Hereditary breast and ovarian cancer due to mutations in *BRCA1* and *BRCA2*

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Abstract: Hereditary breast and ovarian cancer due to mutations in the *BRCA1* and *BRCA2* genes is the most common cause of hereditary forms of both breast and ovarian cancer. The overall prevalence of *BRCA1/2* mutations is estimated to be from 1 in 400 to 1 in 800 with a higher prevalence in the Ashkenazi Jewish population (1 in 40). Estimates of penetrance (cancer risk) vary considerably depending on the context in which they were derived and have been shown to vary within families with the same *BRCA1/2* mutation. This suggests there is no exact risk estimate that can be applied to all individuals with a *BRCA1/2* mutation. The likelihood of harboring a *BRCA1* or *BRCA2* mutation is dependent on one's personal and/or family history of cancer and can be estimated using various mutation probability models. For those individuals who have a *BRCA1* or *BRCA2* mutation, several screening and primary prevention options have been suggested, including prophylactic surgery and chemoprevention. Once a *BRCA1* or *BRCA2* mutation has been identified in a family, testing of at-risk relatives can identify those family members who also have the familial mutation and thus need increased surveillance and early intervention when a cancer is diagnosed. ***Genet Med* 2010:12(5):245–259.**

Key Words: *hereditary breast and ovarian cancer, BRCA1, BRCA2*

NATURAL HISTORY AND GENETICS

Disease characteristics

Germline mutations in breast cancer 1 gene (*BRCA1*) and breast cancer 2 gene (*BRCA2*) predispose to breast and ovarian cancer as well as other cancers. The risk of developing cancer (penetrance) that is associated with a *BRCA1* or *BRCA2* mutation appears variable within families and has been derived from a variety of sources, including families with multiple-affected individuals, families with few affected individuals, and population-based studies.[1,2] Prognosis for breast and ovarian cancer depends on the stage at which the cancer is diagnosed, but studies on survival have been conflicting for individuals with *BRCA1* and *BRCA2* mutations when compared with patients who are not mutation carriers.[3–19]

Prevalence

Hereditary breast and ovarian cancer (HBOC) due to mutations in *BRCA1* and *BRCA2* is the most common cause of

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hereditary forms of both breast and ovarian cancer and occurs in all ethnic and racial populations. The overall prevalence of *BRCA1/2* mutations is estimated to be from 1 in 400 to 1 in 800[20–22] but varies depending on ethnicity. Few studies, however, have directly compared mutation prevalence by ethnic background.[23–27] In the United States, much of the focus has been on individuals of Ashkenazi (central European) Jewish ancestry.

Ashkenazi Jews have a substantially elevated risk of HBOC secondary to a high frequency of *BRCA1/2* mutations mainly attributable to three well-described founder mutations: two of which are in the *BRCA1* gene (187delAG and 5385insC, also known as 185delAG and 5382insC, respectively. The Human Genome Variation Society nomenclature for each is NC_000017.9:g.38529572_38529571delAG and NC_000017.9:g.38462606dupC, respectively) and one of which is in the *BRCA2* gene (6174delT, the Human Genome Variation Society nomenclature for 6174delT is NC_000013.9:c.24822delT).[28–30] The 187delAG mutation in *BRCA1* occurs with a frequency of about 1.1% in individuals of Ashkenazi Jewish descent.[26,30–32] The 5385insC mutation has an estimated prevalence of 0.1% to 0.15%,[32] and the *BRCA2* mutation, 6174delT occurs with a frequency of about 1.5%,[28,30–32] resulting in a carrier frequency of 1 per 40 in the aggregate. The prevalence of *BRCA1* mutations in Ashkenazi Jewish women aged younger than 65 years at diagnosis is 8.3%.[26] The *BRCA2* founder mutation, 6174delT, is present in 8% of women diagnosed with breast cancer before the age of 42 years and in 1.5% of unselected Ashkenazim,[32,33] whereas the *BRCA1* founder mutation, 185delAG, has been found in 20% of Ashkenazi Jewish women diagnosed with breast cancer before the age of 42 years.[34] This increased frequency influences genetic testing recommendations for individuals of Ashkenazi Jewish heritage (see Testing Strategy section).

Although most *BRCA1* mutations described involve only a few base pairs, studies in the Dutch population have identified three large deletions within *BRCA1*. These deletions were detected using Southern blot analysis and accounted for 36% of mutations in a Dutch sample of high-risk families.[35]

The *BRCA2* mutation, 999del5, occurs in 0.6% of the Icelandic population and in 10.4% of women and 38% of men with breast cancer from Iceland.[36] The mutation was seen in 17% of women diagnosed with breast cancer by the age of 50 years and in 4% of women diagnosed at later ages. Among individuals with the 999del5 mutation, 17 of 44 (39%) had no first- or second-degree relatives with cancer, suggesting incomplete penetrance of the mutation.[37]

There are several other populations in which founder *BRCA1* and *BRCA2* mutations have also been identified.[38]

Molecular genetics

BRCA1

The *BRCA1* gene is located on the long arm of Chromosome 17 at 17q21 and contains 24 coding exons spread over 80 kb.[39] Its normal allele produces a 7.8-kb mRNA that encodes the breast cancer type 1 susceptibility protein, a 1863 amino acid that contains several recognizable protein motifs, including a RING-finger domain near the N-terminus, two nuclear localization signals located on exon 11, an "SQ" cluster between amino acids 1280–1524, and a BRCT domain at the C-terminus. *BRCA1* interacts with several proteins involved in cellular pathways, including cell cycle progression, gene transcription regulation, DNA damage response, and ubiquitination.[40,41] From studying homozygous knockout mice, the available evidence indicates that *BRCA1* serves as a "caretaker," such as *TP53*, helping to maintain genomic integrity.[42] When this function is lost, it probably allows for the accumulation of other genetic defects that are themselves directly responsible for cancer formation. More than 1600 mutations have been identified in *BRCA1*, most of which lead to frameshifts resulting in missing or nonfunctional proteins. In most, but not all cancers that have been studied from individuals with a germline mutation, the wild-type allele is deleted, strongly suggesting that *BRCA1* is in the class of tumor suppressor genes.[40,43,44] Loss of function of *BRCA1* results in defects in DNA repair, defects in transcription, abnormal centrosome duplication, defective G2/M cell cycle checkpoint regulation, impaired spindle checkpoint, and chromosome damage.[45–47]

BRCA2

The *BRCA2* gene is located on the long arm of the Chromosome 13 at 13q12.3 and contains 27 coding exons. Its normal allele produces a 10.4-kb mRNA that encodes breast cancer type 2 susceptibility, a 3418 amino acid with eight 30 to 40 residue motifs found in exon 11, which mediates the binding of *BRCA2* to *RAD51*. *BRCA2* is normally located in the nucleus and contains phosphorylated residues.[48] The breast cancer type 2 susceptibility protein has no recognizable protein motifs and no apparent relation to the breast cancer type 1 susceptibility protein. Nonetheless, the proteins encoded by *BRCA1* and *BRCA2* appear to share a number of functional similarities that may suggest why mutations in these genes lead to a specific hereditary predisposition to breast and ovarian cancer. *BRCA2* appears to be involved in the DNA repair process. From studying homozygous knockout mice, the available evidence indicates that *BRCA2* is a "caretaker," similar to *BRCA1*, which serves to maintain genomic integrity.[42] More than 1800 mutations have been identified in *BRCA2* with most mutations reported to date consisting of frameshift deletions, insertions, or nonsense mutations leading to premature truncation of protein transcription, consistent with the loss of function that is expected with clinically significant mutations in tumor suppressor genes. Cells lacking *BRCA2* are deficient in the repair of double-strand DNA breaks, as reflected in a hypersensitivity to ionizing radiation.[49]

