

Hereditary Breast-Ovarian Cancer

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Abstract

Breast cancer (BC) is the most common cancer in women, accounting for 25% of all new cases of cancer. Most BC are sporadic while 5-10% are estimated to be due to an inherited predisposition. Autosomal dominant alterations in two genes, BRCA1 and BRCA2, are likely to account for most familial cases of early-onset BC and/or ovarian cancer (OC), and for 3-4% of all BC. Prevalence of germline BRCA mutations has been estimated to be about 1/600 women in the general population. The lifetime risk of developing hereditary BC (HBC) and/or OC can reach 80%. For a given mutation in the susceptibility gene, disease severity and age at onset show great variability within and between BC families, suggesting the involvement of other genetic as well as non-genetic factors. HBC is not associated with specific phenotypic features and diagnosis relies upon the following characteristics: (1) increasing numbers of affected family members through the same bloodline (either maternal or paternal), (2) early onset of disease, (3) an excess of bilateral disease, (4) an association with ovarian cancer (at any age), (5) and occurrence of BC in male. Genetic testing allows to establish molecular diagnosis, and provides guidelines for a better management of people at high risk of developing BC and/or OC. The strategies of management including surveillance, surgical options and chemoprevention, and the accurate treatment of BC and OC in mutation carriers are still debatable. Studies of cohorts of BRCA1 and BRCA2 mutation carriers are underway in an effort to develop targeted cancer prevention strategies.

Key words

Hereditary breast cancer, hereditary breast and ovarian cancer, BRCA1 gene, BRCA2 gene.

Introduction

Breast cancer (BC) is the most common cancer in women, accounting for 25% of all new cases of cancer. The lifetime-risk of developing BC for

a woman aged over 85 years is about 10%. BC is caused by a complex interplay between host susceptibility and environmental exposure. Although the majority of BC appears to be

sporadic, roughly 10%-20% of cases arise within familial aggregates with varying patterns of apparent disease penetrance (percentage of individuals carrying a given mutation who will develop the disease) and inheritance. In some cases, the susceptibility to BC can be explained by a rare dominant disease allele conferring an eightfold increased lifetime risk of the disease. The existence of such high penetrance alleles has been confirmed by the mapping of the *BRCA1* and *BRCA2* genes (which stands for *BReast Cancer1* and 2).

Disease name/synonyms

Families with hereditary BC can be split into two types: those with the breast-ovarian carcinoma syndrome (Hereditary Breast and Ovarian Cancer, HBOC) and those with site specific BC (Hereditary Breast Cancer, HBC). This distinction is useful at the clinical level but is not supported by molecular genetic studies, since the susceptibility genes, *BRCA1* and *BRCA2*, predispose to both BC and ovarian cancer (OC).

Definition/criteria

Since there are no specific phenotypic features of HBC, the diagnosis relies upon the following characteristics: (1) increasing numbers of affected family members through the same bloodline (either maternal or paternal), (2) early onset of disease, (3) an excess of bilateral disease, (4) a strong association with ovarian cancer (at any age), (5) and occurrence of BC in male. HBC predisposition is inherited in an autosomal dominant fashion and occurs through both male and female transmission. The identification of familial mutation confirms the diagnosis of HBC.

Differential diagnosis

BC is one of the features of other very rare genetic syndromes: [Li-Fraumeni syndrome](#), [Cowden syndrome](#), or [Peutz-Jeghers syndrome](#). A small percentages of OC is attributable to [HNPCC syndrome](#) (Hereditary Non Polyposis Colon Cancer).

Etiology

An autosomal dominant predisposition to BC was suspected for many years and complex segregation analyses have shown that a highly penetrant susceptibility allele could fully explain disease clustering (Claus *et al.*, 1991). One associated locus was subsequently linked to chromosomal region 17q21 and the putative gene was named *BRCA1* (King, 1991). The same region was linked to hereditary OC as this type of tumour was observed in families with an apparent BC predisposition. The *BRCA1* gene was cloned in 1994 and germline mutations were detected in affected members of HBOC families

(Miki *et al.*, 1994). A second locus on chromosome 13q12, called *BRCA2*, was shown to be involved in other family cases not attributed to *BRCA1* and/or with male BC cases. The gene was isolated in 1995 (Tavtigian *et al.*, 1996; Wooster *et al.*, 1994).

