

Prevention and Management of Hereditary Breast Cancer

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INTRODUCTION

It has been 10 years since the *BRCA1* gene was first identified. During this decade, genetic testing for breast cancer susceptibility has been incorporated into the practice of oncology. In this process, the identification of families at the highest hereditary risk for cancer has served as a model to test strategies for prevention or early detection of breast malignancies. An emerging literature has explored primary prevention through risk reducing surgery and chemoprevention, as well as secondary prevention utilizing such approaches as magnetic resonance imaging (MRI) to achieve early detection of breast cancer in women with *BRCA1* or *BRCA2* mutations. Tailored treatments are being explored for newly diagnosed women with *BRCA* mutations. Ultimately, individual risk estimates and clinical management plans will be generated for women carrying *BRCA* mutations, based on consideration of the particular mutation inherited and also on the presence of modifying genetic and environmental factors.

Both *BRCA1* and *BRCA2* are involved in the cellular response to DNA damage and interact with other proteins involved in double-stranded DNA repair.¹ The effects of inherited mutations in these genes are similar, and mutations of both types predispose carriers to female and male breast cancer, and to ovarian cancer.² The risk of male breast cancer is higher in *BRCA2* carriers; ovarian cancer risk is higher in those carrying *BRCA1* mutations. In addition, *BRCA2* mutations appear to predis-

pose both men and women to a wide range of other cancer types.³ The reasons for these tissue-specific differences between the two genes is not clear.

PREVALENCE OF MUTATIONS

Estimates of the frequency of *BRCA1* or *BRCA2* mutations in North America range from one in 150 to one in 800.⁴⁻⁶ Among several ethnic groups the prevalence is considerably higher. Notably, the frequency in those of Ashkenazi Jewish ancestry is one in 50.^{7,8} Other groups with high frequencies of mutations include those from Iceland⁹ and Poland,¹⁰ and common *BRCA1* deletions occur in Dutch breast cancer kindreds.¹¹ These high prevalence rates are due to the presence of founder mutations. Founder mutations are one or more specific mutations in a population that have been inherited from a common ancestor, and which have become amplified through chance effects, often aided by geographic isolation of the population. Among individuals whose origins can be traced to countries or ethnicities associated with particular founder mutations, for example, in the Ashkenazim, testing only for founder mutations may uncover mutations in these kindreds. In the Ashkenazi Jewish population, two mutations in *BRCA1* (185delAG and 5382insC) and one in *BRCA2* (6174delT) account for > 90% of mutations, but nonfounder mutations in both genes have been reported.^{12,13} In the ethnically mixed population of North America, and in most of Europe and Asia, it is still

necessary to screen the entire sequences of both genes for possible mutations. Mutations that result in a truncated protein can be assumed to be deleterious, but missense mutations that result in a single amino acid change are more problematic. Models have been developed to help determine if a mutation which alters only a single amino acid residue is deleterious or is a harmless variant,¹⁴ but these models are not easy to incorporate into clinical practice, given the very large number of missense mutations identified to date.

In general, it is reasonable to offer genetic testing to women with a significantly increased risk of hereditary breast or ovarian cancer by virtue of multiple cases of breast cancer, particularly if cases are early-onset or if breast cancer occurs in a male. While criteria vary, one approach is to offer testing to all women with invasive ovarian or fallopian cancer¹⁵ and women with familial breast cancer (two or more cases of breast cancer diagnosed under age 50 years or family histories of breast and ovarian cancer). The testing thresholds are less stringent for Jewish women, and in general we feel it is reasonable to offer genetic testing to all women of Ashkenazi ancestry with a personal or family history of breast cancer or ovarian cancer.¹⁶ Table 1 summarizes the criteria for testing for *BRCA* mutations.

Penetrance

The lifetime breast cancer risk is about 80% for both *BRCA1* and *BRCA2* carriers¹⁷; however, the risk for Jewish women with the common *BRCA2* founder mutation 6174delT appears to be only about one half of this.^{8,18} It has been observed that the wide range of risk estimates associated with different types of studies performed over the past decade may be influenced by methodologies employed.¹⁹ Alternatively, environmental or other genetic modifying factors may be at play in families.

