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Prevalence of germline mutations in women with breast and/or ovarian cancer in a tertiary care center in Pune, India

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ABSTRACT

In India, the incidence of breast cancer accounted for 1,78,361 cases, whereas ovarian cancer accounts for 45,701 cases, according to Globocan Report 2020. These cancers are known to have a hereditary basis, and >10% of them are associated with pathogenic BRCA1 and BRCA2 mutations. The prevalence of BRCA1 and BRCA2 varies across various Indian studies and is reported to be 2.9–28%. However, gene mutations other than BRCA1 and BRCA2 which are shown to increase the risk of hereditary breast and ovarian cancer (HBOC) are underreported.

Objectives: The objective of this study was to estimate the prevalence of deleterious germline mutations among women with breast and/or ovarian cancer.

Material and Methods: A cross-sectional study was conducted in the department of oncology at a super specialty hospital. Patients were enrolled based on the current National Comprehensive Cancer Network guidelines for genetic risk and evaluation of HBOC. Demographic and clinical information was extracted from the electronic medical records of the hospitals from 2018 to 2021. Next-generation sequencing (NGS) was performed on the extracted DNA using a custom capture kit and classified based on the American College of Medical Genetics.

Results: A total of 94 patients suspected of having HBOC were examined for deleterious germline mutations. The median age of the patient was 46 years (range: 38–57 years). Breast and ovarian cancer patients constituted 64.9% and 35.1%, respectively. The overall mutation detection rate was 25.5%. The positive mutation detection rate was 26.2% and 24.2% in breast and ovarian cancer, respectively, whereas the variant of uncertain significance rate was 18.03% and 24.2%, respectively. Among the pathogenic mutations, BRCA1 was the most common mutation in women with breast cancer (81.3%). In ovarian cancer, it was 50%. BRCA2 mutation was more prevalent in ovarian cancer (50%).

Conclusion: Our study reports a higher prevalence of germline BRCA1 and BRCA2 mutations in breast and ovarian cancer as compared to other studies. Genetic testing can be offered to high-risk women regardless of family history. This will be useful during diagnosis and help physicians in planning subsequent treatment.

Keywords: Next-generation sequencing, Hereditary breast and ovarian cancer, Prevalence, India

INTRODUCTION

In India, the incidence of breast cancer accounts for 1,78,361 cases, and the incidence of ovarian cancer accounts for 45,701 cases according to Globocan Report 2020.[1] These cancers are

known to have a hereditary basis. More than 10% the breast and ovarian cancer patients have pathogenic BRCA1 and BRCA2 mutations.[2,3] It has been observed that mutations in these genes are associated with an increased lifetime risk of developing breast cancer (increased from 50% to 85%) and ovarian cancer (increased from 13% to 50%) in women.[4]

The Anglian Breast Cancer Study Group reported the prevalence of BRCA1 and BRCA2 in women who were screened for breast cancer to be 1:400 and 1:500, respectively.[5] Other than BRCA1 and BRCA2, homologous recombination repair (HRR) genes such as ATM, BRIP1, CHEK2, CDH1, RAD50, RAD51C, PTEN, and PALB2 are also associated with hereditary breast and ovarian cancer (HBOC) syndrome.[6] For instance, one study reported that alterations in germline MSH6 increase the risk of ovarian cancer.[7]

Germline BRCA1, BRCA2, and other HRR gene mutations may also act as prognostic indicators for a variety of tumor types, including breast, ovarian, prostate, and lung cancers.[8,9] They are also good predictors of response for platinum-based (neo)/adjuvant regimens for patients with triple-negative breast cancer (TNBC) or advanced epithelial ovarian cancer.[10] Multiple phase studies have shown that germline and somatic pathogenic mutations in BRCA1 and BRCA2 predict sensitivity to poly ADP-ribose polymerase (PARP) inhibitors as well.[11]

In India, there is a paucity of data regarding the prevalence of BRCA1 and BRCA2 mutations. Available evidence shows rates ranging from 2.9% to 28%.[12,13] A multicentric cross-sectional study conducted in India reported a high prevalence of BRCA mutation among patients with ovarian cancer (25.2%) irrespective of family history.[14] However, gene mutations other than BRCA1 and BRCA2 which are shown to increase the risk of HBOC are underreported. This variation and underreporting could be due to the use of polymerase chain reaction (PCR)-based assays which easily identify the high-risk tumor suppressor genes without major mutation hotspots.[12,15,16]