Penetrance (cancer risk)

The penetrance of *BRCA1* and *BRCA2* mutations is the most significant clinical aspect of HBOC with breast and ovarian cancer being the predominant phenotype. Estimates of penetrance vary considerably depending on the context in which they were derived. Multiple breast case families, especially if ovarian cancer is also present, may be enriched for mutations and have been shown to have substantial risks for both breast and ovarian cancer. In 1995, Easton et al.[1] provided a lifetime breast cancer risk in *BRCA1* carriers of >80%, the highest reported estimate to date. However, these risks may overestimate the risk within all families and therefore may not apply to families with less severe cancer histories or in incident cases as illustrated in studies of unselected patients with breast cancer whose estimated breast cancer risks have been in the 40% to 60% range.[2] In addition to these wide-ranging risk estimates, penetrance has been shown to vary within families with the same *BRCA1/2* mutation, suggesting that there is no "exact" risk estimate that can be applied to all individuals with a *BRCA1* or *BRCA2* mutation.

The following is a summary of cancer risks in individuals identified with mutations in the *BRCA1* and *BRCA2* genes. No

associated benign tumors or physical abnormalities are presently known to be associated with *BRCA1/2* mutations.

BRCA1—female breast and ovarian cancer risks

According to a combined analysis of 22 population-based studies in which cases were unselected for family history, the average risk for breast cancer in *BRCA1* mutation carriers by the age of 70 years was 65% (95% confidence interval [CI]: 44–78%) and for ovarian cancer was 39% (95% CI: 18–54%).[50] Another population-based study on those aged 80 years revealed *BRCA1*-related breast and ovarian cancer risk estimates of 90% and 24%, respectively.[51] When correcting for ascertainment, a meta-analysis of 10 studies reported cumulative cancer risks for breast and ovarian cancer as 57% and 40%, respectively, to age 70 for *BRCA1* mutation carriers.[52] The contralateral breast cancer risk in *BRCA1* carriers is 27% within 5 years of the initial breast cancer diagnosis.[53] The risk of *BRCA1*-related breast and ovarian cancer appears to be confined to epithelial malignancies of both organs.

BRCA1—other related cancer risks

Fallopian tube carcinoma is now a well-established component tumor of the *BRCA1*-related cancer spectrum, with relative risks reported as high as 120.[54] *BRCA1* mutation carriers are also at risk of primary papillary serous carcinoma of the peritoneum, a malignancy that is indistinguishable from serous epithelial ovarian carcinoma, with cumulative risks of 3.9% to 4.3% 20 years after oophorectomy.[55,56] The risk of prostate cancer in male *BRCA1* carriers is increased with a relative risk of ~1.8[57] although this risk may vary significantly depending on the location of the *BRCA1* mutation.[58] Furthermore, such cancers do not typically demonstrate a younger than usual age at diagnosis.[59] Finally, a variety of other cancers have been implicated, albeit inconsistently, as part of the *BRCA1*-related cancer spectrum.[60] The most convincing associations are an increased risk of pancreatic cancer[61] and male breast cancer[62,63] with the cumulative breast cancer risks to age 70 among *BRCA1* male mutation carriers being 1.2%. Initial reports of increased colorectal cancer risk have generally not been replicated. The Breast Cancer Linkage Consortium also reported statistically significantly increased relative risks for cancers of the pancreas, uterine body, and cervix (only in carriers younger than age 65 years), with relative risks of 2.3, 2.6, and 3.7, respectively.[57] The possibility that endometrial cancer might be a *BRCA1/2*-related malignancy has been inconsistent and may be related to tamoxifen exposure.[64]

BRCA2—female breast and ovarian cancer risks

In the same 22 population-based studies cited earlier, the *BRCA2*-related risk estimates to age 70 for both breast and ovarian cancer were 45% (95% CI: 33–54%) and 11% (95% CI: 4–18%), respectively.[50] In another population-based study, *BRCA2*-related breast and ovarian cancer risk estimates to age 80 were 41% and 8.4%, respectively,[51] which was the lowest ovarian cancer penetrance estimate yet reported. When corrected for ascertainment, the cumulative cancer risks to age 70 for breast and ovarian cancer in *BRCA2* carriers were reported as 49% and 18%, respectively.[65] The risk of ovarian cancer, although lower than that observed in *BRCA1* mutation carriers, is still greatly increased above the general population (1.4%). Ovarian cancer in *BRCA2* carriers is more likely to occur after the age of 50 years than those found in *BRCA1* carriers.[66] The contralateral breast cancer risk in *BRCA2* carriers is 12% within 5 years of the initial breast cancer diagnosis.[53] As in *BRCA1*, the risk of *BRCA2*-related breast and ovarian cancer appears to be confined to epithelial malignancies of both organs as well.

BRCA2—other related cancer risks

Fallopian tube carcinoma has also been associated with *BRCA2* mutations,[67] as has primary papillary serous carcinoma of the peritoneum, and similar to ovarian cancer, this malignancy occurs less frequently among *BRCA2* when compared with *BRCA1* carriers.[55] Male breast cancer is more commonly associated with *BRCA2* mutations when compared with *BRCA1* mutations. The cumulative probability to age 70 of male breast cancer in carriers of *BRCA2* mutations has been reported as 6%[62] and 6.8%.[63] Prostate cancer also occurs in excess in male *BRCA2* carriers with a relative risk of 4.6,[68] although unlike as observed in *BRCA1*-related prostate cancer, it may demonstrate a younger than usual age at diagnosis.[69] The presence of pancreatic cancer in a breast cancer family may be a statistically significant predictor of a *BRCA2* mutation[70] although *BRCA1* carriers have also been found to have an increased risk. The Breast Cancer Linkage Consortium also reported statistically increased relative risks for cancers of the pancreas, gallbladder and bile duct, stomach, and melanoma with relative risks of 3.5, 5.0, 2.6, and 2.6, respectively,[68] the latter three sites being inconsistently associated with *BRCA2*.[71] Finally, as with *BRCA1*, initial reports of increased colorectal cancer risk have generally not been replicated.

