



Updated Insights of the BRCA1 and BRCA2 in Breast and Ovarian Cancer

¹Shivam Kumar*, ¹Arvind Kumar Patel, ¹Dharmendra Kumar, ¹Manish Singh

¹Narayan Institute of Pharmacy, Gopal Narayan Singh University, Jamuhar, Sasaram, Rohtas- 821305 (Bihar), India

Keywords

BRCA1 and BRCA2,
Breast cancer, Ovarian
cancer, Tumour
suppressors.

Abstract

The BRCA1 and BRCA2 genes are important tumor suppressor genes that play a vital role in the DNA double-strand break homologous recombination repair process, and mutations in these genes predispose individuals to breast and ovarian cancers. BRCA MGT, which is a genetic testing initiative, has been implemented in the clinical interaction of advanced ovarian cancer patients, leading to advancements in tailored therapy. The interaction between ATM-Chk2 and RAD51 is necessary to activate ATR-Chk1 after DSBs and start homologous recombination. In addition, some females may experience non-random X-chromosome inactivation, leading to hereditary malignancies. BRCA mutations have been the focus of ethnographic research, and they represent a story of gendered activity, hope, and propulsion. Personalization of patient's molecular profiles is becoming more important for creating and administering personalized therapy. The BRCA genes can impact fertility, and ovarian reserve and fertility preservation may be necessary in breast cancer patients with BRCA mutations. The FDA and EMA have approved Niraparib, Rucaparib, and Olaparib for the treatment of platinum-resistant ovarian cancer patients.

*Corresponding Author:

Mr. Shivam Kumar (shiv15gulshan@gmail.com)

ORCID ID: 0009-0008-2232-7203

Article Info

Received: 29 April 2026, Received in revised form: 08 October 2026, Accepted: 08 October 2026,
Available online: 10 October 2026; Volume: 2; Issue: 3; Pages: 447-466.

ISSN: 3049-2955/The authors © 2026, under exclusive license to the Sprout Publication

DOI: [10.63785/cpr.2026.2.3.447466](https://doi.org/10.63785/cpr.2026.2.3.447466)

1. Introduction

BRCA advances our understanding of the genetic basis and molecular pathways underlying breast and ovarian cancers, while the representation of the "BRCA carrier" has become an important symbol of hope, particularly in the context of preventive healthcare and risk management. The implementation of BRCA mainstreaming genetic testing (BRCA MGT) into clinical interactions with patients receiving treatment for advanced ovarian cancer has further strengthened the integration of BRCA genetics into routine oncology practice [1]. These developments in

ovarian cancer research and BRCA genetics have contributed to a more hopeful alliance between genetic information and tailored therapeutic approaches. BRCA1 and BRCA2 are two important tumour suppressor genes that play central roles in the repair of DNA double-strand breaks (DSBs) through the homologous recombination (HR) pathway [2]. Mutations in these breast cancer susceptibility genes are strongly associated with an increased predisposition to breast and ovarian cancers. Such alterations may be inherited as germline mutations or

may arise as somatic alterations through the accumulation of genetic and environmental factors. BRCA mutation carriers are particularly prevalent in certain clinical subgroups, including patients diagnosed with triple-negative breast cancer (TNBC) [3].

BRCA1 performs diverse cellular functions that contribute to its tumour-suppressive activity, including regulation of the cell cycle, DNA repair mechanisms, DNA damage-responsive cell-cycle checkpoints, transcriptional pathways, and apoptosis. These functions are mediated through interactions involving different functional regions of the BRCA1 protein. Numerous studies have demonstrated that breast cancers arising in germline BRCA1 mutation carriers may exhibit distinct phenotypic and molecular characteristics compared with sporadic breast cancers [4]. A significant proportion of germline BRCA1 mutations contribute to hereditary breast and ovarian cancer, with BRCA1 located on chromosome 17q. Frequent allelic deletions involving the BRCA1 locus in breast and ovarian cancers also suggest that alterations in this gene may contribute to the development of sporadic forms of these malignancies. The cloning and characterization of BRCA1 enabled more direct investigation of its contribution to both hereditary and sporadic cancers. Inactivating BRCA1 mutations identified in the germline of families with breast and ovarian cancer susceptibility further supported its role as a tumour suppressor gene [5].

The essential role of the breast cancer type 1 susceptibility protein (BRCA1) in homologous recombination-mediated repair of DNA double-strand breaks. Loss of BRCA1 is associated with genomic instability and activation of p53-dependent apoptosis and is therefore detrimental during embryonic development [6]. However, BRCA1-deficient cancer cells can acquire resistance to apoptosis despite retaining functional p53. Transcriptome-based investigations of ovarian cancer patients with BRCA1 abnormalities identified increased expression of the transmembrane receptor ADRB1 following BRCA1 loss. Increased cAMP production mediated by ADRB1 was found to suppress p53 accumulation and thereby inhibit DNA damage-induced apoptosis, while also increasing expression of the immunosuppressive factor DKK1, which can inhibit cytotoxic T-cell proliferation. Inhibition of ADRB1 effectively eliminated cancer cells by overcoming this apoptotic resistance, revealing a potential mechanism underlying therapeutic resistance in BRCA1-deficient ovarian cancer [7].

For BRCA2 mutation carriers, variation in breast cancer risk is also influenced by common genetic

variants identified through population-based genome-wide association studies (GWAS). Subsequent replication studies have sought to identify genomic loci associated with variation in breast cancer risk among BRCA2 mutation carriers. Inherited BRCA2 mutations substantially increase the lifetime risk of breast cancer. Similar to BRCA1 mutation carriers, women carrying inherited BRCA2 mutations have been reported to have an estimated lifetime breast cancer risk ranging from 56% to 87% [8].

Despite the substantial progress in understanding BRCA1/2 biology, previous reviews have largely focused on individual aspects of BRCA-associated cancer, such as genetic susceptibility, DNA repair mechanisms, or the clinical application of specific targeted therapies. However, there remains a need for an integrated evaluation that connects the molecular functions of BRCA1/2 with genetic testing, tumour characteristics, treatment selection, therapeutic response, resistance mechanisms, and emerging targeted treatment strategies across breast and ovarian cancers [9].

Therefore, the specific objective of this review is to provide a comprehensive and critical synthesis of the current understanding of BRCA1/2, with particular emphasis on their molecular and genetic roles in cancer development, the implications of germline and somatic alterations, BRCA mainstreaming genetic testing, and the clinical relevance of BRCA status in therapeutic decision-making. The review further examines major BRCA-directed treatment strategies, mechanisms of therapeutic resistance, patient-selection considerations, and emerging approaches for improving outcomes in BRCA-associated breast and ovarian cancers. By integrating molecular mechanisms with genetic testing and therapeutic evidence, this review aims to provide a translational perspective that distinguishes it from previous BRCA1/2 reviews and highlights current challenges and future opportunities in personalized management of BRCA-associated malignancies [10].

1. BRCA1/2 Mutations in Breast and Ovarian Cancer

BRCA1 and BRCA2 mutations can occur as either germline or somatic alterations and have different implications for cancer development and clinical management. Germline mutations are present in the reproductive cells and therefore occur throughout the body. They can be inherited from either parent and may be passed on to subsequent generations, contributing to hereditary breast and ovarian cancer. Approximately 5%–10% of epithelial ovarian cancers are associated with germline BRCA1 or BRCA2 mutations [11]. To better understand the molecular

characteristics of these tumours, gene expression profiles of sporadic epithelial ovarian cancers were compared with those of ovarian tumours associated with BRCA1 or BRCA2 mutations using complementary DNA (cDNA) microarrays, allowing molecular patterns shared by hereditary and sporadic tumours to be identified [12].

In contrast, somatic BRCA1/2 mutations are acquired during a person's lifetime and arise within individual cells, particularly tumour cells. Unlike germline mutations, somatic alterations are generally not inherited and are not usually transmitted to offspring. Nevertheless, they may affect homologous recombination-mediated DNA repair and can influence the biological behaviour and therapeutic response of the tumour [13]. The susceptibility to breast cancer can also be inherited as a monogenic trait in approximately 2%–5% of breast cancer cases. Several highly penetrant genes, including BRCA1 and BRCA2, are associated with an increased predisposition to breast cancer. Recognition of these hereditary genetic alterations has contributed to a more precise understanding of breast cancers arising within hereditary cancer syndromes and has important implications for genetic counselling, risk assessment, and family screening [14].

The distinction between germline and somatic BRCA1/2 mutations is also important in treatment selection. Both types of pathogenic alterations can impair homologous recombination repair and may increase tumour sensitivity to platinum-based chemotherapy and PARP inhibitors. Thus, somatic BRCA1/2 mutations may have direct therapeutic significance even in the absence of an inherited cancer predisposition, whereas germline mutations have both therapeutic and hereditary implications [15]. Identification of a germline pathogenic variant may therefore support treatment decisions as well as genetic counselling and risk assessment of family members. In contrast, identification of a somatic mutation primarily provides information about the tumour and may help guide targeted treatment. Distinguishing these two forms of BRCA1/2 alteration is therefore important for understanding cancer risk, selecting appropriate therapeutic strategies, and providing individualized patient management [16].

2. Molecular Mechanism of BRCA1/BRCA2 in DNA Damage Repair

The ATM–Chk2 and ATR–Chk1 pathways are two important kinase signalling pathways involved in the cellular response to DNA damage. The ATM–Chk2 pathway is mainly activated following DNA double-strand breaks (DSBs), whereas the ATR–Chk1 pathway is primarily activated by replication stress

and the accumulation of single-stranded DNA. Although these pathways were initially considered to act independently, it is now recognized that they can work together during the cellular response to DNA damage. Following the occurrence of DSBs, ATM signalling activates several proteins involved in cell-cycle regulation and DNA repair [17].

BRCA1 is an important component of this response and contributes to the processing of damaged DNA and the initiation of homologous recombination repair (HRR). In particular, BRCA1 participates in DNA-end resection, which produces single-stranded DNA at the damaged site and facilitates the subsequent recruitment of HRR proteins. The resulting single-stranded DNA can also stimulate ATR–Chk1 signalling, thereby strengthening the DNA-damage response. BRCA2 acts at a later stage of HRR and has a key role in regulating RAD51. Through its interaction with RAD51, BRCA2 facilitates the loading of RAD51 onto the exposed single-stranded DNA and supports the formation of a stable RAD51 nucleoprotein filament. This filament is essential for locating the homologous DNA sequence, strand invasion, and subsequent repair of the damaged DNA. Therefore, BRCA1 and BRCA2 work in coordination with ATM/ATR signalling and RAD51 to maintain genomic stability and promote accurate repair of DNA double-strand breaks [18].

