Cancer family syndromes and the role of genetic testing have taken center stage in the popular press and the public eye, and the limitations as well as the benefits of genetic testing must be recognized. This report presents guidelines for practitioners who are considering the development of a genetics counseling clinic for patients at risk for breast cancer, as well as for those who currently operate such a clinic.

Approximately 85% to 90% of all breast cancers arise spontaneously. However, two genes have been defined -- BRCA1 cancer-susceptibility gene in 1994 and BRCA2 in 1995 -- that are believed to explain most, but not all, cases of familial breast cancer. New genes continue to be discovered that contribute to breast cancer susceptibility through secondary hormonal effects, such as a newly discovered gene polymorphism that appears to increase breast cancer risk by slowing estrogen metabolism. This is a confusing and constantly changing landscape for us.

The perception that cancer is a genetic disease is common. Not all cancer is inherited, but it does derive from errors in genes regulating growth. Mutations are either inherited (germline) or acquired (somatic). Altered DNA yields altered protein. Most genes in cancer family syndromes such as BRCA1 and BRCA2 are tumor suppressor genes. These genes normally control growth and/or differentiation. If there is a single normal copy, cancer will not occur (Figure).

We can conclude that patients inheriting a cancer family syndrome will have a disproportionate loss of life because of early onset of cancer. The following points are known concerning BRCA1 and BRCA2:

- They are associated with an autosomal dominant inheritance and are highly penetrant.
- Large genes with over 200 known mutations are already described.
- Different mutations will confer different risks of breast cancer, ovarian cancer, and other cancers.
- Different mutations confer different likelihoods of tumor types and age of onset.
- Even the same mutations in the BRCA genes confer different risks on different patient populations.
- We must conclude that there are substantial modifying factors -- presumably genetic, dietary, hormonal -- that affect the likelihood of a given BRCA mutation causing cancer.

BRCA1 and BRCA2 are present in 4% of families.

The frequency of susceptibility allele is 1:800 for BRCA1 and 1:800 BRCA2.

In determining who should be screened, given the cost of genetic screening and counseling -- not to mention the emotional cost -- it is important to focus our cancer family screening efforts on those most likely to benefit.

Clinical clues in the family history include a high numerator to denominator (many affected relatives compared with the total number), early ages of onset, and the presence of multifocal tumors, bilateral tumors, or two primary tumors (eg, breast and ovarian).

Potential benefits of genetic testing include enhanced screening and, potentially, earlier detection; prevention and thus avoidance of medication, lifestyle changes, and prophylactic surgery; and genetic counseling as an educational service. Potential drawbacks to genetic testing include job discrimination, loss of insurance, and misinterpretation of results leading to unnecessary anxiety or false sense of security.

In preparing a patient for testing, the usefulness of the genetic information must be determined before obtaining it. If there is no clear benefit to the patient, she may elect to defer testing or to cryopreserve DNA for potential future use of family members. Many patients come to our High Risk Assessment Clinic for assessment and counseling, and less than 10% undergo testing. All patients are screened beginning at 25 years of age or at 10 years earlier than the age of an affected relative. Screening includes a clinical breast examination, a mammogram (digital if indicated), and breast self-examination instruction. Patients also are counseled in breast cancer prevention strategies such as diet (the positive correlation between fat intake and breast cancer), current chemoprevention (retinoid derivatives), and prophylactic surgery.

Schrag et al constructed a rudimentary model of the effects of prophylactic surgery of the breasts or ovaries using some underlying assumptions that we know to be oversimplifications. Nevertheless, the study is useful for providing estimates of surgical benefits. A 30-year-old woman with a BRCA mutation undergoing prophylactic bilateral simple mastectomies increases her life expectancy by three to five years. Comparatively smaller gains of four to 20 months were expected for a 30-year-old woman undergoing prophylactic oophorectomy. As current chemoprevention trials mature, we may be able to formulate a more sophisticated combined medical and surgical strategies for these patients.

References


Dr Moore is Assistant Professor and Director, High Risk Breast Clinic, Department of Surgery, University of Virginia, Charlottesville, Virginia.