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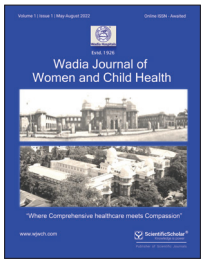

Review Article

Hereditary breast and ovarian cancers: A comprehensive overview of genetic testing, counseling, and treatment

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ABSTRACT

Hereditary breast and ovarian cancers (HBOCs) syndrome is the most common of all hereditary cancers. A harmful *BRCA1* or *BRCA2* mutation can be inherited from one generation to another. Timely genetic testing and genetic counseling are very important in early diagnosis and treatment of the disease. This can help in either avoiding the disease or at least postponing the onset of the disease. This perspective is written for improving the knowledge and counseling skills of health-care providers in offering genetic services for HBOCs.

Keywords: *BRCA1*, *BRCA2*, Breast and ovarian cancer, Genetic counseling, Hereditary breast and ovarian cancers

INTRODUCTION

Hereditary breast and ovarian cancer (HBOC) syndrome is an inheritable syndrome that possibly increases the individuals susceptibility to develop mainly breast and/or ovarian cancer at an early age. It is caused by mutation in *BRCA1* or *BRCA2* genes.[1] Approximately 5–10% of all the breast cancer cases and 20–25% of inheritable breast cancer cases show mutations in *BRCA1* or *BRCA2* genes, whereas in cases of ovarian cancer, mutations are seen in 15% of cases.[2] The protective effect of these *BRCA1* and *BRCA2* gene is due to their ability to produce tumor suppressor proteins. These proteins help in repairing damaged DNA and play an important role in maintaining the stability of the genetic material present in the cell.[3] When there is any mutation in these genes, the protein product is either not produced or does not function correctly. This does not allow the DNA damage to be repaired efficiently. As a result, cells are more likely to develop additional genetic alterations that can lead to cancer. Although breast and ovarian cancers are the predominant cancers associated with *BRCA1* and *BRCA2*, other cancers that have shown some association are prostate, pancreatic, and melanoma.[4]

Health-care providers at primary and secondary health care levels have a diagnostic dilemma when treating women having family history of reproductive cancers. Hence, it is of importance

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that they should be aware of HBOC syndrome. The consensus statement of experts from the Indian Society of Medical and Pediatric Oncology offers practical advice for determining which patients should be referred for genetic counseling and testing, based on their family history, ancestry, and personal history of HBOC.[5]

This perspective is written to improve the knowledge and counseling skills of these health-care providers at primary or secondary health care level. Further, we aim to propose a screening and counseling algorithm which will improve diagnostic ability of these health-care providers and ultimately benefit the society at large [Figure 1].

INHERITANCE AND PREVALENCE OF HBOC

It is an autosomal dominant inheritance which means if a parent carries a mutation in one of these genes that there is a 50% chance (1 in 2) of inheriting the mutation to their offspring. A harmful *BRCA1* or *BRCA2* mutation can be inherited from one generation to another. The effects of mutations in *BRCA1* and *BRCA2* are seen even when a person's second copy of the gene is normal. The prevalence in general population is 1:400. However, higher prevalence of specific *BRCA1* and *BRCA2* mutations are associated with some ethnic groups, such as those of Ashkenazi Jewish descent.[5] The reported prevalence of BRAC1 and BRAC2 among Indian women varies from 16.6% among women with breast cancer and 15.5% and 5.9% among those with ovarian cancer.[6,7]

GENETIC SCREENING FOR HBOC

Since a small proportion of population carries a *BRCA1* or *BRCA2* mutation, genetic testing is not recommended for the general population. *BRCA1* and *BRCA2* testing should be considered for individuals with a family history of a *BRCA1* or *BRCA2* mutation or a personal history of breast or ovarian cancer.

Genetic testing should be considered for individual from a family with a known deleterious *BRCA1/BRACA2* mutation or personal history of breast cancer diagnosed at or below 45 years of age or diagnosed at or below 50 years with an additional primary breast cancer.[8,9] Furthermore, those having one or more close blood relative with breast cancer at any age, or one or more close relative with pancreatic cancer or one or more relative with prostate cancer should be tested. Since the onset of the disease is in adult life, minors (below 18 years) should not be tested.

Table 1 summarizes the criteria for genetic testing based on family history, personal history, and ethnicity.

