International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

Preclinical Evidence Grading of Strategies to Overcome Poly ADP-ribose Polymerase Inhibitor Resistance in Breast Cancer: A Systematic Review

INPLASY202540029
doi: 10.37766/inplasy2025.4.0029
Received: 9 April 2025
Published: 9 April 2025

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ADMINISTRATIVE INFORMATION

Support - This work was funded by the Department of Science and Technology of Hunan Province (HSTD) through a Jun Li program (grant numbers 2022JJ40748).

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202540029

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 9 April 2025 and was last updated on 9 April 2025.

INTRODUCTION

Review question / Objective What is the quality and consistency of preclinical evidence supporting strategies to overcome PARP inhibitor resistance in breast cancer, and which interventions demonstrate the highest translational potential based on experimental outcomes and risk of bias assessment?

Rationale Poly (ADP-ribose) polymerase (PARP) inhibitors have emerged as a promising targeted therapy for BRCA1/2-mutated breast cancers due to their capacity to exploit synthetic lethality in homologous recombination-deficient (HRD) cells. However, despite their initial clinical efficacy, the rapid development of acquired resistance significantly limits long-term treatment outcomes. Resistance mechanisms are diverse, involving restoration of homologous recombination repair, modulation of cell cycle checkpoints, drug efflux, and remodeling of the tumor microenvironment.

Over the past decade, numerous preclinical studies have proposed strategies to overcome PARP inhibitor resistance, including epigenetic modulation, immune activation, metabolic interference, and DNA repair pathway inhibition. Nevertheless, these studies vary widely in their experimental models, mechanistic focus, and outcome metrics, leading to heterogeneity in evidence quality. Currently, there is no standardized framework to evaluate the strength, consistency, and translational relevance of these findings.

Given the urgent clinical need for effective resistance-reversal strategies and the translational gap between preclinical discovery and clinical implementation, a systematic synthesis of existing preclinical evidence is necessary. By applying

rigorous risk of bias assessment tools and the GRADE framework, this study aims to evaluate and rank the most promising therapeutic approaches. The findings will inform future biomarker-guided combination therapy development and facilitate rational design of clinical trials targeting PARP inhibitor resistance in breast cancer.

Condition being studied Breast cancer is the most commonly diagnosed cancer among women worldwide and remains a leading cause of cancer-related mortality. Among its subtypes, triple-negative breast cancer (TNBC) is particularly aggressive and lacks targeted hormonal or HER2-directed therapies, making treatment especially challenging.

Poly (ADP-ribose) polymerase (PARP) inhibitors have demonstrated clinical efficacy in patients with BRCA1/2-mutated breast cancer by exploiting synthetic lethality in tumors with homologous recombination deficiency (HRD). However, a major clinical challenge is the development of acquired resistance to PARP inhibitors, which severely limits their long-term effectiveness. This resistance arises through various mechanisms, including genetic reversion mutations, restoration of DNA repair capacity, and immune evasion, necessitating novel therapeutic strategies to overcome resistance and improve patient outcomes.

This study focuses on the condition of PARP inhibitor-resistant breast cancer and evaluates preclinical strategies designed to reverse this resistance.

METHODS

Search strategy A comprehensive literature search was conducted in March 2025 across PubMed, Web of Science, and Embase to identify eligible studies for this systematic review and to develop an appropriate search strategy. Boolean operators (AND/OR), Medical Subject Headings (MeSH), truncation symbols, and title (TI) and abstract (AB) fields were employed to optimize literature retrieval. The search terms included: breast cancer, triple-negative breast cancer (TNBC), PARP inhibitor, Poly ADP-ribose polymerase inhibitor, olaparib, talazoparib, rucaparib, niraparib, drug resistance, therapeutic resistance, chemoresistance, reversal strategies, overcoming resistance, sensitization, synthetic lethality, preclinical studies, in vitro, in vivo, animal models, and xenografts. Initially, 118 records were identified. After removing duplicates, 88 articles remained for title and abstract screening, from which 60 were excluded for not meeting the inclusion criteria. The full texts of the remaining 28 articles were retrieved for detailed evaluation, and 6 were excluded due to unavailability of full text, use of non-breast cancer models, or lack of assessment of resistance reversal strategies. Ultimately, 22 studies were included in the evidence synthesis (Figure 1). This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.

