Review Article

Hereditary Breast Cancer: The Era of New Susceptibility Genes

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Breast cancer is the most common malignancy among females. 5%–10% of breast cancer cases are hereditary and are caused by pathogenic mutations in the considered reference \( BRCA1 \) and \( BRCA2 \) genes. As sequencing technologies evolve, more susceptible genes have been discovered and \( BRCA1 \) and \( BRCA2 \) predisposition seems to be only a part of the story. These new findings include rare germline mutations in other high penetrant genes, the most important of which include \( TP53 \) mutations in Li-Fraumeni syndrome, \( STK11 \) mutations in Peutz-Jeghers syndrome, and \( PTEN \) mutations in Cowden syndrome. Furthermore, more frequent, but less penetrant, mutations have been identified in families with breast cancer clustering, in moderate or low penetrant genes, such as \( CHEK2 \), \( ATM \), \( PALB2 \), and \( BRIP1 \). This paper will summarize all current data on new findings in breast cancer susceptibility genes.

1. Introduction

Breast cancer is a disease in which breast cells become abnormal and multiply to form a malignant tumor. Breast cancer is the most common form of cancer and the second most common cause of death from a neoplastic disease affecting women. One in 8 women will develop breast cancer in her lifetime in the developed world [1, 2]. There are a number of recognized risk factors for breast cancer development including hormonal, reproductive, and menstrual history, age, lack of exercise, alcohol, radiation, benign breast disease, and obesity [3]. Nevertheless, the key factor to breast cancer development is the early onset of disease. Individual risk increases proportionally with affected relatives with breast cancer and early age of onset [2]. Although approximately 10%–30% of breast cancer cases are attributed to hereditary factors, only 5%–10% of breast cancer cases are identified with a strong inherited component, while only a small fraction of these cases (4%-5%) is explained by mutations in high penetrant genes transmitted in an autosomal dominant manner [4–7].

\( BRCA1 \) and \( BRCA2 \) genes are the most commonly mutated genes, but additional genes associated with hereditary breast cancer are emerging [8]. New advances in genomic technologies have led to parallel testing of multiple genes. Customized next generation sequencing panels are now providing the simultaneous analysis of breast cancer predisposition genes, from high- to intermediate-penetrant genes. Nonetheless, some of these genes have also been associated with increased risk of other cancers, such as ovarian, pancreatic, and colorectal cancer.

2. Patient Eligibility

The implementation of hereditary multigene panel testing arises many issues, such as which are the criteria that patients have to meet in order to undergo the test and the patient clinical management. The utilization of the test must be in compliance with the recommendations for genetic testing identified in the ASCO policy [9].

\( BRCA1 \) and \( BRCA2 \) negative patients with a personal or family history of hereditary cancer can be eligible for customized gene panel testing. Criteria have been amended from the proposed National Comprehensive Cancer Network (NCCN) guidelines and are summarized in Table 1.
Table 1: Criteria of target population for genetic test on customized gene panel modified from (http://www.nccn.org/).

| Individual with breast/ovarian cancer personal history and one of the following: |
|---|
| (i) breast and/or ovarian or pancreatic cancer in at least two blood relatives; |
| (ii) multiple primary breast cancers or bilateral breast cancer, first diagnosed before the age of 50 years; |
| (iii) premenopausal triple negative breast cancer diagnosed at a young age (<45 years); |
| (iv) male breast cancer in a blood relative; |
| (v) ethnicities with high BRCA mutation frequency, such as Ashkenazi Jews, should be tested, even in the absence of family history. |

3. Penetrance

Cancer predisposing genes can be categorized according to their relative risk of a particular type of cancer. High-penetrant genes are associated with a cancer relative risk higher than 5. Low-penetrant genes are presented with relative risk from 1.5 to 5. All genes described, along with their chromosomal position and the phenotypic features, are summarized in Table 2.

3.1. High-Penetrant Genes

3.1.1. BRCA1. BRCA1 encodes a nuclear phosphoprotein, which acts as a tumour suppressor gene through maintaining genomic stability [4]. The encoded protein combines with other tumour suppressors, DNA damage sensors, and signal transducers to form a large multisubunit protein complex, known as the BRCA1-associated genome surveillance complex [10].

BRCA1 inherited mutations predispose to high risk of breast and ovarian cancers. Lifetime risks of breast and ovarian cancer, are as high as 80% and 40%, respectively, among women carrying BRCA1 mutations, while they are characterized by elevated cancer risk at younger ages [11, 12]. While mutations are found throughout the gene’s coding region, extensive population analyses have led to the identification of founder mutations [13–16]. BRCA1-related cancers have distinct pathological features and are generally characterized by the lack of expression of human epidermal growth factor 2, estrogen, and progesterone receptors (triple negative breast cancer) [17].

The recent therapeutic approaches towards BRCA1 carcinomas have increased the clinical utility of BRCA1 genetic analysis. Inhibitors of the poly-ADP ribose polymerase (PARP) inhibitors can provide an alternative route in treatment since they can effectively kill BRCA1-deficient cells [18, 19].

3.1.2. BRCA2. BRCA2 gene is involved in the maintenance of genomic stability and more specifically, the homologous recombination (HR) pathway which repairs double-strand DNA breaks.

Male BRCA2 mutation carriers confer a lifetime risk of prostate, breast, and pancreatic cancers around 20%, 6%, and 3%, respectively. Female BRCA2 mutation carriers face a lifetime risk around 26%–84% for breast cancer and 20% for ovarian cancer [20–22].

BRCA2 is a large gene comprising of 27 exons and mutations can occur throughout the gene. The majority of mutations are frameshifts, but there are a number of missense mutations of which the pathogenicity is usually unclear (variants of unclassified significance-VUS). BRCA2-related tumours usually express estrogen and progesterone receptors and tend to have similar features to sporadic breast cancers, unlike BRCA1-related cancers [23–25].

According to the 2007 ACS guidelines, individuals carrying pathogenic BRCA mutations should undergo a particular surveillance protocol. Annual breast cancer imaging by mammography and/or magnetic resonance imaging (MRI), which is generally a more sensitive detection method, is recommended from the age of 30 [26]. Prophylactic surgeries that include bilateral mastectomy and salpingo-oophorectomy can significantly reduce mortality in these patients [27, 28]. Chemoprophylaxis, such as tamoxifen administration, can also be an alternative route in hormone-dependent tumours [29].

A major limitation of BRCA1 and BRCA2 genetic testing is the number of inconclusive results due to variants of unknown significance (VUSs). VUSs are mainly missense and splice site mutations or can be even silent variants.

The interpretation of such variations can be difficult for physicians and problematic for individuals. The approach towards the evaluation of a VUS variant can be multifactorial, involving the in silico analysis, where specified software is used to predict the phylogenetic conservation and the protein modification caused. Additionally, segregation analysis of the variant with the disease is the main clarification for the pathogenicity of the variant. VUSs with clear data towards pathogenicity require special attention and specialized prevention strategies.

Splicing is an important mechanism during which accurate removal of introns is taking place in pre-mRNA molecules. Apart from the classical splice site sequences, exonic splice enhancers (ESEs) seem to be crucial for correct splicing. ESEs are short (6–8 nucleotides long) exonic motifs that serve as binding sites for specific serine/arginine-rich proteins [30].

