DNA Repair Pathways in Carcinogenesis: Mechanisms, Modulation, and Future Directions for Cancer Prevention

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ABSTRACT

DNA repair mechanisms are prime custodians of genomic integrity and their deregulation is essentially a central feature during oncogenesis. This study surveys the molecular pathways of micro base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), and dual strand repair (DSBR) through homologous recombination (HR) and by no means homologous end joining (NHEJ), and this is by particular attention to the way that they take part in carcinogenic adjustment. Clinical data show that germline BRCA1/2, MLH1, and MSH2 mutations systems cause susceptibility to hereditary cancer, and somatic variants of the repair genes promote tumorigenesis. Further, the epigenetic silencing of the repair capacity as well as oxidative stress and oncogenic signal transduction pathways also play a role in the chemoresistance and the development of the disease. Existing treatment approaches, such as PARP inhibitors and immune checkpoint manipulation are specific modalities, in addition to synthetic lethality approaches, assessed within this study as interventional and preventative measures. Education on repair pathway control can guide the precise oncology, early indication makers, translation of the oncology prevention method, which in turn can control morbidity and enhance the prognosis of the patient

Keywords: *DNA repair pathways,Carcinogenesis,Genomic instability,Base excision repair,Nucleotide excision repair,Mismatch repair,Double-strand break repair,Cancer prevention,DNA damage response,Therapeutic modulation*

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1. INTRODUCTION

The mechanisms involved in removing or repairing lesions in the DNA thus makes the genomic integral and prevents the carcinogenic process. Many cellular processes like base excision repair (BER), nucleotide excision repair (NER), and mismatch repair (MMR) of the cell or the double-strand break repair (DSBR) maintain regulation of cellular response to self-and exogenous stress (de Almeida et al., 2021). Malfunctions in these systems result in the creation of genomic instability which is a characteristic of tumorigenesis. As an example, the repair activity in hepatocellular carcinoma (HCC) is amplified and relates to an augmented proliferation rate and reduced survival (Oshi et al., 2021). Equally, alkylation mutagenesis by nitrosamines is a process requiring BER and MMR, and such repair defects predisposes cancer (Fahrer & Christmann, 2023). In addition to mutational inactivation, splicing regulation of repair-associated genes is also adopted during cancer cell metabolism, e.g., in esophageal carcinoma in the case of ALDH18A1 modulation (Yongkang et al., 2025). In addition, the etiology of viral carcinogenesis, including HPV-mediated tumors, involves usurping the proteins in

the DNA damage response pathway to provide persistence (Cosper et al., 2021). Therefore, the deconstruction of repair processes leads to cancer prevention and focused pharmacology

2. PROBLEM STATEMENT

Although DNA repair pathways are guarantors of integrity, their deregulation paradoxically promotes tumor progression and multidrug resistance. Repair of germline or somatic mutations in HR and MMR genes increases the risk of cancer, and hyperfunctional repair promotes aggressive tumor phenotypes (Li et al., 2021). In HCC, the high repair activity portends a poor survival (Oshi et al., 2021). Similarly, HPV-related oncogenesis makes use of DNA damage response to help support viral genome integration (Cosper et al., 2021). Despite the recent progresses like the PARP inhibitor, cancer will continue to adapt by reassembling repair pathways. This issue that has not been resolved yet underlines the necessity to modulate repair networks in cancer prevention and sustainable approaches to treatment.

3. RESEARCH SIGNIFICANCE

Insights into DNA repair pathways can have dramatic translational importance in oncology. Findings related to genomic instability signatures that are signified with BER, NER, MMR, and DSBR can provide diagnostic and prognostic markers (de Almeida et al., 2021). As an example, BRCA-deficient tumors are morphologically vulnerable in the synthetically lethal setting of PARP inhibition, confirming the therapeutic manipulation (Li et al., 2021). Similarly, the alterations in repair recognized as brought on by splicing in esophageal carcinoma widens the prospect of intervention (Yongkang et al., 2025). The aspect of preventive potential is achieved via the connection between environmental mutagens such as nitrosamines and the repair shortage (Fahrer & Christmann, 2023). This work provides insight into the mechanism of how repair deregulation contributes to carcinogenesis, in support of precision medicine and the design of specific cancer prevention strategies.