Next-generation sequencing (NGS) allows analysis of multiple genes, BRCA, and the common ones mentioned above and has number of advantages over PCR in terms of lower cost, lower inhomogeneous coverage, reduced false-positive pathogenic variants, and reduced dropout of amplicons.[17] NGS is complimented with techniques such as multiplex ligation-dependent probe amplification (MLPA) assay, which is used to highlight large deletions and duplications in the BRCA1 and BRCA2 genes which are usually missed by standard sequencing techniques.[18]

Testing in a larger diverse population is recommended as finding a gene mutation opens up therapeutic possibilities as well as identifies carriers within the family. Data related to germline mutations in Western India are scarce and identifying these mutations will assist doctors in managing patients with breast and ovarian cancer in a more efficient manner. Hence, we used NGS with MLPA to determine the prevalence of germline mutations among women with breast and/or ovarian cancer patients undergoing treatment at a tertiary care center.

Objectives

The objective of this study was to estimate the prevalence of deleterious germline mutations among women with breast and/or ovarian cancer.

MATERIAL AND METHODS

A cross-sectional study was conducted in the department of oncology at a super specialty oncology hospital in Pune, India.

Inclusion criteria

1. Patients diagnosed with breast and/or ovarian cancer
2. Following were the enrollment criteria for this study, which were based on the current National Comprehensive Cancer Network (NCCN) guidelines for genetic risk and evaluation of HBOC:
    - Diagnosed with ovarian cancer at any age
    - Breast cancer at any age and had one or more of the following: at least two close blood relatives with breast cancer; had a first- or second-degree relative with one or more of the following: male breast cancer, pancreatic cancer, ovarian cancer, diagnosed at age ≤50 years, diagnosed with TNBC at age ≤60 years, two or more separate breast cancer primaries-synchronous/metachronous
    - Breast cancer at any age with at least one close blood relative with: Breast cancer age ≤50 years, male breast cancer, pancreatic cancer, or ovarian cancer. Male breast cancer, pancreatic cancer, breast cancer detected before age ≤45 years, and the diagnosis of three or more close blood relatives on the same side of the family.[19]

Exclusion criteria

1. Male patients
2. Female patients with breast and/or ovarian cancer with incomplete information with regards to the gene classification and variants were not eligible and were excluded.

In total, 106 patients diagnosed with breast and ovarian cancer between 2018 and 2021 were referred for genetic testing, among which 94 patients were eligible according to

the abovementioned criteria and were hence included in the study.

Data collection and management

Demographic and clinical information including age and cancer history (both personal and family) was extracted from the electronic medical records (EMRs) available in the hospital from December 2018 to December 2021. Blood samples were collected, coded for confidentiality, stored at the required temperature, and sent to the laboratory for germline mutation testing. DNA was extracted from blood and NGS was performed on the extracted DNA using a custom capture kit covering the complete coding segment of 143 genes with other non-coding or coding pathogenic variants <100 bp documented in ClinVar, Human Gene Mutation Database, BRCA Exchange, and Leiden Open source Variation Database were also included.[20,21] NGS libraries were sequenced to mean >80–100× coverage on the Illumina sequencing platform. The Genome Analysis Toolkit best practice framework for the identification of variants in the sample using Sentieon (v201808.07) was followed and gene annotation of variants was performed using the Variant Effect Predictor program.[22,23] Copy number variants were detected from targeted sequence data using the ExomeDepth method which is a coverage-based approach.[24]

The classification of variations was done based on the American College of Medical Genetics into five categories – class 1 benign, class 2 likely benign, class 3 variant of uncertain significance (VUS), class 4 likely pathogenic (LP), and lastly class 5 pathogenic (P). LP and P variants were defined as deleterious variants.[19]

The treating oncologist informed patients about their mutation test results and post-test genetic counseling was provided as per the local standard of care.

Data analysis

Data extracted from EMR were transferred to Excel format and data were analyzed in STATA 14. The germline mutation positive data were summarized in terms of frequency and percentage.

