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1. RECENT ADVANCES IN BREAST CANCER GENETICS

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INTRODUCTION

Breast cancer is the second most common cancer among women and the second leading cause of cancer death in the US. In 2006, more than 214,000 new breast cancer cases were diagnosed. It is estimated that close to 50,000 women died of the same disease in 2006.¹³ Breast cancer develops in about 12% of women who live to age 90. A positive family history is reported by 15–20% of women with breast cancer. Studies of twins suggest that heritable factors accounts for 25 to 30% of all breast cancers.²⁰ However, less than 7% of all breast cancers are associated with known inherited high penetrance gene mutations. The first two major susceptibility genes for breast cancer, *BRCA1* and *BRCA2*, were identified in 1994 and 1995, respectively.^{23,39} Other tumor susceptibility genes such as *TP53* are known to increase breast cancer risk to an even greater level than *BRCA1* and *BRCA2*. Nonetheless, deleterious mutations of *TP53* are rare and therefore accounts for a much smaller proportion of breast cancer cases.¹⁹ We will review recent developments in the search for additional breast cancer susceptibility genes, recommendations for genetic counseling referral as well as follow-up of *BRCA*- gene mutation carriers.

HIGH PENETRANCE BREAST CANCER SUSCEPTIBILITY GENES

Functional Role of *BRCA1* and *BRCA2* Genes

Mutations and genomic rearrangements within the *BRCA1* and *BRCA2* genes have been clearly associated with breast cancer. These two genes are the best known of a small group of genes that have been associated with the disease (Table 1).

The exact function of the *BRCA1* and *BRCA2* genes is still unknown, more than a decade following their discovery. Mice that lack one copy of either the *Brca1* or the *Brca2* genes do not exhibit any strong tumor predisposition and mice that lack two copies of the *Brca1* gene die in utero.⁹ These traits have limited in vivo analysis of these genes. The *BRCA1* protein may not have one specific function, but its interaction with a variety of other proteins is essential for regulating DNA repair, transcription, and cell cycle progression.⁸ Some functional clues have emerged from in vitro studies of the *BRCA2* gene. After double strand DNA breaks, *BRCA2* induces the translocation of the protein RAD51 into the nucleus and directs RAD51 to the site of the breaks for homologous recombination-directed repair.⁴⁰

Since deleterious mutations alter their function, *BRCA* genes appear to serve as tumor suppressor genes. The inherited mutation represents the first “hit” of Knudson's two-hit model of tumorigenesis. *BRCA*-gene mutations interfere with the DNA repair function of the normal gene, thus resulting in the accumulation of chromosomal abnormalities, and an increased susceptibility to develop malignancy. If the second allele of the gene becomes mutated, this leads to the development of cancer.

Clinical Significance of *BRCA1* and *BRCA2* Genes

These two genes are believed to account for the largest proportion of familial breast cancer cases. Current estimates suggest that 20–25% of familial breast cancer cases are caused by

mutations or genomic rearrangements within these genes. Nevertheless, the frequency of these mutations is relatively rare, occurring in approximately 0.1–0.5% of the general population. This means that the population attributable risk of *BRCA1* and *BRCA2* ranges from a minimum of 3% to a maximum of 7%. Deleterious mutations among individuals of Ashkenazi Jewish descent are 10-fold more common than in the general population. Approximately 2% of Ashkenazi Jews carry a deleterious *BRCA1* or *BRCA2* mutation.³⁵ Therefore, the breast cancer population attributable risk of *BRCA1* and *BRCA2* deleterious mutations among Ashkenazi Jews is probably as high as 15–30%.^{1,10,24,37} Several studies have shown that 90% of deleterious mutation within the *BRCA1* or *BRCA2* genes among of Ashkenazi Jews are one of the following three mutations: *BRCA1* 185deAG, *BRCA1* 5382insC, or *BRCA2* 6174delT. It is therefore recommended to proceed with genetic testing of the three common Ashkenazi mutations among all Ashkenazi Jewish women who develop breast cancer. Additional sequencing of the remainder of the *BRCA* genes should be conducted whenever other features evocative of the hereditary breast and ovarian cancer syndrome are present.