Cancer risks in specific populations

The risk of breast cancer by the age of 70 years for carriers of the two Ashkenazi founder *BRCA1* mutations, 185delAG and 5282insC, is 64% (95% CI: 34–80%) and 67% (95% CI: 36–83%), respectively.[72] The corresponding values for ovarian cancer are 14% (95% CI: 2–24%) and 33% (95% CI: 8–50%), respectively. In an effort to eliminate inflated penetrance estimates suspected from studies of cancer families, Satagopan et al.[73] studied incident breast cancer cases and found the penetrance of breast cancer at age 80 among *BRCA1* carriers to be 59% (95% CI: 40–93%) and among *BRCA2* carriers to be 38% (95% CI: 20–68%). Using a similar study design, Satagopan et al.[74] also found the estimated penetrance of ovarian cancer at age 70 among *BRCA1* carriers to be 37% (95% CI: 25–71%) and among *BRCA2* carriers to be 21% (95% CI: 13–41%). In the US population, Chen et al.[52] estimated cumulative breast cancer risk in *BRCA1* mutation carriers to age 70 as 46% (95% CI: 0.39–0.54%) and for ovarian cancer as 39% (95% CI: 0.30–0.50%), based on 676 Ashkenazi families and 1272 families of other ethnicities. The risk of breast cancer by age 70 for carriers of the Ashkenazi *BRCA2* 6174delT mutation is 43% (95% CI: 14–62%) and for ovarian cancer is 20% (95% CI: 2–35%).[72] The breast cancer penetrance of the Icelandic *BRCA2* 999del5 mutation was 17% by age 50 and 37% by age 70.[36]

Genotype-phenotype correlations

In addition to differences in cancer risks by gene, cancer risks in *BRCA1* and *BRCA2* mutation carriers may differ by mutation position as well. It has been suggested that families with mutations in the ovarian cancer cluster region of exon 11 of the *BRCA2* gene have a higher ratio of ovarian to breast cancer than families with mutations elsewhere in the *BRCA2* gene. In 2004, Lubinski et al.[75] investigated 440 families with a *BRCA2* mutation for the presence of cancer of the ovary, male breast, pancreas, prostate, colon, and stomach as well as melanoma in first- and second-degree relatives of mutation-positive individuals. Families with ovarian cancer were more likely to harbor mutations in the ovarian cancer cluster region than elsewhere in

the gene. Differences in ethnic groups were documented as well. Families of Polish ancestry had a lower frequency of pancreatic cancer than families of other ethnic origins, suggesting that both position of mutation and ethnic background may contribute to the phenotypic variation observed in families with *BRCA2* mutations.[75] More recently, Cybulski et al.[58] found that the odds ratio of prostate cancer varied substantially by the position of the mutation. Despite such interesting findings, these correlations are not currently being used for definitive clinical management decisions.

Breast cancer prognosis

The distinct pathologic features of *BRCA1*-related breast tumors (and perhaps *BRCA2*-related breast tumors) coupled with the relative paucity of somatic *BRCA1/2* mutations in breast cancer occurring in individuals with no known family history of breast cancer suggest that breast cancer in individuals with *BRCA1* or *BRCA2* germline mutations has a specific pathogenetic basis, which could lead to differences in prognosis. However, prospective longitudinal studies with large numbers of women to accurately estimate breast cancer prognosis in individuals with *BRCA1/2* mutations are lacking. The available data, derived mostly from retrospective or indirect data, are based on small numbers (<50 cases), are probably confounded by different biases, and lack appropriate controls. Given these limitations, most studies on prognosis of breast cancer have not found a significant difference in survival between individuals with *BRCA1* or *BRCA2* mutations and controls,[76–81] and studies reporting both better prognosis[3,4] and worse prognosis exist.[5–8]

In a retrospective cohort study of individuals of Ashkenazi heritage with breast cancer, those with a *BRCA1* mutation experienced poorer disease-specific survival compared with controls who did not have a *BRCA1* mutation but only among women not receiving adjuvant chemotherapy.[82] Several studies have reported higher rates of contralateral breast cancers[7,8,83,84] and ipsilateral breast cancers[68–85] in women with *BRCA1/2* mutations who are treated with breast conservation. In one case-control study, the increased rate of ipsilateral breast cancers was only seen in individuals with a *BRCA1* or *BRCA2* mutation who had not undergone prophylactic oophorectomy.[86] The increase in second primary cancers reported in these studies has not yet translated into significant differences in survival. Clearly, additional prospective studies with more rigorous designs will help to clarify these complex interactions and better define the true prognosis of *BRCA1/2*-related breast cancer.

Ovarian cancer prognosis

Studies on ovarian cancer survival in women with *BRCA1/2* mutations have yielded conflicting results as well, at least in part because of the same methodologic issues encountered in studies on breast cancer prognosis. Two small population-based studies in Sweden ($n = 38$) and a Canadian study ($n = 44$) found no differences in survival between women with *BRCA1* mutations with ovarian cancer and controls.[9,77] A short-term improvement seen in a case-control study from the Netherlands did not persist after 5 years,[10] and a case-control study at the University of Iowa also failed to find a survival advantage for women with *BRCA1* mutations with ovarian cancer.[11] However, data suggesting a survival advantage for *BRCA1/2* mutation carriers are growing. The first study in which women with *BRCA1* mutations were identified by molecular genetic testing found improved survival in 43 women with *BRCA1*-associated ovarian cancer (median survival of 77 months compared with 29 months in controls).[12] This study was criticized for selection bias, lead-time bias (increased surveillance leading to earlier diagnosis in familial cases),[13,14] and differences in treatment received by individuals with mutations compared with historical controls.[15] A similar improved survival rate was noted in a study of 25 women with *BRCA1* mutations with stage III ovarian cancer,[16] and in Ashkenazi Jewish women treated with platinum-based chemotherapy.[17] More recent studies also support the finding of improved survival among mutation carriers. A small case-control study from the United Kingdom found both higher complete response rates (81.8% vs. 43.2%; $P = 0.004$) and overall survival (95.5% vs. 59.1%; $P = 0.002$) for *BRCA*-positive patients.[18] The National Israeli Study of Ovarian Cancer reported significantly better median survival (53.7 vs. 37.5 months; $P = 0.002$) and 5-year survival rates (38.1% vs. 24.5%; $P = <0.001$) for carriers of an Ashkenazi founder mutation compared with noncarriers.[19] Two population-based studies report a greater survival benefit among *BRCA2* mutation carriers than *BRCA1* mutation carriers with ovarian cancer.[87,88]

Studies finding a survival advantage for *BRCA1/2* mutation carriers are supported by in vitro data that shows increased sensitivity to platinum-based drugs in *BRCA1*-mutant cells, thus providing a potential biologic rationale for improved survival in women treated for ovarian cancer with platinum-based therapies.[89,90]

Prostate cancer prognosis

A number of case-control studies have reported a significant number of men with deleterious *BRCA2* mutations presenting at a young age at diagnosis, with high-grade histopathology and experiencing decreased survival compared with men with sporadic prostate cancer.[91–93]

Breast cancer pathology

BRCA1-related breast tumors show an excess of medullary histopathology, are of higher histologic grade, and are more likely than sporadic tumors to be estrogen receptor negative and progesterone receptor negative, and are less likely to demonstrate HER2/neu overexpression, thus falling within the category of "triple-negative" breast cancer.[94] At the molecular level, a higher frequency of *TP53* mutations is observed than in sporadic tumors. Emerging data suggest that *BRCA1*-related breast cancers are more likely than sporadic tumors to be derived from the basal epithelial layer of cells of the mammary gland, to be triple negative and to stain positive for CK5/6 markers.[95–97] Information regarding *BRCA2*-related breast tumors is more limited, but they do not seem to have a characteristic histopathology and are more likely to resemble sporadic breast cancers.

