RAD51 and *PALB2* in precision oncology: Clinical implications for HRD associated breast and ovarian cancers (Review)

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Received April 7, 2025; Accepted June 3, 2025

DOI: 10.3892/ijo.2025.5771

Abstract. Maintaining genomic stability is essential for reducing the risk of carcinogenesis. Homologous recombination (HR) is a high-fidelity DNA repair mechanism that addresses double-strand breaks and interstrand crosslinks. The present review examined two key components of HR: *RAD51*, the eukaryotic recombinase and *PALB2*, a scaffolding protein. Their structural and functional roles are explored in the context of breast and ovarian cancer. *RAD51* facilitates homology search and strand invasion, while *PALB2* links *BRCA1* and *BRCA2*, stabilizing *RAD51* filaments. Mutations in these genes compromise HR, increasing susceptibility to various cancers and impacting treatment efficacy by impairing DNA repair. The present review discussed the clinical implications of *RAD51* and *PALB2* mutations, focusing on risk stratification, PARP inhibitor efficacy and emerging therapies. Additionally, it highlighted the potential of *RAD51* and *PALB2* as biomarkers and therapeutic targets, contributing to advances in personalized cancer management.

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Key words: RAD51, PALB2, BRCA, breast cancer, ovarian cancer, *HRR, PARP* inhibitors, theragnostic, genetic testing

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1. Introduction

Cancer develops due to genetic and epigenetic alterations that disrupt normal cellular functions, leading to uncontrolled proliferation and genomic instability. As the second leading cause of global mortality, its incidence continues to rise, driven by errors in cell division, environmental exposures (such as tobacco smoke and UV radiation) and inherited mutations (1). Among the most prevalent malignancies, breast cancer is the most frequently diagnosed cancer in women worldwide, whereas ovarian cancer, although less common, has a higher fatality rate (2). According to the World Health Organization, the global incidence of these cancers is projected to rise from 2.62 million in 2022 to 4.06 million by 2050, with mortality increasing from 873,000 to 1.49 million during the same period (3).

Genetic predisposition plays a central role in the development of these cancers, interacting with environmental

and lifestyle factors. In Asia and India, mortality rates are expected to increase by 67.6 and 100.5%, respectively, by 2050, with similar trends in incidence. Although lifestyle factors contribute to cancer risk, genetic mutations, particularly in *BRCA1* and *BRCA2*, are well-established drivers of hereditary breast and ovarian cancer syndrome (3-5). The increased mortality rates linked to breast and ovarian malignancies can mostly be ascribed to postponed diagnosis and the emergence of therapeutic resistance (6,7). Over 55% of ovarian cancer patients are identified at advanced stages (III/IV), where metastases and chemoresistance markedly restrict curative alternatives (8). Likewise, aggressive variants of breast cancer, including triple-negative breast cancer, often exhibit resistance to standard treatments such as platinum-based chemotherapy and radiotherapy, resulting in unfavorable prognoses (9,10). The evolution of resistance mechanisms entails intricate biochemical pathways that influence drug inflow and efflux, drug inactivation, DNA damage repair and apoptotic signaling. Combating delayed diagnosis via awareness campaigns and therapy resistance with targeted molecular strategies is essential for enhancing outcomes in gynecologic malignancies (6,11). Advances in next-generation sequencing have identified additional susceptibility genes, including *TP53, PTEN, PALB2* and *RAD51*, further expanding the understanding of genetic influences on cancer risk (12-14).

RAD51 and *PALB2* are key components of homologous recombination repair (HRR), a critical pathway for maintaining genomic stability. *RAD51*, located on chromosome 15q15.1, encodes a 339-amino acid protein essential for DNA repair, whereas *PALB2*, on chromosome 16p12.2, functions as a molecular scaffold, linking *BRCA1* and *BRCA2* to stabilize *RAD51* filaments (15-20). Mutations in these genes compromise HRR, increasing susceptibility to breast, ovarian and other cancers. The present review examines their roles in cancer biology, their clinical significance and their potential as therapeutic targets (Fig. 1).

2. Domain organization

RAD51. As a 37-kDa protein composed of 339 amino acids in humans, *RAD51* has a bipartite structure that facilitates its recombinase function. Its structure is highly conserved across species, underscoring its essential role in cellular processes. Among its functional domains, *RAD51* possesses an ATPase domain responsible for DNA strand exchange and repair (21). The N-terminal domain (NTD), spanning residues 1-114, is predominantly unstructured and contains regulatory features. This region includes a conserved BRC repeat-binding motif that mediates a critical interaction with *BRCA2*, a key *RAD51* regulator. The NTD also harbors multiple phosphorylation sites, including Thr13 and Ser14, which are essential for regulating *RAD51* function and facilitating its nuclear-cytoplasmic shuttling. These post-translational modifications allow for precise modulation of *RAD51* activity in response to cellular signals and DNA damage (22,23). The core domain (residues 115-339) is the most conserved and serves as the primary site for recombinase activity. It contains the Walker A and B motifs, which are essential for ATP binding and hydrolysis, as well as the structural components required for recombinase function (Fig. 2).

ATP hydrolysis provides the energy required for *RAD51* filament assembly and strand exchange (24,25). Within this domain, two DNA-binding loops (L1 and L2) facilitate interactions with both single- and double-stranded DNA, aiding in homology recognition and strand invasion during homologous recombination (HR). These loops enable *RAD51* to efficiently bind DNA and mediate repair processes. The core domain of *RAD51* consists of two subdomains connected by a linker and adopts a RecA-like fold, a structural feature shared among recombinases across species. This conservation highlights the evolutionary significance of this fundamental step in DNA repair (26).

RAD51 primarily exists as a quaternary structure in the form of heptameric rings, which undergo conformational changes upon binding to single-stranded DNA (ssDNA). In the presence of ATP, these rings dissociate and reassemble onto ssDNA, forming active nucleoprotein filaments essential for strand invasion and homology searching. The dynamic assembly and disassembly of these filaments serve as a critical regulatory mechanism in HR (27).

PALB2. *PALB2* is a larger protein, comprising 1,186 amino acids, that functions as a molecular scaffold in the HR pathway by coordinating the activities of multiple DNA repair factors. Its structure consists of several distinct domains that contribute to its broad functionality. The N-terminal coiled-coil domain (residues 9-44) interacts with BRCA1, a critical step in assembling the BRCA1-*PALB2*-BRCA2 complex. This interaction enables *PALB2* to recruit BRCA2 and *RAD51* to sites of DNA damage, underscoring its essential role in HR (19,28). Adjacent to the coiled-coil domain, the N-terminal region (residues 1-200) contains an evolutionarily conserved sequence that preferentially binds D-loop structures, which are key intermediates in HR. The C-terminal region (residues 853-1186) features a predicted DNA-binding domain with a strong affinity for both single- and double-stranded DNA. The presence of multiple DNA-binding regions suggests that *PALB2* not only identifies and stabilizes DNA structures requiring repair but also serves as a critical scaffold during the repair process (29,30).