Using the DO-1 antibody, immunocytochemistry (IC) was performed on formalin-fixed, paraffin-embedded tissue sections to investigate p53 expression in familial and sporadic breast cancers. Among the grade-matched tumours examined, p53 positivity was observed in 25/72 (35%) BRCA1-associated tumours and 10/22 (45%) BRCA2-associated tumours. p53 immunostaining was also observed in invasive tumour tissue associated with ductal carcinoma in situ (DCIS) and WAF5 in all BRCA1- and BRCA2-associated tumour cases. In contrast, p53 staining was not detected in any of the normal tissue sections examined. The presence of detectable p53 by immunocytochemistry in breast tumours is commonly associated with increased protein stability resulting from mutations in the TP53 gene [19].

Most female human cells contain two X chromosomes, although only one X chromosome remains functionally active in each cell. During early development, X-chromosome inactivation generally occurs randomly, resulting in tissues containing cells in which either the maternal or paternal X chromosome is active. However, some females may show non-random or skewed X-chromosome inactivation. In individuals carrying a germline mutation in one copy of a tumour-suppressor gene,

such skewed X-chromosome inactivation may result in a greater proportion of cells lacking the functional wild-type allele. Consequently, this phenomenon may influence the expression of tumour-suppressor genes and could contribute to the development of hereditary malignancies [20].

The Rad50/Mre11/Nbs1 (R/M/N or MRN) complex is another important component of the DNA-damage response and is involved in the recognition and processing of DNA double-strand breaks. The MRN complex interacts with BRCA1 and provides an important connection between the early recognition of DNA damage and subsequent BRCA1-mediated repair processes. The complex participates in both homologous recombination (HR) and non-homologous end joining (NHEJ), although its contribution depends on the type and stage of DNA repair [21]. Mre11 possesses nuclease activity, while Rad50 and Nbs1 help regulate and coordinate the activity of the complex. Rad50 or Nbs1 can enhance the endonuclease activity of Mre11, whereas Rad50, but not Nbs1, can stimulate its exonuclease activity.

Through these coordinated activities, the MRN complex contributes to the detection and processing of damaged DNA ends and supports their subsequent repair [22].

Figure 1 illustrates the BRCA1-centered DNA damage response network and its role in maintaining genomic stability. Following DNA damage sensing, ATM-ATR kinase signaling promotes BRCA1 phosphorylation and activation. BRCA1 interacts with key proteins, including BRCA2, RAD51, BRD1A, BRIP1, TOPBP1, CTIP, and ATM, coordinating checkpoint regulation and DNA repair. The pathway connects BRCA1 to homologous recombination through RAD51 and facilitates checkpoint signaling via CHK2 activation and G2-phase control. BRCA1 also influences p53 and WAF1/CDIS pathways and contributes to non-homologous end-joining. Collectively, these interactions regulate cell-cycle progression, repair DNA lesions, and prevent accumulation of genomic instability associated with cancer development and tumorigenesis [23].

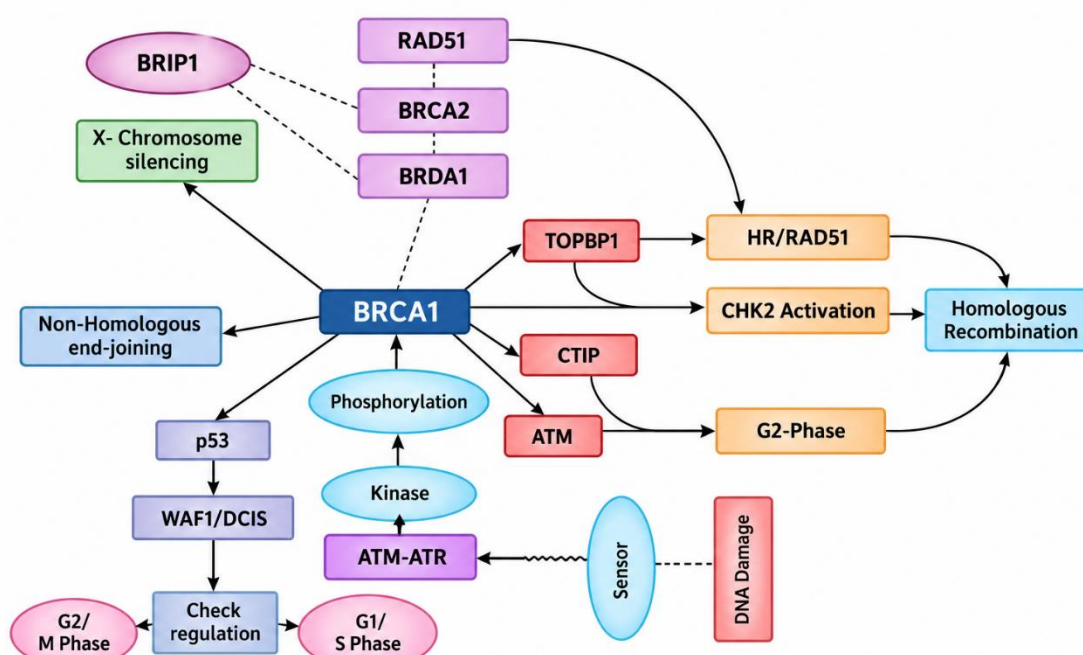


Figure 1: BRCA1 and BRCA2 functions and therapeutic strategy.

3. Clinical Trails

Investigated BRCA1/2 mutations in breast and ovarian cancer populations, including Romanian, Jewish, Gulf-region, Brazilian, and Russian cohorts. Clinical research has also examined BRCA-associated prostate cancer risk, fertility and breast cancer prevention, and the use of genetic testing for patient and family risk assessment. Therapeutic trials have explored PARP inhibition and combination strategies, including

olaparib with durvalumab and tremelimumab, ABT-767, veliparib-based regimens, and ABT-888 with temozolomide. Additional studies have assessed trabectedin in BRCA mutation carriers, letrozole for prevention, INO-5401 vaccination, and chemo-free BRCA-targeted neoadjuvant treatment. Representative registered studies include NCT02317120, NCT00590109, NCT03082976, NCT02953457, NCT01772979, NCT00673335,

NCT04367675, and NCT05209529. Collectively, these trials demonstrate the expanding clinical relevance of BRCA testing, prevention, and personalized treatment strategies [24].

Table 1 summarizes representative clinical trials involving BRCA1 and BRCA2 mutations across breast,

ovarian, and prostate cancers. It includes completed, Phase 1–4, observational, and non-applicable studies evaluating genetic testing, prevention, targeted therapies, vaccination, and neoadjuvant strategies, highlighting the clinical and translational importance of BRCA-directed approaches [11].

Table 1: Clinical trials investigating BRCA1 and BRCA2 mutations, associated cancers, and therapeutic or preventive strategies.

S. No.	Name	Status	Indication	NCT numbers
1.	BRCA1 and BRCA2 Mutation in Romanian Population: a Study of Genotype - Phenotype Correlation at Diagnosis with Prospective Disease Outcome and Survival	Completed/ Phase 4	Breast Cancer, ovarian cancer	NCT02317120
2.	Germline Mutations BRCA1 and BRCA2 in Jewish Women Affected by Breast Cancer	Completed/ Phase 4	Breast Cancer	NCT00590109
3.	Prevalence of Mutations BRCA1 and BRCA2 in Ovarian Cancer Patients in the Gulf Region	Completed/ Phase 4	ovarian cancer	NCT03082976
4.	The IMPACT Study - Identification of Men with a Genetic Predisposition to Prostate Cancer	Completed/ Phase 4	Prostate Cancer in BRCA1 and BRCA2 Carriers	NCT00261456
5.	Use of Recombinant hCG to Prevent Breast Cancer in BRCA1 and BRCA2 Carriers	Completed/ Phase 4	hCG, BRCA1 and BRCA2 mutation	NCT03495609
6.	Study of ABT-767 in Subjects With BRCA1 and BRCA2 Mutations and Solid Tumors or High Grade Serous Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	Completed/ Phase 4	Solid Tumors (e.g. Breast, Ovarian, Prostate, or Pancreatic) and Ovarian	NCT01339650
7.	Establishing the Incidences of BRCA1 and BRCA2 mutation by Combining DHPLC and Direct Sequencing in Ovarian Cancer	Completed/ Phase 4	Ovarian Cancer	NCT00155896
8.	Olaparib, Durvalumab, and Tremelimumab in Treating Patients with Recurrent or Refractory Ovarian, Fallopian Tube or Primary Peritoneal Cancer with BRCA1 or BRCA2 Mutation	Phase 2	BRCA1 and BRCA2 gene mutation	NCT02953457
9.	Genetic Education in BRCA Families	Not applicable	BRCA1 and BRCA2 gene mutation	NCT03544983
10.	Study With Trabectedin in BRCA1 and BRCA2 Mutation Carrier and BRCAness Phenotype Ovarian Cancer (MITO15)	Phase 2	BRCA1 and BRCA2 Mutation Carrier and BRCAness Phenotype	NCT01772979

11.	Evaluation of Tomosynthesis for Characterization and the Management of Breast Lesions (ETOLE)	Not Applicable	BRCA1 and BRCA2 Protein	NCT02959398
12.	A Study to Assess the Safety and Pharmacokinetics of an Inhibitor of Poly ADP-Ribose Polymerase-1 (PARP)	Phase 1	BRCA1 and BRCA2 Protein	NCT00516373
13.	Use of Recombinant hCG to Prevent Breast Cancer in BRCA1 and BRCA2 Carriers	Phase 4	BRCA1 and BRCA2 mutation	NCT03495609
14.	The Link Between BRCA Mutation and Endothelial Function	Not Applicable	BRCA1 and BRCA2 gene mutation	NCT02474264
15.	Letrozole in Preventing Breast Cancer in Postmenopausal Women with a BRCA1 or BRCA2 Mutation (LIBER)	Phase 3	BRCA1 and BRCA2 mutation carrier	NCT00673335
16.	Prospective Cohort Study of Germline Variant Carriers with BRCA1 or BRCA2	Observational Study	BRCA1 and/or BRCA2 Variant Carriers	NCT03296826
17.	INO 5401 Vaccination in BRCA1/2 Mutation Carriers	Phase 1	BRCA1/2 Mutation	NCT04367675
18.	Early Salpingectomy (Tubectomy) With Delayed Oophorectomy in BRCA1/2 Gene Mutation Carriers (TUBA)	Not Applicable	BRCA1 and BRCA2 gene mutation	NCT02321228
19.	ABT-888 and Temozolomide for Metastatic Breast Cancer and BRCA1/2 Breast Cancer	Phase 2	BRCA1 and BRCA2 gene mutation	NCT01009788
20.	Chemo-free BRCA-targeted Neoadjuvant Strategy	Phase 2	BRCA1 and BRCA2 mutation	NCT05209529

4. Patents of BRCA1 and BRCA2

Patents related to BRCA1 and BRCA2 primarily focus on mutation detection, genomic characterization, homologous recombination deficiency, variant classification, and molecularly targeted approaches. These innovations include PCR primers for amplification of BRCA1/2 coding sequences, multiplex PCR-based mutation detection kits, and methods for identifying and mapping genomic rearrangements. Other patented approaches address functional inactivation of the BRCA1/2-associated homologous recombination pathway, construction of high-throughput BRCA mutation libraries, and interactions involving the BRCA1 BRCT domain. Such technologies may support genetic screening, identification of clinically relevant variants, characterization of structural alterations, and patient stratification for

targeted therapies. Collectively, these patents demonstrate the expanding translational and diagnostic importance of BRCA1/2 biology and provide technological foundations for precision oncology, molecular testing, and individualized therapeutic decision-making [25].