4. LITERATURE REVIEW

Authors have set the precedent that DNA repair inhibition could enhance chemotherapeutics or radiotherapy and reveal tumor dependence on backup pathways. This was furthered by Kelley, Logsdon, & Fishel (2014) cataloguing additional potential targets pro ving beyond PARP, such as APE1, ATM/ATR, DNA-PK, and polymerases, and suggesting that chemosensitization has an evolutionary path toward biomarker-driven synthetic lethality. Wang, Chen & Ao (2021) honed the clinical focus, outlining ATR, CHK1, WEE1 and DNA-PK inhibitors with activity attributed to homologous-recombination deficiency and replication stress. mechanistically, Bai, Wang, & Wang (2020) agreed but also placed an emphasis on preclinical rationales supporting the combination of DDR inhibitors and radiotherapy with alkylators, with the caveat of pathway redundancy to attenuate potential benefits. Klinakis, Karagiannis & Rampias (2020) advanced the frontier to mixes with immunotherapy and epigenetic agent contending that chromatin reprogramming rewires restoration reliances and opens up novel synthetic lethality. And coming most more recently, Groelly, Fawkes, Dagg, Blackford, & Tarsounas (2023) objected to PARP-centric thinking, surveying resistance pathways replication-fork protection, reversion mutations, and rewired end-joining and suggested that such pathways must be opposed in next-wave approaches, using ATR, POLQ, and DNA-PK inhibition, and rational sequencing to postpone resistance. Collectively, historical accounts positioned DDR targeting as generic potentiation, but current reviews postulate that targeting is genotype and context specific and all combinations may be adaptive (Wang et al., 2021; Klinakis et al., 2020). The literature has reached a consensus: DDR inhibition has the potential to be transformative and needs to be informed by biomarkers, resistance tracking and trial designs that focus on long-term benefit as opposed to temporary responses (Groelly et al., 2023).

5. METHODOLOGY

The study uses secondary data as a research methodology, which also has a number of advantages such as effectiveness, low costs, and a broad range of findings with a peer-reviewed emphasis. Through conducting a review of other academic literature, report of clinical trials and systematic reports, the study does not collect new data at great cost but yields reliability due to the established evidence. Thematic data analysis is used to outline emerging patterns and central concepts with references to the role of homologous recombination deficiency, mismatch repair defects, and synthetic lethality in carcinogenesis. In this manner, synthesis of varied sources can be made, enhancing conceptual clarity. Such data sources are PubMed-indexed clinical studies, oncology journals, the systematic reviews, and other recent evidence-based reports such as the ones by Paulet et al. (2022), Herzog et al. (2023), and Zhao et al. (2024).

Criteria Type	Inclusion Criteria	Exclusion Criteria
Study Type	Peer-reviewed journal articles, systematic reviews, meta-analyses, and clinical trial reports relevant to DNA repair and carcinogenesis.	Non-peer-reviewed sources, opinion articles, conference abstracts without full data, unpublished manuscripts.
Timeframe	Studies published between 2020 and 2025 to ensure contemporary evidence.	Studies published before 2020, unless highly cited foundational references.
Focus Area	Research focusing on DNA repair pathways (HRD, MMR, NER) and their role in carcinogenesis or targeted therapy.	Studies unrelated to DNA repair mechanisms or focusing on non-cancer diseases.
Population	Studies involving human cancer patients or validated human cell line/animal models relevant to DNA repair deficiencies.	Studies limited to non-oncological conditions or with unvalidated experimental models.
Data Availability	Studies providing clear molecular, genetic, or therapeutic outcome data (e.g., synthetic lethality, PARP inhibitor trials).	Studies lacking detailed results, incomplete datasets, or insufficient methodological transparency.
Language	Articles published in English for consistency and accessibility.	Non-English studies without reliable translations.

