

BRCA1/BRCA2 mutation spectrum analysis in South Asia: a systematic review

Journal of International Medical Research

50(1) 1–13

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DOI: 10.1177/03000605211070757

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Sanjeev Kharel¹ , Suraj Shrestha¹,
Siddhartha Yadav², Prafulla Shakya³,
Sujita Baidya⁴ and Suzita Hirachan⁵

Abstract

Objective: Breast cancer (BC) is the most common form of cancer among Asian females. Mutations in the *BRCA1/BRCA2* genes are often observed in BC cases and largely increase the lifetime risk of having BC. Because of the paucity of high-quality data on the molecular spectrum of *BRCA* mutations in South Asian populations, we aimed to explore these mutations among South Asian countries.

Methods: A systematic literature search was performed for the *BRCA1* and *BRCA2* gene mutation spectrum using electronic databases such as PubMed, EMBASE, and Google Scholar. Twenty studies were selected based on specific inclusion and exclusion criteria.

Results: The 185delAG (c.68_69del) mutation in exon 2 of *BRCA1* was the most common recurrent mutation and founder mutation found. Various intronic variants, variants of unknown significance, large genomic rearrangements, and polymorphisms were also described in some studies.

Conclusions: The South Asian population has a wide variety of genetic mutations of *BRCA1* and *BRCA2* that differ according to countries and ethnicities. A stronger knowledge of various population-specific mutations in these cancer susceptibility genes can help provide efficient strategies for genetic testing.

Keywords

BRCA1, BRCA2, breast cancer, mutation, review, South Asia

Date received: 23 August 2021; accepted: 13 December 2021

¹Maharajgunj Medical Campus, Institute of Medicine, Kathmandu, Nepal

²Department of Oncology, Mayo Clinic, Rochester, MN, USA

³Department of Surgery, National Cancer Hospital and Research Center, Harisiddhi, Lalitpur, Nepal

⁴Kathmandu University School of Medical Sciences, Panauti, Nepal

⁵Department of Surgery, Tribhuvan University Teaching Hospital, Kathmandu, Nepal

Corresponding author:

Sanjeev Kharel, Maharajgunj Medical Campus, Institute of Medicine, Kathmandu, Nepal.

Email: Kharel_sanjeev@iom.edu.np



Introduction

BRCA1 and *BRCA2* are the two human breast and ovarian cancer susceptibility genes discovered in 1994 and 1995, respectively.^{1,2} The *BRCA1* and *BRCA2* genes are located on chromosome 17q and 13q, respectively, and encode factors involved in cell cycle control, gene transcriptional regulation, DNA damage repair, apoptosis, and various other vital cellular processes.³

Globally, breast cancer (BC) is one of the most common cancers. According to global surveys, the overall rate of BC is higher in American and European women compared with Asians, which may be related to the lifestyle of the Asian population.⁴ Though significant differences in incidence and mortality rates between developing and developed countries have been observed, BC comprises a leading cause of death among women worldwide.⁵ In addition, BC is the most common cancer among Asian females.⁶ *BRCA1* and *BRCA2* mutations are observed in approximately 30% of all hereditary or genetic BC cases.⁷ In contrast to western countries where BC incidence peaks among postmenopausal women in their 60s, peaks of BC incidence in Asian countries are observed among premenopausal women in their 40s.⁸

BRCA1 and *BRCA2* are clinically significant because deleterious mutations in these genes are correlated with an increased lifetime risk of BC as high as 60% to 85%, often among people with a positive family history.⁹⁻¹² In addition, women with *BRCA1* mutations have an increased risk of developing ovarian cancer, while men are at increased risk of developing prostate cancer.¹³ Furthermore, carriers of *BRCA2* mutations are at increased risk of gallbladder, bile duct, and stomach cancers, as well as melanoma.¹⁴

The prevalence and distribution of *BRCA1/BRCA2* mutations are variable because of population-specific recurrent or

founder mutations. Accurate identification of the population-specific mutation spectrum is the foremost and most crucial step for assessing cancer risks, applying the importance of genetic testing into clinical practice, establishing preventive measures, and planning for cancer management strategies.¹⁵