A defining feature of *PALB2* is its chromatin association motif (ChAM, residues 395-446), which facilitates chromatin localization and enables the protein to respond to DNA damage (Fig. 3). This domain enables *PALB2* to function as a potential sensor of chromatin state, linking DNA repair processes to broader chromatin organization. *PALB2* contains an MRG15-binding domain (residues 611-764), which interacts with Mrg15, a component of histone acetyltransferase and deacetylase complexes. This association connects *PALB2* to chromatin remodeling processes, where it facilitates gene silencing to support DNA repair (19,31). In the C-terminal portion (residues 853-1186), *PALB2* possesses a WD40 domain that forms a seven-bladed β-propeller structure. This domain serves as the primary interaction site for BRCA2 and is also involved in DNA binding and *RAD51* recruitment. Due to its ability to mediate multiple protein-protein interactions, the WD40 domain plays a key role in establishing *PALB2* as a molecular scaffold essential for assembling the homologous recombination (HR) machinery at sites of DNA damage (19,29,32). Throughout its structure, *PALB2* contains

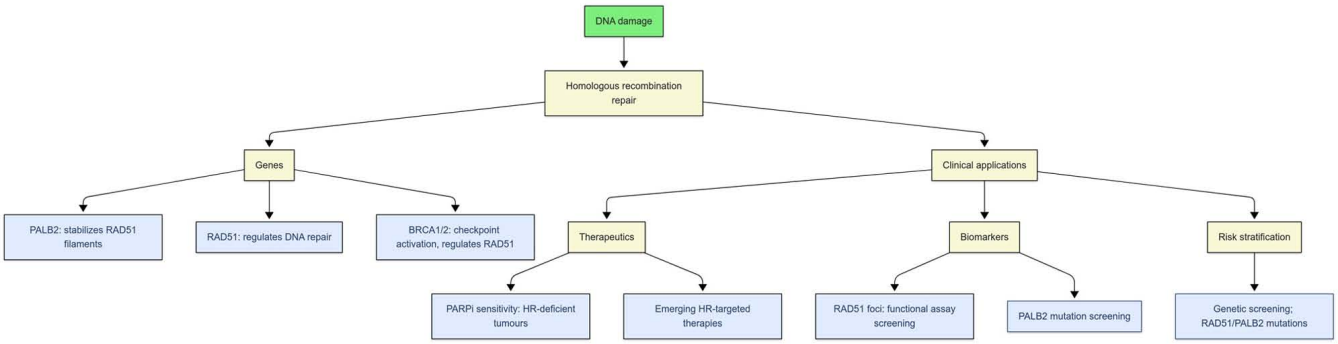


Figure 1. Schematic representation of the current review underscoring the clinical implication of *RAD51* and *PALB2* in breast and ovarian carcinomas.

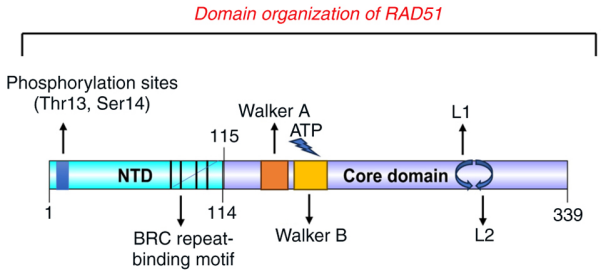


Figure 2. Domain organization of *RAD51*. NTD and Core domain (DOG 1.0 illustrator).

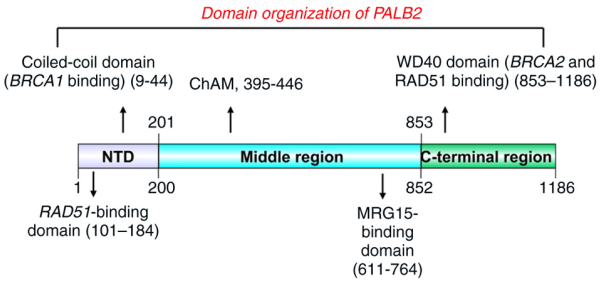


Figure 3. Domain organization of *PALB2*. NTD, Middle region and C-terminal region (DOG 1.0 illustrator).

two *RAD51*-binding domains (residues 101-184 and 850-1186), which facilitate the recruitment of *RAD51* to DNA lesions. This interaction strengthens the connection between *PALB2* and the recombinase components essential for HR, underscoring its central role in orchestrating HR complex assembly and function (19,33).

Similar to other essential DNA repair proteins, *RAD51* and *PALB2* have complex modular structures that reflect their functional roles in HR and their significance in cancer susceptibility. Structural alterations in these proteins can severely affect their function and compromise genomic stability. For instance, mutations in the *RAD51* core domain may impair its ATPase activity or DNA-binding ability, leading to defective HR and an increased cancer risk. Similarly, mutations in the coiled-coil domain of *PALB2* may weaken its binding affinity for BRCA1, while alterations in the WD40 domain could disrupt its interaction with BRCA2, thereby impairing HR activity (32,34-36).

3. Molecular functions

RAD51: orchestrating homologous recombination. *RAD51*, a conserved recombinase, is essential for HR, ensuring genetic integrity in breast, ovarian and prostate tissues. Along with its paralogs (*RAD51*B, *RAD51*C, *RAD51*D, XRCC2 and XRCC3), *RAD51* assembles nucleoprotein filaments on ssDNA, facilitating the search for homologous sequences and strand invasion. This process is fundamental for repairing DNA double-strand breaks (DSBs) and interstrand crosslinks (32,33,37-39).

The functional scope of *RAD51* transcends its traditional role in homologous recombination repair, incorporating essential defense against oxidative damage, a major factor in genomic instability inside cancer cells. Evidence suggests that *RAD51* is overexpressed in high-grade serous ovarian cancer and is associated with unfavorable prognosis. This overexpression seems functionally associated with the regulation of heightened reactive oxygen species (ROS) levels commonly seen in aggressive cancers (40). The reduction or suppression of *RAD51* leads to G_2/M cell cycle arrest, indicating its significance in cellular responses to oxidative stress. Mechanistically, *RAD51* aids in the repair of oxidative DNA damage by participating in homology-directed repair pathways and specialized responses to oxidative stress. The protein seems to regulate mitochondrial function, affecting superoxide production and overall cellular redox balance. The protective function of *RAD51* against oxidative damage may partly elucidate why its overexpression provides survival benefits to cancer cells in microenvironments marked by increased ROS (41,42).

RAD51 constructs a helical nucleoprotein filament on ssDNA, enabling the recognition and invasion of homologous DNA sequences for accurate DNA repair. Binding to ssDNA stabilizes the filament, whereas mutations that destabilize the *RAD51-ssDNA* complex result in deficient DSB repair (43-45). The *RAD51-ssDNA* filament scans neighboring DNA duplexes for homologous sequences. Upon identifying a match, *RAD51* facilitates strand invasion, allowing ssDNA to penetrate the double-stranded template and form a displacement loop (D-loop). This step is critical for *RAD51*-dependent DNA repair, as strand exchange is a key function of the protein. The assembly and disassembly of the *RAD51* filament are regulated by replication protein A (RPA) and *RAD51* paralogs, which modulate filament activity and stability (46-48).