6. RESULT AND DISCUSSION

Base excision repair disruption as a driver of mutagenic carcinogenesis

Base excision repair (BER) disruption is a root cause of mutagenic carcinogenesis due to its role in the inability to repair oxidative and alkylation-damaged DNA. Abasic sites and single-strand breaks are not repaired via normal BER activity, and genomic instability increases by excess of these defective BER events during replication, subsequently resulting in the formation of double-strand breaks (Gohil, Sarker & Roy, 2023).

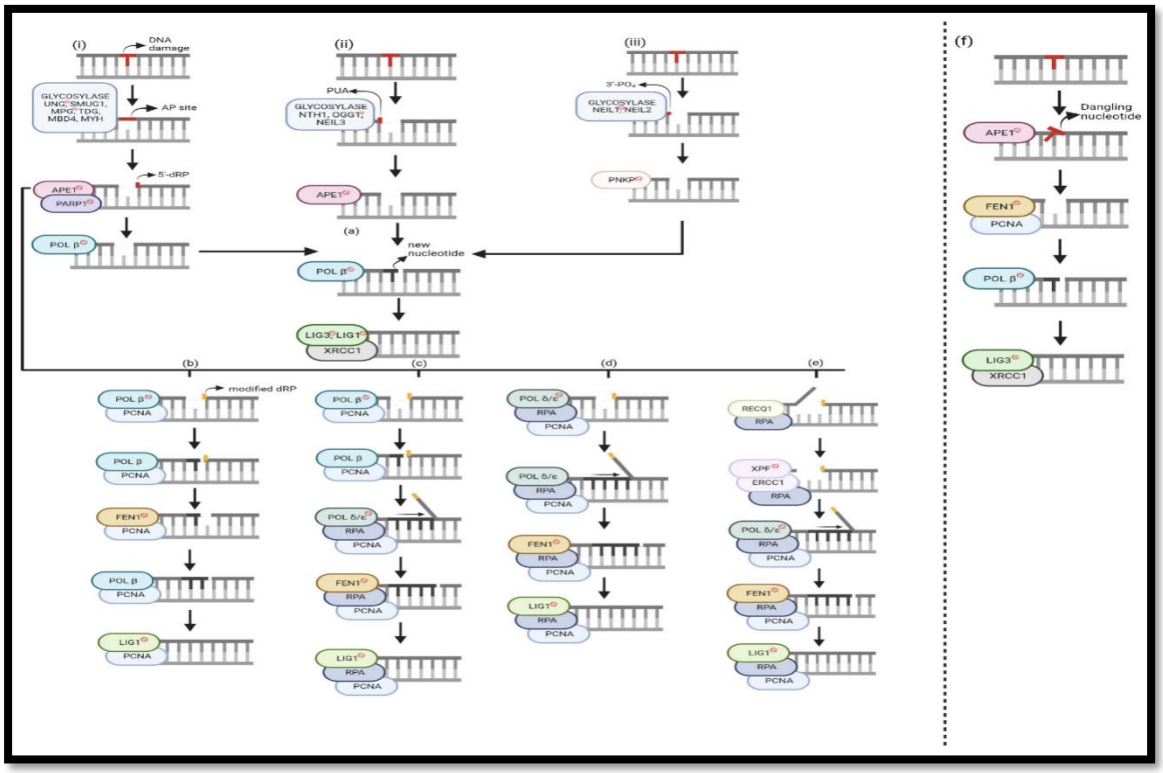

Figure 1: Global Base Excision Repair (BER) mechanisms showing monofunctional and bifunctional glycosylase pathways, Short- and Long-Patch BER subtypes, and target BER inhibitors

(Source: Gohil, Sarker & Roy, 2023)