The developing countries of South Asia inhabit approximately 588 million women over 15 years of age who are at risk of ever-increasing incidence of BC.^{16,17} A lack of awareness and screening protocols, very few diagnostics centers with limited or no access, and lower health care standards have resulted in a higher BC patient mortality rate in developing countries.^{18,19} Moreover, there is a paucity of high-quality data on the epidemiology, biology, and environmental background of *BRCA* mutations in South Asian populations, and the central cancer registries with detailed nationwide data on BC mutations are also lacking in these countries.²⁰ These necessitate a rigorous review of *BRCA1/BRCA2* mutations in this region. Thus, this study was carried out to identify the frequency of *BRCA1* and *BRCA2* gene mutations and explore the spectrum of these mutations among the South Asian population.

Methods

Search strategy

A systematic literature search of the *BRCA1* and *BRCA2* gene mutation spectrum was performed from 10 September to 20 September 2020 using electronic databases like PubMed, EMBASE, and Google Scholar. The electronic databases were searched for peer-reviewed articles published from 1 January 2000 to 1 September 2020. “Breast Neoplasm”, “Hereditary breast and ovarian cancer syndrome”, “*Genes, BRCA1*”, “*Genes, BRCA2*” were the Mesh

terms used, and “Breast cancer,” “Hereditary breast and ovarian cancer,” “*BRCA1* mutation” and “*BRCA2* mutation” were the relevant keywords used, along with the names of all the South Asian countries (Afghanistan, Bangladesh, Bhutan, India, Pakistan, Maldives, Nepal, and Srilanka) connected with Boolean operators “OR” and “AND” wherever appropriate. The search details are further mentioned in Supplementary File 1. Additionally, rigorous manual searches of the reference section of the included articles and the relevant review articles were conducted.

Eligibility criteria

All the peer-reviewed articles published in English, including information on the spectrum of either *BRCA1* or *BRCA2* gene mutations in South Asian women with any form of BC alone or both breast and ovarian cancers, were considered eligible for inclusion in this study. Studies conducted in the South Asian region were also included.

The following exclusion criteria were followed:

1. Studies with insufficient information about a mutation in *BRCA1* and *BRCA2*;
2. Review articles and research protocols;
3. Case series/case reports;
4. Symposium/conference proceedings, commentaries, editorials, letters, views, and opinions;
5. Studies with unclear study designs and unavailable data for risk calculation;
6. Full text unavailable;
7. Articles not in the English language.

For two or more studies that included the same set of patients, we included the study with the larger number of patients.

Data extraction and analysis

Two independent authors (SK and SS) rigorously reviewed the selected studies that met our inclusion criteria and extracted the precise information on headings: author(s), year of publication, number of patients, age at diagnosis, country of origin, clinical phenotype, BC type, method of mutation detection, exon/intron, nucleotide change, amino acid change, mutation type, frequency, and founder mutations. This information was recorded in Microsoft Excel 2013 (Microsoft Corporation, Redmond, WA, USA) (Supplementary Tables S1 and S2). Mutations were classified into different groups according to the original classification the authors used during the study period. All mutations collected were reviewed through the Breast Cancer Information Core database (cBIC) (<https://research.nhgri.nih.gov/projects/bic/>), Leiden Open Variation Database (LOVD) (<http://databases.lovd.nl/shared/genes/BRCA2>); ClinVar (<https://www.ncbi.nlm.nih.gov/clinvar/>), *BRCA* exchange (<https://brcaexchange.org/>), and expert help were taken to tackle any confusion or problems that occurred during data extraction. In addition, to make the comparisons and notations uniform, all the information extracted on *BRCA* mutations incorporated Human Genome Variation Society (HGVS) (<http://www.hgvs.org/rec.html>) nomenclature recommendations, and all mutations are listed as either pathogenic/likely pathogenic, benign, a polymorphism, or a variant of unknown significance (VUS). Recurrent mutations are those reported twice or more in different articles.²¹ Founder mutations were reported as they were designated in our included studies. Any disagreements were resolved with the help of a third reviewer (SY). Ethics approval was not required for this systematic review.

