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New Insights into Breast Cancer Genetics and Impact on Patient Management

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Opinion statement

The combined observation that 20–30% of all patients with breast cancer have a family history of the disease and the results from twin studies showing that 25% of breast cancer cases are heritable, indicate that this malignancy is one of the most commonly inherited cancers. Discovery of the *BRCA1* and *BRCA2* genes more than a decade ago has had a tremendous impact on patient care allowing for early detection and prevention of breast cancer. However, deleterious mutations within the *BRCA1* and *BRCA2* genes cause at most 3–8% of all breast cancer cases. New data indicate that genomic rearrangements within the same genes may occasionally identify additional carriers of nonfunctional *BRCA1* and *BRCA2* genes. Such genomic rearrangements are missed by conventional sequencing. The remainder of the unexplained familial risk is presumably due to other yet unidentified high penetrance genes, but polygenic mechanisms and high frequency low penetrance tumor susceptibility genes are likely to account for a greater proportion of familial breast cancers. In this regard, there is growing evidence that a common variant of the type I TGF-β receptor, *TGFBR1**6A, may account for approximately 5% of all breast cancer cases, a fraction similar to that attributable to *BRCA1* and *BRCA2*. Such genes may also modify the penetrance of the *BRCA1* and *BRCA2* genes. In the next decade, screening for combinations of high and low penetrance genes will likely permit the identification of a large fraction of inherited breast cancer cases and will further reduce the burden of familial breast cancer.

Introduction

One in eight women will be diagnosed with breast cancer in her lifetime and it is expected that more than 214,000 new cases will be diagnosed in the U.S. in 2006 [49]. Most cases of breast cancer are sporadic; however, twin studies have shown that heritable factors may cause 20–30% of all breast cancers [35]. While mutations within the *BRCA1* and *BRCA2* genes are common among women with a strong family history of breast cancer, they account for at most 3–8% of all breast cancer cases. Mutations in the *TP53* and *PTEN* genes, which cause Li-Fraumeni syndrome and Cowden syndrome respectively, are exceedingly rare, and probably account for less than 0.1% of breast cancers. The large effect of heritability in breast cancer suggests major gaps in our knowledge.

Other candidate genes that may cause breast cancer have been identified in the past few years. Cancer susceptibility genes that are associated with an increased risk of breast cancer include *TGFBR1**6A, *CHEK2**1100delC, and *BRIP1* [5,37,41,47]. Many single nucleotide polymorphisms (SNPs) have also been studied and a recent study suggests that 5 of them are associated with breast cancer risk: *CASP8* D302H, *IGFB3* −202 C>A, *PGR* V660L, *SOD2*

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V16A, and TGFB1 *T29C* [Breast Cancer Association Consortium 7]. The respective contribution of these susceptibility genes and candidate SNPs is the focus of several ongoing studies.

These investigations are complicated by the fact that the penetrance of tumor susceptibility genes is highly influenced by other factors such as modifier genes, response to DNA damage, and environmental factors such as exposure to carcinogens, hormonal/reproductive factors, and weight [26].

Genetic testing is currently used to determine if individuals with a personal and/or family history of breast cancer carry mutations or genomic rearrangements within high penetrance breast cancer susceptibility genes. The results of these tests provide useful guidance in deciding how to follow these high risk individuals in order to prevent the occurrence of breast cancer or permit early cancer detection. This article aims to review genes associated with increased breast cancer risk and discuss genetic testing and prevention in individuals with a high risk of developing breast cancer.

High penetrance genes

BRCA1

- While *BRCA1* was cloned more than a decade ago, its exact function is still unknown. This is exemplified by the fact that mice that lack one copy of the *Brca1* gene do not exhibit any strong tumor predisposition. However, mice that lack two copies of the *Brca1* gene die *in utero* [14]. These traits have limited *in vivo* analysis of the *Brca1* gene. 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 [10].
- Deleterious mutations within the *BRCA1* gene are a frequent cause of breast cancer among women with a strong family history of breast cancer and are associated with a significantly increased risk for the disease. A recent analysis of 22 studies involving 8,139 index case patients unselected for family history shows that carrying a deleterious *BRCA1* mutation confers an estimated lifetime risk for developing breast cancer of 65% (95% CI 44–78%) [4]. 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 lifetime risk being 82% by age 80 [26]. Mutations in *BRCA1* are strongly associated with ovarian and fallopian tube cancer [4]. The risk for ovarian cancer for a *BRCA1* mutation carrier is 17% by age 40 and increases to 39% by age 70 and 54% by age 80 [4].

BRCA2

- The *BRCA2* gene was also identified a decade ago, one year after *BRCA1*. The function of *BRCA2* is not as ubiquitous as *BRCA1*. Similarly, to what is observed with *Brca1*, mice that lack one copy of the *Brca2* gene do not exhibit a strong tumor predisposition [14]. Nonetheless, some functional clues have emerged from *in vitro* studies. After a double strand DNA breaks, BRCA2 induces the translocation of the protein Rad51 into the nucleus and directs Rad51 to the site of the break for homologous recombination-directed repair [56].
- A smaller fraction of familial breast cancer cases can be attributed to mutations in *BRCA2* as compared to *BRCA1*. In a combined analysis of 22 studies, *BRCA2* mutation carriers were found to carry a cumulative breast cancer risk by age 70 of

45% (95% CI = 31% – 56%), and for ovarian cancer of 11% (95% CI = 2.4%–19%) [4].

Reliability of current genetic testing for BRCA1 and BRCA2 deleterious mutations

- In a study of 300 women who had been diagnosed with invasive breast cancer at any age, had a 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 tested negative for *BRCA1* and *BRCA2* mutations, as assessed by sequencing of the full coding region of each gene, 35 (11.6%) carried genomic rearrangements within the *BRCA1* or the *BRCA* genes. These mutations were more frequent among individuals under 40 years old [53]. These data strongly 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.