Participant or population The population of interest in this systematic review consists of preclinical models representing breast cancer, with a primary focus on triple-negative breast cancer (TNBC) and other homologous recombination-deficient (HRD) subtypes. These models include:

In vitro systems: BRCA1/2-mutated cell lines (e.g., MDA-MB-436, SUM149PT).

In vivo models: Patient-derived xenografts (PDX, n=9) and genetically engineered mouse models (n=6).

The review specifically addresses resistance to poly ADP-ribose polymerase (PARP) inhibitors (e.g., olaparib, talazoparib) in these models, evaluating strategies to overcome resistance mechanisms such as homologous recombination repair restoration, epigenetic alterations, and immune microenvironment remodeling. Clinical relevance is inferred for patients with BRCA-mutated or HRD breast cancer who develop PARP inhibitor resistance.

Note: As this is a preclinical review, human participants are not directly involved; findings are derived from experimental models.

Intervention In this review, we aim to evaluate a group of interventions that are focused on overcoming resistance to Poly ADP-ribose polymerase (PARP) inhibitors in breast cancer. Specifically, we want to evaluate:

Interventions to Overcome PARP Inhibitor Resistance in Breast Cancer:

Epigenetic Modulation: This includes interventions that target epigenetic processes to alter gene expression patterns and restore sensitivity to PARP inhibitors. For example, inhibiting enhancer of zeste homolog 2 (EZH2), which has been shown to reduce tumor size and extend median survival time in BRCA1-mutant models.

Immune Modulation: This group includes interventions that aim to activate the immune system to enhance the anti-tumor response and overcome resistance. For instance, using STING (stimulator of interferon genes) agonists to increase CD8+ T-cell infiltration and induce a systemic immune response.

Targeting DNA Damage Repair Pathways: Strategies that target other components of the DNA damage repair machinery, such as inhibition

of cyclin-dependent kinases (CDKs) like CDK9/12 or polymerase theta (Polθ), to suppress the restoration of homologous recombination repair and enhance PARP inhibitor efficacy.
Cancer Stem Cell Targeting: Interventions aimed at eradicating cancer stem cells, which are thought to contribute to drug resistance. This includes the use of inhibitors like Notch inhibitors (NIF) to reduce cancer stem cell populations.
Metabolic Interventions: Strategies that target metabolic pathways in cancer cells to disrupt their ability to develop resistance. Examples include the use of oligosaccharides like oligo-fucoidan to reduce glucose uptake and sensitize tumor cells to PARP inhibitors.
Combination Therapies: Evaluating the potential of combining different resistance-reversal strategies (e.g., epigenetic modulation with immune activation) to achieve synergistic effects and overcome complex resistance mechanisms.
Overall, this review seeks to assess the preclinical evidence for a diverse range of interventions aimed at overcoming PARP inhibitor resistance in breast cancer, with the ultimate goal of identifying the most promising strategies for clinical translation.

Comparator In this systematic review, we do not directly apply a comparative intervention to a target population. Rather, we aim to evaluate the preclinical evidence for various interventions that have been proposed to overcome resistance to Poly ADP-ribose polymerase (PARP) inhibitors in breast cancer.

Study designs to be included To address the objective of this systematic review, which is to evaluate the preclinical evidence for strategies to overcome Poly ADP-ribose polymerase (PARP) inhibitor resistance in breast cancer, the following study designs will be included:In Vitro Studies:Cell Line-based Experiments: These studies involve using breast cancer cell lines, particularly those with BRCA1/2 mutations or other characteristics indicative of homologous recombination deficiency (HRD), to test the efficacy of various resistance-reversal strategies. Outcomes measured may include changes in IC50 values, clonogenic.