A recent analysis of 22 studies involving 8,139 index case patients unselected for family history shows that carrying a deleterious *BRCA1* or *BRCA2* mutation confers an estimated lifetime risk for developing breast cancer of 65% (95% CI = 44–78%) and 45% (95% CI = 31–56%), respectively (Antoniou et al., 2003). Importantly, breast cancer risk does not appear to be increased before adulthood. By the age of 40, carrying a deleterious *BRCA1* mutation confers a 20% chance of developing breast cancer, and the risk increases with age, with the maximum lifetime risk being 82% by age 80.¹⁷ Mutations in *BRCA1* are strongly associated with ovarian and fallopian tube cancer.² The risk for ovarian cancer for *BRCA1* mutation carriers is 17% by age 40. It increases to 39% by age 70 and 54% by age 80.² The risks are smaller for *BRCA2* mutation carriers. Hence, current data suggest that *BRCA1* penetrance with respect to both breast and ovarian/fallopian tube cancer is higher than that of *BRCA2*.

Identification of Additional *BRCA1* and *BRCA2* Mutation Carriers

Mutations constitute only one possible mechanism of gene inactivation. Genomic rearrangements and epigenetic modifications such as promoter methylation are additional mechanisms that may lead to gene inactivation. Genomic rearrangements within the *BRCA1* and *BRCA2* genes had not been thoroughly assessed until recently. In a recent study of women with a diagnosis of invasive breast cancer at any age, a strong family history of breast cancer (defined as a family with a minimum of 4 cases of female or male breast cancer, and/or ovarian cancer), and who had no evidence of mutations within the *BRCA1* and *BRCA2* as assessed by sequencing of the full coding region of each gene, 35 of the 300 probands (11.6%) carried genomic rearrangements within these genes. These mutations were more frequent among individuals under 40 years old.³⁶ The same study showed that five percent of the families had a mutation in *CHEK2* and 1% had a mutation in *TP53*.

These provocative results suggest that genomic rearrangements within the *BRCA1* and *BRCA2* genes should be assessed in young probands with a strong family history of breast cancer, especially if the family history also includes male breast cancer and/or ovarian cancer. It is our hope that commercial testing options will expand in the near future so that genomic rearrangement analysis of the *BRCA1* and *BRCA2* genes and testing for *CHEK2* and *TP53* become more widely available. Another exciting development in the field comes from the discovery that a single nucleotide polymorphism (SNP) within the *MDM2* gene promoter (SNP 309) accelerates the age of onset of Li-Fraumeni associated cancers, including breast cancers.⁵ Additional studies are needed to define the true clinical significance of these findings for women with breast cancer.

Current Recommendations for Genetic Counseling and Genetic Testing Referral for Breast Cancer

Identification of candidates for genetic counseling and genetic testing remains a central priority as only a small fraction of the estimated carriers has been identified to date. Individuals fulfilling one or more of the following criteria should be referred to a cancer genetics professional for evaluation: 1) invasive breast cancer or ductal carcinoma in situ diagnosed by age 50 or younger, 2) two primary breast cancers or breast cancer and ovarian cancer in a single individual, 3) two primary breast cancers or breast cancer and ovarian cancer in any close relative from the same side of the family (paternal or maternal), 4) clustering of breast cancer with male breast cancer, thyroid cancer, sarcoma, adrenocortical carcinoma, endometrial cancer, pancreatic cancer, brain tumors, dermatologic manifestations or leukemia/lymphoma on the same side of the family, 5) member of a family with a known mutation in a breast cancer susceptibility gene, 6) breast or ovarian cancer at any age in patient of Ashkenazi Jewish descent, 7) member of a family with a known mutation in a breast cancer susceptibility gene, 8) any male breast cancer, 9) one or more cases of ovarian cancer on the same side of the family. These broad inclusion criteria represent the consensus reached by the members of the National Comprehensive Cancer Network Genetic/Familial Breast and Ovarian Cancer High-Risk Assessment Panel (Table 2).⁷ These criteria include clinical features of the rare Li-Fraumeni and Cowden syndromes in addition to the better known hereditary breast and ovarian cancer syndrome.

Furthermore, there are several tools to estimate an individual woman's breast cancer risk, and the risk that she carries a deleterious mutation within the *BRCA1* or *BRCA2* genes. BRCAPRO is one of the most commonly used software that incorporates several predictive models for inherited or familial breast cancer: the Claus model,⁶ the Couch model,³⁸ the Shattuck-Eidens model,³⁴ the Frank model,¹¹ and a new Bayesian probability model. This software was developed by investigators at the University of Texas Southwestern Medical Center at Dallas and Duke University and is available free of charge at <http://www3.utsouthwestern.edu/cancergene>. This program is particularly useful to calculate a woman's risk of developing breast and/or ovarian cancer and the probability of carrying a mutation within the *BRCA1* or *BRCA2* genes. It has been validated in several studies and appears to predict breast cancer risk equally well in Caucasian and African American women (Nanda, 2005 33971/id; Nanda, 2005 33971/id).⁴

It is important to remember that the autosomal dominant pattern of transmission of the *BRCA1* and *BRCA2* genes means that these genes are transmitted equally well by fathers and mothers. A small family size or transmission through males may mask recognition of the hereditary breast and ovarian cancer syndrome. Hence, in small families or whenever there is a predominance of males in the family, less stringent criteria may be used for referral.