TP53

- *TP53* encodes the tumor suppressor protein p53, which inhibits cell cycle progression in the presence of radiation-induced DNA breaks. *TP53* mutations are associated with a syndrome named Li-Fraumeni syndrome (LFS) and Li-Fraumeni-like syndrome (LFLS) (Table 1).
- In families with LFS, *TP53* is frequently mutated. Studies have shown that although mutations in *TP53* are extremely rare in the general population, those with the mutation will develop cancer at some point. In a study of 100 women who had breast cancer, 4 women below 31 years of age had a mutation in *TP53*, independent of *BRCA*-gene mutation status; 2/37 familial breast cancer cases had features of LFS or LFLS and 2/63 non-familial cases had mutations in *TP53* [32]. In Walsh's study [53] of 300 women with a strong family history of breast cancer who had neither mutations nor genomic rearrangements within the *BRCA1* and *BRCA2* genes, three families had LFS and 7 families had LFLS. Two of the 3 families with LFS and 1 in 7 families with LFLS carried mutations. In addition, out of 21 patients with a family history of breast cancer without LFS or LFLS, none carried mutations in *TP53*. In this selected population, about 1% of families with hereditary breast cancer may carry mutations in *TP53*. Another study suggests that that one in 5000 women with breast cancer harbors a *TP53* mutation [32]. Hence, in the absence of genomic rearrangements within the *BRCA1* and *BRCA2* genes, *TP53* mutations screening should be considered in women with a strong family history of breast cancer and features of LFS or LFLS.

PTEN

- *PTEN* (phosphatase and tensin homolog) is a tumor suppressor gene that inhibits cell growth during the G1 phase of cell cycle by activating the cyclin-dependant kinase inhibitor p27(KIP1) [33]. Mutations in *PTEN* are rare, but are associated with a high penetrance syndrome termed Cowden disease (CD). Individuals with Cowden syndrome have a high risk for developing breast cancer as well as hamartomas and benign tumors in the skin, thyroid, breast, endometrium, and brain. At least three different mutations in *PTEN* have been found in families with CD and early onset breast cancer [51].

Lifestyle factors that affect breast cancer risk

- Many factors influence the penetrance of tumor susceptibility genes, such as environmental factors, carcinogens, hormonal factors, and lifestyle factors. Hormonal

factors that influence breast cancer risk include age at menarche, pregnancy, breast-feeding, and contraceptive use. However, these environmental factors may not be strong enough to change the penetrance of the *BRCA* genes. For example, an early age of onset of menstruation increases a woman's risk of breast cancer [24]. A recent study, though, involving 3947 women showed no correlation between carrying either *BRCA1* or *BRCA2* mutations with age of menarche ($P = 0.97$). However, a matched case-control study with 1311 pairs, showed that for each year that menarche was delayed after age 11 in *BRCA1* carriers, there is a 15% decreased risk of breast cancer ($P_{Trend} = 0.0002$). For women who experienced menarche at 15 years or older, there is a 54% reduced risk of breast cancer compared to those who experienced it before age 11.

- Pregnancy is associated with a protective effect against the early onset of breast cancer in the general population. Although mutations in *BRCA1* or *BRCA2* are associated with a decreased age of breast cancer onset, the protective effects of pregnancy were the same as in wild-type patients. In the general population, childbirth reduces the risk of breast cancer by 23% ($P = 0.009$), and among women negative for either of *BRCA*-gene mutation, the risk is similarly decreased. *BRCA*-gene mutation carriers seem to have a 29% decreased risk of breast cancer after childbirth, with a similar risk reduction to women who do not have a mutation in either gene ($P = 0.26$) [26]. In addition, for women over the age of 40, each additional birth leads to a 14% reduction in the risk for breast cancer in the general population (95% CI = 6–22% $P_{trend} = 0.008$). This trend is seen regardless of *BRCA*-gene mutation status [3].
- It has also been shown that a healthier adolescent lifestyle, measured by adolescent weight within normal limits and physical activity, protects against the risk of early onset of breast cancer. Physical activity among teenagers led to a decrease in early onset breast cancer ($P = 0.025$ in all study participants, and $P = 0.034$ for women with mutations in the *BRCA* genes) [26]. A study on 11,889 females with breast cancer from Taiwan found that both an increased BMI and hip circumference were associated with an increased risk for breast cancer. Compared to a BMI less than 21.6 kg/m^2, having a BMI over 26.2 kg/m^2 resulted in a relative risk of 1.9 (95% CI = 1.0–3.4), and compared to a hip circumference of less than 90 cm, one over 100 cm resulted in a RR = 2.9 (95% CI = 1.1–6.7; $P_{Trend} = 0.0485$) [54]. For *BRCA* carriers, the OR associated with a 35 pounds weight gain after the age of 18 was found to be 4.64 (95% CI = 1.52–14.12; $P_{Trend} = 0.011$) compared to those who gained less than 12 lbs.

Genetic testing

- Genetic testing is carried out for families with a high risk of breast and ovarian cancer (Table 2). The criteria for "high risk" is outlined in the National Comprehensive Cancer Network's (NCCN) Clinical Practice Guidelines in Oncology [1].
- Genetic screening for breast cancer consists of screening for mutations in *BRCA1* and *BRCA2* (Table 3). If the family history is suggestive of either Cowden syndrome of Li-Fraumeni syndrome testing for mutations in *PTEN* or *TP53* may be indicated.

Patient management

- For women with a family history of breast cancer, genetic testing may be a useful tool to guide management options. If a woman has a family history of breast cancer and carries a *BRCA1* or *BRCA2* mutation, medical and surgical interventions have been shown to reduce the risk of cancer. The most effective options include prophylactic bilateral mastectomy and prophylactic salpingo-oophorectomy. However, these

procedures are highly invasive and there are other nonsurgical risk-reducing interventions. Increased surveillance has also been shown to increase early detection.