Table 2 summarizes representative patents associated with BRCA1 and BRCA2, including technologies for PCR-based mutation detection, multiplex screening, genomic rearrangement mapping, homologous recombination pathway assessment, mutation-library construction, BRCA1 molecular interactions, and variant classification. These inventions highlight the development of diagnostic and therapeutic technologies supporting BRCA-focused precision oncology [26].

Table 2: Patents related to BRCA1 and BRCA2 covering mutation detection, genomic analysis, homologous recombination assessment, and therapeutic applications.

S. No.	Patent Title	Patent No.	Published Date	Applicant	Significance and Potential Application	References
1.	PCR Primers for Amplifying Human BRCA1/BRCA2 Coding Sequences and Application	CN105779636B	19-05-2020	Zhang Juyong	Enables PCR amplification of BRCA1/2 coding regions for mutation screening and genetic analysis.	[27]
2.	Multiplex PCR Detection Method and Kit for BRCA1/BRCA2 Mutations	CN105200154B	09-11-2016	Qu Wubin	Enables simultaneous detection of multiple BRCA1/2 mutations, improving genetic screening efficiency.	[28]
3.	Detection, Visualization and High-Resolution Mapping of Genomic Rearrangements in BRCA1/BRCA2 Using Molecular Combing	US20180340235A1	29-11-2018	Aaron Bensimon	Enables detection and mapping of complex BRCA1/2 genomic rearrangements for breast and ovarian cancer analysis.	[29]
4.	Methods for Detecting Inactivation of the Homologous Recombination Pathway in Human Tumors	AU2019200605B2	06-06-2033*	Elodie Manie	Identifies BRCA1/2-associated homologous recombination deficiency to support patient stratification for DNA-repair-targeted therapies.	[30]
5.	Construction of a Tumor BRCA1/2 Mutation Library for High-Throughput Sequencing	CN107312770A	03-11-2017	Chen Yan	Supports high-throughput identification and characterization of BRCA1/2 mutations for genetic profiling.	[31]
6.	Methods and Compositions for Cancer Treatment Relating to BRCA1 BRCT Domain Recognition of Phosphorylated BACH1	US20120295802A1	22-11-2012	Michael B. Yaffe	Targets BRCA1–BACH1 molecular interactions as a potential strategy for cancer therapy development.	[32]
7.	Classification Evaluation Method for BRCA1/2 Gene Variations	CN113823354A	21-12-2021	Liu Zhiyuan	Facilitates clinical interpretation and classification of BRCA1/2 variants to improve genetic risk assessment.	[33]

5. Therapies Related to BRCA1 and BRCA2

Therapeutic strategies associated with BRCA1 and BRCA2 have expanded considerably with the recognition of homologous recombination deficiency as a clinically actionable vulnerability. Current approaches include ovarian- and breast-cancer-specific interventions, PARP inhibitors, preventive strategies, and emerging molecular therapies. Major drug-based approaches include veliparib, talazoparib, olaparib, and APTO-253, which exploit DNA-repair defects and synthetic lethality associated with BRCA1/2 alterations. Clinical investigations have also evaluated fertility preservation, mutation prevalence, geographical variation, and BRCA-associated tumour characteristics. In ovarian cancer, BRCA mutations may increase sensitivity to platinum-based chemotherapy and PARP inhibition. In breast cancer, BRCA1/2 status can guide selection of targeted

treatment, particularly in HER2-negative disease. Additional studies have explored BRCA-related molecular expression, transcriptomic patterns, and alternative therapeutic approaches. Collectively, these strategies demonstrate the increasing integration of BRCA1/2 status into precision oncology and individualized treatment planning [34].

Table 3 summarizes major BRCA1/2-related therapeutic and clinical approaches, including ovarian- and breast-cancer strategies, PARP inhibitor-based treatments, geographical studies, and other molecular interventions. These approaches emphasize the role of BRCA-associated homologous recombination deficiency in treatment selection and support the development of personalized therapeutic strategies [35].

Table 3: Therapeutic approaches related to BRCA1 and BRCA2 in breast and ovarian cancer.

S. No.	Therapy category	Applications	References
1.	Ovarian cancer	BRCA-mutated ovarian cancer characteristics, mutation prevalence, tumour testing, and patient perspectives	[36]
2.	Breast cancer	Fertility preservation, ovarian reserve, and BRCA pathogenic variant prevalence	[37]
3.	Drug therapies	Veliparib, talazoparib, APTO-253, and olaparib for BRCA-associated cancers	[38]
4.	Geographical studies	BRCA1/2 mutation patterns in Brazilian, Italian, and Russian patients	[39]
5.	Other therapies	BRCA1/2 mRNA expression, melphalan, and BRCA-mutated transcriptomic patterns	[40]

5.1 Related to Ovarian Cancer

5.1.1 Clinical Characteristics of Ovarian Cancer Patients with Mutant BRCA1 and 2 Genes

With more than 300,000 new cases and 185,000 fatalities expected in 2020, ovarian cancer remains one of the major health challenges for women worldwide, with Romania being among the 25 countries reporting the highest incidence rates. Homologous recombination (HR) is an important DNA-repair mechanism involved in the repair of DNA double-strand breaks, including those induced by platinum-based chemotherapy.

BRCA1 and BRCA2 are key components of the DNA-damage repair machinery and play an important role in maintaining effective HR-mediated repair. Approximately 20% of ovarian cancers harbour somatic or germline BRCA mutations, which can result in homologous recombination deficiency (HRD)

and increase tumour sensitivity to platinum-based chemotherapy and PARP inhibitors [41].

Among the major PARP inhibitors, olaparib, niraparib, rucaparib, and talazoparib share the ability to inhibit PARP-mediated DNA repair and exploit the vulnerability of tumours with impaired homologous recombination. However, their clinical use differs according to tumour type, BRCA/HRD status, treatment setting, and regulatory indications. Olaparib has been extensively investigated in BRCA1/2-mutated breast and ovarian cancers and has an established role in maintenance and targeted treatment strategies. Niraparib has demonstrated particular clinical relevance in ovarian cancer, including maintenance treatment in patients with advanced disease, with benefit extending to selected patients with HRD [42]. Rucaparib has similarly been developed for BRCA-mutated and HRD-associated ovarian cancers and has been evaluated in both treatment and maintenance settings. Talazoparib is

distinguished by strong PARP-trapping activity and has been particularly investigated in patients with germline BRCA-mutated, HER2-negative advanced or metastatic breast cancer. Thus, although these agents act through the common principle of exploiting defective DNA repair, differences in PARP-trapping potency, tumour indications, patient selection, and treatment settings contribute to their distinct therapeutic relevance. Collectively, these agents illustrate the clinical application of synthetic lethality between PARP inhibition and BRCA1/2-associated homologous recombination deficiency [43].

All gynecologic cancers, ovarian cancer still has the greatest fatality rate, making treatment a challenge, especially with the emergence of platinum-resistant disease. The majority of patients are identified when they are quite sick, necessitating thorough cytoreduction and conventional platinum-based chemotherapy as the mainstays of care. BRCA 1/2 and other related genes have been identified as important regulators of platinum sensitivity thanks to developments in the molecular basis of DNA damage repair. Next generation sequencing was used to retrospectively retrieve patient data from our institute for all patients who underwent testing to check for germline or somatic BRCA mutations [44]. In total, 88 patients were analysed in this study. Advanced FIGO stage IIIC-IV was prevalent at presentation (71.6%), and primary debulking surgery was performed in 58% of patients. A considerable increase in the prevalence of full pathologic responses, a considerably longer overall survival as well as the first and second platinum-sensitive relapses were all associated with BRCA mutant patients, which made up 44% of all cases treated with neoadjuvant chemotherapy. In comparison to BRCA wildtype individuals (54.2 years), the mean age at presentation was considerably lower in the BRCA mutant patients (52 years, $p = 0.045$) [45].

5.1.2 Prevalence of Somatic BRCA1 and BRCA2 Mutations in Ovarian Cancer Among Filipinos

One of the biggest causes of death among women is ovarian cancer. 5,395 (6.2%) of female cancers diagnosed in 2020 had ovarian origins. In terms of gynecologic cancers, it came in second place only behind cervical cancer. Women from Asia and the Pacific had a prevalence rate of 9.2 per 100,000 people. Ovarian cancer has a high mortality rate and a dismal prognosis due to silent growth, delayed or nonexistent symptoms, and advanced stage (III/IV) disease in roughly 70% of women by the time of diagnosis. Breast Cancer Gene 1 (BRCA1), found on Chromosome 17q21, and Breast Cancer Gene 2 (BRCA2), found on Chromosome 13, are the two most

often linked gene mutations [46].

The prevalence of pathogenic somatic mutations in the BRCA1 and BRCA2 genes among patients diagnosed with ovarian cancer. The primary objective is to categorize the identified genetic variants into three distinct groups: benign/no pathogenic variant identified, variant of uncertain significance (VUS), and pathogenic mutations. By accomplishing this objective, the study aims to establish a comprehensive understanding of the genetic landscape associated with ovarian cancer [47].

Furthermore, the relationships between specific mutations detected in BRCA1 and BRCA2 and both histomorphologic findings (microscopic tissue characteristics) and clinical attributes of the patients. This multifaceted approach will shed light on potential correlations between genetic mutations and disease presentation, progression, and response to treatment [48].

