# 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 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.

| Cancer type | Cancer risk in mutation carriers of: | | General Population |
|---|---|---|---|
| | *BRCA1* | *BRCA2* | |
| Cumulative lifetime invasive **breast cancer risk in women** (by age 70) | 57% | 49% | ~12% |
| Cumulative lifetime **ovarian cancer risk (**by age 70) | 40% | 18% | ~1.3% |
| Cumulative lifetime **breast cancer risk in men** (by age 70) | Increased (*controversial*) | 6-7% | 0.1% |
| Lifetime **prostate cancer risk** (by age 70) | n/a | 2-6x increased risk | ~14% |

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.

For a recent review article on HBOC see Moyer VA, U.S. Preventive Services Task Force. Risk assessment, genetic counselling, and genetic testing for BRCA-related cancer in women: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2014; 160(4):271-81.

See www.geneticseducation.ca for the comprehensive *GEC-KO 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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