Role of Low Penetrance Breast Cancer Susceptibility Genes

There is growing genetic evidence that high penetrance germline mutations in genes such as *BRCA1* and *BRCA2* account for a small proportion of familial risk of breast cancer, and much of the remaining variation in genetic risk is likely to be caused by combinations of more common, lower penetrance variants.²⁹

We were the first to identify *TGFBR1**6A, a common variant of the *TGFBR1* gene. This variant has a deletion of three GCG triplets coding for alanine within a nine alanine (9A) repeat sequence of *TGFBR1* exon 1, which results in a six alanine repeat (6A) sequence.²⁷ We have shown that in normal epithelial cells *TGFBR1**6A transmits TGF- β growth inhibitory signals less effectively than *TGFBR1* and is able to switch growth inhibitory signals into growth stimulatory signals in breast cancer cells.^{26,28} Epidemiologically, the *TGFBR1**6A allele is

a candidate tumor susceptibility allele that has been associated with an increased incidence of several types of cancer.^{3,15} A recent meta-analysis of 17 case-control studies that included 6,968 patients with a diagnosis of cancer and 6,145 healthy controls showed that *TGFBRI**6A carriers have a significantly increased risk of breast, colon, ovarian, and prostate cancer as compared with noncarriers.⁴¹ Overall, breast cancer risk is more than twofold higher among *TGFBRI**6A homozygotes (O.R. 2.69, 95% CI 1.54-4.68) than among *TGFBRI**6A heterozygotes (O.R. 1.23, 95% CI 1.06-1.43), which is indicative of a strong allelic dosing effect. More than one in seven healthy individuals and one in six patients with cancer is a *TGFBRI**6A carrier. This establishes *TGFBRI**6A as one of the most common and potentially clinically relevant high-frequency, low-penetrance candidate breast cancer susceptibility allele. The lifelong breast cancer risk incurred by *TGFBRI**6A homozygotes is ~35% compared to 13% for noncarriers; *TGFBRI**6A population attributable risk (PAR) for breast cancer is 4.9 % (2.7–7.2%) (24, 26, 33). This is almost identical to the PAR for *BRCA1* and *BRCA2* combined (3–7%).

In contrast, increased TGF- β circulating levels have been associated with a decreased propensity to develop mammary tumors in animal models.³¹ Similarly, increased TGF- β signaling has been shown to prevent the development of mammary tumors in animal models. A common variant within the human TGF- β 1 (*TGFB1*) gene is represented by the substitutions of Leucine to Proline (T $\rightarrow$ C) at the 10th amino acid position (T29C). Studies have shown that the T $\rightarrow$ C substitution results in higher extracellular TGFB1 secretion and higher TGFB1 circulating levels have been observed in humans that carry this allele. We were the first to propose that various combinations of two naturally-occurring and functionally relevant polymorphisms of the TGF- β signaling pathway may predict breast cancer risk. This proof of concept shows that women with high constitutive TGF- β signaling have a 70% lower risk of breast cancer than women with low TGF- β signaling.¹⁴ This suggests that functional interactions within the TGF- β signaling pathway may act as significant modifiers of breast cancer risk and make contributions to a large portion of a yet unidentified fraction of familial and sporadic breast cancers.