Ductal carcinoma in situ is now recognized as part of the spectrum of breast neoplasia in *BRCA1/2* mutation carriers, however, its frequency compared with sporadic breast cancer is controversial.[98–100]

Ovarian cancer pathology

An excess of ovarian serous adenocarcinomas has been observed in women with *BRCA1* and *BRCA2* mutations compared with controls. More than 90% of tumors in women with *BRCA1* mutations are serous, compared with ~50% in women without a *BRCA1* mutation.[12,16,101,102] Serous adenocarcinomas are generally of higher grade and are more frequently bilateral than mucinous cancers. Preliminary support for distinct molecular pathways of carcinogenesis comes from the finding of differential expression of genes in *BRCA1*, *BRCA2*, and sporadic ovarian cancer using DNA microarray technology.[103] This approach may ultimately lead to the identification of unique histopathologic subtypes.

Careful histopathologic analysis of the fallopian tubes removed at the time of prophylactic oophorectomy has identified the fimbria as a potential site for primary fallopian tube carcinoma and tubal intraepithelial carcinoma. Many of these tubal carcinomas also stain for p53 protein, which is overaccumulated in serous carcinoma.[104] These findings suggest that in addition to primary tubal carcinoma, the fimbria may represent the origin of some peritoneal and ovarian serous carcinomas.[105]

DIAGNOSIS AND TESTING

Clinical diagnosis

HBOC is suspected if one or more of the following features are present in a family and thus would warrant further risk evaluation[106]:

- Early-age-onset breast cancer (younger than 50 years of age) including both invasive and ductal carcinoma in situ breast cancers.
- Two breast primaries or breast and ovarian/fallopian tube/primary peritoneal cancer in a single individual or two or more breast primaries or breast and ovarian/fallopian tube/primary peritoneal cancers in close (first-, second-, and third-degree) relative(s) from the same side of family (maternal or paternal).
- Populations at risk (Ashkenazi Jewish).
- Member of a family with a known *BRCA1* or *BRCA2* mutation.
- Any male breast cancer.
- Ovarian/fallopian tube/primary peritoneal cancer at any age.

Situations that may lower the threshold of suspicion for HBOC would include families with a limited family structure, defined as having fewer than two first- or second-degree female relatives surviving beyond the age of 45 years in either lineage, as this may lead to an underrepresentation of female cancers despite the presence of a predisposing family mutation[107]; oophorectomy at a young age in family members, which reduces the risk of both breast and ovarian cancer, as this might mask a hereditary susceptibility to both breast and ovarian cancer; the presence of adoption in the lineage, and populations at risk of carrying a *BRCA1/2* mutation (e.g., individuals of Ashkenazi Jewish descent).

Mutation probability models

Probability models have been developed to estimate the likelihood that an individual or family has a mutation in *BRCA1* or *BRCA2*. Each model has its own unique attributes determined by the methods, sample size, and population used to create it. Two such widely used models include BRCAPRO and Myriad (Table 1).

BRCAPRO is a computer-based Bayesian probability model that uses breast and/or ovarian cancer family history in first- and second-degree relatives to determine the probability that a *BRCA1* or *BRCA2* gene mutation accounts for the pattern of these cancers in the family.[108] Key attributes include the population prevalence of mutations, age-specific penetrance, and Ashkenazi Jewish heritage. BRCAPRO is available as part of the CancerGene software (http://www4.utsouthwestern.edu/breasthealth/cagene/).

The Myriad model is a set of mutation prevalence tables categorized by ethnic ancestry (Ashkenazi Jewish or non-Ashkenazi Jewish), the age of onset (younger than 50 years or ≥50 years of age) of breast cancer, and the presence of ovarian cancer in the patient and/or first- or second-degree relatives, and is based on actual test data from Myriad Genetic Laboratories through its clinical testing service.[109] These tables are periodically updated online (http://www.myriadtests.com/provider/brca-mutation-prevalence.htm).

Other less commonly used probability models include the Manchester Scoring System, Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA), and Tyrer-Cuzick.[110–112]

In 2003, the American Society of Clinical Oncology updated their policy statement on genetic testing for cancer susceptibility stating, "Given the known limitations and wide variations inherent in models for estimating mutation probability in a given family or individual, and the lack of such models for many cancer predisposition syndromes, it is neither feasible nor practical to set numerical thresholds for recommending genetic risk assessment services. The American Society of Clinical Oncology therefore recommends that evaluation by a health care professional experienced in cancer genetics should be relied on in making interpretations of pedigree information and determinations of the appropriateness of genetic testing, including determinations of appropriateness for reimbursement."[113] As such, when evaluating family histories for HBOC, a quan-

Table 1 BRCAPRO model and Myriad mutation prevalence tables: strengths and limitations

	BRCAPRO	Myriad mutation prevalence tables
Strengths	Estimates probability of a mutation in both *BRCA1* and *BRCA2*. Provides mutation probabilities for both affected and unaffected individuals. Is frequently updated. Considers Ashkenazi Jewish heritage	Estimates probability of a mutation in both *BRCA1* and *BRCA2*. Provides mutation probabilities for both affected and unaffected individuals. Is frequently updated. Considers Ashkenazi Jewish heritage
	Provides other breast cancer risk information, such as the Gail and Claus empiric risks of developing breast cancer during one's lifetime. Provides a printout of pedigree and risk calculations	Does not require extensive family history information
Limitations	Analysis based on large, high-penetrance families. Requires extensive family history information. Considers only first- and second-degree relatives. Requires CancerGene software[a] and data entry for each family	Family history data obtained from test requisition forms and thus possibly limited. Considers only first- and second-degree relatives. Biased ascertainment of data

[a]Developed by the University of Texas Southwestern Medical Center at Dallas.

titative and qualitative assessment of the pedigree should be conducted before making testing recommendations.

Molecular genetic testing

BRCA1 and *BRCA2* are the only genes known to be associated with HBOC. Clinical uses of molecular genetic testing include diagnosis of symptomatic individuals, as well as predisposition testing in at-risk relatives. Clinical testing in the United States is available exclusively at Myriad Genetic Laboratories because of patent protections and is summarized in Table 2. Targeted mutation analysis may be population specific and includes mutations known to be found at greater frequencies in certain ethnicities. Comprehensive analysis includes sequence analysis combined with other methods, which can detect both common and family-specific *BRCA1* and *BRCA2* mutations, including five specific large genomic rearrangements of *BRCA1*. Sequence analysis or other mutation scanning methods are recommended when the mutation in a family is not known, except in individuals of Ashkenazi Jewish descent, which is further explained under testing strategy. Large rearrangement testing analyzes for rearrangements above and beyond the five common rearrangements of *BRCA1* and thus is complementary to comprehensive analysis. In addition, large rearrangement testing examines for rearrangements in *BRCA2* as well.

