified	185 del AG, 4184 del 4, 3596 del 4, K1667R, 22 C to G, IVS10-12 del G, IVS13+2 T to C, IVS7+38 T to C, 5154 C to T, K1183R, S1613G and M1652I	12	3	Saxena, et al. 2006
	2, 5,11 and 8	295 del CA, 4213 del T, 5267 T to G, 185 del G, 2983 C to A	All variations identified with high frequency of 185 del G	15	None	Vaidyanathan, et al. 2009
	2, 11, 12, 13, 14, 16, 17 and 18	Not specified	4162 del AG, 4327 C to T, 1149 del AT, 4399 C to T, 4706 ins 7, 68_69 del AG, 66_67 del AG	12	None	Soumittra, et al. 2009
	2 and 11	185 del AG, 1014 del GT and 3889 del AG	All variations detected	13	None	Hansa, et al. 2012
	20	Not specified	5237 A to C	1	None	Chakraborty, et al. 2013
	2	185 del AG	Not found	-	-	Chakraborty, et al. 2015
	-	c.190 T to C, 1307 del T, g.5331 G to A and c.2612 C to T	Not found	-	-	Kour, et al. 2020

Table 4: [Continued.]

Country	Exons	Variations	Variations detected	No of BRCA 1 variations		References
				Patient	Control	
Sri Lanka	11, 13, 16 & 21	Not specified	856TtoG, 3086delT, 1VS17–2AtoT, 5404delG, IVS7+36TtoC, IVS7+38T-toC, IVS7+41CtoT, IVS7+49del15, IVS7-34CtoT, 2196GtoA, 2201CtoT, 2430TtoC, 2731CtoT, 3232AtoG, 4427TtoC, 4931AtoG, 4956AtoG, 5075GtoA	19	None	Silva, et al. 2008
Nepal	-	185delAG and 1294del40	185delAG	4	None	Bhatta, et al. 2016
Bangladesh	11	Not specified	852GtoC, 711AtoG, 709GtoA	3	None	Nishat, et al. 2019
	2	Not specified	67GtoC, 75CtoA, 48TtoG	5	None	Chowdhury, et al. 2020
Maldives	None					
Bhutan	None					
Afghanistan	None					

METHODOLOGY USED BY DIFFERENT STUDIES OF SAARC COUNTRIES

Pakistan

A case-control study of 341 case subjects with breast cancer and 200 female control subjects has conducted by Liede, et al., in 2002 in which DNA was isolated from peripheral blood. Exon intron boundaries were screened by protein-truncation testing (PTT) and direct sequencing was used for confirmation of all mutant bands detected by PTT. Rashid et al., in 2006 selected the 176 breast cancer families diagnosed with invasive breast cancer; DNA was extracted from blood samples. The entire coding regions of the BRCA1 gene was screened using single strand conformational polymorphism (SSCP) analysis, denaturing high pressure liquid chromatography (DHPLC) analysis, and the protein truncation (PTT). Malik, et al., in 2008 selected the 150 cases of unilateral breast cancer patients; after DNA extraction, Single strand conformational polymorphism (SSCP) was done for exons of BRCA1, and sequence analysis was performed for accepted sequence variant.

53 breast cancer patients were diagnosed by Moatter, et al., in 2011; after DNA extraction, mutational analysis of BRCA1 exons was carried out using single strand conformation polymorphism (SSCP) and protein truncation test (PTT) assay. All BRCA1 sequence variants were confirmed by DNA sequencing. Allele specific PCR was performed by Aziz et al., in 2016 to detect the selected mutations in 120 samples. 523 breast cancer patients were screened by Rashid et al., in 2016 for BRCA1 and BRCA2. Mutation analysis was done by using PTT, SSCP and DHPLC analyses. Samin, et al., in 2018 extracted DNA from 115 subject and exon specific primers were used to amplify BRCA1 exon 2. Sequences were analyzed through the BLAST. BRCA1 variants and BRCA2 variants were studied in 100 breast cancer patients and 100 controls using tetra-ARMS-PCR by Abbas et al., in 2019. Shabana, et al., in 2019 isolated DNA from blood samples of 80 female breast cancers and 80 healthy female by manual method and genotyping was done by PCR-RFLP.