Prophylactic mastectomy

- Prophylactic mastectomy (PM) is the most effective strategy for reducing the risk of breast cancer in high risk individuals. A study by Hartmann et al in 1999 was the first to demonstrate a 90% reduction in breast cancer in high risk families after bilateral PM, regardless of *BRCA1* or *BRCA2* status. Subsequent studies have confirmed this reduction in breast cancer risk [11].

Prophylactic salpingo-oophorectomy

- *BRCA1* and *BRCA2* mutation carriers have a decreased risk of both ovarian and breast cancer after prophylactic salpingo-oophorectomy (PSO). For ovarian cancer, PSO is the best intervention, as screening is virtually ineffective [11]. PSO reduces the risk of ovarian cancer by 85–96% [11,15,23,45]. However, when PSO is performed in premenopausal women, it is also associated with a significant decrease in the risk of breast cancer. In the same studies there was a 53–68% reduced risk of breast cancer after PSO. Eisen et al have shown that a greater risk reduction for breast cancer is achieved when prophylactic surgery is performed prior to age 40 (OR 0.36; 95% CI 0.20–0.64) compared to after age 40 years (OR = 0.53; 95% CI = 0.3–0.91). This risk reduction was observed only in *BRCA1* mutation carriers, probably due to the smaller numbers of *BRCA2* mutation carriers. When PSO is done at an early age, the protective effects are seen for a minimum of 15 years [13]. For *BRCA1/2* mutation carriers, the 10 year breast cancer incidence for a 40-year old woman decreases from 32% to 11% after PSO; at age 50 it decreases from 28% to 19%, and at age 60 the 10 year risk decreases from 25 to 14% [28].
- One concern for many women who consider bilateral PSO as a form of prevention is the onset of premature surgical menopause, which may affect their quality of life. Hormone replacement therapy (HRT) alleviates these symptoms, however when combined with estrogen-progesterone use, it is also associated with an increased risk of breast cancer [46]. Rebbeck et al recently determined that short term HRT usage does not alter breast cancer risk in patients who have undergone bilateral PSO (HR = 0.37; 95% CI = 0.14–0.96) compared to the overall risk of breast cancer after bilateral PSO (HR = 0.40; 95% CI = 0.18–0.92). The impact of long term usage of HRT on the risk of breast cancer for women having undergone bilateral PSO is yet to be studied [44].

Surveillance

- Patients at high risk for breast cancer due to a strong family history or predisposed genetic background should get an annual mammography and breast MRI, as well as semiannual clinical breast exams (CBE). For identifying invasive breast cancer, MRI has a higher sensitivity than mammography and CBE (79.5%, 33.3%, and 17.9%, respectively). The specificities for these methods are 89.8%, 95%, and 98.1%, respectively. The sensitivity rates for any type of tumor detection are: 17.8% for CBE, 40% for mammography, and 71.1% for MRI. The use of MRI screening has been shown to detect invasive tumors at an earlier stage (less than 10 mm) compared to individuals not receiving MRI for screening [30].
- Kriege and colleagues found that the sensitivity of MRI screening is much higher than that of mammography in patients with glandular breast tissue (low breast density) (93.3% vs. 46.7% $P = 0.04$). Although the difference in sensitivity is not as high in

women with dense breast tissue (58.6% MRI vs. 37.9% mammography; $P = 0.3$), MRI still has a higher overall sensitivity compared to mammography[29].

- Because *BRCA1* and *BRCA2* encode proteins that play a role in DNA repair after ionizing radiation, there has been some concern that individuals who carry mutations in either one of these genes would have an increased risk for breast cancer with mammographic screenings [17]. Narod and colleagues conducted the first case control study using 1600 matched cases and controls looking at mammography screening and risk of breast cancer in *BRCA1* and *BRCA2* mutation carriers. They found no association between ever having a mammography and risk of breast cancer for *BRCA1* or *BRCA2* mutation carriers (OR 1.04; 95% CI = 0.84–1.29 vs OR 1.06; 95% CI = 0.67–1.66, respectively) [40]. However, for *BRCA*-gene mutation carriers, the risk for breast cancer before the age of 40 is significantly increased after exposures to chest x-rays that were taken before the age of 20 (HR = 2.61; $P < 0.01$). This risk is also significant for women born after 1949 (HR = 4.64; $P < 0.001$) [2]. Based on these limited studies our recommendation is to avoid non-necessary ionizing radiation in *BRCA*-gene mutation carriers, especially among women 20 years old or younger.

Chemoprevention

- Besides risk-reducing surgeries there are other strategies that may have an impact on breast cancer risk. Medications such as tamoxifen have been used for years in the treatment of breast cancer. Several studies have suggested a significant benefit in reducing the risk of breast cancer in high risk individuals. The NSABP P-1 trial showed that in 13,388 women with a predicted breast cancer risk of over 1.66, use of tamoxifen for 5 years offered a reduction in breast cancer by 43% after a median follow-up of 7 years [16]. In that trial eight women with a *BRCA1* mutation developed breast cancer. Of those, five were in the tamoxifen arm whereas three were in the placebo arm [25] and six of the eight women developed an estrogen receptor (ER) negative breast cancer. In the same study population, 11 women with a *BRCA2* mutation developed breast cancer. Of those, three were in the tamoxifen arm and eight in the placebo arm conferring a 62% reduction in breast cancer risk. Furthermore, six of the breast cancers were found to be ER positive. The number of *BRCA*-gene mutation carriers in this trial is small and precludes any definite conclusion with respect to the benefit of tamoxifen in *BRCA*-gene mutation carriers. It does, however, suggest that *BRCA2*-mutation carriers may derive a benefit from tamoxifen chemoprevention as the majority of breast cancers among *BRCA2* carriers are ER positive. In another chemo-prevention trial, the Royal Marsden trial, there were only four identified *BRCA*-gene mutation positive individuals and therefore a potential benefit from tamoxifen could not be assessed [27]. In another study of 491 women with *BRCA*-gene mutation positive breast cancer, use of tamoxifen significantly decreased the risk of contralateral breast cancer (HR, 0.59; 95% CI, 0.35–1.01) [38]. Other studies have also confirmed the beneficial effect of tamoxifen on breast cancer prevention in *BRCA1*-and *BRCA2*-mutation carriers [20,39].
- In another study Markov modeling of outcomes was performed in a simulated cohort of 30-year old women who tested positive for *BRCA1/2* mutations [19]. Investigators found that the addition of tamoxifen as chemoprevention prolonged survival by 1.8 years over what surveillance would offer.
- Therefore, although the data on tamoxifen chemoprevention in *BRCA*-gene mutation carriers is not overwhelming there seems to be a benefit in reducing the risk of breast cancer. The potential benefit from other chemopreventive strategies, such as raloxifene and aromatase inhibitors, will probably be limited since these agents are