Surveillance of *BRCA*-Mutation Positive Women

Women in their fourth and fifth decade of life who carry deleterious mutations within the *BRCA1* gene have approximately a 30-fold higher risk of breast cancer than women without mutations. For *BRCA2* mutation carriers there is a 10- to 16-fold higher risk.² This has led a fraction of female carriers to elect prophylactic mastectomy, a procedure that has been shown to reduce breast cancer risk by 90% or more.^{12,21,32} However, many women cannot accept the psychological and physical trauma associated with this procedure and a recent study suggests that less than 15% of *BRCA*-mutation carriers undergo prophylactic bilateral mastectomy to reduce breast cancer risk.³⁰ Additional interventions that reduce breast cancer risk among carriers of deleterious mutation within the *BRCA1* and *BRCA2* genes are therefore sorely needed. Both prophylactic salpingo-oophorectomy and tamoxifen have been investigated as breast cancer risk reducing strategies in *BRCA*-mutation carriers. While adjuvant therapy with tamoxifen seems to reduce contralateral breast cancer risk in affected *BRCA*-mutation carriers,^{22,25} its effectiveness as primary prevention in unaffected women has not been investigated. Two separate groups have shown that prophylactic salpingo-oophorectomy significantly reduce breast cancer risk among premenopausal women with mutations within the *BRCA1* and *BRCA2* genes.^{16,33} However, despite the use of these breast cancer risk reduction strategies, breast cancer risk remains a major source of concern for female *BRCA*-mutation carriers who opt against prophylactic mastectomy. Two recent studies of *BRCA*-mutation carriers have highlighted the crucial role of breast MRI as an effective breast cancer screening method. In a study by Kriege et al.¹⁸ performed in the Netherlands, 1909 women at a 15% or more lifetime breast cancer risk (including 358 *BRCA*-mutation carriers)

were screened annually with concurrent mammography and MRI. Of the 45 cancers diagnosed in this cohort, 22 (49%) were identified by MRI alone, with an overall sensitivity of 71% for MRI versus 40% for mammography.¹⁸ In a study by Warner et al performed in Canada, 236 *BRCA*-mutation positive women underwent annual multimodality screening with clinical breast exam, mammography, screening ultrasound, and breast MRI, all performed on the same day. An interval clinical breast exam was performed 6 months later. On the 22 cancers diagnosed, 77% were detected by MRI, and 30% were identified by MRI alone. MRI identified a greater proportion of breast cancers than either mammography (36%) or ultrasound (33%). In these two studies, receiving operating characteristic curves, which reflect both sensitivity and specificity, confirm a greater diagnostic accuracy for MRI as compared with mammography. Consequently, annual mammogram and breast MRI screening are currently recommended starting at age 25 for all female carriers of a deleterious *BRCA* gene mutation.

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CONCLUSIONS

More than a decade following the discovery of the first high penetrance breast cancer susceptibility genes identification of additional *BRCA*-gene mutation carriers remains a major priority. Broad inclusion criteria as well as analysis of genomic rearrangements are likely to facilitate this goal. Low penetrance breast cancer susceptibility genes are emerging as significant contributors to breast cancer risk. Inclusion all these genes into genetic counseling and genetic testing is currently being studied. Future strategies aimed at identifying women at high risk of breast cancer are likely to include a combination of high, moderate and low penetrance breast cancer susceptibility genes.

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Table 1

Breast cancer susceptibility genes

Gene	Associated syndrome	Gene location	Gene frequency	Penetrance
<i>BRCA1</i>	Hereditary breast and ovarian cancer	17q21	Rare	Very high
<i>BRCA2</i>	Hereditary breast and ovarian cancer	13q12.3	Rare	High
<i>TP53</i>	Li-Fraumeni	17p13.1	Very rare	Very high
<i>PTEN</i>	Cowden	10q23.3	Very rare	High
<i>ATM</i>	Ataxia-telangiectasia	11q22-q23	Common	Low to moderate
<i>STK11</i>	Peutz-Jeghers	19p13.3	Very rare	High
<i>TGFBRI</i> *6A	None to date	9q22	Very common	Low to moderate
<i>TGFB1</i> L10P	None to date	19q13.1	Very common	Low
<i>CHEK2</i> *1100delC	None to date	22q12.1	Rare	Moderate
<i>CASP8</i> D302H	None to date	2q33-q34	Common	Low

Table 2
Inclusion criteria for breast and/or ovarian genetic assessment

The presence of one or more of the following criteria warrants referral to a cancer genetics professional:

- Breast cancer onset before the age of 50
 - Two breast cancer primaries or breast and ovarian cancer in a single individual
 - Two breast cancer primaries or breast and ovarian cancers in close relatives from the same side of family (maternal or paternal)
 - Clustering of breast cancer with male breast cancer, thyroid cancer, sarcoma, adrenocortical carcinoma, endometrial cancer, pancreatic cancer, brain tumors, dermatologic manifestations, or leukemia/lymphoma on the same side of the family.
 - Member of the family with a known dictation in a breast cancer susceptibility gene such as *BRCA1*, *BRCA2*, *TP53*, *PTEN*
 - Women of Ashkenazi Jewish descent with breast or ovarian cancer at any age
 - Any male breast cancer
 - One or more ovarian cancer on the same side of family.
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