5.1.3 Tumors Testing in BRCA1 and BRCA2 Mutations with Epithelial Ovarian Cancer

The BRCA1 and BRCA2 genes exhibit germline mutations in high-grade severe ovarian carcinomas (HGSOC), which account for the vast majority of ovarian cancer, can occur up till 18% of patient fatalities[49]. Additionally, somatic BRCA1 and BRCA2 Mutations are present in tumour samples from up to 8% of affected patients[50]. The discovery of poly (ADP-ribose) polymerase-inhibitors (PARPi) has greatly improved the choices for cancer therapy with BRCA1/2 mutations. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved Niraparib, Rucaparib, and Olaparib for the treatment of patients with platinum-sensitive recurrent HGSOC who are in full or partial response to platinum-based chemotherapy [51, 52].

The most crucial factors in determining a patients course of treatment for epithelial BRCA 1/2 mutation is what causes ovarian cancer (EOC). This objective of study was to assess the validity of BRCA tumour testing by comparing tumour DNA with blood DNA sequencing. Patients who underwent germline (gBRCA) and tumour (tBRCA) at the Medical University of Vienna, BRCA mutations are being tested between 2003 and 2019 were identified. The concordance rate was calculated, and the discordant instances were further examined. Out of 140 EOC patients, 47 (33.6%) had a gBRCA mutation and 53 (37.9%) had a tBRCA mutation. 9 more patients with somatic BRCA mutations out of 140 (6.4%) patients and negative germline tests were found through tumour testing. A 93.5% concordance rate and a

96.0% negative predictive value for tumour testing were found when germline and tumour testing were compared. Concordance rate dropped to 90.9% after BRCA mutations of unknown relevance were added to the analysis. The majority of harmful germline BRCA mutations were detected by tumour testing, while three (2.1%) cases were overlooked [53].

5.1.4 An Ethnographic Investigation of Ovarian Cancer Patients in BRCA Gene

Hereditary breast and ovarian cancers are now known to be brought on by the BRCA1 and BRCA2 genes, have been the focus of substantial ethnographic research for the past 20 years or more[54]. Medical sociologists and anthropologists have endeavoured to comprehend the sociocultural and clinical consequences of the genes during this "time of BRCA." Indeed, These genes depict a story of gendered activity, hope, and propulsion into imagined communities to push for funding for research and medical care in addition to one of "migration, marriage," and sorrow [55].

The personalisation of patient's molecular profile is becoming a more important factor in the creation and administration of personalised therapy. It was carried out in two different clinics at a well-known cancer centre in the "conventional" genetic testing environment. The first phase of the study gave an overview of current locations and methods for BRCA genetic testing available. It also gave important insights into the work done by clinical geneticists and genetic consultants, allowing for a fair comparison of the two environments in which the BRCA genes are found. Not only is a BRCA mutation essential to however, it also takes on a more materialist aspect as an embodied practise that extends both inside and outside of the clinic [56].

5.2 Related to Breast Cancer

5.2.1 Ovarian Reserve and Fertility Preservation in Breast Cancer Patients with BRCA Mutations

BRCA1 and BRCA2 mutations may have an impact on female fertility. Premature ovarian insufficiency (POI) is a condition associated with a progressive decline in ovarian function. It may initially present with biochemical changes, such as increased but non-menopausal follicle-stimulating hormone (FSH) levels, reduced fertility, and relatively regular menstruation. As the condition progresses, women may develop an occult clinical stage characterized by reduced fertility despite normal FSH levels and regular menstruation, eventually progressing to more established ovarian insufficiency [57]. Assessment of ovarian function in BRCA mutation carriers can be particularly challenging because bilateral salpingo-

oophorectomy is often recommended as a risk-reducing procedure. Although this surgery can reduce the risk of ovarian and related cancers, it results in loss of ovarian function and consequently has important implications for reproductive potential. Therefore, determining the natural timing of menopause and evaluating ovarian reserve in mutation carriers may have certain limitations [58].

These issues are particularly relevant to the clinical interpretation of BRCA genetic testing. Identifying a BRCA1/2 mutation can provide valuable information not only about an individual's future cancer risk and treatment options but also about reproductive health. For young women with breast cancer or those identified as BRCA mutation carriers before cancer treatment or risk-reducing surgery, genetic testing can facilitate timely counselling regarding fertility, ovarian reserve, and available fertility-preservation options. This information allows patients and healthcare professionals to consider reproductive goals while planning cancer treatment and risk-reducing interventions. Thus, the clinical significance of BRCA testing extends beyond cancer-risk assessment and targeted treatment selection and may also support individualized reproductive decision-making [59].

The relationship between BRCA1/2 mutations, fertility preservation, and ovarian reserve in 67 breast cancer patients aged 18–40 years who underwent oocyte storage for fertility preservation. The study included patients with a BMI between 18 and 28, breast cancer classified according to the American Joint Committee on Cancer (2017), and no evidence of metastasis. No significant differences were observed between the groups with respect to basal FSH levels, duration of ovarian stimulation, number of mature follicles, or total number of retrieved oocytes. The study found no evidence of a reproductive effect associated with BRCA2 mutation. These findings suggest that BRCA2 status alone may not necessarily indicate a reduced ovarian response during fertility preservation. However, reproductive counselling remains important for BRCA mutation carriers because fertility-related decisions may also be influenced by age, planned cancer therapy, future risk-reducing surgery, and individual reproductive goals [60].

5.2.2 BRCA Pathogenic Variant Prevalence in a Significant, Unselected Breast Cancer

BRCA1/2 pathogenic variants play a significant role in determining women with BRCA1/2-associated breast cancer, hereditary breast cancer do not always have lower survival rates than those without such pathogenic variations[61]. However, compared to people with breast cancer that is BRCA1/2 wild-type, those with BRCA1/2-associated breast tumours

benefit from more therapeutic options[62]. The development of novel therapeutics, such as poly (ADP-ribose) polymerase (PARP) inhibitors, which specifically target BRCA1/2-deficient cancer cells, has also increased the range of treatment choices for BRCA1/2 breast cancers [63, 64].

The patients with breast cancer who have tumours caused by BRCA1/2 may benefit from targeted therapy. The effectiveness of the current BRCA screening recommendations in locating these patients is unclear. This study's objectives were to determine a large, clinically relevant breast cancer cohort to determine the incidence of inherited BRCA1/2 pathogenic mutations and to estimate the proportion of BRCA1/2 carriers who were missed by selective screening among those who had the highest likelihood of carrying the gene, as recommended by clinical practise. 5,122 randomly chosen Swedish women diagnosed with breast cancer between 2001 and 2008, were included in the study. Clinical screening underestimated more BRCA2 carriers (34/42, 81.0%) than BRCA1 carriers (23/50, 46%). 1.8% of individuals with breast cancer without any other risk factors had BRCA1/2 mutations. Strict clinical screening of people failed to identify six out of ten BRCA carriers [65].

5.3 Different Drug Therapies

5.3.1 Veliparib in the Treatment of Ovarian Cancer: A Novel Synthetic Technique in BRCA1 and BRCA2

About nearly 90% of all Epithelial ovarian cancers (EOC) are ovarian malignancies. The use of neo (adjuvant) platinum-based chemotherapy and cytoreductive surgery make up the conventional treatment plan. Drug resistance is linked to the recurrence of high grade serous ovarian cancer that has progressed to an advanced stage (HGSOC). One distinguishing feature of HGSOC is a compromised damaging reaction to DNA. Poly (ADP-ribose) polymerase (PARP) inhibitors can prevent breast cancer in people who have the BRCA1 or BRCA2 mutation take advantage of this defect through synthetic lethality and have shown promise as anticancer treatments. A phase I study involving 35 individuals with both refractory solid tumours research using veliparib in combination with metronomic oral cyclophosphamide. Veliparib was given in a variety of regimens ranging from 7 to 21 days and at doses of 20 mg to 80 mg once day, while cyclophosphamide was given at doses of 50 mg or 100 mg once daily on a three-weekly schedule. Phase 2 trial combining veliparib and low-dose cyclophosphamide. During a three-week period, 72 patients with BRCA-mutant ovarian cancer who had previously undergone treatment were arbitrarily chosen to obtain either cyclophosphamide alone a

dosage of 50 mg once daily or cyclophosphamide + veliparib a dosage of 60 mg once daily. The GOG-3005 study, based on NCT00989651 data, compares first-line carboplatin and paclitaxel chemotherapy with veliparib to chemotherapy combined with veliparib chemotherapy with veliparib maintenance therapy to the combination followed by the combination in stage III or IV HGSOC [66].

5.3.2 BRCA1 and BRCA2 in Talazoparib Therapy in Phase II Trial

Patients having genomic BRCA1 and/or BRCA2 (gBRCA1/2) mutation and metastatic HER2-negative breast cancer may benefit from the usage of PARP inhibitors such talazoparib and olaparib is now approved[67]. Niraparib and rucaparib are additional medications in this class that have been authorised for the treatment or maintenance of ovarian cancer[68]. These treatments are based on the theory of synthetic lethality, according to which tumours lacking by obstructing BRCA1 and/or BRCA2 or other homologous recombination (HR)-associated genes, a PARP-dependent single-stranded DNA (ssDNA) repair pathway are made more vulnerable to PARP inhibition. BRCA1, BRCA2, and other related factors are necessary for flawed HR DNA repair, which is consequently reliant on these genes [69, 70].

A PARP inhibitor called talazoparib is effective against BRCA1 and BRCA2 germline mutations leading to advanced breast cancer (gBRCA1/2), however it is unclear what other conditions it can treat. an open-label phase II experiment assessing the effectiveness of talazoparib in people having HER2-negative advanced breast cancer who have already had treatment (n = 13) or other solid tumours (n = 7) that have gene changes that affect other than BRCA1 and BRCA2 homologous recombination (HR) pathway. Four breast cancer patients experienced a partial response according to the RECIST criteria moreover, three other individuals had stable disease for less than six months (clinical benefit rate: 54%). Treatment-associated tumour regression was observed in all individuals who have germline PALB2 (gPALB2; an encoding partner and localizer of BRCA2) mutations [71].

5.3.3 DNA BRCA1/2 Deficiency by APTO-253

The novel indol phenanthroline-imidazoles, APTO-253 precursor was found to destroy cancer cells. It is known that phenanthrolines can combine with a number of doubly charged metals, including Fe, Zn, and Ru have varied binding constants for calf thymus DNA[72, 73]. The precursor was further chemically altered to enhance anticancer action, which produced the new molecule APTO-253. With IC₅₀ values ranging from roughly 0.04 to 2.6 mmol/L, APTO-253 was later

demonstrated to exhibit efficacy against cell lines created from several different types of human cancers, such as leukaemias, lymphomas, colon cancer, and non-small cell lung cancer[74]. Patients with solid tumours were given APTO-253 and it was proceeded into a phase I trial. In each 28-day cycle, the medication was injected intravenously, and the dose was increased in 9 cohorts from 20 to 387 mg/m². In this experiment, 32 individuals were treated, and the sole adverse medication reaction requiring urgent medical attention that affected more than 10% of patients was fatigue [75].

