BRCA 1/2 Mutation Spectrum Analysis in South Asia: A Systematic Review

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Abstract

Background: Breast cancer (BC) is the most common form of all cancers among Asian females. Mutations in *BRCA1/BRCA2* gene are observed in BC cases and also largely increases 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 the spectrum of BRCA gene mutation among the South Asian Population.

Methods: A systematic literature search of electronic databases like PubMed, EMBASE, and Google Scholar on *BRCA1* and *BRCA2* gene mutation spectrum was carried out for peer-reviewed articles providing information on the spectrum of either *BRCA1 or BRCA2* gene mutation on South Asian women with any form of breast cancer.

Results: Twenty studies were selected for review from four South Asian countries showing similar BRCA1/2 gene mutation patterns. 185delAG mutation in exon 2 in *BRCA1* was the most common recurrent mutation and founder mutation found. Various intronic variants, variants of unknown significance, large genomic rearrangements (LGRs) and polymorphisms are also described in some studies.

Conclusions: The prevalence of *BRCA1* mutations is higher than BRCA2 mutations in the South Asian population with a wide variation among different countries and ethnicities. The knowledge of various population-specific mutations in these cancer susceptibility genes can help provide efficient strategies for genetic testing.

Background

BRCA1 and *BRCA2* genes are the two breast and ovarian cancer susceptibility genes discovered in 1994 and 1995, respectively.[1, 2] The locations for *BRCA1* and *BRCA2* genes are chromosome 17q and 13q respectively that encode various factors involved in cell cycle control, gene transcription regulation, DNA damage repair, apoptosis, and other various vital cellular processes.[3]

Globally, Breast cancer is one of the commonest cancers among all cancers. Though significant differences in terms of incidence and mortality rates between developing and developed countries have been observed, breast cancer comprises a leading cause of death among women.[4] In addition, Breast cancer is the commonest cancer among Asian females.[5] Among all hereditary or genetic breast cancer cases, *BRCA1* and *BRCA2* mutations are typically observed in approximately 5 to 10% of the cases.[6] In contrast to western countries where breast cancer incidence peaks among postmenopausal women in their sixties, peaks of breast cancer incidence in Asian countries are observed among the premenopausal women in their forties.[7]

BRCA1 and *BRCA2* genes are clinically significant as deleterious mutations in these genes are correlated with an increase in lifetime risk of breast cancer, as high as 60–85%, and often among people with a

positive family history.[8–11] Mutations in these genes not only predispose to an increased risk of breast cancer, carriers of the mutation in either *BRCA1* or *BRCA2* genes are also at increased risk of various other cancers like prostate, pancreatic, melanoma, and ovarian cancers.[12]

The prevalence and distribution of *BRCA1/2* mutation are however variable due to the population-specific recurrent or founder mutations. Accurate identification of the population-specific mutation spectrum is the foremost and most crucial step to assess cancer risks, applying the importance of genetic testing into clinical practice, founding preventive measures, and planning for cancer management strategies.[13]

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 breast cancer turning this region into the hotspot for breast cancer cases.[14, 15] There is a higher mortality rate of breast cancer patients particularly in developing countries due to a lack of awareness and screening protocols, very few diagnostics centers with limited or no access, and lower health care standards.[16, 17] 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 breast cancer mutation are lacking in countries of South Asia.[18] These necessitate a rigorous review of *BRCA1/2* mutation in this region. Thus, this study was carried with the aim to identify the frequency of *BRCA1* and *BRCA2* gene mutations and to explore the spectrum of BRCA gene mutation among the South Asian Population.

Methods

Search Strategy

A systematic literature search of electronic databases like PubMed, EMBASE, and Google Scholar on *BRCA1* and *BRCA2* gene mutation spectrum was carried out from September 10 to September 20, 2020. The electronic databases were searched for peer-reviewed articles published from January 1, 2000, to September 1, 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 keyword 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 Appendix 1. Additionally, a rigorous manual search of the reference section of the included articles as well as the relevant review articles was conducted.

Eligibility Criteria

All the peer-reviewed articles published in English including information on the spectrum of either *BRCA1 or BRCA2* gene mutation on South Asian women with any form of breast cancer only or both breasts and ovarian cancer were considered eligible for inclusion. Besides, studies conducted in the South Asian region were included.

The following exclusion criteria were included:

1. Studies with insufficient information about a mutation in *BRCA1* and *BRCA2* genes.
2. Review articles, 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, including the same set of patients, we included the study with a larger number of patients.

Data extraction and Analysis

Two independent authors (SK, SS) rigorously reviewed selected studies for systematic review which met our inclusion criteria and extracted the precise information on headings: Author, year of publication, Number of Patients, Age at Diagnosis, Country of Origin, Clinical Phenotype, Breast cancer Type, Method of mutation detection, Exon/Intron, Nucleotide Change, Amino Acid Change, Mutation type, Frequency, and Founder mutations which were recorded in Microsoft Excel 2013 (Microsoft Corp, Redmond, USA). (Table 1 and Table 2) Mutations were classified into different groups according to the original classification 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/) and expert help were taken to tackle confusions and problems during data extraction. While disagreements were resolved with the help of a third reviewer (YS).

