Exploring DNA Damage Responses in Cancer Therapy: Mechanisms, Strategies, and Future Directions

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Abstract

DNA disruption is a pivotal event in carcinogenesis, emanating from intrinsic cellular processes and external environmental agents. When inadequately repaired, it leads to hereditary perturbation and oncogenic transformation. This review presents an extensive outline of the molecular mechanisms underlying DNA impairment and repair, focusing on their application in cancer therapy.

We explore critical repair pathways, highlight advances in therapeutic strategies as seen in PARP inhibitors, and examine emerging innovations including CRISPR-based interventions and biomarker-driven precision oncology. The barriers, such as resistance, toxicity, and tumor heterogeneity, are critically evaluated. Finally, we dive right into the synergistic potential of amalgamating DDR inhibitors with immunotherapies. This review will be a proactive bridge between mechanistic insights with clinical translation, offering a forward-looking perspective on leveraging DDR in cancer treatment. (Figure 1)

Findings:

DDR pathways are crucial in cancer therapy. PARP inhibitors show strong results in HR-deficient tumors. Synthetic lethality, CRISPR tools, and biomarkers enhance precision. Combination therapies improve outcomes, though resistance and toxicity remain challenges.

Conclusion: Optimizing DNA fixing has advanced cancer treatment, but resistance and side effects remain key hurdles. Future progress lies in precision tools, smart biomarkers, and personalized approaches to improve outcomes and access.

Keywords: DNA damage, Repair, Cancer therapy, Mechanisms, Strategies.

Systematic Review Summary – DNA Destruction and Cancer Treatment

Introduction

DNA damage encompasses a spectrum of molecular alterations that compromise the structural and functional fidelity of the genome. These lesions emerge from both endogenous sources, including reactive oxygen species, metabolic byproducts, and replication errors, in addition to exogenous insults, including ionizing radiation, UV light, and genotoxic chemicals. Common types of DNA damage mutations encompass single-strand breaks (SSBs), double-strand breaks (DSBs),[1] base mismatches, nucleotide adducts, and interstrand crosslinks, each posing distinct challenges to cellular homeostasis. If not properly rectified, such damage can precipitate genomic instability, fostering mutations that may culminate in cell death, senescence, or malignant transformation. To counteract these threats, cells initiate an intricate DDR network, comprising surveillance systems, signaling cascades, and repair pathways tailored to specific lesion types. In the realm of oncology, DNA damage plays a dual role: it underpins Carcinogenesis and its subsequent progression through accumulated genetic aberrations, while also serving as a therapeutic target, exploited by DNA-damaging agents like chemotherapy and radiotherapy to selectively eliminate cancer cells. Elucidating pathways leading to DNA impairment and its repair is therefore foundational to advancing cancer prevention, diagnosis, and targeted therapeutic strategies. This review explores how DDR mechanisms and related therapies influence cancer treatment outcomes and the evolution of precision oncology.

Methods:

Criteria for Selection

Inclusion: Peer-reviewed articles (2000–2024) focusing on DDR pathways (e.g., HR, BER), cancer therapies like PARP inhibitors or CRISPR, and studies with clinical or translational relevance.

Exclusion: Non-English texts, unrelated studies, or those without clear outcomes or full data.

Literature Search Strategy

Research was conducted across PubMed, Scopus, Web of Science, Google Scholar, and

ClinicalTrials.gov. Search terms combined "DDR," "cancer," "PARP inhibitors," "CRISPR," and similar phrases, filtering for full-text, relevant articles within the last two decades. (Figure 2)

Study Selection Process

A multi-step review (titles, abstracts, full texts) narrowed down over 600 initial hits to 128 high- relevance studies. Articles were removed if outdated, off-topic, or lacking robust evidence.

Quality Assessment

Each article was reviewed for methodological strength. Trials were checked for sampling size and design quality; preclinical studies were judged on scientific rigor and potential clinical impact.

Data Extraction

Key information included DDR mechanisms, treatment types, patient outcomes (e.g., survival, resistance), and use of biomarkers. Data was compiled using a structured format and cross- checked for accuracy.

Synthesis & Presentation

Findings were grouped into four themes: DDR biology, treatment applications, novel approaches (e.g., synthetic lethality), and future challenges. Diagrams and figures were put to use to communicate insights.

Processes of DNA Damage

DNA is constantly subjected to diverse forms of damage derived from both intrinsic metabolic byproducts and extrinsic environmental sources. These damages, if unrepaired, compromise genomic stability and contribute to carcinogenesis.

Categories of DNA lesions (Figure .3) Base
Modifications:
Oxidative Damage: ROS oxidize bases, forming lesions like 8-oxoG, which can mispair with

adenine, leading to G-to-T transversions.

Alkylation: Alkylating agents add alkyl groups to bases (e.g., O6-methylguanine), disrupting base pairing and replication.

Deamination: Spontaneous or induced loss associated with the amino moiety (e.g., cytosine to uracil), causing mispairing during replication.

Single-Strand Breaks (SSBs):

Result from oxidative attack, ionizing radiation, or enzymatic cleavage during repair, interrupting one DNA strand and potentially leading to repetition Fork Crash if unrepaired.

Double-Strand Breaks (DSBs):

Induced by high-energy radiation, ROS, or replication across SSBs, these are severe lesions that may result in chromosomal rearrangements, a hallmark of cancer.

Interstrand Crosslinks (ICLs):

Induced by bifunctional agents (e.g., cisplatin, psoralens), ICLs link covalently complementary strands, blocking Propagation and the process of transcription.

Intrastrand Crosslinks:

Formed by agents like UV light (e.g., cyclobutane pyrimidine dimers, 6-4 photoproducts), these distort the DNA helix, impeding replication and transcription.

DNA-Protein Crosslinks:

Result from interactions with proteins (e.g., topoisomerase inhibitors), trapping repair enzymes, and stalling replication machinery.[2]

Base Discrepancies and Insertions/Deletions:

Arise from replication errors or polymerase slippage, leading to frameshifts or point mutations if uncorrected by mismatch repair.

DNA Damage Response (DDR)

The DDR represents a conserved cellular signaling framework that orchestrates the detection and reconstruction of DNA damage. Key kinases, including ATM (ataxia-telangiectasia mutated), ATR, and DNA-PKcs, act as sensors and transducers. Upon activation, they activate downstream targets through phosphorylation, such as CHK1, CHK2, and p53, resulting in Cell cycle halting,

- and **Genome repair**
- senescence, or apoptosis, depending on damage severity and cell context.