Ahmed, et al., in 2019 genotyped the selected variations in 300 breast cancer patients and 300 healthy controls by using the allele-specific polymerase chain reaction (PCR). Genetic variant in BRCA1 and 2 was determined by Yousafzai, et al., in 2019 from blood samples of 100 subjects including 50 breast cancer cases and 50 normal subjects. Majeed, et al., in 2020 screened for 5000 women with breast cancer. 302 women were diagnosed with breast cancer; Using Sanger sequencing, DNA extracted from peripheral blood of 100 patients was screened for disease causing variants in the BRCA1.

India

To find out the contribution of BRCA1 mutations to hereditary breast cancer among Indian women, the coding sequence of the BRCA1 gene was studied in 14 breast cancer patients with a positive family history of breast and ovarian cancer. Mutation analysis was carried out by Kumar et al., in 2002 using conformation sensitive gel electrophoresis (CSGE). BRCA1, BRCA2 and CHEK2 germline mutation was studied by Rajkumar, et al., in 2003 in 22 patients with a family history of breast or ovarian cancer and early onset breast cancer. DHPLC was used for mutation analysis.

The distribution and the nature of BRCA1 and BRCA2 germline mutations and polymorphisms were studied by Saxena, et al., in 2006 in the group of 204 breast cancer patients and 140 controls. All coding regions and exon-intron boundaries of the BRCA1 and BRCA2 genes were screened by Heteroduplex analysis followed by direct sequencing of detected variants.

To find out the contribution of BRCA1 and BRCA2 mutations in developing of hereditary breast cancer among Indian women, a mutation analysis of the BRCA1 and BRCA2 genes was carried out by Vaidyanathan, et al., in 2009 in 61 breast or ovarian cancer patients from south India. Mutation analysis was carried out using conformation-sensitive gel electrophoresis (CSGE). Only one study from North East India was performed by Hansa, et al., in 2012 to provide a prevalence of BRCA1 germline mutation. Three mutations were observed in exon 2 and 11.

From the East India, a study expected the carrier frequency of 185delAG (BRCA1) and 6174delT (BRCA2) mutations. The DNA was extracted by Chakraborty, et al., in 2015 from peripheral blood and mutation detection was done using allele specific duplex-multiplex PCR. North Indian breast cancer patients were studied by Kour et al., in 2020 to find the association with four described pathogenic variants of BRCA1and genotyping was done by PCR-RFLP.

Sri Lanka, Bangladesh, Nepal, Maldives, Bhutan and Afghanistan

Sri Lanka, Bangladesh and Nepal have fewer studies on BRCA1 gene related to breast cancer. A total of 130 patients of breast cancer and 40 control subjects from Sri Lanka were analyzed by Silva, et al., in 2008 for BRCA1 mutations. All but exon 11 were screened by single strand conformation analysis (SSCP).

Nishat, et al., in 2019 extracted genomic DNA from the histopathological diagnosed breast cancer tissues of 65 female patients. Two regions of exon11 of BRCA1 gene were amplified and sequenced by using Sanger sequencing. Chowdhury, et al., 2020 extracted genomic DNA from the blood of 50 Bengali Bangladeshi female breast cancer patients. The whole region of exon2 of the BRCA1 gene was amplified and the amplified DNA products were sequenced using Sanger sequencing.

From Nepal, a study was carried out by Bhatta, et al., in 2016 to find the mutations in breast cancer patients. The blood was extracted from 50 breast cancer patients and 20 controls. DNA was subjected to PCR using primers for 185delAG and 1294del40 mutations. There were no studies found from Afghanistan, Bhutan and Maldives in our searching database.