Disruption of ESEs sequences, which can occur in the case of missense mutations or even silent polymorphisms, can result in exon skipping and, therefore, in the production of an alternate, possibly not being fully functional, gene product. Four ESEs, responsive to serine/arginine-rich proteins (SF2/ASF, SC35, SRp40, and SRp55), have been identified in the mammalian cell [31]. ESE motifs, which are scattered throughout the genome, play an important role in exon recognition. A human exon can contain several such motifs, some of which may not be functional [32]. The disruption of these ESEs, which can be caused by synonymous or nonsynonymous genetic variants, can cause
Table 2: Breast cancer susceptibility genes.

| Syndrome | Gene or locus (chromosomal location) | Neoplasm | Lifetime risk |
|----------|--------------------------------------|----------|--------------|
| Hereditary breast/ovarian cancer syndrome | BRCA1 (17q21-22) | Female breast, ovarian cancer | 40–80% |
|         | BRCA2 (13q12-13) | Male and female breast, ovarian, prostate, and pancreatic cancer | 20–85% |
| Li-Fraumeni syndrome | TP53 (17p13.1) | Breast cancer, sarcomas, leukemia, brain tumours, adrenocortical carcinoma, lung cancers | 56–90% |
| Cowden syndrome | PTEN (10q23.3) | Breast, thyroid, endometrial cancer | 25–50% |
|         | Other: benign hamartomas, macrocephaly |          |              |
| Peutz-Jeghers syndrome | STK11 (19p13.3) | Breast, ovarian, cervical, uterine, testicular, small bowel, and colon carcinoma | 32–54% |
|         | Other: Hamartomatous polyps of the small intestine, mucocutaneous pigmentation |          |              |
| Hereditary gastric cancer | CDH1 (16q22.1) | Hereditary diffuse gastric, lobular breast, colorectal cancer | 60% |

**Moderate-penetration mutations**

| Syndrome       | Gene or locus (chromosomal location) | Neoplasm                     | Lifetime risk |
|----------------|--------------------------------------|------------------------------|--------------|
| ATM-related    | ATM (11q22.3)                        | Breast and ovarian cancers   | 15–20%       |
| CHEK2-related  | CHEK2 (22q12.1)                      | Breast, colorectal, ovarian, bladder cancers | 25–37% |
| PALB2-related  | PALB2 (16p12.1)                      | Breast, pancreatic, ovarian cancer, male breast cancers | 20–40% |
| Moderate risk  | BARD1 (2q34-q35), BRIPI (17q22–q24), MREIJA (11q21), NBN (8q21), RAD50 (5q31), RAD51C (17q25.1), XRCC2 (7q36.1), RAD51D (17q11), ABRAXAS (4q21.23) | Breast and ovarian cancers | variable |
| breast/ovarian cancer |                              |                              |              |

the failure of the serine/arginine-rich proteins to bind to the ESE motifs and cause exon skipping. ESEs can be initially assessed by available in silico tools [33], but can only be confirmed experimentally by RT-PCR. Furthermore, in silico data should be treated with caution, since a number of studies have failed to confirm experimentally the initial findings [34, 35].

A major limitation of BRCA1 and BRCA2 genetic testing is the number of inconclusive results due to unclassified sequence variants. A fraction of variants of unclassified significance (VUS) can be determined deleterious, if they lie within ESE motifs and can, therefore, explain the genetic factor in families with family history [35–37].

In many cases, the mutated ESEs might not lead to fully functional transcripts, or even the transcripts produced might be underrepresented, so their actual contribution to pathogenicity can be unclear [38].

3.1.3. TP53. TP53 is a tumour suppressor gene that causes Li-Fraumeni syndrome and affects adults and children. This highly penetrant gene predisposes for a wide spectrum of tumours, including sarcomas, adrenocortical carcinomas, brain cancer, and very early onset breast cancer [39, 40]. Most cancers are manifested from birth through late adulthood [39]. TP53 mutation carriers face a lifetime cancer risk that exceeds 90% [40–42], while the clinical benefit of extensive surveillance of these individuals remains uncertain [43].

Patients with Li-Fraumeni syndrome have an abnormal response to low-dose radiation that should be avoided as a therapeutic approach because of the increased secondary tumour risk [44].

Breast cancer is the most frequent malignancy among female TP53 mutation carriers, with approximately 5% of these cases being diagnosed before the age of 30 [39]. While Li-Fraumeni syndrome accounts for a small fraction of breast cancer cases (~0.1%), TP53 mutation carriers have from an 18- to 60-fold increased risk for early onset breast cancer (diagnosed before the age of 45) when compared to the general population [45–48].

3.1.4. PTEN. Germline mutations in the tumour suppressor PTEN gene are the cause of Cowden syndrome. Cowden syndrome is an autosomal dominant disorder characterized by multiple hamartomas with a high risk of benign and malignant tumours of the thyroid, breast, and endometrium. Mucocutaneous lesions, thyroid abnormalities, fibrocystic disease, multiple uterine leiomyoma, and macrocephaly can also be seen. Affected individuals have a lifetime risk up to 50% for breast cancer, 10% for thyroid cancer, and 5–10% for endometrial cancer. Over 90% of individuals with Cowden syndrome demonstrate germline PTEN mutations.
3.1.5. STK11. Germline mutations in the serine/threonine kinase gene (STK11/LKB1), a tumour-suppressor gene important for mediation of apoptosis and cell cycle regulation, cause Peutz-Jeghers syndrome. Peutz-Jeghers syndrome is an autosomal dominantly inherited syndrome characterized by mucocutaneous pigmentation and hamartomatous polyposis [54]. In addition to an elevated risk of gastrointestinal cancers, an increased risk of cancers at other sites, such as breast [55], small bowel, pancreas, ovary, uterus, stomach, cervix, lung, and testis, has been described [56–61].

STK11 mutation carriers confer a high cumulative risk of any cancer (up to 85%) [62]. In terms of surveillance, Peutz-Jeghers patients should undergo gastrointestinal endoscopy starting from early teens and annual breast MRI starting, at the age of 25–30 [56].

3.1.6. CDH1. The E-cadherin gene (CDH1) is a calcium-dependent cell-cell adhesion molecule expressed in junctions between epithelial cells [63]. CDH1 germline mutations have been associated with hereditary diffuse gastric carcinoma, often with signet ring cell histology. Patients with germline CDH1 mutations carry an increased risk of lobular breast cancer and colorectal cancer [64, 65]. The cumulative risk of gastric cancer in male and female mutation carriers is approximately 67% and 83%, respectively, with a mean age of diagnosis of 40 years [64]. Moreover, women carriers face a 40%–54% lifetime risk of developing lobular breast cancer [66, 67].

Mutations in CDH1 are the genetic cause of up to 48% of the diffusion gastric cancer kindreds [68], while in contrast to other cancer predisposition syndromes, splice-site and missense mutations are common, suggesting that even reduced E-cadherin expression can be deleterious [69].

3.2. Moderate Penetrant Genes

3.2.1. CHEK2. Checkpoint kinase 2 (CHEK2, Chk2), the protein product of the CHEK2 gene, is a serine threonine kinase that is activated in response to DNA damage and plays an important role in transducing the DNA damage signal to downstream repair proteins [70]. CHEK2 protein structure shows three characteristic domains: an N-terminal SQ/TQ cluster domain, a forkhead-associated (FHA) domain, and a serine/threonine kinase domain.

Certain mutations in CHEK2 are reproducibly associated with increased risks of female breast cancer [71]. A particular germline mutation, CHEK2 c.1100delC, has been shown to increase breast cancer risk 2-fold [72]. While it seems to be quite frequent (~3%) in northern European populations (Finish, Dutch) [42, 73], it is rather rare (~0.5%) in southern European populations [74]. Carriers of the CHEK2 c.1100delC mutation have an increased risk of bilateral breast cancer and male breast cancer [75]. A recent study described families with homozygous CHEK2 c.1100delC mutations. Women homozygous for the mutation have a sixfold higher risk of breast cancer when compared to heterozygotes [76].