A recent large study confirmed an 82% lifetime risk for breast cancer and 54% for ovarian cancer for *BRCA1*- and 23% for *BRCA2*-mutation carriers,²⁰ comparable to estimates from meta-analyses.¹⁷ For *BRCA2* carriers, the ovarian cancer risk appears to be greatest for

women who have mutations in the ovarian cancer cluster region, which encompasses nucleotides 3035-6629.²¹ While most of this review will focus on management of breast cancer risk, the increased risk for ovarian (and other) cancers in *BRCA* mutations requires special considerations for screening and prevention.^{22,23}

Contralateral Breast Cancer

After the initial diagnosis of breast cancer in a *BRCA1* or *BRCA2* carrier, the risk of cancer in the opposite breast is approximately 3% per year.²⁴⁻²⁷ The risk is similar for *BRCA1* and *BRCA2* carriers and, in most studies, is not strongly influenced by age. Because of this elevated risk, many carriers with breast cancer may opt to be treated initially with bilateral mastectomy²⁸ if rapid genotyping analysis is made available.²⁹ The incidence of contralateral cancer appears to be reduced by oophorectomy and tamoxifen, each of which appears to reduce risk by approximately 50%.³⁰ It is of interest that bilateral breast cancers (both synchronous and asynchronous) tend to resemble each other in regards to grade and estrogen receptor (ER) -status (article submitted for publication). The reason for this observed concordance between cancers is currently unknown.

Pathology

Initial reports of *BRCA1*-linked cases confirmed an excess of cancers with medullary features, lymphocytic infiltration,³¹ and syncytial growth patterns. *BRCA1*-linked tumors also tended to be of higher grade than nonhereditary cancers, and are more frequently negative for ERs and progesterone receptors (PRs), c-erbB-2, and cyclin D,³²⁻³⁵ and are more likely to be positive for p53 overexpression.³⁶ Ductal carcinoma-in-situ (DCIS) is rare in carriers compared with control patients without mutations.³⁷ Tumors associated with *BRCA2* mutations tend to be similar to their nonhereditary counterparts. Recently, a basaloid phenotype was reported to be present with increased frequency in *BRCA1*-linked breast cancers compared with nonhereditary cancers.³⁸ The basaloid phenotype is characterized by the expression of the stratified epithelial cytokeratins 5 and 6. The phenotype was documented in 40 of 72 *BRCA*-linked specimens that were ER/ErbB-2 negative, compared to fewer than 15% of unselected invasive breast cancers. A Dutch study³⁹ found a similar association with epithelial growth factor receptor expression. Epithelial growth factor receptor is expressed in basilar breast stem cells. In the Dutch study, 14 (67%) of 21 *BRCA1*-linked breast cancers and five of five *BRCA2* breast cancer specimens expressed epithelial growth factor receptor. Only 16% of 430 control tumors expressed epithelial growth factor receptor. These findings are of interest because epithelial growth factor receptor may be a potential target for the treatment or prevention of *BRCA*-linked breast cancers.

Table 1. Who Should be Tested for *BRCA1* or *BRCA2* Mutations?

Familial breast cancer (two or more cases of breast cancer under age 50 years or ovarian cancer any age)
Invasive (nonmucinous) ovarian cancer
Women of Jewish or Polish ancestry with breast cancer*
Unaffected women from a family of the above type where an affected woman is not available
Relatives of known mutation carriers
Male breast cancer
Multiple primary (breast and ovarian) cancer
Cancer of the fallopian tube

*In these groups it is necessary in most cases to test only for the characteristic founder mutations.

Natural History

It is not yet clear if patients with *BRCA1* or *BRCA2* mutations face a worse prognosis than women with breast cancer of similar ages, but without mutations. The basal phenotype, in general, is associated with a relatively poor prognosis⁴⁰ and therefore it might be expected that women with *BRCA1* mutations will experience high recurrence rates. In a recent large study, a decreased relative survival was observed in an Ashkenazi cohort of breast cancer patients with the founder *BRCA1* mutation 185delAG, compared with noncarriers, but the difference was significant only in patients who did not receive chemotherapy.⁴¹ This suggests that the natural history of *BRCA1*-associated cancer might be worse than nonhereditary breast cancer, but that the disparity in survival can be reduced by chemotherapy. There are presently no data that suggest an independent effect of *BRCA2* germline status on survival.