The *RAD51-ssDNA* filament scans adjacent DNA duplexes for homologous sequences. Upon identifying

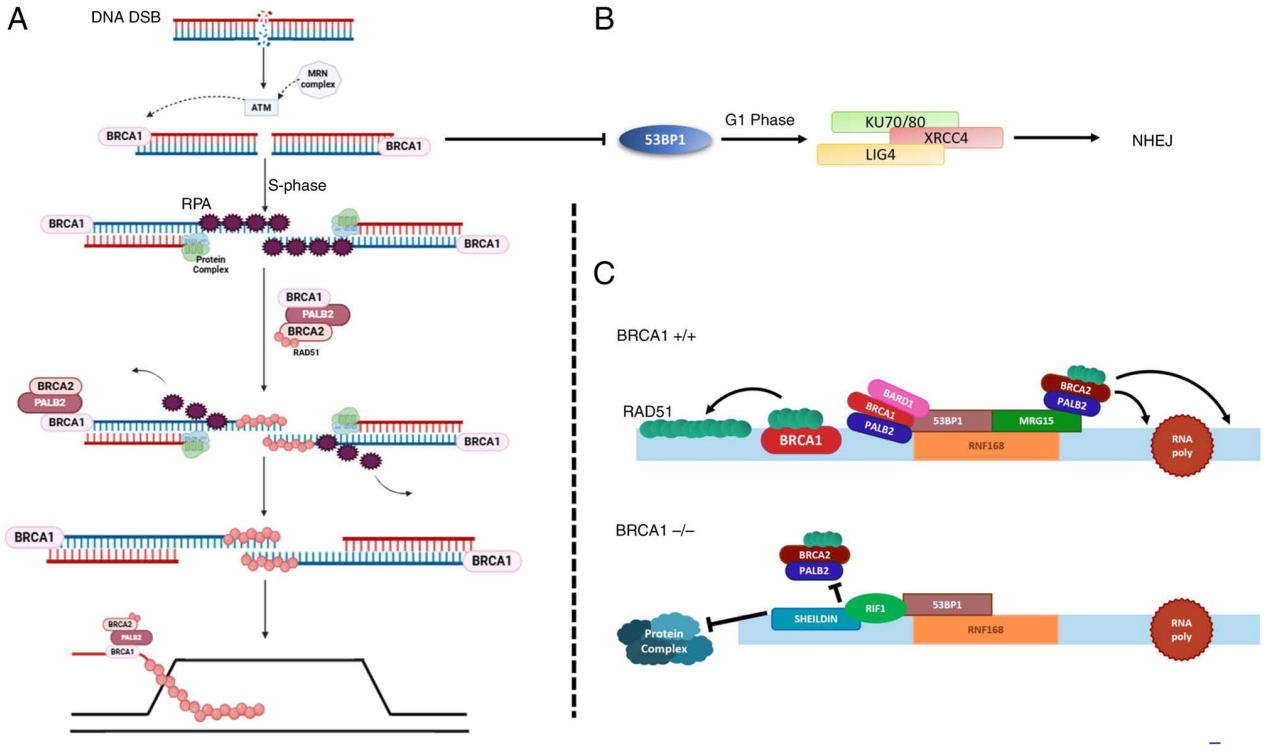


Figure 4. Initiation of HRR and the interaction mechanisms of *RAD51, PALB2* and *BRCA2*. (A) The mechanism of HR initiation and the role of other proteins in facilitating this process. The repair of a double-stranded DNA break requires several essential proteins and complexes. The MRN complex first identifies the DSB and attaches to the location. Subsequently, it recruits *ATM* kinase, which phosphorylates *BRCA1*, facilitating its recruitment to the site of injury. During the S phase, RPA protein complex binds to the exposed single-stranded DNA created by end resection, allowing the *BRCA1-PALB2-BRCA2* complex to load *RAD51* onto the DNA, enabling HRR, where *RAD51* actively searches for a homologous DNA strand to repair the break, with RPA being displaced once *RAD51* is bound. (B) Another possible pathway is via the NHEJ pathway. In the G_1 phase of the cell cycle, NHEJ is primarily triggered if there is a presence of protein 53BP1 which plays a crucial role in the process, and KU70/KU80 heterodimers binds to the broken ends, facilitating the recruitment of the DNA-PKcs, *XRCC4* and LIG4 to finally join the DNA ends back together. (C) The effect of presence and absence of *BRCA1* on *RAD51* and *PALB2*. In the *BRCA* +/+ state, all the interactions and recruitments among the genes and proteins in normal cell is stable. *PALB2* recruit *BRCA1* by direct interaction and it also interacts with *MRG15*, which is a chromodomain containing proteins that bind histone H3K36me3. Sufficient amount of *RAD51* is also loaded onto the DNA and RNF168 acts as stabilizing factor for these interactions. Whereas in the *BRCA* -/- state, the Shieldin complex is active which inhibits the binding of *BRCA2-PALB2-RAD51* complex effectively preventing the *RAD51* recruitment to the damage site leading to impaired HRR. HRR, homologous recombination repair; HR, homologous recombination; MRN, Mre11-Rad50-Nbs1; DSB, double-strand break; *ATM* Ataxia Telangiectasia Mutated; RPA, replication protein A; NHEJ, non-homologous end joining; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; LIG4, Ligase IV; H3K36me3, H3 trimethylated at lysine 36.

homologous regions, *RAD51* facilitates strand invasion, allowing ssDNA to penetrate the double-stranded template and form a D-loop. This step is essential for accurate DNA repair and relies on the ability of *RAD51* to mediate strand exchange. The assembly and disassembly of *RAD51* filaments are regulated by proteins such as RPA and *RAD51* paralogs, which modulate filament stability and function (46-48). The ATPase activity of *RAD51* is critical for its role in DNA strand exchange. Calcium ions regulate this activity by reducing ATP hydrolysis, thereby stabilizing the active *RAD51-ATP-ssDNA* filament, which is necessary for efficient strand exchange (49). Differential extension of dsDNA associated with *RAD51* filaments enhances homology recognition and strand exchange by accelerating the dissociation of non-homologous dsDNA, allowing for the efficient replacement with homologous sequences (50). Proteins such as RTT105 and RAD54 further enhance *RAD51* function; RTT105 promotes *RAD51* assembly and strand exchange, while RAD54 cooperates with *RAD51* to facilitate DNA pairing and unwinding, both of which are essential for homology searching (46,51).

RAD51 paralogs and *BRCA2* play a crucial role in remodeling and stabilizing *RAD51* filaments, ensuring their function in HR. These proteins assist in nucleating and stabilizing *RAD51* filaments on ssDNA, particularly at dsDNA-ssDNA junctions (48,52,53). Beyond its catalytic role, *RAD51* has non-catalytic functions, such as preventing error-prone DNA repair mechanisms that could compromise genomic integrity. Additionally, *RAD51* interacts with various other proteins, including nucleases and helicases, influencing multiple aspects of the DNA repair process (Fig. 4). Mutations in *RAD51* can disrupt HR, leading to genomic instability and increasing the risk of malignancies such as breast and ovarian cancer (24,54,55).

RAD51 activity is closely linked to other DNA repair pathways, including non-homologous end joining (NHEJ) and single-strand annealing (SSA). NHEJ primarily repairs DSBs when homologous templates are unavailable. However, this error-prone mechanism can promote genomic instability, particularly when *RAD51* function is compromised, shifting the repair process toward non-homologous mechanisms. *RAD51* prevents non-conservative repair pathways such as

SSA and alternative end-joining (A-EJ) by occupying ssDNA, thereby inhibiting the annealing step required for these pathways. This function is independent of its role in promoting gene conversion (GC). Silencing or impairing *RAD51* increases SSA and A-EJ activity but does not affect classical NHEJ (C-NHEJ) (56,57). Under low DSB conditions, GC is the preferred repair pathway; however, as DSB load increases, GC is suppressed while SSA becomes more prominent. This shift is not due to *RAD51* availability but is influenced by additional factors such as *53BP1* and *RAD52* (58). *RAD51*-mediated HR can inhibit NHEJ, particularly at replication fork barriers, where *RAD51* acts as an early responder to stalled forks, preventing NHEJ from accessing these sites (59). Some repair mechanisms, such as single-strand template repair in gene editing, can occur independently of *RAD51*, instead relying on proteins such as RAD52 and RAD59 (60).