Another CHEK2 variant, CHEK2 p.I157T, which is located in exon 3 of the gene, is associated with lower breast cancer risk (~1.5) [74, 77]. There is also an increased risk of other malignancies within families carrying CHEK2 mutations including colon, prostate, kidney, and thyroid cancer [78].

Remarkably, many identified rare variants include missense genetic alterations whose functional consequences are rather difficult to assess. In vivo DNA damage assays [79] that can determine their activity can accompany segregation and in silico analyses to determine the pathogenicity of these variants.

3.2.2. PALB2. PALB2, also known as FANCN, is a Fanconi anaemia gene that encodes for a protein that interacts with BRCA2 during homologous recombination and double-strand break repair. It confers breast and ovarian cancers susceptibility [80]. Casadei et al. sequenced PALB2 in high-risk breast cancer families, identifying PALB2 mutations in 33 of 972 families (3.4%) [81]. It is worthwhile to mention that 18 of these 33 families (55%) had a family member with ovarian cancer, who was confirmed to carry the familial PALB2 mutation. Notably, these families had a similar phenotype to BRCA2, with an increased incidence of pancreatic as well as breast and ovarian cancers. Familial pancreatic and/or breast cancer due to PALB2 mutations is inherited in an autosomal dominant pattern, while Fanconi anaemia is an autosomal recessive condition [82, 83].

In another study, rare germline mutations in PALB2 were identified among patients with breast cancer. The first-degree female relatives of these carriers demonstrated significantly higher incidence of breast cancer than relatives of noncarriers, indicating that pathogenic PALB2 mutations confer an estimated 5.3-fold increase in risk. Moreover, the overrepresentation of mutations in the cohort of women with contralateral breast cancer is important to the clinical management of women carrying PALB2 mutation as it implies a significant risk of developing a second primary breast neoplasm [84]. Dansonka-Mieszkowska et al. identified a Polish PALB2 founder mutation in 0.6% of individuals with ovarian carcinoma but only in 0.08% of healthy controls. This mutation was further studied on groups of sporadic and familial breast cancer patients and healthy controls and was estimated that it can increase the risk of familial breast cancer [85].

Recently, PALB2 was reported to be a new pancreatic cancer susceptibility gene as truncating mutations were identified in American patients with familial pancreatic cancer. Mutations in PALB2 were also detected in European families and, interestingly, each of these had also a history of breast cancer [83]. PALB2 mutation carriers of familial pancreatic cancer have to be considered as high-risk individuals with at least 10- to 32-fold increased risk depending on the number of affected family members [86]. Such high-risk family members should be offered screening programs for the early detection and potentially curative operative treatment.
of pancreatic cancer [86], as it has been shown that it can be effective [87, 88].

3.2.3. ATM. The protein deliverable of the ATM gene is a PI3 K-related protein kinase [89]. ATM has multiple complex functions, including a central role in the repair of DNA double-strand breaks, a pathway that includes TP53, BRCA1, and CHEK2 proteins [90].

It is proposed that ATM mutation heterozygotes have a 2-fold higher breast cancer risk compared to the general population. This risk is elevated 5-fold in women under the age of 50 [91]. The gene’s penetrance is approximately 15%, while accurate prediction of who of these mutation carriers will develop breast cancer is not feasible.

It is difficult to assess the clinical utility of genetic testing for ATM at present. However, these ATM mutation carriers may merit different approaches to treatment for breast cancer due to their increased radiosensitivity or efficacy of specific chemotherapies associated with ATM mutations [92].

Homozygous or compound heterozygous ATM mutations cause ataxia telangiectasia, which is characterized by progressive cerebellar ataxia, oculomotor apraxia, immunodeficiency, and general increased risk of malignancies [93]. Lymphoid cancers predominate in childhood, and epithelial cancers, including breast cancer, are seen in adults [94].

3.2.4. BRIPI. BRIPI encodes a protein that was identified as a binding partner of BRCA1 and was investigated as a breast cancer predisposing gene. In 2006, truncating mutations were identified in breast cancer families [95], while the relative breast cancer risk, although there are reports of higher risks in some families, was estimated around 2. BRIPI germline mutations also confer an increased risk of ovarian cancer [96].

Recently, three BRIPI missense mutations have been identified in high-risk Jewish women, who have been tested negative for mutations in BRCA1 and BRCA2 genes, indicating that BRIPI mutations can contribute to breast cancer susceptibility in Jewish high-risk families [97]. Moreover, rare BRIPI mutations have been identified in Spanish and Icelandic ovarian kindreds, indicating that BRIPI behaves like a classical tumor suppressor gene in ovarian cancer [96]. Biallelic mutations of BRIPI cause Fanconi anemia complementation group J, a phenotype different to that caused by biallelic mutations in BRCA2, resulting in much lower rate of childhood solid tumours [2].

3.2.5. RAD51C. RAD51C is an essential gene in homologous recombination, while biallelic missense mutations in the gene cause a Fanconi anemia-like phenotype [98]. RAD51C was investigated as a possible breast and ovarian cancer susceptibility gene in 1100 high-risk families, who were previously tested negative for BRCA1 and BRCA2 mutations. Germline mutations were identified in 1.3% of families with both breast and ovarian cancers, with a mean age of diagnosis of 53 and 60 years, respectively. No pathogenic mutations were identified in families with breast cancer cases only [99]. In a subsequent, but larger, Finnish study, RAD51C mutations were identified in ovarian cancer families only [100], while in a recent Spanish study, identified RAD51C mutations in 1.3% of breast and ovarian cancer families, with mutations in families with breast cancer cases only, were rare [101]. The inclusion of RAD51C gene in routine clinical testing is a controversial matter, mainly due to its low incidence or lack of mutation identification in particular populations.

3.2.6. XRCC2. XRCC2 is a RAD51 paralog and plays an important role in the homologous recombination pathway that repairs double-strand breaks. Failure of these processes will lead to mutations, and as a result XRCC2 might be responsible for cancer predisposition and especially a breast cancer susceptibility gene [102, 103].

An initial exome-sequencing study identified two germline XRCC2 mutations, while a larger-scale genetic analysis revealed ten rare XRCC2 variants in breast cancer families, some of which were definitely pathogenic [104].

Another study suggested that some XRCC2 coding SNPs can influence breast cancer risk and survival. Particularly, the specific XRCC2, p.R188H missense mutation was associated with poor survival prognosis [104].

On the contrary, Hilbers et al. failed to identify unique variants in familial breast cancer patients only, questioning the cancer susceptibility of XRCC2 gene. The only predicted deleterious variant was detected in a control individual, while missense variants were evenly distributed in patients and controls. Although a small relative risk can be attributed to XRCC2 mutations, the actual association needs further evaluation [102, 105].

Since XRCC2 gene is a key mediator in homologous recombination pathway, XRCC2 mutation carriers may benefit from specific targeted therapies such as PARP-inhibitors, but the actual influence of XRCC2 mutations on breast cancer susceptibility requires further investigation.

