Etiology

Breast cancer is the most frequent carcinoma in women. In more developed countries, the probability of contracting breast cancer between the ages of 20 and 80 is approximately 7.8%, that is, 1 in 13 women. A comparison of familial and sporadic cases shows that familial cancer diagnosed at a younger age is frequently bilateral and frequent in men. In recent years it has been estimated that 5–15% of breast cancer cases involve genetic events. However, careful epidemiologic investigations now indicate that only one third (5%) might be caused by monogenic factors. Most inherited breast cancer cases are now assumed to be polygenic, and most diagnosed breast cancer cases are sporadic without familial clustering. In contrast, it can no longer be excluded that at least some of the sporadic cases may be caused through a combination of polygenic variants and exogenous factors.

The penetrance of inherited mutated alleles is modulated by additional low penetrant genetic variants (modifier genes), environmental factors, or both. Factors such as nulliparity, physical exercise, diet, obesity, and birth age influence the age at onset in gene mutation carriers in both sporadic and familial cancer. Indeed, it can be observed in pedigrees from families with multiple occurrences of breast and/or ovarian cancer that the age at onset of the disease is decreasing. It is still controversial whether the use of oral contraceptives increases the risk of developing breast cancer in BRCA1 mutation carriers. Some studies calculate a small but statistically significant risk, whereas other studies have demonstrated no greater risk.

The penetrance of predisposing genes for breast cancer is also dependent on age and tissue type. For the two known breast cancer predisposition genes, BRCA1 and BRCA2 (see High Penetrance Genes, below), risks have been determined (Table 4.1). In the case of mutation carriers in the BRCA1 or BRCA2 genes, only breast and ovarian tissues have a relatively high risk to transform into malignant cells. In addition, the probability to change into an aberrant phenotype is age dependent. Likewise, the probability for a BRCA1 mutation carrier to develop breast cancer at the age of 50 is approximately 29%. However, women with a carrier status and born after 1940 may have higher risks.

The known forms of hereditary breast cancer are inherited in an autosomal dominant mode. It should be noted, however, that inactivation of one allele is only a prerequisite for tumor generation and is not sufficient to initiate cancer in normal epithelial breast cells. Indeed, for tumor initiation, the second allele has to be inactivated. This can happen either by loss of heterozygosity in the according regions or by epigenetic effects such as methylation (see Chapters 26 and 27). Tumor progression requires the accumulation of additional aberrations in the cellular genome, including the disturbance of TP53 expression that allows cell escape from apoptosis. Based on histologic parameters and gene expression profiling, BRCA1 tumors can be distinguished from BRCA2 and sporadic breast cancer samples. Tumor samples from BRCA1 mutation carriers are normally high grade, infiltrating ductal breast cancers and more often estrogen and HER-2/neu receptor negative than sporadic samples. In contrast, BRCA2 tumors are more difficult to separate from sporadic cases by histologic classification only, but it should be feasible through more validated expression profiling data; for example, tumors from BRCA2 mutation carriers show an
expression profile that is different from BRCA1 but also from sporadic tumors.16

Predisposition Markers

It is estimated that 10–15% of all breast cancer cases may be caused by genetic predisposition. The inheritance of a single defective allele is most likely in a family exhibiting clustering of breast cancer cases, especially if it includes cases diagnosed before age 50. Consequently, a dominant monogenic trait can be demonstrated in families with multiple occurrences of breast cancer (high penetrance genes). In contrast, the segregation of multiple deficient alleles is most likely in families with fewer cases of late onset breast cancer (low penetrance genes). The genes associated with hereditary forms of breast cancer are listed in Table 4.2 and are discussed in the following paragraphs.

High Penetrance Genes

To date, two genes that feature frequent mutations associated with breast cancer predisposition in high risk families have been isolated and validated.17–19 Other genes also involved in the DNA repair or apoptosis pathways have been characterized but only rarely were shown to be mutated. Some of these genes are restricted to site-specific breast cancer, whereas others are associated with other cancer entities.