only being used in postmenopausal women. However, future trials will address these issues.

Low penetrance genes

- Cancer due to *BRCA1* or *BRCA2* mutations account for only about 3–8% of all breast cancer cases. Other genes have been identified as breast cancer susceptibility genes, which may account for a proportion of the remainder of heritable breast cancer cases. These genes include *BRIP1*, *CHEK2**1100delC, and *TGFBR1**6A. They are considered low penetrance breast cancer susceptibility genes because only a small fraction of individuals who carry these genes will ultimately develop cancer.

CHEK2

- CHEK2 is a cell cycle checkpoint protein that mediates mitotic block in the presence of ionizing radiation-induced DNA damage. Thus inactivating mutations in *CHEK2* would promote cancerous growth in the presence of DNA damage. The *CHEK2**1100delC mutation abolishes kinase activity of the protein, thereby blocking signaling by *CHEK2*.
- The *CHEK2**1100delC variant is present in 1.1% of the population. In contrast, 5.1% of breast cancer patients who are wildtype for the *BRCA* genes carry this mutation. Women carriers of *CHEK2**1100delC have a two-fold increased risk for breast cancer compared to the normal population [36].
- The role of *CHEK2**1100delC in male breast cancer is controversial. Meijers-Heijboer's study in 2002, which included patients from the UK, North America, the Netherlands, and Germany, found the *CHEK2**1100delC mutation in 13.5% of patients from families with male breast cancer [36]. The risk for breast cancer in men who carry *CHEK2**1100delC is increased ten-fold, and 9% of male breast cancer cases are estimated to arise from *CHEK2**1100delC. Other studies have not been able to link *CHEK2**1100delC to male breast cancer cases [50,53].

BRIP1

- BRIP1 (also known as *BACH1*) encodes a helicase that functionally interacts with the *BRCA1* gene to contribute to DNA repair [8]. A recent study found that *BRIP1* was mutated in 9 out of 1,212 individuals (0.74%) with breast cancer who had a family history of breast cancer. Within these 9 people, there were five different types of truncating mutations. These patients carried wildtype *BRCA* genes. In the control group, which consisted of 2,081 people chosen from a 1958 Birth Cohort Collection in Great Britain, only 2 people (0.1%) had truncating mutations ($P = 0.0030$), conferring an estimated relative risk of breast cancer associated with *BRIP1* truncated mutations to be 2.0 (95% CI = 1.2–3.2; $P = 0.012$) [47].

TGF-b pathway variants

- Transforming growth factor beta (TGF-b) has a dual role in cancer development. In normal mammary epithelial and breast carcinoma cells, TGF-b inhibits cell proliferation, however, as the tumor progresses TGF-b enhances invasion and metastasis [52]. Thus, loss-of-function mutations in the TGF-b signaling pathway in the early stages of oncogenesis would contribute to tumor growth due to the lack of growth inhibitory signals. Gain-of-function mutations benefit the late steps in tumor metastasis.
- *TGFBR1**6A is a common variant of *TGFBR1*, which received its name from the three alanine deletion from a nine alanine tract in the receptor's signal sequence.

TGFBR1*6A has been shown to mediate TGF-b growth inhibitory signals less efficiently in reporter assays and growth inhibition assays in mink lung epithelial cells [9,43]. Importantly, *TGFBR1**6A has been shown to switch TGF-b growth inhibitory signals into growth stimulatory signals in MCF-7 breast cancer cells, which strongly suggests that *TGFBR1**6A provide a selective growth advantage to cancer cells in the TGF-b-rich tumor microenvironment [42]. A recent meta-analysis of 17 case-control studies that included 13,113 individuals has shown that *TGFBR1**6A carriers have a 22% increased risk of cancer. With respect to breast cancer this study showed that *TGFBR1**6A homozygotes have almost a three-fold increased risk as compared with non-carriers (OR 2.69, 95% CI 1.54–4.68) [57]. Given the high *TGFBR1**6A carrier frequency in the general population (14.1%), the population attributable breast cancer risk is 4.9% (2.7–7.2%) (Table 4).