3.2.7. NBS1, RAD50, and MRE11. The MRE11-RAD50-NBS1 (MRN) protein complex plays an important role in sensing and early processing of double-strand breaks, thus maintaining genomic integrity [106, 107]. This protein complex integrates DNA repair with checkpoint signalling through the ATM, BRCA1, and CHEK2 proteins [106]. Based on the complex’s important role in preventing malignancies, a number of studies have screened breast and/or ovarian cancer families for germline mutations in the coding regions of the aforementioned genes. Potentially pathogenic mutations have been identified in all three genes. Specifically, MRE11 and NBS1 mutations in highly conserved amino acids that have not been identified in controls have been described in Finish high-risk families [107, 108]. In respect to RAD50, a relatively common low-risk allele was identified in patients and controls, as well as a small number of unique rare pathogenic alleles. The interesting finding is the increased genomic instability in peripheral blood T-lymphocytes drawn from these mutation carriers [106]. Analyzing breast cancer patients’ tumours can lead to the identification of MRE11 germline mutations based on the reduced or lack of expression of all three (MRN) proteins [109]. NBN mutation carriers confer elevated risks
for a numerous types of cancers, including breast cancer [8, 106, 108, 110–112], which can be estimated to a 2- to 3-fold increase [110], while family relatives display a higher rate of various forms of cancers [112, 113].

Even minor disturbances of complexes’ activity have profound effects on the genomic integrity and, thus, all three components have been implicated in recessive genetic instability disorders. More importantly, individuals carrying biallelic hypomorphic NBN mutations suffer from the Nijmegen breakage syndrome, being susceptible to several types of cancer. Approximately 40% of them will develop a malignancy before the age of 21 [110].

Germline mutations in NBS1, RAD50, and MRE11 genes, although seen in low frequencies and can be population specific, can be qualified as novel candidates for breast cancer susceptibility in a subset of non-BRCA1 and BRCA/2 families. However, their clinical impact is yet to be determined.

3.2.8. BARD1. BARD1 (BRCA1-associated RING domain) was identified initially as a protein interacting with BRCA1 in DNA double-strand break repair and apoptosis initiation. BARD1 mutations have been detected in breast, ovarian, and endometrial cancers. Initial BARD1 mutational analysis in familial and sporadic cases revealed four different germline mutations not followed by subsequent loss of heterozygosity [114]. More recent studies have been successfully identified BARD1 mutations in high-risk families [8, 115]. BARD1 mutations can confer cancer susceptibility, but larger studies are essential to confirm that.

3.2.9. ABRAXAS. ABRAXAS (also known as ABRAI, CCDC98, or FAM175A) codes a protein that is an essential component of BRCA1 holoenzyme complex as it binds to BRCA1 BRCT motifs via its phosphorylated C-terminus. ABRAXAS as well as the other members of this complex (RAP80, BRCC36, BRCC45, and MERIT40/NBA1) is involved in DNA damage checkpoints in response to double-strand breaks.

Recently, proteomic analysis revealed the binding of ABRAXAS to the BRCA1 BRCT (BRCA1 carboxyl-terminal) repeats, which are essential elements in tumour suppression. Due to the close interaction to BRCA1, ABRAXAS might be a cancer susceptibility gene and might play a role in hereditary breast and ovarian carcinoma [116].

Although there is only a small number of studies, ABRAXAS constitutes a good candidate for yet unexplained cases with strong family history. A missense alteration, p.R361Q, resulting in abnormal DNA response, was identified in 3 out of the 125 Finish, BRCA1 and BRCA2 negative, families and one out of the 991 unselected breast cancer cases studied. The missense allele segregated with the disease in the two families, while no ABRAXAS genetic alterations were identified in the healthy controls studied [117].

Therefore, based on these preliminary data, ABRAXAS can be considered as a new breast cancer susceptibility gene.

3.2.10. RAD51D. RAD51D is one of the five paralogs of RAD51 protein family. RAD51 family members are similar to bacterial RecA and Saccharomyces cerevisiae Rad51, which are known to be involved in DNA repair pathway. Its gene product complexes with other RAD51 protein members, while it is an important element in homologous recombination in the eukaryotic cells along with other gene products [118, 119].

Loss-of-function mutations in RAD51D gene seem to predispose to ovarian cancer, while there is doubtable association to breast cancer susceptibility. RAD51D pathogenic mutations are generally rare, contributing to approximately 0.5%–0.9% of breast/ovarian probands of BRCA1 and BRCA2 negative families [120, 121]. Another study successfully identified deleterious RAD51D mutations in 0.8% of unselected patients previously diagnosed with ovarian, peritoneal, or fallopian tube cancer [122]. Interestingly, there seems to be a higher prevalence of RAD51D mutations in families where there is elevated ovarian cancer burden (2 or more ovarian cancer cases) [120, 121].

The ovarian cancer relative risk for carriers of RAD51D mutations is estimated to be 6.3, while the relative risk for breast cancer is not statistically significant [120]. A single RAD51D splice mutation has been identified to have founder effect within the Finnish population [123].

PARP inhibitors can be considered as a therapeutic alternative for RAD51D mutation carriers, as RAD51D-deficient are sensitive to PARP inhibitors [120].

4. Low Penetrant Breast Cancer Loci

A number of common breast cancer susceptibility loci have been associated with a slightly increased or decreased risk of breast cancer. These can follow the polygenic model, or can act synergistically with environmental factors or lifestyle, to account for a small fraction of familial breast cancer cases.

Most of these low-susceptibility loci have been highlighted through genome wide association studies (GWAS) and initially included a number of loci. In the final breast cancer assessment risk, six SNPs showed statistically significant association: MAP3K1, FGFR2, LSP1, TNRC19, and H19 [124–128].

Moreover, a particular SNP in CASP8 was identified to confer a slightly increased susceptibility in a candidate-gene study [129, 130].

Although the actual contribution of low power, common susceptibility loci in hereditary breast cancer is debatable, the identification of such alleles can explain a subset of breast cancer cases.

5. Benefits of Genetic Testing

The knowledge of a patient’s genetic susceptibility for breast cancer can orientate appropriately clinical management. This information can provide the following options.

(i) Modify breast cancer surveillance options and age of initial screening.

(ii) Suggest specific risk-reduction measures (e.g., consider prophylactic salpingo-oophorectomy after
childbearing and/or prophylactic bilateral mastectomy, for women with increased risk for breast and/or ovarian cancer).

(iii) Clarify familial cancer risks, based on gene-specific cancer associations.

(iv) Offer treatment guidance (e.g., avoidance of radiation-based treatment methods for individuals with a TP53 mutation).

(v) Identification of other at-risk family members.

(vi) Provide customized, gene-specific, treatment options (e.g., PARP-inhibitors in BRCA1-mutation carriers).

(vii) Preimplantation diagnosis.

6. Future Perspectives

In the last few years a significant progress has been made in broadening the spectrum of cancer-related genes. The potentials of new sequencing technologies, from whole genome to exome sequencing, can accelerate the discovery of new susceptibility genes, not only for breast cancer, but also for other cancers too. Targeted capture and massively parallel sequencing of specific genes can successfully identify families at risk for developing breast and/or ovarian cancer, while it seems that this technique is now ready to be applied in a clinical setting. Knowing the genetic defect can provide the route to customized, targeted therapies with extremely beneficial outcome.

(vii) Preimplantation diagnosis.

References

[1] J. Ferlay, D. M. Parkin, and E. Steliarova-Foucher, “Estimates of cancer incidence and mortality in Europe in 2008,” European Journal of Cancer, vol. 46, no. 4, pp. 765–781, 2010.

[2] F. Laloo and D. G. Evans, “Familial breast cancer,” Clinical Genetics, vol. 82, no. 2, pp. 105–114, 2012.

[3] X. R. Yang, J. Chang-Claude, E. L. Goode et al., “Associations of breast cancer risk factors with tumor subtypes: a pooled analysis from the breast cancer association consortium studies,” Journal of the National Cancer Institute, vol. 103, no. 3, pp. 250–263, 2011.

