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REVIEW ARTICLE

Hereditary breast cancer: new genetic developments, new therapeutic avenues

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Abstract Six genes confer a high risk for developing breast cancer (*BRCA1/2*, *TP53*, *PTEN*, *STK11*, *CDH1*). Both BRCA1 and BRCA2 have DNA repair functions, and *BRCA1/2* deficient tumors are now being targeted by poly(ADP-ribose) polymerase inhibitors. Other genes conferring an increased risk for breast cancer include *ATM*, *CHEK2*, *PALB2, BRIP1* and genome-wide association studies have identified lower penetrance alleles including *FGFR2*, a minor allele of which is associated with breast cancer. We review recent findings related to the function of some of these genes, and discuss how they can be targeted by various drugs. Gaining deeper insights in breast cancer susceptibility will improve our ability to identify those families at increased risk and permit the development of new and more specific therapeutic approaches.

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Introduction

This is an exciting time in the study of hereditary factors involved in breast cancer susceptibility. In particular, the introduction of novel treatment trials that aim to tailor the patient's genotype to the drug has highlighted the importance of understanding the high penetrance genes involved in breast cancer, and a wealth of information is available to guide the management of mutation carriers. Excellent reviews exist on the management of patients with an inherited predisposition to cancer (Lynch et al. 2008; Robson and Offit 2007), and our goal is not to review this aspect. In this review, we will focus on new developments in the pathogenesis of *BRCA1* and *BRCA2*-related breast cancer, and on the function of other breast cancer susceptibility genes. We will discuss how a better understanding of inherited breast cancer pathophysiology can lead to novel potential therapies for patients affected by inherited breast cancer.

BRCA1

BRCA1 was mapped in 1990 (Hall et al. 1990) and cloned in 1994 (Miki et al. 1994). Constitutional mutations in *BRCA1* cause hereditary breast and ovarian cancer syndrome. This tumor suppressor acts as a hub protein and is involved in genomic stability, DNA repair, DNA damage response and cell cycle checkpoint control, chromatin remodeling, transcriptional regulation and protein ubiquitylation (see Narod and Foulkes 2004, for a review). BRCA1 facilitates DNA repair by its involvement in homologous recombination and nucleotide excision repair. Its precise functions and their relationship to cancer pathogenesis continue to be extensively investigated and recent findings in

this respect include the further refinement of the BRCA1 double-strand break recognition mechanism. Through its C-terminal domains, BRCA1 forms three distinct and mutually exclusive complexes with the proteins Abraxas, BACH1 (BTB and CNC Homology 1) or CtIP (C-terminal binding protein Interacting Protein). It seems that the protein RAP80 (Receptor-Associated Protein, 80 kDa) may recruit BRCA1-Abraxas and BRCA1-CtIP complexes to damaged DNA (Kim et al. 2007a; Sobhian et al. 2007; Wang et al. 2007a). It also appears that the BRCA1-CtIP complex interacts with the MRN complex (composed of MRE11, RAD50, and NBS1) to facilitate double-strand break resection, in order for homologous recombination-mediated DNA double-strand break repair to occur (Chen et al. 2008; Sartori et al. 2007). However, the ubiquitinated targets on damaged DNA which are recognized by RAP80 are not known, and further elucidation of the pathway will be important in elucidating the role of BRCA1 in DNA repair (see Wu et al. 2008, for a review).