BRCA1 variations among different populations of SAARC

Pakistan and India

Pakistan and India are considered two major countries of South Asia. Pakistani population has a variety of ethnicity. Punjabis cover the largest ethnic group in the country at 44.15%, while other important ethnic groups include Pashtun 15.42%, Sindhi 14.1%, Mohajir 7.57%, Baloch 3.57%, and others 4.66%.[10] India is the second most populated country in the world,

Table 5: Variations studied in SAARC countries with in exons of BRCA1 gene

Exons	Variations	Country	Ethnicity (no of subject)	References
2	185delAG	Pakistan	Punjabi (1)	Liede, et al. 2002
			Pathan (2)	Rashid, et al. 2006
			Not specified (1)	Aziz, et al. 2016
			Punjabi (1)	Samin, et al. 2018
		India	North India (1)	Kumar, et al. 2002
			North India (1)	Saxena, et al. 2006
			South India (8)	Vaidyanathan, et al. 2009
			North-East India (1)	Hansa, et al. 2012
		Nepal	Nepalese (4)	Bhatta, et al. 2016
	185insA	Pakistan	Punjabi (1)	Liede, et al. 2002
			Punjabi (3)	Rashid, et al. 2006
	68-69delAG	India	South India (3)	Soumittra, et al. 2009
	66-67delAG		South India (1)	Soumittra, et al. 2009
	48TtoG	Bangladesh	Bengali (1)	Chowdhury, et al. 2020
	67GtoC		Bengali (2)	Chowdhury, et al. 2020
	75CtoA		Bengali (2)	Chowdhury, et al. 2020
5	295delCA	India	South India (1)	Vaidyanathan, et al. 2009
6	271TtoG	Pakistan	Mohajir (1)	Moatter, et al. 2011
7	550delA	Pakistan	Not specified (1)	Rashid, et al. 2006
	465GtoA	India	North India (1)	Kumar, et al. 2002
8	589delCT	Pakistan	Punjabi (1)	Rashid, et al. 2006

Table 5: [Continued.]

11	2080insA	Pakistan	Pashtun (3)	Liede, et al. 2002
	1912TtoG		Mohajir (1)	Liede, et al. 2002
	1616delAAAT		Mohajir (1)	Liede, et al. 2002
	4184del4		Sindhi (1), Punjabi (4)	Liede, et al. 2002
		India	North India (1)	Saxena, et al. 2006
	1476delG	Pakistan	Punjabi (1)	Liede, et al. 2002
	2041insA		Punjabi (2)	Liede, et al. 2002
	3889delAG	Pakistan	Punjabi (2)	Liede, et al. 2002
		India	North-East India (9)	Hansa, et al. 2012
	1127delA	Pakistan	Punjabi (1)	Liede, et al. 2002
	2266delG		Punjabi (1)	Liede, et al. 2002
	2722CtoG		Kashmiri (1)	Liede, et al. 2002
	3405CtoT		Mohajir (1)	Liede, et al. 2002
	894delG		Mohajir (1)	Liede, et al. 2002
	1956delA		Punjabi (1)	Liede, et al. 2002
	1770insT		Baloch (1)	Liede, et al. 2002
	1013delTG		Mohajir (1)	Liede, et al. 2002
	2388delG		Mohajir (1)	Liede, et al. 2002
			Pashtun (1)	Rashid, et al. 2006
	Q491X		Punjabi (1)	Rashid, et al. 2006
	Q531X		Not specified (1)	Rashid, et al. 2006
	3812insT		Not specified (1)	Rashid, et al. 2006
	1123TtoG		Pashtun (1)	Moatter, et al. 2011
	E1250X		Not specified (1)	Shabana, et al. 2019
	1033GtoT		Baloch (1)	Yousafzai, et al. 2019
	1181GtoA		Baloch (1)	Yousafzai, et al. 2019
	1267inAT		Baloch (1)	Yousafzai, et al. 2019
	1682CtoT		Baloch (1)	Yousafzai, et al. 2019
	1847CtoT		Baloch (1)	Yousafzai, et al. 2019
	2612CtoT		Baloch (1)	Yousafzai, et al. 2019
	3748GtoT		Baloch (1)	Yousafzai, et al. 2019
	1027delA	India	North India (1)	Kumar, et al. 2002
	3596del4		North India (1)	Saxena, et al. 2006
	2983CtoA		South India (1)	Vaidyanathan, et al. 2009
	4213delT		South India (1)	Vaidyanathan, et al. 2009
	1149delAT		South India (1)	Soumittra, et al. 2009
	1014delGT		North-East India (3)	Hansa, et al. 2012
	3086delT	Sri Lanka	Sinhalese (1)	Silva, et al. 2008
	856TtoG		Sinhalese (1)	Silva, et al. 2008
	2196GtoA		Sinhalese (1)	Silva, et al. 2008
	2201CtoT		Sinhalese (1)	Silva, et al. 2008
	2430TtoC		Sinhalese (1)	Silva, et al. 2008
	2731CtoT		Sinhalese (1)	Silva, et al. 2008
	3232AtoG		Sinhalese (1)	Silva, et al. 2008
	3667AtoG		Sinhalese (1)	Silva, et al. 2008
	4427TtoC		Sinhalese (1)	Silva, et al. 2008
	4931AtoG		Sinhalese (1)	Silva, et al. 2008
	4956AtoG		Sinhalese (1)	Silva, et al. 2008
	5075GtoA		Sinhalese (1)	Silva, et al. 2008
	852GtoC	Bangladesh	Bengali (1)	Nishat, et al. 2019
	711AtoG		Bengali (1)	Nishat, et al. 2019
	709GtoA		Bengali (1)	Nishat, et al. 2019
12	4284delAG	Pakistan	Mohajir (2)	Liede, et al. 2002
	Q1395X		Punjabi (1)	Rashid, et al. 2006
	4162del5	India	South India (1)	Soumittra, et al. 2009
13	1452delA	Pakistan	Not specified (1)	Malik, et al. 2008
	4327CtoT	India	South India (1)	Soumittra, et al. 2009
14	4399CtoT	India	South India (1)	Soumittra, et al. 2009