PRIMARY PREVENTION

Primary prevention refers to preventing cancers from occurring in the first place, whereas secondary prevention refers to strategies devoted to early detection. Possible avenues of primary prevention of breast cancer include measures such as lifestyle change, chemoprevention, and prophylactic surgery. Because of the rarity of *BRCA* mutation carriers among the breast cancer population, most studies to date have been retrospective and observational.

Prophylactic Mastectomy

It is not surprising that mastectomy is an effective way to prevent breast cancer. This was shown in a small prospective study and in historical cohort studies of primary and contralateral breast cancers. Meijers-Heijboer et al⁴² observed no cases of breast cancer among 76 women who underwent prophylactic mastectomy after 3 years. Rebbeck et al⁴³ observed breast cancer in two of 191 women after mastectomy, compared with 184 of 378 women who retained their breasts. Metcalfe et al²⁴ studied 491 women treated for hereditary breast cancer. Only one contralateral breast cancer was observed among 146 women who had undergone a contralateral mastectomy versus 33 expected ($P < .0001$). These studies suggest that the residual breast cancer risk following mastectomy is almost zero. Currently, total mastectomy is generally recommended over subcutaneous, or nipple-sparing mastectomy, but data about the failures of subcutaneous mastectomy are largely anecdotal and based on a much older literature. Technical advances in skin sparing techniques and availability of approaches such as muscle-containing flaps or implantable prostheses have broadened the surgical options available to women considering these procedures.⁴⁴

Reproductive Factors

Several reproductive factors have been found to modify the risk of breast cancer in *BRCA1* and *BRCA2* carriers.

Breast-feeding for 1 year or more (cumulative) reduced the risk of breast cancer by about one half in *BRCA1* carriers, but had no effect in *BRCA2* carriers.⁴⁵ Increasing parity is a risk factor for breast cancer in *BRCA2* carriers, but not in *BRCA1* carriers (article submitted for publication). A marginal increase in breast cancer risk has been reported among users of oral contraceptives, but only for women who began use before 1975 and reported 5 or more years of contraceptive use.⁴⁶ These associations have been based on single studies and need to be confirmed.

Oophorectomy for Breast Cancer Risk Reduction

To date, the established cofactors for *BRCA1*-associated breast cancers are hormonally-associated.⁴⁷ Antihormonal approaches include tamoxifen, raloxifene and other SERMs, ovarian ablation (oophorectomy, radiation, or chemical ablation), and aromatase inhibition. Of these, only tamoxifen and oophorectomy have been well studied in the context of *BRCA1* and *BRCA2* mutations. The rationale for the antihormonal approach comes from the observation that oophorectomy prevents breast cancer in *BRCA1* and *BRCA2* carriers. Cohort studies estimated the reduction in breast cancer risk associated with a premenopausal oophorectomy to be about 50%.⁴⁸⁻⁵⁰ A recent case-control study reported that the risk reduction might be even greater if the oophorectomy is performed before age 40 years, and that the duration of protection is approximately 15 years (article submitted for publication). Short-term use of estrogen in young women following oophorectomy might abrogate some of the breast cancer protection associated with oophorectomy; however, such interventions in symptomatic young women may be of enormous benefit in improving quality of life. Studies of the relative breast cancer risks associated with hormone replacement therapy in young *BRCA* mutation carriers after oophorectomy are now underway. There are no empirical data on the degree of protection against breast cancer offered by other forms of ovarian ablation (eg, radiation, gonadotropin-releasing hormone agonists [GnRH]). A GnRH agonist may be preferred by a woman who wishes to preserve her fertility, but the use of these drugs in *BRCA* carriers is not widespread, and the effectiveness in reducing breast cancer risk is unknown. There remains concern that these nonsurgical approaches to ovarian ablation do not address risk for tubal or ovarian cancers, which are known to be increased in *BRCA* mutation carriers.

Tamoxifen

On theoretical grounds, tamoxifen should not reduce the incidence of ER-negative breast cancers—and most breast cancers which occur in *BRCA1* (but not *BRCA2*) carriers are estrogen-receptor negative. The National Surgical Adjuvant Breast and Bowel Project

P1 trial attempted to address this issue; however only eight *BRCA1* carriers with breast cancer were identified in the follow-up period.⁵¹ No protective effect was seen with tamoxifen, but the number of cases was too small for the study to be definitive. In a large case-control study, tamoxifen was found to reduce the incidence of contralateral breast cancer in affected *BRCA1* and *BRCA2* carriers by about one half.³⁰ To the extent that contralateral cancers in carriers are representative of all new primary breast cancers, the results of this study might be extrapolated to the prevention of first primary breast cancers. But this conclusion would be invalid if the two primary cancers were not independent; for example, if tamoxifen were given only to ER-positive patients, and if the ER status of bilateral cancers were highly correlated, as appears to be the case from preliminary studies (article submitted for publication), then the results of the case-control study would support a protective effect of tamoxifen only against ER-positive breast cancers.