About small chemical APTO-253 has anti-proliferative effects on cell lines generated from a variety of human cancers. In order to uncover synthetic interactions with a high potential for death combination research, we aimed to understand the modes of action for APTO-253 and the source of resistance. Raji investigated the cellular pharmacology of APTO-253 in lymphoma cells, and a subline that was resistant to the drug. APTO-253 was discovered to intracellularly transform into a complex called Fe(253)₃, which contains three molecules of APTO-253 and one molecule of iron. The intracellular concentration of Fe(253)₃ was approximately 18 times higher than Fe(253)₃ appears to be the most active form, and it is that of the original drug. Since cells treated with APTO-253 experienced DNA damage, we wondered if cells lacking in homologous recombination would also experience DNA damage. In numerous isogenic paired cell lines, loss of BRCA1 or BRCA2 activity resulted in APTO-253 hypersensitivity of a magnitude equal to that of olaparib, a PARP inhibitor. Raji cells with 16-fold acquired resistance accumulated 16-fold less iron (253)₃. Drug efflux pump ABCG2 overexpression is an important mechanism of resistance, according to RNA-sequence data. ABCG2 inhibition reversed APTO-253 resistance in Raji/253R, and ABCG2 overexpression rendered HEK-293 cells resistant to the drug. The restricted number of medications that can take advantage of homologous recombination flaws now includes APTO-253 [76].

5.3.4 Olaparib: A Novel Treatment of Metastatic Breast Cancer by BRCA1/2 Mutation

Breast cancer is the malignancy in which women are most frequently diagnosed worldwide. Year the United States, there will likely be 268,600 new cases diagnosed in 2019. Since 2006, death rates have decreased by an average of 1.8% annually, although the number of newly diagnosed cases has mostly stayed constant[77]. 6% of all new cases of breast cancer are metastatic, with a 27% 5-year overall survival rate[78]. Only single-agent chemotherapy with one of the following recommended drugs is

currently available for patients with metastatic TNBC: eribulin, liposomal, doxorubicin, capecitabine, gemcitabine, paclitaxel, and vinorelbine[79]. Olaparib (Lynparza) was given routine approval by the US Food and Drug Administration (FDA) on January 8 for patients with gBRCAm, HER2-negative metastatic breast cancer. The therapeutic effects of olaparib approval for oncology advanced practitioners, its usage in treating patients with metastatic breast cancer, and its role in treating individuals who have a gBRCAm mutation.

Most common malignancy in women is breast cancer are frequently diagnosed by worldwide. Risk for breast cancer can increase as a result of genetic abnormalities. The tumour suppressor genes BRCA1 and BRCA2 have inherited germline mutations in 5% to 10% of instances of breast cancer (gBRCAm) are to blame. Patients with a gBRCAm now have another therapy option thanks to olaparib, a poly (ADP-ribose) polymerase (PARP) inhibitor was approved to treat metastatic, HER2-negative breast cancer. When PARP is inhibited, at replication forks, the PARP-DNA complex is entrapped, causing single-strand breaks to become double-strand breaks (DSBs). Cell apoptosis is the result of PARP entrapment and the buildup of DSBs. BRCA1/2 deficient cells, which results in synthetic lethality, are more vulnerable to PARP inhibition's effects because they are unable to repair DNA damage. The phase III OlympiAD trial exhibit a benefit for survival without advancement, but there is no benefit for total survival, which led to the approval of olaparib. the therapeutic implications of olaparib's approval for oncology advanced practitioners, its use in the care of those with a gBRCAm mutation, and its role in the supervision of those with metastatic breast cancer [80].

5.4 Geographical Based Therapies

5.4.1 BRCA1/2 Pathogenic Mutation in Brazilian Individuals with Non-Selected Ovarian Cancer

The most fatal gynaecological malignancy is ovarian cancer. Ovarian cancer will likely cause 14,070 fatalities in the United States and 22,240 new cases, ranking it as the fifth most deadly cancer for women[81]. In most cases, the disease is diagnosed in its advanced clinical stages, which contributes to the high mortality. Even though certain high risk populations can get some limited benefits from screening[82]. The most frequent existence of germline BRCA1 or BRCA2 pathogenic mutations is known as the Hereditary Breast and Ovarian Cancer Syndrome (HBOC). Ovarian cancer risk existed for those who carried the harmful BRCA1 and BRCA2 mutations of around 45 and 20% till the age of 80, respectively [83].

The patients with ovarian cancer frequently carry pathogenic (P) and likely pathogenic (LP) BRCA1/2 germline mutations. These variations haven't, however, been thoroughly defined in Brazilian ovarian cancer patients. The clinical characteristics and results of germline genetic testing for the BRCA1/2 genes in ovarian cancer patients someone had genetic testing counselling at the A.C. Camargo Cancer Centre (Brazil) between 2015 and 2017 were evaluated in this retrospective investigation. 33 P and LP variations were discovered in 158 patients (20.8%), including 27 in BRCA1 and 6 in BRCA2, along with six mutations of questionable clinical importance. The Multiplex Ligation dependent Probe Amplification (MLPA) data were missing in 13% of the patients. BRCA1 three P variations were discovered in many patients: c. 3331_3334delCAAG (p.Gln1111Asnfs5*), 5266dupC (p.Gln1756Profs*74), and 211A > G (p.Arg71Gly). One LP variant in BRCA1-c.4153 4154delCT (p.Leu1385Ilefs*5) had not yet been reported [84].

5.4.2 Ovarian and Breast Cancer Effected by BRCA-Related Variant in Rome

The homologous recombination mechanism, which involves two genes named BRCA1 and BRCA2, is used to fix double-strand DNA breaks (HR). Genomic instability can be caused by pathogenic variations (PVs) in one of these genes that render the BRCA proteins inactive or dysfunctional. Due to the negative effects of these PVs, an individual is more likely to acquire cancer[85]. BRCA1 and BRCA2 deleterious germline PV carriers have a higher lifetime chance of having specifically, 60-80% for breast cancer (BC) and 26-54% and 10-23% for BRCA1 and BRCA2, respectively, for ovarian cancer (OC). For BRCA1 and BRCA2 PVs, the probability of BC in carrier men is 1% and 6%, respectively. Additionally, an increased PVs may have an impact on prostate and pancreatic cancer risk in these genes [86].

Increased risk of breast and ovarian cancer over the course of a lifetime is BRCA1 or BRCA2 carriers are connected to pathogenic variations (PVs). Among many racial and ethnic groupings, the frequency of germline mutations in BRCA1 and BRCA2 varies greatly. According to several studies, Italian BC and OC families have a controversial rate of variation that runs from 8% to 37%. We consistently examined hundreds of persons employing Next-generation sequencing (NGS)-based in vitro diagnostic (IVD) methods with either sporadic or family history of cancer. With the help of NGS, we discovered some new PVs and a few variations with unclear significance (VUS), which were subsequently evaluated in silico with the aid of specialised tools. We provide comprehensive information on BRCA1/2 mutations found in 517 out of 2351 BC and OC individuals. The

prevalence and range of Patients with BC and/or OC who underwent testing at Policlinico Gemelli Foundation Hospital and who are largely from Central and Southern Italy were discovered to have BRCA1/2 mutations. In addition to giving a general overview of the frequency of variance in various Italian regions, this study provides information that may be useful in the clinical care of patients [87].

5.4.3 BRCA1 and BRCA2 Mutation in Breast Cancer and Ovarian Cancer Patients in Russia

BRCA1 and BRCA2 germline mutations, respectively, have an impact on the incidence rates of breast and ovarian cancer (BC and OC) by 5-8% and 10-20%. Healthy females with known that people with BRCA1 or BRCA2 mutations follow their health and think about having preventive surgery[88, 89]. Regardless regardless of whether they show signs of a BRCA1 or BRCA2-driven illness, The spectrum of BRCA1 and BRCA2 mutations in Slavic, Jewish, and Icelandic people is often restricted to a few recurrent alleles, hence it is advised that all BC and OC patients undergo a number of ethnicity-specific BRCA1 and BRCA2 PCR testing [90].

High prevalence of the founder allele in Slavic countries reflects the range of BRCA1 and BRCA2 mutations. A substantial collect data of patients from Russia with breast cancer and ovarian cancer who performed full-length BRCA1 and BRCA2 testing or founder mutation testing analyses. The four founder mutations detected in the most popular test, which were discovered in 399/8533 (4.7%) consecutive BC patients, 230/2317 (9.9%) OC patients, and 30/118 (25.4%) women with a combination of BC and OC. (BRCA1: 4153delA, 4153delA, 185delAG; BRCA2: 6174delT). The quantity of known mutation carriers increased noticeably as a result of the addition of four additional test for recurrent BRCA1 mutations (BRCA1; 3819del5, and 3875del4) (OC: 34/1289 (2.6%); BC: 16/993 (1.6%); BC+OC: 2/39 (5.1%)). 785 women underwent sequence of the entire coding areas of BRCA1 and BRCA2, the majority of whom had BRCA-driven disease-related clinical symptoms but were negative for all of the aforementioned founder alleles [91].

5.5 Other therapies

5.5.1 Clinical significance of BRCA1 and BRCA2 mRNA expression in ovarian cancer

Tumor-suppressor genes BRCA1 and BRCA2 control gene transcription, apoptosis, the arrest of cell division, and the homologous recombination repair of DNA damage[92]. 5 to 10% of all epithelial OCs are genetic, and BRCA1/2 mutations account for at least

two-thirds of these[93]. According to current theory, Pathogenic BRCA mutations have better outcomes in OC patients survival rates, probably as a result of improved responses to poly(ADP)-ribose polymerase inhibitors (PARP) and platinum-based chemotherapy[93]. Although There are limited facts concerning on BRCA-expression in OCs with BRCA-wildtype, they might have clinical significance. We questioned if the transcriptome-level expression of BRCA1/2 may serve as an accurate predictor of the clinical prognosis for OC patients following the platinum response [94, 95].