Table 5: [Continued.]

15	S1503X	Pakistan	Punjabi (1) Punjabi (5)	Liede, et al. 2002 Rashid, et al. 2006
16	4837AtoG 4706ins7	Pakistan India	Mohajir (1) Baloch (1) South India (1)	Moatter, et al. 2011 Yousafzai, et al. 2019 Soumittra, et al. 2009
17	5149delCTAA K1667R 5154CtoT	Pakistan India	Punjabi (1) North India (1) North India (1)	Rashid, et al. 2006 Saxena, et al. 2006 Saxena, et al. 2006
18	5267TtoG 5120del3	India	South India (1) South India (1)	Vaidyanathan, et al. 2009 Vaidyanathan, et al. 2009
20	5376insA 5231delG 5237AtoC	Pakistan India	Not specified (1) Mohajir (1) Not specified (1)	Rashid, et al. 2006 Moatter, et al. 2011 Chakraborty, et al. 2013
21	5308insG 5404delG	Pakistan Sri Lanka	Baloch (1) Sinhalese (1)	Yousafzai, et al. 2019 Silva, et al. 2008
24	R1835X	Pakistan	Punjabi (2)	Rashid, et al. 2006

Table 6: Variations studied in SAARC countries with in introns of BRCA1 gene

Intron	Country	Ethnicity	Reference
IVS14-1GtoA	Pakistan	Pashtun (1), Punjabi (2)	Liede, et al. 2002
		Punjabi (1)	Rashid, et al. 2006
IVS20-1GtoC		Not specified (1)	Rashid, et al. 2006
IVS7+38TtoC	India	North India (1)	Saxena, et al. 2006
	Sri Lanka	Sinhalese (1)	Silva, et al. 2008
IVS13+2TtoC	India	North India (1)	Saxena, et al. 2006
IVS10-12delG		North India (1)	Saxena, et al. 2006
IVS7-2AtoT	Sri Lanka	Sinhalese (1)	Silva, et al. 2008
IVS7+36TtoC		Sinhalese (1)	Silva, et al. 2008
IVS7+41CtoT		Sinhalese (1)	Silva, et al. 2008
IVS7+49del15		Sinhalese (1)	Silva, et al. 2008
IVS7-34CtoT		Sinhalese (1)	Silva, et al. 2008

but general information on BRCA1 is not available now. The prevalence of breast cancer in India is increasing so rapidly and become the number one cancer in females.[6]

The earlier studies by Liede, et al., in 2002 from Pakistan and Kumar et al., in 2002 from India found out the variation of BRCA1 (185delAG) in only one patient from their study sample (Table 5).

