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Editorial

Trends of germline mutations in women with breast and ovarian carcinoma

Satinder Kaur[1], Megha Nandwani[2]

[1]Department of Gynaecological Oncology, Dharamshila Narayana Superspeciality Hospital, New Delhi, [2]Department of Gynaecological Oncology, Chittaranjan National Cancer Institute, Kolkata, West Bengal, India.

***Corresponding author:**
Satinder Kaur,
Department of Gynaecological Oncology, Dharamshila Narayana Superspeciality Hospital, New Delhi, India.

satinder31@gmail.com

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The GLOBOCAN statistics of 2020 have ranked breast carcinoma as number one among women in India with an incidence of 26.3%. Carcinoma ovary has also seen rising trends and ranks third among female cancers with an incidence of 6.7% in Indian women.[1] The most prevalent cancer in the world is breast carcinoma, accounting for 7.8 million cases over the past 5 years.[1] Both these cancers are often associated with germline mutations that most commonly involve breast cancer gene 1 (BRCA1) and breast cancer gene 2 (BRCA2) genes. When patients of carcinoma breast and ovary are subjected to molecular genetic testing, it is seen that 66% of cases with BRCA1 positive and 34% of cases with BRCA2 positive status are associated with hereditary breast-ovarian cancer syndrome (HBOC).[2] The mean cumulative risk of breast cancer is 57% in BRCA1 mutation carriers and 49% in BRCA2 mutation carriers, while ovarian cancer risk in women with BRCA1 and BRCA2 mutations is 40% and 18%, respectively.

The prevalence of BRCA1 and BRCA2 mutations in the general population is reported to be around 0.2–0.3%.[3] It has been noted that substantial variation of the BRCA gene has been seen in different geographical areas as well as race or ethnicity. In the United States itself, the variants observed in African Americans are not seen in any other racial groups.[4,5]

India is a diverse country with multiple ethnic societies dwelling on the same island, and thus, a diverse spectrum of germline mutations is seen in patients with HBOC. Many authors have studied the prevalence of these mutations in the Indian population. Gupta *et al.*[6] reported the prevalence of pathogenic variants in women with ovarian cancer as 15.7% with BRCA1 and 5.9% with BRCA2 mutations. Singh *et al.*[7] sequenced 1010 unrelated patients and their families across India with an indication of breast or ovarian cancer. They included 14 genes for sequencing and found out that 30% of patients have germline mutations and out of these, 84.9% of the mutations were detected in BRCA1 and BRCA2.

Kulkarni *et al.*[8] also have highlighted the prevalence of germline mutations in breast and ovarian carcinoma in their study that has been published in the present issue of this journal. The study was conducted at a tertiary cancer center in Pune, India. Ninety-four patients of HBOC were screened using the next-generation sequencing (NGS) method for genetic testing. They found that 25.5% of the patients had pathogenic germline patients, which is much higher than Western data. The most common mutation reported was BRCA1 in 70.8% of cases, whereas BRCA2 was found in 20.8% of the study population. The pathogenic mutations observed in the present study were in four genes that are BRCA1, BRCA2, checkpoint kinase 2, and tumor protein 53. There are limited data on genetic testing of germline mutations in India and this study contributes to

helping us identify the variants and prevalence of BRCA genes in Indian women.

The importance of germline testing in patients with breast and ovarian cancer cannot be more stressed. From the decision of treatment regimens, genetic counseling, and screening strategies to prophylactic surgeries, all depend on the results of genetic sequencing. In this study, National Comprehensive Cancer Network guidelines[9] have been used for genetic testing in patients and the classification of variations in genetic mutations is based on the American College of medical genetics. This may miss out on many patients with both BRCA and non-BRCA mutations, who would have otherwise benefitted. Familial risk assessment tools along with genetic counseling should be used for appropriate assessment as suggested by the US Preventive Services Task Force.

The study underscores the need for increased awareness about the role of genetic testing in breast and ovarian cancer management. It highlights the potential benefits of incorporating NGS techniques and multigene panel testing in routine clinical practice. The molecular analysis of germline mutations can be reliably tested using the NGS as it is a sensitive and quicker method.[10] Kulkarni *et al*.[8] used the same method for the detection of BRCA testing and have been able to identify sixteen different types of pathogenic mutations. This study did not use the multiplex ligation-dependent probe amplification (MLPA) technique which is required for the detection of alterations in the copy number of specific deoxyribonucleic acid sequences. Studies have shown that approximately 5–10% of all BRCA1/2 mutations are large deletions or duplications. Therefore, if MLPA is not employed in the testing process, these mutations could potentially be missed in that subset of patients.

The findings of the study revealed several important insights. The prevalence of pathogenic BRCA1 mutations was higher in women with breast cancer (81.3%), while BRCA2 mutations were more prevalent in ovarian cancer (50%). The notable finding in the study was that most of the cases with non-BRCA gene mutations were classified as variants of uncertain significance (VUS) type of variation. VUS was seen in 18.03% and 24.2% of breast and ovarian cancer cases, respectively. The significance of a VUS can change as more information becomes available through ongoing research and scientific advancements. Therefore, VUS results should be interpreted very cautiously.

Genetic counseling plays a pivotal role in guiding individuals at risk of carrying BRCA mutations. By providing information about the significance of genetic testing, the implications of test results, and available preventive measures, genetic counselors can empower individuals and families to make informed decisions. In this study, no pre-test counseling was done, though the treating oncologist did inform the patient about the results and post-test counseling was provided. Genetic counseling by trained healthcare professionals helps facilitate informed decision-making and more personalized care of patients with hereditary cancer syndromes. Strengthening the genetic counseling infrastructure in India, both in terms of trained professionals and support services is essential to effectively manage the prevalence of BRCA mutations.

This study contributes significantly to the existing knowledge regarding the prevalence of BRCA gene mutations in breast and ovarian cancer patients in India. Although the findings of this study are comparable to other Indian and Western literature, due to the small sample size and focus on a single tertiary care center, it is difficult to generalize the results and draw meaningful conclusions. The emphasis on genetic testing especially in patients with positive family history is appropriately conveyed. Collaborating data from various cross-sectional and prospective studies across the country, research articles, and multicentric data will give us more insight into a comprehensive understanding of the prevalence and impact of BRCA mutations in the Indian population. This will help in the formulation of regional recommendations and guidelines specific to the needs of our population.

This study provides valuable insights into the prevalence of germline mutations, particularly BRCA1 and BRCA2, in breast and ovarian cancer patients in India. In the Indian scenario, the prevalence of germline mutations in patients with hereditary breast and ovarian cancer seems to be higher as compared to the Western literature. Seeing the trends and the advancements in treatment policies, consideration must be given to recommend genetic testing irrespective of family history. The availability of cost-effective models for genetic sequencing to cover the diverse Indian population is the need of the hour. This data is thought-provoking and highlights the importance of incorporating genetic testing in our everyday practice to strategize screening, prevention, and treatment of hereditary breast-ovarian tumors.

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