Selenium

A theoretical approach to cancer prevention in *BRCA* carriers involves reducing the rate of chromosome breakage. Both *BRCA1* and *BRCA2* are involved in the DNA damage response pathway and heterozygous carriers have increased rates of chromosome aberrations. One study, if replicated, provides a clinical test of this hypothesis; *BRCA1* carriers were found to experience high levels of bleomycin-induced chromosome breaks, and the frequency of breaks could be returned to normal by supplementation with oral sodium selenite.⁵²

SECONDARY PREVENTION

The goal of screening is to identify breast cancer at a stage when a surgical cure is likely. Traditionally, this includes small breast cancers (< 1 cm) that are node negative and with no evidence of distant spread. For these women, cure can be expected in the great majority of cases. But *BRCA1*-associated breast cancers are typically of high grade and are ER-negative, and so prognosis might be expected to be worse than average. Among *BRCA1* carriers there was little correlation between tumor size and lymph-node positivity in one study; about one third of *BRCA1* carriers had lymph node metastases detected at diagnosis, regardless of tumor size.⁵³ Therefore, it may be problematic to predict the benefits of screening using survival data generated from a comparison group of noncarriers.

A number of advisory groups in the United States and Europe have published recommendations for surveillance for women at hereditary risk for breast cancer and ovarian cancer.⁵⁴⁻⁵⁶ In general, these guidelines called for annual mammography beginning around age 25 to 30 years, as

well as monthly breast self-examinations (BSE) and clinical breast examination (CBE) once to twice a year.

Studies in the general population have not supported the use of BSE as a means to decrease breast cancer mortality.⁵⁷⁻⁵⁹ Nevertheless, most cancers in *BRCA* carriers have been detected by BSE or by CBE. In a Canadian study, six invasive cancers were found in 1,044 women at increased risk for breast cancer. Only two were found by mammography; all six were found by CBE or BSE.⁶⁰ In a later study of 678 women at risk for hereditary breast cancer, six of 26 cancers were detected by physical examination (and were mammographically occult).⁶¹

BRCA-associated tumors may be particularly hard to detect mammographically. Pushing margins, breast density, and mutation status contribute independently to false-negative mammograms in *BRCA* heterozygotes.⁶² Studies in the United States and United Kingdom of women younger than 50 years with a family history of breast cancer reported sensitivities of 63% to 70%⁶³ and 44%,⁶⁴ respectively. Goffin et al⁶⁵ found that only two (25%) of eight breast cancers in *BRCA1* carriers were detectable by mammogram at diagnosis, versus 27 (77%) of 35 from noncarrier controls ($P = .01$). In a large cohort at a single center, less than half of 12 breast tumors diagnosed in *BRCA* mutation carriers were found by mammogram.⁶⁶

In women at increased hereditary risk for breast cancer, a generally higher sensitivity has been reported for ultrasound than for mammography—47% versus 43% in a large German study⁶⁷ and 60% versus 33% in a Canadian study.⁶⁸ Thus, ultrasound may play a role as an additional screening modality.

Breast MRI offers the promise of a greatly improved sensitivity of detection of breast cancers in those at high risk (Table 2). Early studies reported sensitivities in the range of 100% for invasive breast cancer, but later studies, which included DCIS, reported lower sensitivities.⁶⁷⁻⁷⁵ In the largest series reported to date, the sensitivity of MRI was 83% for invasive disease, but was only 71% overall.⁷² However, the benefit attributable to finding cases of DCIS (*v* early invasive cancers) has not been established. In a study with longitudinal follow-up, MRI detected nine breast tumors that were missed by the other screening modalities.⁶⁸ Of note, only two (9%) of the 22 women with breast cancer detected in this Canadian trial had lymph node metastases, and none of these occurred in the incident screens. However, when MRI is used, false-positive findings have been noted; in the first year of screening the false-positive rate is on the order of 10% at most centers. An additional 10% to 20% of women will undergo additional studies for “probably benign” lesions, a small proportion of which will ultimately be found to be malignant.⁷⁶ Thus, we feel that MRI now has an established role in screening *BRCA* mutation carriers, recognizing that the