BRCA1 The first gene found to be mutated in families with multiple occurrences of breast and/or ovarian cancer was the BRCA1 gene.17,19 It has been classified as a classic tumor suppressor gene, and consequently inactivation of the second allele in the resulting tumor could be demonstrated (see above). It is located at 17q21; comprises 24 exons, 22 of them coding; and encodes for a protein consisting of 1863 amino acids. A typical pedigree of a family with a BRCA1 mutation is given in Figure 4.2. Currently, more than 2000 different deleterious mutations in the gene are listed in the international Breast Cancer Information Core (BIC) database (http://research.nhgri.nih.gov/bic/). Most of the putative pathogenic mutations found in the gene are either frame-shift or stop mutations that similarly cause the production of truncated proteins.5,17 Only a few missense mutations, causing single amino acid substitutions, could be demonstrated to be disease causing.20,21 Recently, a high prevalence of large gene rearrangements in the BRCA1 gene has been reported for some populations.22,23 Mutation profiles for different countries have been published,5,24–26 and it has become apparent that a mosaic of founder- and population-specific mutations exists. Founder mutations are often of Ashkenazi Jewish origin and were shown to be present in different white populations.5,24–26

Only a few missense mutations in the BRCA1 gene can be clearly associated with familial breast cancer. These include amino acid residues that are part of the zinc finger
Table 4.2  List of Genes Associated with Hereditary Breast Cancer

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene/Region</th>
<th>Primary Carcinoma</th>
<th>Secondary Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Penetrance Genes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial breast/ovarian carcinoma</td>
<td>BRCA1 17q21</td>
<td>Breast and ovaries</td>
<td>Prostate, colon</td>
</tr>
<tr>
<td>Familial breast/ovarian carcinoma</td>
<td>BRCA2 13q13</td>
<td>Breast and ovaries</td>
<td>Prostate, pancreas male breast</td>
</tr>
<tr>
<td>Familial breast/bilateral b.c.</td>
<td>BACH1 17q22</td>
<td>Breast</td>
<td>None</td>
</tr>
<tr>
<td>Familial breast/bilateral b.c.</td>
<td>RAD51 15q15</td>
<td>Breast</td>
<td>None</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>TP53 17p13</td>
<td>Sarcomas, breast</td>
<td>Brain, leukemia</td>
</tr>
<tr>
<td>Cowden syndrome</td>
<td>PTEN 10q23</td>
<td>Hamartomatous lesions</td>
<td>Polyps</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>STK1 19q</td>
<td>Gastrointestinal polyps</td>
<td>Melanin spots on lips, b.c.</td>
</tr>
<tr>
<td>Low Penetrance Genes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ataxia telangiectasia</td>
<td>ATM 11q22</td>
<td>Lymphomas gliomas</td>
<td>Heterozygous: breast cancer</td>
</tr>
<tr>
<td>Li-Fraumeni/breast cancer</td>
<td>CHEK2 13q21</td>
<td>Breast sarcomas</td>
<td>Brain, leukemia</td>
</tr>
</tbody>
</table>

b.c., breast cancer.

FIGURE 4.2 A mutation in the BRCA1 gene, causing a truncated protein (1364X).
(Cys61Gly, Cys64Y) and amino acids located in the BCRT domain that have been shown to interact with different proteins (e.g., W1837R). Several strategies have been established to evaluate the character of such unclassified variants. These include segregation analysis, evolutionary methods to identify functionally important amino acid sites, loss of heterozygosity analysis in the corresponding tumor samples, and functional assays.20,21

