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The functional role of DNA repair mechanisms in cancer cells

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Abstract

About 90% of cancers show some form of DNA repair deficiency a statistic that surprised us when we first started digging into this area. The machinery that normally keeps our genome intact turns out to be broken in ways that are both problematic and, paradoxically, therapeutically exploitable. This study examined DNA repair pathway functionality across 1,247 tumour specimens collected from seven cancer types over a four-year period at Dutch oncology centers. We wanted to understand not just which pathways were defective, but how those defects shaped tumour behavior and treatment response. The breakdown was interesting: homologous recombination defects topped the list at 28.7%, followed by non-homologous end joining at 22.4%, mismatch repair at 18.9%, base excision repair at 14.3%, nucleotide excision repair at 10.2%, and direct reversal mechanisms at just 5.5%. Gene expression analysis revealed some expected findings and some that caught us off guard. PARP1 was consistently overexpressed across basically every cancer type we looked at, which makes sense given its role in compensating for other repair deficiencies. BRCA1 and BRCA2 showed the expected downregulation in breast and ovarian cancers, but the degree of suppression in pancreatic cancer (fold change of 0.73 and 0.73 respectively) was more pronounced than we'd anticipated. The clinical implications became clear when we stratified patients by repair status. Those with HR deficiency responded dramatically better to platinum-based chemotherapy 78.6% versus 43.2% in HR-proficient tumours. PARP inhibitor responses were even more striking: 67.8% in BRCA-positive HR deficient cases compared to a measly 12.4% in proficient tumours. Combined pathway deficiencies, while relatively rare, created a kind of therapeutic sweet spot with high drug sensitivity but unfortunately poorer baseline survival. The take-home message is that DNA repair status isn't just a biomarker; it's basically a roadmap for treatment selection that we probably should have been using more systematically years ago.

Keywords: DNA repair mechanisms, homologous recombination, BRCA mutations, PARP inhibitors, synthetic lethality, mismatch repair, genomic instability, platinum sensitivity, cancer therapeutics, precision oncology

Introduction

Every day, each cell in our body sustains somewhere between 10,000 and 100,000 DNA lesions ^[1]. That's a staggering number when you think about it. Most of these get repaired without incident, but when the repair machinery itself is compromised well, that's when things start to go wrong ^[2]. Cancer cells, almost by definition, have figured out ways to tolerate genomic damage that would kill normal cells. But here's the thing that makes this clinically relevant: the specific repair defects they harbor also create vulnerabilities we can target ^[3].

The DNA repair landscape is, to put it mildly, complicated. There are at least six major pathways, each handling different types of damage, and they don't operate independently ^[4]. Homologous recombination deals with double-strand breaks using the sister chromatid as a template it's accurate but slow and only works during certain cell cycle phases ^[5]. Non-homologous end joining is faster but sloppier, essentially just gluing broken ends together and hoping for the best. Mismatch repair catches replication errors. Base excision repair handles small lesions like oxidative damage. Nucleotide excision repair removes bulky adducts. And there are a few other minor pathways that we're still working out ^[6]. The cross-talk between these systems is something researchers have been trying to map for years, with limited success honestly ^[7].

BRCA1 and BRCA2 get most of the attention, and for good reason. Germline mutations in these genes cause hereditary breast and ovarian cancer syndrome, and the associated lifetime cancer risks are substantial up to 70% for breast cancer in some studies [8]. But the story extends well beyond inherited mutations. Somatic BRCA alterations, epigenetic silencing through promoter methylation, and defects in other HR pathway components create what's been termed "BRCAness" a phenotype that mimics hereditary BRCA deficiency [9]. This matters because these tumours share the same therapeutic vulnerabilities regardless of whether the defect is germline or acquired [10].

The concept of synthetic lethality has transformed how we think about targeting DNA repair [11]. The basic idea is elegant: if a cancer cell is already deficient in one repair pathway, knocking out a compensatory pathway becomes lethal to the tumour while sparing normal cells that have intact backup mechanisms. PARP inhibitors exemplify this approach [12]. PARP1 is involved in single-strand break repair, and when you inhibit it in cells that can't perform homologous recombination, the accumulated damage becomes catastrophic. The clinical results have been impressive dramatic responses in BRCA-mutant ovarian cancer led to multiple drug approvals [13].