Results

We identified 493 studies from electronic database search and 4 additional studies from manual searching of reference lists and related systematic reviews. After duplicates 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 PRISMA diagram detailing the identification and selection process is given in Figure 1.

BRCA1 and BRCA2 mutations

This study screened a total of 1,768 female breast cancer patients and 573 breast cancer families for exploring the mutations in the *BRCA1* gene while 1,347 female breast cancer patients and 573 breast cancer families for the *BRCA2* gene as shown in Table 1 and 2. [13, 19–37]

Bangladesh

Only one study (**Akter et. al 2019**) found the frequency of pathogenic mutation in *BRCA1* and *BRCA2* as 4.65% (2/43) and 9.30% (4/43) respectively.

India

In 2002, **Kumar et al.** and **Saxena et al.** carried out a mutational analysis of *BRCA1* and *BRCA2* genes. Only 3 patients (21.42%) out of 14 patients with a positive family history of breast or ovarian cancer had *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 S et al.** found that. out of 100 sporadic breast cancer cases analyzed, only exon 2 of both *BRCA1 and BRCA2* in 6 different patients, 2 (2%) in *BRCA1* and 4 (4%) in *BRCA2* showed alterations. 185delAG, a frameshift mutation of *BRCA1* in exon 2 was found to be the founder mutation among 2 patients.

Saxena S et al. in 2006 found 18 sequence variants (9 distinct *BRCA1* and 9 distinct *BRCA2* variants) . K118R, a polymorphism with an amino acid change Lysine to Arginine was the most common missense polymorphism mutation reported among 16 patients. While in the same year **Syamala V et al.** revealed a total of 13 distinct germline *BRCA2* sequence variants in 94 patients.

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

In 2012, **Juwle A et al. observed** BRCA*1* and *BRCA2* mutations in 26 of 50 (52%) women diagnosed with early-onset breast cancer. Mutations in the *BRCA1* gene were observed in 17 (34 %) patients and the *BRCA2* gene in 12 (24 %) patients. A missense mutation 5076G>A was found among six breast cancer women.

Singh AK et al. (2015) identified 12 sequence variants of *BRCA1 gene* in the study group, including ten frameshifts, one missense, and one nonsense mutation.

In **2016, Mannan A** et al. conducted a multi-gene sequencing among 141 unrelated patients. Fifty-one pathogenic cases (36.2%) out of which 19 novel mutations were detected. 68_69delAG, c.5074+1G4A, c.3352C4T and c.4837_4838delinsGCC were recurrent mutations seen in *BRCA1*. While, 13/24 cases (54%) were found to have sequence variation; 69% (9 out of 13 cases) were identified in the *BRCA1* gene,

and 31% (4 out of 13 cases) in the *BRCA2* gene in a study by **Darooei et al.in 2017** that carried out a whole gene sequencing.

In 2018, **Mehta et al.** and **Shah et al.** carried out the mutational analysis. The frequency of mutations in *BRCA1* and *BRCA2* gene was 20 patients (15.9%) and 7 (5.6%) respectively in a study by **Mehta et al**., while 11 cases with *BRCA1* gene mutations (31.4%) followed by 15 with *BRCA2* gene mutations (42.9%), and both *BRCA1* and *BRCA2* mutations in nine cases (25.7%) were found in a study by **Shah et al.** with a missense mutation (87.8% of 35 cases) being the commonest.

Pakistan

Liede et al. (2002) found that 6.7 % of breast cancer cases had either *BRCA1 or BRCA2* mutation with 65% accounting for *BRCA1*. IVS14-1G>A, 2080insA, 4284delAG, and 4184del4 in the *BRCA1* gene while 3337C>T in the *BRCA2* gene were common mutations seen in most breast cancer cases.

Rashid et al. (2006) , a BRCA mutation screening study found 39 cases of breast cancer. A frameshift mutation 185delAG in exon 2 was described as a founder mutation and found among 2 families while a nonsense mutation 4627 C>A was described as a founder mutation among 5 families.

Moatter et al. (2011) studied 53 Pakistani breast cancer patients consisting of 23 early-onset breast cancer cases and 30 breast cancer patients with family history and found only four mutations (two frameshifts, one missense, and a polymorphism mutation) in *the BRCA1* gene.

In a study by Rashid et al. 2019, 110 in *BRCA1* and 23 in *BRCA2*, totaling 133 deleterious mutations (24.7%) were found. Frameshift mutations c.3770_3771del in exon 11 was the most common *BRCA1* mutation found among ten families followed by c.5503C>T a nonsense mutation among 9 families, exon 1-2 deletion a large genomic rearrangement among 7 families, c.685del a frameshift mutation among seven families and an intronic variant IVS14-1G>A, splice site mutation was found among five families, while c.5222_5225del a frameshift mutation found among 4 families were the most common *BRCA2* mutations among breast cancer families. Large group rearrangements commonly found were deletion in exon 1-2 observed in seven breast cancer families.

