



Comparison of Patient Susceptibility Genes Across Breast Cancer: Implications for Prognosis and Therapeutic Outcomes

This article was published in the following Dove Press journal:
Pharmacogenomics and Personalized Medicine

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Abstract: Hereditary breast cancer syndromes affect a small (10–15% of cases) but significant group of patients. BRCA1 and BRCA2 are the most familiar and well-studied genes associated with inherited breast cancer. However, mutations in the high-penetrance genes, *TP53*, *PTEN*, *CDH1*, *MSH1*, *MLH1*, *MSH6*, *PMS2*, *PALB2*, and *STK11*, and in the moderate-penetrance genes, *CHEK2*, *ATM*, and *BRIP1*, also correlate with high lifetime risks of breast cancer and other malignancies as well. Advances in breast cancer genetics have led to an improved perception of diagnosis and screening strategies. The specific considerations and challenges involved in treating this unique population have become a fertile ground for research. Indeed, these genes and downstream molecular pathways have now become potential therapeutic targets in breast cancer patients, including those with BRCA1 or BRCA2 mutations. This review describes the variety of hereditary breast cancer genes, from their molecular origins to the prognosis and multidisciplinary clinical decision-making processes. Key publications and other reported recent clinical trials and guidelines are provided.

Keywords: breast cancer, BRCA, TP53, PTEN, CDH1, Lynch syndrome

Introduction

Breast cancer is the major cause of cancer death among women worldwide.¹ Most breast cancer cases are sporadic rather than inherited. Approximately 10–15% of breast cancer cases are associated with hereditary syndromes, and the majority of them will carry a deleterious mutation in *BRCA1/2*^{2,3} (Figure 1). Patients with pathogenic mutations other than *BRCA* can be detected by commercial multigene panel testing. These genes may be related to highly penetrant syndromes, such as Cowden (*PTEN*) and Li-Fraumeni (*p53*). Mutation carriers in one of these genes have a lifetime breast cancer risk above 50%.^{4–6} The relatively low cost of gene sequencing has allowed widespread use of panel testing that examines a variety of cancer-causing genes. When analyzing test results of more than 60,000 patients with breast cancer, and after excluding *BRCA*-positive patients and those with syndromic genes (*PTEN*, *TP53*), more than 6% of them were found to have a pathogenic mutation in other genes, including *CHEK2*, *PALB2* and *ATM*. High or moderately increased risks were associated with pathogenic variants in *PALB2* (odd ratio [OR], 7.46), *RAD51D* (OR, 3.07), *ATM* (OR, 2.78), *BARD1* (OR, 2.16), and *CHEK2* (OR, 1.48).⁷ The increased use of panel testing is directly associated

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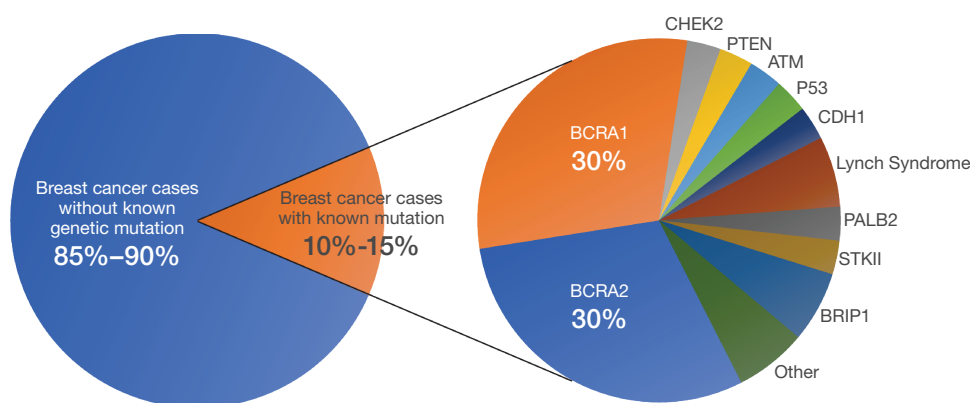


Figure 1 Breast cancer patients with genetic mutations. Approximately 10–15% of breast cancer cases are associated with hereditary syndromes, and the majority of them will carry a deleterious mutation in *BRCA1* and *BRCA2*. Other rare highly penetrant syndromes are Cowden (PTEN) and Li-Fraumeni (p53). After excluding *BRCA*-positive and syndromic genes, there are pathogenic mutation in other genes.

with escalation in the diagnosis of patients with mutations in moderate- and low-penetrance genes. While extensive data are available for *BRCA1/2* mutation carriers, information on less common genes and their management is limited.