Table 2. Comparison of MRI, Mammography, and Ultrasound in Screening Women at High Risk for Breast Cancer

Study	No. of Subjects	No. of Cancers	Sensitivity	Specificity	Lymph-Node Positive (%)
Tilanus-Linthorst et al ⁶⁹	109	3	MRI-100%	MRI-94%	0
Robson et al ⁷¹	54	3	MRI-100%	MRI-83%	0
Stoudjesdijk et al ⁷⁰	139	9	MRI-100% MAM-42%	MRI-93% MAM-96%	50
Warner et al ⁶⁸	236	22	MRI-77% MAM-36% US-33%	MRI-95% MAM-99.8% US-96%	9
Kuhl et al ⁶⁷	462	51	MRI-96% MAM-43% US-47%	MRI-95% MAM-94% US-88%	35
Kriege et al ⁷²	1,909	51	MRI-71% MAM-40%	MRI-90% MAM-95%	21

NOTE. Adapted from Table in Morris EA, Liberman L, Ballon DJ, et al: MRI of occult breast carcinoma in a high-risk population. AJR Am J Roentgenol 181:619-626, 2003.

Abbreviations: MRI, magnetic resonance imaging; MAM, mammogram; US, ultrasound.

addition of mammography and/or ultrasound may further improve the sensitivity of MRI screening.⁷⁷

SCREENING FOR HEREDITARY OVARIAN CANCER

Screening for ovarian cancer using serial CA-125 levels and abdominal ultrasound has been proposed as a method of reducing mortality through early detection. There have been no randomized trials of screening in *BRCA1* carriers, but observational cohort studies have been disappointing. Liede et al⁷⁸ identified seven incident ovarian/peritoneal cancers in a historic cohort of 33 *BRCA* carriers who underwent regular screening examinations. Six of the seven cases were stage III at the time of diagnosis. For the majority of cases, the ultrasound findings were normal before diagnosis and the women presented with pain or abdominal distension. In a randomized trial of CA-125 and ultrasound in women at average risk, Jacobs et al⁷⁹ identified 16 ovarian cancers in the screened group. Eleven of the 16 tumors were diagnosed at stage III or IV. Neither CA-125 nor ultrasound have proven to be sensitive means of detecting stage I and stage II ovarian cancers. Mok et al⁸⁰ reported that serum levels of prostasin are elevated in women with ovarian cancer, and proposed that this may qualify as a new tumor marker, possibly in combination with CA-125. New techniques for identifying patterns of serum proteins generated by mass spectroscopy are promising for the development of new sensitive and specific screening tests for ovarian cancer.⁸¹ Petricoin et al⁸¹ were able to identify all 50 malignant ovarian cancers in a set of 116 serum samples, including 18 stage I cases. The specificity of the test was 95%. However, it is not yet known how long the mean duration of stage I ovarian cancer is, and therefore the optimal screening interval has not yet been defined.

Breast Cancer Treatment

Currently, the typical management of most women with hereditary breast cancer differs little from the management of nonhereditary cancers. However, because of

the 32% estimated 10-year risk of contralateral breast cancer in *BRCA1* carriers²⁴ and the 13% ovarian cancer risk,⁸² some women with stage I or II breast cancer may choose to undergo prophylactic (risk-reducing) oophorectomy and/or contralateral mastectomy as part of their initial treatment plan. With regard to radiation or chemotherapy, relatively little research has been completed on the assessment of various treatment approaches for hereditary breast cancer. This can be explained by the relative rarity of mutations among unselected breast cancer patients (less than 5% of the total) and, until recently, the limited availability of genetic testing. Nevertheless, it has been possible to create historic cohorts of treated patients with mutations and to compare outcomes associated with different treatments. In this type of study, mutation carriers are identified at a recent date and the tumor characteristics, medical history, and clinical outcomes are recorded and analyzed using survival analysis. The principal limitation of this type of study is that there is expected to be an association between survivorship and genetic testing, that is, the longer a patient survives following a diagnosis of breast cancer, the more likely she is to receive testing. This potential survivorship bias can be eliminated by using archived tumor banks from unselected cohorts, in which archived specimens can be analyzed for founder mutations (eg, in the Ashkenazim). Of course, these studies are not randomized, and if one wishes to evaluate the effect of a particular treatment, then survivorship must be adjusted for other treatments received and for the prognostic features of the tumors.