Understanding the DDR machinery is critical for designing therapeutics that exploit cancer- specific vulnerabilities while maintaining normal tissue. (Figure 4)

DNA Repairing Paths in Cancer

DNA rejuvenate conduits are indispensable for maintaining genomic integrity. In cancer, the following pathways are frequently dysregulated, either through loss-of-function mutations or compensatory upregulation, providing exploitable vulnerabilities for therapy.

Fanconi Anemia (FA) Pathway: Repairs ICLs during replication. UHRF1 recruits FANCD2/FANCI, which orchestrates endonuclease cleavage (e.g., ERCC1, XPF) and DSB repair via nucleases, polymerases, and ligases.

Nucleotide Excision Repair (NER): Fixes bulky DNA lesions. Global-genome NER (GG- NER) uses XPC to detect helix distortions, while Transcription-mediated NER (TC-NER) senses RNA polymerase stalling. TFIIH unwinds DNA, XPG/XPF excise the lesion, and polymerases/ligases fill the gap.

Base Excision Repair (BER): Corrects small base lesions. DNA glycosylases create an abasic site (AP), processed employing short-patch (1 nucleotide) or long-patch (2–10 nucleotides) BER. PARP-1/2 and APE1/2 facilitate repair, with XRCC1 and ligases sealing the gap.

Mismatch Repair (MMR): Resolves replication errors. MSH2/MSH6 (MutSα) or MSH2/MSH3 (MutSβ) recognize mismatches or indels, recruiting EXO1 to excise ~150 nucleotides, followed by polymerase δ and ligase I repair.

Double-Stranded Break (DSB) Repair:

- **Non-Homologous End-Joining (NHEJ):** Ku70/Ku80 protects DSB ends, DNA-PKcs recruits XRCC4/XLF/ligase IV for ligation, with Artemis processing incompatible ends.
- **Homology-Directed Repair (HDR):** MRN/CtIP resects DNA ends, RAD51 (with BRCA2) uses sister chromatid as a template for accurate repair, regulated by 53BP1 and ATM.

- **Alternative Pathways (A-EJ/SSA):** Error-prone; MMEJ uses short homology (2–20 nt), SSA uses longer stretches (>25 nt), involving PARP-1, MRN, and RAD52.

Strategies for Therapeutic Management

A profound comprehension of DNA repair biology has enabled the design of therapies that exploit cancer-specific deficiencies in the DDR. The selective targeting of these [3] vulnerabilities enhances the efficient operation and treatment while minimizing unintended consequences to normal tissues.

(Figure 5: Bar graph comparing PFS and ORR for PARP inhibitors vs. chemotherapy in BRCA- mutated cancers.)

Recent meta-analyses of Phase two and three trials underscore the clinical success of DDR- targeting agents, particularly in homologous recombination-deficient (HRD) cancers. For example, in BRCA-mutated ovarian cancer, poly (ADP-ribose) polymerase (PARP) inhibitors demonstrate a pooled response rate of 57% (95% CI: 52–62%) and a median PFS of 11.0 months— nearly double that of standard chemotherapy (5.5 months; $p < 0.001$).

CRISPR-based synthetic lethal screens have further expanded the breadth of DDR-targeted therapy, uncovering novel vulnerabilities in HR-proficient tumors. These discoveries are accelerating the evolution of new agents and biomarker-driven strategies, projected to double DDR-therapy utilization by 2030.

Radiotherapy and Chemotherapy

Conventional therapies such as radiotherapy and alkylating agents (e.g., cisplatin, cyclophosphamide) act by inducing DNA lesions—predominantly double-strand breaks or crosslinks. Radiotherapy introduces DSBs through ionizing radiation, while alkylating agents form covalent adducts that disrupt replication.[4]

Despite their broad utility, these therapies are limited by resistance mechanisms and off-target effects in normal tissues. Combining them with DDR inhibitors or radiosensitizers has shown promise in improving tumor selectivity and reducing toxicity. Research is ongoing to refine combination regimens and dosing schedules to get the most out of the therapeutic index.

Addressing DNA Repair with Smaller Molecule Inhibitors

Small-molecule modulators targeting the DDR have transformed cancer therapeutics by selectively inducing lethality in genetically prone tumor cells. These agents interfere with key DDR enzymes, augmenting the cytotoxic effects of DNA damage while preserving cells that are normal with intact repair systems.

PARP Inhibitors: PARP enzymes facilitate by detection and initiation of repair of single-strand breaks (SSBs). Inhibitors include niraparib, Olaparib, and rucaparib prevent PARP-mediated repair, leading to the amassing of SSBs that convert into double-strand breaks during replication. In homologous recombination-deficient (HRD) tumors, particularly BRCA1/2-mutant, this synthetic lethality results in apoptosis.

ATM/ATR and DNA-PK Inhibitors: ATM and ATR are central DDR kinases elicited by DSBs and replicative stress, respectively. DNA-PKcs is essential for NHEJ. Pharmacological inhibition of these kinases sensitizes tumor cells to genetically toxic substances and can potentiate radiotherapy. Early-phase clinical trials have demonstrated promising efficacy in multiple tumor types, especially when paired with chemotherapy or immune checkpoint blockers.

Synthetic Mortality and Precision Medicine

The concept of **synthetic lethality** forms the foundation of several targeted cancer therapies. It describes a situation so which the concurrent disruption of two genes causes cell demise.[5], whereas the loss of either gene alone is tolerable. This principle enables targeted destruction of cancer cells harboring specific repair deficiencies, sparing normal cells.

A prototypical example is the utilization of **PARP inhibitors** in tumors with BRCA1/2 mutations. While BRCA loss impairs homologous recombination (HR), cancer cells compensate via PARP- dependent SSB repair. PARP inhibition removes this backup pathway, resulting in cell death. (Figure 6: Diagram illustrating synthetic lethality — BRCA-deficient cancer cell relies on PARP; PARP inhibition results in lethal DSB accumulation.)