In this review, we aim to describe clinical implications, management and prognosis of patients with known germline gene mutations, including those in moderate-penetrance genes.

High-Penetrance Genes in Breast Cancer *BRCA*

BRCA1/2 pathogenic mutations are associated with elevated risk for breast, ovarian⁸ and peritoneal cancer in women, with breast cancer and prostate cancer in men, and, to a lesser degree, with pancreatic cancer. *BRCA1/2* mutations exhibit an autosomal dominant pattern of transmission, and they are rare in the general population (1 to 500), but they account for more than 5% of all breast cancer cases.⁹ The frequency of *BRCA1/2* approximates 1 in 40 in the Ashkenazi Jewish population.¹⁰ Penetrance is variable, even within families with the same variant.^{11,12} In general, the cumulative breast cancer risk up to age 80 years is above 50% for *BRCA1/2* carriers.^{3,13,14} Moreover, they also bear a significant increase in the risk of contralateral breast cancers,^{3,15} which is greater with earlier age at diagnosis, and *BRCA1* (rather than *BRCA2*) pathogenic mutation.¹⁶ A protective effect was reported in women undergoing bilateral salpingo-oophorectomy,³ however, a more recent publication suggested that this association is a result of bias and does not actually exist.¹⁷ *BRCA* mutation carriers commonly develop breast cancer at a young age¹⁸ and bilateral disease is more frequent than

in non-carriers.¹⁹ *BRCA1* breast cancer is often “triple negative” (TNBC).²⁰ The prognosis of *BRCA*-associated breast cancers, however, is relatively similar to that of sporadic breast cancers,²¹ with inconsistent data from meta-analyses showing worse overall survival (OS) on the one hand^{22,23} and some suggesting better OS among triple negative breast cancer patients on the other hand.²⁴ In addition, *BRCA1/2* mutation carriers have an estimated 8–62% lifetime risk for ovarian cancer.⁸

Therapeutic Outcomes Surgery

A bilateral mastectomy reduces this risk of developing breast cancer in healthy carriers, but an overall survival effect in comparison to surveillance has not been clearly demonstrated.²⁵ A recent report suggested a survival benefit in *BRCA1* carriers.²⁶ Contralateral prophylactic mastectomy is a risk-reducing procedure performed in patients diagnosed with a unilateral breast cancer. While there is no clear survival benefit for most *BRCA1/2* breast cancer patients,^{25,27–29} some evidence suggests a disease-free survival (DFS) and OS benefit in younger patients with early-stage disease.^{30,31} A meta-analysis including 4 studies (N=2555) reported an association between contralateral prophylactic mastectomy and reduced mortality,³⁰ however those studies bear some bias since healthier women are selected for risk-reducing surgery. Interestingly, the rates of performing a contralateral prophylactic mastectomy have increased over the past few years.^{31,32} The NCCN guidelines panel recommends considering risk-reducing mastectomy on a case-by-case basis. When counseling patients on contralateral risk-reducing mastectomy, one should consider the various

risks relevant to the specific patient, such as the prognosis of the present breast cancer and the likelihood of developing a contralateral breast cancer, as well as the risks associated with the surgery itself. A risk-reducing salpingo-oophorectomy (BSO) is recommended after completion of childbearing.³³

Radiation

The risk of recurrent cancer in ipsilateral breast is roughly 15% in 10 years in *BRCA1/2* mutation carriers who had undergone breast lumpectomy. This risk is relatively lower than that of the contralateral breast³⁴ as a result of irradiation of the affected breast.^{34,35} Therefore, ipsilateral whole breast radiation is strongly recommended to all *BRCA1/2* mutation carriers undergoing breast-conserving surgery. This reduction in risk also raised the hypothesis that radiation to the contralateral breast may have a risk-reducing role in *BRCA1/2* carriers wishing to refrain from undergoing a prophylactic mastectomy. A non-randomized Phase II trial that evaluated prophylactic breast irradiation for the contralateral breast in *BRCA* mutation carriers showed reduction in the incidence of breast cancer ($P=0.011$).³⁶