BRCA2 regulates the HR activity of *RAD51* through two *RAD51*-binding domains: A core domain containing eight BRC repeats and a C-terminal *RAD51*-binding domain (CTRBD) with a phosphorylation site. The CTRBD enhances HR by stabilizing *RAD51* oligomers and nucleofilaments, thereby improving HR efficiency. Mutant *BRCA2* lacking *RAD51*-interacting mutations in the CTRBD fails to support HR when tested with the full-length protein but retains partial function when fused to an essential *BRCA2* domain. Exogenous CTRBD expression promotes HR without affecting NHEJ efficiency and confers resistance to DNA-damaging treatments. This resistance depends on endogenous *BRCA2*, demonstrating the potential of therapeutic strategies aimed at enhancing CTRBD activity. The expression of CTRBD facilitates *RAD51* foci formation, indicating efficient DNA repair. These findings suggest that peptides derived from CTRBD could serve as protective agents for normal tissues during cancer therapy or as sensitizers to enhance the efficacy of existing treatments in tumor cells (61-64).

PALB2: interaction with BRCAs and RAD51. PALB2 functions as a tumor suppressor and plays a critical role in the DNA damage response. It interacts with *BRCA1* and *BRCA2*, forming a complex essential for recruiting and loading *RAD51* onto DNA, thereby acting as a scaffold to initiate HR (20,38,65,66). The ability of *PALB2* to interact with chromatin and form oligomers is necessary for assembling the *BRCA2-RAD51* repair complex at sites of DNA damage, independent of other DNA damage checkpoint proteins (67,68). The N-terminal coiled-coil motif of *PALB2* regulates its self-association, a process critical for its function in HR. This self-interaction competes with the *PALB2-BRCA1* interaction, enabling a switch that activates HR when required (68,69). In collaboration with *BRCA2*, *PALB2* stimulates polymerase η (Polη) in recombination-associated DNA synthesis at blocked replication forks, demonstrating its role beyond D-loop formation (70).

Additionally, *PALB2* participates in the G_2/M checkpoint response, linking *BRCA1* and *BRCA2* in checkpoint activation and maintenance to prevent chromosomal abnormalities following DNA damage (66). *PALB2* also interacts with *RNF168*, which connects the HR machinery to histone ubiquitylation, facilitating the assembly of HR complexes at DNA breaks (71,72). Beyond its role in HR repair, *PALB2* is involved in the Fanconi anemia (FA) pathway, a crucial response to interstrand DNA crosslinks. Biallelic *PALB2* mutations not only disrupt HR repair but also contribute to the development of FA, a genetic disorder associated with increased cancer susceptibility, particularly breast and ovarian cancers. This link underscores the multifaceted role of *PALB2* in tumorigenesis through diverse DNA repair mechanisms (20,73,74).

4. Synergistic interaction with other HRR genes

RAD51 and PALB2. PALB2 plays a critical role in homologous recombination by acting as a key partner of *RAD51*. Its primary function is to facilitate the loading of *RAD51* onto ssDNA, enabling strand invasion. This interaction promotes the formation of the *RAD51* filament on ssDNA, a process essential for homology searching and DNA repair. *PALB2* enhances *RAD51* activity and serves as a molecular bridge between *BRCA1* and *BRCA2*, stabilizing the *RAD51* filament and optimizing its recombinase function (33,38,75) (Fig. 4A and B).

BRCA1-PALB2-BRCA2-RAD51 complex. The intricate structure of this protein complex highlights the coordinated function of the HR repair pathway. BRCA1 serves as the primary sensor of DNA DSBs, facilitating the recruitment of *PALB2* to the damage site. Acting as a molecular scaffold, *PALB2* aids in the localization of BRCA2, which, in turn, facilitates the loading of *RAD51* onto ssDNA at the break site. *RAD51* then assembles into nucleoprotein filaments that catalyze the search for homologous sequences and initiate strand invasion, a defining step of HR repair (38,76,77). The interdependence of these components is evident in how each protein enhances the function of the others. The BRCA1-*PALB2* interaction strengthens the ability of *BRCA1* to recognize DNA damage, thereby improving the capacity of *BRCA2* to load *RAD51*. This series of interactions results in repair efficiency that surpasses the combined effectiveness of the individual proteins. Mutations in any of these genes can severely disrupt the HR repair process, leading to genomic instability and an increased risk of malignancies (38,66,68) (Fig. 4A and B).

RAD51 paralogs (XRCC2, RAD51C). RAD51 paralogs, such as XRCC2 and *RAD51*C, interact synergistically with *RAD51* to enhance its function. These proteins share structural similarities with *RAD51* and are essential for stabilizing *RAD51* nucleoprotein filaments on ssDNA, thereby improving the efficiency of homology searching and strand exchange (25,48,57). Together with other paralogs, XRCC2 and *RAD51*C form distinct protein complexes that operate at different stages of the HR process. The BCDX2 complex (*RAD51*B-*RAD51*C-*RAD51*D-XRCC2) facilitates *RAD51* binding to ssDNA, while the CX3 complex (*RAD51*C-XRCC3) plays a key role in resolving Holliday junctions. The division of functions among these paralogs enhances the robustness and efficiency of the HR pathway (78,79).

BRCA1-FANCN/RAD51 interaction. The interaction between *BRCA1, FANCN* (*PALB2*) and *RAD51* establishes a crucial link between the FA pathway and HR repair. *FANCN/PALB2*

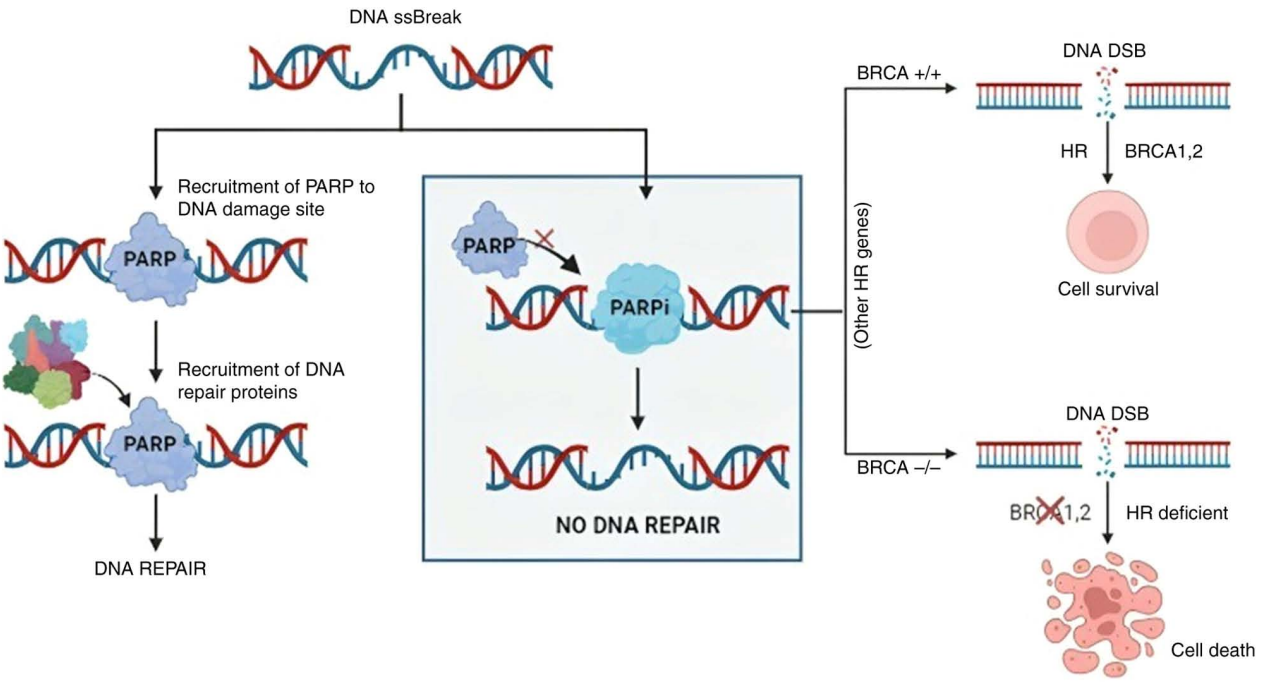


Figure 5. Synthetic lethality exhibits PARPi. PARP, poly-(ADP-ribose) polymerase; PARPi, PARP inhibitors; HR, homologous recombination; ss, single-stranded.

