HEREDITARY BREAST AND OVARIAN CANCER

Bottom line: Breast cancer is relatively common in the general population (12% lifetime risk) and the majority of cases occur sporadically. About 5-10% of breast cancer is due to an inherited gene change. Mutations in the genes BRCA1 or BRCA2 are the most common cause of hereditary breast and ovarian cancer (HBOC) and BRCA1 and BRCA2 mutation carriers have a significant increased lifetime risk for breast and ovarian cancer in addition to other cancers. Risk-reducing surgeries and, for some women, chemoprevention, can reduce mortality from breast and ovarian cancers in both BRCA1 and BRCA2 carriers. Individuals with family histories of breast or ovarian cancer that are at high risk (generally >10%) to carry a BRCA1 or BRCA2 gene mutation can be offered referral to genetics services for a discussion of the benefits, harms and limitations of genetic testing, while women whose family histories suggest a low risk of carrying a BRCA1 or BRCA2 gene mutation can be reassured and offered screening following provincial guidelines.

WHAT IS HEREDITARY BREAST AND OVARIAN CANCER SYNDROME?

Approximately 80% of breast cancer occurs sporadically. About 10-15% of breast cancer is familial (when shared familial risk factors e.g. genes, environment, cause a higher incidence of cancer) and about 5-10% is hereditary (due to a single gene mutation). Harmful mutations in BRCA1 and BRCA2 appear to account for ~30% of high-risk breast cancer families. HBOC is an autosomal dominant cancer predisposition syndrome. Individuals with HBOC have a high risk for breast and ovarian cancers and a moderate risk for other cancers (Table 1). Not all individuals who inherit a mutation in BRCA1 or BRCA2 will develop cancer (reduced penetrance) and the signs and symptoms, type, and age of onset of cancer will vary within families (variable expressivity).

It is estimated that the general population prevalence of pathogenic mutations in the BRCA1 and BRCA2 genes is 1 in 300 to 1 in 500. Founder mutations are observed in individuals of Ashkenazi Jewish ethnicity occurring at an estimated frequency of about 1 in 50.

WHO SHOULD BE OFFERED GENETIC TESTING?

These are general guidelines to identify patients at high risk for HBOC. You should consider referring your patient to your local genetics centre or hereditary cancer program for further assessment if s/he has a family or personal history of:

- Breast cancer diagnosis at a young age (<35-45 years) [both invasive and ductal carcinoma in situ]
- Ovarian cancer at any age [epithelial]
- Male breast cancer
- Multiple primaries in the same individual e.g. bilateral breast cancer (particularly if the diagnosis was before age 50), breast and ovarian cancer
- Breast cancer diagnosis AND a family history of two or more additional HBOC- related cancers, including breast, ovarian, prostate (Gleason ≥7) and pancreatic cancer
- High risk ethnicity (Ashkenazi Jewish, Icelandic) and a personal and/or family history of breast, ovarian or pancreatic cancer
- Triple negative breast cancer diagnosed <age 60

OR if s/he has a personal

- Probability of 10% or higher to carry a BRCA mutation

Eligibility criteria for genetic testing vary among organizations. In general, criteria are based on clinical features that increase the likelihood of a hereditary cancer susceptibility syndrome.

If possible, testing is first offered to the affected individual in the family at highest risk to carry a mutation in order to maximize the likelihood of detecting a mutation. For example, this might be the youngest individual with breast cancer in a family with multiple cases of breast and ovarian cancer.
See the [GEC-KO point of care tool](https://www.geneticseducation.ca) which can be used in your practice to help identify patients that would benefit from referral to genetics or your local hereditary cancer program.

**HOW WILL GENETIC TESTING HELP YOU AND YOUR PATIENT?**

*If a mutation is identified (a positive test result):*

- Clinical intervention can improve outcomes. (See *GECKO Messenger for Screening and Management*)
  - Risk-reducing mastectomy lessens the risk of breast cancer by at least 90%
  - Annual magnetic resonance imaging plus mammography increases detection rate for breast cancer
  - Risk-reducing salpingo-oophorectomy decreases the risk of ovarian cancer by at least 80% and, if performed prior to menopause, can reduce the risk of breast cancer by at least 50%
  - Chemoprevention, e.g. tamoxifen, may be considered for some women as a risk-reducing option.
- Other at-risk family members can be identified and given accurate risk assessments
- Positive health behaviours can be reinforced

*If a mutation is not identified and testing was for a known familial mutation (true negative):*

- Your patient is not considered to be at increased risk of developing hereditary cancer but may still be at increased risk of cancer depending on family history
- You can provide reassurance to your patient and their children

Table 1. Significant lifetime cancer risks for individuals who have inherited a mutation in the BRCA1 or BRCA2 gene as compared to the general population.

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Cancer risk in mutation carriers of:</th>
<th>General Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BRCA1</td>
<td>BRCA2</td>
</tr>
<tr>
<td>Cumulative lifetime invasive breast cancer risk in women (by age 70)</td>
<td>57%</td>
<td>49%</td>
</tr>
<tr>
<td>Cumulative lifetime ovarian cancer risk (by age 70)</td>
<td>40%</td>
<td>18%</td>
</tr>
<tr>
<td>Cumulative lifetime breast cancer risk in men (by age 70)</td>
<td>Increased (controversial)</td>
<td>6-7%</td>
</tr>
<tr>
<td>Lifetime prostate cancer risk (by age 70)</td>
<td>n/a</td>
<td>2-6x increased risk</td>
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</tbody>
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NOTE: The literature suggests that there is also an increased lifetime risk for other cancers such as melanoma and pancreatic cancer in BRCA mutation carriers.


See [www.geneticseducation.ca](https://www.geneticseducation.ca) for the comprehensive *GECKO Messenger* with references and more on risks, benefits, limitations, screening and management, as well as for the made for practice *point of care tool.*

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