**Introduction**

Hereditary genetic mutations cause about 5% of breast cancers. In these cases, the hereditary predisposition may be so strong that nongenetic risk factors have only a minor impact on the likelihood of disease, and family histories reveal evidence of an autosomal dominant inheritance pattern of breast cancer. About 90% of these rare hereditary cancers are caused by a mutation of either \textit{BRCA1}, which was cloned in 1994, or \textit{BRCA2}, which was cloned in 1995. Identification of these genes has permitted the rapid development of programs for genetic counselling, risk assessment and genetic testing for families affected with hereditary breast cancer. This review will focus on the clinical indications of hereditary breast cancer, pathogenetic mechanisms, laboratory tests for mutations of \textit{BRCA1} and \textit{BRCA2}, and issues of clinical management.

**Clinical indications of \textit{BRCA1}- and \textit{BRCA2}-associated breast cancer**

A hereditary breast and ovarian cancer syndrome should be suspected whenever there is premenopausal onset, multiple family members are affected, more than one primary tumour is found or there is concurrent ovarian cancer in the patient’s history. Breast and ovarian cancer can occur within the spectrum of malignant diseases found in a number of different syndromes. Proving that the cause is genetic, and which gene is implicated, requires genetic testing. Whereas private testing is available simply by submitting a specimen and paying the cost of the test, publicly funded clinical services use combinations of criteria (Table 1) to determine which patients are at increased risk and therefore eligible for testing. Most programs only offer testing to women at high risk, sometimes arbitrarily defined as a greater than 25% lifetime risk of breast cancer, or greater than 10% chance of detecting a mutation. A detailed assessment of a 3-generation family history and review of pathology records are essential components for determining which patients are at increased risk and therefore eligible for testing. Although patients are likely to have accurate knowledge of breast cancers diagnosed in the family, recall of ovarian and other cancers is less accurate; therefore, it is important to retrieve pathology records for these diagnoses. Different risk models are available for use, but since each has limitations, several may be applied in an effort to accurately estimate risk based on pedigree information.
Pathogenetic mechanisms: BRCA1 and BRCA2

Cancer results from sequences of genetic mutations that lead to a loss of control over cellular growth, differentiation, division and programmed cell death. The major types of genes implicated in transformation to malignancy are oncogenes, tumour suppressor genes (TSGs) and DNA repair genes (Table 2). Oncogenes are rarely associated with hereditary cancer syndromes (the oncogene RET, associated with familial medullary thyroid carcinomas and other syndromes, is a notable exception). Hereditary cancers are usually associated with mutations of TSGs (e.g., Li–Fraumeni syndrome and P53) or DNA repair genes (e.g., hereditary nonpolyposis colorectal cancer, MSH2 and MLH1). BRCA1 and BRCA2 are classified as TSGs, based on the autosomal dominant pattern of inheritance and cellular functions identified to date. Inheritance of a mutation of one of these genes is an early step in a pathway of genetic mutations that lead to breast cancer.5–8

BRCA1 is a large gene on chromosome 17, with 24 exons spanning approximately 100 000 base pairs of genomic DNA (Fig. 1). A detailed description of this gene is provided by entry 113705 of the online index OMIM (www3.ncbi.nlm.nih.gov/htbin-post/Omim). When the BRCA1 protein was described, it did not have an obvious homology with any other known proteins, and therefore its functions were a mystery. They are still not clearly understood. BRCA1 is strongly expressed in testis, thymus and ovary, as well as breast tissue. It is transcribed from 22 exons (5592 base pairs) and consists of 1863 amino acids. Several regions of the protein have predicted tertiary structures that suggest specific functions (motifs), as shown in Fig. 1. BRCA1 has multiple functions in the cell.8-10 It has DNA-binding and nuclear-localizing regions and it interacts with TP53, RB, ATM, BRCA2, and other proteins involved in DNA repair and transcriptional regulation. In response to DNA damage, the BRCA1 protein is phosphorylated by the ATM protein and then localizes to the nucleus, where it becomes part of a multiprotein DNA repair complex to mediate homologous DNA repair. This process requires the function of another