acts as a bridge between these pathways, facilitating their cooperation in specific repair scenarios, particularly in resolving DNA interstrand crosslinks (ICLs). *BRCA1* interacts with *FANCN/PALB2*, which subsequently associates with *BRCA2* and *RAD51*, enabling the recruitment of HR factors to sites of ICL damage processed by the FA pathway. This interaction ensures a coordinated response to complex DNA damage, highlighting the interconnected nature of DNA repair mechanisms (20,80-82).

5. Antagonistic interactions with other HRR genes

53BP1-RAD51 interplay. The antagonistic relationship between *53BP1* and *RAD51* highlights the intricate balance among DNA repair mechanisms. While *RAD51* facilitates HR, *53BP1* promotes NHEJ, an error-prone repair pathway that directly joins DNA ends without requiring extensive homology. Although NHEJ is less accurate than HR, it provides a rapid response in time-sensitive situations (58,83,84). *53BP1* competes with *BRCA1* for binding at DNA damage sites, potentially inhibiting the recruitment of HR factors such as *RAD51*. This competition is cell cycle-dependent, with *53BP1* favoring NHEJ during the G_1 phase, whereas *BRCA1* counteracts *53BP1* in the S and G_2 phases to facilitate HR. The interplay between these pathways ensures the selection of an appropriate repair mechanism based on the cell cycle stage and the nature of the DNA damage (85-88) (Fig. 4B).

Srs2 and RAD51. While several interactions enhance *RAD51* function, certain proteins exert antagonistic effects. Srs2 acts as a major anti-recombinase by specifically targeting *RAD51* filaments, promoting their disassembly and disrupting the *RAD51-ssDNA* filament. Srs2 interacts with *RAD51* and stimulates ATP hydrolysis within the filament, thereby reducing *RAD51* availability for recombination. This antagonistic activity is counteracted by the *RAD55-RAD57* complex, which inhibits Srs2 and helps maintain *RAD51* filament stability (89,90).

PARP Inhibitors and BRCA1/2 mutations. The use of PARP inhibitors (PARPi) in *BRCA1/2*-mutated cells exemplifies the concept of synthetic lethality, an approach leveraged in cancer treatment. PARPi selectively target cells with HR repair deficiencies, particularly those harboring *BRCA1/2* mutations (Fig. 5). These inhibitors function by preventing the repair of single-strand breaks, which can accumulate and lead to DSBs that require HR for resolution (91-96). However, the effectiveness of these drugs may be compromised by compensatory DNA repair pathways. *RAD51* paralogs, such as *XRCC2*, can partially restore HR functions in *BRCA*-mutated cells, reducing their sensitivity to PARPi. This resistance highlights the antagonistic interplay between DNA repair mechanisms and the challenges associated with targeting specific pathways for cancer treatment (91,97,98).

6. *RAD51* and *PALB2* and its association with various types of cancer

Mutations in *RAD51* and its paralogs have been associated with an increased susceptibility to breast cancer. Biallelic alterations in *RAD51C* have been linked to Fanconi anemia, while monoallelic alterations elevate the risk of breast and ovarian cancer (99-101). Similarly, *RAD51D* mutations have been implicated in ovarian cancer predisposition, with *RAD51C* and *RAD51D* mutations specifically associated with an increased risk of ovarian cancer (102,103). Additionally, variants in *RAD51B* have been linked to both breast and ovarian cancer, further emphasizing the critical role of *RAD51*

Table I. A summary of *RAD51* and *PALB2* and its association with various cancer.

Gene	Associated disease	Summary
RAD51	Breast cancer	Overexpression of *RAD51* is common in breast cancer and is linked to more genomic instability, aggressive tumor behavior and a poor outcome. Changes or problems with *RAD51* can make homologous recombination repair less effective. This makes tumors more vulnerable to DNA-damaging agents but also makes treatment less effective.
	Ovarian cancer	*RAD51* dysregulation in ovarian cancer is associated with HRD, which affects the efficacy of platinum-based chemotherapy and PARP inhibitors. Elevated *RAD51* expression is indicative of resistance to these therapies and correlates with poorer clinical outcomes.
	Prostate cancer	Mutations or altered expression of *RAD51* and its paralogs are associated with prostate cancer, potentially contributing to genomic instability and influencing sensitivity to DNA-damaging therapies.
	Pancreatic cancer	Overexpression enhances proliferation and aerobic glycolysis through HIF1α, which is associated with reduced survival rates. Homologous recombination deficiency in *PALB2*-mutant tumors increase sensitivity to PARP inhibitors.
PALB2	Breast cancer	Germline mutations in *PALB2* are associated with a substantial increase in breast cancer risk, with affected individuals experiencing a lifetime risk of up to 53%. *PALB2* serves as a crucial scaffold connecting *BRCA1* and *BRCA2*; its absence disrupts homologous recombination, resulting in heightened susceptibility and affecting the response to PARP inhibitors.
	Ovarian cancer	*PALB2* mutations are infrequent in ovarian cancer; however, they still present an elevated risk. Tumors exhibiting *PALB2* loss frequently demonstrate HRD, which can be therapeutically targeted using DNA-damaging agents and PARP inhibitors.
	Prostate cancer	Germline mutations associated with aggressive phenotypes. Biallelic inactivation leads to homologous recombination deficiency, allowing for the stratification of patients for PARP inhibitor therapy. Somatic alterations affect the capacity for DNA repair.
	Pancreatic cancer	Germline mutations in *PALB2* are linked to a moderately elevated risk of pancreatic cancer. The compromised DNA repair capacity in these instances may guide targeted treatment approaches.

HRD, homologous recombination deficiency; PARP, poly-(ADP-ribose) polymerase; HIF1α, hypoxia-inducible factor 1α.

in these malignancies (104). *PALB2* mutations are recognized as significant risk factors for breast cancer. Studies suggest that the lifetime risk for female carriers of *PALB2* mutations may be comparable to that of *BRCA2* mutation carriers (105,106). Although *PALB2* mutations are relatively rare, they play a notable role in hereditary breast cancer. By contrast, *RAD51C* mutations are less commonly observed in familial breast cancer cases (65,107) (Table I).

In ovarian cancer, *RAD51* and *PALB2* mutations influence not only cancer susceptibility but also treatment outcomes. Ovarian cancers with *RAD51*- and *PALB2*-deficient homologous recombination, along with other repair dysfunctions, exhibit increased sensitivity to platinum-based chemotherapy and PARPi. This sensitivity arises from synthetic lethality, wherein the simultaneous deficiency of two DNA repair pathways, HR and base excision repair, leads to cell death (Fig. 5). However, the restoration of *RAD51* function has been associated with acquired resistance to these therapies, underscoring the dynamic nature of HR pathway alterations in cancer progression and treatment (108-112). Elevated *RAD51* levels correlate with poor prognosis and reduced progression-free survival in ovarian cancer patients. *RAD51* also serves as a predictive biomarker for platinum resistance, indicating poorer treatment outcomes (38,113) (Table I).