Ongoing research continues to identify newly synthesized deadly interactions beyond BRCA. High-throughput CRISPR-Cas9 screens have revealed candidate gene pairs in TP53-mutated and ATM-deficient tumors, widening the clinical scope of precision oncology.[6]

Emerging Technologies

CRISPR-Based Therapies

The advent of CRISPR-Cas9 genome editing has transformed cancer research and therapeutic design by enabling precise genetic modifications. In oncology, CRISPR offers dual utility: 1) functional genomics screens to locate novel cancer targets, and 2) direct correction or disruption of oncogenic drivers.

CRISPR-mediated knockouts of DNA DDR genes in cancer models have been instrumental in mapping synthetic lethal interactions, aiding drug development. In parallel, targeted editing of oncogenes or tumor suppressors holds potential for curative interventions.

Despite these advances, translation to the clinic faces technical and ethical hurdles. Off-target effects, immunogenicity, and inefficient delivery—especially in solid tumors—remain major challenges. Approaches to mitigate these include high-fidelity Cas9 variants, non-viral delivery systems (e.g., nanoparticles), and inducible editing platforms. Continued innovation is essential to safely harness CRISPR in DDR-targeted therapies.

Biomarker-Guided Therapy

Biomarkers are essential for stratifying patients in DDR-targeted therapy. Mutations in genes such as **BRCA1/2**, **ATM**, and **TP53** serve as predictive indicators for sensitivity or resistance to specific agents, particularly PARP inhibitors. Genomic assays evaluating **HRD**—including RAD51 foci assays, copy number analysis, and mutational signatures—inform treatment decisions and clinical trial design. Next-generation sequencing (NGS) platforms enable real-time profiling and adaptive treatment strategies.[7]

Incorporation of biomarker data into treatment planning enables precision oncology, reducing toxicity while enhancing therapeutic efficacy. Concomitant diagnostics are increasingly essential in regulatory approvals and reimbursement models.

DDR and Immunotherapy

Recent advances have illuminated a compelling link between DNA repair deficiencies and tumor immunogenicity. When DDR pathways are compromised, cells accumulate DNA damage and mutational burdens at an accelerated rate. This genomic instability often leads to the generation of neoantigens—mutated peptides presented on tumor cell surfaces—which can be recognized by the

immune system. As a result, DDR-deficient tumors frequently exhibit enhanced sensitivity to ICIs such as PD-1 and PD-L1 antibodies.

Moreover, combining DDR inhibitors with immunotherapeutic agents is showing promise in Preliminary and clinical settings. A key mechanism underpinning this synergy involves the phenomenon of “viral mimicry.” Inhibiting DDR processes can result in the cytosolic accumulation of double-stranded DNA, which engages innate immune sensors like cGAS-STING. This activation results in type 1 interferon signaling, effectively tricking the system of immunity into treating the tumor as a virally infected cell and amplifying the anti-tumor immune response. [1]

This intersection of DDR and immunity opens exciting avenues for rational combination strategies, particularly in neoplasms with low baseline immunogenicity. Trials are underway to evaluate PARP inhibitors in conjunction with ICIs, and early results indicate enhanced efficacy across multiple cancer types, including ovarian, lung, and triple-negative breast cancers. [8] Continued exploration of the DDR-immune interface promises to expand the therapeutic arsenal and offer new hope for patients with otherwise refractory tumors. (Figure 7- Overview of DNA Injury Types and Corresponding Cellular Repair Pathways)

Current Trends in Clinical Applications PARP Inhibitors in Clinical Practice

Poly(ADP-ribose) polymerase (PARP) inhibitors have emerged as a cornerstone in the treatment of homologous recombination-deficient (HRD) cancers, particularly those with **BRCA1/2** mutations. Agents such as **olaparib**, **rucaparib, and niraparib** have received regulatory approval for utility in ovarian, breast, and prostate cancers, demonstrating significant improvements in clinical outcomes.

In pivotal phase III trials:

Olaparib showed a 60% response rate in BRCA-mutant ovarian cancer, extending median PFS to

11.2 months compared to **5.4 months** with placebo.

Niraparib improved PFS in both BRCA-mutant and wild-type HRD subgroups, suggesting broader applicability beyond BRCA status.

Rucaparib displayed durable responses in heavily pre-treated patients, highlighting its role in recurrent disease.[9]

Table 1. Summary of Key Clinical Trial Outcomes for Endorsed PARP Inhibitors

Drug	Cancer Type	Response Rate (RR)	Progression-Free Survival (PFS)	Overall Survival (OS)
Olaparib	Ovarian (BRCA+)	60%	11.2 months	34.5 months
Niraparib	Ovarian (BRCA+)	55%	9.3 months	31.2 months
Rucaparib	Ovarian (BRCA+)	54%	10.8 months	28.7 months

Table 1 summarizes these key outcomes, including response rates, median PFS, and overall survival (OS).

Source for Table 1 (click here)

Ongoing clinical trials are exploring PARP inhibitors in additional tumor types, including **pancreatic, lung, and endometrial cancers**, along with the **adjuvant setting**. Investigations are also focused on identifying predictive biomarkers beyond BRCA, such as genomic scarring, ATM mutations, and RAD51 foci.

Combination Therapies

The assimilation juggling PARP inhibitors with additional therapeutic approaches is an area of intense investigation to overcome resistance, enhance efficacy, and expand the therapeutic window.

Combinations under clinical evaluation include:

PARP inhibitors + (ICIs): The synergy between DNA damage and immune activation is mediated via the **cGAS-STING** pathway. DNA damage induces cytosolic DNA accumulation, promoting Type 1 interferon regulation and enhancing T-cell-mediated tumor clearance. Early- phase studies, such as **MEDIOLA** and **TOPACIO**, have reported encouraging response rates in platinum-resistant cancers.

PARP inhibitors + chemotherapy: DNA-damaging agents (e.g., cisplatin, topotecan) exacerbate replication stress, and when coupled with impaired repair due to PARP inhibition, this drives tumor cell apoptosis. However, overlapping toxicities—especially **myelosuppression**—require dose optimization and staggered scheduling.

PARP inhibitors + radiotherapy: PARP inhibition sensitizes tumor cells to Radiation from ions by preventing the Remodeling of DNA strand breaks. This radiosensitization has shown promise in preclinical glioblastoma and lung cancer models.[10]

Triplet combinations: Trials combining **PARP inhibitors + chemotherapy + ICIs** are underway, aiming for multimodal synergy. However, the complexity of Toxicology underscores the need for **biomarker-guided patient selection**.