Results

We identified 493 studies from electronic database searches and four additional studies from manual searching of reference lists and related systematic reviews. After duplicate removal, we screened 170 articles by titles and abstracts. After screening, 57 full-text articles were retrieved and assessed against the predefined inclusion criteria, leaving 20 articles eligible to be included in the review. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram detailing the identification and selection process is shown in Figure 1.

BRCA1 and BRCA2 mutations

This study screened a total of 1768 female BC patients and 573 BC families for exploring the *BRCA1* mutations, and 1347 female BC patients and 573 BC families for *BRCA2* mutations (Supplementary File 2).^{15,21–39}

Bangladesh

One study (Akter et al. 2019) found the frequency of pathogenic mutations in *BRCA1* and *BRCA2* to be 4.65% (2/43) and 9.30% (4/43), respectively.²¹

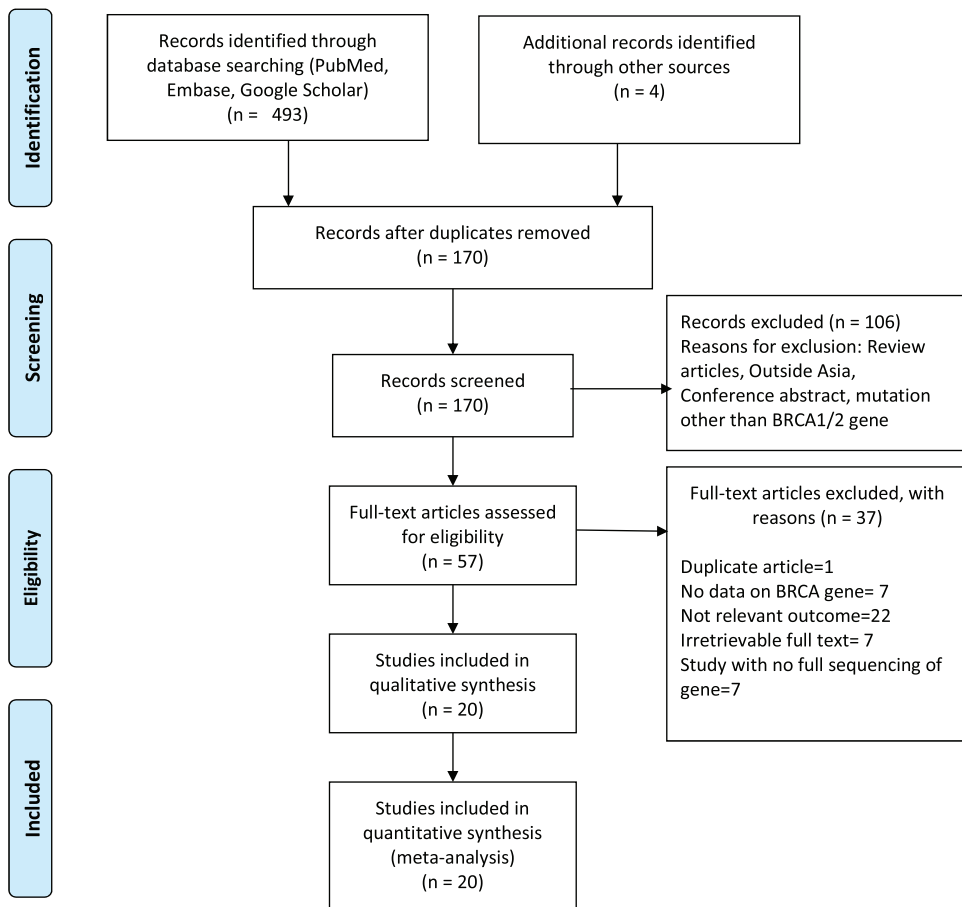


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram detailing the identification and selection process for relevant studies.

India

In 2002, Kumar et al. and Saxena et al. carried out a mutational analysis of *BRCA1* and *BRCA2*.^{22,23} Only 3 (21.42%) out of 14 patients with a positive family history of breast or ovarian cancer had a *BRCA1* mutation in the study by Kumar et al., while six sequence variants (two in *BRCA1* and four in *BRCA2*) were found in a study by Saxena et al.