The role of BRCA1 in chromosomal integrity is further underlined by the finding that the heterodimer formed by the association of BRCA1 and BARD1 (BRCA1-Associated Ring Domain 1) is necessary for the accumulation of TPX2, a critical factor in microtubule stabilization and mitotic spindle assembly (Joukov et al. 2006). Improved understanding of the transcriptional regulation mechanisms of BRCA1 is likely to lead to new therapeutic interventions (reviewed in Murray et al. 2007). In that respect, it has recently been shown that SUMO1 (Small Ubiquitin-like Modifier 1) mediates repression of transcription of BRCA1 regulated genes by chromatin remodelling (Park et al. 2007). *BRCA1* gene expression is itself regulated by multiple E2F transcription factors and repressive "pocket proteins", and it has recently been shown that the *BRCA1* terminator fine-tunes its expression by forming a loop and interacting with its promoter (Tan-Wong et al. 2008). The role of the BRCA1 cofactor COBRA1, which is a component of the human negative elongation factor (NELF) and acts as a transcriptional co-repressor in estrogen-mediated gene expression, seems to be involved in tumor suppression by regulatory pathways common to BRCA1 (Aiyar et al. 2007; Sun et al. 2008).

The basal phenotype

For some time, *BRCA1*-related tumors have been recognized to possess immunohistochemical features that separate them from sporadic breast cancers (Karp et al. 1997; Lakhani et al. 1998). Their frequent expression of markers expressed in the basal cells of the breast [such as cytokeratin 5/6 (CK5/6) and annexin VIII] led to the use of the term "basal breast cancer", although this does not imply that the tumors arise from basal cells (Perou et al. 2000). Among *BRCA1*-related breast cancers, 44% were ER-negative, CK5/6 and CK14 positive (adjusted odds ratio of 148 compared with ER positive, cytokeratin negative breast cancers), whereas this phenotype was seen in only 2% of breast cancers from *BRCA1/2*-negative controls (Lakhani et al. 2005). For more detailed reviews on the basal phenotype please see (Rakha et al. 2007). Expression arrays have also contributed to the refinement of the basal phenotype in *BRCA1* related tumors (Sorlie et al. 2003). A recent mouse model of hereditary breast cancer has been created by the generation of conditional mouse models with tissue-specific mutation of *BRCA1* and/or *p53* in basal epithelial cells (Liu et al. 2007). These mice develop mammary carcinomas reminiscent of the basal phenotype, and could potentially be used to predict the response of breast cancer to new therapeutic means. It has recently been shown that *BRCA1*-mutant tumors fail to express ER (estrogen receptor) alpha due to the loss of *BRCA1*-mediated transcriptional activation of *ESR1* (Hosey et al. 2007), suggesting a link between *BRCA1* loss of expression and the development of the basal phenotype, and also potentially explaining the mechanism for a decreased response to anti-estrogen drugs in some *BRCA1* deficient tumors. In another study, Saal et al. (2008) showed that *PTEN* expression is frequently compromised in *BRCA1*-associated breast cancers with the basal phenotype. These data could be consistent with a model of oncogenesis involving an inherited *BRCA1* mutation, followed by a somatic *TP53* mutation, then loss of the second *BRCA1* allele, and finally disruption of *PTEN* causing aberrant PTEN-PI3K pathway signaling (Foulkes 2008).

A possible intermediate in the development of the basal-like phenotype could be *SOX2*, an embryonic transcription factor over-expressed in a number of basal-like tumors from *BRCA1* mutation carriers (Rodriguez-Pinilla et al. 2007). It has been suggested that BRCA1 functions as a stem cell regulator based on the clinico-pathological features of breast cancer related to *BRCA1* germline mutations and fundamental understandings of BRCA1 biology (Foulkes 2004). Some studies have now provided some support for this hypothesis (reviewed in Stingl and Caldas 2007); it was shown that in culture, depletion of BRCA1 impairs differentiation of mammary epithelial cells (Furuta et al. 2005), and more recently it was demonstrated that BRCA1 is required for the differentiation of ER-negative stem cells to ER-positive luminal cells, in vitro and in primary human mammary epithelial cells implanted in mice (Liu et al. 2008). Moreover, in breast tissue from *BRCA1* mutation carriers, LOH at the *BRCA1* locus was associated with the expression of a progenitor-specific gene (*ALDH1*) and absence of ER-positivity in entire lobules which were histologically normal. This suggests that BRCA1 is required for the differentiation of progenitor cells (Liu et al. 2008).