Srilanka

Silva et al. (2008) studied 130 Srilankan breast cancer patients and found 19 sequence variants in *BRCA1*. In **2017, Silva et al.** found the prevalence of pathogenic and likely pathogenic variants of *BRCA2* as 23 % and 6.3 % respectively. c.6728C>T in exon 11, a missense pathogenic *BRCA2* mutation was found among three Srilankan young breast cancer patients

Various intronic variants and variants of unknown significance are described in some studies. The most common intronic variant was IVS14-1G>A/ c.4485-1G>A, found among six Pakistani breast cancer families in a study by Rashid et al. 2006 and reported previously in Breast Cancer Information Core Database (BIC).

Akter et al. showed a similar frequency in germline VUS (Variation of Unknown Significance) mutation as *BRCA1* and *BRCA2* mutation while Syamala V. et al. found all Exonic or Intronic sequence variations were VUS. Four unclassified variants of unknown clinical significance (942G>A G275S, 3238G>A S1040N, 5002T>C M1628T, and 5076G>A M1652I) observed in nine patients in the *BRCA1* gene, and nine missense mutations of unknown clinical significance in nine patients in *BRCA2* gene were found in a study by Juwle et al. Similarly, Darooie et al. also found four VUS, one in *BRCA1* and three in *BRCA2* gene. Most of the missense mutations as VUS were described in a study by Mehta et al. while Silva et al. found two intronic VUS (Variant of uncertain significance) (c.1910-74T>C, c.1910-51G>T) and other two VUSs. (c.2324C>T, c.5104C>T). VUS is clearly detailed in Table 1 and Table 2.

Recurrent mutations are those repeatedly reported twice or more in different articles. 185delAG mutation in *BRCA1* was the most common recurrent mutation among Pakistani and Indian breast cancer women. [13,20,21,25,29,33]

Discussion

To our knowledge, this is the first review done systematically to explore the spectrum of *BRCA1* and *BRCA2* gene mutation among South Asian breast cancer female patients.

BRCA-associated breast cancers are seen at younger ages among Asian patients. A study in Korea showed approximately 50% of breast cancer patients younger than 40 years of age with *BRCA1/2* mutations.[38] This finding is consistent with most of the studies of our review.

The study on the Bangladeshi Population found an enriched pathogenic *BRCA2* mutation than *BRCA1* similar to Finnish, Chinese, and Cyprian BC patients. [19,39,40] While studies on Indian and Pakistani people showed a higher frequency of *BRCA1* mutation than *BRCA2* mutation [21,22,30,33,13,25] as observed in Saudi Arabia and most studies among white populations. [41-43] . In contrast, *BRCA2* mutations are found to have a higher incidence among Asian populations except for Indians and Pakistanis. While *BRCA1* mutations are found more in other ethnicities. [44,45] Similarly, a comprehensive analysis among Asian countries showed a higher frequency of *BRCA1* mutations than that of *BRCA2* mutations (622 vs 583). But in some Asian countries; in China, Hong Kong, Korea, and the Philippines, *BRCA2* mutations had a higher frequency than that of *BRCA1* mutations.[46]

BRCA1/2 germline mutations with familial breast cancer in Asian patients have a prevalence ranging from 8.0% to 31.8%. While early-onset breast cancer 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 breast cancer, 3.5% of cases of sporadic patients, and 0.38% of healthy populations. [44,47]

Recurrent mutations are those repeatedly reported. 185delAG BRCA1 mutation was first reported on Askanazi Jews and then on Chile, Russia, and Israel populations, [48-51] and is described as a founder

mutation in Egyptian and Hungarian patients. [52,53] In addition, 185delAG mutation in exon 2 is the second globally frequent *BRCA1* mutation, described in all Asia, America, Africa, and European populations.[54] 3889delAG in exon 12 was previously reported among the Chinese and Malaysian populations. [55,56] 5382insC(c.5266dupC) in exon 20 was reported first on the Danish Population; common in European countries and is the most frequent *BRCA1* mutation in the world described as a founder mutation in Russians and Turkish Population. [54,57] This mutation is seen in only one family in the study by Rashid et al. 2019.

3889delAG/c.3770_3771del in exon 11 and c.5503C>Tin exon 14 which were found among the Pakistani population was described previously among Turkish and Filipinos. [13,58,59] A missense mutation 5076G>A in exon 16 with AA change M1652I found among early-onset breast cancer patients of Indian ethnicity, was reported earlier in a study by Thompson et. al. [60] c.390C>A *BRCA1* mutation found mainly among Japanese and Korean patients was the second most reported mutation of Asia. c.7480C>T (no. of cases: 53; BIC entries: 11) followed by c.1399A>T (no. of cases: 29; BIC entries: 2) and c.3744_3747delTGAG (no. of cases: 26; BIC entries: 8). were *BRCA2* mutations found commonly mainly in Korean and Chinese patients [46]. In a study by Kwong et al., two mutations were referred to as recurrent mutations. One c.470_471delCT mutation of *BRCA1* gene observed among Chinese and Korean patients populated in Hong Kong, Malaysia, and the USA and described previously in Japanese and Pakistani patients. While another one c.981_982delAT *BRCA1* gene is described in Chinese patients. These recurrent mutations contributed 20.6% of all *BRCA1* mutations.[61] 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 breast cancer-causing pathogenic mutations in *BRCA1* and *BRCA2* genes are often the nonsense, frameshift, and splicing mutations that lead to the production of a truncated protein.[62]