[4] E. B. Claus, N. Risch, and W. D. Thompson, “Genetic analysis of breast cancer in the cancer and steroid hormone study,” The American Journal of Human Genetics, vol. 48, no. 2, pp. 232–242, 1991.

[5] B. Newman, M. A. Austin, M. Lee, and M. C. King, “Inheritance of human breast cancer: evidence for autosomal dominant transmission in high-risk families,” Proceedings of the National Academy of Sciences of the United States of America, vol. 85, no. 9, pp. 3044–3048, 1988.

[6] J. M. Hall, M. K. Lee, B. Newman et al., “Linkage of early-onset familial breast cancer to chromosome 17q21,” Science, vol. 250, no. 4988, pp. 1684–1689, 1990.

[7] Y. Miki, J. Swensen, D. Shattuck-Eidens et al., “A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1,” Science, vol. 266, no. 5182, pp. 66–71, 1994.

[8] T. Walsh, M. K. Lee, S. Casadei et al., “Detection of inherited mutations for breast and ovarian cancer using genomic capture and massively parallel sequencing,” Proceedings of the National Academy of Sciences of the United States of America, vol. 107, no. 28, pp. 12629–12633, 2010.

[9] C. M. Waters, A. C. Hoover, L. C. McClain, T. T. Moore, C. T. Rogers, and K. Thornton, “Current guidelines and best practice evidence for intensified/enhanced breast cancer screening in women with BRCA mutations,” Journal for Nurse Practitioners, vol. 5, no. 6, pp. 447–453, 2009.

[10] Y. Wang, D. Cortez, P. Yazdi, N. Neff, S. J. Elledge, and J. Qin, “BASC, a super complex of BRCA1-associated proteins involved in the recognition and repair of aberrant DNA structures,” Genes and Development, vol. 14, no. 8, pp. 927–939, 2000.

[11] P. L. Welch and M. C. King, “BRCA1 and BRCA2 and the genetics of breast and ovarian cancer,” Human Molecular Genetics, vol. 10, no. 7, pp. 705–713, 2001.

[12] A. Antoniou, P. D. Pharoah, S. Narod et al., “Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unsellected for family history: a combined analysis of 22 studies,” The American Journal of Human Genetics, vol. 72, no. 5, pp. 1117–1130, 2003.

[13] S. Armaou, I. Konstantopoulou, T. Anagnostopoulou et al., “Novel genomic rearrangements in the BRCA1 gene detected in greek breast/ovarian cancer patients,” European Journal of Cancer, vol. 43, no. 2, pp. 443–453, 2007.

[14] I. Konstantopoulou, T. Rampias, A. Ladopoulou et al., “Greek BRCA1 and BRCA2 mutation spectrum: two BRCA1 mutations account for half the carriers found among high-risk breast/ovarian cancer patients,” Breast Cancer Research and Treatment, vol. 107, no. 3, pp. 431–441, 2008.

[15] G. Johannesdottir, J. Gudmundsson, J. T. Bergthorsson et al., “High prevalence of the 999del5 mutation in icelandic breast and ovarian cancer patients,” Cancer Research, vol. 56, no. 16, pp. 3663–3665, 1996.

[16] B. B. Roa, A. A. Boyd, K. Volcik, and C. S. Richards, “Ashkenazi jewish population frequencies for common mutations in BRCA1 and BRCA2,” Nature Genetics, vol. 14, no. 2, pp. 185–187, 1996.

[17] F. Fostira, M. Tsitlaidou, C. Papadimitriou et al., “Prevalence of BRCA1 mutations among 403 women with triple-negative breast cancer: implications for genetic screening selection criteria: a Hellenic Cooperative Oncology Group Study,” Breast Cancer Research and Treatment, vol. 134, no. 1, pp. 353–362, 2012.

[18] H. E. Bryant, N. Schultz, H. D. Thomas et al., “Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase,” Nature, vol. 434, no. 7035, pp. 913–917, 2005.

[19] H. Farmer, H. McCabe, C. J. Lord et al., “Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy,” Nature, vol. 434, no. 7035, pp. 917–921, 2005.

[20] S. Chen et al., “Characterization of BRCA1 and BRCA2 mutations in a large United States sample,” Journal of Clinical Oncology, vol. 24, no. 6, pp. 863–871, 2006.

[21] D. Easton, “Cancer risks in BRCA2 mutation carriers: the breast cancer linkage consortium,” Journal of the National Cancer Institute, vol. 91, no. 15, pp. 1310–1316, 1999.

[22] S. Thorlacius, J. P. Struwing, P. Hartge et al., “Population-based study of risk of breast cancer in carriers of BRCA2 mutation,” The Lancet, vol. 352, no. 9137, pp. 1337–1339, 1998.
[23] S. R. Lakhani, J. Jacquemier, J. P. Sloane et al., “Multifactorial analysis of differences between sporadic breast cancers and cancers involving BRCA1 and BRCA2 mutations,” Journal of the National Cancer Institute, vol. 90, no. 15, pp. 1138–1145, 1998.

[24] W. D. Foulkes, “BRCA1 and BRCA2: chemosensitivity, treatment outcomes and prognosis,” Familial Cancer, vol. 5, no. 2, pp. 135–142, 2006.

[25] S. A. Narod and W. D. Foulkes, “BRCA1 and BRCA2: 1994 and beyond,” Nature Reviews Cancer, vol. 4, no. 9, pp. 665–674, 2004.

[26] D. Saslow et al., “American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography,” CA: a Cancer Journal for Clinicians, vol. 57, no. 2, pp. 75–89, 2007.

[27] T. R. Rebeck, T. Friebel, H. T. Lynch et al., “Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE study group,” Journal of Clinical Oncology, vol. 22, no. 6, pp. 1055–1062, 2004.

[28] N. D. Kauff, J. M. Satagopan, M. E. Robson et al., “Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation,” The New England Journal of Medicine, vol. 346, no. 21, pp. 1609–1615, 2002.

[29] M. C. King, S. Wieand, K. Hale et al., “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,” Journal of the American Medical Association, vol. 286, no. 18, pp. 2251–2256, 2001.

[30] B. R. Graveley, “Sorting out the complexity of SR protein functions,” RNA, vol. 6, no. 9, pp. 1197–1211, 2000.

[31] L. Cartegni, S. L. Chew, and A. R. Krainer, “Listening to silence and understanding nonsense: exonic mutations that affect splicing,” Nature Reviews Genetics, vol. 3, no. 4, pp. 285–298, 2002.

[32] B. J. Blencowe, “Exonic splicing enhancers: mechanism of action, diversity and role in human genetic diseases,” Trends in Biochemical Sciences, vol. 25, no. 3, pp. 106–110, 2000.

[33] L. Cartegni, J. Wang, Z. Zhu, M. Q. Zhang, and A. R. Krainer, “ESEfinder: a web resource to identify exonic splicing enhancers,” Nucleic Acids Research, vol. 31, no. 13, pp. 3568–3571, 2003.

[34] P. J. Whaley, C. A. Pettigrew, B. L. Brewer, L. C. Walker, A. B. Spurle, and M. A. Brown, “Effect of BRCA2 sequence variants predicted to disrupt exonic splice enhancers on BRCA2 transcripts,” BMC Medical Genetics, vol. 11, no. 1, article 80, 2010.

[35] M. Menéndez, J. Castellsague, M. Mirete et al., “Assessing the RNA effect of 26 DNA variants in the BRCA1 and BRCA2 genes,” Breast Cancer Research and Treatment, vol. 132, no. 3, pp. 979–992, 2012.