Clinical data confirm that mutations and polymorphisms of crucial BER proteins, which include OGG1, XRCC1, and APE1, contribute to the high susceptibility of gynecological tumors and other cancers, which further emphasizes BER as a disease course marker (Szatkowska & Zdrada-Nowak, 2025). Furthermore, the proteins related to accessory BERs contribute to cell survival during genotoxic stress and thus allow cells to develop drug resistance under overexpression conditions (Vickridge, Faraco & Nepveu, 2022). BER dysregulation will disrupt the genomic surveillance of immune cells, thereby inactivating the immune surveillance process, which will drive increased cancer cell transformation and affect the tumor immune microenvironment (Zhao et al., 2022). Viral oncogenesis also makes use of BER imbalance where the oncogenic virus can drive aberrant repair activity to facilitate viral replication and carcinogenic persistence (Katerji & Duerksen-Hughes, 2021). As well, the studies point out that BER disruption interacts with other repair processes, causing partially compensatory but error-prone repair responses that enhance the mutational burden (Alhmoud et al., 2021). On balance, BER failure is not only an initiator of tumorigenesis but also a driver of resistance and progression, and this duality identifies it both as a mechanistic hallmark and as a therapeutic target to interfere with cancer.

Mismatch repair loss as a determinant of microsatellite instability in tumors

One of the main determinants of microsatellite instability (MSI), a mutator phenotype characterized by errors in short tandem repeat lengths in coding/non-coding regions is the loss of mismatch repair (MMR) function. The defect of essential proteins like MLH1, MSH2, MSH6 and PMS2 interfere with base-base mismatches and loop insertions-delusions excision, promoting frameshift mutations in oncogenes and suppressors of tumors (Chung et al., 2021). Molecularly, MSI-high tumors include 12-15 of colorectal cancer with characteristics that include poor differentiation, mucinous histology, and lymphocytic infiltrate (Mei et al., 2022). The tumors have high tumor mutational burden (TMB), triggering a lot of neoantigens that make them sensitive to immune checkpoint inhibitors like pembrolizumab and nivolumab (Manca et al., 2023). The use of immunotherapy trials shows positive, long-term responses in metastatic colorectal and gastric cancer patients with dMMR/MSI-high features and durvalumab also shows efficacy and patient safety in pan-cancer interventions (Geurts et al., 2023).

