



Universal Germline Genetic Testing in Epithelial Ovarian Cancer: Promises and challenges

Rima Sanjay Pathak¹ Rajiv Sarin¹

¹Department of Radiation Oncology, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India

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Address for correspondence Rima Sanjay Pathak, MD, 1128, Homi Bhabha Block, Department of Radiation Oncology, Tata Memorial Hospital, Dr. Earnest Borges Road, Parel, Mumbai 400012, Maharashtra, India (e-mail: drrimapathak@gmail.com).

Epithelial ovarian cancer (EOC) is the third most common cancer among Indian women. Despite the advances in their management, EOC patients have the highest mortality among gynecological cancers.¹ Globally, nearly 70% of EOC is present in stage III/IV and this reflects poor survival outcomes. This makes cancer prevention and early detection a high research priority. The presence of pathogenic germline mutation with a predisposition to cancer development and a personal or family history of cancer are among the most important risk factors for the development of EOC.

Across different parts of the world, EOC has been reported to have the highest prevalence of germline genetic mutations (10–40%) among all the cancers occurring in females.^{2–4} This variation in prevalence is partly determined by the selection criteria for genetic testing. Recognizing this high probability of underlying germline mutations, various professional societies and NCCN, have recommended germline genetic testing for EOC.^{5,6} These guidelines suggest using different criteria based on family history, age at diagnosis, or histology.^{5,6}

Various societies suggest using different criteria to select patients for genetic testing for several reasons such as the high cost of testing, prolonged wait times for genetic counseling, and the adverse impact these results may have on health insurance, psychosocial and mental state, and family dynamics. Selection based on family history, age at diagnosis, or histological characteristics help to enrich the cohort for genetic counseling and testing. However, it is being increasingly recognized that germline pathogenic or likely pathogenic variants may be identified in EOC patients who do not fulfill certain genetic testing criteria.^{7,8} This is due to incomplete penetrance, paternal inheritance, unreliable family history, or small family size.

Moreover, the frequency and spectrum of *BRCA1/2* and other gene mutations vary in different geoeethnic groups.^{2,3,9} The frequency and the type of mutations associated with various histologies also differ.⁹

A study from Ontario evaluating physician practices showed that genetic testing rates and referrals reduce with the increasing complexity of testing criteria.¹⁰ Research studies employing germline multigene panel testing of large unselected EOC populations could provide a more reliable estimate of the prevalence of germline mutations and the most commonly mutated genes in EOC cases in the population. This information would facilitate genetic counseling and help frame evidence-based guidelines for genetic testing, which is an expensive test with a turn-around time of 4 to 6 weeks.

This study provides the much-required detailed information of the prevalence in unselected Indian ovarian cancer patient population (15.5%) while also providing estimates for various enriched subgroups of patients who are ≤ 50 years (22.2%), serous epithelial ovarian cancers (25.2%), or those with a family history of cancer (55.6%).¹¹ The results show that the prevalence of germline mutations is much higher than most solid tumors. Contrary to expectations, subgroups such as non-serous (13.8%), older than 50 years (20.8%), or those without a family history (20.2%) also had a clinically relevant prevalence of germline mutation.¹¹ This implies that several patients will be unable to qualify for the genetic test if any selection criteria are used. Identifying the maximum number of index EOC cases will not only help to personalize their therapy, provide cancer surveillance, and ensure future cancer prevention but also extend the benefit of identifying family members who have inherited the mutation and through culturally sensitive and evidence-

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based genetic counseling, testing, and risk management approaches.^{12,13} The recent negative results of the UK Collaborative Trial of Ovarian Cancer Screening study of lack of benefit of ovarian cancer screening using annual transvaginal ultrasound or longitudinal CA-125¹⁴ highlights the continued relevance of timely risk-reducing salpingo-oophorectomy for women with germline *BRCA1/2* mutations.

With patients enrolled from three centers in Delhi, two in Mumbai, and one each in Bengaluru and Hyderabad, major goethnic groups within India are likely to be represented. However, with a relatively small cohort of 239 cases and the non-inclusion of several large and small Indian states, several goethnic groups with a different population prevalence of germline *BRCA* mutations and founder mutations would be under-represented. Furthermore, it is unclear if this represents a consecutive patient cohort or some form of selection was present. As seen previously in many studies that selecting patients based on any criteria can inflate the prevalence leading to erroneous estimates. In addition to the *BRCA1/2* genes, mutations in other genes associated with the development of ovarian cancer such as *PALB2*, *PRIB1*, the core *RAD* genes, *CHEK2* among others were not reported even though a 94 gene NGS panel was used.^{2,7,11} Moreover, copy number variation or large genomic rearrangement were not reported, which potentially lead to underestimation of the prevalence.

Are we ready to implement genetic counseling and testing in unselected EOC population? As per the GLOBOCAN 2018 data, more than 36,000 ovarian cancer patients are diagnosed every year in India, with the vast majority being EOC.¹ Currently, in India, there are a limited number of trained genetic counselors and pre-test genetic counseling will be the rate-limiting step if unselected population testing is implemented. Therefore, before the implementation of unselected population testing, building the required capacity and infrastructure by adopting the mainstreaming pathway is required. Here, the primary care physician/oncologist provides pre-test counseling for patients without a significant family history or psychosocial issues and detailed post-test counseling of mutation carriers in the cancer genetics clinic. Such a model has been adopted in the UK and Malaysia and has been shown to improve access to genetic testing by reducing waiting times for counseling.¹⁵

Thus, this study provides important information on the prevalence of germline mutations among ovarian cancer patients from India and leads to the realization of many challenges with its practical implementation across the country. There is a need for such studies to generate the prevalence of germline mutations in other cancer-predisposing genes in ovarian cancers of different histologies and other common cancers among Indian patients. This is among the first few steps toward the expansion of access to genetic testing among cancer patients and their family members in India.

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Conflict of Interest

Dr. Rima Sanjay Pathak is a member on the Data safety and monitoring at Tata Memorial Centre, Mumbai.

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