Table 1: Outline of criteria for hereditary breast and ovarian cancer syndromes

<table>
<thead>
<tr>
<th>≥1 cancer</th>
<th>≥2 cancers, same side of family</th>
<th>≥3 cancers, same side of family</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashkenazi Jewish and breast cancer &lt;50 years of age or ovarian cancer at any age</td>
<td>Breast cancer &lt;60 years of age and a first or second-degree relative with ovarian cancer or male breast cancer</td>
<td>3 or more cases of breast or ovarian cancer at any age</td>
</tr>
<tr>
<td>Male breast cancer</td>
<td>Breast and ovarian cancer in the same individual, or bilateral breast cancer with the first case at &lt;50 years of age</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 cases of breast cancer, both at &lt;50 years of age, in first or second-degree relatives</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 cases of ovarian cancer, any age, in first or second-degree relatives</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ashkenazi Jewish and breast cancer at any age, and any family history of breast or ovarian cancer</td>
<td></td>
</tr>
</tbody>
</table>

The possibility of a hereditary breast and ovarian cancer syndrome should be considered if a review of 3 generations of the family history finds any of these criteria.

Table 2: Types of genes commonly implicated in carcinogenesis

<table>
<thead>
<tr>
<th>Gene</th>
<th>Functions of typical protein products</th>
<th>Mechanism in hereditary cancer</th>
<th>Examples of syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncogene (mutated versions of normal protooncogenes)</td>
<td>Tyrosine kinases (intracellular metabolism), growth factors, growth factor receptors, hormones, hormone receptors, extracellular proteins</td>
<td>Gain of function: abnormal structure or expression; not commonly implicated as the primary event in hereditary cancer</td>
<td>Familial medullary thyroid carcinoma (RET)</td>
</tr>
<tr>
<td>Tumour suppressor</td>
<td>Transcriptional regulation, cell cycle control</td>
<td>Loss of function: loss of ability to regulate down-regulate cell division, inhibit cell cycling or induce differentiation (or both)</td>
<td>Hereditary breast cancer (BRCA1 and BRCA2); Li – Fraumeni syndrome (P53)</td>
</tr>
<tr>
<td>DNA repair</td>
<td>Components of DNA repair complexes (e.g., mismatch repair)</td>
<td>Loss of function: repair complexes fail to function properly</td>
<td>Hereditary nonpolyposis colorectal cancer (HNPPC; MSH2, MLH1 and others); also BRCA1, BRCA2</td>
</tr>
</tbody>
</table>
TSG, P53, to arrest the cell cycle so that the repair mechanisms can function before the cell divides. BRCA1 therefore appears to be a critical component of a complex of enzymes that act to repair DNA damage caused by inaccurate replication, oxidative compounds, genotoxic drugs, radiation and other mechanisms. BRCA1 also appears to suppress estrogen-mediated proliferation of breast epithelial cells. Thus, BRCA1 is important in embryonic proliferation of tissues. Also, inactivation of BRCA1 interferes with DNA repair in breast tissue and increases exposure of the breast to estrogen hormones. Gene expression studies have confirmed that mutations of BRCA1 are associated with an abnormal pattern of cellular gene expression affecting hundreds of genes, and the tumour cells accumulate many chromosomal abnormalities.

BRCA2 is on chromosome 13. It is an even larger gene, with a total of 27 exons and 10 254 base pairs coding for a BRCA2 protein with 3418 amino acids. A detailed description of this gene is provided by entry 600185 of the online index OMIM (www3.ncbi.nlm.nih.gov/htbin-post/Omim). The general organization of BRCA2 is very similar to BRCA1 (Fig. 1), so the 2 genes are probably ancestrally related. Because the expression and known functions of BRCA2 protein appear to be similar to those of BRCA1, and because BRCA2 protein interacts with BRCA1, it is thought that BRCA1 and BRCA2 are involved in the same functional pathways. However, BRCA2 tumours have a different pattern of cellular protein expression, cellular phenotypes and histologic appearance.

BRCA1 and BRCA2 both fit the classic definition of TSGs (Fig. 2). Tumour suppressor genes are associated with cancer through loss of function and often have a “gatekeeper” role as a defence against mutation of other critical genes. Both functional copies (alleles) of a TSG need to be lost before the associated malignant transformation can proceed. Loss of the 2 normal alleles is usually a 2-step process (Knudson hypothesis). First one copy is

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**Fig. 1: Structure and functional interactions of BRCA1 and BRCA2 proteins.**
lost, often through a deletion, frameshift or point mutation. Descendants of that cell have only 1 remaining functional allele. Then in one of those cells, the second normal copy is lost. This second loss can occur through a variety of mechanisms and is much more likely to occur once the first mutation has taken place. Descendants of the cells with no functional TSG can progress to malignancy. In sporadic cancer, both mutations are acquired after conception. In hereditary cancer syndromes, the first mutation is inherited, so that the fetus already has loss of the first normal allele in all cells from the time of conception. This means that the second acquired mutation is highly likely to occur sometime in the life of the individual. Clinically, this results in a high risk for tumours and also an earlier average age of onset.