The success of these regimens will depend on careful titration, predictive biomarker identification, and real-time pharmacovigilance.

Overcoming Resistance Mechanisms

Despite initial efficacy, many tumors eventually develop endurance to DDR-targeted therapies. Understanding these mechanisms is crucial for designing second-line strategies and improving patient outcomes.

Common resistance mechanisms include:

Restoration of homologous recombination: Through secondary (reversion) mutations in BRCA1/2 or RAD51, which fix the comprehension frame and protein function, thereby nullifying synthetic lethality.

Upregulation of drug efflux pumps: Overexpression of **P-glycoprotein (ABCB1)** reduces intracellular drug concentrations, lowering therapeutic effectiveness.

Compensatory activation of alternative repair pathways, Such as BER or NHEJ.

Altered PARP trapping dynamics: Mutations affecting PARP1-DNA complex stability can reduce cytotoxicity without altering catalytic inhibition.

Strategies to overcome resistance:

Combination therapies targeting secondary DDR components (e.g., **ATR**, **CHK1**, **WEE1**

inhibitors) are being tested in resistant models.

Emerging agents targeting RAD51, **POLQ**, and **SLFN11** may prevent recombination recovery and enhance synthetic lethality.

Liquid biopsies and ctDNA are getting acclimated to monitor resistance evolution and guide real- time therapy adaptation.

As resistance pathways are often multifactorial, adaptive clinical trials employing longitudinal genomic profiling and AI-driven decision support are crucial for next-generation therapeutic planning.

Discussion

The preceding ten years have witnessed a paradigm shift in oncology through the strategic targeting of DNA repair mechanisms. DDR inhibitors, such as PARP inhibitors, have revolutionized therapy algorithms for Individuals with BRCA mutations and beyond. However, clinical adoption is hindered by resistance, toxicity, and access-related challenges.

Expert consensus emphasizes the need for Biomarker-driven investigation designs, particularly those integrating longitudinal molecular profiling, patient-reported outcomes (PROs), and real- time pharmacovigilance. Future trials should incorporate stratified cohorts, allowing dynamic reclassification based on evolving tumor biology during treatment.

Additionally, the intersection of DDR with immune modulation, epigenetics, and tumor metabolism represents a fertile ground for innovation. Integrating these domains through multi- omics approaches and machine learning could set the route for next-generation precision oncology.

Challenges and Limitations

Despite promising clinical outcomes, the therapeutic exploration of the DDR faces significant limitations that must be tackled to ensure durable responses and widespread applicability.

Toxicity and Off-Target Effects

DDR-targeting agents, especially when combined with chemotherapy or radiotherapy, may damage normal tissues with high proliferative rates, such as bone marrow, gastrointestinal mucosa, and hair follicles, leading to hematologic toxicity, gastrointestinal symptoms, and alopecia.

Novel agents with increased tumor specificity, targeted delivery platforms (e.g., antibody-drug conjugates, nanoparticle formulations), and intermittent dosing schedules are under development to mitigate off-target effects.

Tumor Heterogeneity

Intra and inter-tumoral heterogeneity significantly influence therapeutic responses. Subclonal variation in DDR gene expression and Epigenetic modulation might give rise to mixed or incomplete responses, even within a single tumor mass.
Advances in single-cell sequencing, liquid biopsies, and spatial transcriptomics are getting acquainted with characterizing this heterogeneity and tailoring real-time therapeutic strategies.

Resistance Mechanisms

Both constitutive and emergent resistance remain formidable challenges. Mechanisms include:

- Genetic recurrent alterations in BRCA1/2 restore homologous recombination.
- Upregulation of compensatory repair pathways (e.g., BER, NHEJ).
- Drug efflux via ABC transporters.
- Microenvironmental modulation, including hypoxia-mediated DDR suppression.

Integrated biomarker monitoring and computational models are being developed to predict resistance trajectories and guide adaptive treatment approaches.

Conclusion

DDR-targeted therapy signifies a paradigm shift in oncology. With innovations in genome editing, omics, and computational modeling, cancer therapy is entering an era of precision and adaptability. Integrating DDR inhibitors with immunotherapy and personalized biomarkers will transform cancer care, provided challenges in resistance and equity are addressed.

Limitations

- Therapeutic Toxicity:

  We acknowledge that DDR-targeting agents, particularly in combination with chemotherapy or radiotherapy, may lead to significant off-target effects in normal tissues, limiting their clinical tolerability.

- Tumor Heterogeneity:

  The variability in DDR gene expression, Epigenetic governance across and within tumors, presents a major challenge, potentially resulting in heterogeneous treatment responses.

- Emergence of Resistance:

  Despite initial efficacy, resistance mechanisms—such as BRCA reversion mutations, activation of alternate repair pathways, and drug efflux—remain a significant barrier to sustained therapeutic benefit.

- Delivery and Specificity Limitations:

  Novel interventions like CRISPR and small-molecule inhibitors face challenges related to delivery efficiency, off-target activity, and specificity in solid tumor environments.

- Limited Biomarker Scope:

  While BRCA mutations guide current DDR therapies, there is something to strive for broader, more inclusive biomarker identification to enable wider clinical application.

- Ethical and Translational Barriers:

  The clinical translation of gene-editing and next-generation DDR-targeted therapies is hindered by unresolved ethical, regulatory, and safety considerations.

- Lack of Real-World Data:

  Many findings are derived from controlled clinical trials or preclinical models, with limited validation in real-world, diverse patient populations.

- Access and Equity Concerns:

  We recognize that high costs and infrastructure requirements may restrict access to advanced DDR therapies in resource-limited settings.

Future Directions

- Development of next-generation inhibitors targeting POLQ, RAD51, and WRN.
- Omics integration and AI to predict therapeutic outcomes.
- Immunogenomics to optimize DDR-immunotherapy combinations.
- Expanding access in resource-limited settings.

Financial Support

This study didn't obtain any external funding or financial support.

Ethical Approval

Ethical approval was not required for this study.

Informed Consent

Informed consent did not apply to this review.

Data Availability

Data sharing is not pertinent**,** since no new data was created or examined in this study.