[36] J. D. Fackenthal and O. I. Olopade, “Breast cancer risk associated with BRCA1 and BRCA2 in diverse populations,” Nature Reviews Cancer, vol. 7, no. 12, pp. 937–948, 2007.

[37] J. D. Fackenthal, L. Cartegni, A. R. Krainer, and O. I. Olopade, “BRCA2 T2722R is a deleterious allele that causes exon skipping,” The American Journal of Human Genetics, vol. 71, no. 3, pp. 625–631, 2002.

[38] C. T. Moseley, P. E. Mullis, M. A. Prince, and J. A. Phillips, “An exonic splice enhancer mutation causes autosomal dominant GH deficiency,” Journal of Clinical Endocrinology and Metabolism, vol. 87, no. 2, pp. 847–852, 2002.

[39] J. N. Weitzel, K. D. Gonzalez, K. A. Noltner et al., “Beyond Li fraumeni syndrome: clinical characteristics of families with p53 germline mutations,” Journal of Clinical Oncology, vol. 27, no. 8, pp. 1250–1256, 2009.

[40] A. Chompret, L. Brugières, M. Ronsin et al., “P53 germline mutations in childhood cancers and cancer risk for carrier individuals,” British Journal of Cancer, vol. 82, no. 12, pp. 1932–1937, 2000.

[41] K. E. Nichols, D. Malkin, J. E. Garber, J. F. Fraumeni, and F. P. Li, “Germ-line p53 mutations predispose to a wide spectrum of early-onset cancers,” Cancer Epidemiology Biomarkers and Prevention, vol. 10, no. 2, pp. 83–87, 2001.

[42] M. Gage, D. Wattendorf, and L. R. Henry, “Translational advances regarding hereditary breast cancer syndromes,” Journal of Surgical Oncology, vol. 105, no. 5, pp. 444–451, 2012.

[43] C. R. M. Lammens, E. M. A. Bleiker, N. K. Aaronson et al., “Regular surveillance for Li-fraumeni syndrome: advice, adherence and perceived benefits,” Familial Cancer, vol. 9, no. 4, pp. 647–654, 2010.

[44] F. Laloo, J. Varley, D. Ellis et al., “Prediction of pathogenic mutations in patients with early-onset breast cancer by family history,” The Lancet, vol. 361, no. 9363, pp. 1101–1102, 2003.

[45] T. Walsh, S. Casadei, K. H. Coats et al., “Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer,” Journal of the American Medical Association, vol. 295, no. 12, pp. 1379–1388, 2006.

[46] M. Olivier, D. E. Goldgar, N. Sodha et al., “Li–Fraumeni and related syndromes: correlation between tumor type, family structure, and TP53 genotype,” Cancer Research, vol. 63, no. 20, pp. 6643–6650, 2003.

[47] J. M. Birch, J. Heighway, M. D. Teare et al., “Linkage studies in a Li-Fraumeni family with increased expression of p53 protein but no germ line mutation in p53,” British Journal of Cancer, vol. 70, no. 6, pp. 1176–1181, 1994.

[48] J. E. Garber and K. Offit, “Hereditary cancer predisposition syndromes,” Journal of Clinical Oncology, vol. 23, no. 2, pp. 276–292, 2005.

[49] C. Eng, “Will the real Cowden syndrome please stand up: revised diagnostic criteria,” Journal of Medical Genetics, vol. 37, no. 11, pp. 828–830, 2000.

[50] T. M. Starin, J. P. W. van der Veen, and F. Arwert, “The Cowden syndrome: a clinical and genetic study in 21 patients,” Clinical Genetics, vol. 29, no. 3, pp. 222–233, 1986.

[51] J. Li, C. Yen, D. Liaw et al., “PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer,” Science, vol. 275, no. 5298, pp. 1943–1947, 1997.

[52] C. Eng, “Role of PTEN, a lipid phosphatase upstream effector of protein kinase B, in epithelial thyroid carcinogenesis,” Annals of the New York Academy of Sciences, vol. 968, pp. 213–221, 2002.

[53] D. C. Allain, “Genetic counseling and testing for common hereditary breast cancer syndromes a Paper from the 2007 William Beaumont hospital symposium on molecular pathology,” Journal of Molecular Diagnostics, vol. 10, no. 5, pp. 383–395, 2008.

[54] I. P. M. Tomlinson and R. S. Houlston, “Peutz-Jeghers syndrome,” Journal of Medical Genetics, vol. 34, no. 12, pp. 1007–1011, 1997.

[55] M. G. F. van Lier, A. Wagner, E. M. H. Mathus-Vliegen, E. J. Kuipers, E. W. Steyerberg, and M. E. Van Leerdam, “High cancer risk in peutz-jeghers syndrome: a systematic review and surveillance recommendations,” American Journal of Gastroenterology, vol. 105, no. 6, pp. 1258–1265, 2010.

[56] A. D. Beggs, A. R. Latchford, H. F. A. Vasen et al., “Peutz-Jeghers syndrome: a systematic review and recommendations for management,” Gut, vol. 59, no. 7, pp. 975–986, 2010.
[57] S. B. Gruber, M. M. Entius, G. M. Petersen et al., “Pathogenesis of adenocarcinoma in Peutz-Jeghers syndrome,” Cancer Research, vol. 58, no. 23, pp. 5267–5270, 1998.

[58] W. Lim, S. Olschwang, J. J. Keller et al., “Relative frequency and morphology of cancers in STK11 mutation carriers,” Gastroenterology, vol. 126, no. 7, pp. 1788–1794, 2004.

[59] F. M. Giardiello, S. B. Welsh, and S. R. Hamilton, “Increased risk of cancer in the Peutz-Jeghers syndrome,” Gastroenterology, vol. 121, no. 6, pp. 1348–1353, 2001.

[60] N. Hearle, V. Schumacher, F. H. Menko et al., “Frequency and spectrum of cancers in the Peutz-Jeghers syndrome,” Clinical Cancer Research, vol. 12, no. 10, pp. 3209–3215, 2006.

[61] G. Graziano, B. Humar, and P. Guilford, “The role of the E-cadherin gene (CDH1) in diffuse gastric cancer susceptibility: from the laboratory to clinical practice,” Annals of Oncology, vol. 14, no. 12, pp. 1705–1713, 2003.

[62] P. D. P. Pharoah, P. Guilford, and C. Caldas, “Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary diffuse gastric cancer families,” Gastroenterology, vol. 121, no. 6, pp. 1348–1353, 2001.

[63] G. Keller, H. Vogelsang, I. Becker et al., “Diffuse type gastric and lobular breast carcinoma in a familial gastric cancer patient with an E-cadherin germline mutation,” American Journal of Pathology, vol. 155, no. 2, pp. 337–342, 1999.

[64] K. N. Kangarlaris and S. B. Gruber, “Clinical implications of founder and recurrent CDH1 mutations in hereditary diffuse gastric cancer,” Journal of the American Medical Association, vol. 297, no. 21, pp. 2360–2372, 2007.

[65] I. Kluijt et al., “Familial gastric cancer: guidelines for diagnosis, treatment and periodic surveillance,” Familial Cancer, vol. 11, no. 3, pp. 363–369, 2012.

[66] A. R. Brooks-Wilson, P. Kaurah, G. Suriano et al., “Germline E-cadherin mutations in hereditary diffuse gastric cancer: assessment of 42 new families and review of genetic screening criteria,” Journal of Medical Genetics, vol. 41, no. 7, pp. 508–517, 2004.