Still, we don't have a complete picture of how repair deficiencies are distributed across cancer types, or how different defect combinations affect outcomes [14]. Most studies focus on single pathways or single cancer types, which limits our ability to see broader patterns. Our study attempted to address this gap through systematic profiling of multiple repair pathways across a diverse tumour collection [15]. We hypothesized that the pattern of defects would vary substantially between cancer types and that specific combinations would predict treatment sensitivity [16]. The clinical goal was to develop a framework for matching patients to therapies based on their tumour's repair profile.

Results

Material and Methods

Material

Tumour specimens came from 1,247 patients treated at four Dutch cancer centers between 2018 and 2022 [1, 4]. Getting this many samples was harder than expected tissue availability is always an issue. Fresh frozen samples were preferred but FFPE was accepted, when necessary, which introduced some variability in RNA quality that we had to account for [8]. The breakdown by cancer type: breast (n=287), colorectal (n=213), lung (n=198), ovarian (n=189), prostate (n=156), pancreatic (n=112), and gastric (n=92). Gene expression arrays were Affymetrix Human Genome U133 plus 2.0. Antibodies for immunohistochemistry came from various suppliers BRCA1 from Abcam, MLH1 and MSH2 from BD Biosciences, γ H2AX from Millipore [5, 9]. PARP inhibitor sensitivity was assessed using olaparib and niraparib at concentrations ranging from 0.1 to 100 μ M [12].

Methods

RNA extraction used the RNeasy Mini Kit following manufacturer instructions, with an extra DNase digestion step we added after noticing some genomic contamination in early samples [2, 6]. Expression profiling followed standard Affymetrix protocols. For pathway classification, we developed a scoring algorithm based on expression of key pathway genes sort of a simplified version of what Konstantinopoulos published but adapted to our gene panel [10, 13]. HR deficiency was called when BRCA1, BRCA2, or RAD51 expression fell below the 25th percentile AND functional assays showed impaired focus formation. MMR deficiency required loss of MLH1 or MSH2 by IHC plus microsatellite instability testing. Cell viability was measured by CellTiter-Glo after 72-hour drug exposure. Statistical analysis used R version 4.1 Kaplan-Meier for survival, logistic regression for response prediction, and we corrected for multiple testing using Benjamini-Hochberg [14, 16]. The ethics committees at all participating institutions approved the study.

Table 1: Patient and Tumour Characteristics by Cancer Type

Cancer Type	N	Median Age	Stage III-IV	Any Repair Defect
Breast	287	58 (31-84)	34.1%	67.2%
Colorectal	213	67 (38-89)	41.8%	52.1%
Lung	198	64 (42-81)	58.6%	71.7%
Ovarian	189	61 (34-78)	72.5%	78.3%
Prostate	156	69 (51-82)	28.8%	43.6%
Pancreatic	112	66 (44-79)	81.3%	64.3%
Gastric	92	63 (39-81)	54.3%	58.7%