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Conflicts of Interest

The authors affirm that no disagreements of concern exist.

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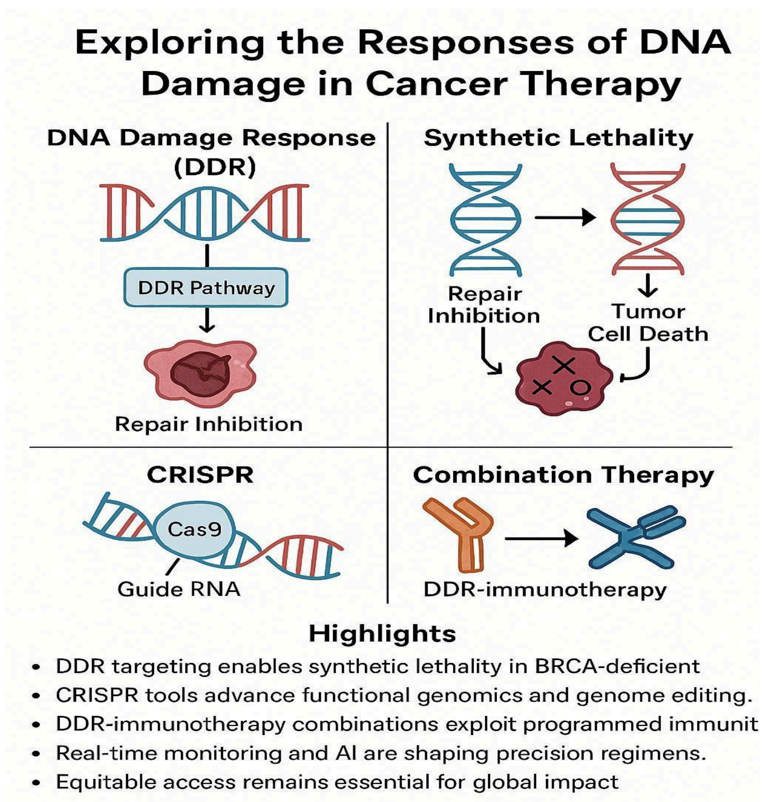
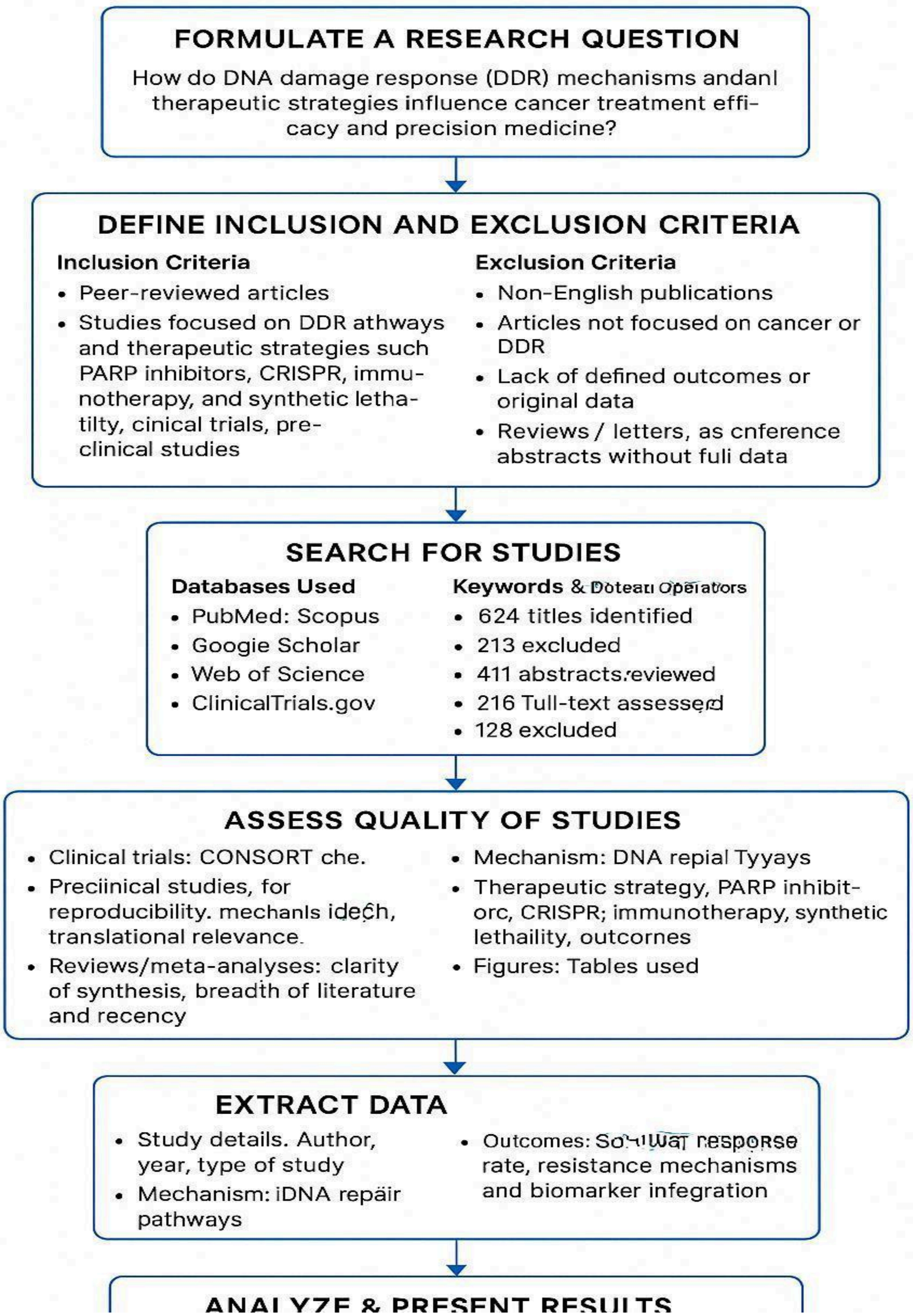


Figure 1 - Targeting DNA Damage Responses for Cancer Therapies

Source - OpenAI. (2025). ***Exploring the responses of DNA damage in cancer therapy*** **[AI- generated image]. ChatGPT. https://chat.openai.com**

Figure 2- "Structured workflow of a Systematic Review in DNA Damage and Cancer Therapy"