[67] G. Suriano, M. J. Oliveira, D. Huntsman et al., “E-cadherin germline missense mutations and cell phenotype: evidence for the independence of cell invasion on the motile capabilities of the cells,” Human Molecular Genetics, vol. 12, no. 22, pp. 3007–3016, 2003.

[68] T. H. Stracker, T. Usui, and J. H. J. Petrini, “Taking the time to make important decisions: the checkpoint effector kinases Chk1 and Chk2 and the DNA damage response,” DNA Repair, vol. 8, no. 9, pp. 1047–1054, 2009.

[69] M. Weischer, S. E. Bojesen, C. Ellervik, A. Tybjørg-Hansen, and B. G. Nordestgaard, “CHKE2 *1000delC genotyping for clinical assessment of breast cancer risk: meta-analyses of 26,000 patient cases and 27,000 controls,” Journal of Clinical Oncology, vol. 26, no. 4, pp. 542–548, 2008.

[70] D. Easton, “CHKE2 *1000delC and susceptibility to breast cancer: a collaborative analysis involving 10,860 breast cancer cases and 9,065 controls from 10 studies,” The American Journal of Human Genetics, vol. 74, no. 6, pp. 1175–1182, 2004.

[71] S. Narod et al., “Estimating survival rates after ovarian cancer among women tested for BRCA1 and BRCA2 mutations,” Clinical Genetics, vol. 83, no. 3, pp. 232–237, 2012.

[72] C. Cybulski, B. Gorski, T. Hugerszki et al., “Effect of CHEK2 missense variant 1157T on the risk of breast cancer in carriers of other CHEK2 or BRCA1 mutations,” Journal of Medical Genetics, vol. 46, no. 2, pp. 132–135, 2009.

[73] L. Mellemkjær, C. Dahl, J. H. Olsen et al., “Risk for contralateral breast cancer among carriers of the CHEK2 *1100delC mutation in the WECARE Study,” British Journal of Cancer, vol. 98, no. 4, pp. 728–733, 2008.

[74] M. A. Adank, M. A. Jonker, Kluijt I et al., “CHEK2 *1100delC homozygosity is associated with a high breast cancer risk in women,” Journal of Medical Genetics, vol. 48, no. 12, pp. 860–863, 2011.

[75] C. Cybulski, D. Wokölczechy, T. Hugerszki et al., “A deletion in CHEK2 of 5,395 bp predisposes to breast cancer in Poland,” Breast Cancer Research and Treatment, vol. 102, no. 1, pp. 119–122, 2007.

[76] C. Cybulski, B. Górska, T. Hugerszki et al., “CHEK2 is a multigorgan cancer susceptibility gene,” The American Journal of Human Genetics, vol. 75, no. 6, pp. 1131–1135, 2004.

[77] W. Roeb, J. Higgins, and M. C. King, “Response to DNA damage of CHEK2 missense mutations in familial breast cancer,” Human Molecular Genetics, vol. 21, no. 12, pp. 2738–2744, 2012.

[78] N. Rahman, S. Seal, D. Thompson et al., “PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene,” Nature Genetics, vol. 39, no. 2, pp. 165–167, 2007.

[79] S. Casadei, B. M. Norquist, T. Walsh et al., “Contribution of inherited mutations in the BRCA2-interacting protein PALB2 to familial breast cancer,” Cancer Research, vol. 71, no. 6, pp. 2222–2229, 2011.

[80] S. Jones, R. H. Hruban, M. Kamiyama et al., “Exomic sequencing identifies PALB2 as a pancreatic cancer susceptibility gene,” Science, vol. 324, no. 5924, p. 217, 2009.

[81] E. P. Slater, P. Langer, E. Niemczyk et al., “PALB2 mutations in European familial pancreatic cancer families,” Clinical Genetics, vol. 78, no. 5, pp. 490–494, 2010.

[82] M. Tischkowitz, M. Capanu, N. Sabbaghian et al., “Rare germline mutations in PALB2 and breast cancer risk: a population-based study,” Human Mutation, vol. 33, no. 4, pp. 674–680, 2012.

[83] A. Dansonka-Miszewska, A. Kluska, J. Moe et al., “A novel germline PALB2 deletion in Polish breast and ovarian cancer patients,” BMC Medical Genetics, vol. 11, no. 1, article 20, 2010.

[84] R. E. Brand, M. M. Lerch, W. S. Rubinstein et al., “Advances in counselling and surveillance of patients at risk for pancreatic cancer,” Gut, vol. 56, no. 10, pp. 1460–1469, 2007.

[85] P. Langer, P. H. Kann, V. Fendrich et al., “Five years of prospective screening of high-risk individuals from families with familial pancreatic cancer,” Gut, vol. 58, no. 10, pp. 1410–1418, 2009.

[86] M. I. Canto, M. Goggins, R. H. Hruban et al., “Screening for early pancreatic neoplasia in high-risk individuals: a prospective controlled study,” Clinical Gastroenterology and Hepatology, vol. 4, no. 6, pp. 766–781, 2006.

[87] R. T. Abraham, “PI 3-kinase related kinases: “big” players in stress-induced signaling pathways,” DNA Repair, vol. 3, no. 8–9, pp. 883–887, 2004.

[88] M. Ahmed and N. Rahman, “ATM and breast cancer susceptibility,” Oncogene, vol. 25, no. 43, pp. 5906–5911, 2006.
D.J. Thompson, S. Duedal, J. Kirner et al., “Cancer risks and mortality in heterozygous ATM mutation carriers,” Journal of the National Cancer Institute, vol. 97, no. 11, pp. 813–822, 2005.

K. Gudmundsdottir and A. Ashworth, “The roles of BRCA1 and BRCA2 and associated proteins in the maintenance of genomic stability,” Oncogene, vol. 25, no. 43, pp. 5864–5874, 2006.

H. H. Chun and R. A. Gatti, “Ataxia-telangiectasia, an evolving phenotype,” DNA Repair, vol. 3, no. 8-9, pp. 1187–1196, 2004.

D. Morrell, E. Cromartie, and M. Swift, “Mortality and cancer incidence in 263 patients with ataxia-telangiectasia,” Journal of the National Cancer Institute, vol. 77, no. 1, pp. 89–92, 1986.

S. Seal, D. Thompson, A. Renwick et al., “Truncating mutations in the Fanconi anemia J gene BRIP1 are low-penetrance breast cancer susceptibility alleles,” Nature Genetics, vol. 38, no. 11, pp. 1239–1241, 2006.

T. Rafnar, D. F. Gudbjartsson, P. Sulem et al., “Mutations in BRIP1 confer high risk of ovarian cancer,” Nature Genetics, vol. 43, no. 11, pp. 1104–1107, 2011.

I. Catucci, R. Milgrom, A. Kushnir et al., “Germline mutations in BRIP1 and PALB2 in Jewish high cancer risk families,” Familial Cancer, vol. 11, no. 3, pp. 483–491, 2012.

F. Vaz, H. Hanenberg, B. Schuster et al., “Mutation of the RAD51C gene in a Fanconi anemia-like disorder,” Nature Genetics, vol. 42, no. 5, pp. 406–409, 2010.

K. P. Pennington and E. M. Swisher, “Hereditary ovarian cancer: beyond the usual suspects,” Gynecologic Oncology, vol. 124, no. 2, pp. 347–353, 2012.

L. M. Peltari, T. Heikkinen, D. Thompson et al., “RAD51C is a susceptibility gene for ovarian cancer,” Human Molecular Genetics, vol. 20, no. 16, pp. 3278–3288, 2011.