- Several polymorphisms have been found in the *TGFB1* gene. Two specific polymorphisms modulate the level of circulating TGF-b: $Arg^{25}Pro$ (resulting from a C to T substitution at position 509) and $Leu^{10}Pro$ (resulting from a T to C substitution at position 29) [18,55]. The $Leu^{10}Pro$ variant results in increased levels of TGFB1 secretion [12,55]. In a cohort study of 3,075 White American women over the age of 65 the authors found that the risk of breast cancer decreased 64% in *TGFB1*CC* carriers compared to subjects that were *TGFB1**CT or *TGFB1**TT [58]. However, two studies have shown that there is no correlation between woman carrying the C allele and the risk of breast cancer [21,31]. A recent study using patients from the Shanghai Cancer Registry, could not correlate breast cancer risk with *TGFB1**CC or CT [48]. Thus, the association between this SNP and breast cancer remains to be clarified.
- We have recently investigated the combined genetic assessment of *TGFBR1**6A and *TGFB1* T29C. Patients and controls were divided into three groups based on combination of these two functionally-relevant variants and categorized into high, intermediate, and low constitutive TGF-b signalers. Low signalers had a 70% increased breast cancer risk as compared with high signalers (OR 1.69, 95% CI 1.08–2.66), which is consistent with the known role of TGF-β in animal models of breast cancer. Importantly, this approach was able to predict breast cancer risk in 30% of the population. If ongoing studies confirm this association, TGF-β pathway analysis may become a useful clinical tool to predict breast cancer risk in the near future [22].
- The field of breast cancer susceptibility genes is rapidly evolving. Integration of novel breast cancer susceptibility genes is likely to provide effective new means of breast cancer prevention within the next few years.

Reference and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. NCCN Clinical Practice Guidelines in Oncology. 2006http://www.nccn.org/professionals/physician_gls/PDF/genetics_screening.pdf. 2006. Ref Type: Electronic Citation

2. Andrieu N, Easton DF, Chang-Claude J, Rookus MA, Brohet R, Cardis E, Antoniou AC, Wagner T, Simard J, Evans G, Peock S, Fricker JP, Nogues C, Van't VL, Van Leeuwen FE, Goldgar DE. Effect of chest X-rays on the risk of breast cancer among BRCA1/2 mutation carriers in the international

BRCA1/2 carrier cohort study: a report from the EMBRACE, GENEPSO, GEO-HEBON, and IBCCS Collaborators' Group. J Clin Oncol 2006a;24:3361–3366. [PubMed: 16801631]

3. Andrieu N, Goldgar DE, Easton DF, Rookus M, Brohet R, Antoniou AC, Peock S, Evans G, Eccles D, Douglas F, Nogues C, Gauthier-Villars M, Chompret A, Van Leeuwen FE, Kluijt I, Benitez J, Arver B, Olah E, Chang-Claude J. Pregnancies, breast-feeding, and breast cancer risk in the International BRCA1/2 Carrier Cohort Study (IBCCS). J Natl Cancer Inst 2006b;98:535–544. [PubMed: 16622123]
4. Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, Loman N, Olsson H, Johannsson O, Borg A, Pasini B, Radice P, Manoukian S, Eccles DM, Tang N, Olah E, Anton-Culver H, Warner E, Lubinski J, Gronwald J, Gorski B, Tulinius H, Thorlacius S, Eerola H, Nevanlinna H, Syrjakoski K, Kallioniemi OP, Thompson D, Evans C, Peto J, Lalloo F, Evans DG, Easton DF. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 2003;72(5):1117–1130. [PubMed: 12677558]
5. Baxter SW, Choong DY, Eccles DM, Campbell IG. Transforming growth factor beta receptor 1 polyalanine polymorphism and exon 5 mutation analysis in breast and ovarian cancer. Cancer Epidemiol Biomarkers Prev 2002;11:211–214. [PubMed: 11867510]
6. Birch JM, Hartley AL, Tricker KJ, Prosser J, Condie A, Kelsey AM, Harris M, Jones PH, Binchy A, Crowther D. Prevalence and diversity of constitutional mutations in the p53 gene among 21 Li-Fraumeni families. Cancer Res 1994;4:1298–1304. [PubMed: 8118819]
7. Breast Cancer Association Consortium Commonly studied single-nucleotide polymorphisms and breast cancer: results from the Breast Cancer Association Consortium. J Natl Cancer Inst 2006;98:1382–1396. [PubMed: 17018785]
8. Cantor SB, Bell DW, Ganesan S, Kass EM, Drapkin R, Grossman S, Wahrer DC, Sgroi DC, Lane WS, Haber DA, Livingston DM. BACH1, a novel helicase-like protein, interacts directly with BRCA1 and contributes to its DNA repair function. Cell 2001;105:149–160. [PubMed: 11301010]
9. Chen T, de Vries EG, Hollema H, Yegen HA, Vellucci VF, Strickler HD, Hildesheim A, Reiss M. Structural alterations of transforming growth factor-beta receptor genes in human cervical carcinoma. Int J Cancer 1999;82:43–51. [PubMed: 10360819]
10. Deng CX. BRCA1: cell cycle checkpoint, genetic instability, DNA damage response and cancer evolution. Nucleic Acids Res 2006;34:1416–1426. [PubMed: 16522651]
11. Domchek SM, Friebel TM, Neuhausen SL, Wagner T, Evans G, Isaacs C, Garber JE, Daly MB, Eeles R, Matloff E, Tomlinson GE, Van't VL, Lynch HT, Olopade OI, Weber BL, Rebbeck TR. Mortality after bilateral salpingo-oophorectomy in BRCA1 and BRCA2 mutation carriers: a prospective cohort study. Lancet Oncol 2006;7:223–229. [PubMed: 16510331]
12. Dunning AM, Ellis PD, McBride S, Kirschenlohr HL, Healey CS, Kemp PR, Luben RN, Chang-Claude J, Mannermaa A, Kataja V, Pharoah PD, Easton DF, Ponder BA, Metcalfe JC. A transforming growth factorbeta1 signal peptide variant increases secretion in vitro and is associated with increased incidence of invasive breast cancer. Cancer Res 2003;63:2610–2615. [PubMed: 12750287]
13. Eisen A, Lubinski J, Klijn J, Moller P, Lynch HT, Offit K, Weber B, Rebbeck T, Neuhausen SL, Ghadirian P, Foulkes WD, Gershoni-Baruch R, Friedman E, Rennert G, Wagner T, Isaacs C, Kim-Sing C, Ainsworth P, Sun P, Narod SA. Breast cancer risk following bilateral oophorectomy in BRCA1 and BRCA2 mutation carriers: an international case-control study. J Clin Oncol 2005;23:7491–7496. [PubMed: 16234515]
14. Evers B, Jonkers J. Mouse models of BRCA1 and BRCA2 deficiency: past lessons, current understanding and future prospects. Oncogene 2006;25:5885–5897. [PubMed: 16998503]
15. Finch A, Beiner M, Lubinski J, Lynch HT, Moller P, Rosen B, Murphy J, Ghadirian P, Friedman E, Foulkes WD, Kim-Sing C, Wagner T, Tung N, Couch F, Stoppa-Lyonnet D, Ainsworth P, Daly M, Pasini B, Gershoni-Baruch R, Eng C, Olopade OI, McLennan J, Karlan B, Weitzel J, Sun P, Narod SA. Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a BRCA1 or BRCA2 Mutation. JAMA 2006;296:185–192. [PubMed: 16835424]
16. Fisher B, Costantino JP, Wickerham DL, Cecchini RS, Cronin WM, Robidoux A, Bevers TB, Kavanah MT, Atkins JN, Margolese RG, Runowicz CD, James JM, Ford LG, Wolmark N. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 2005;97:1652–1662. [PubMed: 16288118]