In 2004, Hedau et al. found that out of 100 sporadic BC cases analyzed, only exon 2 of both *BRCA1* and *BRCA2* in six patients (two (2%) in *BRCA1* and four (4%) in *BRCA2*) showed alterations.²⁴ 185delAG (c.68_69del), a frameshift mutation of *BRCA1* in exon 2, was found to be the founder mutation among two patients.

Saxena et al. in 2006 found 18 sequence variants (9 distinct *BRCA1* and 9 distinct *BRCA2* variants). K1183R (c.3548_3549delinsGG), a variant leading to a lysine to arginine amino acid change, was the most common missense polymorphism reported among 16 patients.²⁵ However, the significance remains uncertain. In the same year, Syamala et al. revealed 13 distinct germline *BRCA2* sequence variants in 94 patients.²⁶

Vaidyanathan et al. in 2009 found eight *BRCA1* (20.5%) mutations with the majority (6/8; 75%) being frameshift mutations. They found only one *BRCA2* mutation.²⁷ In the same year, Soumittra et al. found that 13 of the 71 samples analyzed had a deleterious mutation. Ten mutations were in *BRCA1* and three were in *BRCA2*.²⁸

In 2012, Juwle et al. observed *BRCA1* and *BRCA2* mutations in 26 of 50 (52%) women diagnosed with early onset BC.²⁹ Mutations in *BRCA1* were observed in 17 (34%) patients and mutations in *BRCA2* in 12 (24%) patients. A missense mutation 5076G>A (c.4957G>A) was found among six women with BC.

Singh et al. (2015) identified 12 sequence variants of *BRCA1* in the study group, including 10 frameshifts, 1 missense, and 1 nonsense mutation.³⁰

In 2016, Mannan et al. conducted a multi-gene sequencing analysis among 141 unrelated patients.³¹ Fifty-one pathogenic cases (36.2%) included 19 novel mutations. 185delAG (c.68_69del), IVS17+1G>A (c.5074+1G>A), 3471C>T (c.3352C>T), and S1566fs (c.4837_4838delinsGCC) were recurrent mutations seen in *BRCA1*. Furthermore, 13/24 cases (54%) were found to have sequence variation; 69% (9 of 13 cases) were identified in *BRCA1* and 31% (4 of 13 cases) in *BRCA2* in a study by Darooei et al. in 2017 that performed whole genome sequencing.³²

In 2018, Mehta et al. and Shah et al. carried out mutational analyses.^{33,34} The frequency of mutations in *BRCA1* and *BRCA2* was 20 patients (15.9%) and 7 patients (5.6%), respectively, in a study by Mehta et al. Eleven cases with *BRCA1* mutations (31.4%), 15 with *BRCA2* mutations (42.9%), and 9 cases (25.7%) with both *BRCA1* and *BRCA2* mutations were found in a study by Shah et al. A missense mutation (87.8% of 35 cases) was the most common.

Pakistan

Liede et al. (2002) found that 6.7% of BC cases had either *BRCA1* or *BRCA2* mutations, with 65% of those cases accounting for *BRCA1*. IVS14-1G>A (c.4485-1G>A), 2080insA (c.1961dup), 4284delAG (c.4165_4166del), and 4184del4 (c.4065_4068del) in *BRCA1* and 3337C>T (c.3109C>T) in *BRCA2* were common mutations seen in most BC cases.³⁵

Rashid et al. (2006) conducted a *BRCA* mutation screening study in 39 cases of BC. A frameshift mutation, 185delAG (c.68_69del) in exon 2, was described as a founder mutation and found among two

families, while a nonsense mutation, 4627 C>A (c.4508C>A), was described as a founder mutation among five families.³⁶

Moatter et al. (2011) studied 53 Pakistani BC patients consisting of 23 early onset BC cases and 30 BC patients with a family history.³⁷ They found only four mutations (two frameshifts, one missense, and a polymorphism mutation) in *BRCAl*.

