

# The role of BRCA1 AND BRCA2 in hereditary breast cancer

## Review Article

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**Abbreviations:** National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial, (NSABP-P1); prophylactic mastectomy, (PM); prophylactic oophorectomy, (PO)

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## Summary

**BRCA1 and BRCA2 account for most cases of hereditary breast cancer in the United States and Europe. These are suppressor genes that are inherited in an autosomal dominant fashion. Several studies showed that the histologic and molecular phenotype of BRCA-associated tumors is different from that of nonhereditary tumors. There is a difference in steroid receptor status between BRCA1 and 2 tumors regard to chemoprevention of breast cancer with antiestrogens. 93-100% of BRCA2 associated breast cancers are ER/PR<sup>+</sup>. Breast cancers associated with BRCA1 mutations are frequently of a higher grade and are hormone receptor-negative in one third of them. A higher proportion of cancers related to a BRCA1 mutation have atypical or typical medullary histologic features. The lifetime cumulative risk of invasive breast cancer for individuals with BRCA1 or BRCA2 mutations ranges from 50% to 87%. Familial breast cancer, however, accounts for fewer than 10% of all breast cancers, and BRCA1-related and BRCA2-related familial disease constitutes only two-thirds to three-fourths of these cases. Among women younger than 35 years old with breast cancer, 10% to 15% have a BRCA1 mutation. Woman with BRCA 1/2 mutations already affected by the disease have a risk, to age 70, of contralateral breast cancer that ranges between 50% and 64%. It has been difficult to determine whether germline BRCA 1/2 status has an effect on breast cancer outcome and the results from several studies remain controversial. There are preliminary data that BRCA 1/2 related tumors may have a faster growth rate than sporadic tumors. In these women prophylactic mastectomy, chemoprevention with tamoxifen or prophylactic oophorectomy are reasonable options. Genetic testing for BRCA 1/2 mutations should be done in those with a significant family history of breast or ovarian cancer, those with a diagnosis of breast or ovarian cancer below 50 years of age and those with a blood relative who is known to have a mutation in BRCA 1 or 2. Ongoing clinical trials will determine who the optimal subjects are for screening, how screening and counseling should be conducted and what type of societal involvement is needed so that genetic screening can be used without exposing the subject to unexpected risks and consequences.**

## I. Introduction

In the European Union, the number of breast and ovarian cancer cases diagnosed every year is 115/100.000 and 18/100.000, respectively.

Genetic susceptibility as a result of highly penetrant germ line inactivation in cancer predisposition genes characterizes approximately 5-10% of breast cancers, 10% of ovarian cancer and 25% of the early onset of breast cancer (Nooster et al, 1994; Palma et al, 2006).

Recent advances in molecular genetics have identified a number of genes associated with inherited susceptibility to cancer and have provided a means to begin identifying individuals and families with an increased risk of cancer. One of the most exciting and highly anticipated breakthroughs in cancer genetics was the cloning of BRCA1 and BRCA2 in early nineties (Nooster et al, 1994; Palma et al, 2006).

Breast cancer is the most prevalent type of cancer in women and several epidemiologic studies have identified

some risk factors for breast cancer, including a family history of the disease. There is a clearly documented two to fourfold increase in risk of breast cancer among women with one or more first-degree relatives with the disease. (Pharoah et al, 1997).

The magnitude of the risk increases with the number of affected relatives in the family, the closeness of the relationship and the age at which the affected relative was diagnosed. The younger the age at diagnosis, the more likely it is that a genetic component is present (Coditz et al, 1993).

Studies of families with a hereditary pattern of breast cancer have also revealed an association with ovarian cancer among some individuals with a genetic predisposition for breast cancer. Families in which both breast and ovarian cancers are present in the same lineage have significantly increased likelihood of carrying a cancer-predisposing mutation. (Couch et al, 1997; Shattuck Eidens et al, 1997).

## **II. Hereditary breast cancer syndrome**

The majority of breast cancers are sporadic occurring, in women without a family history of breast cancer.

Approximately 15% to 20% of breast cancers are associated with some family history of breast cancer but no evidence of autosomal transmission. Only a small proportion of all breast cancer up to 10% are attributable to germline mutation in single, highly penetrant cancer susceptibility genes, such as BRCA1 and BRCA2. These cancers result from a strong genetic predisposition and cancer susceptibility in these families is transmitted in an autosomal dominant fashion (Claus, 1996).

BRCA1 or BRCA2 have been estimated to include approximately 45% breast cancer susceptibility syndromes that are transmitted as a dominant autosomic trait, accounting for about 40% cases of families with both early onset breast cancer (Wooster and Weber, 2003).

Although the exact function of BRCA1 and BRCA2 and their role in breast carcinogenesis are not completely known, it appears that they may not only function as tumor-suppressor genes but also play a role in DNA repair. The genes perform multiple discrete functions and tumor is initiated when genetic instabilities lead to increased mutations in these genes (Hall et al, 1990).