The resulting loss of functional BRCA1 or BRCA2 protein cannot be detected reliably by immunohistochemistry at present. Therefore, routine pathology studies cannot be used to identify tissues with inactivating BRCA1 or BRCA2 mutations. However, sporadic, BRCA1- and BRCA2-related tumours can be differentiated by computer-assisted analysis of the pattern of expression of specific proteins, and this type of gene-expression analysis may be applied to tumour classification in the future.

Clinically, there is currently no consensus of opinion on whether BRCA1- or BRCA2-associated tumours have a better or worse prognosis than sporadic tumours.

Most clinically significant mutations of BRCA1 and BRCA2 are caused by deletions or insertions of nucleotides (1, 2, or multiples other than 3). During protein synthesis, the reading frame of triplet codons for amino acid incorporation is then shifted by 1 or 2 positions, so that inevitably there is a premature stop instruction that abruptly truncates the synthesized protein product somewhere after the mutation. Less commonly, a single nucleotide can be altered so that it codes for a stop (nonsense mutation), which in BRCA1 is often due to C-to-T transitions in CpG islands and is associated with premature degradation of the faulty RNA. A mutation of a single nucleotide may also change a specific amino acid in a functionally critical region (missense mutation). Other types of mutations alter splice sites between introns and exons, or result in large deletions and duplications (e.g., duplication of all of exon 13). These larger mutations often arise because of erroneous recombination between similar stretches of repeat sequences in the DNA.

Although many mutations occur in exon 11,
which is the largest exon in both \textit{BRCA1} and \textit{BRCA2}, mutations are found throughout both genes and no particular “hotspots” are recognized. In \textit{BRCA1}, even mutations near the end of the protein can be associated with strong family histories. This does not appear to be true for \textit{BRCA2}, because several mutations near the end of the gene do not appear to be clinically significant. Many mutations are catalogued in detail in a Web-based data registry that is openly accessible and maintained by the NIH (breast cancer information core [BIC] registry) at \url{www.nhgri.nih.gov/Intramural_research/Lab_transfer/Bic/} [accessed May 15, 2001]).

Both genes have “founder” mutations that are associated with specific ethnic backgrounds (Table 3).14–16 These founder mutations can be very common and occur in many ethnicities. A founder mutation arises as a new mutation in an individual and passes to the affected person’s many descendants within that population. This usually occurs either through catastrophic loss, with repopulation from a few ancestors (one or more of whom carry a mutation) or through migration of a population into a new territory, with one or more of the migrants carrying a mutation. Examples of the former include the Ashkenazi Jewish founder mutations. Examples of the latter are found in French Canadian and Icelandic14 descendants. At least 8 different founder mutations have been documented in French Canadian families,15 whereas founder mutations consisting of large deletions or duplications are prominent in Dutch kindreds.16 About 2.5% of Ashkenazi Jews carry a \textit{BRCA1} 185delAG, \textit{BRCA1} 5382insC or \textit{BRCA2} 6174delT founder mutation.17–21 Almost 10% of Icelandic patients having breast cancer carry a specific mutation of \textit{BRCA2},14 and large genetic rearrangements occurring as founder mutations may account for up to 30% of hereditary breast and ovarian cancer in Dutch kindreds.19 For this reason, ethnicity must be carefully determined during review of the family history.

**Laboratory tests for mutations of \textit{BRCA1} and \textit{BRCA2}**

Testing for \textit{BRCA1} and \textit{BRCA2} generally follows 1 of 2 approaches (Figs. 3 and 4): complete automated sequencing of all exons, or a 2-step protocol starting with a screening technique that is followed by limited sequencing for particular exons and potential mutations. The availability, cost and providers of testing have in part been determined by patent rights held by Myriad Genetics Inc. of Salt Lake City.

Automated sequencing has the advantage of a complete sequence analysis of all coding regions of the genes and definitive identification of the actual mutation in the coding sequence. Therefore, this test is predicted to detect missense mutations (single nucleotide changes leading to a change of amino acid) as well as most protein truncation mutations arising by frameshift or nonsense mutations. Sequencing will also pick up polymorphisms (sequence variants found in normal people and not associated with disease), but these are not usually clinically significant. Sequencing may not, however, pick up certain types of mutations resulting from larger rearrangements, such as complete duplications of exons or large deletions.