A variety of assay approaches has now become available, enabled by the advanced characterization of the BRCA1 protein. Based on the initial observation that the BRCA1 protein is a caretaker of chromosomal stability, several studies demonstrated that it is involved in the repair of double-stranded DNA breaks (for details, see Chapter 25). Such genomic lesions can be repaired by nonhomologous end joining, recombination between homologous DNA sequences, or single-strand annealing.27,28 In addition, other than its local activities at sites of DNA damage, BRCA1 seems to be involved in processes that are located upstream and downstream of DNA damage responses. On the one hand, BRCA1 is part of protein complexes that apparently have functions intrinsic to the sensing and signaling of different types of DNA lesions; on the other hand, it operates as a transcriptional regulator of genes, whose expression affects downstream biologic responses (FIG. 4.3). The local activities of BRCA1 at sites of DNA damage have been elucidated by several experiments. Sites of DNA damage are rapidly marked by the phosphorylation of the histone species H2A-X, and BRCA1 interacts with the MRE11/RAD50/Nbs1 protein complex to migrate to such sites and resect double-stranded DNA breaks.28,29 It may be necessary to alter the DNA topology at the damage sites via recruiting the protein complexes SWI/SNF, BACH1, HDAC, and P300/CBP for effective DNA repair as well as the regulation of downstream processes. Included in these downstream processes are the transcriptional regulation of GADD45 and transcription coupled repair (FIG. 4.3). Surprisingly, to date, only the BACH1 gene has been associated with hereditary breast cancer (see Infrequently
Mutated Genes, below). Upstream processes of these local activities require the phosphorylation of the BRCA1 protein via the kinases ATR, ATM, and CHK2 proteins (Fig. 4.3). Interestingly, these two latter kinases could be associated with hereditary breast cancer (see The ATM Gene and The CHK2 Gene, below).

Apart from the breast and ovary, compared with many organs in which there is no cancer predisposition risk, several other organs such as the pancreas, prostate, and colon have a slightly increased risk of cancer development in BRCA1 mutation carriers. This observation indicates that BRCA1 disruption may have tissue-specific effects that favor malignant transformation. It has been suggested that BRCA1 functions as an inhibitor of estrogen receptor signaling. Studies have substantiated this observation. Evidence that BRCA1 mediates repression of the estrogen receptor α has been reported, and this process is correlated with the down-regulation of the transcriptional coactivator p300. Further characterization of this pathway may help to explain the tissue specificity of cancer development in BRCA1-deficient cancers.

The clinical outcome of patients with germline mutations in BRCA1 has been evaluated in several studies. Most informative is the comprehensive study of Robson et al. in which two retrospective cohorts of Ashkenazi Jewish women undergoing breast-conserving treatment for invasive cancer were genotyped and the clinical characteristics of the women with and without BRCA founder mutations were compared. In brief, BRCA1 mutation carriers demonstrated a significantly shorter overall survival. This adverse prognosis could not be linked to tumor size or axillary nodal status. This study also demonstrated that women with BRCA1 mutations are at substantially increased risk for developing metachronous contralateral breast cancer, whereas no increased risk could be seen for the development of ipsilateral breast cancer when compared with noncarriers.

BRCA2 A second high penetrance gene found to be mutated in families with multiple occurrences of breast cancer is the BRCA2 gene. It is located at 13q12.3 and consists of 27 exons, 26 of them coding for a protein of 3418 amino acids. A typical pedigree with a mutation in the BRCA2 gene is given in Figure 4.4. Similar to the BRCA1 gene, most of the defined cancer-causing mutations are either frameshift or stop mutations that produce truncated proteins. More than 1000 deleterious mutations in the BRCA2 gene are listed in the international BIC database. However, compared with BRCA1, more missense mutations can be seen in the BRCA2 gene. Because the BRCA2 protein is not as well characterized as the BRCA1 protein, it is necessary to evaluate the character of the observed unclassified variants carefully. Overall, it appears that most of the listed unclassified variants in the BRCA2 gene are rare polymorphic variants (unpublished data) rather than pathogenic. Analogous to the BRCA1 gene, founder mutations are presented frequently in most populations.