In Pakistani population Aziz et al., in 2016 concluded that 185del AG and 4627C>A of BRCA1 may help in developing the mutations only in certain ethnic groups or specified locations whereas, another study by Ahmed et al., in 2019 described the presence of 185delAG in Pathan and 4627C>A, in Punjabi populations. Another study detected the BRCA1 185delAG and 185insA mutation in Pakistani population, 1 of 46 Punjabi had positive result for 185del AG.[9] Two studies by Malik et al., in 2008 and by Moatter et al., in 2011 on Pakistani population included exon-2 in their research had not found the patients to be positive for 185delAG. The 185delAG variant has been found to be the most common mutation in BRCA1 in India, as few selected studies exposed with limited sample ranges from 19 to 204. The variable frequencies were found in the studied groups from North India such as: 7.14% by Kumar et al., in 2002, 0.49% by Saxena, et al., in 2006 and from South India 16.4% by Vaidyanathan, et al., in 2009. From the East India, the mutation of 185delAG was not found in any patients with or without family history.[6]

As Table 5 shows that the major exon 11 of BRCA1 gene is detected in different studies at larger distribution of Variations. Liede, et al., in 2002 conducted the 16 Variations on exon 11 with high frequency of 2080insA in Pashtun and 4184del4 in Punjabi. Other variations on exon 11 have found in Mohajir families. A variation S1503X on exon 15 is detected by Rashid et al., in 2006 in 5 Punjabi families and two intronic variant (IVS14-1GtoA, IVS20-1GtoC) are also detected [Table 6].

From India, two studies from North India by Kumar et al., in 2002 and Saxena, et al., in 2006 and two studies from South India by Vaidyanathan, et al., in 2009 and Soumittra, et al., in 2009 had detected the variations on exon 11. Hansa, et al., in 2012 observed the three variations, 185delAG in 1, and 1014delGT in 3 and 3889delAG in 9 patients from North-East Indian patients with exons 2 and 11.

Additionally, mutations in exon 6 (271TtoG), exon 20 (5231delG) and exon 11 (1123TtoG) were reported first time in the Pakistani population.[19]Other studies had been investigated the different mutation of BRCA1 gene in breast cancer patients of Pakistani population and suggested that BRCA1 has highly contributor in developing the breast cancer.[16]

A study by Chakraborty, et al., in 2013 conducted a novel mutation (5237AtoC), which was found in BRCA1 on exon 20 of a breast cancer patient. In silico analysis performed that suggested an alteration of BRCA1 structure due to this mutation.

The contribution of BRCA1 variations are presented in Figure 2 and 3.

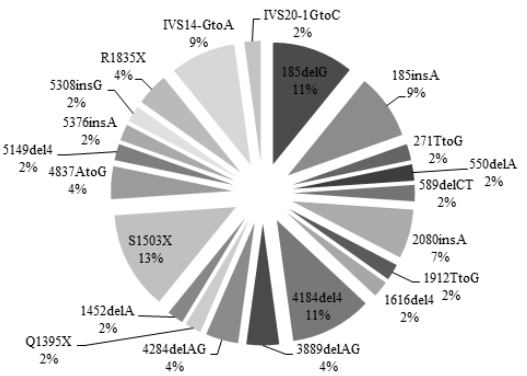

Figure 2: The percentage% of BRCA1 variations in Pakistani populations as calculated from collected data in Table 5