Germline *PALB2* mutations are linked to an increased risk of prostate cancer, particularly in its aggressive forms. Genome-wide association studies have identified *RAD51B*, a *RAD51* paralog, as a susceptibility gene for prostate cancer. Additionally, somatic alterations in *RAD51* and *PALB2* contribute to HRD in a subset of prostate cancers, potentially influencing treatment strategies, including the use of PARPi (38,114,115). In prostate cancer, *RAD51* expression is frequently upregulated, enhancing DNA repair capacity and contributing to therapy resistance, particularly against radiation and chemotherapy. *EGFR* signaling regulates *RAD51* expression, promoting DNA repair and epithelial-mesenchymal transition (EMT), which drive intrinsic resistance in prostate cancer cells (116). Furthermore, the *Jak2-Stat5a/b* signaling pathway is essential for *RAD51* expression and its inhibition sensitizes prostate cancer cells to radiation by impairing HR-mediated DNA repair (117) (Table I).

PALB2 functions as a tumor suppressor and plays a critical role in homologous recombination by facilitating the

recruitment of *BRCA2* and *RAD51* to sites of DNA damage. It enhances the recombinase activity of *RAD51*, which is essential for assembling the synaptic complex during HR (118,119). Mutations in *PALB2* lead to HRD, increasing the susceptibility of cancer cells to DNA-damaging agents such as PARP inhibitors. In prostate cancer, biallelic *PALB2* inactivation is associated with HRD and serves as a criterion for stratifying patients for PARPi therapy (119) (Table I).

In pancreatic cancer, *RAD51* overexpression has been shown to promote cancer cell proliferation and regulate aerobic glycolysis by targeting hypoxia-inducible factor 1α (HIF1α). This overexpression correlates with poor survival outcomes in pancreatic cancer patients (120,121). A study identified novel germline missense variants of *PALB2* (*p.Ser64Leu* and *p.Pro104Leu*) in patients with familial pancreatic cancer. These variants impair the DNA damage response by disrupting the recruitment of *PALB2* and *RAD51* to DNA damage foci, leading to defective homologous recombination and increased cellular sensitivity to ionizing radiation and PARP inhibitors. These findings suggest that patients harboring these *PALB2* variants may benefit from personalized treatments incorporating these therapeutic agents (122) (Table I).

7. Mutational landscape of *RAD51* and *PALB2*

In the *RAD51* gene analysis, a total of 65,779 samples across all tissue types were examined, including 5,718 samples specifically related to breast cancer (123). Among these, 28 samples contained mutations, accounting for ~0.49% of the breast cancer cases analyzed. In the case of the *PALB2* gene, 69,198 total samples were analyzed across all tissue types, with 5,856 samples from breast cancer cases (123). Of these, 153 samples exhibited mutations, representing ~2.61% of the breast cancer cases tested. Regarding gene expression in breast cancer, 1,104 expression profiles were recorded for both *RAD51* and *PALB2*. *RAD51* was overexpressed in 109 cases, while *PALB2* was overexpressed in 187 cases (16.94%) and under-expressed in 7 cases (0.63%; Tables II and III).

For ovarian cancer, 65,779 total samples were analyzed for *RAD51*, including 1,340 ovarian cancer-specific samples. Among these, 23 cases (1.72%) carried mutations. In the case of *PALB2*, 69,198 total samples were analyzed, with 1,524 related to ovarian cancer, among which 29 cases (1.9%) harbored mutations. Regarding gene expression in ovarian cancer, 266 expression profiles were recorded, with *RAD51* overexpressed in 6 cases (2.26%). *PALB2* was overexpressed in seven cases (2.63%) and under-expressed in 10 cases (3.76%; Tables II and III) (123).

In prostate cancer, *RAD51* mutations were detected in 0.95% (31/3,258) of samples, with overexpression observed in 2.81% (14/498) of cases. *PALB2* mutations were found in 3.72% (142/3,819) of samples, with 6.22% (31/498) showing overexpression and 1.41% (7/498) showing under-expression. In pancreatic cancer, *RAD51* mutations were identified in 0.64% (17/2,656) of samples, with 2.23% (4/179) exhibiting overexpression. *PALB2* mutations occurred in 1.23% (36/2,935) of cases, with 4.47% (8/179) showing overexpression and 1.68% (3/179) showing under-expression (Tables II and III) (123).

Table II. Gene mutation analysis of *RAD51* and *PALB2* genes on breast, ovarian, prostate and pancreatic cancers among all other cancer types (https://cancer.sanger.ac.uk/cosmic/gene/analysis).

Gene	Sample type, n	Mutation, n	Mutation percentage
RAD51	All cancer types, 65,779	369	0.56
	Breast cancer, 5,718	28	0.49
	Ovarian cancer, 1,340	23	1.72
	Prostate cancer, 3,258	31	0.95
	Pancreatic cancer, 2,656	17	0.64
PALB2	All cancer types, 69,198	1,272	1.84
	Breast cancer, 5,856	153	2.61
	Ovarian cancer, 1,524	29	1.9
	Prostate cancer, 3,819	142	3.72
	Pancreatic cancer, 2,935	36	1.23

8. Clinical significance of *RAD51* and *PALB2* in breast and ovarian cancer

The growing understanding of *RAD51* and *PALB2* mutations has markedly advanced the management of hereditary cancer syndromes. Current guidelines from the National Comprehensive Cancer Network (NCCN; https://www.nccn.org/guidelines/category_1) and the American Society of Clinical Oncology (ASCO; https://www.asco.org/search?q=genetic_testing) recommend genetic testing for individuals with specific cancer histories, including early-onset breast cancer, male breast cancer, triple-negative breast cancer and familial cancer predispositions (4,124,125). These mutations confer substantial cancer risks, with *PALB2* variations associated with a 2- to 4-fold increase in breast cancer risk (33-58% lifetime risk) (19,123), whereas *RAD51* variants have been linked to increased risks of breast, ovarian, pancreatic and prostate cancers (18,100,110,122,126,127). Genetic test results range from pathogenic to benign, necessitating expert molecular genetic interpretation and genetic counseling (128,129). Management strategies for mutation carriers include enhanced surveillance protocols such as early mammography, ultrasound, MRI and targeted screenings (130). Preventive surgeries, including risk-reducing mastectomy or risk-reducing salpingo-oophorectomy, can reduce the risk of certain cancers by >90% (131-133). Additionally, chemoprevention strategies using selective estrogen receptor modulators such as tamoxifen and raloxifene, or aromatase inhibitors, are being explored as preventive measures (134-136). Critically, these genetic insights have revolutionized cancer treatment, particularly through targeted therapies such as PARP inhibitors, which exploit synthetic lethality in homologous recombination-deficient cancers (Fig. 5) (137). Personalized chemotherapy selection, including platinum-based regimens, has further refined treatment approaches (138). Investigational therapies, such as ATR inhibitors (139,140) and WEE1 inhibitors (141), hold promise for expanding treatment options. Ultimately, these advances contribute to more precise and

Table III. Gene expression analysis of *RAD51* and *PALB2* in carcinomas such as breast, ovary, pancreas and prostate (https://cancer.sanger.ac.uk/cosmic/gene/analysis).