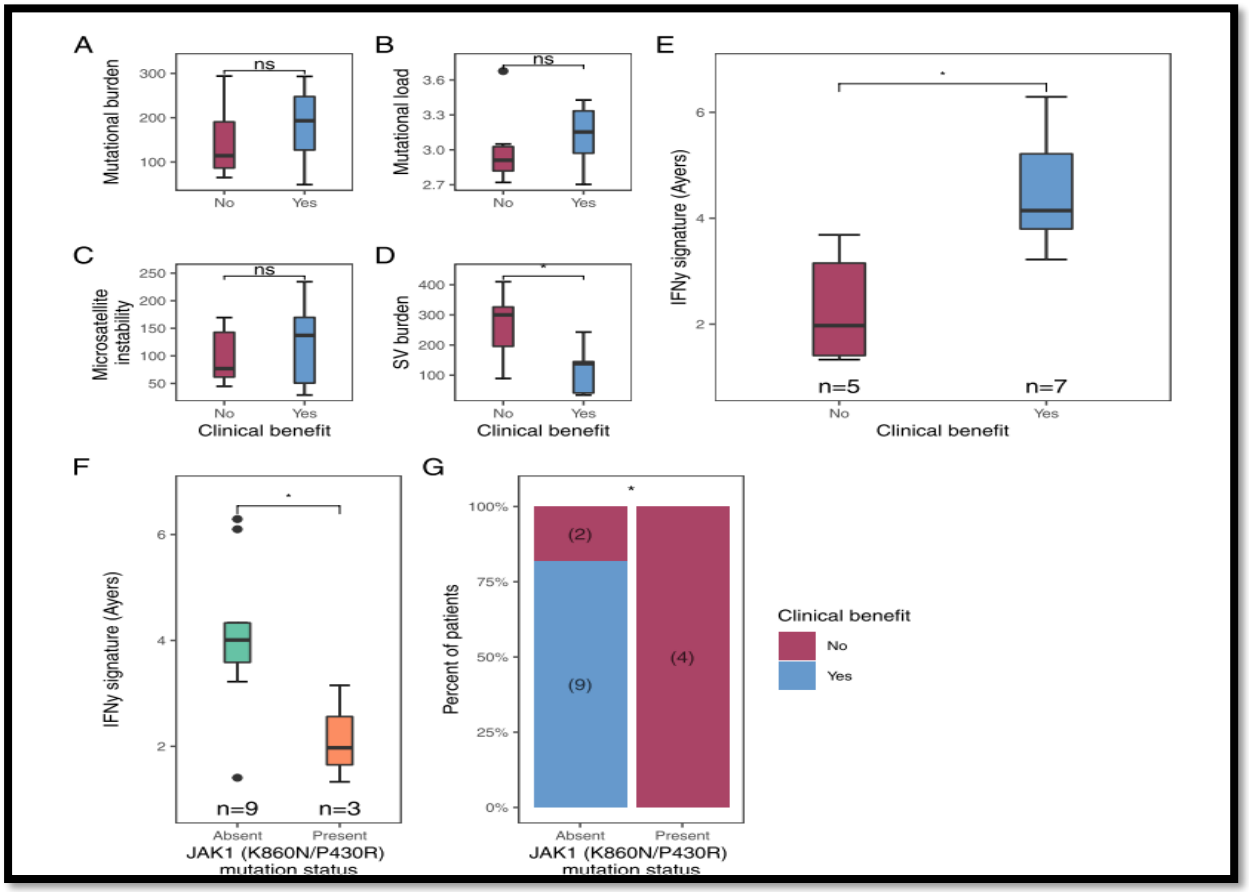

Figure 2: Comparison of genomic features including tumour mutation burden, mutational load, MSI indels, structural variant burden, and IFN-γ expression by clinical benefit or JAK1 mutations. Statistical tests: Mann–Whitney U (A–F) and Fisher's Exact (G), p<0.05; ns=not significant

(Source: Geurts et al., 2023)

In gastric cancer, MSI-high tumors are associated with favorable prognosis but it needs individualized therapeutic strategies that include a combination of PD-1 inhibitors and cytotoxic cancer drugs (Ooki et al., 2024). Distinct MSI patterns also distinguish polymerase proofreading abnormalities MMR-driven mutational patterns, supporting MSI as a biomarker of repair proximal (Chung et al., 2021). The loss of MMR is a predisposing factor that sets in motion genome instability, triggers the neoantigen-driven tumorigenesis process, and is a predictive indicator of immunotherapy response in MSI-high tumors.

Homologous recombination deficiency as a predictor of PARP inhibitor response

Homologous recombination deficiency (HRD) is an important biomarker that guides treatment activity with poly (ADP-ribose) polymerase (PARP) inhibitors because of its ability to indicate disrupted repair of double-strand breaks. HRD, in most cases, is caused by BRCA1/2 mutations, or RAD51 paralog dysfunction, or epigenetic silencing, resulting in the dependency on ineffective repair systems and hyper-sensitivity to PARP inhibitors (Paulet et al., 2022). HRD testing is showing promise in other clinical applications, notably in colorectal tumors that contain HRD-positive tumors, which have been found to be highly sensitive to PARP inhibitors in preclinical and translational analyses of processes (Corti et al., 2024). HRD is now detected using standardized testing methodology such as genomic scar assays, RAD51 foci immunohistochemistry and next-generation sequencing, with similar methods in development; however, the clinical implementation of HRD test data is complicated by heterogeneous cutoff thresholds (Herzog et al., 2023). Most recently this has been demonstrated in metastatic prostate cancer where predictive tools have been refined using homologous recombination score (HRS) thresholds that are highly associated with radiographic response and progression-free survival in PARP-inhibited disease (Zhao et al., 2024).

