GENE MESSENGER

is a collection of up-to-date, definitive, short reviews on genetics topics which have made headlines, with recommendations regarding referral for genetic services or testing. A team of family physicians, genetic counselors, and geneticists has designed Gene Messenger to provide practical information to help family physicians and their patients make informed choices about rapidly emerging genetic discoveries. Gene Messenger was created by the GenetiKit research team.

Hereditary breast and ovarian cancers

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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* or *BRCA2* gene mutations are at a much higher risk of developing the disease.

Statistics

Twenty percent of breast cancer is familial (family history of breast cancer). Approximately 5% to 10% of breast cancer is hereditary—a gene mutation has been inherited, which puts the patient at an increased risk of cancer. Two-thirds of these hereditary cancers occur in individuals with *BRCA1* or *BRCA2* mutations, which are germline mutations. The remaining 10% to 15% is due to some other factor involving the family, such as an environmental factor, chance, or an undiscovered gene mutation. The consequences of having a *BRCA* mutation are outlined in **Table 1**.

Table 1. Estimated risk of developing cancer by age 70 in *BRCA* mutation carriers compared with the general population.

TYPE OF CANCER	*BRCA* MUTATION CARRIERS (%)	GENERAL POPULATION (%)
Breast (women)	50–85	11
Breast (men)	≤6	Rare
Ovarian (*BRCA*1)	40–60	1.5
Ovarian (*BRCA*2)	10–20	1.5

BRCA—breast cancer gene.

BRCA genes

- More than 2600 mutations have been found on chromosome 17 in *BRCA1* and on chromosome 13 in *BRCA2*.
- These gene mutations have the following characteristics:
  — autosomal dominant transmission and
  — a carrier frequency of approximately
  -1 per 800 people in the general (White) population and
  -1 per 40 to 50 people in the Ashkenazic Jewish population (3 common mutations in Ashkenazic Jews).
- Both genes are tumour suppressors.
- Mutation of these genes leads to the following:
  — an inability to regulate cell death and
  — uncontrolled cell growth leading to cancer.

Who should be offered referral?

Referral for genetic counseling or testing should be offered to patients who meet the following criteria:

- multiple cases of breast or ovarian cancer on same side of the family, especially
  — in closely related relatives,
  — in more than 1 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;
- an Ashkenazic Jewish heritage, particularly with relatives with breast or ovarian cancer;
- a family member with primary cancer in both breasts, especially if diagnosed before age 50;
- a family member with ovarian cancer;
- a family history of 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 a substantial risk. In Ontario, for example, testing eligibility criteria reflect a 10% or higher risk of mutation; affected individuals in a family who are the highest risk are tested first. Genetic testing is generally not offered to unaffected individuals unless a mutation has been identified in the family.

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 breast and ovarian cancers; and magnetic resonance imaging enhances surveillance for breast cancer.
- Family members at risk can be identified.
- Positive health behaviour can be reinforced.

Negative test result

- Gives reassurance to individuals and their children.

Harms and limitations of genetic testing

There are potential negative aspects to genetic testing for the mutated *BRCA* 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 toward health.

There are also cases of uninformative test results (variants of unknown significance). In these cases, genetic testing does not detect the gene mutations, even in families with a strong history of breast or ovarian cancer. This underlines our incomplete understanding of inherited susceptibility to cancer.

Bottom line

Increasing age is still the main risk factor for breast cancer. 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 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.

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Acknowledgment

This project was funded by the Canadian Institutes of Health Research.

Competing interests

None declared

Additional resources

Predictive Cancer Genetics Steering Committee. *Ontario physicians' guide to referral of patients with family history of cancer to a familial cancer genetics clinic or genetics clinic*. Toronto, ON: Ontario Medical Association; 2001. Available from: **www.oma.org/pcomm/OMR/nov/01genetics.htm.**

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For a listing of cancer 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.**

GenetiKit KNOWLEDGE IN TRANSLATION

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