Greater response to platinum-based chemotherapy, Better survival in patients with OC is associated with BRCA1 and BRCA2 mutations. However, it is still unclear how BRCA1/2 mRNA expression in OC works. The clinical features of 201 epithelial OCs and 12 non-cancerous fallopian tubes for the manifestation of BRCA1/2 mRNA. OCs had higher levels of BRCA1/2 mRNA expression than controls ($P = 0.011$ and $P = 0.001$, respectively). In BRCA1 mutant OCs, BRCA1 mRNA expression was reduced ($P = 0.014$), although BRCA2 mRNA expression was higher ($P = 0.001$). Low BRCA1 and BRCA2 expression were linked to higher overall survival (OS) and progression-free survival (PFS) ($P = 0.012$, $P = 0.004$, and $P = 0.001$, respectively). This effect, according to a subgroup study, was limited to tumours with the BRCA1-wildtype gene. The predictive effect of BRCA1-expression for OS was validated by Cox-regression ($P = 0.028$). Only high-grade serous OCs showed independence of the prognostic significance of BRCA2-expression for PFS ($P = 0.045$) and OS ($P = 0.015$). Increased platinum sensitivity because tissues with low BRCA1/2 expression have less capacity to repair DNA damage. In this context, both measures may also be potential indicators of PARP sensitivity, particularly in tumours containing BRCA-wildtype DNA [96].

5.5.2 Molecularly focused therapy for hereditary breast and ovarian cancer

A significant study model for individualised therapy strategies for certain germline mutations is the hereditary breast and ovarian cancer (HBOC) syndrome, which is connected to the pathogenic mutations of the breast cancer 1 (BRCA1) and breast cancer 2 (BRCA2) genes. Multiple incidences of breast and ovarian cancer in the same family branch, together with additional tumours (prostate, pancreatic, and stomach carcinoma), early onset (36 years), bilaterality, and an autosomal dominant inheritance pattern, are characteristics of HBOC. Women with metastatic and non-metastatic breast cancer may benefit from treatment interventions if a BRCA gene mutation is discovered. Treatment with

poly (ADP-ribose) polymerase (PARP) inhibitors, which prevent cancer cells from repairing their damaged DNA and result in cell death, is remarkable in the therapeutic scenario of BRCA+ breast cancer. The data supporting the utility of BRCA1/2 status as a diagnostic, prognostic, and predictive biomarker in the personalised treatment of hereditary BRCA + malignancies [97].

5.5.3 BRCA-Related Ovarian Carcinoma is Melphalan

The majority of deaths from gynecologic cancers globally are caused by ovarian cancer. About 60–70% of patients eventually experience recurrence despite the best debulking surgery, adequate firstline chemotherapy with Taxane-platinum doublets, bevacizumab- or poly (adenosine diphosphate-ribose-polymerase inhibitors (PARPi)-based maintenance therapy)[98, 99]. A nitrogen alkylating agent like mustard is called melphalan that can be given intravenously or orally and is primarily used to treat multiple myeloma. Since there is very little evidence available on using melphalan to treat epithelial ovarian cancer (EOC)[100]. The effectiveness and side effects of melphalan in platinum-resistant EOC with intensive pretreatment. In addition, we sought to demonstrate higher melphalan sensitivity in patients with BRCA1/2 deficiency [101].

Melphalan, a bifunctional alkylating drug, has demonstrated selective efficacy in reports of ovarian epithelial cancer cases that lack the BRCA gene (EOC). Melphalan therapeutic advantage in the general platinum-resistant EOC group is unclear how BRCA status should be categorised. Our goal was to evaluate the effectiveness of melphalan in treating individuals following platinum-based therapy with recurrent EOC. Between February 2007 and July 2020, patients with recurrent EOC who received melphalan were included in this retrospective observational analysis study. Recurrence of the disease while receiving treatment or within six months of finishing platinum-based chemotherapy. There were 75 platinum-resistant EOC patients in all. (Age range: 41–82) The median age was 69. Prior to melphalan, prior treatments had an average of 4 (with a range of 1–7). We found that with overall survival (OS), progression-free survival (PFS), and follow-up of 32 months on average (range: 1-62) were, respectively, 3.6 months (range 2.9-4.7) and 9.5 months (range 8.0-14.1). The highest proportion of melphalan-treated EOC patients who had undergone extensive pre-treatment [102].

5.5.4 Breast and Ovarian Cancers with BRCA1 and BRCA2-Mutated Transcriptome Patterns

The BRCA1 and BRCA2 genes play a major role in

maintaining genomic integrity and cancer suppression by promoting DNA repair by homologous recombination and activating replication[103]. 5-15% of individuals with ovarian cancer (OV) (10–25%) and breast cancer (BC) had mutations in the BRCA1 or BRCA2 gene. The cumulative risk for breast and ovarian malignancies with mutation carriers is around 70% and 14-44%, respectively[104, 105]. In-depth research is also being done on how BRCA1 and BRCA2 affect survival, but the findings are conflicting. Most studies report that people with breast cancer who have BRCA1 mutations have a worse clinical outcome than BRCA2 mutation carriers and non-carriers [106].

Breast and ovarian cancers recognised danger elements and primary causes of BRCA1 and BRCA2 gene mutations. The disease-related changes in the transcriptome and functional landscapes (breast vs ovarian malignancies), genes, and mutation type have received little attention to date (germline vs. somatic). Systematic analysis of the relationships between outcome, gene expression, illness clinical characteristics and treatment of BRCA1 and BRCA2 germline and somatic mutations. From the TCGA dataset, we examined RNA-seq data from breast and ovarian cancers utilising transcriptome and phenotypic "portrayal" through the use of functional annotation and multi-layer self-organizing maps. The analysis was focussed on BRCA1/2 mutations. The findings showed that the examined tumours landscapes of the BRCA1- and BRCA2-dependent transcriptome differed significantly. According to research, the characteristics of both somatic and germline mutations of both genes by the dysregulation of many biological processes and by diverse relationships with phenotypic traits and poly(ADP-ribose) polymerase (PARP)-inhibitor gene signatures [107].

7. Challenges and Limitations of BRCA1/2-Targeted Therapy

Despite the significant therapeutic advances associated with BRCA1/2-directed treatment, several challenges continue to influence treatment response and clinical outcomes. One of the major concerns is the development of acquired or primary resistance to targeted therapies, particularly poly(ADP-ribose) polymerase (PARP) inhibitors. Resistance may occur through restoration of homologous recombination repair, secondary or reversion mutations in BRCA1/2, alterations in DNA-damage response pathways, changes in drug transport, or other mechanisms that allow tumour cells to overcome the synthetic lethal effect of PARP inhibition. Consequently, patients who initially respond to treatment may eventually experience disease progression, highlighting the need

for better strategies to prevent or overcome therapeutic resistance.

Appropriate patient selection is another important consideration in BRCA-targeted therapy. Although BRCA1/2 mutations are important biomarkers for treatment selection, patients with the same mutation may demonstrate different treatment responses and clinical outcomes. Differences in germline and somatic mutations, tumour type, mutation status, genomic background, homologous recombination deficiency, previous treatment exposure, and disease stage can influence therapeutic response. Therefore, comprehensive molecular characterization and careful clinical assessment are important for identifying patients who are most likely to benefit from BRCA-directed treatment.

Genetic testing also plays an important role in the identification and management of patients with BRCA1/2-associated cancers. Germline testing can identify inherited BRCA1/2 mutations and may provide information relevant to both treatment selection and familial cancer-risk assessment, whereas tumour-based testing can identify somatic alterations that may have therapeutic implications. However, interpretation of genetic test results can be complicated by variants of uncertain significance, differences between germline and somatic findings, technical limitations, and differences in testing accessibility. Appropriate genetic counselling and standardized testing approaches are therefore important to ensure accurate interpretation and effective clinical decision-making.

Current BRCA-targeted therapeutic approaches also have several limitations. Although PARP inhibitors have demonstrated substantial clinical benefit in selected patients, their effectiveness is not uniform across all BRCA1/2-mutated tumours, and resistance and disease progression remain significant clinical concerns. Treatment-related adverse effects, the possibility of cumulative toxicity, differences in response between tumour types, and the emergence of resistance may restrict long-term therapeutic benefit. In addition, the clinical significance of individual BRCA1/2 variants and the optimal treatment strategy for patients with different molecular and clinical characteristics are not always clearly established. These limitations emphasize the need for continued research into predictive biomarkers, mechanisms of resistance, combination therapies, and individualized treatment strategies to improve the efficacy and durability of BRCA1/2-targeted therapy.

Conclusion

BRCA1 and BRCA2 genes are important tumour

suppressor genes that play diverse roles in the cell cycle and DNA repair mechanisms. Germline mutations in these genes predispose individuals to breast and ovarian cancer, and these mutations affect undiscovered molecular processes. The advancements in BRCA genetics have led to tailored therapy for patients with advanced ovarian cancer, and the BRCA carrier symbolizes hope in preventive health measures. The ATM-Chk2 and RAD51 pathways are activated by DNA damage and are responsible for coordinating cellular responses to DNA damage. Females with a germline mutation in one copy of a tumour suppressor gene may experience nonrandom X-chromosome inactivation, resulting in the emergence of hereditary malignancies. Personalized therapy based on the patient's molecular profile is becoming increasingly important, and the BRCA genes have been focused of substantial ethnographic research. Lastly, the BRCA1 and BRCA2 genes could impact fertility, and studies have been conducted to evaluate ovarian reserve and fertility preservation in breast cancer patients with BRCA mutations.