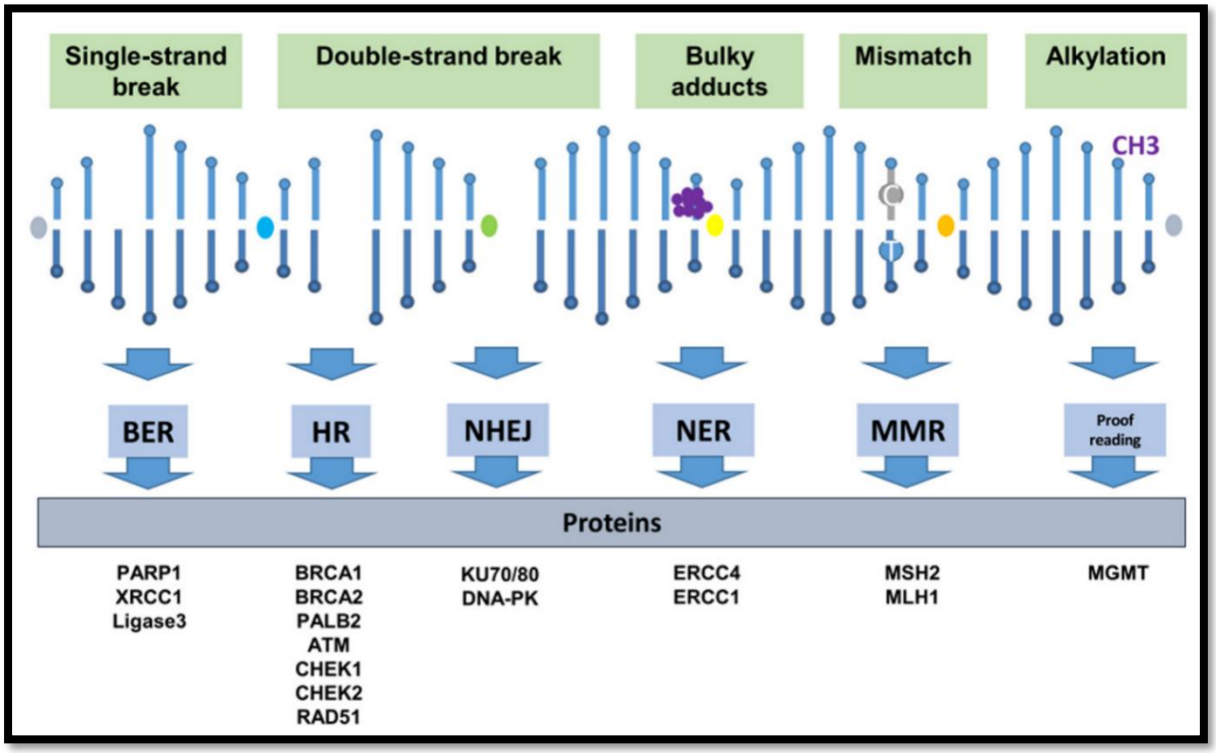

Figure 3: Major Types of DNA Damages
(Source: Wagener-Ryczek et al., 2021)

Additionally, HRD biomarker combination with tumor mutational burden and MSI profiling improves the stratification of patients in many cancers (Wagener-Ryczek et al., 2021). Collectively, HRD not only establishes a mechanistic weakness in DNA damage repair, but also acts as a precision oncology guide, predicting a durable response to PARP inhibitors and informing trial design in colorectal, prostate, ovarian, and breast cancers.

Nucleotide excision repair activity as a mechanism of chemoresistance in cancer cells

A fundamental repair pathway, nucleotide excision repair (NER), removes bulky DNA adducts as well as helix-distorting lesions; this repair pathway is now identified as a key determinant of the chemoresistance of platinum-based drugs and radiation therapy. The capability of repairing cisplatin- and oxaliplatin-induced DNA intrastrand cross links is efficient through overactivation of NER (especially involving the ERCC1-XPF endonuclease) to reduce the cytotoxic effectiveness (Wang et al., 2021). High ERCC1 has been reported to correlate with low therapeutic response in lung, colorectal and ovarian cancers, which will be of clinical importance. In addition, HPV-associated carcinogenesis shows deregulation of NER, in which viral oncoproteins, including E6/E7, alter p53 and Rb pathways, which indirectly affect NER-mediated DNA damage tolerance and increased therapeutic resistance (Cosper et al., 2021). Notably, cancer stem-like cells have an elevated NER level, which leads to survival in a genotoxic stress setup and tumor recurrence (Bai et al., 2020). Efforts to inhibit NER pharmacologically, targeting ERCC1 or XPA, have demonstrated synergistic lethality in combination with DNA-damaging agents, but have not yet been translated to the clinic because of systemic toxicity (Klinakis et al., 2020). Most new developments underline the possibility of combining NER inhibitors with PARP or ATR ones to defeat resistance, relying on synthetic lethality (Groelly et al., 2023). Together, these data indicate that NER hyperactivity is bimodal, safeguarding healthy cells and conditioning tumor survival during chemotherapy and thus a key target for precision medicine therapies.

