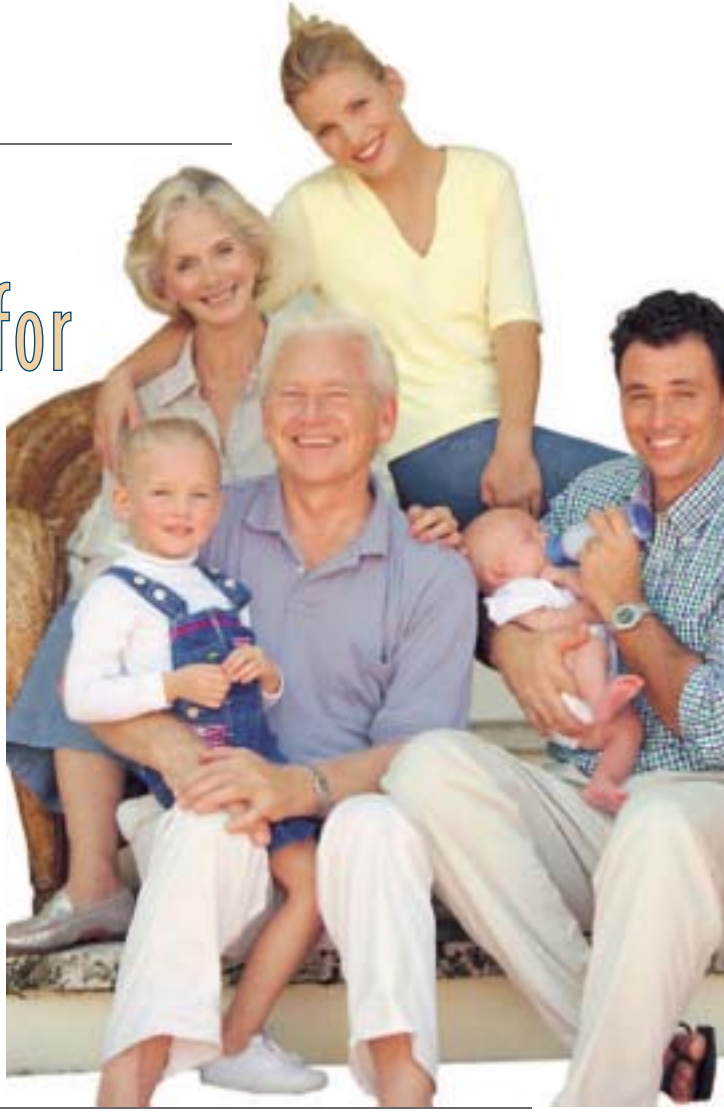
Genetic Counselling for BRCA 1 and 2



By Dawna Gilchrist, MD, FRCPC, FCCMG

Approximately 5% to 10% of breast cancer (BC) is hereditary in nature. Since the discovery of the genes BRCA 1 and 2 in the early 1990s, genetic counselling and testing of high-risk individuals and families have become widely available. In order for patients to be truly informed, issues of clinical and laboratory limitations, as well as the pros and cons of testing, must be clearly explained.

Prior to the early 1990s, it was known that some families had an excess of BC, and sometimes ovarian cancer (OC). It seemed likely, therefore, these families harboured a mutation to a gene or genes that predisposed them to breast, ovary and possibly other cancers.

In 1994, the gene BRCA 1 was discovered, followed shortly thereafter by BRCA 2.[1,2] Everyone has these genes and they normally work to protect us from cancer. Approximately 1 in 1,000 individuals, however, carries a mutation to BRCA 1 or 2.[3]

Women who carry a mutation in BRCA 1 or 2 have a 50% to 85% chance of developing BC, compared to 12% overall population risk.[4] Those with a mutation in BRCA 1 have as much as a 50% risk of developing OC — the risk is 20% to 30% for women with BRCA 2 mutations. The risk of OC in the general pop-

ulation is 1.5% to 2%. Men may transmit these mutations, and are at increased risk for BC (especially those with BRCA 2 mutations). There is also an increased risk — 20% to 35% — for prostate cancer, compared to a 5% to 10% overall population risk. Mutation carriers for both genes have an increased risk for colon cancer of a few per cent over the general population. Some BRCA 2 mutation families may have a small increased risk for cancers of the stomach, pancreas, gallbladder and melanoma.