In a 2019 study by Rashid et al., 133 deleterious mutations (24.7%) were found, including 110 in *BRCAl* and 23 in *BRCA2*.¹⁵ Frameshift mutation 3889delAG (c.3770_3771del) in exon 11 was the most common *BRCAl* mutation found among 10 families, followed by nonsense mutation 5622C>T (c.5503C>T) among 9 families, exon 1-2 deletion among 7 families, frameshift mutation 804delT (c.685del) among 7 families, and intronic variant IVS14-1G>A (c.4485-1G>A) was found among 5 families. Frameshift mutation 5450delGTAA (c.5222_5225del) was found among four families and was the most common *BRCA2* mutation among BC families. Large group rearrangements commonly found were deletions in exon 1-2, which were observed in seven BC families.

Sri Lanka

Silva et al. (2008) studied 130 Sri Lankan BC patients and found 19 sequence variants in *BRCAl*.³⁸ In 2017, Silva et al. found the prevalence of pathogenic and likely pathogenic variants of *BRCA2* as 23% and 6.3%, respectively.³⁹ c.6728C>T in exon 11, a missense pathogenic *BRCA2* mutation, was found among three Sri Lankan young BC patients.

Various intronic variants and VUS are described in some studies. The most common intronic variant was IVS14-1G>A (c.4485-1G>A), found among six Pakistani BC families in a study by Rashid et al.¹⁵ and reported previously in

the Breast Cancer Information Core Database (BIC).

Akter et al. showed a similar frequency in germline VUS as *BRCAl* and *BRCA2* mutations,²¹ while Syamala et al. found all exonic or intronic sequence variations were VUS.²⁶ Four unclassified variants of unknown clinical significance [942G>A (c.823G>A), 3238G>A (c.3119G>A), 5002T>C (c.4883T>C), and 5076G>A (c.4957G>A)] were observed in nine patients in *BRCAl*, and nine missense mutations of unknown clinical significance in nine patients in *BRCA2*, were found in a study by Juwle et al.²⁹ Similarly, Darooie et al. also found four VUS, one in *BRCAl* and three in *BRCA2*.³² Most of the missense mutations as VUS were described in a study by Mehta et al.³³, while Silva et al. found two intronic VUS (c.1910-74T>C and c.1910-51G>T) and another two VUS [(S775F (c.2324C>T) and P1702S (c.5104C>T)] in *BRCA2*.³⁹ VUS are outlined in detail in Tables S1 and S2.

The 185delAG (c.68_69del) mutation in *BRCAl* and W31X (c.92G>A) mutation in *BRCA2* were the most common recurrent mutations among Pakistani and Indian female BC patients.^{15,22,23,27,31,35} (Tables S3 and S4)

Discussion

This review was done systematically to explore the spectrum of *BRCAl* and *BRCA2* gene mutations among female South Asian BC patients.

BRCA-associated BCs are seen at younger ages among Asian patients. A study in Korea showed approximately 50% of BC patients younger than 40 years of age have *BRCAl/2* mutations.⁴⁰ This finding is consistent with most of the studies in our review.

The study on the Bangladeshi population found an enriched pathogenic *BRCA2* mutation similar to that of Finnish,

Chinese, and Cyprian BC patients.^{37,41,42} Studies on Indian and Pakistani people showed a higher frequency of *BRCA1* mutations than *BRCA2* mutations,^{15,23,24,27,32,35} as also observed in Saudi Arabia and most studies among white populations.^{43–45} In contrast, *BRCA2* mutations have a higher incidence among Asian populations other than Indians and Pakistanis. In general, *BRCA1* mutations are found more in other ethnicities.^{46,47} Similarly, a comprehensive analysis among Asian countries showed a higher frequency of *BRCA1* mutations than that of *BRCA2* mutations (622 vs 583). Yet, in some Asian countries, such as China, Hong Kong, Korea, and the Philippines, *BRCA2* mutations had a higher frequency.⁴⁸

BRCA1/2 germline mutations with familial BC in Asian patients have a prevalence ranging from 8.0% to 31.8%. Early onset BC patients have a prevalence ranging from 2.8% to 21.4%. A recent Chinese cohort study found *BRCA* mutations in 9.1% of cases with at least one risk factor for hereditary BC, 3.5% of cases of sporadic patients, and 0.38% of healthy populations.^{46,49}