The contribution of LGR in Asian high-risk breast cancer patients has been described by a few studies. LGRs accounted for 6.3% of all mutations in *BRCA1/2* genes in a Malaysian cohort. [63] 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. [64] Our review also included few studies accounting for LGRs. LGR mutation del exon 1-2 found among seven BC families was previously reported in Omani Population.[65] Increasing reports on polymorphisms, rare sequence variant, and missense mutations as likely pathogenic along with large genomic rearrangements (LGRs) were found among different ethnics' groups.[46]

K118R, a common missense polymorphism mutation found in our study was previously reported by Thompson et al. [60] The frequency of VUS differs according to the ancestry of individuals and testing laboratories. African-American population showed the highest rate of VUS, 21% followed by 15% European and 5-6% in the USA among the population with European ancestry. [66,67] VUS accounting 40% of total variants are not distinctly established and classified even with recent testing, NGS 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.[68]

The results of *BRCA1* and *BRCA2* genes are not very different between different countries within South Asia. The similarity in the race, ethnicity among various south Asian countries might be one of the many reasons for the similar BRCA1/2 gene mutation pattern as shown in Table 1 and Table 2.

With recent advancement in genetic testing, NGS (Next Gene Sequencing) methodology can analyze the entire human genome in a day which can more accurately identify various mutations which predispose an individual at increased risks for development of various cancers. Though much progress has been made after the development of NGS, still many mutations in BRCA1 and BRCA2 and their role in pathogenicity are yet to be elucidated. Thus, a better understanding of mutations in these genes with consideration of different ethnic populations is crucial.[46] Moreover, genetic profile from the assessment in the clinical settings gives information on the degree of admixture and susceptibility to genetic disease. [69,70]

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. [46]

Limitations

Lack of uniform nomenclature, different diagnostic interventions used, non-specific terminologies, and unavailability of complete data 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 lead to the differences in the frequency of pathogenic variants. So, the recurrent and common mutations may not be the true reflection among breast cancer patients of South Asia. Furthermore, studies were included from four countries of South Asia only.

Future implications

The knowledge of the local mutation spectrum pattern can help the concerned authorities/researchers make possible plans for future epidemiological study in the larger population and also help to conduct pilot screening studies for genetic testing and mutational analysis among women at risk and different ethnic groups of 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.

Conclusions

The prevalence of *BRCA1* mutations is higher than BRCA2 mutations in the South Asian population with a wide variation of gene mutations in different countries and ethnicities. The improved knowledge of the

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

Abbreviations

DNA**- Deoxy**-Ribo Nucleic Acid

VUS - Variation of Unknown Significance

LGRs**-** Large Genomic Rearrangements

BC- Breast Cancer

NGS- Next Gene Sequencing

BIC- Breast Cancer Information Core.

Declarations

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Competing Interest: None to declare.

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Authors Contributions: SK and SS were involved in conceptualization of the study along with designing the study search strategy, reviewed study abstracts, extracted data from full text articles, and drafted the initial manuscript. SY, PS, and SH were involved in editing and revising the manuscript. All the authors read and approved the final version of the manuscript.

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References

1. Miki Y, Swensen J, Shattuck-Eidens D, et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science. 1994;266:66–71.
2. Wooster R, Bignell G, Lancaster J, Swift S, Seal S, Mangion J, Collins N, Gregory S, Gumbs C, Micklem G. Identification of the breast cancer susceptibility gene BRCA2. Nature. 1995;378:789–92.
3. Wang F, Fang Q, Ge Z, Yu N, Xu S, Fan X. Common BRCA1 and BRCA2 mutations in breast cancer families: a meta-analysis from systematic review. Mol Biol Rep. 2012;39:2109–18.
4. World Health Organization. (2015) Global Status Report on Noncommunicable Diseases 2014.https://books.google.com/books/about/Global_Status_Report_on_Noncommunicable.html?hl=&id=INoOrgEACAAJ.
5. Shin H-R, Carlos MC, Varghese C. Cancer control in the Asia Pacific region: current status and concerns. Jpn J Clin Oncol [Internet]. 2012 Oct;42(10):867–81. Available from: http://dx.doi.org/10.1093/jjco/hys077. Accessed 22 Dec 2020.
6. Valencia OM, Samuel SE, Viscusi RK, Riall TS, Neumayer LA, Aziz H. The Role of Genetic Testing in Patients With Breast Cancer. JAMA Surgery. 2017;152:589.
7. Leong SPL, Shen Z-Z, Liu T-J, Agarwal G, Tajima T, Paik N-S, Sandelin K, Derossis A, Cody H, Foulkes WD. Is breast cancer the same disease in Asian and Western countries? World J Surg. 2010;34:2308–24.
8. Al-Moundhri MS, Al-Ansari A, Al-Mawali K, Al-Bahrani B. BRCA1 gene Molecular Alterations in Omani Breast Cancer Patients. Gulf J Oncolog. 2013;1:45–51.
9. Giordano A, Normanno N. (2009) Breast Cancer in the Post-Genomic Era. Springer Science & Business Media.
10. Seong M-W, Cho S, Noh D-Y, Han W, Kim S-W, Park C-M, Park H-W, Kim SY, Kim JY, Park SS. Comprehensive mutational analysis of BRCA1/BRCA2 for Korean breast cancer patients: evidence of a founder mutation. Clin Genet. 2009;76:152–60.