BRCA2

BRCA2 was cloned in 1995 (Wooster et al. 1995), and plays an important role in homologous recombination, both in meiosis and repair of double-strand breaks (Thorslund and West 2007). It seems to regulate the RAD51 and DCM1 recombinases to perform this function (Thorslund et al. 2007). BRCA2 also interacts with DSS1 and PALB2 (discussed later). When both *BRCA2* alleles are inactivated, a Fanconi anemia (FA) phenotype can occur (Howlett et al. 2002; Offit et al. 2003). *BRCA2*-associated breast cancers are predominantly moderate to high-grade invasive ductal carcinomas and tissue microarrays have shown that they demonstrate a luminal phenotype (Bane et al. 2007). Two new interesting findings are that *BRCA2* mutations might be a cause of Li–Fraumeni-like syndrome (Evans et al. 2008), and that *BRCA2* mutations increase the risks for certain childhood tumors (Magnusson et al. 2008).

Treatment of *BRCA1/2* deficient tumors

In vitro, breast cancer cell lines which have lost *BRCA1* become resistant to anti-cancer agents targeting the microtubules (such as vinca alkaloids and taxanes), but are more sensitive to agents which cause double-strand breaks (such as etoposide, bleomycin and radiation) and interstrand cross-linking agents such as platinum-based drugs. Currently there is a relative paucity of clinical correlations, but trials are underway to try to extend our understanding of the role of platinum drugs in the treatment of both *BRCA1*-related breast cancer and non-hereditary "basal-like" breast cancers (Foulkes 2006). Poly(ADP-ribose) polymerase 1 (PARP) is a nuclear protein which localizes the site of DNA damage and provides the first step in double-strand break DNA repair. At DNA damage sites, PARP attaches poly(ADP-ribose)-branched chains to DNA, which in turn recruit repair proteins and cell cycle checkpoint mediators (Ratnam and Low 2007). To specifically target *BRCA1/2* deficient tumors which already have impaired double-strand break DNA repair, PARP inhibitors have been shown to be effective in vitro (Bryant et al. 2005; Farmer et al. 2005) and are now entering clinical trials (Donawho et al. 2007).

TP53

TP53, which codes for the protein p53, is constitutionally mutated in Li–Fraumeni syndrome, an autosomal dominant predisposition to breast cancer, soft tissue sarcomas and osteosarcoma, brain tumors, adrenocortical cancer, Wilms tumor, and many rarer tumors, such as phyllodes tumors. The p53 protein is one of the most widely studied tumor suppressors, since its association with tumorigenesis was demonstrated in 1979. It can induce both apoptotic death and cell cycle arrest and recent studies continue to elucidate the mechanisms of action of p53 (reviewed in Aylon and Oren 2007). One important question surrounds the mechanisms which lead to cell cycle arrest to permit DNA repair, or to apoptosis. It seems that binding of the Hzf zinc finger protein promotes the activation of genes important for cell-cycle arrest genes, rather than apoptosis (Tanaka et al. 2007). Conversely, if DNA damage is more important, the chromatin-associated protein CAS/CSE1L binds with p53, promoting the transcription of pro-apoptotic genes (Das et al. 2007).

Activation of, or restoration of, p53 by various means has been a longstanding goal in cancer therapy, and it is hoped that some of those treatments might be brought to clinical use in the near future, such as the use of the anti-malarial drug quinacrine (Friedman et al. 2007; Kim et al. 2007b) which reactivates the expression of *TP53* by inactivating NFκB, a transrepressor of *TP53* (Gurova et al. 2005). Nevertheless, there are risks to this approach, in that over-expression of wild-type p53 may have unwanted consequences in stem cells (Sharpless and DePinho 2004).