In another approach, a screening method can be used in conjunction with selective sequencing. Although cost is a significant factor in choosing this approach, some screening methods can also provide technical advantages. One common method is the protein truncation test (PTT). This technique depends on the in vitro generation of protein products from fragments of the gene (Figs. 3 and 4). Because the end result of the test is to detect a protein truncation, this screening technique preferentially detects a type of mutation that is almost always clinically significant. The truncation may be detected even if it is produced by a large deletion or duplication not found by sequencing. However, the PTT does not detect missense mutations, and any positive result must be confirmed by a sequence analysis of the region in question to confirm the exact nature of the

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Population</th>
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<tbody>
<tr>
<td>185delAG of \textit{BRCA1}</td>
<td>Ashkenazi Jewish</td>
</tr>
<tr>
<td>5382insC of \textit{BRCA1}</td>
<td>Ashkenazi Jewish</td>
</tr>
<tr>
<td>6174delT of \textit{BRCA2}</td>
<td>Ashkenazi Jewish</td>
</tr>
<tr>
<td>del3,8kbEx8-13 of \textit{BRCA1}</td>
<td>Dutch</td>
</tr>
<tr>
<td>del5,10bpEx22 of \textit{BRCA1}</td>
<td>Dutch</td>
</tr>
<tr>
<td>R1443X of \textit{BRCA1}</td>
<td>French Canadian</td>
</tr>
<tr>
<td>8765delAG of \textit{BRCA2}</td>
<td>French Canadian</td>
</tr>
<tr>
<td>999del5 of \textit{BRCA2}</td>
<td>Icelandic</td>
</tr>
</tbody>
</table>
mutation (Fig. 4). Sometimes the follow-up sequence analysis gives negative results because the mutation is a large deletion or duplication. In that case, further testing by additional techniques such as Southern blot analysis is required. This latter type of analysis is laborious and may not be available. Regardless of laboratory technique, it is standard practice to confirm the presence of a mutation by a second analysis of a separate extraction of DNA before it is reported.

It is important to recognize the limitations of genetic testing. All commonly used techniques to date depend on using the polymerase chain reaction to amplify fragments of the gene before analysis. This approach may fail when the genetic rearrangement exceeds the scale of the fragments or when the mutation falls in the overlap regions between the fragments scanned. Another limitation is that occasionally the gene itself does not have a mutation, but a mutation or abnormal degree of methylation in upstream regulatory regions results in failure to express the protein. In this situation, even complete sequencing of the gene will fail to detect the cause. The sensitivity of testing, by complete sequencing or by screening plus sequencing, is probably in the range of 85%. This means that an estimated 15% of patients receive a false-negative result with current technology. Thus, all current laboratory protocols for testing BRCA1 and BRCA2 are laborious, costly and fail to detect some mutations.

In the future, it is likely that laboratory protocols will combine tests for expression of functional BRCA1 and BRCA2, and related proteins, as in gene expression arrays, with chip-based diagnostic

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**Fig. 3: Steps in the laboratory analysis for mutations of BRCA1 gene.**