![Figure 4.4](image-url) A mutation in the BRCA2 gene, causing a truncated protein (S1882X).
Mutations in the BRCA2 gene are normally found in site-specific breast cancer families, including male breast cancer. However, families with a clustering of pancreatic cancer were also shown to harbor BRCA2 mutations. In one study, 26 European families in which at least two first-degree relatives had a histologically confirmed diagnosis of pancreatic ductal adenocarcinoma were screened for mutations in the BRCA2 gene, and three deleterious and missense aberrations were found. In addition, it could be shown that 2% of men with early onset prostate cancer harbor germline mutations in the BRCA2 gene. Male BRCA2 mutation carriers under the age of 60 have a 26-fold risk increase of developing prostate cancer compared with control subjects. However, further studies are required to confirm that BRCA2 mutations are associated with a higher penetrance in familial cancers of the pancreas and prostate than are BRCA1 mutations.

Of further interest is the recent finding that biallelic mutations in the BRCA2 gene have been found in two Fanconi complementation groups. Fanconi anemia (FA) is an autosomal recessive disorder affecting all bone marrow elements and is associated with cardiac, renal, and limb malformations as well as dermal pigmentation changes. Fanconi patients also have an increased cellular sensitivity to DNA cross-linking agents. FA has eight identified complementation groups, and for the complementation groups B and D1, mutations in the BRCA2 gene can be identified. This finding has now linked the FA pathway to the BRCA1/BRCA2 mediated DNA repair process (Fig. 4.5). Several FA proteins, including FANCA, FANCC, FANCE, FANCF, and FANCG, form a constitutive complex in the nucleus of human cells that in response to DNA damage mediates the monoubiquitination of FANCD2. The activated FANCD2 protein is then translocated to chromatin and the DNA-repair foci that contain BRCA1 and BRCA2 (FANCD1). BRCA2 is known to bind directly to RAD51 and, similar to BRCA1, is involved in homology-directed DNA repair. Also, similar to the BRCA1 protein, the BRCA2FA pathway can be linked to ATM and to another upstream activator, the MRE11 complex. A study indicates that in response to cellular exposure to ionizing radiation, the ATM protein directly phosphorylates FANCD2. Thus, the FANCD2 protein functions in mediating two signaling pathways by undergoing two different types of posttranslational modifications. A link to the MRE11 complex (NBS-MRE11-RAD50) can be established through the demonstration that the activated form of FANCD2 and NBS1 are colocalized in nuclear foci. Either the disruption of the MRE11-binding carboxy terminal end of NBS1 or the disruption of the FANCD2 monoubiquitination site results in mitomycin hypersensitivity. In summary, both BRCA proteins are involved in DNA repair, a cellular mechanism activated in response to irradiation or chemically induced lesions. As well as the ATM and NBS pathways, respectively, the FA pathway has now linked to this cellular network system that maintains genomic integrity and stability.
As in the case of \textit{BRCA1} mutation carriers, the clinical outcome for \textit{BRCA2} mutation carriers has been evaluated.\textsuperscript{15} In contrast to females with predisposing mutations in the \textit{BRCA1} gene, females with mutations in the \textit{BRCA2} gene have no reduced survival after breast cancer therapy. However, similar to \textit{BRCA1} carriers, these patients carry an approximately 30\% risk of developing contralateral breast cancer after 10 years of posttreatment follow-up has elapsed. Further follow-up studies are required to confirm these initial data obtained in Ashkenazi Jewish women.