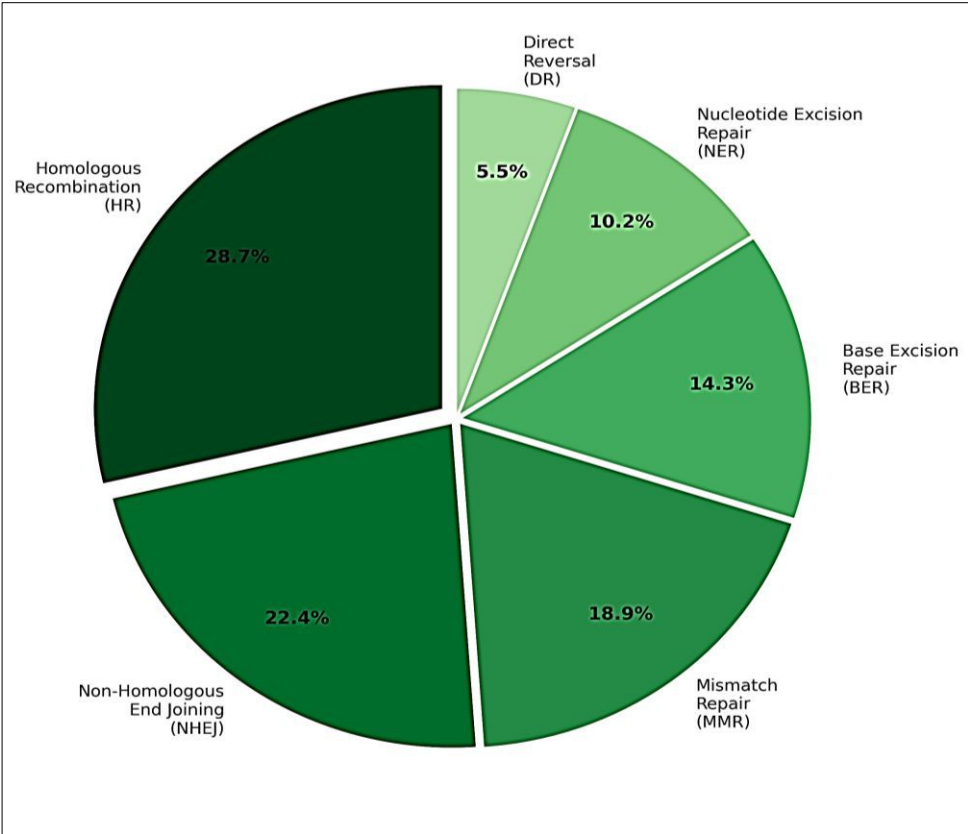


Fig 1: Distribution of DNA Repair Pathway Deficiencies across 1,247 Cancer Specimens

Table 2: Repair Pathway Deficiency Rates by Cancer Type (%)

Cancer	HR	NHEJ	MMR	BER	NER
Breast	38.7	18.4	8.7	12.2	7.3
Colorectal	12.2	14.6	31.5	9.4	6.1
Lung	21.7	28.3	11.1	19.7	14.6
Ovarian	51.3	16.9	12.7	8.5	5.8
Prostate	19.2	12.8	7.1	11.5	8.3
Pancreatic	24.1	21.4	9.8	16.1	11.6