A. Osorio, D. Endt, F. Fernández et al., “Predominance of pathogenic missense variants in the RAD51C gene occurring in breast and ovarian cancer families,” Human Molecular Genetics, vol. 21, no. 13, pp. 2889–2898, 2012.

F. S. Hilbers, J. T. Wijnen, N. Hoogerbrugge et al., “Rare variants in XRCC2 as breast cancer susceptibility alleles,” Journal of Medical Genetics, vol. 49, no. 10, pp. 618–620, 2012.

C. E. Tambini, K. G. Spink, C. J. Ross, M. A. Hill, and J. Thacker, “The importance of XRCC2 in RAD51-related DNA damage repair,” DNA Repair, vol. 9, no. 5, pp. 517–525, 2010.

D. J. Park, F. Lesueur, T. Nguyen-Dumont et al., “Rare mutations in XRCC2 increase the risk of breast cancer,” The American Journal of Human Genetics, vol. 90, no. 4, pp. 734–739, 2012.

W. Y. Lin, N. J. Camp, L. A. Cannon-Albright et al., “A role for XRCC2 gene polymorphisms in breast cancer risk and survival,” Journal of Medical Genetics, vol. 48, no. 7, pp. 477–484, 2011.

K. Heikkinen, K. Rapakko, S. M. Karpinnen et al., “RAD50 and NBS1 are breast cancer susceptibility genes associated with genomic instability,” Carcinogenesis, vol. 27, no. 8, pp. 1593–1599, 2006.

K. Heikkinen, S. M. Karpinnen, Y. Soini, M. Mäkinen, and R. Winquist, “Mutation screening of Mre11 complex genes: indication of RAD50 involvement in breast and ovarian cancer susceptibility,” Journal of Medical Genetics, vol. 40, no. 12, article e131, 2003.

S. Desjardins, J. C. Beauparlant, Y. Labrie et al., “Variations in the NBN/NBS1 gene and the risk of breast cancer in non-BRCA1/2 French Canadian families with high risk of breast cancer,” BMC Cancer, vol. 9, article 181, 2009.

J. Bartkova, J. Tommiska, L. Oplustilova et al., “Aberrations of the MRE11-RAD50-NBS1 DNA damage sensor complex in human breast cancer: MRE11 as a candidate familial cancer-predisposing gene,” Molecular Oncology, vol. 2, no. 4, pp. 296–316, 2008.

N. Bogdanova, S. Feshchenko, P. Schürmann et al., “Nijmegen Breakage Syndrome mutations and risk of breast cancer,” International Journal of Cancer, vol. 122, no. 4, pp. 802–806, 2008.

S. Nseir, C. Di Pompeo, S. Soubrier et al., “Effect of ventilator-associated tracheobronchitis on outcome in patients without chronic respiratory failure: a case-control study,” Critical Care, vol. 9, no. 3, pp. R238–245, 2005.

E. Seemanova, “An increased risk for malignant neoplasms in heterozygotes for a syndrome of microcephaly, normal intelligence, growth retardation, remarkable facies, immunodeficiency and chromosomal instability,” Mutation Research, vol. 238, no. 3, pp. 321–324, 1990.

E. Seemannová, P. Jarolím, P. Seeman et al., “Cancer risk of heterozygotes with the NBN founder mutation,” Journal of the National Cancer Institute, vol. 99, no. 24, pp. 1875–1880, 2007.

C. Ghimenti, E. Sensi, S. Presciuttiini et al., “Germline mutations of the BRCA1-associated ring domain (BARD1) gene in breast and breast/ovarian families negative for BRCA1 and BRCA2 alterations,” Genes Chromosomes and Cancer, vol. 33, no. 3, pp. 235–242, 2002.

M. Ratajska, E. Antoszewska, A. Piskorz et al., “Cancer predisposing BARD1 mutations in breast-ovarian cancer families,” Breast Cancer Research and Treatment, vol. 131, no. 1, pp. 89–97, 2012.

B. Wang, S. Matsuoka, B. A. Ballif et al., “Abraxas and RAP80 form a BRCA1 protein complex required for the DNA damage response,” Science, vol. 316, no. 5828, pp. 1194–1198, 2007.

S. Solyom, B. Aressy, K. Pylkas et al., “Breast cancer-associated Abraxas mutation disrupts nuclear localization and DNA damage response functions,” Science Translational Medicine, vol. 4, no. 122, Article ID 122ra23, 2012.

W. D. Heyer, K. T. Ehmnsen, and J. Liu, “Regulation of homologous recombination in eukaryotes,” Annual Review of Genetics, vol. 44, pp. 113–139, 2010.

D. Schild, Y. C. Lio, D. W. Collins, T. Tsonomdo, and D. J. Chen, “Evidence for simultaneous protein interactions between human Rad51 paralogs,” The Journal of Biological Chemistry, vol. 275, no. 22, pp. 16443–16449, 2000.

C. Loveday, C. Turnbull, E. Ramsay et al., “Germline mutations in RAD51D confer susceptibility to ovarian cancer,” Nature Genetics, vol. 43, no. 9, pp. 879–882, 2011.

D. J. Osher, K. de Leeeneer, G. Michils et al., “Mutation analysis of RAD51D in non-BRCA1/2 ovarian and breast cancer families,” British Journal of Cancer, vol. 106, no. 8, pp. 1460–1463, 2012.

A. Wickrampayake, G. Bernier, C. Pennil et al., “Loss of function germline mutations in RAD51D in women with ovarian carcinoma,” Gynecologic Oncology, vol. 127, no. 3, pp. 552–555, 2012.

L. M. Peltari, J. Kiiski, R. Nurminen et al., “A Finnish founder mutation in RAD51D: analysis in breast, ovarian, prostate, and colorectal cancer,” Journal of Medical Genetics, vol. 49, no. 7, pp. 429–432, 2012.

D. F. Easton, K. A. Pooley, A. M. Dunning et al., “Genome-wide association study identifies novel breast cancer susceptibility loci,” Nature, vol. 447, no. 7148, pp. 1087–1093, 2007.

D. J. Hunter, P. KRAFT, K. B. Jacobs et al., “A genome-wide association study identifies alleles in FGFR2 associated with risk
of sporadic postmenopausal breast cancer,” *Nature Genetics*, vol. 39, no. 7, pp. 870–874, 2007.

[126] S. Ahmed, G. Thomas, M. Ghoussaini et al., “Newly discovered breast cancer susceptibility loci on 3p24 and 17q23,” *Nature Genetics*, vol. 41, no. 5, pp. 585–590, 2009.

[127] G. Thomas, K. B. Jacobs, P. Kraft et al., “A multistage genome-wide association study in breast cancer identifies two new risk alleles at 1p11.2 and 14q24.1 (RAD51L1),” *Nature Genetics*, vol. 41, no. 5, pp. 579–584, 2009.

[128] W. Zheng, J. Long, Y. T. Gao et al., “Genome-wide association study identifies a new breast cancer susceptibility locus at 6q25.1,” *Nature Genetics*, vol. 41, no. 3, pp. 324–328, 2009.

[129] A. Cox, A. M. Dunning, M. Garcia-Closas et al., “A common coding variant in CASP8 is associated with breast cancer risk,” *Nature Genetics*, vol. 39, no. 3, pp. 352–358, 2007.

[130] R. L. Milne, M. M. Gaudet, A. B. Spurdle et al., “Assessing interactions between the associations of common genetic susceptibility variants, reproductive history and body mass index with breast cancer risk in the breast cancer association consortium: a combined case-control study,” *Breast Cancer Research*, vol. 12, no. 6, article R110, 2010.