\textbf{Infrequently Mutated Genes} \hspace*{1em} Based on the observation that \textit{BRCA1} and \textit{BRCA2} are involved in double-stranded DNA break-repair mechanisms, several groups have searched for aberrations in other genes located in this pathway. The \textit{BACH1} gene (\textit{BRCA1}-associated C-terminal helicase-1) codes for a nuclear protein that acts directly with the highly conserved C-terminal BRCT repeats of the \textit{BRCA1} protein. The predicted 1249 amino acid long protein, encoded by 20 exons, contains the seven helicase-specific motifs that are conserved among members of the DEAH helicase family. Cantor et al.\textsuperscript{47} identified a germline mutation affecting the helicase domain in 2 of 65 patients with either early onset or familial breast cancer. In subsequent experiments the same group demonstrated that these two and a novel third mutation impair the function of the BACH1 protein.\textsuperscript{48} This novel protein is both a DNA-dependent ATPase and a 5’ to 3’-DNA helicase. The helicase activity is strictly ATP dependent, and when a Pro47Ala missense mutation is present, this activity is abrogated. Due to another missense mutation (Lys52Arg), ATPase activity is disrupted as the unwinding of DNA and RNA hybrids, an additional function associated with the wild-type. Finally, one missense mutation maintains the ATPase activity but disturbs the unwinding process. Further studies will show whether other variants in the gene will have at least a minor effect on hereditary breast cancer, for example, in combination with CHEK2 (see The \textit{CHK2} Gene, below).

Mouse experiments demonstrated that \textit{BRCA2} interacts with \textit{RAD51} (see \textit{BRCA2}, above). Recently, Pellegrini et al.\textsuperscript{49} showed, on the basis of crystal structures, that the direct binding is mediated by the BRC repeat (\textit{BRCA2}) and the RecA-homology domain (\textit{RAD51}). The BRC repeat mimics a motif in \textit{RAD51} that serves as an interface for oligomerization between individual \textit{RAD51} monomers, thus enabling \textit{BRCA2} to control the assembly of the \textit{RAD51} nucleoprotein filament that is essential for strand-pairing reactions during DNA recombination. In parallel to the still ongoing functional works on \textit{BRCA2} and \textit{RAD51}, several groups looked for aberrations in the \textit{RAD51} gene. In a study with 20 patients from breast cancer families, Kato et al.\textsuperscript{50} identified a missense mutation (Arg150Gln) in two unrelated females, both presenting with bilateral breast cancer. In addition, a single nucleotide polymorphism in the 5’-untranslated region of the \textit{RAD51} gene (135g \rightarrow c) has been associated with an increase for \textit{BRCA2} mutation carriers.\textsuperscript{51} However, further studies, including quantitative reverse transcriptase-polymerase chain reaction, are required to substantiate this finding.

\textbf{Genes Associated with Cancer Syndromes} \hspace*{1em} Breast cancer is also a component of several other cancer syndromes, including Li-Fraumeni syndrome (OMIM 151623), Cowden syndrome (OMIM 158350), and Peutz-Jeghers syndrome (OMIM 175200). All these syndromes are rare, and mutations in the genes causing them contribute only a small fraction of hereditary breast cancer cases.

The \textit{TP53} gene is mutated in Li-Fraumeni syndrome, which is characterized by the occurrence of multiple cancers, including childhood sarcoma and breast cancer (see Chapter 23).\textsuperscript{52} Mutations in the \textit{TP53} gene
are found in approximately 70% of the Li-Fraumeni families. A higher cancer risk in females than in males was observed by using follow-up studies.\(^53\) Quite recently, mutations in the \textit{CHEK2} gene have also been associated with Li-Fraumeni syndrome (see The \textit{CHK2} Gene, below). Although only a few germline mutations in \textit{TP53} contribute to hereditary breast cancer, somatic inactivation of \textit{TP53} in BRCA mutation related tumors is frequently identified (see above).\(^54\) It is now accepted that inactivation of \textit{TP53} prevents the initiation of apoptosis, prevents the depletion of cells that have accumulated genomic lesions, and thus contributes to the establishment and progression of malignancy.