These two large genes (*BRCA1* has 24 exons of which 22 code for a protein of 1863 amino-acids, *BRCA2* has 27 exons of which 26 code for 3418 amino-acids) share only a slight homology and are not similar to any other known genes. Nonetheless, they appear to share some functional similarities. Their proteins of nuclear localization are expressed in a wide range of tissues and are especially critical in DNA damage repair. *BRCA1* has been shown to play a role in cell cycle-checkpoint control, ubiquitylation and chromatin remodeling (Venkiteshraman, 2002). The exact mechanism by which inactivation of these genes might lead to malignant transformation of cells remains unknown (Kennedy *et al.*, 2002).

Mutations are spread throughout the genes and most of them cause premature truncation of the proteins, due to nonsense, small deletions or insertions, splice or large rearrangements. The missense mutations, except in some functional domains (RING or BRCT in *BRCA1*), are of unknown clinical significance.

Several hundreds of distinct mutations have been described for both *BRCA* genes (see the Breast Information Core [BIC] web site <http://research.nhgri.nih.gov/projects/bic/>) revealing no mutational hotspots. The majority of mutations are unique and each family tends to have its own mutation, which makes the first molecular analysis difficult in a given family. However, a number of "founder" mutations common in defined populations, such as individuals of Ashkenazi Jewish descent, have been identified

Tumours arising in members of *BRCA* families revealed loss of heterozygosity (LOH) at the locus with retention of the disease-predisposing allele leading to complete inactivation of two copies as expected with tumour suppressor gene (Collins *et al.*, 1995; Smith *et al.*, 1992). LOH is seen commonly at the *BRCA1* or *BRCA2* locus in sporadic cancer, the remaining allele is almost never mutated, although protein level can be reduced. Thus, *BRCA*-linked disease might be mainly restricted to the heritable syndrome.

BRCA2 has recently been identified as identical to the Fanconi Anemia gene *FANCD1*. Children homozygote for *BRCA2* exhibit features of FA and early onset leukaemia (less than 5 years of age) and other types of pediatric tumours (Howlett *et al.*, 2002).

Clinical aspects of *BRCA*-associated breast and ovarian cancers

BRCA1-related BC are usually infiltrating ductal carcinomas (relative deficit of *in situ* lesions) with an increased frequency of medullary or atypical medullary types. The tumours are often of higher grade than sporadic cancers and usually hormone receptor-negative. *TP53* gene mutations and absence of Her-2/neu overexpression appears to be common (Breast Cancer Linkage Consortium, 1997). *BRCA2*-associated BC have not consistently revealed a specific pattern of tumour characteristics (Lakhani *et al.*, 1998).

Gene expression profiling by cDNA microarray have shown different sets of genes expression in *BRCA1*-, *BRCA2*- and sporadic breast tumours, suggesting functional differences between the tumour types (Hedenfalk *et al.*, 2001).

Prognosis

The prognosis of *BRCA*-associated BC is still controversial with a worsening trend at least for *BRCA1* (Evans *et al.*, 2004). Local recurrences following tumorectomy seem to be of a higher frequency without data about a worsening survival. Breast tissue of mutation carriers remains at risk for the development of new primary malignancies after a first treatment.

BRCA-associated OC, fallopian tube and peritoneal cancers cannot be readily distinguished from sporadic cancers, although mucinous tumours are distinctly underrepresented as are tumours of borderline malignancy (Risch *et al.*, 2001). Five-year survival for OC appears to be better for *BRCA1*-mutation patients in Ashkenazi Jewish women (Cass *et al.*, 2003).