While approximately 5% to 10% of all BC and OC is due to genetic mutations, not all of these mutations occur in BRCA 1 or 2.[3] There are other rare genetic syndromes in which BC (*i.e.*, Cowden, Li-Fraumeni) and OC can occur in hereditary non-polyposis colon cancer syndrome.[3]

Unfortunately, many families who seem as if they should carry a mutation in BRCA 1 or 2 do not. In these cases, a mutation in a gene that predisposes them to cancer must exist, but it must be in a gene that has not yet been defined, and for which there is no molecular diagnostic test. Because of the multiple complexities, it is strongly recommended that counselling be conducted by knowledgeable individuals and testing initiated only when patients are fully informed.[5] This generally requires referral to a medical genetics clinic or a specialized cancer genetics clinic.

Who might have a hereditary cancer syndrome?

In general, members of those families with multiple cases of BC and/or OC — in a distribution consistent with autosomal dominant inheritance — are the most likely candidates. Early age of onset of cancer is another important clue, and the occurrence of BC and OC in the same family is extremely suggestive. The Ashkenazi Jewish (AJ) population is known to harbour a high prevalence of BRCA 1 and 2 mutations (approximately 1% of each mutation). The index of suspicion is, therefore, higher in this group.

A case

In Figure 1, we see a family referred to a clinical genetics office for counselling and potential genetic testing. The proband (marked by the arrow) is a young, unaffected woman whose sister has died of OC — onset, age 27. The proband's mother survives after getting BC at age 43. A maternal aunt has died of OC at the age of 35 and

Dr. Gilchrist is associate professor of medicine and medical genetics, University of Alberta, Edmonton.

the maternal grandmother died of BC at the age of 39. By the criteria outlined above, this side of the family is virtually diagnostic of BC/OC syndrome, and testing for mutations in BRCA 1 and 2 is indicated.

There is also concern, however, on the paternal side of the family, which is AJ. The proband's father is cancer-free, but his sister died of BC, which struck at age 67. No further information is known regarding the family, as they all died in the Holocaust. While a single case of post-menopausal BC is most likely to be sporadic in origin, this family history is incomplete and, because of the Jewish heritage, testing for the common AJ mutations in BRCA 1 and 2 would be indicated.

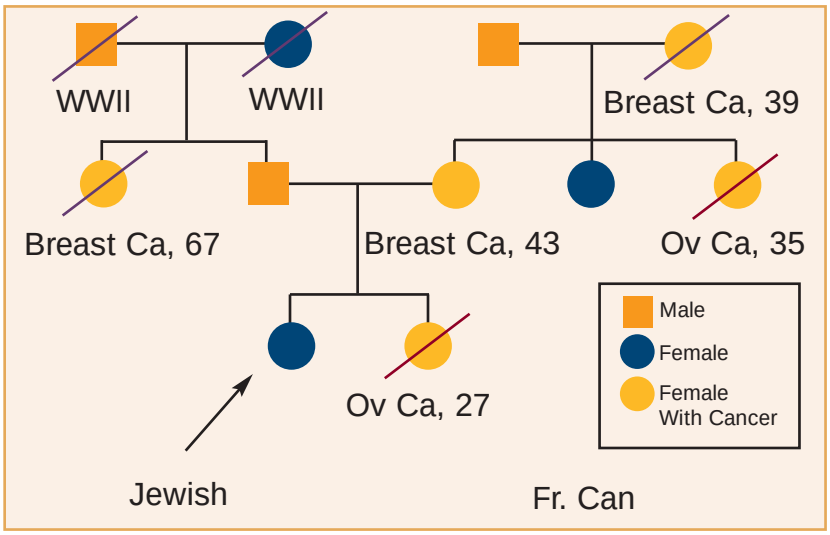


Figure 1. Pedigree of proband's family, showing relevant history. Shaded individuals are affected with either breast (Breast Ca) or ovarian (Ov Ca) cancer, at age of onset as indicated. Proband is highlighted with an arrow. Her mother is the only surviving affected family member.

Table 1

Screening recommendations for breast/ovary cancer syndrome

- Self breast exam, once monthly (both females and males)
- Physician breast exam, twice yearly (both females and males)
- Mammogram, yearly, starting age 25-35
- Transvaginal ultrasound of the ovaries, starting age 25-35
  - — Yearly (no family history of ovarian cancer)
  - — Every six months (family history of ovarian cancer)
- Routine population screening for colon–fecal occult blood and sigmoidoscopy OR colonoscopy every five years, starting at age 50
- Routine population screening for prostate cancer — digital prostate exam and prostate-specific antigen yearly starting at age 50

Genetic counselling

The proband is referred by her family physician or another physician involved in her care. The genetics clinic then contacts her to confirm her willingness to be seen and to obtain information to construct a pedigree. The clinic also needs to obtain medical records with family members' permission. It is extremely important to validate the cancers reported in the family — particularly with respect to gynecological or other intra-abdominal cancer. In general, the more remote the cancer death (both in years and closeness of relationship), the more likely the information may not be accurate.