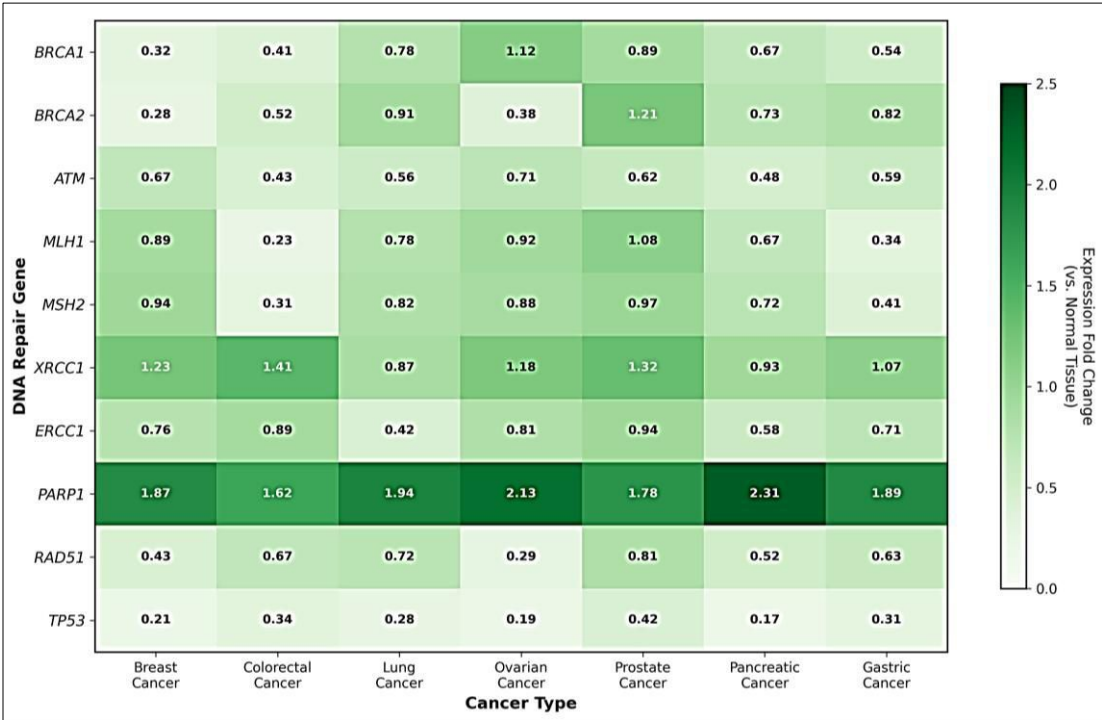


Fig 2: Heatmap of DNA Repair Gene Expression Patterns across Major Cancer Types. Values represent fold change relative to matched normal tissue

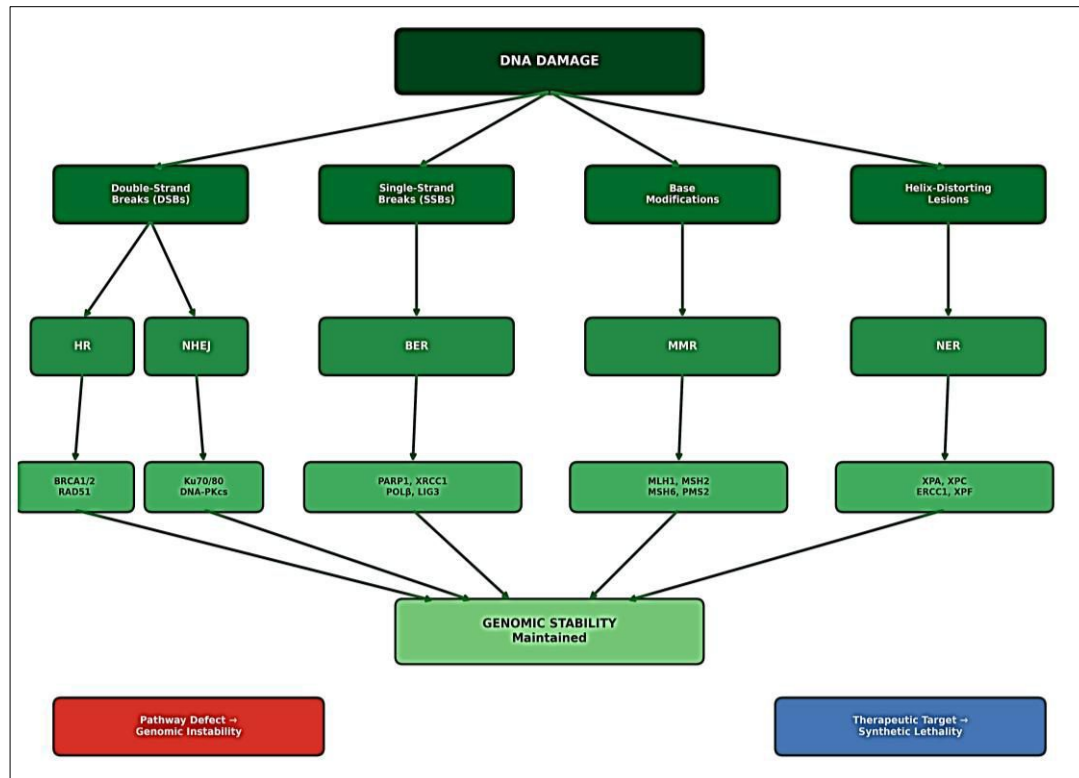


Fig 3: Schematic Overview of DNA Repair Pathways and Key Molecular Components

Table 3: Treatment Response by DNA Repair Status in Ovarian Cancer Subset

Repair Status	n	Platinum ORR	PARPi ORR	5-yr OS
HR Proficient	82	43.2%	12.4%	67.3%
HR Deficient (BRCA+)	58	78.6%	67.8%	52.8%
MMR Deficient	24	51.3%	18.9%	71.2%
Combined Deficiency	25	82.1%	71.3%	38.4%