PTEN

PTEN (phosphatase tensin homolog on chromosome ten) has been identified as a tumor suppressor following the study of a region marked by LOH (10q23) in various tumors (Li et al. 1997). It is constitutively mutated in Cowden syndrome, a syndrome characterized by macrocephaly, specific cutaneous findings, and a susceptibility to dysplastic gangliocytoma of the cerebellum, as well as breast and thyroid cancer (Liaw et al. 1997). Mutations in *PTEN* also cause the related syndrome, Bannayan–Riley–Ruvalcaba syndrome, characterized by macrocephaly, multiple lipomas, intestinal hamartomatous polyps, vascular malformations, and abnormal pigmentation of the penis.

PTEN acts as a tumor suppressor and a growth regulator, mainly by down-regulating the phosphatidylinositol-3-kinase (PI3K) signal transduction cascade (reviewed in Goberdhan and Wilson 2003). The PI3K signal transduction cascade regulates cell survival, motility, epithelial-mesenchymal transition, angiogenesis, growth and metabolic fluxes which are emerging as important players in oncogenesis (DeBerardinis et al. 2008). Loss of expression of *PTEN*, secondary to loss of *TP53* expression, could be involved in *BRCA1* associated oncogenesis, as described above. Other functions such as cell migration and stem-cell self renewal have also been described (Chow and Baker 2006). Recently described additional functions of PTEN

include the maintenance of chromosome integrity (Shen et al. 2007) and regulation of phospholipase C and D (Alvarez-Breckenridge et al. 2007). It was also recently discovered that regulation of PTEN activity through degradation or nuclear targeting is tightly regulated by its level of ubiquitination (Trotman et al. 2007; Wang et al. 2007b).

An important recent finding is that the loss of *PTEN* expression (or activating mutations in *PIK3CA* which encodes an activator of the PI3K signal transduction cascade) plays a major role in trastuzumab resistance (Berns et al. 2007). *PTEN* loss sensitizes tumors to the inhibition of mammalian target of rapamycin (mTOR) (Mills et al. 2001; Neshat et al. 2001; Podsypanina et al. 2001). It was also shown that rapamycin inhibits tumor progression in mouse model of HER2-positive breast cancer (Mosley et al. 2007) and clinical trials with mTOR inhibitors are showing promise for breast cancer (Gligorov et al. 2007). Inhibition of mTOR is also a mechanism of action of metformin, which inhibits growth of breast cancer cells (Dowling et al. 2007).

STK11

Another gene conferring increased risk of breast cancer is *STK11* (*LKB1*), encoding a serine/threonine kinase. *STK11* is mutated in the autosomal dominant condition Peutz–Jeghers syndrome, characterized by perioral pigmentation and hamartomatous polyposis (Hemminki et al. 1998). Patients with Peutz–Jeghers syndrome have around a 30–50% risk of developing breast cancer by age 70 (Giardiello et al. 2000; Hearle et al. 2006; Lim et al. 2004). Like other tumor suppressors (*TSC1*, *TSC2*, *PTEN* and *NF1*), *STK11* exerts its effect in part through inhibition of the mTOR pathway (Wullschleger et al. 2006). As in the case of *PTEN*, rapamycin could also be a potential therapeutic agent for patients with Peutz–Jeghers syndrome (Katajisto et al. 2007).

CDH1

Another autosomal dominant cancer syndrome, familial diffuse gastric cancer, predisposes affected women to lobular breast cancer. It is caused by mutations in *CDH1*, encoding E-cadherin, which is important for cell-to-cell adhesion (Becker et al. 1994). However, in individuals with lobular breast cancer and a family history of breast cancer but not gastric cancer, mutations in *CDH1* are found at a low frequency (Masciari et al. 2007). Upregulation of E-cadherin by various drugs (Bocca et al. 2007; Gapter et al. 2008; Wang et al. 2008) might be beneficial for breast cancer treatment as it can act as an invasion suppressor (Frixen et al. 1991).