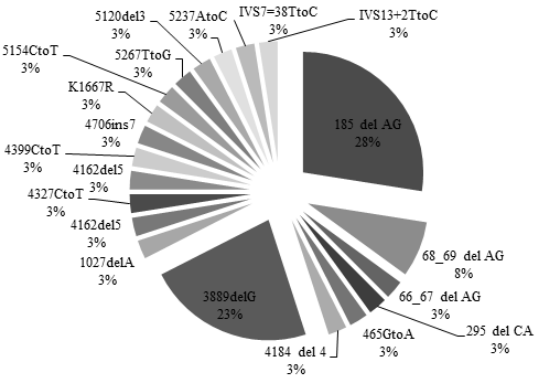

Figure 3: The contribution of BRCA1 variations in Indian populations as calculated from collected data in Table 5

Sri Lanka, Bangladesh, Nepal, Maldives, Bhutan and Afghanistan

The first report on BRCA1 mutations and polymorphisms in Sri Lankan breast cancer patients were identified by Silva et al., in 2008. The 19 sequence variants in BRCA1 gene were found. One intronic variant (IVS7+38TtoC) was found common variation in India and Sri Lanka (Table 7). A total of 5 mutations 48TtoG, 67GtoC and 75CtoA in exon 2 of BRCA1 were identified in Bangladesh.[8] And in another study, 3 novel mutations were found in a patient, 2/3 mutant sequences had effect on amino acid coding.[20] In Nepalese, The prevalence of 185delAG in breast cancer patients was found to be 8% but 1294del40 was not appeared.[5]

As Table 7 shows the 185delAG is the common variation of BRCA1 gene from Pakistan, India and Nepal populations.

From other three countries of SAARC (Maldives, Bhutan and Afghanistan), no study was found regarding the BRCA1 or breast cancer in our searched range.

Table 7: Most common variations of BRCA1 gene found from different populations of SAARC countries

Variation	No of Patients[Ethnicity]				
	Pakistan	India	Sri Lanka	Bangladesh	Nepal
185delAG	5 [2 Punjabi, 2 Pathan and 1 not specified]	11 [2 North India, 8 South India and 1 North-East India]	-	-	4 [Nepalese]
4184del4	5 [1 Sindhi, 4 Punjabi]	1 [North India]	-	-	-
3889delAG	2 [Punjabi]	9 [North East India]	-	-	-
IVS7+38 T to C	-	1 [North India]	1 [Sinhalese]		

DISCUSSION

The studies of hereditary or sporadic breast cancer among the SAARC populations are well considered. Most of studies conducted on hereditary breast cancer and only three studies conducted on sporadic breast cancer, one study by Malik et al., in 2008 from Pakistan, one study by Saxena, et al., in 2006 from India and one study by Silva et al., in 2008 from Sri Lanka (Table 1,2 and 3). In our review, Genetic epidemiological studies improve our knowledge of population heredities of BRCA1. There have been unique founder variations identified in SAARC population. Recently, most of data was created from studies of high risk families and case controls. Studies of unselected breast cancer patient in SAARC are developing. Usually, these studies provide more information, despite the use of inadequate and different methods for variations detection. Most of studies have focused on early onset breast cancer; however the majority of cases follow before age of 50 years in South Asian countries.

Until, it is not yet cleared that how much variations among these countries are contributing to genetic factors, or what ratio of all cases of breast cancer are familial. The studies show the prevalence of BRCA1 variations may be equivalent or higher in Asia than in South Asian countries. Diagnosis of hereditary breast cancer in young age patients from SAARC populations, it is expected that BRCA1 variations will account for greater proportion of all breast cancer in South Asia.

Pakistan and India as counterpart of SAARC countries have well range in standard of cancer screening and treatment. In other SAARC countries, due to scarcity of resources or lack of awareness against the breast cancer, genetic screening is not common. However, beside BRCA1 association studies common risk factors are explored by different studies.

The present study was conducted to find the relationship and prevalence of BRCA1 gene among breast cancer patients with in population and ethnic groups of SAARC countries. Due to limited researches on related study, exact result was not concluded. There is a need for larger collective studies for further insight into mutational spectra of BRCA 1 gene.

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CONFLICT OF INTEREST
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AUTHORS' CONTRIBUTION

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All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.