Gene Name	Gene expression, n	Overexpressed, n	Overexpressed, %	Underexpressed, n	Underexpressed, %
RAD51	All cancers				
	65,779				
	Breast cancer				
	1,104	109	9.87	-	-
	Ovarian cancer				
	266	6	2.26	-	-
	Pancreas cancer				
	179	4	2.23	-	-
	Prostate cancer				
	498	14	2.81	-	-
PALB2	All cancer types				
	69,198				
	Breast cancer				
	1,104	187	16.94	7	0.63
	Ovarian cancer				
	266	7	2.63	10	3.76
	Pancreas cancer				
	179	8	4.47	3	1.68
	Prostate cancer				
	498	31	6.22	7	1.41

individualized cancer prevention and treatment strategies, improving patient outcomes.

PARP inhibitors play a crucial role in the treatment of breast and ovarian malignancies, particularly in individuals with *BRCA* mutations or HRD. These drugs leverage synthetic lethality by inhibiting two DNA repair pathways, inducing cytotoxicity in cancer cells while sparing normal cells (142). They have demonstrated significant efficacy in improving progression-free survival, especially in *BRCA*-mutated cancers (143). PARPi have shown potential beyond *BRCA*-mutated cancers, offering benefits to patients with additional HRR pathway deficiencies or platinum-resistant tumors (144). Efforts to enhance their efficacy have led to combination therapies involving chemotherapy, antiangiogenic agents and immunotherapy (145).

Several PARPi have been approved or are in late-stage clinical trials for breast and ovarian cancer treatment. Olaparib has demonstrated efficacy as a monotherapy in *BRCA*-related tumors in phase II trials (146). Talazoparib was approved by the FDA in October 2018 for treating metastatic germline *BRCA1/2*-mutated breast cancer. Rucaparib and niraparib have been approved for ovarian cancer treatment (147). Veliparib is in late-stage clinical development and has been investigated in combination with chemotherapy agents such as carboplatin, paclitaxel and temozolomide (145). These inhibitors have demonstrated efficacy across various clinical settings, including neoadjuvant, adjuvant and metastatic treatments for breast and ovarian cancer (148). Numerous clinical trials have assessed the efficacy and safety of PARPi across different cancer types: SOLO-1 trial (NCT01844986) evaluated Olaparib as a maintenance treatment for newly diagnosed advanced ovarian cancer with *BRCA* mutations. This phase III trial showed a significant improvement in progression-free survival compared with placebo (149). OlympiA trial (NCT02032823) is investigating Olaparib in the adjuvant setting for high-risk HER2-negative breast cancer patients with *BRCA1/2* mutations, including potential cases with *RAD51* and *PALB2* mutations (150). TAPUR trial (NCT02693535) is exploring Olaparib in various solid tumors, including those with mutations in HRR genes such as *RAD51* and *PALB2* (151). EMBRACA trial (NCT01945775) examined Talazoparib in patients with advanced breast cancer and germline *BRCA* mutations. This phase III study demonstrated superior progression-free survival compared with chemotherapy (152). ARIEL2 trial (NCT01891344) assessed Rucaparib in patients with platinum-sensitive, high-grade ovarian cancer. This phase II trial developed a tumor genomic profiling assay to quantify HR loss of heterozygosity using next-generation sequencing (153). Phase III trial (NCT02470585) evaluated Veliparib in combination with platinum-based chemotherapy for locally advanced or metastatic breast cancer, yielding favorable outcomes (152). PRIMA study (NCT02655016) investigated Niraparib as a maintenance therapy for newly diagnosed advanced ovarian cancer. This phase III trial demonstrated improved progression-free survival across multiple biomarker-defined subgroups (154). These trials have revealed varying efficacy and safety profiles among different PARPi. For instance, Niraparib has been associated with a higher incidence of grade ≥3 adverse events compared with other PARP inhibitors (155). Expanding the indications for PARPi beyond *BRCA* mutations could benefit a broader patient population with DNA repair deficiencies (Fig. 6).

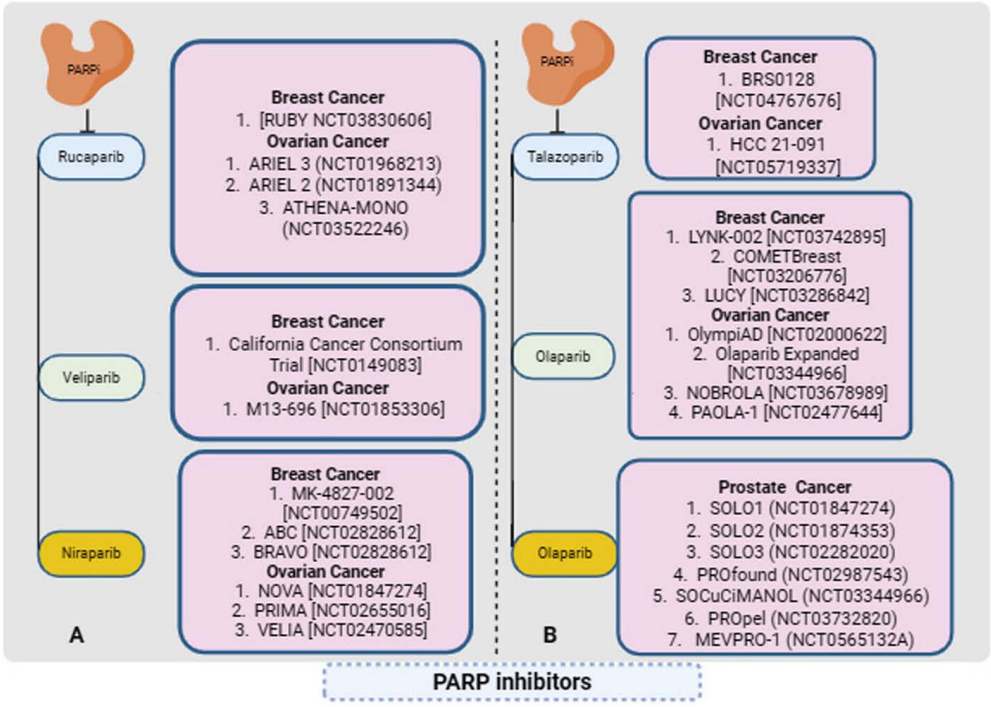


Figure 6. Clinical trials of key PARP inhibitors in breast, ovarian, and prostate cancers. PARP, poly-(ADP-ribose) polymerase; PARPi, PARP inhibitors.

9. Therapeutic implications

For *PALB2*-mutated tumors lacking HR, treatment options extend beyond *BRCA1/2* mutations due to their heightened sensitivity to PARP inhibitors (155-157). Similarly, *RAD51* overexpression contributes to resistance against neoadjuvant endocrine therapy in estrogen receptor (ER)-positive breast carcinoma. This therapy resistance, associated with poor prognosis, is partly due to inadequate *BRCA2* methylation, which fails to suppress *RAD51* expression (156,158). Inhibiting *RAD51* may enhance the efficacy of DNA-damaging agents and help overcome chemoresistance. *RAD51* inhibitors could improve chemotherapy effectiveness while preserving genomic integrity and immune function (55,157). As a key regulator of HRR, *RAD51* plays a crucial role in therapeutic resistance and cancer progression. Depletion of damage-specific DNA binding protein 2 (*DDB2*) leads to *RAD51* destabilization, rendering triple-negative breast cancer cells more sensitive to PARPi due to compromised HR repair (157). Polymorphisms in *RAD51* and *XRCC3* have been associated with an increased risk of breast cancer and poor radiotherapy outcomes, highlighting the role of genetic variability in treatment response (159,160).