In women the overall range of risk of breast cancer associated with mutations in the BRCA1 or BRCA2 gene is from 40% - 85% over a lifetime, whereas the lifetime risk in the general population is approximately 12.5%, and differ in populations 2% in Japan and 14% in USA (Begg, 2002).

In women who are BRCA1 or BRCA2 mutation carriers and have a history of breast cancer, the lifetime risk of contralateral breast cancer is also elevated, at 40% to 60% (Meijers et al, 2002).

BRCA1 and BRCA2 mutation carriers have a very elevated risk of ovarian cancer, ranging from 15% to 40%, compared with an approximate risk of 2% in the general population (Easton et al, 1995).

It is generally accepted, that carriers of mutations in BRCA1 or BRCA2 have an excessive risk for both breast

and ovarian cancer that warrants consideration of more intensive preventive and screening strategies.

Men with BRCA1 or BRCA2 mutation have an elevated risk of breast cancer, although the overall risk is low.

An increasing body of research has shown that there are differences in the breast cancer phenotype found in breast carcinoma obtained from BRCA1 mutation carriers compared with those found in BRCA2 mutation carriers and that these cancers may also have characteristics distinct from sporadic cases. For example, when compared with sporadic cases, BRCA1 mutations associated breast cancers are more likely to be invasive ductal, high-grade carcinoma with lymphocyte mutation. DCIS by itself or with invasive components is found less often in BRCA1 mutation-positive tumors. In addition aneuploidy, estrogen and progesterone receptor negativity and positive status for P53 overexpression and erb-2 are more likely to be observed in tumors from mutation cancers (BCLC 1997; Boyd et al, 2000).

Unlike with BRCA1 mutation carriers, no distinct phenotype for breast cancers in BRCA2 mutation carriers has emerged. However, one important finding is that, compared with breast cancers from BRCA1 mutation carriers, BRCA2 mutation-positive tumors have a higher rate of steroid receptor positivity (Chappuis P et al, 2000).

The literature provides no consensus about the survival rates for cases of breast cancer in BRCA1 mutation carriers compared with sporadic cases of breast cancer. Several studies have shown that survival rates are less favorable compared with sporadic cases. This finding is consistent with the histopathological features in mutation carriers, which suggest a more adverse prognosis. However, other studies have shown that survival rates are similar. Limited data for BRCA2 mutation carriers suggest that their survival after breast cancer is equivalent to that observed for the general population, however most studies are needed (Phillips et al, 1999).

## **III. Assessment of hereditary breast cancer-genetic testing**

Hereditary patterns of cancer are often characterized by early age at onset, high penetrance, bilaterality in paired organs and association with other types of tumors. In many families, an apparent pattern of vertical transmission consistent with autosomal dominant inheritance, in which the genetic mutation is transmitted to 50%. Individuals who belong to populations such as Ashkenasi people, may also have an increased chance of carrying a BRCA1 or BRCA2 mutation, especially in the setting of a family history of breast or ovarian cancer or both (Malone et al, 2000). Individuals who have only a family history of breast and/or ovarian cancer may also be at risk. For this reason, risk assessment and counseling are considered to be integral components of genetic screening for hereditary breast cancer.

These individuals should be considered to accurately determine their risk and to offer screening and general prevention recommendations.

The selection of appropriate candidates for genetic testing is based on personal and familial characteristics that determine the individual's prior probability of being a mutation carrier, and on the psychosocial degree of readiness of the person to receive genetic test results. Statistical models based on personal and family history characteristics have been developed to estimate a person's chance of having a BRCA1 or BRCA2 mutation (Parmigiani et al, 1998; Berry et al, 2002). These models may aid the counselor in making genetic testing decisions. The potential benefits, limitations and risks of genetic testing are also important considerations in the decision-making process.

There are two types of definitive results for which it is clear whether the patient has elevated cancer risks. True positive results indicate that a deleterious, risk-conferring mutation was identified. True negative results mean that an individual has tested negative for a deleterious mutation. In such cases, cancer risks are thought to be reduced to the level of general population. False negative results can occur as a laboratory error, as can false positive results.

Uninformative results arise when BRCA1 and BRCA2 analysis fails to reveal the presence of a deleterious mutation and hereditary risk cannot be ruled out. In these instances, the individual and her relatives need to be counseled that they may still be at increased risk for hereditary breast cancer and should be managed on the basis of the pattern of cancers observed in their family.

For patients who belong to families with known BRCA1 and BRCA2 mutations, post-test counseling should point out that although the individual has not inherited the mutation, a negative test result does not eliminate the risk of developing cancer, therefore, they should be encouraged to adhere to population screening guidelines for cancer. In addition, in the context of these results, there is no reason to recommend ovarian screening or consideration of prophylactic surgery.

If the patient does not belong to a family with a known BRCA1 or BRCA2 mutation, a negative result must be interpreted with caution. The patient may carry an undetected BRCA1 or BRCA2 mutation or a mutation in another susceptibility gene. Post-test counseling and management of these patients must be highly individualized and based on family and personal medical history.