RESULTS

Ninety-four patients suspected of having HBOC were tested for deleterious germline mutations. Breast cancer patients constituted 64.9% ($n = 61$) and ovarian cancer 35.1% ($n = 33$). The median age was 46 years, with an interquartile range of 38 years to 57 years. Among breast cancers, more than half had TNBC (57.3%, 35/61), 32.8% (20/61) were estrogen receptor positive or/and progesterone receptor positive or/and human epidermal growth factor receptor 2 negative (ER+/PR+/HER2–), and 4.9% (3/61) were HER-2 positive (HER2+). More than three-fourths (75.7%, 25/33) of ovarian cancer patients had high-grade serous and 24.2% (8/33) had low-grade serous.

The overall mutation detection rate for ovarian cancer was 25.5% ($n = 24$), as depicted in [Figure 1]. For breast cancer patients, the positive mutation detection rate was 26.2% (16/61) of cases and the VUS rate was 18.03% (11/61); however, in cases of ovarian cancer, the positive mutations and VUS rates were 24.2% (8/33) of patients in both the groups [Figure 2].

We further analyzed the types of mutation observed in patients with a positive family history of breast and/or ovarian cancer. The cohort who had a significant family history of any cancer was 10.6% (10/94), whereas 33.3% (8/24) of patients, who had the pathogenic mutation, had a family history.

Among breast cancer women with pathogenic mutations, 75% had a history of cancer in their families (1st or 2nd relatives), whereas, in women with ovarian cancer, it was 25%. Similarly, BRCA1 mutations account for 75% of all gene mutations, while BRCA2 mutations are responsible for 25% of the mutation [Table 1].

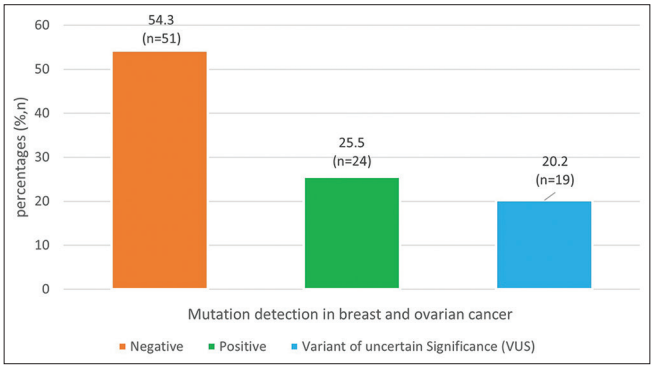

Figure 1: Prevalence of pathogenic (positive mutations) among breast and ovarian cancer patients tested for hereditary breast and ovarian cancer panel.

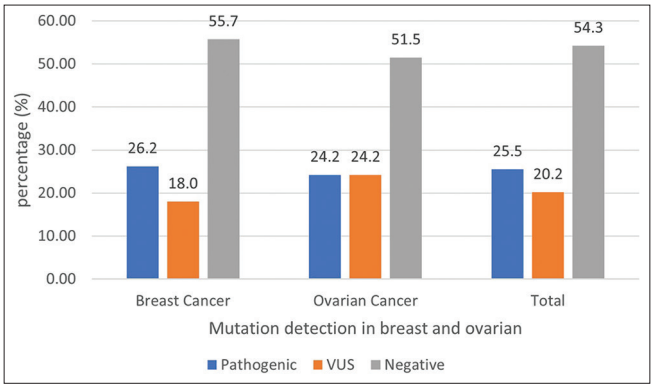

Figure 2: Distribution of breast and ovarian cancer patients tested for hereditary breast and ovarian cancer panel.

Frequency of BRCA1, BRCA2, and other pathogenic mutations among patients with breast and ovarian cancer

Pathogenic mutations were observed in four genes including BRCA1, BRCA2, CHEK2, and Transformation-related protein 53 (TP53) in this cohort. The most common mutation found was BRCA1 (70.8%, *n* = 17). BRCA2 mutations were seen in 20.8% (n = 5) of patients and non-BRCA mutation, was seen in 8.4% (n = 2).

In five patients, more than one mutation was reported. Of these, three patients with BRCA1 had additional mutations in MSH6, MutL protein homolog 1 (MLH1), and PALB2, respectively. One patient with BRCA2 harbored TP53 and PTPN11 mutations. All the additional mutations which were along with BRCA1 and BRCA2 were reported to be VUS. However, one patient reported TP53 along with PTEN was a pathogenic mutation.

