

Review Article

Hereditary Breast Cancer: The Era of New Susceptibility Genes

Paraskevi Apostolou and Florentia Fostira

Molecular Diagnostics Laboratory, INRASTES, National Center for Scientific Research "Demokritos", Athens, Greece

Correspondence should be addressed to Florentia Fostira; florentia@rrp.demokritos.gr

Received 10 December 2012; Accepted 21 February 2013

Academic Editor: Francesco Baudi

Copyright © 2013 P. Apostolou and F. Fostira. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

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 *BRIPI*. 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 around 1.5, whereas intermediate-penetrant genes confer relative cancer risks 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
Genes with high-penetrance mutations			
Hereditary breast/ovarian cancer syndrome	<i>BRCA1</i> (17q12–21)	Female breast, ovarian cancer	40–80%
	<i>BRCA2</i> (13q12-13)	Male and female breast, ovarian, prostate, and pancreatic cancer	20–85%
Li-Fraumeni syndrome	<i>TP53</i> (17p13.1)	Breast cancer, sarcomas, leukemia, brain tumours, adrenocortical carcinoma, lung cancers	56–90%
Cowden syndrome	<i>PTEN</i> (10q23.3)	Breast, thyroid, endometrial cancer Other: benign hamartomas, macrocephaly	25–50%
Peutz-Jeghers syndrome	<i>STK11</i> (19p13.3)	Breast, ovarian, cervical, uterine, testicular, small bowel, and colon carcinoma Other: Hamartomatous polyps of the small intestine, mucocutaneous pigmentation	32–54%
Hereditary gastric cancer	<i>CDH1</i> (16p22.1)	Hereditary diffuse gastric, lobular breast, colorectal cancer	60%
Moderate-penetrance mutations			
<i>ATM</i> - related	<i>ATM</i> (11q22.3)	Breast and ovarian cancers	15–20%
<i>CHEK2</i> - related	<i>CHEK2</i> (22q12.1)	Breast, colorectal, ovarian, bladder cancers	25–37%
<i>PALB2</i> -related	<i>PALB2</i> (16p12.1)	Breast, pancreatic, ovarian cancer, male breast cancers	20–40%
Moderate risk breast/ovarian cancer	<i>BARD1</i> (2q34-q35), <i>BRIP1</i> (17q22-q24), <i>MRE11A</i> (11q21), <i>NBN</i> (8q21), <i>RAD50</i> (5q31), <i>RAD51C</i> (17q25.1), <i>XRCC2</i> (7q36.1), <i>RAD51D</i> (17q11), <i>ABRAXAS</i> (4q21.23)	Breast and ovarian cancers	variable

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 will express some clinical manifestation by their 20s [49–53].

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 diffuse 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 anemia 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. BRIP1. *BRIP1* 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. *BRIP1* germline mutations also confer an increased risk of ovarian cancer [96].

Recently, three *BRIP1* missense mutations have been identified in high-risk Jewish women, who have been tested negative for mutations in *BRCA1* and *BRCA2* genes, indicating that *BRIP1* mutations can contribute to breast cancer susceptibility in Jewish high-risk families [97]. Moreover, rare *BRIP1* mutations have been identified in Spanish and Icelandic ovarian kindreds, indicating that *BRIP1* behaves like a classical tumor suppressor gene in ovarian cancer [96]. Biallelic mutations of *BRIP1* 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 Finnish 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 *BRCA2* 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 *ABRA1*, *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 doubtful 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*, *LSPI*, *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 results. Nevertheless, this era of new genes while opening new roads in cancer susceptibility still needs to be treated with caution. Genetic counseling for most of these new genes can be complicated, while extreme prevention strategies, such as prophylactic surgeries cannot be recommended with current data. Further evaluation and genetic analysis in large series of patients will determine actual cancer risks.