Eligibility criteria Primary research articles published in English between 2015 and 2025 were included in this systematic review. Eligible studies must have investigated preclinical strategies aimed at overcoming PARP inhibitor resistance in breast cancer, including in vitro (cell line-based) and in vivo (animal model-based) studies. The selected studies had to evaluate the efficacy of reversal strategies, such as combination therapy, gene regulation approaches, metabolic modulation, and immune-based interventions, in restoring sensitivity to PARP inhibitors. Studies were required to report at least one quantitative outcome measure, including changes in IC50 values, clonogenic survival, apoptosis rates, DNA damage repair markers, or tumor growth inhibition in animal models. Only studies employing breast cancer models—particularly triple-negative breast cancer or other homologous recombination-deficient (HRD) subtypes—were considered. Articles that included an appropriate control group, such as cells or animals treated with PARP inhibitors alone, were deemed eligible. Studies providing mechanistic insights into the molecular pathways underlying resistance reversal were also included. All eligible references were required to be full-text original research articles.
Excluded from this review were studies that did not specifically investigate PARP inhibitor resistance in breast cancer or did not evaluate strategies to overcome resistance. Research focusing on cancer types other than breast cancer, including ovarian, prostate, or pancreatic cancers, was excluded unless breast cancer-specific data were provided. Studies that only explored the mechanisms of resistance without assessing a reversal strategy were also excluded. Articles lacking experimental validation, such as bioinformatics-only analyses or computational modeling without in vitro or in vivo confirmation, were not considered. Clinical studies, case reports, reviews, guidelines, expert opinions, conference abstracts, and non-peer-reviewed articles were excluded to ensure methodological rigor. Additionally, studies with insufficient or incomplete data, such as those lacking quantitative outcome measures (e.g., IC50 values, apoptosis rates, DNA damage markers, or tumor growth data), were not included. Non-English publications and studies where full-text access was unavailable were also excluded from the final analysis.

Information sources PubMed: A comprehensive database of biomedical literature maintained by the National Library of Medicine at the National Institutes of Health.
Web of Science: A multidisciplinary citation database that includes peer-reviewed journals, books, and conference proceedings in the sciences, social sciences, arts, and humanities.
Embase: A biomedical and pharmacological database that covers a wide range of medical subjects, including clinical trials, drug information, and health policy.

Main outcome(s) The outcomes reported in the preclinical studies will cover a range of time points, from short-term effects observed within days or

weeks of treatment initiation to longer-term survival data spanning months. The timing of outcomes will be critical in assessing the durability of any therapeutic effects and the potential for resistance evolution over time.

Effect Measures:

Tumor Size and Growth Inhibition: One of the primary effect measures will be the reduction in tumor size or growth inhibition observed in animal models treated with resistance-reversal strategies in combination with PARP inhibitors. This will be quantified using metrics such as tumor volume, tumor weight, or percentage tumor growth inhibition.

Survival Outcomes: For studies with longer follow-up periods, survival outcomes such as median survival time, progression-free survival, and overall survival will be evaluated. These metrics will provide insights into the potential impact of resistance-reversal strategies on long-term patient outcomes.

Biomarkers of Resistance and Sensitivity: Changes in biomarkers related to PARP inhibitor resistance and sensitivity will also be examined. This may include markers of DNA damage repair pathways, cell cycle regulation, drug efflux pumps, and the tumor immune microenvironment.

Immune Activation and Infiltration: Immune-based interventions will be evaluated based on their ability to activate anti-tumor immune responses, such as increased CD8+ T-cell infiltration and cytokine production.

Combination Therapy Effects: For studies evaluating combination therapies, the synergistic effects of combining resistance-reversal strategies with PARP inhibitors will be assessed. This may include evaluation of dose-response relationships and determination of optimal therapeutic ratios.

Safety and Toxicity: While the primary focus of this review will be on efficacy, safety and toxicity profiles of the evaluated strategies will also be considered. This will be important in assessing the feasibility of translating these preclinical findings into clinical practice.

Quality assessment / Risk of bias analysis The risk of bias in the included studies was assessed using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) tool for in vivo studies and the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool for in vitro studies . The SYRCLE tool evaluates key domains such as randomization, allocation concealment, blinding, baseline characteristics, selective reporting, and data completeness, while ROBINS-I assesses bias due to confounding, selection, intervention classification, missing data, and outcome measurement. Each study was independently reviewed by a single reviewer, with a second reviewer verifying the assessments. Studies were categorized as low, moderate, or high risk of bias based on predefined criteria. High-quality studies demonstrated clear randomization (for in vivo models), well-defined control groups, complete outcome reporting, and robust statistical analyses. Studies with unclear randomization, inadequate blinding, incomplete outcome data, or evidence of selective reporting were classified as having a moderate or high risk of bias.