Among patients with breast cancer (*n* = 16) harboring pathogenic mutations, BRCA1 was the most common mutation seen in 81.3% (13/16). According to subtypes, 62.5% (10/16) had triple-negative disease and 18.8% (3/16) had ER/PR+ and HER2− disease. BRCA2 was seen in only one patient with BRCA2 who had ER/PR+ and HER2− subtype. Non-BRCA mutations were seen in two patients with breast cancer and had triple-negative and ER/PR+ and HER2− disease subtypes. Among patients with ovarian cancer, BRCA1 and BRCA2 mutations were distributed equally (50%, *n* = 4). BRCA1 patients had high- and low-grade serous ovarian carcinoma whereas all BRCA2 patients had high-grade serous ovarian carcinoma, as mentioned in [Table 2].

Identification and distribution of different types of pathogenic variants in BRCA1, BRCA2, and other non-BRCA genes

Sixteen different types of pathogenic mutation were detected in BRCA1 and five in BRCA2. One recurrent mutation reported in BRCA1 was seen in c.68_69del. This mutation was detected in three patients in our cohort. The distribution of the pathogenic variants is shown in [Table 3].

VUS in breast and ovarian cancer

The prevalence of VUS in our cohort was 20.2% (19/94) and among these, 57.9% (11/19) was found in breast cancer patients and 42.1% (8/19) in ovarian cancer. VUS in BRCA made up a minority of cases (21.1%, 4/19) with one breast cancer of triple-negative subtype and three high-grade serous ovarian cancer. The majority of VUS was seen in non-BRCA genes (78.9%, 15/19) [Table 4].

DISCUSSION

Our study used a multigene HBOC panel and found that 25.5% of breast and ovarian cancers harbored pathogenic germline mutations. This is a higher prevalence of mutations as compared to a large cohort study conducted among

Table 1: Details of mutation among breast and/or ovarian cancer patients with family history.

Breast or Ovarian Cancer	Subtypes	Gene	Exon	Mutation	Age at diagnosis (in years)
Breast Cancer	ER+/PR+/HER2−	BRCA1	10	c. 1504_1508del	50
Breast Cancer	TNBC	BRCA1	2	c. 68_69del	30
Breast Cancer	TNBC	BRCA1	18	c. 5196del	30
Breast Cancer	TNBC	BRCA1	24	5566C>T	30
Breast Cancer	ER+/PR+/HER2−	BRCA2	10	1301_1304del	42
Breast Cancer	TNBC	BRCA1	Int-17	c. 5137+1G>A	39
Ovarian Cancer	High grade serous	BRCA2	Int-2	c. 68-1_81del	55
Ovarian Cancer	High grade serous	BRCA1	6	484del	53

TNBC: Triple-negative breast cancer, ER+: Estrogen receptor positive, PR+: Progesterone receptor positive, HER−: Human epidermal growth factor receptor 2 negative

Table 2: Pathogenic mutations observed in breast cancer subtypes and ovarian cancer.

Gene	Breast cancer (*n*=16)		Ovarian cancer (*n*=8)	
Sub-types	TNBC (*n*=11)	ER/PR+and HER2− (*n*=5)	High grade serous (*n*=6)	Low grade serous (*n*=2)
BRCA1 *n* (%)	10 (62.5)	3 (18.8)	2 (25)	2 (25)
BRCA2 *n* (%)	0 (0)	1 (6.3)	4 (50)	0 (0)
Non-BRCA *n* (%)	1 (6.3)	1 (6.3)	0 (0)	0 (0)

TNBC: Triple-negative breast cancer, ER+: Estrogen receptor positive, PR+: Progesterone receptor positive, HER−: Human epidermal growth factor receptor 2 negative

Table 3: Distribution of various pathogenic variants.