Molecular diagnosis

Since most *BRCA* mutations result in truncated proteins, the protein truncation test (PTT) is widely used. Other different methods of pre-screening (SSCP, DGGE, HA, DHPLC...) followed by sequencing of abnormal fragment detect the point mutations. Direct DNA sequencing allows the analysis of the entire coding region. As deletions, duplications or other genomic rearrangements account for about 10% of all mutations, analysis by quantitative multiplex PCR of short fluorescent fragments (QMPSF), Southern blot or quantitative PCR should be part of a routine mutation detection protocol (Casilli *et al.*, 2002).

Nonetheless, none of the currently available technique can guarantee the identification of all cancer-predisposing mutations in the two genes. Testing is still complicated, costly and time-consuming. However, founder mutations in certain populations facilitate carrier detection.

Epidemiology

Prevalence

Prevalence of germline *BRCA* mutations has been estimated to be about 1/600 women in the general population, with a range of 1/400 and 1/1400 (Antoniou *et al.*, 2001), whereas three specific founder mutations are carried by 1/40 in individuals of Ashkenazi origin (Tonin *et al.*, 1996). Some founder mutations have been also described in other populations, such as the 999del5 in Iceland (Johannesdottir *et al.*, 1996). Approximately, 5-10% of all BC are due to high-risk susceptibility genes and about 3 to 4% of all BC -about 10% of BC diagnosed before the age of 35 and 10% of OC- result from mutations in *BRCA* genes. *BRCA1* and *BRCA2* are responsible for approximately 95% of families cases segregating both BC and OC, and for 65% of families cases segregating only BC cases (Ford *et al.*, 1998), and a high proportion of cases of Ashkenazi descent (Newman *et al.*, 1998). Incidence of *BRCA2* mutation in male BC has been estimated to be 20% (Haraldsson *et al.*, 1998). Additional high-penetrance genes that increase susceptibility to BC may exist. However, genetic heterogeneity and the rarity of high-penetrance genes make genes difficult to identify. The majority of familial BC might be due to other genes conferring lower risks. Thus, mutations (1100delC) in the *CHEK2* gene has been shown to account for about 5% of all cases of familial BC (defined by two cases or more of BC in relatives before the age of 60 years and no detectable *BRCA* mutation), but the penetrance is lower than 20% (Meijers-Heijboer *et al.*, 2002). In contrast, this allele has a very high penetrance in families affected with Li-Fraumeni syndrome, the disease it was initially associated with.

Cancer risks in individuals with deleterious *BRCA* mutations

Estimates of penetrance of germline *BRCA1* or *BRCA2* mutation varies among series depending on the methods of ascertainment, the study design and the ethnic groups. However, it is clear that the lifetime risk of BC may be as high as 80% (50% before the age of 50 in case of *BRCA1* and 25% in case of *BRCA2*) in families with multiple cases of the disease (Ford *et al.*, 1998), although lower risk estimates (60%) have also been reported in family history of few cases (Antoniou *et al.*, 2003) or in Ashkenazi population (Struewing *et al.*, 1997). The risk of contra-lateral BC is approximately 40% at 10 years (Metcalfe *et al.*, 2004).

BRCA2 has been associated with an increased risk for male BC although the absolute risk remains low (lifetime risk of 5%) (Ford *et al.*,

1998). Some male BC cases have been also described in families with *BRCA1* mutations.

The lifetime risk of OC, including fallopian tube and primary peritoneal cancer, may be higher among *BRCA1* carriers (28%-66%) than among *BRCA2* carriers (16%-27%) and may occur at later ages in *BRCA2* carriers (Risch *et al.*, 2001). In addition, carriers of deleterious *BRCA* mutations are at a 4- fold increased risk of prostate cancer in comparison with the general population, however absolute risk remains low in these carriers (Ford *et al.*, 1998; Breast Cancer Linkage Consortium, 1999).