References

1. Lincoln, S., et al., Proffered Papers and Posters Presented at the Seventh International Symposium on Hereditary Breast and Ovarian Cancer—BrcA: From the Personal to the Population. *Current Oncology*, 2018. 25(3): p. 224-262.
2. Maioru, O.-V., et al., Developments in Genetics: Better Management of Ovarian Cancer Patients. *International Journal of Molecular Sciences*, 2023. 24(21): p. 15987.
3. Paul, A. and S. Paul, The breast cancer susceptibility genes (BRCA) in breast and ovarian cancers. *Front. Biosci. (Landmark Ed)*, 2014. 19(4): p. 605-618.
4. Deng, C.-X., BRCA1: cell cycle checkpoint, genetic instability, DNA damage response and cancer evolution. *Nucleic Acids Research*, 2006. 34(5): p. 1416-1426.
5. Mehta, A., et al., Germline BRCA1 and BRCA2 deleterious mutations and variants of unknown clinical significance associated with breast/ovarian cancer: a report from North India. *Cancer Manag Res*, 2018. 10: p. 6505-6516.
6. Zhang, J., The role of BRCA1 in homologous recombination repair in response to replication stress: significance in tumorigenesis and cancer therapy. *Cell & Bioscience*, 2013. 3(1): p. 11.
7. Yue, W., et al., The Apoptotic Resistance of BRCA1-Deficient Ovarian Cancer Cells is Mediated by cAMP. *Frontiers in Cell and Developmental Biology*, 2022. Volume 10 - 2022.
8. Coignard, J., et al., A case-only study to identify genetic modifiers of breast cancer risk for BRCA1/BRCA2 mutation carriers. *Nature Communications*, 2021. 12(1): p. 1078.
9. Moser, S.C. and J. Jonkers, Thirty Years of BRCA1: Mechanistic Insights and Their Impact on Mutation Carriers. *Cancer Discov*, 2025. 15(3): p. 461-480.
10. Mehrgou, A. and M. Akouchekian, The importance of BRCA1 and BRCA2 genes mutations in breast cancer development. *Med J Islam Repub Iran*, 2016. 30: p. 369.
11. Georgy, D.M., et al., From mutation to treatment: The dual role of BRCA1 and BRCA2 in gynecological malignancy development and management a systematic review. *Biochemistry and Biophysics Reports*, 2026. 46: p. 102564.
12. Jazaeri, A.A., Molecular profiles of hereditary epithelial ovarian cancers and their implications for the biology of this disease. *Mol Oncol*, 2009. 3(2): p. 151-6.
13. Kim, S.I., et al., Germline and Somatic BRCA1/2 Gene Mutational Status and Clinical Outcomes in Epithelial Peritoneal, Ovarian, and Fallopian Tube Cancer: Over a Decade of Experience in a Single Institution in Korea. *Cancer Res Treat*, 2020. 52(4): p. 1229-1241.
14. Chang-Claude, J., Inherited genetic susceptibility to breast cancer. *IARC Sci Publ*, 2001. 154: p. 177-90.

Acknowledgement

Thankful to Narayan Institute of Pharmaceutical Sciences, Gopal Narayan Singh University, Jamuhar, Sasaram, 821305, Bihar, INDIA, for their support throughout writing this article.

Author Contribution

SK: Study Conception and Design; **AKP:** Data Collection; **DK:** Data Analysis; **MS:** Manuscript Drafting.

Consent for publication

Not applicable.

Funding

None.

Conflict of interest

The author declared no conflict of interest, financial or otherwise.

AI declaration: No any AI tools are used for generating scientific data, results, or conclusions.

15. Arafa, A.T., et al., Germline-Somatic Interactions in BRCA-Associated Cancers: Unique Molecular Profiles and Clinical Outcomes Linking ATM to TP53 Synthetic Essentiality. *Clin Cancer Res*, 2025. 31(9): p. 1730-1745.
16. Ceyhan-Birsoy, P., Ozge, M. Misyura, and D. Mandelker, A Clinical Approach to Detecting Germline Pathogenic Variants From Tumor-Only Sequencing. *JNCI Cancer Spectrum*, 2020. 4(3).
17. Yan, W., et al., Activation of the ATM-Chk2 DNA damage response pathway by Newcastle disease virus enhances viral replication. *Veterinary Research*, 2026. 57(1): p. 24.
18. Creeden, J.F., et al., Homologous recombination proficiency in ovarian and breast cancer patients. *BMC Cancer*, 2021. 21(1): p. 1154.
19. Tan, P., et al., Immunohistochemical expression of p53 protein in invasive breast carcinoma: clinicopathologic correlations. *Oncol Rep*, 1999. 6(5): p. 1159-63.
20. Amos-Landgraf, J.M., et al., X Chromosome Inactivation Patterns of 1,005 Phenotypically Unaffected Females. *The American Journal of Human Genetics*, 2006. 79(3): p. 493-499.
21. Lamarche, B.J., N.I. Orazio, and M.D. Weitzman, The MRN complex in double-strand break repair and telomere maintenance. *FEBS Letters*, 2010. 584(17): p. 3682-3695.
22. Majka, J., et al., ATP Hydrolysis by RAD50 Protein Switches MRE11 Enzyme from Endonuclease to Exonuclease*. *Journal of Biological Chemistry*, 2012. 287(4): p. 2328-2341.
23. Wu, J., L.-Y. Lu, and X. Yu, The role of BRCA1 in DNA damage response. *Protein & Cell*, 2010. 1(2): p. 117-123.
24. Pourmasoumi, P., A. Moradi, and M. Bayat, BRCA1/2 Mutations and Breast/Ovarian Cancer Risk: A New Insights Review. *Reproductive Sciences*, 2024. 31(12): p. 3624-3634.
25. Ellison, G., et al., A reliable method for the detection of BRCA1 and BRCA2 mutations in fixed tumour tissue utilising multiplex PCR-based targeted next generation sequencing. *BMC Clin Pathol*, 2015. 15: p. 5.
26. Ewald, I.P., et al., Genomic rearrangements in BRCA1 and BRCA2: A literature review. *Genet Mol Biol*, 2009. 32(3): p. 437-46.
27. Ozcelik, H., et al., Long-range PCR and next-generation sequencing of BRCA1 and BRCA2 in breast cancer. *The Journal of Molecular Diagnostics*, 2012. 14(5): p. 467-475.
28. Wang, F., et al., Tumor immune microenvironment and mutational analysis of tracheal adenoid cystic carcinoma. *Annals of Translational Medicine*, 2020. 8(12).
29. Bensimon, A., et al., Methods for the detection, visualization and high resolution physical mapping of genomic rearrangements in breast and ovarian cancer genes and loci brca1 and brca2 using genomic morse code in conjunction with molecular combing. 2014, Google Patents.
30. Manie, E., M.-H. Stern, and T. Popova, Methods for detecting inactivation of the homologous recombination pathway (BRCA1/2) in human tumors. 2021, Google Patents.
31. Scherer, K.H., Grating-based X-ray phase-contrast mammography. 2016: Springer.
32. Sinha, S. and S.M. Wang, Classification of VUS and unclassified variants in BRCA1 BRCT repeats by molecular dynamics simulation. *Computational and structural biotechnology journal*, 2020. 18: p. 723-736.
33. Ernst, C., et al., Performance of in silico prediction tools for the classification of rare BRCA1/2 missense variants in clinical diagnostics. *BMC medical genomics*, 2018. 11: p. 1-10.
34. Xie, Y., et al., Combined strategies with PARP inhibitors for the treatment of BRCA wide type cancer. *Frontiers in Oncology*, 2024. Volume 14 - 2024.
35. Qi, W., et al., BRCA1/2 Reversion Mutations and Cancer Therapy Resistance. *Biology*, 2026. 15(11): p. 866.
36. Vergote, I., et al., Current perspectives on recommendations for BRCA genetic testing in ovarian cancer patients. *European Journal of Cancer*, 2016. 69: p. 127-134.
37. Prokurotaite, E., et al., Impact of Breast Cancer and Germline BRCA Pathogenic Variants on Fertility Preservation in Young Women. *Life*, 2023. 13(4): p. 930.
38. Sendur, M.A.N., et al., Talazoparib in patients with BRCA mutant metastatic breast or ovarian carcinoma: results of early access program. *BMC Cancer*, 2025. 25(1): p. 1897.
39. Fernandes, G.C., et al., Prevalence of BRCA1/BRCA2 mutations in a Brazilian population sample at-risk for hereditary breast cancer and characterization of its genetic ancestry. *Oncotarget*, 2016. 7(49): p. 80465-80481.
40. Arakelyan, A., et al., Transcriptome Patterns of BRCA1- and BRCA2- Mutated Breast and Ovarian Cancers. *International Journal of Molecular Sciences*, 2021. 22(3): p. 1266.
41. Zhang, M., et al., The Role of Cancer-Associated Fibroblasts in Ovarian Cancer. *Cancers*, 2022. 14(11): p. 2637.

42. Fu, X., et al., Mechanism of PARP inhibitor resistance and potential overcoming strategies.
43. Colombo, I., S. Lheureux, and A.M. Oza, Rucaparib: a novel PARP inhibitor for BRCA advanced ovarian cancer. *Drug Des Devel Ther*, 2018. 12: p. 605-617.
44. Havasi, A., et al., Ovarian Cancer—Insights into Platinum Resistance and Overcoming It. *Medicina*, 2023. 59(3): p. 544.
45. Kubelac, P., et al., The clinical features associated with mutated BRCA1 and 2 genes in ovarian cancer patients. *J Buon*, 2019. 24(4): p. 1538-1543.
46. Ren, Y., et al., Global, regional, and national burden of ovarian cancer in women aged 45 + from 1990 to 2021 and projections for 2050: a systematic analysis based on the 2021 global burden of disease study. *Journal of Cancer Research and Clinical Oncology*, 2025. 151(8): p. 225.
47. Chao, A., et al., Prevalence and clinical significance of BRCA1/2 germline and somatic mutations in Taiwanese patients with ovarian cancer. *Oncotarget*, 2016. 7(51): p. 85529-85541.
48. Bernardo, C.J., et al., Prevalence of Somatic BRCA1 and BRCA2 Mutations in Ovarian Cancer among Filipinos using Next Generation Sequencing. *PJP*, 2023.
49. Stratton, J.F., et al., Contribution of BRCA1 mutations to ovarian cancer. *New England Journal of Medicine*, 1997. 336(16): p. 1125-1130.
50. Shi, T., et al., Survival benefit of germline BRCA mutation is associated with residual disease in ovarian cancer. *Cellular Physiology and Biochemistry*, 2018. 47(5): p. 2088-2096.
51. Pennington, K.P., et al., Germline and Somatic Mutations in Homologous Recombination Genes Predict Platinum Response and Survival in Ovarian, Fallopian Tube, and Peritoneal Carcinomas DNA Repair Mutations and Outcomes in Ovarian Cancer. *Clinical Cancer Research*, 2014. 20(3): p. 764-775.
52. Mathews, C.A., et al., Maintenance olaparib after platinum-based chemotherapy in patients (pts) with newly diagnosed advanced ovarian cancer (OC) and a BRCA mutation (BRCAm): Efficacy by surgical and tumor status in the Phase III SOLO1 trial. 2019, American Society of Clinical Oncology.
53. Bekos, C., et al., Reliability of tumor testing compared to germline testing for detecting BRCA1 and BRCA2 mutations in patients with epithelial ovarian cancer. *Journal of Personalized Medicine*, 2021. 11(7): p. 593.
54. Gibbon, S., et al., Breast cancer gene research and medical practices: transnational Genes & Diseases, 2024. 11(1): p. 306-320.
- perspectives in the time of BRCA. 2014: Routledge.
55. Mozersky, J. and S. Gibbon, Chapter Mapping Jewish Identities: Migratory Histories and the Transnational Re-Framing of 'Ashkenazi BRCA Mutations' in the UK and Brazil. *Breast Cancer Gene Research and Medical Practices*, 2014.
56. Therond, C., et al., The narrative paradox of the BRCA gene: an ethnographic study in the clinical encounters of ovarian cancer patients. *Anthropology & Medicine*, 2020. 27(4): p. 449-464.
57. Sousa, V., G. Livera, and M. Misrahi, Genetics of Premature Ovarian Insufficiency: From Molecular Architecture to Precision Medicine. *International Journal of Molecular Sciences*, 2026. 27(19): p. 8662.
58. Tschernichovsky, R. and A. Goodman, Risk-Reducing Strategies for Ovarian Cancer in BRCA Mutation Carriers: A Balancing Act. *The Oncologist*, 2017. 22(4): p. 450-459.
59. McCarthy, A.M. and K. Armstrong, The role of testing for BRCA1 and BRCA2 mutations in cancer prevention. *JAMA Intern Med*, 2014. 174(7): p. 1023-4.
60. Porcu, E., et al., Impact of BRCA1 and BRCA2 mutations on ovarian reserve and fertility preservation outcomes in young women with breast cancer. *Journal of Assisted Reproduction and Genetics*, 2020. 37(3): p. 709-715.
61. Foulkes, W.D., BRCA1 and BRCA2: chemosensitivity, treatment outcomes and prognosis. *Familial cancer*, 2006. 5(2): p. 135-142.
62. Niravath, P., B. Cakar, and M. Ellis, The role of genetic testing in the selection of therapy for breast cancer: a review. *JAMA oncology*, 2017. 3(2): p. 262-268.
63. Ferri, M., et al., Targeting Wnt-driven cancers: Discovery of novel tankyrase inhibitors. *European Journal of Medicinal Chemistry*, 2017. 142: p. 506-522.
64. Robson, M., et al., Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *New England Journal of Medicine*, 2017. 377(6): p. 523-533.
65. Li, J., et al., Prevalence of BRCA1 and BRCA2 pathogenic variants in a large, unselected breast cancer cohort. *International journal of cancer*, 2019. 144(5): p. 1195-1204.
66. Boussios, S., et al., Veliparib in ovarian cancer: a new synthetically lethal therapeutic approach. *Investigational new drugs*, 2020. 38(1): p. 181-193.