17. Friedenson B. Is mammography indicated for women with defective BRCA genes? Implications of recent scientific advances for the diagnosis, treatment, and prevention of hereditary breast cancer. MedGenMed 2000;2:E9. [PubMed: 11104455]

18. Grainger DJ, Percival J, Chiano M, Spector TD. The role of serum TGF-beta isoforms as potential markers of osteoporosis. Osteoporos Int 1999;9:398–404. [PubMed: 10550458]

19. Grann VR, Jacobson JS, Thomason D, Hershman D, Heitjan DF, Neugut AI. Effect of prevention strategies on survival and quality-adjusted survival of women with BRCA1/2 mutations: an updated decision analysis. J Clin Oncol 2002;20:2520–2529. [PubMed: 12011131]

20. Gronwald J, Tung N, Foulkes WD, Offit K, Gershoni R, Daly M, Kim-Sing C, Olsson H, Ainsworth P, Eisen A, Saal H, Friedman E, Olopade O, Osborne M, Weitzel J, Lynch H, Ghadirian P, Lubinski J, Sun P, Narod SA. Tamoxifen and contralateral breast cancer in BRCA1 and BRCA2 carriers: an update. Int J Cancer 2006;118:2281–2284. [PubMed: 16331614]

21. Jin Q, Hemminki K, Grzybowska E, Klaes R, Soderberg M, Zientek H, Rogozinska-Szczepka J, Utracka-Hutka B, Pamula J, Pekala W, Forsti A. Polymorphisms and haplotype structures in genes for transforming growth factor beta1 and its receptors in familial and unselected breast cancers. Int J Cancer 2004;112:94–99. [PubMed: 15305380]%20;

22. Kaklamani VG, Baddi L, Liu J, Rosman D, Phukan S, Bradley C, Hegarty C, McDaniel B, Rademaker A, Oddoux C, Ostrer H, Michel LS, Huang H, Chen Y, Ahsan H, Offit K, Pasche B. Combined genetic assessment of transforming growth factor-beta signaling pathway variants may predict breast cancer risk. Cancer Res 2005;65:3454–3461. [PubMed: 15833881]

23. Kauff ND, Satagopan JM, Robson ME, Scheuer L, Hensley M, Hudis CA, Ellis NA, Boyd J, Borgen PI, Barakat RR, Norton L, Castiel M, Nafa K, Offit K. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med 2002;346:1609–1615. [PubMed: 12023992]

24. Kelsey JL, Gammon MD, John EM. Reproductive factors and breast cancer. Epidemiol Rev 1993;15:36–47. [PubMed: 8405211]

25. King MC, Wieand S, Hale K, Lee M, Walsh T, Owens K, Tait J, Ford L, Dunn BK, Costantino J, Wickerham L, Wolmark N, Fisher B. Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. JAMA 2001;286:2251–2256. [PubMed: 11710890]

26. King MC, Marks JH, Mandell JB. Breast and Ovarian Cancer Risks Due to Inherited Mutations in BRCA1 and BRCA2. Science 2003;302:643–646. [PubMed: 14576434]

27. Kote-Jarai Z, Powles TJ, Mitchell G, Tidy A, Ashley S, Easton D, Assersohn L, Sodha N, Salter J, Gusterson B, Dowsett M, Eeles R. BRCA1/BRCA2 mutation status and analysis of cancer family history in participants of the Royal Marsden Hospital tamoxifen chemo-prevention trial. Cancer Lett. 2006

28. Kramer JL, Velazquez IA, Chen BE, Rosenberg PS, Struewing JP, Greene MH. Prophylactic oophorectomy reduces breast cancer penetrance during prospective, long-term follow-up of BRCA1 mutation carriers. J Clin Oncol 2005;23:8629–8635. [PubMed: 16314625]

29. Kriege M, Brekelmans CT, Obdeijn IM, Boetes C, Zonderland HM, Muller SH, Kok T, Manoliu RA, Besnard AP, Tilanus-Linthorst MM, Seynaeve C, Bartels CC, Kaas R, Meijer S, Oosterwijk JC, Hoogerbrugge N, Tollenaar RA, Rutgers EJ, de Koning HJ, Klijn JG. Factors affecting sensitivity and specificity of screening mammography and MRI in women with an inherited risk for breast cancer. Breast Cancer Res Treat. 2006

30. Kriege, et al. Efficacy of MRI and Mammography for Breast-Cancer Screening in Women with a Familial or Genetic Predisposition. N Engl J Med 2004 July 29;351:427–437. [PubMed: 15282350] 2004