11. Marchina E, Fontana MG, Speziani M, Salvi A, Ricca G, Di Lorenzo D, Gervasi M, Caimi L, Barlati S. BRCA1 and BRCA2 genetic test in high risk patients and families: counselling and management. Oncol Rep. 2010;24:1661–7.
12. Dutil J, Colon-Colon JL, Matta JL, Sutphen R, Echenique M. Identification of the prevalent BRCA1 and BRCA2 mutations in the female population of Puerto Rico. Cancer Genet. 2012;205:242–8.
13. Rashid MU, Muhammad N, Naeemi H, Khan FA, Hassan M, Faisal S, Gull S, Amin A, Loya A, Hamann U. Spectrum and prevalence of BRCA1/2 germline mutations in Pakistani breast cancer patients: results from a large comprehensive study. Hereditary Cancer in Clinical Practice. 2019. https://doi.org/10.1186/s13053-019-0125-5.
14. CIA.The world factbook; 2014, https://wwwciagov/library/publications/the-world-factbook/geos/bghtml/.
15. Shetty P. India faces growing breast cancer epidemic. Lancet. 2012;379:992–3.
16. da Costa Vieira RA, Biller G, Uemura G, Ruiz CA, Curado MP. Breast cancer screening in developing countries. Clinics. 2017;72:244–53.
17. Ramathuba DU, Ratshirumbi CT, Mashamba TM. (2015) Knowledge, attitudes and practices toward breast cancer screening in a rural South African community. Curationis. https://doi.org/10.4102/curationis.v38i1.1172.
18. Moore MA, Shin H-R, Curado M-P, Sobue T. Establishment of an Asian Cancer Registry Network - problems and perspectives. Asian Pac J Cancer Prev. 2008;9:815–32.
19. Akter H, Sultana N, Martuza N, et al. Novel mutations in actionable breast cancer genes by targeted sequencing in an ethnically homogenous cohort. BMC Med Genet. 2019. https://doi.org/10.1186/s12881-019-0881-0.
20. Kumar BV, Lakhotia S, Ankathil R, Madhavan J, Jayaprakash PG, Nair MK, Somasundaram K. Germline BRCA1 mutation analysis in Indian breast/ovarian cancer families. Cancer Biol Ther. 2002;1:18–21.
21. Saxena S, Szabo CI, Chopin S, Barjhoux L, Sinilnikova O, Lenoir G, Goldgar DE, Bhatanager D. BRCA1 and BRCA2 in Indian breast cancer patients. Hum Mutat. 2002;20:473–4.
22. Hedau S, Jain N, Husain SA, et al. Novel germline mutations in breast cancer susceptibility genes BRCA1, BRCA2 and p53 gene in breast cancer patients from India. Breast Cancer Res Treat. 2004;88:177–86.
23. Saxena S, Chakraborty A, Kaushal M, et al. Contribution of germline BRCA1 and BRCA2 sequence alterations to breast cancer in Northern India. BMC Med Genet. 2006;7:75.
24. Syamala V, Sreeja L, Syamala VS, Vinodkumar B, Raveendran PB, Sreedharan H, Kuttappan R, Balakrishnan L, Ankathil R. Novel germline mutations in BRCA2 gene among 96 hereditary breast and breast–ovarian cancer families from Kerala, South India. J Cancer Res Clin Oncol. 2007;133:867–74.
25. Vaidyanathan K, Lakhotia S, Ravishankar HM, Tabassum U, Mukherjee G, Somasundaram K. BRCA1 and BRCA2 germline mutation analysis among Indian women from south India: identification of four

novel mutations and high-frequency occurrence of 185delAG mutation. J Biosci. 2009;34:415–22.