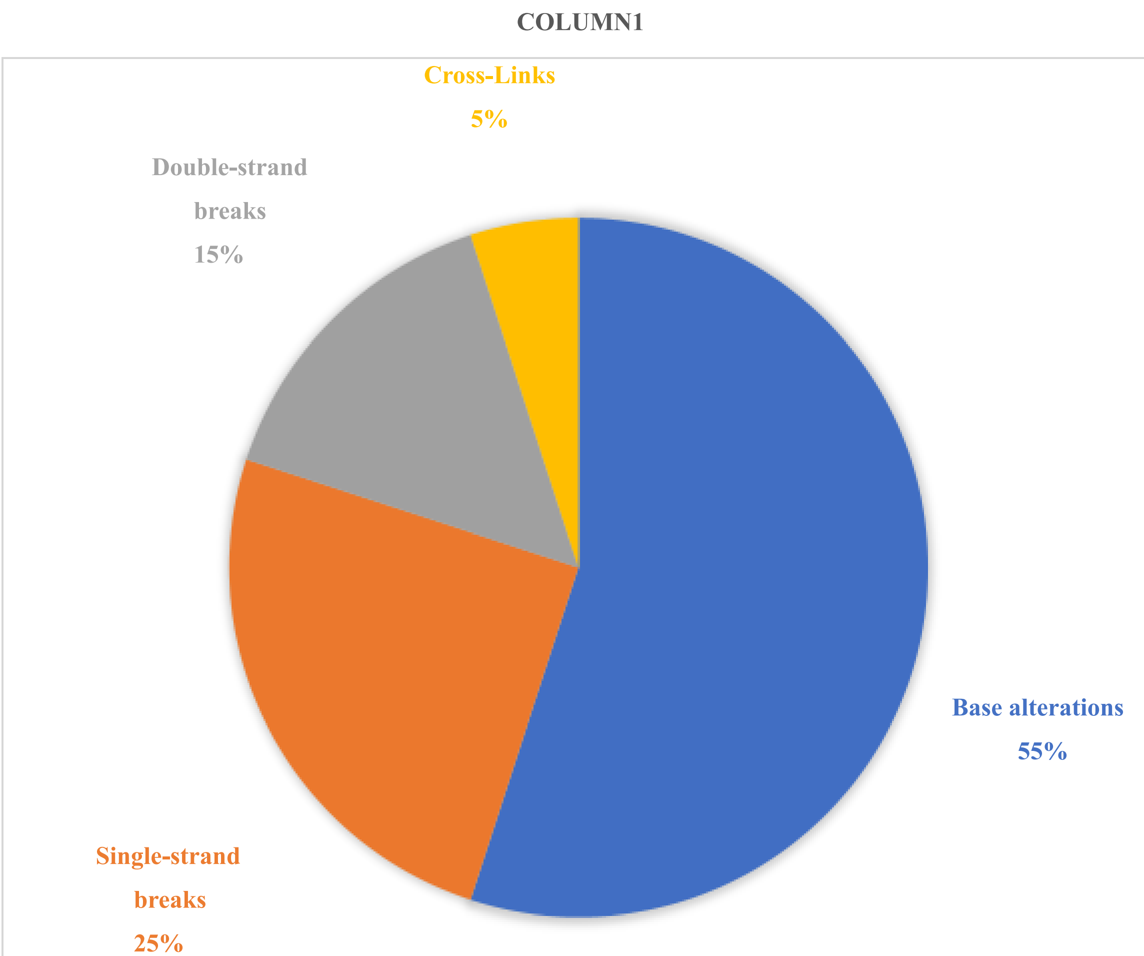


Figure 3: Pie chart showing the relative proportions of common DNA damage types

Source: Self-Created

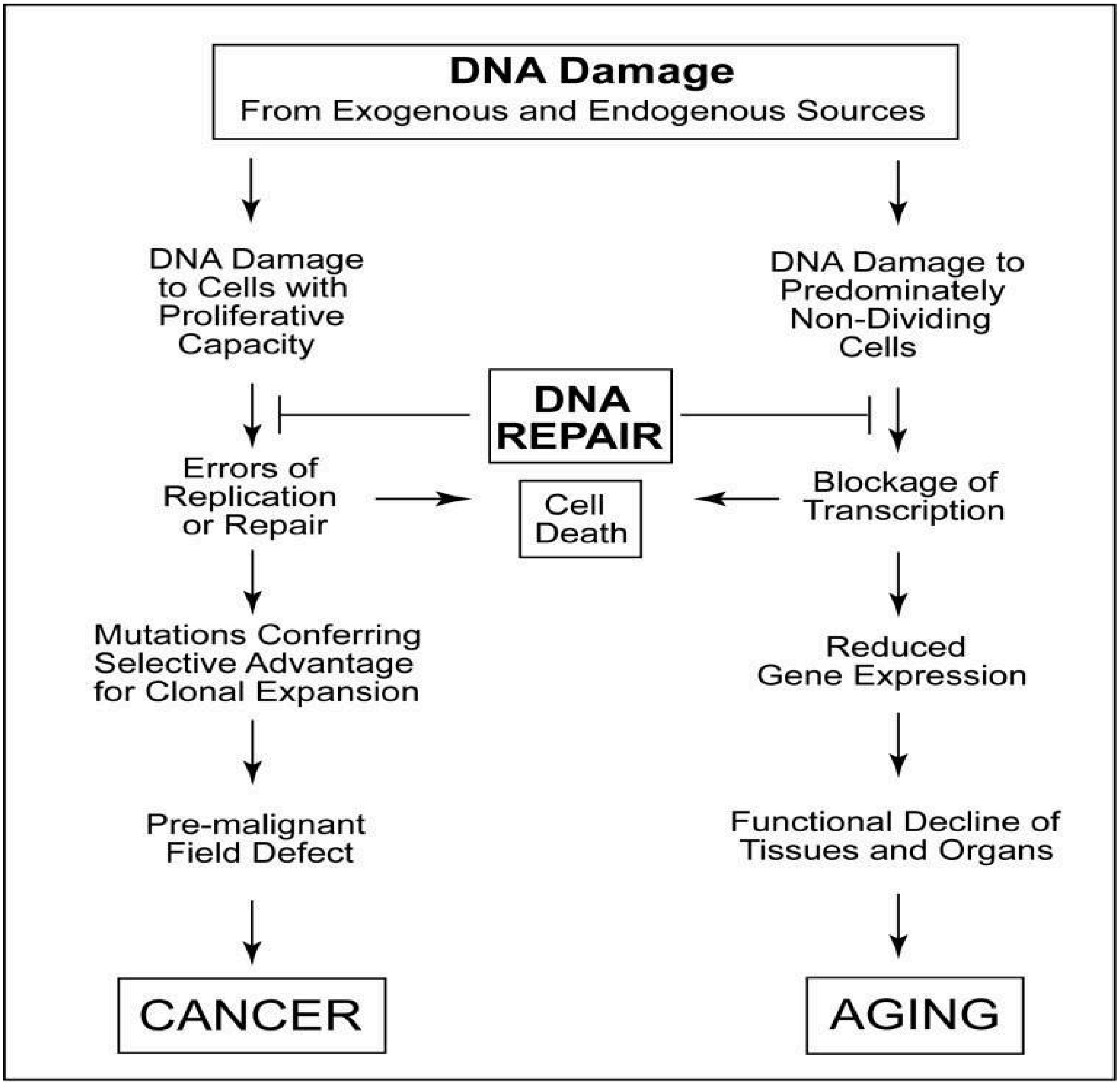


Figure 4- Pathways Linking DNA Damage to Cancer Development and Aging.