31. Krippl P, Langsenlehner U, Renner W, Yazdani-Biuki B, Wolf G, Wascher TC, Paulweber B, Bahadori B, Samonigg H. The L10P polymorphism of the transforming growth factor-beta 1 gene is not associated with breast cancer risk. Cancer Lett 2003;201:181–184. [PubMed: 14607332]

32. Lalloo F, Varley J, Moran A, Ellis D, O'dair L, Pharoah P, Antoniou A, Hartley R, Shenton A, Seal S, Bulman B, Howell A, Evans DG. BRCA1, BRCA2 and TP53 mutations in very early-onset breast cancer with associated risks to relatives. Eur J Cancer 2006;42:1143–1150. [PubMed: 16644204]

33. Li DM, Sun H. PTEN/MMAC1/TEP1 suppresses the tumorigenicity and induces G1 cell cycle arrest in human glioblastoma cells. Proc Natl Acad Sci U S A 1998;95:15406–15411. [PubMed: 9860981]
34. Li FP, Fraumeni JF Jr, Mulvihill JJ, Blattner WA, Dreyfus MG, Tucker MA, Miller RW. A cancer family syndrome in twenty-four kindreds. Cancer Res 1988;48:5358–5362. [PubMed: 3409256]
35. Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, Pukkala E, Skytthe A, Hemminki K. Environmental and heritable factors in the causation of cancer–analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med 2000;343:78–85. [PubMed: 10891514]
36. Meijers-Heijboer H, vanden OA, Klijn J, Wasielewski M, de SA, Oldenburg R, Hollestelle A, Houben M, Crepin E, van Veghel-Plandsoen M, Elstrodt F, van DC, Bartels C, Meijers C, Schutte M, McGuffog L, Thompson D, Easton D, Sodha N, Seal S, Barfoot R, Mangion J, Chang-Claude J, Eccles D, Eeles R, Evans DG, Houlston R, Murday V, Narod S, Peretz T, Peto J, Phelan C, Zhang HX, Szabo C, Devilee P, Goldgar D, Futreal PA, Nathanson KL, Weber B, Rahman N, Stratton MR. Lowpenetrance susceptibility to breast cancer due to CHEK2(*)1100delC in noncarriers of BRCA1 or BRCA2 mutations. Nat Genet 2002;31:55–59. [PubMed: 11967536]
37. Meijers-Heijboer H, van GB, van Putten WL, Henzen-Logmans SC, Seynaeve C, Menke-Pluymers MB, Bartels CC, Verhoog LC, van den Ouweland AM, Niermeijer MF, Brekelmans CT, Klijn JG. Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med 2001;345:159–164. [PubMed: 11463009]
38. Metcalfe K, Lynch HT, Ghadirian P, Tung N, Olivotto I, Warner E, Olopade OI, Eisen A, Weber B, McLennan J, Sun P, Foulkes WD, Narod SA. Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. J Clin Oncol 2004;22:2328–2335. [PubMed: 15197194]
39. Narod SA, Brunet JS, Ghadirian P, Robson M, Heimdal K, Neuhausen SL, Stoppa-Lyonnet D, Lerman C, Pasini B, de los RP, Weber B, Lynch H. Tamoxifen and risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers: a case-control study. Hereditary Breast Cancer Clinical Study Group. Lancet 2000;356:1876–1881.
40. Narod SA, Lubinski J, Ghadirian P, Lynch HT, Moller P, Foulkes WD, Rosen B, Kim-Sing C, Isaacs C, Domchek S, Sun P. Screening mammography and risk of breast cancer in BRCA1 and BRCA2 mutation carriers: a case-control study. Lancet Oncol 2006;7:402–406. [PubMed: 16648044]
41. Pasche B, Kaklamani V, Hou N, Young T, Rademaker A, Peterlongo P, Ellis N, Offit K, Caldes T, Reiss M, Zheng T. TGFBR1*6A and cancer: a meta-analysis of 12 case-control studies. J Clin Oncol 2004;22:756–758. [PubMed: 14966109]
42. Pasche B, Knobloch TJ, Bian Y, Liu J, Phukan S, Rosman D, Kaklamani V, Baddi L, Siddiqui FS, Frankel W, Prior TW, Schuller DE, Agrawal A, Lang J, Dolan ME, Vokes EE, Lane WS, Huang CC, Caldes T, Di CA, Hampel H, Nilsson I, von HG, Fodde R, Murty VV, de la CA, Weghorst CM. Somatic acquisition and signaling of TGFBR1*6A in cancer. JAMA 2005;294:1634–1646. [PubMed: 16204663]
43. Pasche B, Kolachana P, Nafa K, Satagopan J, Chen YG, Lo RS, Brener D, Yang D, Kirstein L, Oddoux C, Ostrer H, Vineis P, Varesco L, Jhanwar S, Luzzatto L, Massague J, Offit K. TbetaR-I(6A) is a candidate tumor susceptibility allele. Cancer Res 1999;59:5678–5682. [PubMed: 10582683]
44. Rebbeck TR, Friebel T, Wagner T, Lynch HT, Garber JE, Daly MB, Isaacs C, Olopade OI, Neuhausen SL, van V, Eeles R, Evans DG, Tomlinson G, Matloff E, Narod SA, Eisen A, Domchek S, Armstrong K, Weber BL. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J Clin Oncol 2005;23:7804–7810. [PubMed: 16219936]
45. Rebbeck TR, Lynch HT, Neuhausen SL, Narod SA, Van't VL, Garber JE, Evans G, Isaacs C, Daly MB, Matloff E, Olopade OI, Weber BL. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med 2002;346:1616–1622. [PubMed: 12023993]
46. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321–333. [PubMed: 12117397]
47. Seal S, Thompson D, Renwick A, Elliott A, Kelly P, Barfoot R, Chagtai T, Jayatilake H, Ahmed M, Spanova K, North B, McGuffog L, Evans DG, Eccles D, Easton DF, Stratton MR, Rahman N. Truncating mutations in the Fanconi anemia J gene BRIP1 are low-penetrance breast cancer susceptibility alleles. Nat Genet 2006;38:1239–1241. [PubMed: 17033622]

48. Shin A, Shu XO, Cai Q, Gao YT, Zheng W. Genetic polymorphisms of the transforming growth factor-beta1 gene and breast cancer risk: a possible dual role at different cancer stages. Cancer Epidemiol Bio-markers Prev 2005;14:1567–1570.