Strategy of data synthesis Data from the included studies will be extracted by a single reviewer using Microsoft Excel in accordance with the PRISMA guidelines. To ensure accuracy, all extracted data will be saved in duplicate. The extracted data will include the last name of the first author, study design, year of publication, breast cancer subtype, experimental models (cell lines and/or animal models), intervention strategy, control groups, key outcome measures (such as IC50 values, apoptosis rates, clonogenic survival, DNA damage markers, and tumor growth inhibition in vivo), statistical significance (p-values), and quality assessment scores.

The risk of bias in the included studies will be assessed using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) tool for in vivo studies and the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool for in vitro studies. Each study will be independently reviewed by a single reviewer, with a second reviewer verifying the assessments. Studies will be categorized as low, moderate, or high risk of bias based on predefined criteria.

The overall strength of evidence for each intervention strategy will be evaluated using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) system. This approach will consider factors such as study design, risk of bias, consistency of results, directness of evidence, precision of estimates, and publication bias. Evidence from well-designed in vivo studies with strong methodological rigor will initially be rated high, while evidence from in vitro studies will be rated moderate due to inherent limitations in clinical applicability. If the risk of bias for either in vivo or in vitro experiments is rated as moderate rather than low, the overall GRADE rating will be correspondingly downgraded. Additionally, studies with significant inconsistency in results, imprecision, or indirectness will be further downgraded. Conversely, studies demonstrating large effect sizes, dose-response relationships, or strong mechanistic plausibility will be upgraded. Based on the GRADE criteria, evidence will be

categorized as high, moderate, low, or very low quality.

Subgroup analysis Subgroup analysis in this systematic review will be conducted to explore the nuanced effects of various strategies aimed at overcoming Poly ADP-ribose polymerase (PARP) inhibitor resistance in breast cancer. The analysis will be structured around key dimensions, including intervention type, study design, breast cancer subtype, and evidence strength, to provide a comprehensive understanding of the preclinical evidence base.
Intervention Type: Studies will be subgrouped based on the specific resistance-reversal strategy employed, such as epigenetic modulation, immune modulation, targeting DNA damage repair pathways, cancer stem cell targeting, metabolic interventions, and combination therapies. This will allow for an assessment of the efficacy and potential synergies of different approaches.
Study Design: In vitro and in vivo studies will be analyzed separately to evaluate the direct effects of interventions on cancer cells and their therapeutic efficacy in a more physiologically relevant setting. This will help to determine the translatability of preclinical findings to clinical practice.
Breast Cancer Subtype: Studies focusing on BRCA1/2-mutated breast cancer and non-BRCA1/2-mutated breast cancer will be analyzed as distinct subgroups. This will provide insights into the specific challenges and opportunities associated with overcoming PARP inhibitor resistance in different genetic contexts.
Evidence Strength (GRADE): Studies will be categorized based on their GRADE rating, with high-quality evidence being analyzed separately from moderate- to low-quality evidence. This will help to identify the most robust findings and to highlight areas where further research is needed to strengthen the evidence base.

Sensitivity analysis Exclude Studies with High Risk of Bias: By removing studies that are deemed to have a high risk of bias based on the SYRCLE and ROBINS-I tools, the sensitivity analysis will help determine if the overall conclusions of the review are influenced by the inclusion of these potentially flawed studies.
Assess the Impact of Heterogeneity: If significant heterogeneity is detected among the included studies (as measured by the I^2 statistic), sensitivity analyses will be conducted to explore the sources of this heterogeneity. This may involve excluding studies that contribute disproportionately to the heterogeneity or analyzing subgroups of studies with more homogeneous characteristics.
Evaluate the Robustness of Effect Sizes: Sensitivity analyses will also be used to assess the stability of the effect sizes calculated for different interventions. By comparing the effect sizes obtained from the full set of studies with those obtained from a reduced set of studies (after excluding outliers or studies with high risk of bias), the review will determine if the findings are consistent andreliable.

Language restriction English-only articles will be included.

Country(ies) involved China.

Keywords breast cancer, poly ADP-ribose polymerase inhibitor, drug resistance, preclinical strategies; evidence grading.

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