For families with strong histories of breast and ovarian cancer, an undetected gene alteration may still be present and autosomal dominant risks may still apply. Risk management in these patients must be individualized, based on the patient's personal and family history of cancer. The individual can also be informed that the significance of the mutation may become clarified through further research and should also be encouraged to periodically consult with a cancer genetics service to see if the variant has been reclassified (Nooster et al, 1994; Palma et al, 2006).

## **IV. Screening recommendations**

A plan of individualized risk management should be discussed with the patient who is found to carry a BRCA1 or BRCA2 mutation.

An aggressive surveillance plan should be considered by women with BRCA1 and BRCA2 mutation, both before and after menopause. The emphasis is on initiating screening considerably early than standard recommendations as a reflection of the early age of onset seen in hereditary breast/ovarian cancer.

Recent reports have demonstrated that MRI may be more sensitive than mammography. These women must begin imaging studies at 25 years old. In addition, because interval breast cancers found in mutation carriers undergoing annual imaging studies, a shorter screening interval every 6 months may be indicated (Brekelmans et al, 2001).

However, because some cancers may be missed by mammography and MRI, the importance of breast physical examinations should not be discounted beginning at age of 18 years old. Frequent clinical performed exams (two or four times per year). are an important component of the management plan for mutation carriers. A pelvic examination, CA-125 determination and concurrent trans vaginal ultrasound, should be performed every 6 to 12 months, starting at ages 30 to 35 (Warner et al, 2001).

This management detects I or II clinical stage of ovarian cancer in max 10% of BRCA1/2 carriers, so this method is of low effectiveness (Eisinger et al, 2004).

The clinical management of these subjects must be performed in a multidisciplinary approach by a team of different specialists.

## **V. Management of hereditary breast cancer**

### **A. Chemoprevention**

An important question for many BRCA1 and BRCA2 mutation carriers is whether tamoxifen is effective in reducing breast cancer risk. Because several studies have shown a reduction in breast cancer risk for premenopausal mutation carriers who have undergone oophorectomy, it is possible that tamoxifen may be similarly efficacious because the drug blocks estrogen receptors. In retrospective case-control study of more than 200 mutation carriers with breast cancer who received tamoxifen in the adjuvant setting, it was found that, tamoxifen reduced the risk of contralateral breast cancer for BRCA1 and BRCA2 mutation carriers by 50%. However, complete information regarding the estrogen receptor status of patients was not included; thus it is unclear whether risk reduction is equivalent in these groups (Narod et al, 2000).

A number of studies investigated the possible activity of hormone deprivation in reducing breast cancer incidence in women at risk of developing breast cancer.

Briefly in the NSABP-P1 Trial (Fisher et al, 1998) more than 13,000 "high-risk" women were randomised between 1992 and 1997 to receive tamoxifene 20mgr/d or placebo for 5 years and, overall, a 50% reduction of

invasive breast cancer incidence was found with tamoxifen.

The later published data from IBIS-I trial also demonstrates the reduction of breast cancer risk by 32% in tamoxifen group (Cuzick et al, 2002).

Small studies performed with BRCA1 mutation carriers with breast cancer, however, provide preliminary data suggesting that tamoxifen may still play a role in risk reduction in this group, but further studies are needed.

## B. Surgical approach

The option of prophylactic mastectomy (PM) should be discussed with women with an inherited susceptibility to breast cancer. Two studies with different lengths of follow up demonstrated that PM substantially reduces the risk of breast cancer in mutation carriers. It will be important to continue to follow carriers longer to determine if any of them develop breast cancer later (Meijers-Heijboer 2001; Scheuer et al, 2002).

It is important to note that occult cancers have been detected at the time of prophylactic surgery, so careful pathological analysis of the tissue is important.

In general, the current evidence suggests that PM reduces the risk of breast cancer by more than 90% among women with BRCA1 and BRCA2 mutation (Schrag et al, 1997).

Two studies support that prophylactic oophorectomy (PO) reduce the risk of breast cancer in both BRCA1 and A2 mutation carriers. In particular, findings from a study by Rebbeck et al, (2002) reveals that PO reduced the risk of breast cancer by more than 50%. A prospective study by Kauff et al, showed a trend for risk reduction for breast cancer and a statistically significant decreased risk for the combined endpoints of breast and ovarian cancers (Rebbeck et al, 1999; Kauff ND 2002).

Although prophylactic surgery is at present, the most effective means of reducing risk, this may not be the preferred option for some women.

PO will induce surgical menopause in premenopausal women, if not appropriately managed can interfere significantly with a woman's quality of life.

The decision to proceed with PM involves multiple consideration.

However, the surgery is extensive and requires many weeks for recuperation. Moreover, body image can be markedly affected.

Patients who are likely to carry mutations must be able to weigh the benefits, risks and limitations of BRCA1 and BRCA2 testing before deciding to proceed. The benefits must be balanced against a number of important limitations of testing. These include the possibility of finding a mutation of uncertain significance or missing a mutation because of limited test sensitivity.

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