With this caveat in mind, the impact of germline *BRCA* status on ipsilateral local recurrence rates after breast conserving surgery has been controversial. Concern has been expressed that ionizing radiation may pose a special hazard for women with *BRCA* mutations, who are deficient in their ability to repair radiation-induced DNA breaks.⁸³ However, there are no empirical data to suggest that this is the case for therapeutic radiation or mammog-

raphy. Radiotherapy appears not to increase the risk of cancer in the opposite breast²⁴ and the incidence of local reactions to radiation has not been found to be exceptional in *BRCA* carriers.⁸⁴ Ipsilateral recurrence rates have been reported to be similar in mutation carriers and women without mutations in large clinic-based studies.^{84,85} Metcalfe et al²⁴ estimated the 10-year cumulative incidence of ipsilateral recurrence to be 34% in *BRCA* carriers with breast conserving surgery who did not receive radiotherapy, but was only 9% in those who did ($P = .01$ for difference; ipsilateral recurrences include both local recurrences and new primary ipsilateral cancers). Similar findings were observed in studies of unselected Ashkenazi women undergoing lumpectomy and radiation therapy.^{27,36} However, other studies of women who have survived long periods of time after their initial breast cancer diagnosis have suggested a significant late risk of ipsilateral second primary malignancies.⁸⁶⁻⁸⁸ In combination, these studies suggest that *BRCA*-associated breast cancer is as likely as nonhereditary disease to be sterilized by adjuvant radiation therapy, but the breast tissue remains at risk indefinitely due to the underlying hereditary predisposition. While breast conserving treatment remains an option for women with *BRCA*-associated breast cancer, they must be monitored for second primary cancers.

Most women with *BRCA1*-associated breast cancer will have high-grade, ER-negative tumors, and are therefore candidates for chemotherapy.^{89,90} It has been suggested that *BRCA1*-associated tumors are highly sensitive to certain chemotherapy agents such as mitomycin⁹¹ and platinum,⁹² or to chemotherapy in the setting of adjuvant⁴¹ or neoadjuvant administration.⁹³ Chemotherapy sensitivity and taxane resistance may be related to the involvement of *BRCA1* in apoptotic response.⁹⁴⁻⁹⁶ This may be due to the inability of cancer cells to repair DNA effectively (the cells are homozygous null for *BRCA1* protein).

The majority of *BRCA1*-associated tumors are ER-negative and in general, hormonal ablative treatments are not indicated for these patients. However, oophorectomy has been shown to prevent primary breast cancers, local recurrences, and contralateral breast cancers. There

is also preliminary data that suggests that breast cancers, which arise in women who have previously undergone oophorectomy, are not more likely to have an aggressive phenotype (size, node positivity, ER-status) than are tumors in women with intact ovaries (article submitted for publication). There are no data yet which show that oophorectomy or ovarian ablation will prevent distal recurrence or death, and these are important areas of future research.

A Decade of *BRCA1*

Following the discovery of *BRCA1* in 1994, it was by no means clear that interventions in this genetically defined population at highest known risk for breast cancer would translate to a clinical benefit. Subsequent experience has begun to document the efficacy of medical and surgical interventions following genetic testing. A decade after the cloning of these two genes, significant questions remain regarding the molecular pathogenesis of *BRCA1*- and *BRCA2*-associated breast tumors, as well as the environmental and other genetic factors that modify these effects. The function of the proteins encoded by *BRCA1* and *BRCA2* remains to be fully elucidated, and this gap in knowledge continues to hamper efforts to develop molecularly targeted therapies. In the United States, the lack of comprehensive federal legislation banning genetic discrimination and the uneven reimbursement for genetic testing and follow-up care remain challenges.⁹⁷ Nonetheless, advances in early detection and prevention of *BRCA*-associated tumors offers cause for optimism among families carrying mutations of these highly penetrant, but predictable, breast cancer susceptibility genes.

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The authors indicated no potential conflicts of interest.

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