ATM

Ataxia-telangiectasia is an autosomal recessive disorder causing cerebellar ataxia, progressive neurological deterioration, oculocutaneous telangiectasia, sensitivity to radiation and an increased risk of cancer. It is caused by biallelic mutations in the *ATM* gene (Savitsky et al. 1995), which encodes a checkpoint kinase which phosphorylates p53 and BRCA1. Female heterozygotes for mutations in *ATM* do not have the ataxia-telangiectasia phenotype, but have an increased susceptibility to breast cancer, with a relative risk of approximately twofold (Renwick et al. 2006; Thompson et al. 2005). Activation of ATM is being proposed as a new therapeutic avenue in oncology (Brew et al. 2006; Krishnan et al. 2007).

CHEK2

The *CHEK2* gene codes for a serine threonine kinase, involved in cell-cycle control and DNA repair, that is activated by *ATM* in response to double-strand DNA breaks (Matsuoka et al. 1998). CHEK2 phosphorylates BRCA1 and possibly influences its role in DNA repair (Lee et al. 2000; Schneider et al. 2004). The *CHEK2* mutation 1100delC has been associated with a twofold to threefold increase in breast cancer risk (CHEK2 Breast Cancer Case-Control Consortium 2004; Weischer et al. 2007). Other *CHEK2* mutations have also been associated with breast cancer susceptibility (Laitman et al. 2007; Shaag et al. 2005; Walsh et al. 2006). If selective inhibition of certain CHEK2 functions can be achieved, this strategy could be used in chemoprevention interventions (reduction of normal-cell apoptosis in cancer chemotherapy), as is being studied for p53 using pifithrin-alpha (reviewed in Zhou and Bartek 2004).

NBS1 and *RAD50*

Data also suggest that the gene involved in Nijmegen breakage syndrome (*NBS1*), another DNA repair defect, and the gene *RAD50* (part of the MRN complex, composed of MRE11, RAD50 and NBS1), specifically the *RAD50* 687delT mutation which is only present in the Finnish population, may confer an increased susceptibility to breast cancer (Bogdanova et al. 2008; Heikkinen et al. 2006). The MRN complex, upstream of ATM, is involved in recognition and repair of DNA double-strand breaks (Lavin 2007). However, a subsequent study where 435 UK and 46 Finnish familial breast cancer patients were sequenced for *RAD50* mutations and 544 Finnish familial breast cases were genotyped for 687delT (Tommiska et al. 2006) found