Source- Chantelmao. (2017, May 17). *Types of DNA Damage* [Image]. Wikimedia Commons.

https://commons.wikimedia.org/wiki/File:Types_of_DNA_Damage.jpg

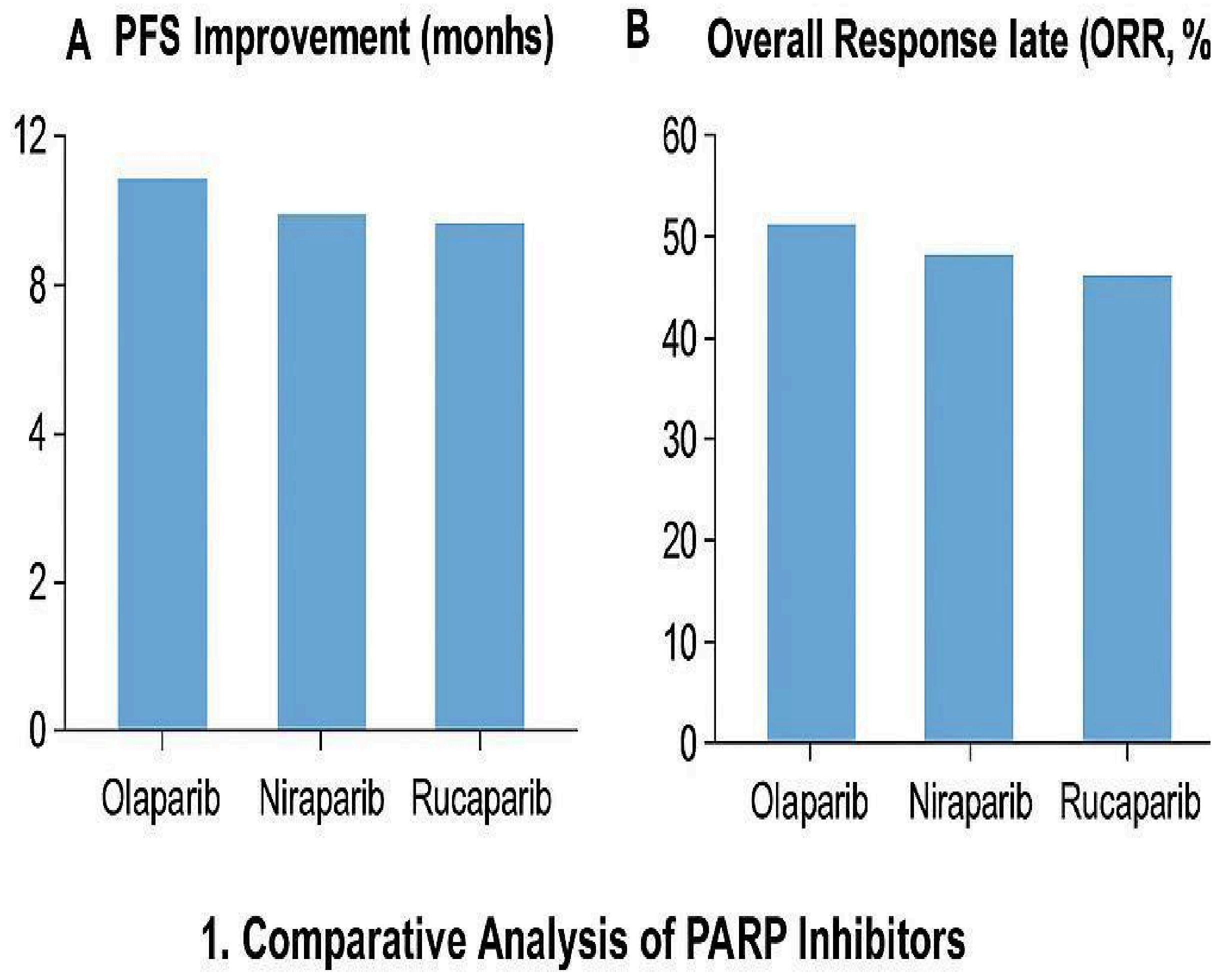


Figure 5: Bar graph comparing PFS and ORR for PARP inhibitors vs. chemotherapy in BRCA-mutated cancers.