Treatment in the Neoadjuvant Setting

The contribution of platinum-based therapy to pathologic complete (pCR) response was explored in women with *BRCA1/2* mutations and TNBC. All patients with TNBC were more likely to achieve a pCR with the addition of carboplatin to neoadjuvant chemotherapy. However, patients without a germline *BRCA* mutation exhibited a much larger increase in pCR rate than *BRCA*-mutated patients.^{37,38} For example, in the BrighTNess trial, the addition of carboplatin increased the pCR rate among *BRCA*-wild type patients from 29% to 59% compared to an increase from 41% to 50% in *BRCA* carriers.³⁹ Moreover, in the outcomes analysis from the GeparSixto trial, the absolute improvement in DFS with the addition of carboplatin was greater among *BRCA*-wildtype patients compared to *BRCA*-mutated patients.⁴⁰ A systematic review of TNBC patients undergoing neoadjuvant treatment reported that platinum is associated with significantly increased pCR in *BRCA1/2* wild type patients, but not in *BRCA1/2*-mutation carriers.⁴¹ This phenomenon may be attributed to the higher sensitivity of tumors with *BRCA1/2* mutation to other alkylating chemotherapies, such as cyclophosphamide. Therefore, decisions regarding the addition of platinum agents in the neo-adjuvant setting should be individualized regardless of *BRCA* status and

with consideration of clinical response to chemotherapy and initial stage.

In cells with a *BRCA1/2* mutation, inhibition of poly (ADP-ribose) polymerase (PARP) causes irreversible DNA damage.⁴² In the neoadjuvant setting, the use of single-agent oral talazoparib for 6 months resulted in 53% of the participants achieving pCR.⁴³ This strategy may be more widely adopted in the future, pending the results of larger trials. Since there are different resistance mechanisms to PARP inhibitors and chemotherapy (including platinum),⁴⁴ future strategies may incorporate sequential use of PARP inhibitors in the neoadjuvant setting, with the addition of chemotherapy to patients not achieving pCR.

Treatment in Metastatic Disease

The use of the PARP inhibitor Olaparib in *BRCA1/2*-metastatic patients with triple-negative breast cancer was assessed in the OlympiAD trial. Patients randomly assigned to Olaparib experienced an improved PFS compared to those assigned to chemotherapy.⁴⁵ A recent update of that trial suggested an OS benefit for olaparib in patients who had not received chemotherapy for metastatic disease, with longer OS compared with chemotherapy-treated patients.⁴⁶ Similarly, talazoparib improved PFS compared to single-agent chemotherapy in the TNBC subgroup of the EMBRACA trial.⁴⁷ Interestingly, the EMBRACA trial showed improvement in PFS in HR positive patients as well. In the BROCADE trial, patients with metastatic HER2-negative and a germline *BRCA* mutation demonstrated improved PFS with the addition of the PARP inhibitor Veliparib to chemotherapy (comprised of carboplatin/paclitaxel).⁴⁸ The TNT randomized trial compared docetaxel with carboplatin as a first-line treatment in women with metastatic TNBC. The overall response rates were similar, but carboplatin resulted in a higher response rate (68% versus 33%) and improved PFS (6.8 versus 4.4 months) among *BRCA1/2*-mutation carriers.⁴⁹

Overall, these studies clearly demonstrate the role of PARP inhibitors and platinum agents in the treatment of metastatic *BRCA1/2* carriers.

TP53 – Li Fraumeni Syndrome

Li Fraumeni syndrome (LFS) is a rare, highly penetrant, autosomal dominant syndrome associated with a germline mutation in the tumor protein *p53* gene.⁵⁰ It constitutes approximately 1% of all hereditary breast cancer cases.⁵¹ *p53* mutation carriers are at increased risk of developing

various cancers, including soft tissue sarcomas, premenopausal breast cancers, tumors of the brain, lung, skin, pancreas, adrenal cortex, and leukemia in childhood or early adulthood,⁵² with a lifetime cancer incidence of nearly 100%.⁵³ The lifetime risk of breast cancer in female mutation carriers approaches 50% by age 60 years. The mean age at onset is approximately 35 years, and a first diagnosis of breast cancer is rare after 50.⁵⁴

There are no data on the benefit of risk-reduction mastectomies, although they seem like a reasonable option when extrapolating data from *BRCA1/2* carriers. The NCCN guidelines panel recommends a case-by-case discussion that considers family history, life expectancy and reconstructive options.