49. Smigal C, Jemal A, Ward E, Cokkinides V, Smith R, Howe HL, Thun M. Trends in breast cancer by race and ethnicity: update 2006. CA Cancer J Clin 2006;56:168–183. [PubMed: 16737949]

50. Syrjakoski K, Kuukasjarvi T, Auvinen A, Kallioniemi OP. CHEK2 1100delC is not a risk factor for male breast cancer population. Int J Cancer 2004;108:475–476. [PubMed: 14648717]

51. Tsou HC, Teng DH, Ping XL, Brancolini V, Davis T, Hu R, Xie XX, Gruener AC, Schrager CA, Christiano AM, Eng C, Steck P, Ott J, Tavtigian SV, Peacocke M. The role of MMAC1 mutations in early-onset breast cancer: causative in association with Cowden syndrome and excluded in BRCA1-negative cases. Am J Hum Genet 1997;61:1036–1043. [PubMed: 9345101]

52. Wakefield LM, Roberts AB. TGF-beta signaling: positive and negative effects on tumorigenesis. Curr Opin Genet Dev 2002;12:22–29. [PubMed: 11790550]

53. Walsh T, Casadei S, Coats KH, Swisher E, Stray SM, Higgins J, Roach KC, Mandell J, Lee MK, Ciernikova S, Foretova L, Soucek P, King MC. Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer. JAMA 2006;295:1379–1388. [PubMed: 16551709]

54. Wu MH, Chou YC, Yu JC, Yu CP, Wu CC, Chu CM, Yang T, Lai CH, Hsieh CY, You SL, Chen CJ, Sun CA. Hormonal and body-size factors in relation to breast cancer risk: a prospective study of 11,889 women in a low-incidence area. Ann Epidemiol 2006;16:223–229. [PubMed: 15996484]

55. Yokota M, Ichihara S, Lin TL, Nakashima N, Yamada Y. Association of a T29->C polymorphism of the transforming growth factor-beta1 gene with genetic susceptibility to myocardial infarction in Japanese. Circulation 2000;101:2783–2787. [PubMed: 10859282]

56. Yoshida K, Miki Y. Role of BRCA1 and BRCA2 as regulators of DNA repair, transcription, and cell cycle in response to DNA damage. Cancer Sci 2004;95:866–871. [PubMed: 15546503]

57. Zhang HT, Zhao J, Zheng SY, Chen XF. Is TGFBR1*6A Really Associated With Increased Risk of Cancer? J Clin Oncol 2005;23:7743–7744. [PubMed: 16234535]

58. Ziv E, Cauley J, Morin PA, Saiz R, Browner WS. Association between the T29->C polymorphism in the transforming growth factor beta1 gene and breast cancer among elderly white women: The Study of Osteoporotic Fractures. JAMA 2001;285:2859–2863. [PubMed: 11401606]

Table 1

Criteria for Li-Fraumeni Syndrome (LFS) and Li-Fraumeni-like syndrome (LFLS)

Li-Fraumeni Syndrome (LFS)	Sarcoma <45 yo with 1st degree relative < 45yo with cancer and 1st or 2nd degree relative < 45yo with any cancer [34].
Li-Fraumeni-like syndrome (LFLS)	Sarcoma, brain tumor or adrenocortical carcinoma < 45yo or childhood leukemia and 1st or 2nd degree relative with LFS tumor and 1st or 2nd degree relative < 60yo with cancer [6].

Table 2

Criteria for genetic testing for BRCA gene mutations

• Early age (< 40) at the onset of breast cancer with or without a family history of breast cancer
• 2 primary breast cancers or breast and ovarian cancer in a single patient or 2 primary breast or breast and ovarian cancers in close relatives from the same side of the family
• a clustering of breast cancer with male breast cancer, thyroid cancer, sarcoma, adrenocorticoid cancer, endometrial cancer, pancreatic cancer, brain tumors, dermatologic manifestations, or leukemia/lymphoma on the same side of the family
• A member of the family with known mutations in breast cancer susceptibility genes
• Population at risk (such as the Ashkenazi Jewish population)
• Any male breast cancer
• Personal history of ovarian cancer

Table 3

Results of genetic screening for *BRCA1/2* mutations

Result	Interpretation
Positive for deleterious mutation	Individual has high risk of breast and ovarian cancer
Negative for a mutation	Result interpreted with caution especially in the setting of a strong family history
Mutation of unknown significance	Mutation has not been definitively shown to be deleterious either because it is rare or because it may not completely track with the family history of the individual
Mutation favoring benign polymorphism	Although not certain these mutations seem to not be associated with a high risk for breast and ovarian cancer

Table 4

Clinical relevance of low-penetrance breast cancer susceptibility genes

	Population frequency	Hazard ratio (95% C.I)	Population attributable risk (PAR)
*TGFBR1*6A*	0.5% homozygotes	O.R. 2.69 (1.54–4.68)	4.9% (2.7%–7.2%) of all breast cancers
	14.1% heterozygotes	O.R. 1.23 (1.06–1.43)	
CHEK2	0.5% heterozgotes	O.R. 1.5 (1.2–1.8)	Less than 0.5% of all breast cancers

J Clin Onc 57, 23:7743-7743; Am J Hum Genet 2004, 74:1175-82; Clin Cancer Res 2006, 12:4832-4835.