Once the chart is complete, the proband will be given an appointment and seen by a

Table 2

Prophylactic options for breast/ovary cancer syndrome:

Surgical

- Bilateral total mastectomy reduces the chance of BC by 90%.
- Bilateral pre-menopausal oophorectomy reduces the chance of BC by 50%.
- Bilateral oophorectomy reduces the chance of OC by approximately 50%. The lining of the pelvic cavity cannot be removed and there is still a chance for primary peritoneal carcinomatosis.

Hormonal manipulation

- Tamoxifen has been shown to reduce the risk of BC when given to post-menopausal women at high risk of BC for multiple reasons. (The Gail model has nine risk factors. The biggest risk factor is age. Family history is only one risk factor).
- Studies in the use of tamoxifen and other agents to modify estrogen are currently ongoing, both in sporadic and hereditary BC and OC patients.

clinical geneticist and/or genetic counsellor. The former is a physician with specialty or subspecialty training in medical genetics. The latter is an individual trained in the non-diagnostic forms of genetic counselling, often with a Master's degree in this area. Usually, the proband is allowed to bring family or friends to the appointment. In our case, the proband would be encouraged to bring both parents.

Genetic counselling involves discussion of the family history and an explanation of the probable genetic risk involved. In this case, the most likely possibility on the maternal side is a mutation in BRCA 1. The remaining possibilities are a mutation in BRCA 2 or a mutation in a cancer predisposition gene which is, as yet, not characterized. As the paternal side of the family is AJ, there is a 1% chance of a mutation in BRCA 1 and a 1% chance of a mutation in BRCA 2.

The proband's specific risk is based on the basics of autosomal dominant inheritance. If the patient's mother carries a mutation to a gene that predisposes her to cancer, the proband's risk of having that mutation is 50%. Likewise, if the proband's father

carries a common AJ mutation, then the patient is at 50% risk of carrying that same mutation.

BRCA 1 and 2 are both lengthy genes and multiple mutations have been reported in both. Our testing is incomplete, in that we cannot test for mutations in potential cancer predisposition genes currently unknown. Genetic testing, therefore, is most informative when commenced with a living, affected family member.

The first test in this family is not on the unaffected proband. On the maternal side, the mother would be most suitable. No live affected individual is available from the father's side of the family, but, as we are looking only for the common AJ mutations, testing of the father would be suitable. If the father had been unavailable, we could have tested the proband for the AJ mutations, but this might not have given us as much information regarding the paternal side of the family.

The pros and cons of testing would be explained to the proband and her parents. Potential for knowledge gained regarding the specifics of the genetic cause of cancer in this family is on both sides of the equation. Within a family, some individuals want to know as much as possible about the cancer while others may wish to ignore it completely. Knowledge of genetic predisposition may alleviate concerns for some and provoke feelings of anxiety and depression in others. Family dynamics may be affected.

Based on the maternal family history, "at-risk" individuals would be well-advised to follow surveillance recommendations (see Table 1).[6] Should a mutation be found, at-risk individuals — such as the proband — may proceed with molecular diagnostics to obtain their own mutation status. If the mutation is present, the at-risk individual might be more motivated to pursue surveillance. He/she would be reassured about following population recommendations if he/she did not have the mutation. Similarly, options for prophylaxis (see Table 2) may be on or off the table depending on mutation status.[7,8] Of course, mutation testing for the proband and other at-risk individuals depends on an informative test result (*i.e.*, the finding of a mutation in the mother and/or father). If

the test result is non-informative (*i.e.*, no mutation is found in BRCA 1 or 2), no further testing is possible.

On the con side, issues of discrimination may arise based on a molecular diagnosis. Individuals who are known to carry a mutation predisposing them to a genetic disease may have difficulty obtaining life or disability insurance. Such knowledge might pose a barrier in emigration. In the U.S., the most common reason not to proceed with genetic testing is the fear of losing health-care coverage.