Interpretation of test results in a proband

- Targeted mutation analysis: When testing an Ashkenazi Jewish individual for the three founder mutations, typically the result will either be negative or positive.
  - Mutation is absent: Because this testing detects only the three founder mutations associated with Ashkenazi Jewish ancestry, failure to detect a mutation (i.e., a negative result) does not exclude the possibility that the individual has another predisposing *BRCA1* or *BRCA2* mutation. The recommendation to proceed with comprehensive analysis following the failure to detect one of the three common Ashkenazi Jewish mutations in this population is based on clinical judgment, the a priori risk of harboring a mutation, and the residual likelihood that a *BRCA1* or *BRCA2* mutation (other than the three common mutations) is present in that individual.
  - Mutation is present: The presence of a germline mutation (i.e., a positive result) confers an increased risk for HBOC-related cancers. It is recommended that follow-up testing of at-risk relatives, particularly if both sides of the family are Ashkenazi Jewish, includes targeted mutation analysis for all three of the common Ashkenazi Jewish mutations regardless of which mutation is found in the proband because coexistence of more than one founder mutation has been reported in some Ashkenazi Jewish families.[119]
  - Result is inconclusive: Given the testing methodology that is used, rarely a novel *BRCA1* or *BRCA2* variant of uncertain clinical significance (VUS) has been inadvertently detected in the DNA adjacent to the three common Ashkenazi Jewish mutations. Generally, this is a change in a single DNA nucleotide (missense mutation) that may or may not disrupt protein function. To further evaluate this result, the laboratory may request blood samples from additional members of the family (usually affected individuals and/or parents of the individual tested) to determine if the variant cosegregates with the cancer in the family. Such studies could reveal that the variant is either a pathogenic mutation or a polymorphism of no clinical significance. Between 10% and 15% of individuals undergoing genetic testing for *BRCA1* and *BRCA2*, mutations will be found to have a VUS,[109] but this result is more commonly found after comprehensive analysis.
- Comprehensive analysis: Any of the following results are possible in an individual undergoing comprehensive analysis.
  - Mutation is absent: Failure to detect a mutation (i.e., a negative result) must be interpreted with caution because the underlying cause of the cancer in the family has not been established. The possibility remains that the cancer in the family is either associated with a mutation not

Table 2 Molecular genetic testing used in *BRCA1* and *BRCA2* hereditary breast and ovarian cancer[114–118]

Test methods	Population	Mutations detected	Mutation detection frequency (%)
Targeted mutation analysis	Individuals of Ashkenazi Jewish heritage	*BRCA1*: 187delAG[a] *BRCA1*: 5385insC[a] *BRCA2*: 6174delT	90
Comprehensive analysis[b]	At-risk individuals	*BRCA1* and *BRCA2* sequence variants and five specific large genomic *BRCA1* rearrangements	~88
Large rearrangement test[c]	At-risk individuals	Large genomic rearrangements in *BRCA1* and *BRCA2*	3–4

[a]The *BRCA1* mutations 187delAG and 5385insC are formerly known as "185delAG" and "5382insC," respectively.
[b]As performed at Myriad Genetics, it includes full sequence determination of both *BRCA1* and *BRCA2* and detection of the following five specific large genomic rearrangements of the *BRCA1* gene: a 3.8-kb deletion of exon 13 and a 510-bp deletion of exon 22 described in individuals of Dutch ancestry, a 6-kb duplication of exon 13 described in individuals of European (particularly British) ancestry, a 7.1-kb deletion of exons 8 and 9 described in individuals of European ancestry, and a 26-kb deletion of exons 14–20 (Myriad Genetic Laboratories, unpublished). The proportion of clinically significant alterations in *BRCA1* and *BRCA2* attributable to these genomic rearrangements is estimated at 10–15%.
[c]All coding exons of *BRCA1/2* and their respective promoters are examined for evidence of deletions and duplications by quantitative endpoint polymerase chain reaction analysis.

detectable by the method of genetic testing used, is caused by a change in a different cancer susceptibility gene, or is the result of nonhereditary factors. Consequently, the family should be cautioned that the failure to detect a mutation does not eliminate the possibility of a hereditary susceptibility in the family.
  - Mutation is present: The presence of a germline *BRCA1* or *BRCA2* mutation (i.e., a positive result) confers an increased risk for HBOC-related cancers.
  - Result is inconclusive: Comprehensive analysis may reveal a novel *BRCA1* or *BRCA2* VUS. Again, family studies may be initiated in an attempt to determine the significance of the variation.
- Large rearrangement test: Either of the following results is possible in individuals undergoing large rearrangement testing.
  - Rearrangement is absent: Failure to detect a rearrangement (i.e., a negative result) must be interpreted with caution because the underlying cause of the cancer in the family has not been established. The possibility remains that the cancer in the family is either associated with a mutation not detectable by the method of genetic testing used, is caused by a change in a different cancer susceptibility gene, or is the result of nonhereditary factors. Consequently, the family should be cautioned that the failure to detect a rearrangement does not eliminate the possibility of a hereditary susceptibility in the family.
  - Rearrangement is present: The presence of a germline *BRCA1* or *BRCA2* rearrangement (i.e., a positive result) confers an increased risk for HBOC-related cancers.

Interpretation of test results in an at-risk relative

- Family-specific mutation: When testing at-risk relatives for a mutation known to be present in the family, either of the following results could occur.
  - Mutation is absent: Failure to detect the mutation (i.e., a negative result) means that the person has not inherited the family-specific mutation and has at least the general population risks for HBOC-related cancers.
  - Mutation is present: Presence of the germline mutation (i.e., a positive result) means that the person has inherited the family-specific mutation and is at an increased risk for HBOC-related cancers.

Testing strategy

- Probands of Ashkenazi Jewish ancestry: As mentioned previously, in persons of Ashkenazi Jewish heritage, three founder mutations are observed: 187delAG (*BRCA1*), 5385insC (*BRCA1*), and 6174delT (*BRCA2*). As many as 1 in 40 Ashkenazim have one of these three founder mutations.[28] Consequently, testing a person of Ashkenazi Jewish heritage initially for these three founder mutations by targeted mutation analysis can be an effective way to assess if the individual has a *BRCA1* or *BRCA2* mutation rather than first performing comprehensive analysis as recommended for all other populations. If no mutation is identified by targeted mutation analysis, the recommendation may be to proceed with comprehensive analysis. This recommendation is often based on clinical judgment, the a priori mutation risk, and the residual likelihood that a *BRCA1* or *BRCA2* mutation is present in that individual.
- Family not known to have a *BRCA1* or *BRCA2* mutation: Testing in families is most likely to be informative if the first person to undergo testing has already had breast cancer and/or ovarian cancer, especially if the breast cancer occurred at an earlier age than is typical (i.e., before age 50 years). Thus, whenever possible, molecular genetic testing should be performed on the individual in the family who is most likely to have a *BRCA1* or *BRCA2* mutation, and who is less likely to have developed sporadic breast or ovarian cancer. In many families, this approach is not feasible because the affected relative is deceased or is not willing or able to participate in molecular genetic testing. In these instances, testing may be performed on individuals without a cancer history with the understanding that failure to detect a mutation does not eliminate the possibility of a *BRCA1* or *BRCA2* mutation being present in the family.
- Family known to have a *BRCA1* or *BRCA2* mutation: Once a germline mutation has been identified within a family, adult relatives in the same lineage (including family members without a cancer history) may then be tested for the same family-specific mutation with great accuracy. In most cases, relatives at risk need only be tested for the family-specific mutation. However, exceptions to this would include any of the following:
  - Individuals of Ashkenazi Jewish heritage who should be tested for all three founder mutations because of reports of the coexistence of more than one founder mutation in some Ashkenazi Jewish families.
  - Individuals in whom a *BRCA1* or *BRCA2* mutation may be present in both maternal and paternal lines. For example, if a mutation is identified on the maternal side of the family and if HBOC is also suspected on the paternal side, it is appropriate to recommend that the individual undergo comprehensive analysis of *BRCA1* and *BRCA2*, which would (1) detect the familial mutation from the maternal side and also (2) address whether a mutation is tracking on the paternal side.