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Fig. 4: (4a) A gel from a protein truncation assay for part of exon 11 in BRCA1. The first lane indicates the position of standardized size markers. The last lane provides the result for a known positive control specimen for this fragment. The stained bands in each lane are radiolabelled protein fragments separated by size. Smaller fragments move farther through the gel than larger fragments. The normal protein products from the assay are present as the heavy bands at the top of each lane. Two patients have abnormally small fragments. The sequencing results for the second of these 2 specimens (the right-hand one) are illustrated in 4b and 4c. (4b) Black-and-white image of part of a 4-colour electrophoretogram produced by an automated DNA sequencer (ABI 310). A normal DNA sequence will usually be read as a series of peaks, each of a colour specific to the nucleotide (A, C, G or T). Two different peaks in 1 location indicate a heterozygous base-pair difference. At the point indicated by arrows, the patient has a deletion of a single adenine (A) nucleotide. This results in a shift of the reading frame for the mutated allele. The normal sequence in this region is AAG-TAAAAGACATGACA. The deletion of the last of the 4 As results in a mutated sequence of AAGTAAAAGACATGAC. Following from the site of the deletion, there are 2 peaks at each position (1 reading from the normal allele, 1 from the abnormal allele) because of the frameshift. Above the graph are the bases as called by the sequencing software and the operator. At the mutation and following, the N base codes indicate combinations of nucleotides detected. (4c) Following analysis of the electrophoretogram, the called base-pair sequence is compared to a normal control. This figure illustrates, from the top down, the normal sequence in this region, the sequence from the patient obtained by forward sequencing (from beginning toward end) and the patient sequence obtained by reverse sequencing (from end toward beginning). Bidirectional sequencing is often helpful in clarifying the exact position and nature of a mutation, because the sequencing process may work more accurately from one direction than the other. The abnormal base codes indicate identified combinations of base pairs: R = purine (A and G), M = amnio (A and C), W = weak bonds (A and T), K = keto (G and T), Y = pyrimidine (C and T). The next step is to determine the effect of the frameshift on amino acid sequence. The normal codon sequence in this region is: aaa (codon 690) aga cat gac agc gat act ttc cca gag ctg aag. In this case, the 2190delA deletion causes a frameshift at codon 691 that leads to a premature stop a few codons later at position 700. Instead of reading leucine from a CTG codon, the mutated sequence provides a termination instruction from a TGA codon. Reading from the deletion, the codons are: aat gca gac ata ctt tcc cag agc tga (700 = stop). The mutation is then compared to reported mutations by referring to the Breast Cancer Information Core registry, a Web site maintained by the United States National Institutes of Health. To date, this particular mutation has been identified at least 6 times in association with hereditary cancer and would therefore be reported as a clinically significant mutation.
assays that provide high-throughput screening for the causative genetic mutations.

All putative mutations need to be compared to known mutations listed in the BIC registry and other sources. If the mutation is a frameshift, nonsense or splice-site mutation that causes a protein truncation and it has been previously reported in association with a positive family history, it can be reliably interpreted to be clinically significant and a likely cause of the clinical history. If, on the other hand, the laboratory result identifies a missense mutation (single amino acid change that is not a premature stop), the result must be interpreted with caution; only if there is a reported association with cancer in other families can it be considered to be causal. The clinical significance of novel mutations can sometimes be determined by more complete family studies, where all members of a family (those unaffected and those affected) are genotyped in order to determine if the putative mutation cosegregates with the appearance of cancer.

**Clinical management**

Patients are often strongly motivated to seek counselling and testing. Many appear to overestimate their actual risk. Undoubtedly, some are so influenced by their family history that they rarely pass a day without thinking of their risk. Patients who request counselling are usually not deterred by insurance concerns, but family issues commonly arise. In the latter situation, it is imperative that rights to privacy and confidentiality are maintained. Compassionate, informed and nondirective counselling is essential in all stages of the counselling process.

The outcomes from counselling and testing vary. About half of all hereditary breast cancers are caused by a mutation of BRCA1, and about 30% are related to BRCA2. In practical terms, there is little difference in the clinical importance between a BRCA1 mutation and a BRCA2 mutation: both result in strongly increased risk for breast and ovarian cancer, and some increase in risk for other cancers, including prostate and pancreatic cancer. Families with breast and ovarian cancer, and with very early onset of breast cancer (<35 years of age) are more likely to have a mutation of BRCA1 than BRCA2. Male breast cancer is more likely to occur with BRCA2 mutations, but it is found in association in both BRCA1 and BRCA2 families. It is important not to overlook the risk for ovarian cancer in BRCA1 and BRCA2 families, particularly because ovarian cancer is more difficult to detect and treat than breast cancer. Ovarian and other non-breast cancers appear to be more likely in families with mutations clustered in specific regions (e.g., ovarian cancer-cluster region of exon 11 of BRCA2).

Because of the adverse implications for under- or overinterpretation of a laboratory result, clinical interpretation must be carefully coordinated with the reporting laboratory. Laboratory results fall into 1 of 3 categories: positive, negative or inconclusive.