Breast/Ovarian cancer	Pathogenic gene mutation	Variants	Frequency
Ovarian cancer	BRCA-1	c. 833T>A	1
Breast cancer	BRCA-1	c. 68_69del	2
Ovarian cancer	BRCA-1	c. 68_69del	1
Ovarian cancer	BRCA-1	2269del	1
Breast cancer	BRCA-1	2866_2870del	1
Breast cancer	BRCA-1	5129T>A	1
Breast cancer	BRCA-1	5566C>T	1
Breast cancer	BRCA-1	c. 122del	1
Breast cancer	BRCA-1	c. 1504_1508del	1
Breast cancer	BRCA-1	c. 2338C>T	1
Breast cancer	BRCA-1	c. 2410_2413del	1
Breast cancer	BRCA-1	c. 2679_2682del	1
Breast cancer	BRCA-1	c. 4357+2T>C	1
Ovarian cancer	BRCA-1	c. 4571C>A	1
Breast cancer	BRCA-1	c. 5137+1G>A	1
Breast cancer	BRCA-1	c. 5196del	1
Breast cancer	BRCA-2	1301_1304del	1
Ovarian cancer	BRCA-2	484del	1
Ovarian cancer	BRCA-2	880G>T	1
Ovarian cancer	BRCA-2	c. 486del	1
Ovarian cancer	BRCA-2	c. 68-1_81del	1
	Non-BRCA		
Breast cancer	CHEK2	938delinsTT	1
Breast cancer	TP53	c. 1042G>A	1
	Total		24

BRCA1: Breast Cancer Gene 1, BRCA2: Breast Cancer Gene 2, CHEK2: Checkpoint Kinase 2, TP53: Tumour Protein 53

Table 4: Frequency of VUS in breast and ovarian cancer.

Gene	Breast cancer (*n*=11)	Ovarian cancer (*n*=8)
VUS BRCA2 *n* (%)	1 (9.1%)	3 (37.5%)
VUS Non-BRCA *n* (%)	10 (90.9%)	5 (62.5%)

VUS: Variant of uncertain significance

high-risk Chinese individuals.[25] BRCA1 and BRCA2 were observed as the most commonly mutated genes in our study. It was more frequent in the breast than in ovarian cancer. This finding has been endorsed by numerous other studies as well.[5,14,26,27] A study conducted by Valarmathi *et al*. in India reported the prevalence of deleterious germline BRCA1 mutation among breast cancer as 16% which is lower as compared to our study.[28] Other than BRCA1 and BRCA2, other non-BRCA genes such as CHEK2 and TP53 were identified as pathogenic variants which were also found in Matta *et al*.'s study.[29] A common recurrent founder mutation in BRCA1 was c.68_69del which is also reported in two different studies conducted in India.[30,31]

Multigene panel testing is associated with a higher frequency of VUS.[32] The VUS prevalence in our study was 20.2%; however, VUS in BRCA2 and other non-BRCA genes was reported to be similar to that of Gupta *et al*.'s study.[14]

The prevalence of germline pathogenic BRCA1 and BRCA2 mutations among patients who have a family history seems to be higher in breast cancer as compared to ovarian cancer patients. These findings are corroborated by Singh *et al*.'s study which was conducted on over 1000 Indian patients with breast and/or ovarian cancer and reported that positive family history has significantly increased the possibility of detecting mutation among breast cancer (basically in triple negatives) as compared to ovarian cancer.[31]

The strength of our study lies in the inclusion of patients of all ages in the adult groups and those with or without relevant family history. Angeli *et al*. reported that presently selection of patients for genetic testing is based on family history and age of onset.[33] However, studies suggest different models to select patients for multigene panel test.[34] These study results emphasize that genetic testing is important irrespective of family history. Furthermore, BRCA positivity has recently been approved as a biomarker to predict sensitivity to both platinum chemotherapy and PARP inhibitors.[35] Therefore, testing is important from the aspect of prevention and risk reduction and in planning further treatment.

The high prevalence rate of a germline mutation in an unselected cohort also emphasizes that local guidelines be developed for genetic testing in India which can also be included as part of the National Health Programme, that is National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Disease and Stroke.

There are several limitations to our study. First, the findings of this study cannot be generalized due to a small sample size and hospital-based cross-sectional study, which may include a referral bias. Furthermore, our study does not capture the diversity of mutations, as it is not representative of the genetic variation seen across India. Hence, multicenter studies involving different parts of India would provide the true prevalence of germline mutation in breast and ovarian cancer patients. This has been addressed to some extent by the study of Gupta *et al.* but was restricted only to patients with ovarian cancer.[14]

However, despite these limitations, our study adds information regarding the prevalence of germline mutation in breast and ovarian cancer and emphasizes the need and scope of germline testing in the Indian population.