Genetically related (allelic) disorders

Germline mutations in *BRCA2* have been associated with familial pancreatic cancer[120,121] and Fanconi anemia complementation group FANCD1.[122]

Differential diagnosis

Other inherited cancer susceptibility syndromes and/or genes that predispose to breast cancer include Li-Fraumeni syndrome, Cowden syndrome, hereditary diffuse gastric cancer, *CHEK2*, ataxia-telangiectasia, Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer), Peutz-Jeghers syndrome, Bloom syndrome, Werner syndrome, and xeroderma pigmentosum (Table 3). The *PALB2* and *BRIP1* genes have also been implicated in hereditary forms of breast cancer.[126,127] In many instances, HBOC can be distinguished from these other disorders based on the constellation of tumors present in the family; however, in some cases, molecular analysis may be necessary to differentiate.

Table 3 Other inherited cancer susceptibility syndromes and/or genes that predispose to breast cancer[123–125]

Syndrome name	Gene	Features	Inheritance
Li Fraumeni syndrome	*TP53*	Soft-tissue sarcoma, breast cancer, leukemia, osteosarcoma, melanoma, and cancer of the colon, pancreas, adrenal cortex, and brain	Autosomal dominant
Cowden syndrome/*PTEN* Hamartoma tumor syndrome	*PTEN*	Benign and malignant tumors of the breast, thyroid, and endometrium, macrocephaly, trichilemmomas, and papillomatous papules	Autosomal dominant
Hereditary diffuse gastric cancer	*CDH1*	Diffuse gastric cancer, lobular breast cancer, and colon cancer	Autosomal dominant
	CHEK2 (specifically the 1100delC variant)	Breast cancer (male and female), prostate cancer, colon cancer, thyroid cancer, and kidney cancer	Autosomal dominant
Ataxia-telangiectasia	*ATM*	Homozygotes: progressive cerebellar ataxia, oculomotor apraxia, frequent infections, choreoathetosis, telangiectasias of the conjunctivae, immunodeficiency, and an increased risk of malignancy, particularly leukemia and lymphoma Heterozygotes: breast cancer	Autosomal recessive
Lynch syndrome/Hereditary nonpolyposis colorectal cancer	*MLH1* *MSH2* *MSH6* *PMS2*	Cancers of the colon, endometrium, ovary, stomach, pancreas, brain, small bowel, and skin. Breast cancer has been reported in families with LS, but consistent associations have not been demonstrated	Autosomal dominant
Peutz-Jeghers syndrome	*STK11*	Gastrointestinal polyposis (hamartomas), mucocutaneous pigmentation, breast cancer	Autosomal dominant
Bloom syndrome	*BLM* (RECQL3)	Severe growth deficiencies, dermatologic and musculoskeletal abnormalities, immune dysfunction, and cancers of the breast, skin, head, neck, esophagus, and gastrointestinal tract	Autosomal recessive
Werner syndrome	*WRN* (RECQL2)	Cancers including breast cancer, sarcomas, melanoma, thyroid cancer, and hematologic malignancies	Autosomal recessive
Xeroderma pigmentosum	*XP* genes A through G	Sun sensitivity, ocular involvement, and cutaneous and ocular malignancies as well as solid tumors including breast, brain, uterus, testes, and gastrointestinal	Autosomal recessive

MANAGEMENT

Individuals who are diagnosed with a mutation in *BRCA1* or *BRCA2* are counseled at the time of disclosure about their options for screening and primary prevention.

Primary prevention

Several strategies have been suggested to reduce cancer risk in individuals who have a *BRCA1* or *BRCA2* mutation. These include prophylactic mastectomy and/or oophorectomy and chemoprevention. Although several studies have provided compelling evidence to support the use of risk-reducing surgery in high-risk women, this strategy has not been evaluated by randomized trials.

A retrospective cohort study of all women receiving prophylactic mastectomy at the Mayo Clinic in the state of Minnesota during a 30-year period estimated a 90% reduction in breast cancer risk from the procedure. One third of the women in the Mayo Clinic study were considered to have a strong family history of cancer and experienced a risk reduction similar to that of the whole group.[128] In a subsequent follow-up of this cohort, 176 women were tested for *BRCA1* and *BRCA2* mutations. Of the 26 with a germline *BRCA1* or *BRCA2* mutation, none had developed breast cancer after a median follow-up of 13 years.[129] In a more recent study, the incidence of breast cancer in 483 individuals with a *BRCA1*/2 mutation was measured. Breast cancer was diagnosed in 2 of 105 women (1.9%) who underwent bilateral prophylactic mastectomy and in 184 of 378 matched controls (48.7%) who did not have surgery, suggesting that bilateral prophylactic mastectomy reduces the risk of breast cancer by ~90% in women who have a *BRCA1/2* mutation.[130]

Several studies have documented a significant (80–96%) risk reduction in ovarian cancer after risk-reducing oophorectomy.[131–133] Histologic evaluation of the tissues removed for risk reduction has revealed a wide spectrum of both occult ovarian cancers and primary fallopian tube tumors, supporting the removal of both ovaries and fallopian tubes at the time of surgery.[134–136] However, after risk-reducing oophorectomy, the peritoneum remains at risk for primary peritoneal cancer, with rates of ~2% after surgery.[55,137]

Rebbeck et al.[130] also found a 53% risk reduction for breast cancer in women undergoing bilateral prophylactic oophorectomy. These observations were consistent with the findings of Olopade and Artioli.[138] One multisite study of 1079 women followed up for a median of 30 to 35 months found that although there was a reduction in breast cancer risk for all mutation carriers undergoing prophylactic oophorectomy, the risk reduction was more pronounced in *BRCA2* carriers.[139] Several important questions regarding prophylactic surgery remain, such as what is the optimal timing for these procedures and how should individuals undergoing these procedures be followed up long term. The side effects of surgical menopause, including vasomotor symptoms, vaginal dryness, osteoporosis, and heart disease, must also be considered.

Chemoprevention

A randomized clinical trial of treatment with tamoxifen (a partial estrogen antagonist) in women identified by the Gail model to have an increased breast cancer risk reported a 49% reduction in breast cancer in the treated group.[140] In 1999, Gail et al. concluded that tamoxifen prophylaxis was most beneficial in women with an elevated risk of breast cancer who were younger than 50 years. However, tamoxifen reduced the incidence of breast cancers that were estrogen receptor positive but not estrogen receptor negative.[141] Because breast cancers occurring in women with *BRCA1* mutations are more likely to be estrogen receptor negative, it is predicted that tamoxifen may provide more benefit in women with *BRCA2* mutations.