Among *BRCA* mutation carriers, there is an interindividual variability in cancer risk as to the age of disease onset and tumor site. Specific mutations (type and location within the gene) might be associated with disease severity or might preferentially predispose to OC rather than BC. It is clear that certain families have a very high risk of OC –sometimes, only OC are observed in the families- while others have a low risk (Gayther *et al.*, 1997; Grade *et al.*, 1997). Other factors, including genes involved in hormone or carcinogen metabolism, or personal characteristics such as reproductive history and exogenous exposures, may modify cancer risks (reviewed in Narod, 2002). Lower age at onset in the recent generations (anticipation) might be attributable to greater awareness and better screening, preferential ascertainment or possible contributing “environmental” factors (King *et al.*, 2003).

Genetic counselling

Accurate genetic diagnosis requires the expertise of a genetic professional who is familiar with the counselling and the management of families at hereditary risk.

The geneticist can determine if a patient is an appropriate candidate for genetic testing on the basis of her personal and family histories of cancer. Genetic testing is usually offered to women who exceed a 10%-20% probability of having a mutated *BRCA* allele (not recommended if <10%). Many models, such as the models by Couch, Shattuck-Eidens, Frank, BRCAPRO and BODICEA (Antonioni *et al.*, 2004) are available (others are currently being developed) to assess the personal likelihood of carrying a *BRCA1/2* mutation and to discriminate at the 10%-20% likelihood level. However, the geneticist’s judgement is also of great importance. Furthermore, none of these models take into account the histo-pathological characteristics of the tumors. For example, genetic testing can be considered in the following cases:

- Three or more cases of BC occurring before the age of 60 and/or OC

occurring at any age in three successive generations;

- Two cases of BC diagnosed before the age of 50 -at any age if bilateral- in first degree relatives, or second degree if the filiations is paternal;
- One case of BC occurring before the age of 50 and one case of OC occurring at any age;
- Two cases of OC occurring at any age.

Before undergoing genetic testing, all patients give written informed consent in accordance with national regulations (based on the declaration of Helsinki

<http://www.med.or.jp/english/helsinki.html>.

The first step in testing is to identify the specific mutation running in a given family. This involves taking blood from an affected member of the family who is the most likely to harbour a germline mutation (index case). Otherwise, the meaning of negative result could never be interpreted completely in the absence of a known family mutation.

A positive result (a deleterious mutation has been identified in either *BRCA1* or *BRCA2*) confirms a very high risk of developing BC, contra-lateral BC and OC and allows the patient to have specific management according to her needs and the family members of the appropriate branch to be tested. Testing for a known mutation is easy and much less expensive than a full gene study.

The absence of a deleterious mutation in the index case (no known family mutation) suggests that the cancer family history, or at least the personal history of the index case, is probably not caused by a mutation in *BRCA1* or *BRCA2*. Nevertheless, as described above, there are limitations in current molecular technology. Furthermore, a mutation may arise in another susceptibility gene(s) not yet identified. Thus, this negative test result does not rule out the possibility of hereditary predisposition.

A variant of uncertain significance can be found in about 10% of cases. In general, it refers to a missense mutation that may or may not affect the function of the gene product. In the absence of functional assay, the results are considered negative and are of no use in management.

Individuals with a negative test for a known mutation do not inherit the family mutation. They are usually considered to have a risk of developing cancers similar to that of the general population. They cannot transmit the mutation to their children.

As testing is still complicated, costly and time-consuming, it is important to minimize unnecessary testing while optimising the usefulness of test results. Thus, testing should

be limited to individuals with a family history of BC or OC.

Management

Treatment of BC

The different options for treatment of the primary breast tumour are still debatable. Given the high risk for subsequent ipsilateral or contralateral breast cancer and the possible worsened outcome associated with conservative treatment, radical surgical approaches, such as bilateral prophylactic mastectomies, should be discussed, especially in *BRCA1*-mutation carriers. However, no significant data are currently available to justify modification of treatment.