Therapeutic Outcomes

Radiation

Carriers are at increased risk of developing secondary malignancies in radiation fields.^{55,56} Women with LFS who develop breast cancer are generally recommended to undergo mastectomy rather than lumpectomy and radiation, given the risks of radiation-induced malignancies in this syndrome.

Systemic Treatment

HER2 is positive in 64% to 83% of breast cancers among *TP53* carriers.⁵⁷ Patients with *TP53* mutations have limited response to chemotherapy in both the neoadjuvant and adjuvant settings.^{58,59} Clinical decisions regarding chemotherapy in this patient population should be made on a case-by-case basis while considering the limited response and the secondary malignancy risk.

PTEN (Cowden Syndrome)

The germline *PTEN* mutations detected in Cowden syndrome clinically present as multiple hamartomas and contain an increased risk for breast, thyroid, endometrium, kidney and colorectal malignancies.⁶⁰ The *PTEN* gene is a negative regulator of the phosphoinositide-3-kinase (PI3K), and a mammalian target of rapamycin (mTOR) signaling pathways, which are known to be involved in cell proliferation, cell cycle progression, and apoptosis.⁶¹

A decrease in *PTEN* expression may be associated with poor outcomes in BC.^{62,63} There are no data on the benefit of risk-reducing mastectomies although they seem to be a reasonable option when extrapolating data from *BRCA1/2* carriers. The NCCN guidelines panel recommends a case-by-case discussion that considers family history, life expectancy and reconstructive options.

Therapeutic Outcomes

Systemic Therapy

Trials that evaluated the addition of Everolimus to chemotherapy and trastuzumab reported a potential benefit in women with *PTEN* mutations.⁶⁴ Studies that evaluated the addition of AKT inhibitor treatment to chemotherapy in TNBC reported an association between *PTEN* alterations and response to AKT inhibitor treatment, both in the early and advanced settings.^{65,66} It was recently suggested that the *PTEN* gene has a role in maintaining genomic stability^{67,68} and PARP inhibitor sensitization.^{69–71} A phase II trial that evaluated Talazoparib (PARPi) for *BRCA1/2* wild type HER2- breast cancer patients with *PTEN* gene mutations exhibited response or stability.⁷²

CDHI (Hereditary Diffuse Gastric Cancer Syndrome)

Hereditary diffuse gastric cancer syndrome is associated with germline pathogenic variants in the cadherin 1 gene (*CDHI*).^{73,74} The lifetime cumulative risk for advanced diffuse-type gastric cancer is 70% for males and 56% for females by the age of 80 years.⁷⁵ Germline *CDHI* mutations are associated with the development of lobular breast cancer in women, with a cumulative lifetime risk estimated to be as high as 50% to 60%.^{73,76,77} *CDHI* somatic mutations do not impact prognosis of lobular breast cancer patients, however, the presence of *CDHI* plus *ERBB2* mutations leads to worse prognosis.⁷⁸

Therapeutic Outcomes

Systemic Therapy

Invasive lobular carcinoma (ILC) is relatively resistant to chemotherapy compared to invasive ductal carcinoma. The cause might be the luminal A phenotype. Indeed, adjuvant endocrine therapy is preferred for this patient population.⁷⁹ Since the PI3K pathway is activated upon E-cadherin loss, lobular cancer cells were hypothesized to be sensitive to AKT inhibitors.⁸⁰ Therefore, it is reasonable to consider the use of AKT inhibitors in the metastatic setting. More clinical trials are warranted, perhaps with combinations of effective hormonal treatments.