A positive result is reported when the laboratory identifies a mutation that is identical to a previously documented and reported mutation, or a mutation that is interpreted to cause a premature truncation of the protein product. Patients who receive a positive result have strong confirmation of an increased lifetime risk for cancers associated with the gene and therefore should be referred for discussion of the options for clinical management. The actual risk for an individual patient will vary with the type of mutation (BRCA1 or BRCA2), and site of the mutation in the gene. Apparently identical mutations can be associated with variable family histories (i.e., the expression of a mutation can vary depending upon the genetic background and other factors). Therefore, it is not possible to provide highly specific risk estimates unless the mutation is well characterized (e.g., founder mutations in certain ethnic populations) or there is extensive knowledge of the individual family. Most patients are told that their lifetime risk is between 40% and 85% for breast cancer, and between 16% and 40% for ovarian cancer. These estimates may be further increased if the family history is very strong or there is other concurrent evidence of increased risk (e.g., patient history of biopsy with atypical hyperplasia) or may be decreased (e.g., advanced age with no diagnosis of cancer and a weak family history). For patients with a known mutation, management strategies are modified to increase the chance of early detection of cancer, and primary prevention through surgery, chemoprevention or other strategies may be chosen.
A negative result is reported when the laboratory fails to find a known familial mutation in the patient tested. In this situation, a mutation has already been found in another family member, and cosegregation with cancer has been demonstrated or assumed. With a negative result, the pedigree-based estimate of risk is substantially revised, and most patients are told that their lifetime risk of breast or ovarian cancer is not significantly increased above that of the baseline population. Subsequent management for surveillance and early detection is modified accordingly.

Unfortunately, an inconclusive result is the most common outcome of testing. In this situation, a person at high risk is tested, but no mutation is found and no other family member is known to have a mutation. Therefore, it is unclear whether (a) the result is a false-negative one, (b) the family history of breast cancer is due to a mutation of another cancer-causing gene or (c) the cancer is of sporadic rather than hereditary origin. These patients are placed in the unsatisfactory situation of knowing that they still have an estimate of increased risk (based upon their family history) but no laboratory confirmation of a known genetic mutation. Consideration should still be given to clinical management programs that optimize prevention and early detection.

Options in clinical management continue to be developed for patients at high risk.\textsuperscript{4,30–32} Whereas protocols utilizing regular mammography and clinical examination may facilitate early detection, providers must consider that primary prevention may be an appropriate choice for women who live in fear of breast or ovarian cancer. Bilateral prophylactic mastectomy\textsuperscript{31,32} appears to reduce preexisting risk for a diagnosis of breast cancer by 90% to 95%, with an estimated survival benefit of 2 to 3 years for women at high risk. Ovariectomy appears to reduce the risk of a diagnosis of ovarian cancer by only 40% to 50%; however, because ovarian cancer is less curable than breast cancer, the survival benefit is similar — 2 to 2.5 years. Failures of prophylactic surgery appear to be due to either undetected cancer at the time of surgery or the presence of residual normal tissue that undergoes malignant transformation later in life. Another option that should be considered is chemoprevention. Tamoxifen may reduce the risk of breast cancer by at least 40% and appears to confer a survival benefit despite concerns about the possible induction of endometrial cancers. Tamoxifen, raloxifene and a variety of other compounds are currently being assessed in clinical trials for evidence of effectiveness in this role.\textsuperscript{4,33,34} Unfortunately, changes in lifestyle such as weight loss, reduction in dietary fat and alcohol intake, and increased physical exercise, probably have a relatively small protective effect in the face of high genetic predisposition.

The potential benefits of genetic counselling and testing appear to be clear for women who are confirmed to be a low risk. However, women who receive a positive result may also directly benefit from an increased feeling of control, understanding their family history and a sense of justification for any surveillance and prevention measures they adopt. Women who receive an inconclusive result may be relieved by the failure to find a mutation but are still left with no clear explanation for their family history of breast cancer.

**Summary**

Less than 5% of breast cancers are hereditary, but over 90% of hereditary breast cancers are caused by a mutation of either \textit{BRCA1} or \textit{BRCA2}. The mutation may be inherited from either the maternal or the paternal side of the family. Clinicians should consider specific criteria in the family history to determine when a patient may benefit from counselling and appropriate testing. Testing is generally offered only to patients who are at high risk and is currently estimated to have a sensitivity of about 85%. Test protocols are primarily oriented to detecting frameshift and nonsense mutations that cause premature protein truncations. Missense mutations also occur, but they are less common and sometimes not clearly of clinical significance. Laboratory results need to be correlated with the clinical picture, and genetic counselling is a critical component in maximizing the benefits of testing.

In the future, application of more refined clinical criteria, as well as expected improvements in laboratory techniques, will undoubtedly lead to significantly better outcomes and options in surveillance and management for hereditary breast and ovarian cancer syndromes caused by mutations of \textit{BRCA1} and \textit{BRCA2}.
References


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