Prevention and surveillance in individuals carrying a *BRCA* mutation

*Surveillance options for women with *BRCA* mutation*

Screening guidelines for mutation carriers are largely based upon expert opinion. They are extrapolated from the guidelines given to the general population and are based on the same concept, namely the earliest the cancer is detected, the highest is the chance of survival. However, it is unknown if this concept actually applies equally to *BRCA* cancers. Mammography is the mainstay of BC surveillance, with no evidence that radiation exposure may increase cancer risk, and is annually recommended, although the sensitivity in younger women is significantly reduced. The high-grade nature of *BRCA*-associated BC may predispose to the development of disease in the intervals between mammographic examinations. Therefore, breast ultrasonography may be added every six months, although there is no evidence that it improves early tumor detection. Studies increasingly suggest that breast MRI may be more sensitive with acceptable specificity. Thus, this very useful tool could be included in the screening of *BRCA*-mutation women.

Annual transvaginal ultrasonography with color flow Doppler, clinical pelvic exams and CA 125 measurement, starting at age 30-35, may be recommended.

The effectiveness of both BC and OC screening programs has not been proved.

There are no established guidelines for HBC or other malignancies screenings in male *BRCA* mutation carrier. However, it seems reasonable to initiate this screening slightly earlier than in the general population, especially for prostate cancer.

Prophylactic surgical options

Bilateral prophylactic mastectomy has been reported to be at least 90% effective in reducing BC incidence (Hartmann *et al.*, 2001; Rebbeck *et al.*, 2004). This procedure is variably considered because of the significant psychosocial consequences.

Salpingo-oophorectomy procedure is more frequently used in women who have completed childbearing and are nearing menopause, in order to reduce not only coelomic epithelial cancer but also breast cancer risk. The risk of developing BC decreases even more when the procedure is performed at earlier ages (before the age of 45) (Rebbeck *et al.*, 2002). There are no data to address the question of hormone replacement therapy (HRT) for treating menopausal symptoms. The consequences of premature oestrogen deprivation on the quality of life and its long-term health risks have not been defined.

Chemoprevention

Chemoprevention for the prevention of BC is currently limited. Tamoxifen was shown to reduce the risk of contralateral BC in germline *BRCA* carriers (Narod *et al.*, 2000). In a very small subset of *BRCA1* mutation carriers, there is no significant result (King *et al.*, 2001). It is not surprising given the greater prevalence of oestrogen receptor-negative tumours reported among these patients. The crucial issue is the risk-benefit of tamoxifen as a preventive agent since side effects include an increased risk of endometrial cancer, thrombo-embolic events and a decreased quality of life for young women. Optimal dose, duration, and age at first use are unknown. Tamoxifen is perhaps not the ideal candidate drug for primary prevention of BC. Other selective oestrogen receptor modulator (SERM) or other drugs are currently being investigated.

Unresolved questions

The restricted tissue expression of the germline *BRCA*-mutations to predominantly breast and ovarian cells has not yet been clearly explained. Several hypotheses emphasizing the role of oestrogen have been proposed.

Somatic *BRCA1* and *BRCA2* mutations are practically absent in sporadic BC, unlike some other tumour-suppressor genes, such as *RB1* and *APC*, involved in both hereditary and sporadic forms of cancer. This contradicts with the classic two-hit model of tumorigenesis and remains unresolved.

Conclusion

Although inherited BC or OC due to a mutation in *BRCA1* or *BRCA2* are rare in the general population, it is important for clinicians to

recognize a HBC/HBOC syndrome within families and individuals, since identification of such a disease will have an impact on cancer screening, surveillance and management of the affected individuals and of at high risk family members. Generally, the family history, when extended through 3 generations, allows identifying a hereditary cancer syndrome. Molecular genetic testing may confirm HBC/HBOC diagnosis. Patients have to be informed of the possibilities concerning presymptomatic testing, risk assessment, surveillance, prevention and psychological support with respect to the potential benefits and limitations. Predictive medicine should be used with care.

Research has significantly progressed over the past ten years, but considerable work still needs to be done to optimise the benefits of testing. The management of individuals at hereditary risk for BC and OC cancer is being continuously refined and many studies on potential chemoprevention are now in progress worldwide. Factors that affect the penetrance of *BRCA* mutations must urgently be determined in order to characterize protective factors.

Other large prospective studies are needed to rapidly validate the methods of surveillance and prevention in this group at « high risk », so that these methods could be adapted to very large populations

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