People considered for genetic testing for *BRCA1* and *BRCA2* mutations should be counseled regarding the potential uncertainties before undergoing testing by the genetic counselor.[5]

GENETIC COUNSELING FOR HBOC

A pre-test counseling is done in which detailed personal and family medical history is obtained. Differences between sporadic

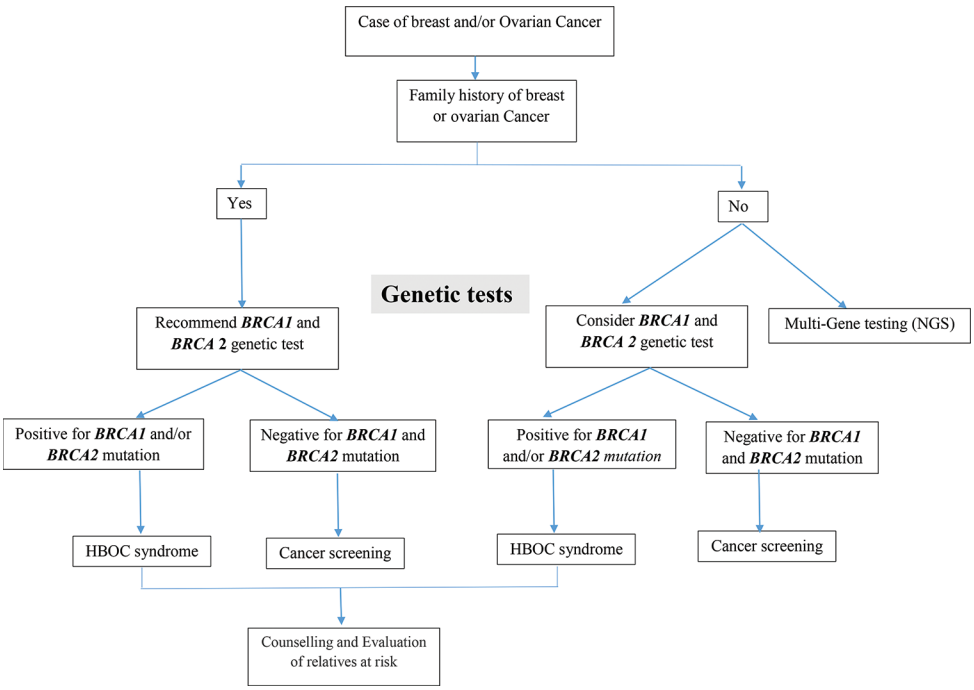

Figure 1: Proposed algorithm for hereditary breast and ovarian cancers screening and counseling. NGS: Next generation sequencing, HBOC: Hereditary breast and ovarian cancer.

Table 1: Summarizing the criteria for genetic testing based on family history, personal history, and ethnicity.

Criteria for genetic testing	Details
Limited or no family history	Diagnosed at or below age 60 with triple (ER, PR, and HER2) negative breast cancer
Family history of breast cancer	(a) Close blood relative with breast cancer at or below age 50 (b) Two or more close blood relatives with breast cancer at any age, including one with invasive ovarian cancer
Family history of pancreatic or prostate cancer	Two or more close blood relatives with pancreatic or prostate cancer at any age
Ethnic group with higher mutation frequency	Individuals of Ashkenazi Jewish descent
Personal history of invasive ovarian or breast cancer	Considered for genetic testing
Personal history of prostate cancer	At any age with one or more close blood relatives with breast cancer (at or below 50), invasive ovarian, pancreatic, or prostate cancer at any age
Genetic counseling	Individuals considered for *BRCA1* and *BRCA2* mutations testing should be counseled about potential uncertainties before testing

ER: Estrogen receptor, PR: Progesterone receptor, HER2: Human epidermal growth factor receptor 2

and hereditary cancer are explained. Transmission risk of HBOC and family risk assessment needs to be done in counseling session. Appropriate test should be selected after discussing the benefits and limitations of genetic testing to make an informed decision. A post-test counseling is also recommended in which the medical implications of a positive or a negative test result, psychosocial assessment, and support and possible options for cancer risk management, including enhanced screening and surgery along with available support services should be discussed.

GENETIC TESTING FOR HBOC

For sample collection, approximately 5–6 mL of peripheral blood sample is collected in ethylenediaminetetraacetic acid vacutainer. The sample sent to laboratory should reach preferably within 24–48 h and it usually takes about a month to get the test results. The DNA extracted from blood sample is subjected to mutation studies.

TYPES OF GENETIC TESTING

Following different approaches can be adopted for genetic testing based on the history:

BRCA1/BRCA2 mutations study by sequencing

This involves complete *BRCA1* and *BRCA2* gene mutation testing by Sanger sequencing or next- generation sequencing (NGS). All the coding exons as well as exon-intron boundaries are analyzed in both genes. All the variations are compared against the available databases and further classified as Class 1 to Class 5 indicating benign to pathogenic nature of the mutation.