PALB2

Partner and localizer of *BRCA2* (*PALB2*) is a breast cancer susceptibility gene that encodes the *BRCA2*-interacting protein.^{81,83} *PALB2* bi-allelic mutations cause Fanconi anemia and predispose to pediatric malignancies, including

medulloblastoma, Wilm's tumor and acute myeloid leukemia.⁸² Mono-allelic mutations of *PALB2* cause familial breast and pancreatic cancer,^{83,84} prostate cancer in men, and ovarian cancer in women.⁸⁵ Mutation carriers have a cumulative risk of breast cancer ranging between 33% to 58% by age 70 years.^{86,88} *PALB2* is considered to be a moderate- to high-risk gene associated with hereditary breast cancer.^{85–87} Breast cancer risk associated with a *PALB2* pathogenic variant appears to be influenced by a family history of breast cancer and other environmental factors. Women with no family history of breast cancer have a cumulative risk of 33%, compared to 58% in women with two or more family members with breast cancer. Breast cancers in patients with *PALB2* mutations have phenotypic characteristics relatively similar to *BRCA1/2* mutant tumors: 50% are grade III, 40% are triple-negative phenotype, 58% are estrogen receptor-negative and 93% are HER2-negative.⁸⁸

Systemic Therapy

Increased sensitivity to PARP inhibitors in *PALB2*-deficient cells demonstrates the synthetic lethal interaction between *PALB2* loss and DNA-damaging agents.⁸⁹ Furthermore, one preclinical study demonstrated response in *PLAB2*-mutated cells to other DNA-damaging agents, such as platinum.⁹⁰ These preliminary findings warrant validation in clinical studies.

STK11 (LKB1, Peutz-Jeghers Syndrome)

Peutz-Jeghers syndrome (PJS) is a rare disorder associated with pathogenic variants in the serine/threonine kinase 11 gene (*STK11*, also called *LKB1*).⁹¹ Mucocutaneous pigmented lesions occur in about 95% of affected patients. Additionally, hamartomatous polyps in the gastrointestinal tract are hallmark features.⁹² This syndrome is associated with an elevated risk for breast cancer.⁹² The cumulative risk of breast cancer is approximately 55%, and the diagnosis tends to occur at a younger age (mean 37 years).⁵

MSH1, MLH1, MSH6, PMS2, and EPCAM (Lynch Syndrome)

Lynch syndrome, also known as hereditary nonpolyposis colon cancer (HNPCC), is associated with pathogenic variants in mismatch repair genes. The primary cancers associated with Lynch syndrome involve the colon, endometrium, ovaries and stomach.^{93–96} No statistical increase in breast cancer risk was found in 13 out of 21 studies, an

increased risk was reported in 8 and 1 prospective study identified a fourfold increased risk for breast cancer.^{96–98} Subsequent studies have found that the breast cancer risk may vary based on genotype. For example, in a study on *MLH1* and *MSH2* families in the United Kingdom, the cumulative breast cancer risk until age 70 years in *MLH1* carriers was 18.6%, whereas the comparable risk in *MSH2* carriers was 11.2%.⁹⁹ In another study on pathogenic variants among women with Lynch syndrome, breast cancer risks were elevated in *MSH6* and *PMS2* carriers but not in *MLH1* or *MSH2* carriers.^{100,102}

Systemic Therapy

Mismatch repair errors characteristic of the MSI phenotype are rare in breast cancer,¹⁰¹ being found in fewer than 2% of cases.¹⁰² High numbers of MSI tumors have been recently found to be susceptible to immunotherapy,¹⁰³ leading to the use of pembrolizumab (an anti-PD-1 agent) for high MSI metastatic solid tumors.¹⁰⁴

Moderate Penetrance Genes for Breast Cancer CHEK2

The checkpoint kinase 2 (*CHEK2*) gene is associated with a DNA damage repair response.¹⁰⁵ Several *CHEK2* variants have been identified, including single polymorphism (1100delC) which has emerged as being associated with low-to-moderate penetrance breast cancer sensitivity.¹⁰⁶ The 1100delC variant is also linked to increased risk for colorectal cancer, especially with a family history of colon cancer.¹⁰⁷ Other common malignancies associated with *CHEK2* include male breast cancer,¹⁰⁸ stomach, prostate, kidney and thyroid cancer, and also sarcoma.^{109,110} The 1100delC variant is associated with a two- to threefold increased risk of breast cancer, predominantly among caucasian women of northern or eastern european descent.^{46,111–115} The cumulative risk of breast cancer to age 80 years in women with this variant is about 32%, whereas the cumulative risk to age 49 years is about 6%.⁸⁵