26. Soumittra N, Meenakumari B, Parija T, Sridevi V, Nancy KN, Swaminathan R, Rajalekshmy KR, Majhi U, Rajkumar T. Molecular genetics analysis of hereditary breast and ovarian cancer patients in India. Hereditary Cancer in Clinical Practice. 2009. https://doi.org/10.1186/1897-4287-7-13.
27. Juwle A, Saranath D. BRCA1/BRCA2 gene mutations/SNPs and BRCA1 haplotypes in early-onset breast cancer patients of Indian ethnicity. Med Oncol. 2012;29:3272–81.
28. Pandey AKSA. BRCA1 Gene's EXON 11 and Breast Carcinoma: A Mutational Hot Spot for Familial Patients and Prone to Metastases in Northern India. Journal of Clinical Experimental Pathology. 2015. https://doi.org/10.4172/2161-0681.1000219.
29. Mannan AU, Singh J, Lakshmikeshava R, et al. Detection of high frequency of mutations in a breast and/or ovarian cancer cohort: implications of embracing a multi-gene panel in molecular diagnosis in India. J Hum Genet. 2016;61:515–22.
30. Darooei M, Poornima S, Salma BU, Iyer GR, Pujar AN, Annapurna S, Shah A, Maddali S, Hasan Q. Pedigree and BRCA gene analysis in breast cancer patients to identify hereditary breast and ovarian cancer syndrome to prevent morbidity and mortality of disease in Indian population. Tumour Biol. 2017;39:1010428317694303.
31. Mehta A, Vasudevan S, Sharma SK, Kumar D, Panigrahi M, Suryavanshi M, Gupta G. Germline BRCA1 and BRCA2 deleterious mutations and variants of unknown clinical significance associated with breast/ovarian cancer: a report from North India. Cancer Management Research. 2018;10:6505–16.
32. Shah ND, Shah PS, Panchal YY, Katudia KH, Khatri NB, Ray HSP, Bhatiya UR, Shah SC, Shah BS, Rao MV. Mutation analysis of BRCA1/2 mutations with special reference to polymorphic SNPs in Indian breast cancer patients. Appl Clin Genet. 2018;11:59–67.
33. Liede A, Malik IA, Aziz Z, Rios Pd P, de L, Kwan, Narod E SA. Contribution of BRCA1 and BRCA2 mutations to breast and ovarian cancer in Pakistan. Am J Hum Genet. 2002;71:595–606.
34. Rashid MU, Zaidi A, Torres D, et al. Prevalence of BRCA1 and BRCA2 mutations in Pakistani breast and ovarian cancer patients. Int J Cancer. 2006;119:2832–9.
35. Moatter T, Aban M, Khan S, Azam I, Pervez S. BRCA1 status in Pakistani breast cancer patients with moderate family history. J Coll Physicians Surg Pak. 2011;21:680–4.
36. Silva WD, De Silva W, Karunanayake EH, Tennekoon KH, Allen M, Amarasinghe I, Angunawala P, Ziard MH. Novel sequence variants and a high frequency of recurrent polymorphisms in BRCA1gene in Sri Lankan breast cancer patients and at risk individuals. BMC Cancer. 2008. https://doi.org/10.1186/1471-2407-8-214.
37. Silva SD, De Silva S, Tennekoon KH, Dissanayake A, De Silva K, Jayasekara L. Novel and reported pathogenic variants in exon 11 of BRCA2 gene in a cohort of Sri Lankan young breast cancer patients. Fam Cancer. 2017;16:329–38.
38. Han S-A, The KOHBRA Research Group and the Korean Breast Cancer Society, Kim S-W, et al. The prevalence of BRCA mutations among familial breast cancer patients in Korea: results of the Korean Hereditary Breast Cancer study. Fam Cancer. 2013;12:75–81.

39. Hartikainen JM, Kataja V, Pirskanen M, Arffman A, Ristonmaa U, Vahteristo P, Ryynänen M, Heinonen S, Kosma V-M, Mannermaa A. Screening for BRCA1 and BRCA2 mutations in Eastern Finnish breast/ovarian cancer families. Clin Genet. 2007;72:311–20.
40. Ikeda N, Miyoshi Y, Yoneda K, Shiba E, Sekihara Y, Kinoshita M, Noguchi S. Frequency ofBRCA1 andBRCA2 germline mutations in Japanese breast cancer families. Int J Cancer. 2001;91:83–8.
41. Janavičius R, Rudaitis V, Mickys U, Elsakov P, Griškevičius L. Comprehensive BRCA1 and BRCA2 mutational profile in Lithuania. Cancer Genet. 2014;207:195–205.
42. Thomassen M, Gerdes A-M, Cruger D, Jensen PKA, Kruse TA. Low frequency of large genomic rearrangements of BRCA1 and BRCA2 in western Denmark. Cancer Genet Cytogenet. 2006;168:168–71.
43. Bu R, Siraj AK, Al-Obaisi KAS, Beg S, Al Hazmi M, Ajarim D, Tulbah A, Al-Dayel F, Al-Kuraya KS. Identification of novel BRCA founder mutations in Middle Eastern breast cancer patients using capture and Sanger sequencing analysis. Int J Cancer. 2016;139:1091–7.
44. Kim H, Choi DH. Distribution ofBRCA1andBRCA2Mutations in Asian Patients with Breast Cancer. Journal of Breast Cancer. 2013;16:357.
45. (2000) Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. British Journal of Cancer 83:1301–1308.
46. Kwong A, Shin VY, Ho JCW, et al. Comprehensive spectrum of BRCA1 and BRCA2 deleterious mutations in breast cancer in Asian countries. J Med Genet. 2016;53:15–23.
47. Lang G-T, Shi J-X, Hu X, et al. The spectrum of BRCA mutations and characteristics of BRCA-associated breast cancers in China: Screening of 2,991 patients and 1,043 controls by next-generation sequencing. Int J Cancer. 2017;141:129–42.
48. Levy-Lahad E, Catane R, Eisenberg S, et al. Founder BRCA1 and BRCA2 mutations in Ashkenazi Jews in Israel: frequency and differential penetrance in ovarian cancer and in breast-ovarian cancer families. Am J Hum Genet. 1997;60:1059–67.
49. Gallardo M, Silva A, Rubio L, et al. Incidence of BRCA1 and BRCA2 mutations in 54 Chilean families with breast/ovarian cancer, genotype–phenotype correlations. Breast Cancer Res Treat. 2006;95:81–7.
50. Anisimenko MS, Mitrofanov DV, Chasovnikova OB, Voevoda MI, Kovalenko SP. BRCA1 gene mutations frequency estimation by allele-specific real-time PCR of pooled genomic DNA samples. Breast. 2013;22:532–6.
51. Laitman Y, Borsthein RT, Stoppa-Lyonnet D, et al. Germline mutations in BRCA1 and BRCA2 genes in ethnically diverse high risk families in Israel. Breast Cancer Res Treat. 2011;127:489–95.
52. Ibrahim SS, Hafez EE, Hashishe MM. Presymptomatic breast cancer in Egypt: role of BRCA1 and BRCA2 tumor suppressor genes mutations detection. Journal of Experimental Clinical Cancer Research. 2010. https://doi.org/10.1186/1756-9966-29-82.
53. Looij MV der, Van der Looij M, Szabo C, et al. Prevalence of founderBRCA1 andBRCA2 mutations among breast and ovarian cancer patients in hungary. Int J Cancer. 2000;86:737–40.