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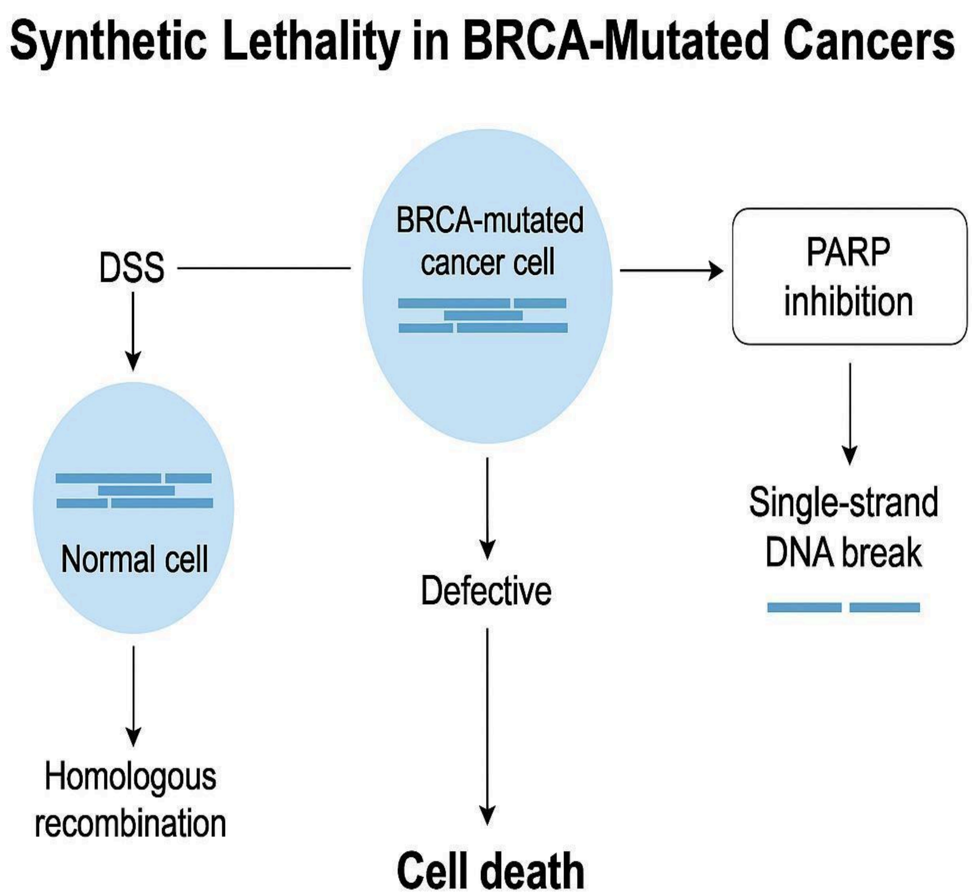

Figure 6: Diagram illustrating synthetic lethality — BRCA-deficient cancer cell relies on PARP; PARP inhibition results in lethal DSB accumulation.

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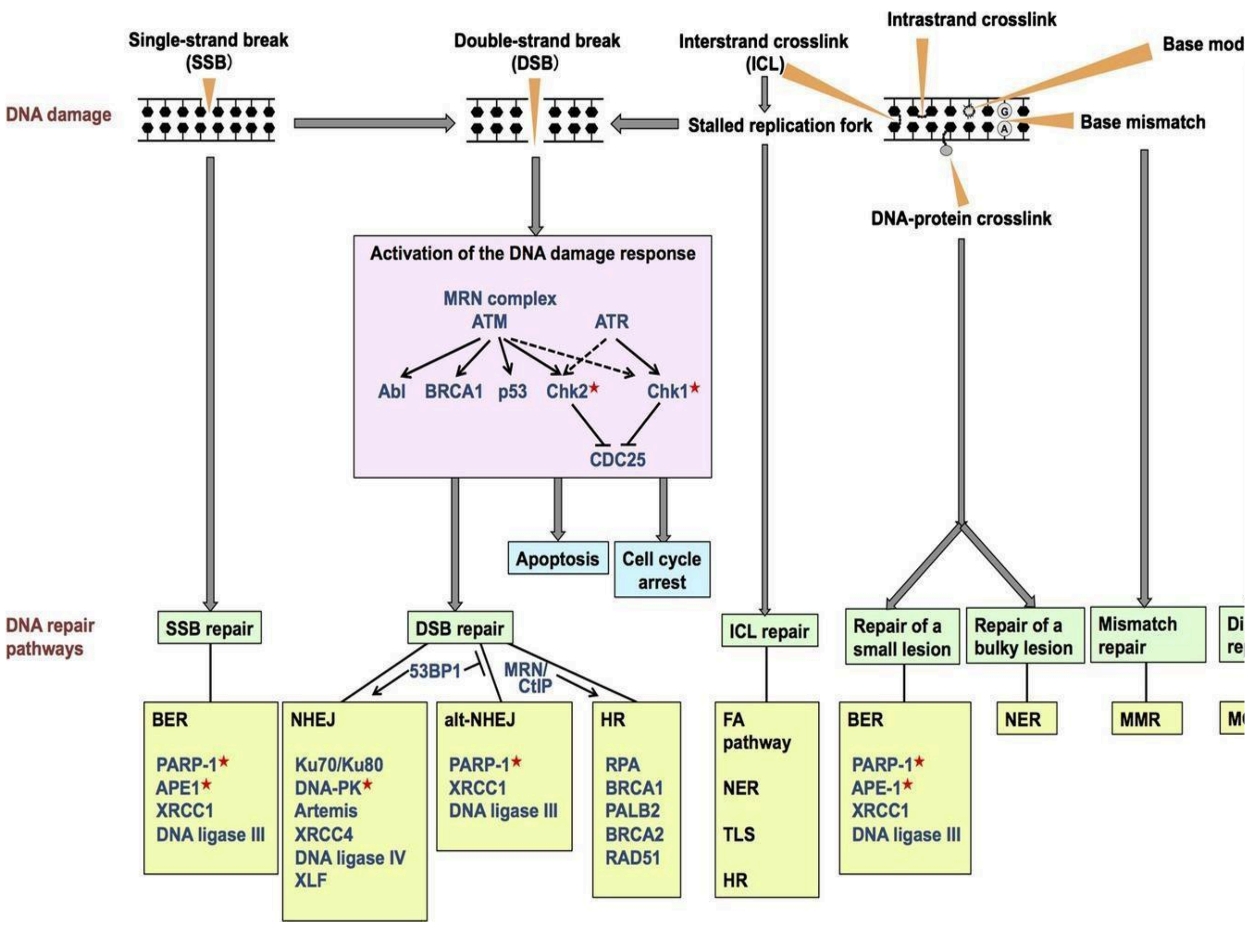

Figure 7- Overview of DNA Damage Types and Corresponding Cellular Repair Pathways Current Trends in Clinical Applications

Source- https://doi.org/10.1002/em.22087