BRCA1/2 deletion duplication by multiplex probe ligation assay (MLPA)

The large rearrangements in *BRCA1/2* cannot be detected by sequencing and needs MLPA studies. However, the frequency of these mutations is very low.

A comprehensive *BRCA* analysis

Sequencing and large deletion duplication studies both are done together.

Hereditary cancer panel

All the genes reported to be associated with breast and ovarian cancer along with *BRCA 1&2* are tested by NGS platform, usually by whole exome sequencing.

Targeted approach

BRCA1 or *BRCA2* mutation if identified in an individual with breast and/or ovarian cancer,[10] then that specific mutation only can be tested in other family members to assess their risk.

Interpretation of results of genetic testing

Interpretation of the test result is very crucial and has to be correlated clinical and family history.

Positive test result indicates that a person has inherited a known harmful mutation in *BRCA1* or *BRCA2* gene, and hence, the individual will be at an increased risk of developing certain cancers. A positive test result cannot tell whether or when an individual will actually develop cancer. Also, some women who inherit a harmful *BRCA1* or *BRCA2* mutation may never develop breast or ovarian cancer.[11] A positive genetic test result may have important health and social implications for family members and future generations as genetic test results are applicable not only to the individual being tested but also to person's blood relatives. Inherited harmful *BRCA1*or *BRCA2* mutations, irrespective of whether or not it develops cancer in an individual, may pass the mutation on to their sons and daughters. There is

50% chance of inheriting a parent's mutation to next generation.

Negative test result can be more difficult to understand than a positive result because what the result means depends in part on an individual's family history of cancer and whether a *BRCA1* or *BRCA2* mutation has been identified in a blood relative. Hence in such cases clinical correlation is very important. If a close blood relative of the tested person is known to carry a harmful *BRCA1* or *BRCA2* mutation, a negative test result is clear meaning that person does not carry the harmful mutation that is responsible for the familial cancer, and thus cannot pass it on to their children. Such a test result is called a true negative and the associated risk of cancer in them is same as of general population. If the tested person has a family history of breast or ovarian cancer but complete *BRACA1&2* gene testing identifies no mutation, a negative result in such individuals should be interpreted with caution. As other genes and possibility of large deletion duplications in them cannot be ruled out by complete gene sequencing. The likelihood that genetic testing will miss a known harmful *BRCA1* or *BRCA2* mutation though very low, but cannot be neglected.

As per the latest American College of Medical Genetics (ACMG) guidelines,[8] the variants can be of five types as mentioned in Table 2.

Table 2: Variant classification as per ACMG 2020.

S. No.	Type of variant	Interpretation
1.	Pathogenic	Variant that is certain to disrupt gene function or to be disease causing
2.	Hypomorphic (R) or likely pathogenic variant (D)	Recessive: Variant that reduces gene function, but that only causes a biochemical abnormality - or disease - if in trans to a LoF allele. Dominant: likely LoF, or variant of functionally important consequence
3.	Variant of potential interest, possibly pathogenic	Rare variant that could affect gene function based on biological knowledge aided by bioinformatic tools, i.e., a variant of potential biological significance
4.	Likely benign	Lower frequency variant with no reason to suspect a recessive or hypomorphic role, or likely neutral after functional/family studies
5.	Benign	High frequency variant with no reason to suspect a recessive or hypomorphic role, or certainly neutral after functional family studies

ACMG: American college of medical genetics, LoF: Loss of function

HBOC syndrome management

Surveillance for BRCA1- and BRCA2-associated hereditary cancers

In a family with HBOCs, breast awareness should start at the age of 18 years. Clinical breast examinations should be done every 6–12 months, starting at the age of 25 years. Breast cancer screening by annual breast magnetic resonance imaging (MRI) (preferred) or Mammogram if MRI unavailable or individualized based on family history should start at the age of 25–29 years. At the age of 30–75 years annual mammogram and breast MRI screening is suggested. At age above 75 years individualized management for women with a *BRCA* mutation who are treated for breast cancer, annual Mammography and breast MRI should continue. Screening for ovarian cancer with transvaginal ultrasound, tumor marker studies such as serum CA-125 concentration and discussion about options of risk-reducing medicine and surgery between 35 and 40 years and on completion of child bearing and lifestyle modification is suggested. For men, breast self-examination training and education for disease awareness should start at age of 35 years. Furthermore, clinical breast examination needs to be advised every 12 months beginning at the age of 35. Furthermore, at the age of 40, recommendation of prostate screening for *BRCA*2 carriers and consideration of prostate screening for *BRCA1* carriers needs to be done. The screening for melanoma by dermatologist should be individualized based on family history.