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. Lalloo 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 unselected 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. Anagnostopoulos 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. Tsitlidou, 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. Struewing, 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. 665–676, 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. Rebbeck, 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. Whiley, C. A. Pettigrew, B. L. Brewster, L. C. Walker, A. B. Spurdle, 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. Castellsagué, 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 exon 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 germline 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. 5308, 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," *The New England Journal of Medicine*, vol. 316, no. 24, pp. 1511–1514, 1987.
- [60] A. D. Spigelman, V. Murday, and R. K. S. Phillips, "Cancer and the Peutz-Jeghers syndrome," *Gut*, vol. 30, no. 11, pp. 1588–1590, 1989.
- [61] F. M. Giardiello, J. D. Brensinger, A. C. Tersmette et al., "Very high risk of cancer in familial Peutz-Jeghers syndrome," *Gastroenterology*, vol. 119, no. 6, pp. 1447–1453, 2000.
- [62] 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.
- [63] F. 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.
- [64] 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.
- [65] 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.
- [66] K. N. Kangelaris 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.
- [67] I. Kluijdt et al., "Familial gastric cancer: guidelines for diagnosis, treatment and periodic surveillance," *Familial Cancer*, vol. 11, no. 3, pp. 363–369, 2012.
- [68] 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.
- [69] 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.
- [70] 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.
- [71] M. Weischer, S. E. Bojesen, C. Ellervik, A. Tybjærg-Hansen, and B. G. Nordestgaard, "CHEK2 *1100delC 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.
- [72] D. Easton, "CHEK2 *1100delC 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.
- [73] 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.
- [74] C. Cybulski, B. Gorski, T. Huzarski et al., "Effect of CHEK2 missense variant I157T 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.
- [75] 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.
- [76] M. A. Adank, M. A. Jonker, Kluijdt 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.
- [77] C. Cybulski, D. Wokołorczyk, T. Huzarski 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.
- [78] C. Cybulski, B. Górski, T. Huzarski et al., "CHEK2 is a multiorgan cancer susceptibility gene," *The American Journal of Human Genetics*, vol. 75, no. 6, pp. 1131–1135, 2004.
- [79] 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.
- [80] 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.
- [81] 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.
- [82] 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.
- [83] 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.
- [84] 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.
- [85] A. Dansonka-Mieszkowska, A. Kluska, J. Moes et al., "A novel germline PALB2 deletion in Polish breast and ovarian cancer patients," *BMC Medical Genetics*, vol. 11, no. 1, article 20, 2010.
- [86] 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.
- [87] 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.
- [88] 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.
- [89] 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.
- [90] M. Ahmed and N. Rahman, "ATM and breast cancer susceptibility," *Oncogene*, vol. 25, no. 43, pp. 5906–5911, 2006.

- [91] D. 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.
- [92] 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.
- [93] H. H. Chun and R. A. Gatti, "Ataxia-telangiectasia, an evolving phenotype," *DNA Repair*, vol. 3, no. 8-9, pp. 1187–1196, 2004.
- [94] 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.
- [95] 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.
- [96] 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.
- [97] 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.
- [98] 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.
- [99] K. P. Pennington and E. M. Swisher, "Hereditary ovarian cancer: beyond the usual suspects," *Gynecologic Oncology*, vol. 124, no. 2, pp. 347–353, 2012.
- [100] L. M. Pelttari, 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.
- [101] A. Osorio, D. Endt, F. Fernandez 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.
- [102] 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.
- [103] 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.
- [104] 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.
- [105] 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.
- [106] K. Heikkinen, K. Rapakko, S. M. Karppinen et al., "*RAD50* and *NBS1* are breast cancer susceptibility genes associated with genomic instability," *Carcinogenesis*, vol. 27, no. 8, pp. 1593–1599, 2006.
- [107] K. Heikkinen, S. M. Karppinen, Y. Soini, M. Mäkinen, and R. Winqvist, "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.
- [108] S. Desjardins, J. C. Beaudarlant, 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.
- [109] 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.
- [110] 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.
- [111] 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.
- [112] 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.
- [113] E. Seemanová, P. Jarolim, 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.
- [114] C. Ghimenti, E. Sensi, S. Presciuttini 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.
- [115] 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.
- [116] 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.
- [117] 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.
- [118] W. D. Heyer, K. T. Ehmsen, and J. Liu, "Regulation of homologous recombination in eukaryotes," *Annual Review of Genetics*, vol. 44, pp. 113–139, 2010.
- [119] D. Schild, Y. C. Lio, D. W. Collins, T. Tsomondo, 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.
- [120] 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.
- [121] D. J. Osher, K. de Leeneer, 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.
- [122] A. Wickramanyake, 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.
- [123] L. M. Pelttari, 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.
- [124] 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.
- [125] 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. Ghousaini 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.