Table 1 High and moderate penetrance breast cancer susceptibility genes

Gene	Syndrome associated with gene	Breast cancer risk, relative risk (RR), or odds ratio (OR) (95% CI)	Mutation frequency in non-founder populations	Strategies for therapeutic targeting
BRCA1	Hereditary breast and ovarian cancer	Cumulative risk by 70 years is 65% (51–75%) (Antoniou et al. 2003)	≈1/400 (≈5% of unselected breast cancer patients)	PARP-1/2 inhibitors, to target *BRCA1/2* deficient tumors which have already impaired DSB DNA repair (Bryant et al. 2005; Farmer et al. 2005)
BRCA2		Cumulative risk by 70 years is 45% (33–54%) (Antoniou et al. 2003)		
TP53	Li–Fraumeni syndrome	RR 18.1 (8.6–33.2) between 20 and 44 years (Garber et al. 1991)	<1/10,000 (<0.25% of unselected breast cancer patients) (Borresen et al. 1992; Sidransky et al. 1992)	Restoration of *TP53* expression (Friedman et al. 2007; Kim et al. 2007b)
PTEN	Cowden syndrome	Cumulative lifetime risk is 25–50% (Longy and Lacombe 1996; Starink et al. 1986)	<1/10,000	mTOR inhibition (Gligorov et al. 2007; Mosley et al. 2007)
STK11	Peutz–Jeghers syndrome	Cumulative risk by 70 years is 30–50% (Giardiello et al. 2000; Hearle et al. 2006; Lim et al. 2004)	<1/10,000	mTOR inhibition (Katajisto et al. 2007)
CDH1	Familial diffuse gastric cancer	RR 6.6 (5.9–7.3) (Pharoah et al. 2001)	<1/10,000	Up-regulation of E-Cadherin (encoded by *CDH1*) might be beneficial for cancer treatment (Bocca et al. 2007; Gapter et al. 2008; Wang et al. 2008)
ATM	Ataxia-telangiectasia	RR 2.37 (1.51–3.78) (Renwick et al. 2006)	1/33–333 (FitzGerald et al. 1997; Swift et al. 1986; Thompson et al. 2005)	Activation of ATM (Brew et al. 2006; Krishnan et al. 2007)
CHEK2		OR 2.6 (1.3–5.4) for 1100delC mutation (Meijers-Heijboer et al. 2002)	1/100–200 in certain populations (Mehenni et al. 2006; Vahteristo et al. 2002; Weischer et al. 2007)	Selective inhibition could be used in chemoprevention (Zhou and Bartek 2004)
NBS1	Nijmegen Breakage syndrome	OR 3.1 (1.4–7.0) in Russian population; OR 9.7 (1.3–73.2) in Byelorussian population (Steffen et al. 2006), for 657del5 mutation	Probably rare in most other populations	
RAD50		OR 4.3 (1.5–12.5) for 687delT in Finnish (Heikkinen et al. 2006)	Not observed in other populations	
BRIP1	Fanconi anemia	RR 2.0 (1.2–3.2) (Seal et al. 2006)	<1/1,000	In cells deficient for the FA pathway, inhibition of ATM results in cell death (Garcia and Benitez 2008; Kennedy et al. 2007)
PALB2		RR 2.3 (1.4–3.9) (Rahman et al. 2007)	<1/1,000	

only one novel truncating *RAD50* mutation in one UK family and did not find a significant association with *RAD50* 687delT and breast cancer in their Finnish cohort. The *NBS1* 657del5 mutation has been studied in various populations (Buslov et al. 2005; Carlomagno et al. 1999), but has only been shown to be significantly associated with breast cancer in Polish and Byelorussian populations (Bogdanova et al. 2008; Steffen et al. 2006).

BRIP1 and *PALB2*

Another DNA repair defect, FA, is related to breast cancer. In particular, three genes (*BRCA2*, *BRIP1* and *PALB2*) result in FA when both alleles are inactivated and lead to increased risk for breast cancer in monoallelic mutation carriers. Recent reviews describe the link between the FA and the BRCA networks (Wang 2007). The relative risks conferred by *BRIP1* and *PALB2* mutations are approximately two (95% CI 1.2–3.2) and 2.3 (95% CI 1.4–3.9), respectively (Rahman et al. 2007; Seal et al. 2006). It remains puzzling why these particular FA genes are associated with an increased susceptibility to breast cancer, while other known FA genes seem not to be (Berwick et al. 2007; Seal et al. 2003). The FA proteins linked to breast cancer susceptibility appear to have different functions in the FA–BRCA pathway (Patel 2007), as PALB2 is involved in homologuous recombination (like BRCA2), but BRIP1 is not, although it does interact with BRCA1. The components of the FA network could eventually become the targets of novel anti-cancer agents (Garcia and Benitez 2008). For example, in cells deficient for the FA pathway, inhibition of ATM results in cell death (Kennedy et al. 2007).

Modifier genes and low penetrance genes

Breast cancer risks vary widely amongst *BRCA1/2* mutation carriers (see Table 1). Indeed, in a recent study by Begg et al. (2008), it was demonstrated that a younger age of onset of breast cancer and the occurrence of contralateral breast cancer were both independently associated with a higher risk of breast cancer in family relatives of *BRCA1/2* mutation carriers. The 135G→C polymorphism in the 5′ untranslated region of the gene coding for the BRCA1/2 interacting protein RAD51 affects splicing of this gene and increases the risk of breast cancer in *BRCA2* mutation carriers (Antoniou et al. 2007). Microarray studies in irradiated lymphoblastoid cell lines from patients with or without *BRCA1/BRCA2* mutations have identified novel potential modifier genes (Walker et al. 2007). It will be interesting to see if these novel potential modifier genes associate with increased breast cancer risk in larger international studies.