54. Karami F, Mehdipour P. (2013) A comprehensive focus on global spectrum of BRCA1 and BRCA2 mutations in breast cancer. Biomed Res Int 2013:928562.
55. Zhang J, Pei R, Pang Z, Ouyang T, Li J, Wang T, Fan Z, Fan T, Lin B, Xie Y. Prevalence and characterization of BRCA1 and BRCA2 germline mutations in Chinese women with familial breast cancer. Breast Cancer Res Treat. 2012;132:421–8.
56. Thirthagiri E, Lee SY, Kang P, et al. Evaluation of BRCA1 and BRCA2 mutations and risk-prediction models in a typical Asian country (Malaysia) with a relatively low incidence of breast cancer. Breast Cancer Res. 2008. https://doi.org/10.1186/bcr2118.
57. Tereschenko IV, Basham VM, Ponder BAJ, Pharoah PDP. BRCA1 and BRCA2 mutations in Russian familial breast cancer. Hum Mutat. 2002;19:184–4.
58. Balcı A, Huusko P, Pääkkönen K, Launonen V, Üner A, Ekmekçi A, Winqvist R. Mutation analysis of BRCA1 and BRCA2 in Turkish cancer families: a novel mutation BRCA2 3414del4 found in male breast cancer. Eur J Cancer. 1999;35:707–10.
59. De Leon Matsuda ML, Liede A, Kwan E, Mapua CA, Cutiongco EMC, Tan A, Borg A, Narod SA. BRCA1 and BRCA2 mutations among breast cancer patients from the Philippines. Int J Cancer. 2002;98:596–603.
60. Thompson D, Easton D. The Genetic Epidemiology of Breast Cancer Genes. Journal of Mammary Gland Biology Neoplasia. 2004;9:221–36.
61. Kwong A, Ng EKO, Wong CLP, Law FBF, Au T, Wong HN, Kurian AW, West DW, Ford JM, Ma ESK. Identification of BRCA1/2 Founder Mutations in Southern Chinese Breast Cancer Patients Using Gene Sequencing and High Resolution DNA Melting Analysis. PLoS ONE. 2012;7:e43994.
62. Pohlreich P, Zikan M, Stribrna J, et al. High proportion of recurrent germline mutations in the BRCA1 gene in breast and ovarian cancer patients from the Prague area. Breast Cancer Res. 2005;7:R728–36.
63. Kang P, Mariapun S, Phuah SY, Lim LS, Liu J, Yoon S-Y, Thong MK, Taib NAM, Yip CH, Teo S-H. Large BRCA1 and BRCA2 genomic rearrangements in Malaysian high risk breast-ovarian cancer families. Breast Cancer Res Treat. 2010;124:579–84.
64. Kwong A, Ng EKO, Law FBF, Wong HN, Wa A, Wong CLP, Kurian AW, West DW, Ford JM, Ma ESK. Novel BRCA1 and BRCA2 genomic rearrangements in Southern Chinese breast/ovarian cancer patients. Breast Cancer Res Treat. 2012;136:931–3.
65. Al-Moundhri MS, Al-Bahrani B, Burney IA, Nirmala V, Al-Madhani A, Al-Mawaly K, Al-Nabhani M, Thomas V, Ganguly SS, Grant CS. The Prognostic Determinants of Gastric Cancer Treatment Outcome in Omani Arab Patients. Oncology. 2006;70:90–6.
66. Lindor NM, Goldgar DE, Tavtigian SV, Plon SE, Couch FJ. BRCA1/2 Sequence Variants of Uncertain Significance: A Primer for Providers to Assist in Discussions and in Medical Management. Oncologist. 2013;18:518–24.
67. Eccles BK, Copson E, Maishman T, Abraham JE, Eccles DM. Understanding of BRCA VUS genetic results by breast cancer specialists. BMC Cancer. 2015;15:936. doi:10.1186/s12885-015-1934-1.