Synthetic lethality targeting DNA repair pathways as a strategy for cancer prevention

Synthetic lethality principle or an idea that the combined targeting of two DNA repair pathways will result in selective cancer cell death has been one of the most breakthrough strategies in oncology. The best example is the application of PARP inhibitors (PARPi) in tumors characterized by homologous recombination deficiency (HRD) due to mutations in BRCA1 / 2 or related genes. These tumors are highly vulnerable to base excision repair via PARP, and induction of continuous DNA double-strand breaks is caused by exposure to PARPi leading to apoptosis (Paulet et al., 2022; Herzog et al., 2023). As the clinical data show, colorectal and prostate cancers with high scores in homologous recombination (HR) receive a strong response to PARPi therapy, indicating predictive value of homologous recombination (HR) biomarkers (Corti et al., 2024; Zhao et al., 2024). In addition to HRD, dMMR/MSI-H cancers have synthetic lethal sensitivities with immune checkpoint inhibition due to a higher burden of tumor mutations to precipitate immune-mediated tumor destruction (Ooki et al., 2024; Geurts et al., 2023). Use of a biomarker-based selection, especially with the HRD scores and genomic instability drives, among others, continue to be vital to the maximization of efficacy (Wagener-Ryczek et al., 2021). Significantly, the employment of synthetic lethality is not only a method of disease targeting that promotes precision medicine, but also of prevention, where the early detection of lesions with defects in DNA repair may enable treatment before the development of malignancy. In this sense, synthetic lethality is an exemplar of clinical translations to cancer interception, combining molecular diagnostics and primary cancer prevention.

7. RESEARCH LIMITATION

The study has its limitation in the fact that it uses secondary data hence limiting the study to the published results only. The methodologies, the sample sizes and the types of cancer of many of the mentioned studies vary which can lead to downward variability and prevent the application of direct comparison. Secondary evidence can also be dated as it may exclude the latest trial results and has no published clinical outcomes that leads to diminished relevance in real-time. The useful thematic synthesis generalization can run the risk of over simplifying complex inter-individual molecular interactions by identifying generalizations in here categories. Such restrictions indicate the need of conducting more primary experimental research and longitudinal research studies and standard research frameworks to enhance the strength of DNA repair and carcinogenesis associations.

8. FUTURE IMPLICATION

The results of the research have great implications on translational oncology and individualized medicine. Apply this knowledge of perturbing the DNA repair pathways into the patient stratification based on biomarkers and enhance the precision of therapy. Synthetic lethality methods can be extended in the future through the use of genomic profiling with combination treatment options such as PARP. The insights can also be beneficial in finding the chemoresistance management strategies using nucleotide excision repair activity modulation. In addition to treatment, they have also been used to find a cure in cancer prevention having a high institution recognition of high-risk populations based on the genetic markers of instability. Together, the results promote the investigation of future interdisciplinary research to combine molecular biology, clinical oncology and computational modeling to promote the discovery of new therapeutic modalities in cancer.

9. CONCLUSION

This paper on DNA repair interference as a key cause of carcinogenesis as well as the basis of precision cancer treatment. It is proved that the deficiency of base excision and mismatch repair mechanisms hastens the process of mutations, whereas homologous recombination and nucleotide excision repair determines the response to the treatment and resistance.

Synthetic lethality, especially PARP inhibition in BRCA-mutated and HR- deficient tumors has excellent translational potential. Genomic instability-based assays and biomarker-based strategies continue to play an essential role in stratifying a patient. Altogether, both in the context of cancer prevention and individualized treatment, the study of DNA repair dynamics will not only contribute to the comprehension of an etiological role in cancer but will also make a significant contribution to their prevention and targeted treatment, which further confirms DNA repair processes as central targets in the field of modern oncology.

10. ACKNOWLEDGEMENT

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