Modifier genes could independently act as low penetrance genes for breast cancer susceptibility and, in the past two years, numerous genome-wide association studies have looked at breast cancer susceptibility, and have identified new loci such as *FGFR2* (see Table 2 and Antoniou et al. 2008; Easton et al. 2007; Ellis et al. 2006; Gold et al. 2008; Huijts et al. 2007; Hunter et al. 2007; Murabito et al. 2007; Stacey et al. 2007, 2008). Other individuals looked at a few single nucleotide polymorphisms (SNPs) in large cohorts (Cox et al. 2007a, b). *FGFR2* encodes a receptor tyrosine kinase and is involved in tumorigenesis in various models such as prostate and urothelial cancer (Grose and Dickson 2005). Farnesyl transferase inhibitors, which act downstream of FGFR2 on Ras signaling, have shown promise in clinical trials (Gligorov et al. 2007). These findings are important for the understanding of the pathophysiology of

Table 2 Low penetrance breast cancer susceptibility genes and loci

Gene or locus	Per allele odds ratio (95% CI)	Minor allele frequency in Northern Europeans	References
FGFR2	1.26 (1.23–1.30)	0.38	Easton et al. (2007)
TOX3 (*TNRC9*)	1.14 (1.09–1.20)	0.46	
MAP3K1	1.13 (1.09–1.18)	0.28	
LSP1	1.06 (1.02–1.11)	0.3	
Locus on 8q	1.06 (1.01–1.11)	0.4	
Locus on 2q35	1.11 (1.03–1.20)	0.11–0.52 in various populations	Stacey et al. (2007)
Locus on 16q12	1.27 (1.19–1.36)	0.30–0.54 in various populations	
Loci on 5p12	1.19 (1.13–1.26), higher for ER-positive tumors	0.20–0.31 in various populations	Stacey et al. (2008)
Locus on 6q22.33	1.41 (1.25–1.59)	0.21 in Ashkenazi Jews	Gold et al. (2008)
TGFB1	1.07 (1.02–1.13)	0.68	Cox et al. (2007a)
CASP8 (protective)	0.89 (0.85–0.94)	0.13	

Genes describe the region where SNPs have been associated with breast cancer risk, and risks refer to specific SNPs (see references for details)

breast cancer, but at present have limited clinical impact, since each locus confers no more than a per allele odds ratio of 1.4 for breast cancer. It should be noted that these risks may be additive or multiplicative, and further large multicenter studies will be important if the eventual goal is to use these data in novel risk prediction models. Network modeling has permitted the association of *HMMR*, encoding a hyaluronan-mediated motility receptor which is involved in centrosome function in conjunction with BRCA1, with breast cancer susceptibility (Pujana et al. 2007). In addition, the study of microRNAs and their link with the p53 network might lead to the identification of new breast cancer susceptibility genes (He et al. 2007). Powerful molecular approaches are permitting the elucidation of the spectrum of somatic mutations in breast cancers, leading to a better understanding of breast cancer pathophysiology and potentially leading to new therapeutic avenues in the future (Greenman et al. 2007; Sjoblom et al. 2006; Wood et al. 2007).

Conclusion

Novel technologies for the large scale detailed analysis of the genome are permitting a better understanding of oncogenesis and are unraveling new cancer susceptibility loci. At the same time, as we decipher the pathways leading to cancer formation in hereditary breast cancer, and gain more in-depth information about stem cell regulation, novel therapeutic strategies are emerging. It is hoped that that by using a combination of these approaches, further progress will be made in making prevention and treatment tailored to hereditary breast cancer a reality in the near future.

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