



☆ Topic: Hereditary breast/ovarian cancer

☆ **Summary:** Breast cancer is more common in older women but 1 in every 250 women in their 30s could develop breast cancer over the next 10 years. The causes are not yet known, although a diet high in fat, excess alcohol use and smoking are contributing factors. Women who carry the *BRCA1* and *BRCA2* gene mutations are at much higher risk of developing the disease.

☆ **Bottom line:** Increasing age is still the main risk factor for breast cancer but 5% to 10% of breast cancer is due to an inherited *BRCA1* or *BRCA2* mutation. People with “high risk” family histories of breast or ovarian cancer should be offered referral to genetics services, with a discussion of the benefits, harms and limitations of genetic testing. Risk reduction mastectomy and salpingo-oophorectomy can reduce mortality from breast and ovarian cancers in *BRCA1* and *BRCA2* carriers. Women with “low risk” family histories should be reassured and offered screening as per general population guidelines.

✓ The Disease

- Approximately 80% of breast cancer occurs sporadically and 20% is inherited. About 5-10% is hereditary (due to a single gene mutation) and 10-15% is familial (when a combination of genetic and environmental risk factors are shared in a family). Genetic testing is available for hereditary breast and ovarian cancer. About two-thirds of hereditary breast and ovarian cancer is related to mutations in the *BRCA1* and *BRCA2* genes, which are germline mutations. The consequences of having a *BRCA* mutation are outlined in Table 1.

✓ The BRCA Genes

- More than 2600 mutations have been found in the *BRCA1* gene (located on chromosome 17) and the *BRCA2* gene (located on chromosome 13)
- The mutations have the following characteristics:
 - Autosomal dominant transmission
 - A carrier frequency of approximately 1/800 in the general (White) population and 1 per 40 to 50 people in the Ashkenazi Jewish population
 - Both genes are tumor suppressors.
 - Mutation leads to the following:
 - an inability to regulate cell death
 - uncontrolled growth leading to cancer

✓ Consequences of having a faulty gene/ BRCA mutation (Table 1)

	Estimated Risk in BRCA Mutation Carriers (by Age 70)	In General Population
Breast Cancer (in women)	50 - 85%	11%
Ovarian Cancer (<i>BRCA1</i>)	40 - 60%	1.5%
Ovarian Cancer (<i>BRCA2</i>)	10 - 20%	1.5%
Breast Cancer (in men)	up to 6%	Rare

✓ Who should be considered for testing?

- Referral for genetic counseling or testing should be offered to patients who meet the following criteria:
 - Multiple cases of breast and/or ovarian cancer in family, especially
 - in closely related relatives
 - in more than one generation, and
 - when breast cancer is diagnosed before age 50
 - A family member with breast cancer diagnosed before age 35;
 - A family member with both breast and ovarian cancers;
 - A person with Ashkenazi Jewish heritage with a personal or family history of breast or ovarian cancer;
 - A family member with primary cancer in both breasts if one or both cancers diagnosed before age 50;
 - A family member with ovarian cancer;
 - A family member with male breast cancer; or
 - A family member with an identified *BRCA1* or *BRCA2* mutation.

Testing for the faulty genes, *BRCA1* and *BRCA2*, involves a blood test, which is usually available at regional genetic centres and some cancer centres. The test is covered by most provincial health plans if there is substantial risk. In Ontario, for example, testing eligibility reflects a 10% or higher risk of mutation; affected individuals in a family who are at highest risk are tested first. Genetic testing is generally offered to affected individuals, where possible, unless a mutation has already been identified in the family.¹

✓ Benefits of genetic testing

- Positive test result
 - Clinical intervention can improve outcomes: risk reduction mastectomy reduces risk of breast cancer; salpingo-oophorectomy reduces risk of ovarian and breast (if done premenopausally) cancer; and magnetic resonance imaging enhances surveillance for breast cancer^{2,3}
 - Family members at risk can be offered testing and identified.
 - Positive health behaviours can be reinforced.
- Negative test result
 - Gives reassurance to individuals and their children.

✓ Harms/limitations of testing

- There are potential negative aspects to genetic testing for mutations in the *BRCA1* and *BRCA2* genes:
 - Positive test result
 - Adverse psychological reaction leading to family issues and distress
 - Job or insurance discrimination
 - Confidentiality issues, especially among family members
 - Incomplete penetrance – having the mutation does not necessarily mean the patient will get the disease
 - Negative test result
 - Adverse psychological reaction, which can include survivor guilt
 - Might lead to a complacent attitude to health

There are also cases of uninformative test results (when no mutations are detected, hereditary cancer cannot be ruled out entirely) and unclear results (when variants of unknown significance are detected in *BRCA1* or *BRCA2*).

★Web Resources: www.genetests.org

★Review Articles:

1. Predictive Cancer Genetics Steering Committee. Ontario physicians' guide to referral of patients with family history of cancer to a familial cancer genetics clinic. Toronto, ON: Ontario Medical Association; 2001. Available at: www.oma.org/pcomm/OMR/nov/01genetics.htm
2. Horsman D, Wilson BJ, Avar D, et al, on behalf of the National Hereditary Cancer Task Force. Clinical Management Recommendations for Surveillance and Risk-Reduction Strategies for Hereditary Breast and Ovarian Cancer Among Individuals Carrying a Deleterious *BRCA1* or *BRCA2* Mutation. *J Obstet Gynaecol Can* 2007;29(1):45–60.
3. Narod SA, Offit K. Prevention and management of hereditary breast cancer. *J Clin Oncol*. 2005; 23:1656-1663.

For a listing of genetics clinics in Canada, along with their respective contact and referral information, visit the Canadian Association of Genetic Counsellors website at www.cagc-accg.ca.

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