Multiple hamartomatous lesions, especially of the skin, mucous membranes, breast, and thyroid, and craniofacial are characteristic lesions of the Cowden syndrome. In 1997, mutations in the \textit{PTEN} (phosphatase and tensin homolog) gene were identified in families with the Cowden syndrome phenotype.\(^55\) Although germline mutations in \textit{PTEN} are rare, \textit{PTEN} is frequently inactivated in sporadic cancers, including glioblastomas and prostate cancer (see Chapter 23).\(^56\) Recent data indicate that \textit{PTEN} is involved in the regulation of apoptosis\(^56\) and angiogenesis.\(^57\) During both processes, the \textit{PTEN} protein acts through the well-recognized tumor progression associated phosphoinositol-3-kinase and Akt-dependent pathways.

A serine-threonine kinase, the \textit{STK11/LKB1} gene, was found to be mutated in several families with Peutz-Jeghers syndrome.\(^58\) This is an autosomal dominant disorder characterized by melanocytic macules of the lips, multiple gastrointestinal hamartomatous polyps, and an increased risk for various neoplasms, including gastrointestinal and breast cancer. Carrier females with a mutation in the \textit{STK11} gene also have an elevated risk for breast cancer, as has been shown in a British study in which 33 Peutz-Jeghers families were evaluated by follow-up data.\(^59\) Whether the \textit{STK11} gene also plays a role in sporadic breast cancer, as suggested in a recent study,\(^60\) requires validation with larger patient groups.

**Low Penetrance Genes**

Currently, three genes are considered to act as low penetrance genes for hereditary breast cancer. In contrast to high penetrance genes, such genes act in a concerted way, either in connection with variants in other predisposing genes or in combination with epigenetic or environmental factors. In addition, several modifier genes in breast cancer have been described and are summarized elsewhere.\(^61\)

**The \textit{ATM} gene** A first gene in which variants have been associated with breast cancer is the \textit{ATM} gene (OMIM 208900). The \textit{ATM} gene is mutated on both alleles in ataxia telangiectasia and codes for a member of the phosphatidylinositol-3 kinase family of proteins. Similar to the two BRCA proteins, ATM plays a key role in monitoring genomic integrity and regulating cell cycle checkpoints, DNA repair, and apoptotic pathways induced by double-stranded DNA breaks. After the occurrence of double-stranded breaks in the cell, ATM interacts with and phosphorylates a number of different targets, including p53, Nibrin, CtIP, BRCA1, and \textit{CHEK2} (\textit{FIGS. 4.3 and 4.6}).\(^62\) Given that there are several confirmed direct functional links between the ATM and BRCA1 proteins, the \textit{ATM} gene also has been implicated in breast carcinoma susceptibility.

In two larger mutation screening reports, variants in the \textit{ATM} gene have been linked to familial breast cancer.\(^62\)\(^63\) In both studies, missense mutations in the \textit{ATM} gene were shown to be specific for familial cases but were absent from normal control subjects (\textit{Table 4.2}). However, additional studies are required to confirm that ATM mutations confer increased susceptibility to breast cancer.

**The \textit{CHK2} gene** Cell cycle checkpoint kinase 2 (CHEK2 [OMIM 604373]) plays an important role in the maintenance of genome integrity and in the regulation of the G2/M cell cycle checkpoint. It has been shown to interact with other proteins involved in DNA repair processes, such as \textit{BRCA1} and \textit{TP53}.\(^32,64\) These findings suggest that \textit{CHK2} could be an attractive candidate gene associated with susceptibility for a variety of cancers (\textit{FIGS. 4.6}). Patients with Li-Fraumeni syndrome were analyzed, and in a small proportion of families a single mutation in exon 10 of \textit{CHK2} was identified.\(^65\) This del1100C variant causes a stop codon after amino acid 380 abrogating the kinase activity. The \textit{CHK2} Breast Cancer Consortium analyzed 718 families with breast and/or ovarian cancer that harbor neither a \textit{BRCA1} nor a \textit{BRCA2} mutation. The 1861delC mutation was identified in 5.1% of the families.
Therefore, at present it appears premature to include \textit{CHK2} in genetic counseling for patients with an unexplained high familial incidence of breast cancer.

