Clinical features

Hereditary breast and ovarian cancer syndrome (HBOC) is an adult-onset, cancer predisposition syndrome. HBOC is characterized by a high risk of breast and ovarian cancers, and an increased risk of other cancers such as prostate, pancreatic, and melanoma. Individuals with HBOC tend to develop cancer at an earlier age than the general population, and have higher risk for bilateral breast cancer, a second primary tumor in a different tissue, and cancer recurrence. HBOC is not associated with any unique physician exam findings.

Absolute lifetime cancer risks associated with HBOC

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>HBOC Lifetime Risk</th>
<th>General Population Lifetime Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>55-85% in females, 6% in males</td>
<td>12.3% in females, &lt;1% in males</td>
</tr>
<tr>
<td>Ovarian</td>
<td>25-45%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>2-4%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Prostate</td>
<td>20%</td>
<td>15%</td>
</tr>
</tbody>
</table>

Prevalence of HBOC

About 5-10% of breast cancers and 10-15% of ovarian cancers can be attributed to HBOC. In the Ashkenazi Jewish population, up to 25% of ovarian cancer can be attributed to HBOC. An estimated 1 in 500-1,000 individuals in the general population have a disease-causing BRCA1 or BRCA2 mutation. About 1 in 40 individuals of Ashkenazi Jewish ancestry carry a BRCA1 or BRCA2 mutation. Statistical algorithms are available to determine the likelihood of a BRCA1 or BRCA2 mutation based on personal and family history.

Diagnosis

Identification of a mutation in BRCA1 or BRCA2 by genetic testing is sufficient for the diagnosis of HBOC. Criteria have been developed to identify individuals who would most benefit from genetic testing, based on red flags in the personal and family cancer history. In general, additional evaluation is warranted when at least one of the following features is present in a patient or family:

- 2 or more consecutive generations affected with breast cancer
- History of breast cancer (invasive or DCIS) < 50 y or triple-negative breast cancer < 60 y
- 2 primary tumors in the breast and/or ovary/fallopian tube/peritoneum in a single individual
- Ashkenazi Jewish ancestry
- Male breast cancer at any age
- Ovarian/fallopian/peritoneal cancer at any age

See the USPSTF and NCCN guidelines below and the BRCA1 and BRCA2 testing criteria factsheet for additional information about testing criteria.

Genetics & inheritance

HBOC is caused by a mutation in the BRCA1 or BRCA2 gene. When functioning normally, these genes are thought to serve as “caretakers” of the genome, correcting sporadic DNA errors due to faulty cell division or environmental exposures. Individuals with a mutation in BRCA1 or BRCA2 accumulate more DNA damage that can lead to cancer.

HBOC is an autosomal dominant condition. First-degree relatives of a BRCA1 or BRCA2 mutation carrier have a 50% chance of also carrying the mutation. Men and women are equally likely to inherit, and pass on, a mutation.
Clinical testing

BRCA1 and BRCA2 genetic testing detects most cases of HBOC. Sequencing identifies 88-90% of individuals with a detectable BRCA1 or BRCA2 mutation and deletion/duplication analysis 10-12%. Individuals with Ashkenazi Jewish ancestry are typically offered testing for three mutations in BRCA1 and BRCA2 that commonly occur in that population with reflex to full sequencing and deletion/duplication analysis if indicated.

Expanded testing using a multi-gene panel that includes other cancer predisposition genes may identify additional families with hereditary breast cancer. Early estimates suggest that about 5-15% of people meeting criteria for testing of the BRCA1 and BRCA2 will have a mutation in a different gene.

Management

Increased surveillance (clinical breast exam, mammogram, and MRI) and consideration of risk reducing interventions (such as chemoprevention and preventive mastectomy or oophorectomy) are recommended. See the NCCN guidelines below.

Other genes that contribute to breast and ovarian cancer

There are other hereditary cancer syndromes that increase the risk for breast cancer, such as Cowden syndrome and Li-Fraumeni syndrome. The presentation of these syndromes in a family may overlap with that of HBOC, but can sometimes be distinguished based on characteristic features, such as physical exam findings. In addition, a number of common genetic susceptibility variants are thought to increase breast cancer risk to a lesser extent than BRCA1 and BRCA2. There are likely other genes that contribute to breast and ovarian cancer which have not yet been identified. See GeneReviews for more information about the genetic differential diagnosis for HBOC.

Select guidelines & resources

Resources
GeneReviews (2013): BRCA1 and BRCA2 Hereditary Breast and Ovarian Cancer
American Society of Clinical Oncology (2014): Hereditary Breast and Ovarian Cancer
National Cancer Institute (2015): Genetics of Breast and Gynecologic Cancers PDQ – High-Penetrance Breast and/or Gynecologic Cancer Susceptibility Genes

Guidelines
American College of Medical Genetics & National Society of Genetic Counselors (2014): Referral indications for cancer predisposition assessment
National Society of Genetic Counselors (2007): Risk Assessment and Genetic Counseling for Hereditary Breast and Ovarian Cancer: Recommendations of the National Society of Genetic Counselors