CONCLUSION

Our study results suggest a higher prevalence of germline BRCA1 and BRCA2 mutations in breast and ovarian cancer as compared to other studies in India. Genetic testing to any high-risk woman regardless of family history should be recommended, which will be useful at diagnosis and help physicians in planning the treatment and estimating risk prevention in family members.

Ethics

This study was approved by the institutional review board of our hospital and all the patient information was coded and kept confidential.

Declaration of patient consent

Patient's consent not required as patient's identity is not disclosed or compromised.

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Nil.

Conflicts of interest

There are no conflict of interest.

REFERENCES

1. International Agency for Research on Cancer (IARC), World Health Organization. Latest Global Cancer Globocan; 2020 (India). Available from: https://gco.iarc.fr/today/data/factsheets/populations/356-india-fact-sheets.pdf [Last accessed on 2022 Oct 25].
2. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature 2011;474:609-15.
3. Koboldt DC, Fulton RS, McLellan MD, Schmidt H, Kalicki-Veizer J, McMichael JF, *et al*. Comprehensive molecular portraits of human breast tumours. Nature 2012;490:61-70.
4. Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips KA, Mooij TM, Roos-Blom MJ, *et al*. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. JAMA 2017;317:2402-16.
5. Anglian Breast Cancer Study Group. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Anglian Breast Cancer Study Group. Br J Cancer 2000;83:1301-8.
6. Cao WM, Gao Y, Yang HJ, Xie SN, Ding XW, Pan ZW, *et al*. Novel germline mutations and unclassified variants of BRCA1 and BRCA2 genes in Chinese women with familial breast/ovarian cancer. BMC Cancer 2016;16:64.
7. Kaufman B, Shapira-Frommer R, Schmutzler RK, Audeh MW, Friedlander M, Balmaña J, *et al*. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol 2015;33:244-50.
8. Lee YC, Lee YC, Li CY, Lee YL, Chen BL. BRCA1 and BRCA2 gene mutations and lung cancer sisk: A meta-analysis. Medicina (Lithuania) 2020;56:212.
9. Stone L. The IMPACT of BRCA2 in prostate cancer. Nat Rev Urol 2019;16:639.
10. Swisher EM, Lin KK, Oza AM, Scott CL, Giordano H, Sun J, *et al*. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): An international, multicentre, open-label, Phase 2 trial. Lancet Oncol 2017;18:75-87.
11. Menezes MC, Raheem F, Mina L, Ernst B, Batalini F. PARP inhibitors for breast cancer: Germline BRCA1/2 and beyond. Cancers (Basel) 2022;14:4332.
12. Hansa J, Kannan R, Ghosh SK. Screening of 185DelAG, 1014DelGT and 3889DelAG BRCA1 mutations in breast cancer patients from North-East India. Asian Pac J Cancer Prev 2012;13:5871-4.
13. 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.
14. Gupta S, Rajappa S, Advani S, Agarwal A, Aggarwal S, Goswami C, *et al*. Prevalence of BRCA1 and BRCA2 mutations among patients with ovarian, primary peritoneal, and fallopian tube cancer in India: A multicenter cross-sectional study. JCO Glob Oncol 2021;7:849-61.
15. Francis AM, Ramya R, Ganesan N, Kumarasamy P, Paul SF, Munirajan AK, *et al*. Analysis of BRCA1 gene exon 2 mutation in breast cancer patients in a South Indian population. Res J Pharm Technol 2018;11:4592-6.
16. Verma A, Nag S, Hasan Q, Selvakumar VP. Mainstreaming genetic counseling for BRCA testing into oncology clinics-Indian perspective. Indian J Cancer 2019;56:38.