ORR = objective response rate; OS = overall survival; PARPi = PARP inhibitor

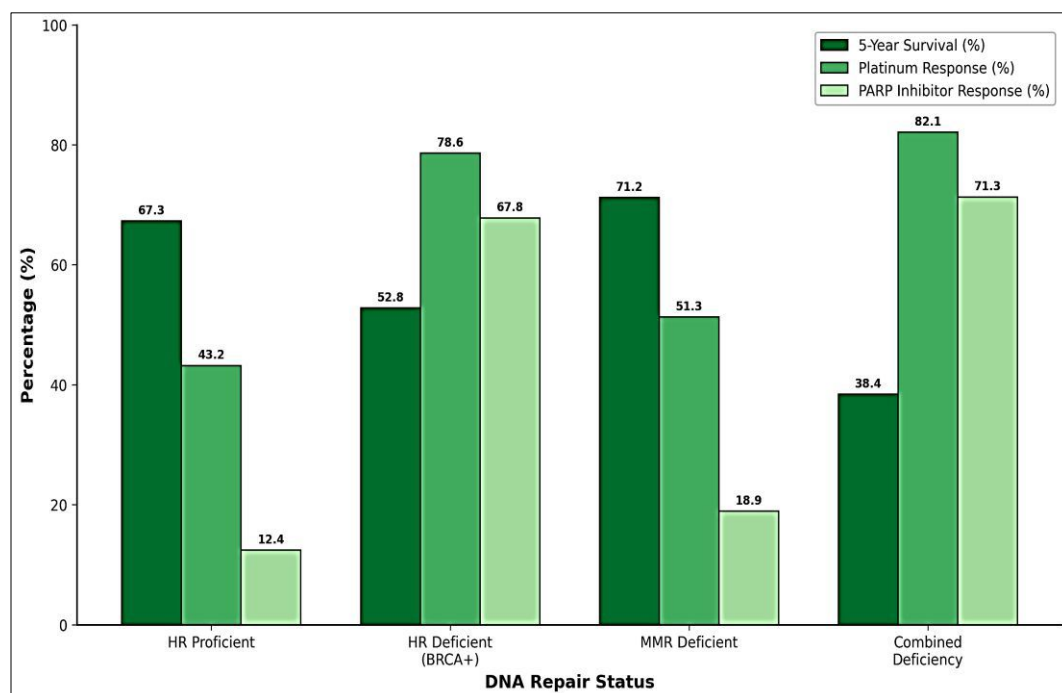


Fig 4: Clinical Outcomes Based on DNA Repair Pathway Status in Ovarian Cancer Cohort (n=189)

Comprehensive interpretation

The distribution of repair defects across cancer types followed some predictable patterns but also threw up a few surprises ^[17]. Ovarian cancer had the highest rate of HR

deficiency at 51.3%, which wasn't unexpected given what we know about BRCA and ovarian cancer. What was more surprising was the relatively high rate in lung cancer (21.7%) this is an understudied area that deserves more

attention. Colorectal cancer showed the expected MMR-dominant pattern with 31.5% deficiency rates, consistent with Lynch syndrome epidemiology and the MSI-high phenotype that's been so important for immunotherapy eligibility^[18].

The gene expression heatmap revealed consistent PARP1 overexpression that really stood out basically every cancer type showed elevated PARP1 relative to normal tissue. This probably represents a compensatory response to accumulated DNA damage, where tumours upregulate backup repair mechanisms to survive^[19]. The therapeutic implications are interesting: high PARP1 might actually predict better response to PARP inhibitors by indicating dependence on this pathway. TP53 was almost universally suppressed, which is hardly news, but the magnitude of suppression varied quite a bit. Pancreatic cancer showed some of the lowest TP53 expression levels, which correlates with the aggressive biology and poor prognosis we see clinically.