Therapeutic Outcomes

Systemic Treatment

Mutations in the *CHEK2* gene have been associated with a lack of benefit from anthracycline in breast cancer.^{116,117} The H371Y variant was associated with better response.¹¹⁸ In clinical studies of women with the *CHEK2* 1100delC mutation, no differences in response to chemotherapy were observed when compared to non-carriers.^{118,119}

Table I Common Genes and Clinical Recommendations

Gene	Surgery Recommendations	Radiation Recommendations	Systemic Treatment Recommendations
<i>BRCA1/2</i>	Discuss bilateral risk-reduction mastectomy.	Radiation post-lumpectomy per indication. Consider radiation to contralateral breast.	Consider PARPi/platinum in the presence of metastases.
<i>TP53</i>	Discuss bilateral risk-reduction mastectomy.	Consider avoiding radiation due to high risk of secondary malignancies. Risk-benefit ratio should be discussed.	Limited response to chemotherapy. Check HER2 status. Consider risk for secondary malignancy.
<i>CDH1</i>	Insufficient evidence for risk-reduction mastectomy, manage by family history.		Adjuvant endocrine therapy is preferred. Consider Akt inhibitors in a clinical trial setting.
<i>PTEN</i>	Insufficient evidence for risk-reduction mastectomy, manage by family history.		Consider Akt inhibitors and PARP inhibitors in a clinical trial setting.
<i>MSH1, MLH1, MSH6, PMS2, and EPCAM</i>	Insufficient evidence for risk-reduction mastectomy, manage by family history.	Consider risk for secondary malignancy.	Consider immunotherapy in the presence of metastases.
<i>PALB2</i>	Discuss bilateral risk-reduction mastectomy.		Offer recruitment to a clinical trial with PARPi.
<i>CHEK2</i>	Insufficient evidence for risk-reduction mastectomy, manage by family history.		
<i>ATM</i>	Insufficient evidence for risk-reduction mastectomy, manage by family history.	Avoid radiation in deleterious <i>ATM</i> missense variants. Risk-benefit ratio should be discussed in other variants.	
<i>BRIP1</i>	Insufficient evidence for risk-reduction mastectomy, manage by family history.		Offer recruitment to a clinical trial with PARPi.

Radiation

Patients with a *CHEK2* mutation are not characterized by any distinct radiosensitivity.¹²⁰ Therefore, planning modifying radiotherapy for women with breast cancer who have this mutation is unwarranted.¹²¹

ATM

The ataxia-telangiectasia mutated (*ATM*) gene encodes a protein kinase involved in DNA repair. Heterozygotic carriers are at a twofold increased risk of developing breast cancer than non-carriers, with a cumulative lifetime breast cancer risk of about 30%.^{85,122-124} *ATM* pathogenic variants have also been associated with increased risks for pancreatic and ovarian cancer.^{93,125}

Rare pathogenic variants in the *ATM* gene may be associated with a substantially higher risk of breast cancer.^{123,126} The risk of second primary breast cancer is not clear.¹²⁷

Therapeutic Outcomes

Radiation

Radiation toxicity in *ATM* mutation carriers is a subject of controversy. Upon activation by ionizing radiation, ATM phosphorylates the proteins that control the pathways involved in DNA repair, including BRCA.¹²⁸ Studies have suggested that radiation exposure may cause contralateral breast cancer in women who carry deleterious *ATM* missense variants.¹²⁹ However, the rarity of these variants implies that *ATM* mutations could explain only a small fraction of second primary breast cancers.¹²⁹ Contrarily, no evidence of breast radiation toxicity in *ATM* mutation carriers has been reported, suggesting that breast-conserving therapy can be safely considered in this patient population.¹³⁰ Moreover, a meta-analysis including 5 studies showed that radiation therapy is safe in *ATM* mutation carriers diagnosed with cancer.¹³¹ Currently, NCCN and