17. Desmond A, Kurian AW, Gabree M, Mills MA, Anderson MJ, Kobayashi Y, *et al*. Clinical actionability of multigene panel testing for hereditary breast and ovarian cancer risk assessment. JAMA Oncol 2015;1:943-51.
18. Negură L, Carasevici E, Artenie V, Negură A. Using MLPA for large genomic rearrangements detection in breast cancer predisposition genes. Rev Med Chir Soc Med Nat Iasi 2009;113:1182-90.
19. Daly MB, Pilarski R, Berry M, Buys SS, Farmer M, Friedman S, *et al*. NCCN guidelines insights: Genetic/familial high-risk assessment: Breast and ovarian, version 2.2017. J Natl Compr Cancer Netw 2017;15:9-20.
20. Stenson PD, Mort M, Ball EV, Evans K, Hayden M, Heywood S, *et al*. The human gene mutation database: Towards a comprehensive repository of inherited mutation data for medical research, genetic diagnosis and next-generation sequencing studies. Hum Genet 2017;136:665-77.
21. Cline MS, Liao RG, Parsons MT, Paten B, Alquaddoomi F, Antoniou A, *et al*. BRCA Challenge: BRCA Exchange as a global resource for variants in BRCA1 and BRCA2. PLoS Genet 2018;14:e1007752.
22. Freed D, Aldana R, Weber J, Edwards J. The sentieon genomics tools-a fast and accurate solution to variant calling from next-generation sequence data. Biorxiv 2017. DOI: 10.1101/115717
23. McLaren W, Pritchard B, Rios D, Chen Y, Flicek P, Cunningham F. Deriving the consequences of genomic variants with the Ensembl API and SNP effect predictor. Bioinformatics 2010;26:2069-70.
24. Plagnol V, Curtis J, Epstein M, Mok KY, Stebbings E, Grigoriadou S, *et al*. A robust model for read count data in exome sequencing experiments and implications for copy number variant calling. Bioinformatics 2012;28:2747-54.
25. Shao D, Cheng S, Guo F, Zhu C, Yuan Y, Hu K, *et al*. Prevalence of hereditary breast and ovarian cancer (HBOC) predisposition gene mutations among 882 HBOC high-risk Chinese individuals. Cancer Sci 2020;111:647-57.
26. Fernandes GC, Michelli RA, Galvão HC, Paula AE, Pereira R, Andrade CE, *et al*. Prevalence of BRCA1/BRCA2 mutations in a Brazilian population sample at-risk for hereditary breast cancer and characterization of its genetic ancestry. Oncotarget 2016;7:80465-81.
27. Soumittra N, Meenakumari B, Parija T, Sridevi V, Nancy KN, Swaminathan R, *et al*. Molecular genetics analysis of hereditary breast and ovarian cancer patients in India. Hered Cancer Clin Pract 2009;7:13.
28. Valarmathi MT, Agarwal A, Deo SS, Shukla NK, Das SN. BRCA1 germline mutations in Indian familial breast cancer. Hum Mutat 2003;21:98-9.
29. Matta BP, Gomes R, Mattos D, Olicio R, Nascimento CM, Ferreira GM, *et al*. Familial history and prevalence of BRCA1, BRCA2 and TP53 pathogenic variants in HBOC Brazilian patients from a public healthcare service. Sci Rep 2022;12:18629.
30. Valarmathi MT, Sawhney M, Deo SS, Shukla NK, Das SN. Novel germline mutations in the BRCA1 and BRCA2 genes in Indian breast and breast-ovarian cancer families. Hum Mutat 2004;23:205.
31. Singh J, Thota N, Singh S, Padhi S, Mohan P, Deshwal S, *et al*. Screening of over 1000 Indian patients with breast and/or ovarian cancer with a multi-gene panel: Prevalence of BRCA1/2 and non-BRCA mutations. Breast Cancer Res Treat 2018;170:189-96.
32. Schroeder C, Faust U, Sturm M, Hackmann K, Grundmann K, Harmuth F, *et al*. HBOC multi-gene panel testing: Comparison of two sequencing centers. Breast Cancer Res Treat 2015;152:129-36.
33. Angeli D, Salvi S, Tedaldi G. Genetic predisposition to breast and ovarian cancers: How many and which genes to test? Int J Mol Sci 2020;21:1128.
34. Antoniou AC, Pharoah PP, Smith P, Easton DF. The BOADICEA model of genetic susceptibility to breast and ovarian cancer. Br J Cancer 2004;91:1580-90.
35. Yang D, Khan S, Sun Y, Hess K, Shmulevich I, Sood AK, *et al*. Association of BRCA1 and BRCA2 mutations with survival, chemotherapy sensitivity, and gene mutator phenotype in patients with ovarian cancer. JAMA 2011;306:1557-65.

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