Genetic counselling is always recommended prior to predictive molecular diagnostics (*i.e.*, mutation testing in unaffected, at-risk individuals). Molecular testing for genetic disorders of adult onset is not recommended in minors, except that some form of prevention or early treatment is available.[9]

Genetic testing

The technical complexities of screening for mutations in the BRCA 1 and BRCA 2 genes far exceed those of any other type of testing. The complications include the involvement of more than one possible gene — each of which is relatively large — and the presence of more than 1,000 different catalogued mutations on each gene. Some mutations are more difficult to detect than others.

Results Counselling

The lab reports that the proband's father does not carry any of the common AJ mutations. The proband's mother has a mutation in BRCA 1.

The medical genetics clinic will now recall the proband and her family to discuss the results. The father's result means the BC in his sister is most likely to have been sporadic, and the proband's risk for BC, therefore, is not likely to be increased by the paternal history. There is, however, the proviso that the rest of the family history is unknown. Should there have been other individuals in the paternal family with BC and/or OC, there might be a mutation to a cancer predisposition gene that was not one of the common AJ mutations.

The mother carries a mutation in BRCA 1 known to be associated with BC and OC. It is assumed the deceased affected individuals carry the same mutation. The proband is at 50% risk for having this mutation, as are the mother's surviving sister and any offspring of the proband's deceased sister and aunt. There may also be more distant relatives at risk in the grandmother's circle of relatives. The family is encouraged to pass on this information as far as possible within the family. The proband is offered genetic testing, and other at-risk individuals in the family may avail themselves of the options of counselling and testing as well.

Because the mother has a BRCA 1 mutation, she is also at risk for OC and increased risk for another BC (approximately five times the sporadic recurrence risk). Recommendations for sur-

veillance (see Table 1) and options for prophylaxis (see Table 2) are again discussed. Should the proband find she, too, has the mutation, these recommendations and options may also apply to her. If she is found to not have the mutation, the recommendation would be self breast exam monthly and mammograms starting at the age of 50 (population recommendations).

It is important to remember males in BRCA mutation families are also at risk for BC and at an increased risk for prostate cancer. As well, both sexes are at a slightly increased risk of colon cancer. Mutations can be passed through males, as well as through females (*i.e.*, from grandmother to father to daughters and sons).

Depending on the centre, specialized clinics and/or patient support groups may be available to BRCA mutation carriers. Unfortunately, genetic testing cannot predict when or where cancer will occur or how serious it will be, nor is there any special diet, exercise or treatment that will absolutely prevent disease. When cancer occurs, the treatment for these patients is the same as for a sporadic case.

Where to refer patients

Medical genetics clinics are available in most university centres in Canada, as well as in a few larger hospitals. Specialized cancer genetics clinics may also be available.

The future

A decade ago, we had no tests whatsoever for hereditary forms of BC and OC, and we had a far poorer understanding of its natural history. Our current information base and ability to test is still incomplete, however, we gain more information every year. This will eventually lead to complete understanding, full testing and, perhaps, a cure. Dx

References

1. Miki Y, Swensen J, Shattuck-Eidens D, et al: A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 1994; 266:66-71.
2. Wooster R, Bignell G, Lancaster J, et al: Identification of the breast cancer susceptibility gene BRCA2. Nature 1995; 378:789-92.
3. Emery J, Lucassen A, Murphy M: Common hereditary cancers and implications for primary care. Lancet 2001; 358:56-63.
4. Ford D, Easton DF, Stratton M, et al: Genetic heterogeneity and penetrance analysis for the BRCA1 and BRCA2 genes in breast cancer families. Am J Hum Genet 1998; 62:676-89.
5. Statement of The American Society of Human Genetics on Genetic Testing for Breast and Ovarian Cancer Predisposition. Am J Hum Genet 1994; 55:i-iv.
6. Cancer Genetics Studies Consortium: Recommendations for follow-up care of individuals with an inherited predisposition to cancer: BRCA 1 and BRCA 2. JAMA 1994; 277:997-1003.
7. Eisen A, Rebbeck TR, Wood WC, et al: Prophylactic surgery in women with a hereditary predisposition to breast and ovarian cancer. J Clin Onc 1994; 18:1980-95.
8. Fisher B, Costantino JP, Wickerham DL, et al: Tamoxifen for the prevention of breast cancer: Report of the national surgical adjuvant breast and power project P-1 study. J Natl Can Inst 1998; 90:1371-88.
9. ASHG/ACMG Report: Ethical, legal and psychosocial implications for genetic testing in children and adolescents. Am J Hum Genet 1995; 57:1233-41.