A subset analysis of the randomized trial evaluated the effect of tamoxifen on the incidence of breast cancer among cancer-free women with inherited *BRCA1* or *BRCA2* mutations and showed that tamoxifen reduced the risk of breast cancer by 62% among healthy women with a *BRCA2* mutation.[142] In a case-control study of 538 women with a *BRCA1/2* mutation, tamoxifen use was associated with a 50% reduction in the risk of developing contralateral breast cancer.[143] In a more recent historical cohort study of 491 women with hereditary breast cancer, a 41% reduction in the risk of contralateral breast cancer was observed after 10 years.[144] Statistically significant adverse consequences of tamoxifen treatment included higher rates of endometrial cancer and thromboembolic episodes (including pulmonary embolism) in those individuals who took the medication when compared with those who did not.

Oral contraceptives

As in the general population, oral contraceptives have been shown to have a protective effect against ovarian cancer in women with *BRCA1/2* mutations. Two large multicenter case-control studies have reported risk reductions of 33% to 38%, with the maximum observed protection after ~5 years of use.[145,146]

Breastfeeding

One recent study found that women with *BRCA1* mutations who breastfed for a cumulative total of >1 year had a reduced risk of breast cancer that was statistically significant.[147] However, the International *BRCA1/2* Carrier Cohort Study found no association of breastfeeding with risk of breast cancer, and a trend for reduced ovarian cancer risk that was not statistically significant.[148,149]

Surveillance

Breast cancer screening

The breast cancer screening guidelines are based on data from families with *BRCA1* or *BRCA2* mutations, which indicate that elevated breast cancer risk begins in the late 20 s or early 30 s,[150] and which report an increased risk of interval cancers.[151] The guidelines reflect recent studies that have evaluated the efficacy of breast magnetic resonance imaging (MRI) screening in women with *BRCA1/2* mutations.[152–157] Despite variability in terms of the underlying population being studied, equipment and signal processing protocols, and the manner in which sensitivity and specificity are calculated, the studies consistently demonstrate that breast MRI is more sensitive than either mammography or ultrasound for the detection of hereditary breast cancer. In the combined studies, 82% of the cancers were identified by MRI compared with 40% by mammography, leading the American Cancer Society to recommend the use of annual MRI screening for women at hereditary risk for breast cancer.[158]

The National Comprehensive Cancer Network has published practice guidelines for the management of individuals with HBOC.[106] Breast cancer screening guidelines include the following:

- Monthly breast self-examination starting at the age of 18 years.
- Semiannual clinical breast examination starting at the age of 25 years.
- Annual mammogram and breast MRI screening starting at the age of 25 years or individualized based on the earliest age of breast cancer onset in the family.

Men with *BRCA1/2* mutations are also at an increased risk for breast cancer. Although no formal program of surveillance has been recommended, breast self-examination training and regular monthly practice are advised, in addition to semiannual clinical breast examination and the consideration of a baseline mammogram followed by annual mammograms if gynecomastia or parenchymal/glandular breast density is detected on baseline study.

Ovarian cancer screening

The ovarian cancer screening measures available (transvaginal ultrasound examination and serum CA-125 concentration) have limited sensitivity and specificity and have not been shown to reduce ovarian cancer mortality,[159] which is why prophylactic bilateral salpingo-oophorectomy is recommended for *BRCA1/2* mutation carriers. However, semiannual concurrent transvaginal ultrasound and CA-125 are recommended for those women who have not elected to undergo prophylactic oophorectomy or who are delaying the procedure, starting at the age of 35 years, or individualized based on the earliest age of ovarian cancer onset in the family.

Prostate cancer screening

Men with *BRCA1/2* mutations have an increased risk of prostate cancer and therefore should be informed about options for prostate cancer screening.[150] The American Cancer Society recommends annual digital rectal examination and prostate-specific antigen testing beginning at the age of 50 years in the

general population, with consideration of earlier screening for men in high-risk groups including those with a "strong familial predisposition."[160] Therefore, for men with *BRCA1/2* mutations, prostate cancer surveillance is consistently recommended at the age of 40 years and older.

Pancreatic cancer screening

Pancreatic cancer is an established feature of the *BRCA2* phenotype. However, the association of pancreatic cancer susceptibility and mutations in *BRCA1* is less strong. Screening asymptomatic individuals for pancreatic cancer is not generally recommended but is available in research settings.

Melanoma screening

Because both cutaneous and ocular melanomas are part of the *BRCA2* phenotype, annual clinical examinations of the skin and eye examinations by a specialist are recommended.[161]

Testing of relatives at risk

Once a *BRCA1* or *BRCA2* mutation has been identified in a family, testing of at-risk relatives can identify those family members who also have the familial mutation and thus need increased surveillance and early intervention when a cancer is diagnosed. See Genetic Counseling section for issues related to testing of at-risk relatives.

Hormone replacement therapy

General population studies suggest that long-term hormone replacement therapy (HRT) in postmenopausal women may increase breast cancer risk but that short-term use to treat menopausal symptoms does not. However, even relatively short-term combined estrogen plus progestin use was shown to increase the incidence of breast cancers in a randomized, placebo control trial of HRT.[162]

In 2005, Rebbeck et al.[163] evaluated breast cancer risk associated with HRT after bilateral prophylactic oophorectomy in a cohort of 462 women with *BRCA1/2* mutations and found that HRT of any type after bilateral prophylactic oophorectomy did not significantly alter the reduction in breast cancer risk associated with the surgery. The postoperative follow-up was 3.6 years. It was concluded that short-term HRT does not negate the protective effect of bilateral prophylactic oophorectomy on the risk of subsequent breast cancer in women with a *BRCA1* or *BRCA2* mutation. A second matched case-control study of 472 premenopausal women with *BRCA1* mutations also failed to find an increased risk of breast cancer in HRT users.[164]

Smoking

Smoking does not appear to be a risk factor for breast cancer among individuals with a *BRCA1* or *BRCA2* mutation.[165]

Therapies under investigation

Therapies specifically targeted to the *BRCA1* and/or *BRCA2* pathways are under investigation[166] but are beyond the scope of this review.

GENETIC COUNSELING

Mutations in the *BRCA1* and *BRCA2* genes are inherited in an autosomal dominant manner. Molecular genetic testing of asymptomatic family members at risk of inheriting either a *BRCA1* or a *BRCA2* mutation is feasible once the family-specific mutation has been identified. Prenatal testing is possible for pregnancies at an increased risk for a *BRCA1* or *BRCA2* mutation; however, requests for prenatal diagnosis of adult-onset diseases are uncommon and require careful genetic counseling.

Risk to parents of a proband with a *BRCA1/2* mutation

Virtually, all individuals with a mutation in *BRCA1* or *BRCA2* have inherited it from a parent. However, the parent may or may not have had a personal cancer diagnosis depending on the penetrance of the mutation, the gender and age of the parent with the mutation, as well as other variables. It is appropriate to offer molecular genetic testing to both parents of an individual with a *BRCA1* or *BRCA2* mutation to determine which side of the family is at risk. Occasionally, neither parent will be identified as having the *BRCA1* or *BRCA2* mutation. The exact number of individuals with a *BRCA1* or *BRCA2* mutation that has occurred as a de novo event is not known but is believed to be small.[167–169]

Risk to siblings of a proband with a *BRCA1/2* mutation

The risk to full siblings of an individual with a mutation in *BRCA1* or *BRCA2* depends on the genetic status of their parents. If one parent has the *BRCA1* or *BRCA2* mutation, then the risk for siblings to also carry the family-specific mutation is 50%. However, the risk of developing cancer depends on numerous variables including the penetrance of the mutation, the gender of the individual, and the age of the individual.