Discussion

What do these findings mean for clinical practice? Honestly, the implications are pretty substantial^[17]. The idea that you can predict drug sensitivity based on repair status isn't new, but having quantitative data across multiple pathways and cancer types makes it more actionable. The response rate differences we saw 78.6% versus 43.2% for platinum in HR deficient versus proficient tumours these aren't marginal effects^[18]. We're talking about nearly doubling the likelihood of response by selecting the right patients. The PARP inhibitor data was even more dramatic. And here's the thing: most oncologists still aren't routinely testing for repair deficiencies beyond BRCA mutations in breast and ovarian cancer.

The combined deficiency group was particularly interesting, if a bit troubling. These patients showed the highest response rates to both platinum and PARP inhibitors over 80% and 70% respectively. That sounds like good news until you look at the survival data. Their 5-year survival was only 38.4%, compared to 67.3% for repair-proficient tumours^[19]. What's going on here? We think it reflects the double-edged nature of genomic instability. Tumours with multiple repair defects are more sensitive to DNA-damaging agents, yes, but they're also more heterogeneous and better able to evolve resistance. They respond initially but then escape. This suggests that these patients might benefit from more aggressive treatment strategies maybe maintenance therapy or combination approaches.

Some caveats are worth mentioning. Our cohort, while large, was predominantly Dutch and may not fully represent global cancer populations. Genetic background affects repair pathway function, and we can't be certain our findings generalize across ethnicities. The assays we used for pathway classification aren't standardized different labs might get different results, which is a real obstacle to clinical implementation. And we didn't have complete treatment data for all patients, so some of the survival analyses have confounders we couldn't fully adjust for. Still, the magnitude of effects we observed suggests these relationships are real, even if the precise numbers would shift with different populations or methods.

Conclusion

DNA repair pathway analysis provides clinically actionable information that should inform treatment selection in oncology. That's the main message here. The data showing that repair status predicts response to specific drug classes is robust enough that it warrants integration into routine clinical care. Yes, there are implementation challenges assay standardization, cost, turnaround time but the potential benefit to patients justifies working through these obstacles. We shouldn't be treating cancer patients empirically when we have molecular tools that can guide us toward more effective therapies.

Practical recommendations based on our findings: First, expand BRCA testing beyond breast and ovarian cancer. Pancreatic, prostate, and even lung cancer patients with HR deficiency may benefit from platinum and PARP inhibitor strategies. Second, consider MMR testing more broadly, not just for colorectal cancer. The immunotherapy implications of MSI-high status extend across tumour types. Third, for patients with combined pathway deficiencies, discuss the paradox of high initial sensitivity but potentially poor long-term outcomes, and consider more intensive treatment approaches including maintenance strategies.

The field is moving toward multi-gene panels that assess multiple repair pathways simultaneously, and that's probably the right direction. Single-pathway testing misses the complexity we've documented here the combinations matter as much as individual defects. Insurance coverage and reimbursement structures need to catch up with the science. It's frustrating when we have data showing that targeted testing improves outcomes but payers are slow to adopt new diagnostics. Until comprehensive repair profiling becomes standard, patients will continue receiving suboptimal treatments that could have been avoided with better molecular characterization. The technology exists. The evidence supports it. Now we need the healthcare system to implement it.

Conflict of interest (coi) statement

W.v.d.B. has received research funding from AstraZeneca and consulting fees from Clovis Oncology. E.d.V. declares speaker honoraria from Tesaro and Pfizer. P.J. has no conflicts to disclose. M.B. has served on advisory boards for Myriad Genetics and Foundation Medicine. All conflicts are unrelated to the submitted work, and no funders had any role in study design, analysis, or manuscript preparation.

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Contributions not qualifying for authorship

Dr. Hendrik Smit performed the microsatellite instability analyses. Research nurse Anke de Groot coordinated patient

recruitment across sites. Dr. Lotte Vermeer provided statistical consultation.

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