Prophylactic surgeries

Bilateral mastectomy with nipple sparing and immediate breast reconstruction for women between 30 years and 40 years. Recently, many breast conservative surgeries have emerged. However, they should be offered with proper preoperative counseling, as there are many reports on higher rates of ipsilateral breast cancer recurrence in carriers of *BRCA* mutation treated with breast conservation surgeries.[6,12] Bilateral salpingo-oophorectomy should be considered in from age 35 to 40 years for *BRCA1* mutation carriers and 40 to 45 years for *BRCA2* mutation carriers (ideally after completion of family).

Nonsurgical alternatives

Nonsurgical options like chemoprevention using Tamoxifen or aromatase inhibitors are being studied as options for primary prevention, but they lack sufficient data on efficacy and side effect profile from prospective trials in young premenopausal women.[7,13]

Risk to relatives

Advice about possible inherited cancer risk to relatives, options for risk assessment, and management should be

discussed along with genetic counseling and consideration of genetic testing for at risk relatives.

Reproductive options

For patients of reproductive age group advice about options for prenatal diagnosis and assisted reproductive technology (ART) including preimplantation genetic diagnosis also risk associated, limitations and benefits of these technologies should be discussed with proper genetic counseling.

CONCLUSION

Early screening, evaluating, and testing can help to initiate timely medical intervention. The proposed algorithm is a valuable tool for primary and secondary health care providers, enhancing their ability to identify individuals at risk for HBOC syndrome. By offering clear guidelines for genetic testing and counseling based on family history, personal history, and ethnicity, it simplifies decision-making processes and ensures timely referrals. This approach helps in early detection and management of hereditary cancers, improving patient outcomes. Moreover, the algorithm educates and empowers health-care providers to offer comprehensive care and support to patients and their families, ultimately benefiting the broader community. Early screening, evaluating, and testing can help to initiate timely medical intervention.

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Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

REFERENCES

1. Petrucelli N, Daly MB, Pal T. BRCA1- and BRCA2-associated hereditary breast and ovarian cancer. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJ, *et al*., editors. GeneReviews®. Seattle, WA: University of Washington, Seattle; 1993-2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1247 [Last accessed on 2024 Apr 03].
2. Bahsi T, Erdem HB. Spectrum of BRCA1/BRCA2 variants in 1419 Turkish breast and ovarian cancer patients: A single center study. Turk J Biochem 2020;45:83-90.
3. Prakash R, Zhang Y, Feng W, Jasin M. Homologous recombination and human health: The roles of BRCA1, BRCA2, and associated proteins. Cold Spring Harb Perspect Biol 2015;7:a016600.
4. National Cancer Institute. BRCA gene changes: Cancer risk and genetic testing. Available from: https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet [Last accessed on 2024 Apr 03].
5. Malhotra H, Kowtal P, Mehra N, Pramank R, Sarin R, Rajkumar T, *et al*. Genetic counseling, testing, and management of HBOC in India: An expert consensus document from Indian Society of medical and pediatric oncology. JCO Glob Oncol 2020;6:991-1008.
6. 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.
7. Tanriverdi O, Meydan N, Barutca S. Long-term effect of trastuzumab on QT dispersion in adjuvant treatment for patients with Her2 receptor positive breast cancer: A pilot study. Med Oncol 2012;29:3265-71.
8. Petrucelli N, Daly MB, Pal T. BRCA1- and BRCA2-associated hereditary breast and ovarian cancer. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJ, *et al*., editors. GeneReviews®. Seattle, WA: University of Washington, Seattle; 1993-2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1247 [Last accessed on 2024 Apr 03].
9. Gogia A, Nithin SG, Pramanik R, Gupta R, Deo SV, Mathur S, *et al*. Prevalence of BRCA1 and BRCA2 mutations in an unselected cohort of Indian women with breast cancer. J Clin Oncol 2023;41:e13004.
10. 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.
11. NCCN guidelines: Breast cancer. Available from: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1419 [Last accessed on 2024 Apr 03].
12. Co M, Liu T, Leung J, Li CH, Tse T, Wong M, *et al*. Breast conserving surgery for BRCA mutation carriers-a systematic review. Clin Breast Cancer 2020;20:e244-50.
13. Singer CF. Non-surgical prevention strategies in women with hereditary breast and ovarian cancer syndromes. Horm Mol Biol Clin Investig 2020;41.