Recurrent mutations are those repeatedly reported. The 185delAG (c.68_69del) *BRCA1* mutation was first reported in Ashkenazi Jews, then in Chilean, Russian, and Israeli populations.^{50–53} 185delAG (c.68_69del) is described as a founder mutation in Egyptian and Hungarian patients.^{54,55} In addition, this mutation in exon 2 is globally the second most frequent *BRCA1* mutation, described in all Asian, American, African, and European populations.⁵⁶ The 3889delAG (c.3770_3771del) mutation in exon 12 of *BRCA1* was previously reported among the Chinese and Malaysian populations.^{57,58} In exon 20, 5382insC (c.5266dupC) was reported first in the Danish population. It is common in European countries, is the most frequent

BRCA1 mutation in the world, and is described as a founder mutation in Russian and Turkish populations.^{49,56} This mutation was seen in only one family in the study by Rashid et al. 2019. In European countries, 5382insC (c.5266dup) is the most important and prevalent *BRCA1* mutation even though Asian and American BC patients rarely have it.⁵⁹ The three most well-characterized founder mutations in Ashkenazi Jews are two in *BRCA1* (185delAG (c.68_69del) and 5382insC (c.5266dup)) and one in *BRCA2* (6174delT (c.5946delT)).^{60–62} Screening for these three founder mutations alone is now part of routine clinical practice for Ashkenazi Jewish individuals.⁶³ The 5382insC (c.5266dup) mutation in *BRCA1* exon 20 is the second most frequently reported mutation in the BIC database, being prevalent in central and eastern Europe.⁶³ However, the mutation pattern among BC patients has varied widely according to the countries. Additionally, in the BC families who were genotyped from Boston, Massachusetts, USA, 6697delTC (c.6468_6469del) was the most frequent mutation accompanying the three major Ashkenazi Jew insertions/deletions.⁵⁶

In exon 11 and exon 14 of *BRCA1*, 3889delAG (c.3770_3771del) and 5622C>T (c.5503C>T), respectively, which were found among the Pakistani population, were previously described among Turkish and Filipino individuals.^{15,64,65} A missense mutation 5076G>A (c.4957G>A) in exon 16 with amino acid change M1652I (c.4956G>A) was found among early onset BC patients of Indian ethnicity. This was reported earlier in a study by Thompson et al.⁶⁶ The Y130X (c.390C>A) *BRCA1* mutation, found mainly among Japanese and Korean patients, was the second most reported mutation in Asia. *BRCA2* mutations that are commonly found mainly in Korean and Chinese patients were 7708C>T

(c.7480C>T) (53 cases; 11 BIC entries), K467X (c.1399A>T) (29 cases; two BIC entries), and 3972del4 (c.3744_3747delTGAG) (26 cases; eight BIC entries).⁴⁸ In a study by Kwong et al., two mutations were referred to as recurrent mutations. The 589delCT (c.470_471delCT) mutation of *BRCA1* was observed among Chinese and Korean patients in Hong Kong, Malaysia, and the USA, and described previously in Japanese and Pakistani patients. *BRCA1* 1100delAT (c.981_982delAT) is described in Chinese patients. These recurrent mutations were 20.6% of all *BRCA1* mutations.⁶⁷ These mutations are also described in our study, but have low frequency in South Asian regions. As seen in our study and in accordance with BIC, most of the BC-causing pathogenic mutations in *BRCA1* and *BRCA2* are often nonsense, frameshift, and splicing mutations that lead to the production of a truncated protein.⁶⁸

The contribution of large genomic rearrangements (LGRs) in Asian high-risk BC patients has been described in a few studies. LGRs accounted for 6.3% of all mutations in *BRCA1/2* in a Malaysian cohort.⁶⁹ A study from southern China found LGRs in 0.7% (4/555) of high-risk breast or ovarian cancer patients in *BRCA* genes and accounted for 5.8% of overall *BRCA1/2* mutations in the study cohort.⁷⁰ Our review also included a few studies accounting for LGRs. LGR mutation del exon 1-2, found among seven BC families, was previously reported in the Omani population.⁷¹ An increasing number of reports on polymorphisms, rare sequence variants, and missense mutations as likely pathogenic, along with LGRs, were found among different ethnic groups.⁴⁸