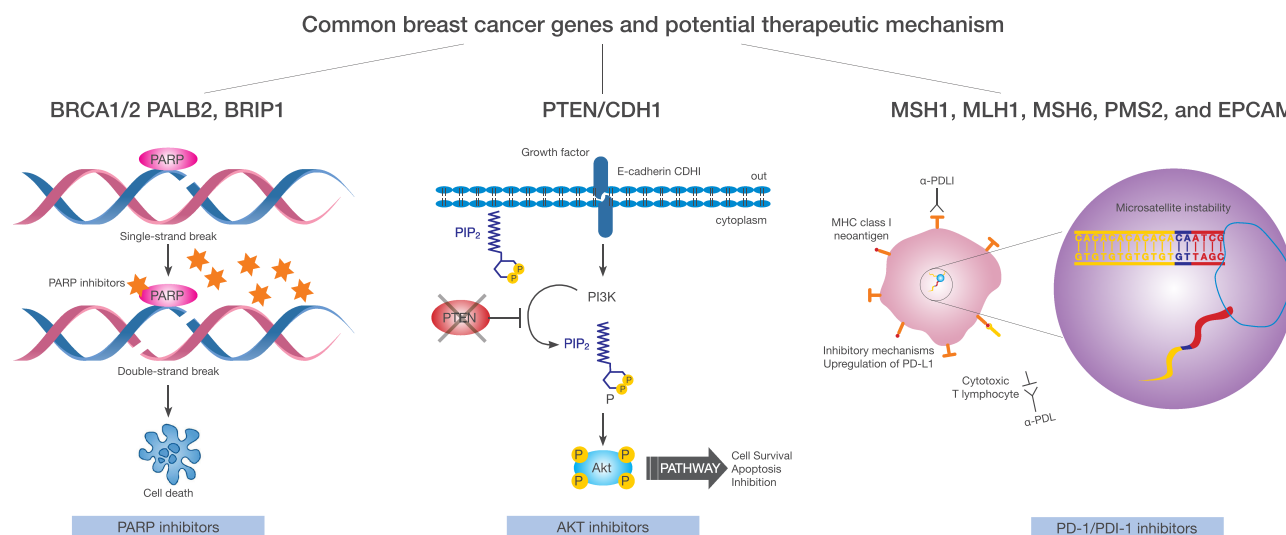


Figure 2 Breast cancer susceptibility genes and potential therapeutic mechanisms. In Patients with BRCA1/2, PALB2 and BRIP1 mutations, PARPi and platinum should be considered. In patients with PTEN and CDH1 mutations AKT inhibitors in a clinical trial setting may be reasonable. In patients with Lynch syndrome immunotherapy has an emerging role.

ESMO guidelines do not recommend against radiation in this patient population.¹³²

Systemic Treatment

ATM mutations may potentially have increased sensitivity for platinum chemotherapy. However, in vitro killing of tumor cells by platinum drugs has not been demonstrated.¹³³ Checkpoint kinase 1 (Chk1) is downstream of ATM in the DNA damage-induced cell-cycle arrest. Therefore, inhibitors of Chk1 may act as chemosensitizers in ATM-mutated cancers.¹³⁴

BRIP1

BRIP1 (*BRCA1* interacting protein C-terminal helicase 1) is a DNA repair gene that interacts with BRCA1.¹³⁷ *BRIP1* is a protein that supports *BRCA1* to repair damaged DNA. *BRIP1* inactivating mutations are hypothesized to be associated with a marginal increased risk of breast cancer, and have more frequently been linked with a moderately increased risk of ovarian cancer.^{136–139} It has been postulated that BRIP1 is a potential target for PARP inhibitors and platinum agents.¹³⁵

Conclusion

In this review, we summarized common breast cancer hereditary syndromes, including BRCA1/2, as well as the less common culpable genes, *TP53*, *PTEN*, *CDH1*, *MSH1*, *MLH1*, *MSH6*, *PMS2*, *PALB2*, *STK11*, *CHEK2*, *ATM*, and *BRIP1*, that are frequently diagnosed in accessible multi-gene panels. We presented an overview of gene carrier

prognosis, and indicated our recommendations for clinical decision-making with regard to surgery, radiation and systemic treatment (Table 1 and Figure 2). In this unique population of breast cancer patients, clinicians must strongly consider the patient's family history, life expectancy and any risk for other secondary malignancies. Participation in clinical trials should be encouraged. Moreover, patients are strongly advised to attend multi-disciplinary clinics for surveillance, risk reduction and primary prevention.

Acknowledgments

We would like to thank Esther Eshkol for English editing.

Disclosure

Dr Amir Sonnenblick reports personal fees from Eli Lilly, Pfizer, and Roche; grants from Novartis, outside the submitted work. The authors report no other conflict of interest in this work.

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