67. Mateo, J., et al., A decade of clinical development of PARP inhibitors in perspective. *Annals of Oncology*, 2019. 30(9): p. 1437-1447.
68. Lord, C.J. and A. Ashworth, BRCAness revisited. *Nature Reviews Cancer*, 2016. 16(2): p. 110-120.
69. Tomao, F., et al., Parp inhibitors as maintenance treatment in platinum sensitive recurrent ovarian cancer: an updated meta-analysis of randomized clinical trials according to BRCA mutational status. *Cancer Treatment Reviews*, 2019. 80: p. 101909.
70. Sachdev, E., et al., PARP inhibition in cancer: an update on clinical development. *Targeted oncology*, 2019. 14(6): p. 657-679.
71. Gruber, J.J., et al., A phase II study of talazoparib monotherapy in patients with wild-type BRCA1 and BRCA2 with a mutation in other homologous recombination genes. *Nature Cancer*, 2022. 3(10): p. 1181-1191.
72. Wijaya, K., N. Yoshioka, and H. Inoue, DNA binding of iron (II) complexes with 1, 10-phenanthroline and 4, 7-diphenyl-1, 10-phenanthroline: salt effect, ligand substituent effect, base pair specificity and binding strength. *Journal of inorganic biochemistry*, 2003. 94(3): p. 263-271.
73. Yoshioka, N. and H. Inoue, DNA binding of iron (II) mixed-ligand complexes containing 1, 10-phenanthroline and 4, 7-diphenyl-1, 10-phenanthroline. *Journal of inorganic biochemistry*, 1999. 77(3-4): p. 239-247.
74. Huesca, M., et al., A novel small molecule with potent anticancer activity inhibits cell growth by modulating intracellular labile zinc homeostasis. *Anticancer Activity of ML-133. Molecular cancer therapeutics*, 2009. 8(9): p. 2586-2596.
75. Cercek, A., et al., Phase 1 study of APTO-253 HCl, an inducer of KLF4, in patients with advanced or metastatic solid tumors. *Investigational new drugs*, 2015. 33: p. 1086-1092.
76. Tsai, C.-Y., et al., APTO-253 is a new addition to the repertoire of drugs that can exploit DNA BRCA1/2 deficiency. *Molecular cancer therapeutics*, 2018. 17(6): p. 1167-1176.
77. Saeed, S., et al., Cancer and how the patients see it; prevalence and perception of risk factors: a cross-sectional survey from a tertiary care centre of Karachi, Pakistan. *BMC public health*, 2019. 19: p. 1-7.
78. Domchek, S.M., et al., Abstract PD6-11: An open-label, multitumor, phase II basket study of olaparib and durvalumab (MEDIOLA): Results in germline BRCA-mutated (g BRCA m) HER2-negative metastatic breast cancer (MBC). *Cancer Research*, 2018. 78(4_Supplement): p. PD6-11-PD6-11.
79. Litton, J.K., et al., Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. *New England Journal of Medicine*, 2018. 379(8): p. 753-763.
80. Caulfield, S.E., C.C. Davis, and K.F. Byers, Olaparib: a novel therapy for metastatic breast cancer in patients with a BRCA1/2 mutation. *Journal of the advanced practitioner in oncology*, 2019. 10(2): p. 167.
81. Siegel, R.L., K.D. Miller, and A. Jemal, *Cancer statistics*, 2019. CA: a cancer journal for clinicians, 2019. 69(1): p. 7-34.
82. Rosenthal, A.N., et al., Evidence of stage shift in women diagnosed with ovarian cancer during phase II of the United Kingdom Familial Ovarian Cancer Screening Study. *Journal of Clinical Oncology*, 2017. 35(13): p. 1411.
83. Kuchenbaecker, K.B., et al., Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. *Jama*, 2017. 317(23): p. 2402-2416.
84. Cotrim, D.P., et al., Prevalence of BRCA1 and BRCA2 pathogenic and likely pathogenic variants in non-selected ovarian carcinoma patients in Brazil. *BMC cancer*, 2019. 19(1): p. 1-9.
85. Lakhani, S.R., et al., Prediction of BRCA1 status in patients with breast cancer using estrogen receptor and basal phenotype. *Clinical cancer research*, 2005. 11(14): p. 5175-5180.
86. Iqbal, J., et al., The incidence of pancreatic cancer in BRCA1 and BRCA2 mutation carriers. *British journal of cancer*, 2012. 107(12): p. 2005-2009.
87. Santonocito, C., et al., Spectrum of germline BRCA1 and BRCA2 variants identified in 2351 ovarian and breast cancer patients referring to a reference cancer hospital of Rome. *Cancers*, 2020. 12(5): p. 1286.
88. Domchek, S.M., et al., Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. *Jama*, 2010. 304(9): p. 967-975.
89. Ludwig, K.K., et al., Risk reduction and survival benefit of prophylactic surgery in BRCA mutation carriers, a systematic review. *The American Journal of Surgery*, 2016. 212(4): p. 660-669.
90. Paluch-Shimon, S., et al., Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening. *Annals of Oncology*, 2016. 27: p. v103-v110.

91. Sokolenko, A.P., et al., Frequency and spectrum of founder and non-founder BRCA1 and BRCA2 mutations in a large series of Russian breast cancer and ovarian cancer patients. *Breast Cancer Research and Treatment*, 2020. 184(1): p. 229-235.
92. Roy, R., J. Chun, and S.N. Powell, BRCA1 and BRCA2: different roles in a common pathway of genome protection. *Nature Reviews Cancer*, 2012. 12(1): p. 68-78.
93. Risch, H.A., et al., Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer. *The American Journal of Human Genetics*, 2001. 68(3): p. 700-710.
94. Sabatier, R., et al., Ovarian cancer patients at high risk of BRCA mutation: the constitutional genetic characterization does not change prognosis. *Familial cancer*, 2016. 15(4): p. 497-506.
95. Kotsopoulos, J., et al., Ten-year survival after epithelial ovarian cancer is not associated with BRCA mutation status. *Gynecologic oncology*, 2016. 140(1): p. 42-47.
96. Tsibulak, I., et al., BRCA1 and BRCA2 mRNA-expression prove to be of clinical impact in ovarian cancer. *British journal of cancer*, 2018. 119(6): p. 683-692.
97. Ponti, G., et al., Hereditary breast and ovarian cancer: from genes to molecular targeted therapies. *Critical Reviews in Clinical Laboratory Sciences*, 2023: p. 1-11.
98. Conteduca, V., et al., The emerging role of anti-angiogenic therapy in ovarian cancer. *International journal of oncology*, 2014. 44(5): p. 1417-1424.
99. Rao, H.-L., et al., Increased intratumoral neutrophil in colorectal carcinomas correlates closely with malignant phenotype and predicts patients' adverse prognosis. *PloS one*, 2012. 7(1): p. e30806.
100. Hasan, J. and G.C. Jayson, Oral melphalan as a treatment for platinum-resistant ovarian cancer. *British journal of cancer*, 2003. 88(12): p. 1828-1830.
101. Fan, F.S. and C.-F. Yang, Complete response to orally administered melphalan in malignant pleural effusion from an occult female genital organ primary neoplasm with BRCA1/2 mutations: a case report. *Journal of Medical Case Reports*, 2018. 12(1): p. 1-6.
102. Conteduca, V., et al., Melphalan as a Promising Treatment for BRCA-Related Ovarian Carcinoma. *Frontiers in oncology*, 2021. 11: p. 716467.
103. Lord, C.J. and A. Ashworth, The DNA damage response and cancer therapy. *Nature*, 2012. 481(7381): p. 287-294.
104. Ricci, M.T., et al., Referral of ovarian cancer patients for genetic counselling by oncologists: need for improvement. *Public health genomics*, 2015. 18(4): p. 225-232.
105. Shah, S., et al., Epithelial ovarian cancer: Providing evidence of predisposition genes. *International Journal of Environmental Research and Public Health*, 2022. 19(13): p. 8113.
106. Hennessy, B.T., et al., Somatic mutations in BRCA1 and BRCA2 could expand the number of patients that benefit from poly (ADP ribose) polymerase inhibitors in ovarian cancer. *Journal of Clinical Oncology*, 2010. 28(22): p. 3570.
107. Arakelyan, A., et al., Transcriptome patterns of brca1-and brca2-mutated breast and ovarian cancers. *International journal of molecular sciences*, 2021. 22(3): p. 1266.