K1183R (c.3548_3549delinsGG), a common missense mutation in *BRCA1* and a VUS found in our study, was previously reported by Thompson et al.⁶⁶ The frequency of VUS differs according to the ancestry of individuals and testing

laboratories. The African American population showed the highest rate of VUS (21%), followed by European (15%) and Americans with European ancestry (5%–6%).^{72,73} VUS accounting for 40% of total variants are not distinctly established and classified, even when next-generation sequencing (NGS) was used. The use of VUS in a clinical setting is quite challenging, and the clinical and genetic significance of VUS has not been clearly delineated in the literature to date.⁷⁴

The *BRCA1* and *BRCA2* gene mutation frequencies are not very different between different countries within South Asia. The similarity in race and ethnicity among these countries is one of many possible reasons for the similar mutation pattern, as shown in Tables S1 and S2.

With recent advancements in genetic testing, NGS methodology can be used to analyze the entire human genome in a single day. This can more accurately identify the various mutations that predispose an individual to increased risks for developing various cancers. Though much progress has been made after the development of NGS, many *BRCA1* and *BRCA2* mutations and their roles in pathogenicity are yet to be elucidated. Thus, a better understanding of mutations in these genes with consideration of different ethnic populations is crucial.⁴⁸ Moreover, genetic profiles from clinical assessments provide information on the degree of admixture and susceptibility to genetic disease.^{75,76} For optimizing efficient strategies for genetic testing for *BRCA1* and *BRCA2* mutations, information on the high frequency of these mutations among Asian populations with those residing in various parts of the world is of great need.⁴⁸

A lack of uniform nomenclature, differences in diagnostic interventions used, non-specific terminologies, and unavailability of complete datasets caused variation in reporting. Thus, the authors' consensus

and expert help were considered while entering data. Similarly, the differences in ascertainment, like age at diagnosis or family history, led to the varied frequencies of pathogenic variants. Therefore, the recurrent and common mutations may not be a true reflection of South Asian BC patients. Furthermore, studies were included from only four South Asian countries. Additionally, the majority of the BC cases were sporadic with an estimated frequency ranging from 90% to 95%. The remaining cases (5%–10%) included familial BCs.⁷⁷ However, the majority of included studies provided no information on whether the mutation was sporadic or germline/familial.

The knowledge of the local mutation spectrum pattern can help the concerned authorities and researchers make possible plans for future epidemiological studies in the larger population. It can also help to conduct pilot screening studies for genetic testing and mutational analysis among women and different ethnic groups within the country. In addition, the establishment of an Asian registry of *BRCA1/BRCA2* mutation carriers seems paramount to allow more organized research work to be done on this population. Having an understanding of the most recurrent *BRCA1* and *BRCA2* mutations of our ethnicities or population can help improve and speed up the diagnosis, treatment, and follow-up processes for BC patients. Elucidating the founder effect of *BRCA1/2* genes can significantly impact the management of hereditary cancer families on a national and international healthcare system level, making genetic testing more affordable and cost-effective.

Conclusions

The South Asian population has a wide variety of genetic mutations of *BRCA1* and *BRCA2*, differing according to the countries and ethnicities. An improved

knowledge of the *BRCA1/BRCA2* mutation spectrum can help clinicians deliver proper genetic counseling and cancer management to women diagnosed with or at high risk of developing BC.

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Doi: 1) 10.21203/rs.3.rs-290397/v1(<https://www.researchsquare.com/article/rs-290397/v1>)

2) 10.21203/rs.3.rs-290397/v1 (<https://europepmc.org/article/ppr/ppr356734>)

Author contributions

SK and SS were involved in the conceptualization of the study, along with designing the study search strategy, reviewing study abstracts, extracting data from full-text articles, and drafting the initial manuscript. SY, PS, SB, and SH were involved in editing and revising the manuscript. All the authors read and approved the final version of the manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID iD

Sanjeev Kharel  <https://orcid.org/0000-0001-9591-3168>

Supplemental material

Supplemental material for this article is available online.

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