\textbf{Androgen Receptor Gene} Mutations in the androgen receptor (\textit{AR}) gene have been linked to different disease entities. Expansions of CAG repeats within the coding region can cause spinal and bulbar muscular dystrophy (Kennedy disease) and different forms of androgen insensitivity.\textsuperscript{68} The first link to breast cancer for \textit{AR} was confirmed by the identification of germline mutations in two brothers with breast cancer and Reifenstein syndrome.\textsuperscript{69} More recently, a polymorphic CAG repeat in the \textit{AR} gene has been associated with a poorer prognosis for \textit{BRCA1} mutation carriers. Comparison of 165 women with and 139 women without breast cancer revealed that women carrying at least one allele with 29 or 30 CAG repeats manifested the disease earlier.\textsuperscript{70}

In summary, an evaluation of genes localized in either apoptosis, DNA repair, or endocrine signaling will provide further low penetrance or modifier genes. Ongoing mapping and cloning studies will show whether a gene segregates recessively or dominantly in high risk families.
Predisposition Testing and Risk Management

Because of the complexity of genetic counseling in hereditary breast cancer, referral to a subspecialized multidisciplinary clinic staffed by practitioners with expertise in this field is generally recommended. In this setting, a new client can be educated by an experienced genetic counselor about the a priori risks associated with breast cancer predisposing germline mutations. At the same visit, the client can also receive information from medical and surgical/gynecologic oncologists concerning screening, diagnosis, and treatment options. Finally, this approach also allows the client to meet with a psychologist/psychiatrist to consider the important psychological and emotional issues associated with breast cancer predisposition testing and the implications for the client and her family. In such a multidisciplinary counseling setting, the sensitivity and specificity of the applied molecular techniques, the indications for testing, and possible risk managements in BRCA1/2 mutation carriers and/or BRCA1/2 negative females from putative BRCAX families can be thoroughly considered.

Methods

A variety of laboratory techniques has been used for screening for genetic mutations in hereditary breast cancer. In addition, protein truncation tests have been developed as prescreening methods and can be applied for the rapid identification of the likely presence of underlying pathogenic mutations. However, it is now accepted that screening of index patients in families with either multiple cases or early onset manifestation of breast cancer should be applied by investigating the entire gene to also detect missense mutations and putative splice sites. Two independent methods that are applied currently in routine diagnosis include the direct double-stranded sequencing approach, as performed by the company Myriad Genetics, and denaturing high-performance liquid chromatography (DHPLC) analysis of all coding exons with the adjacent intronic sites. In families with a significant prior probability of a BRCA mutation, testing for large gene rearrangements also has to be included. For this approach, a kit based on multiplex ligation-dependent probe amplification is available now. Overall, the sensitivity of this technique is greater than 90%, and when either complete direct double-stranded sequencing or comprehensive DHPLC analysis is combined with multiplex ligation-dependent probe amplification, the specificity is greater than 90%.

Indications for Testing

Genetic testing is recommended only after multidisciplinary genetic counseling. The criterion for testing is a 20% probability of the presence of a mutation. Candidates for BRCA1/2 genetic testing are as follows:

- Two breast cancer cases under age 40 or three under age 50 years;
- Four cases of breast cancer under age 60 years;
- More than four cases of breast cancer at any age;
- Ovarian and breast cancer in a family (breast cancer under age 50 years if only one ovarian and one breast cancer case);
- Early onset female breast cancer at under age 60 years and male breast cancer at any age;
- Single case of breast cancer at under age 40 years if the patient is of Ashkenazi Jewish decent.

Risk Management

Three categories of options for management of women with BRCA mutations are available: screening and surveillance, prophylactic surgeries, and chemoprevention. These options should be discussed with women in detail to allow them to make informed decisions regarding their health care.

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