Published 2015 Nov 25.

68. Federici G, Soddu S. Variants of uncertain significance in the era of high-throughput genome sequencing: a lesson from breast and ovary cancers. J Exp Clin Cancer Res. 2020;39:46. https://doi.org/10.1186/s13046-020-01554-6.
69. Mardis ER. Next-generation DNA sequencing methods. Annu Rev Genomics Hum Genet. 2008;9:387–402.
70. Royal CD, Novembre J, Fullerton SM, Goldstein DB, Long JC, Bamshad MJ, Clark AG. Inferring genetic ancestry: opportunities, challenges, and implications. Am J Hum Genet. 2010;86:661–73.

Tables

Due to technical limitations the Tables are available as a download in the Supplementary Files.

Figures

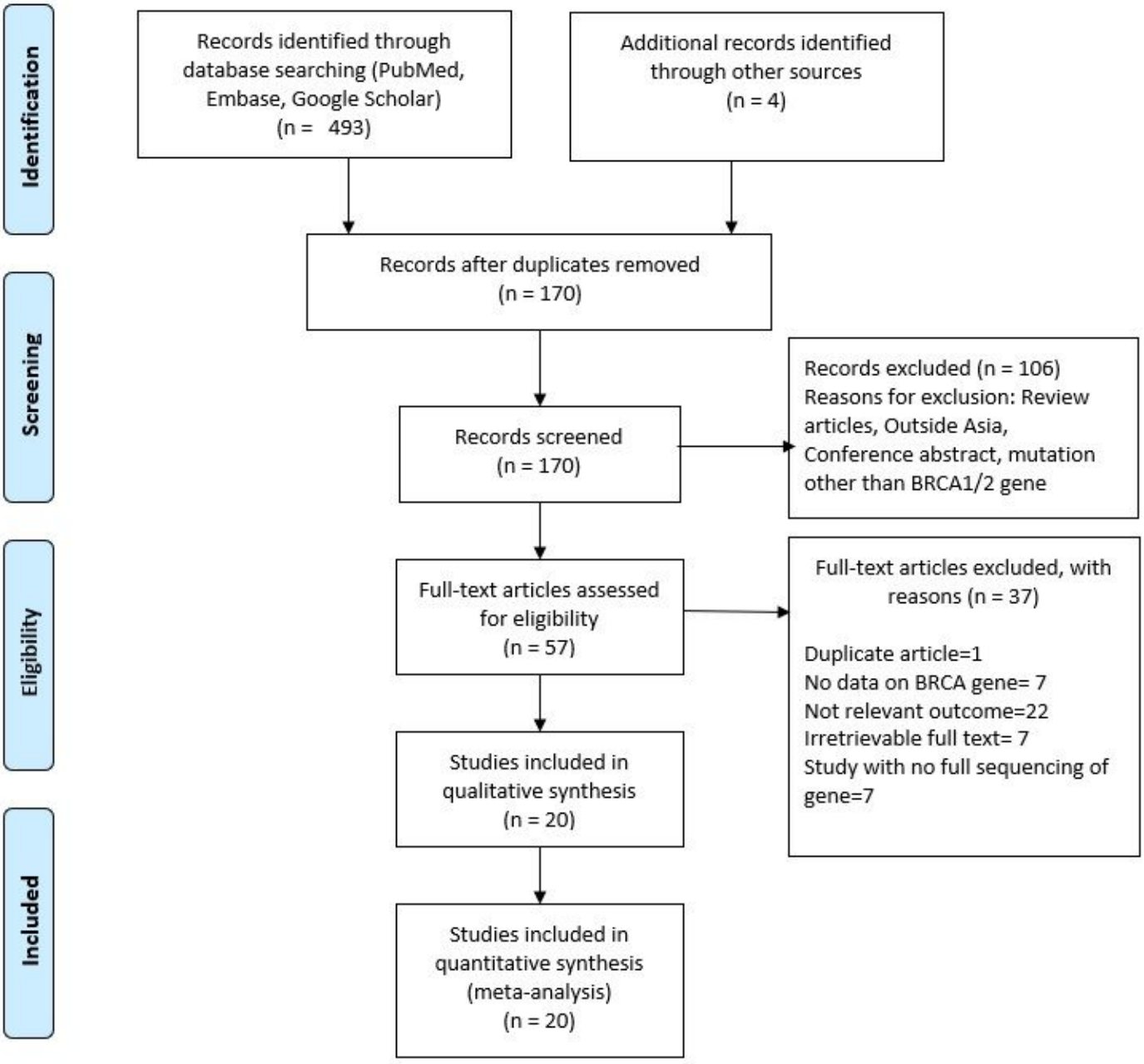

Figure 1

The PRISMA diagram detailing the identification and selection process

Supplementary Files

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