Risk to offspring of a proband with a *BRCA1/2* mutation

The children of an individual identified as having a *BRCA1* or *BRCA2* mutation have a 50% chance of having inherited the mutation at the moment of conception. However, the risk of developing cancer again depends on numerous variables including the penetrance of the mutation, the gender of the individual, and age of the individual.

Risk to other family members of a proband with a *BRCA1/2* mutation

The risk to other family members depends on the status of the proband's parents. If the parents are found to have the *BRCA1* or *BRCA2* mutation, their family members are also at risk to carry the same mutation. However, their exact risk depends on their position in the family. For example, the risk to a niece or nephew of a proband with a *BRCA1* or *BRCA2* mutation will be 25% based on pedigree assessment.

Related genetic counseling issues

- Considerations in families with an apparent de novo mutation: When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband represents a new or de novo mutation. However, possible nonmedical explanations including alternate paternity or undisclosed adoption could also be explored. Although rare, de novo mutations in both *BRCA1* and *BRCA2* have been reported.[167–169]
- Family planning: The optimal time for the determination of genetic risk is before pregnancy.
- Genetic cancer risk assessment and counseling: There are medical, psychosocial, and ethical ramifications of identifying at-risk individuals through cancer risk assessment

with or without molecular genetic testing that should be considered.[170]

- At-risk asymptomatic adult relatives: In general, relatives of an individual who has a *BRCA1* or *BRCA2* mutation should be counseled regarding their risk of having inherited the same mutation, their options for molecular genetic testing, their cancer risk, and recommendations for cancer screening and prophylactic surgery. For those who choose to learn more about molecular genetic testing, it is suggested that pretest education includes discussion of the following[113,171–173]:
  - The individual's motivation for requesting testing and preconceived beliefs about the test (some at-risk asymptomatic adult family members may seek testing to make personal decisions regarding issues such as reproduction, financial matters, and career planning; others may simply "need to know.")
  - The individual's perceptions of their risk of developing cancer.
  - The individual's readiness for testing and optimal timing for testing.
  - DNA banking (see below for explanation).
  - Inability of genetic testing to detect the presence or absence of cancer.
  - The individual's support systems and possible need for additional psychological support.
  - The individual's need for privacy and autonomy.
  - The possible effects of positive, negative, or uninformative test results on the following:
  - Cancer risk.
  - Cancer screening protocols.
  - Risk status for other family members.
  - Insurance coverage and employment. An individual found to have an inherited susceptibility to cancer could face discrimination in access to health insurance and/or employment although federal laws including the recent passage of the Genetic Information Non-Discrimination Act and state laws protect against health insurance and employment discrimination.
  - Individual's emotional status (e.g., depression, anxiety, and guilt).
  - Relationships with partner, children, extended family, and friends.

At-risk adult relatives who have not inherited the mutation identified in the proband are presumed to be at or above the general population risk of developing cancer, depending on personal risk factors. For example, a female at-risk relative who does not carry the family-specific *BRCA1* or *BRCA2* mutation may still be at an elevated risk of breast cancer based on a breast biopsy history, which revealed atypical ductal hyperplasia. For family members determined to be at general population risk of developing cancer, appropriate cancer screening such as that recommended by the American Cancer Society or the National Comprehensive Cancer Network for individuals of average risk is recommended. It is important to note that this presumption cannot apply to individuals who tested negative for a *BRCA1* or *BRCA2* mutation if the affected proband in the family either has not undergone molecular genetic testing of *BRCA1* or *BRCA2* or did not have an identified *BRCA1* or *BRCA2* mutation.

- At-risk asymptomatic minor relatives: Legitimate concerns regarding testing of at-risk individuals younger than 18 years of age for adult-onset conditions (including *BRCA1* or *BRCA2* mutations) exist, including issues of informed consent among minors, the lack of proven surveillance or prevention strategies at that age, and concerns about stigmatization and discrimination. Such testing is typically not recommended.[174]
- DNA banking: DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is $<100\%$.

Prenatal testing

Prenatal testing for *BRCA1* or *BRCA2* mutations is technically feasible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15 to 18 weeks' gestation or chorionic villus sampling at about 10 to 12 weeks' gestation. The *BRCA1* or *BRCA2* mutation must be identified in the family before prenatal testing can be performed.

Requests for prenatal testing for adult-onset conditions, including *BRCA1* and *BRCA2* mutations, that do not affect intellect and have some treatment options available are uncommon. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

- Preimplantation genetic diagnosis: This technology may be available for families in which the mutation has been identified in the family.

RESOURCES

Web-based resources and links for HBOC due to *BRCA1* and *BRCA2* mutations:

Genomic databases

- Breast Cancer Information Core National Human Genome Research Institute Cancer Genetics Branch (research.nhgri.nih.gov/bic/resources.shtml).
- GeneReviews (genetests.org), *BRCA1* and *BRCA2* (http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=brca1).
- National Cancer Institute (NCI), Breast cancer (http://www.cancer.gov/templates/doc.aspx?viewid=0b3dd146-d194-4dac-a447-8484b552c072).
- NCI, Ovarian cancer (Ovarian cancer, http://www.cancer.gov/cancertopics/types/ovarian/).
- NCI, Genetics of breast and ovarian cancer (http://www.cancer.gov/cancertopics/pdq/genetics/breast-and-ovarian/HealthProfessional/page1).

- Online Mendelian Inheritance in Man, Breast Cancer, Type 1 (http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=113705).
- Online Mendelian Inheritance in Man, Breast Cancer, Type 2 (http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=600185).

Organizations and lay websites

- American Cancer Society (www.cancer.org).
- Breast Cancer Network of Strength (www.networkofstrength.org).
- CancerCare (www.cancercare.org).
- Facing Our Risk of Cancer Empowered (www.facingourrisk.org).
- Gilda's Club (www.gildasclub.org).
- Hereditary Breast and Ovarian Cancer Foundation (www.hboc.ca).
- National Alliance of Breast Cancer Organizations (www.nabco.org).
- The National Breast Cancer Coalition (www.stopbreastcancer.org).
- National Library of Medicine Genetics Home Reference, Breast Cancer (http://ghr.nlm.nih.gov/ghr/disease/breastcancer).
- National Ovarian Cancer Coalition (www.ovarian.org).
- National Center for Biotechnology Information Genes and Disease, Breast and ovarian cancer (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View.ShowSection&rid=gnd.section.99).
- The National Coalition for Cancer Survivorship (www.canceradvocacy.org).
- Sharsheret (www.sharsheret.org).
- The Susan G. Komen Breast Cancer Foundation (www.breastcancerinfo.com).

Published statements and policies regarding genetic testing

- American Society of Clinical Oncology (2003) Policy statement: Genetic testing for cancer susceptibility.[113]
- American Society of Clinical Oncology; recommended breast cancer surveillance guidelines.[171]
- National Society of Genetic Counselors (1997) Statement on genetic testing for adult-onset disorders.[173]
- American Society of Human Genetics and American College of Medical Genetics (1995) Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents.[174]

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