Pharmacologically targeting *RAD51* has been shown to reduce B02-induced clonogenic survival and increase prostate cancer radioresistance. Conversely, *RAD51* activators, such as RS-1, exploit *RAD51* overexpression to induce synthetic lethality in cancer cells (116,119). The role of *PALB2* in enhancing *RAD51* activity suggests that targeting *PALB2* or its interactions could serve as a viable therapeutic strategy. Disrupting *BRCA1*-independent mechanisms of *PALB2* localization may improve treatment outcomes in *BRCA1*-mutant tumors that have regained HR function and developed resistance to PARPi (33). Combining *RAD51* or *PALB2* inhibitors with other therapies, such as radiation or PARPi, could enhance treatment efficacy. For instance, inhibiting *Jak2-Stat5a/b* signaling reduces *RAD51* expression and sensitizes prostate cancer cells to radiation while sparing surrounding healthy tissue, making it a potential adjuvant therapy (118). *RAD51* is also emerging as a potential biomarker and therapeutic target in pancreatic cancer. Inhibiting *RAD51* may increase cancer cell susceptibility to DNA-damaging agents, including ionizing radiation and PARPi, by impairing their DNA repair capacity (121,160). A novel *RAD51* inhibitor, CYT-0851, has demonstrated promising anticancer activity in preclinical models of pancreatic cancer, leading to significant tumor growth inhibition and, in some cases, tumor regression (161). Patients with *PALB2* mutations may be particularly responsive to DNA-damaging therapies, such as ionizing radiation and PARPi, due to their impaired DNA repair capabilities (120). Similarly, targeting *RAD51* with inhibitors such as CYT-0851 could enhance the efficacy of existing treatments and help overcome drug resistance in pancreatic cancer (161).

10. Commercial insights

The understanding of *RAD51* and *PALB2* functions presents several commercial potentials, particularly in oncology, where they act as therapeutic targets. Commercial tests that look for changes in *PALB2* and *RAD51* may help find individuals early who are more likely to get breast and ovarian cancer, allowing for proactive treatment plans. Myriad Genetics (https://myriad.com/gene-table/) provides genetic testing panels encompassing *BRCA1*, *BRCA2* and additional genes associated with hereditary cancer, such as *RAD51* and *PALB2* (162). *RAD51* and *PALB2* are still experimental biomarkers in clinical decision-making, with

minimal incorporation into FDA-approved instruments. *RAD51* and *PALB2* are essential elements of the HRR pathway and their modifications, such as mutations, loss of heterozygosity (LOH), or diminished *RAD51* foci formation, can signify HRD, which correlates with susceptibility to PARPi and platinum-based treatments. HRD scores, which integrate genomic instability indicators such as LOH, telomeric allelic imbalance (TAI) and large-scale state transitions (LST), are used to detect HRD-positive cancers, exemplified by FDA-approved assessments such as Myriad Genetics' myChoice® CDx. This test computes a Genomic Instability Score using LOH, TAI and LST to inform PARPi therapy in ovarian cancer, although it does not directly evaluate *RAD51* or *PALB2* functionality. *PALB2* mutations are incorporated in several next-generation sequencing (NGS) panels, such as Myriad's myRisk® and Tempus xT, which emphasize germline or somatic mutations instead of functional testing (163-166). *PALB2* mutations are infrequently incorporated into expanded germline panels (such as Invitae Multi-Cancer Panel) and are not typically evaluated in regular HRD testing due to their low prevalence (~2-3%) and difficulties in variant interpretation (165,167). The therapeutic value of *RAD51* focuses on functional tests such as *RAD51* foci measurement, which assesses homologous recombination repair proficiency in real time. Preclinical and early-phase trials indicate that *RAD51*-Low scores (≤10% foci-positive cells) accurately predict sensitivity to platinum and PARPi in ovarian and triple-negative breast malignancies (168-170). Nonetheless, these assays do not possess FDA approval and encounter challenges in standardization, especially in formalin fixed and paraffin embedded samples, where preanalytical factors and scoring thresholds (such as 10 vs. 20% cutoff) influence reproducibility (167,170). Conversely, genomic scar-based HRD diagnostics such as myChoice® prevail in clinical use, although their incapacity to identify dynamic HR restoration (such as *BRCA1/2* reversion mutations) (170). Current experiments (such as MITO16A/MaNGO-OV2) are assessing *RAD51* foci in conjunction with genomic scores; nevertheless, widespread implementation is contingent upon standardized methodologies and validation in prospective cohorts (163,167). Consequently, whereas *PALB2* is progressively incorporated into NGS panels for therapeutic selection and *RAD51* shows promise as a functional biomarker, their regular clinical application necessitates further validation and incorporation into standardized HRD testing protocols (165,166).

11. Limitations

Notwithstanding the therapeutic promise of *RAD51* and *PALB2* as biomarkers, numerous obstacles impede their clinical application. The low mutation frequency of *PALB2* (1-3% in hereditary breast cancers) restricts cost-effectiveness in population-wide screening, hence requiring tailored testing in high-risk groups (171). Second, ~50% of *PALB2* and *RAD51* variations are categorized as variants of unknown significance (VUS) owing to insufficient functional data, hence confounding risk stratification and therapeutic decision-making (172,173). Functional assays, including *RAD51* foci quantification, encounter standardization challenges, especially in archival formalin fixed and paraffin embedded samples, where preanalytical factors (such as fixation duration) and laboratory HRD scoring thresholds (such as <20% *RAD51*-positive cells) affect reproducibility (98,163,172). Moreover, HRD genomic scar assays, although indicative of PARP inhibitor efficacy, may not adequately reflect the dynamic restoration of homologous recombination through *BRCA1/2* reversion mutations or epigenetic modifications. Future methods must emphasize the integration of multigene HRD panels (such as *RAD51C/D, PALB2*) with functional assays to clarify VUS and evaluate real-time HR proficiency. High-throughput clustered regularly interspaced short palindromic repeats-mediated mutagenesis and AI-based categorization systems may expedite the annotation of VUS. Overcoming these constraints necessitates joint endeavors to integrate mechanistic insights with scalable diagnostic tools, hence enhancing tailored therapy methods for HRD-associated malignancies (98,163,174,175).

12. Conclusion

The present review highlighted the critical roles of *RAD51* and *PALB2* in HRR-mediated genomic stability and their significant effect on breast and ovarian cancer pathogenesis. Mutations in these genes substantially increase cancer risk, underscoring their importance in genetic testing protocols for early risk stratification. The clinical effectiveness of PARPi in HRR-deficient tumors further emphasizes the need to identify *RAD51* and *PALB2* mutations to inform personalized treatment strategies. However, resistance mechanisms present a major challenge, necessitating alternative therapeutic approaches, such as *RAD51* inhibition or combinatorial treatment modalities.

Future research should focus on improving functional assays to assess HRR status and expanding clinical trials to include *RAD51*- and *PALB2*-mutated patient groups. These efforts, combined with the development of tailored therapies, are expected to refine precision oncology strategies and improve outcomes for patients with HRR-deficient cancers. The evolving understanding of *RAD51* and *PALB2* not only deepens insights into cancer biology but also paves the way for transformative therapeutic advancements.

Acknowledgements

Not applicable.

Funding

This research has been funded by Scientific Research Deanship at University of Ha'il-Saudi Arabia through project number (RG-24 173).

Availability of data and materials

Not applicable.

Authors' contributions

Conceptualization was by MN and MK. Data curation was by SA. Formal Analysis was by ME-T. Initial screening and

content curation was by AK. Methodology was by TG and AA. Supervision was by KA. SG wrote the original draft. Writing, reviewing and editing was by MN, SR and FA. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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