

RAD51 as a Therapeutic Target and Predictive Biomarker in Breast Cancer Radiotherapy: A Systematic Review and Translational Synthesis

RAD51 in Breast Cancer Radiotherapy

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Abstract

Background: Treatment-resistant breast cancer (BC) is a significant clinical issue. The prognostic and predictive value of RAD51 expression in BC and radiotherapy (RT) remains inconsistent. This review examines the clinical and translational evidence regarding RAD51's role in BC risk and RT resistance, as well as its potential as a predictive biomarker and therapeutic target.

Main body: This systematic review synthesised clinical and translational evidence on RAD51's role in BC risk and RT resistance. A systematic literature search was conducted in PubMed, Scopus, Google Scholar, and IASJ (2014–2024) following PRISMA 2020 guidelines. Given the significant variability in study designs, outcome measures, and experimental models, a meta-analysis was not achievable. This review encompasses 25 studies. Seventeen studies have shown that RAD51 may be a therapeutic target for treatment-resistant BC cells in vitro and in vivo. Six studies revealed that RAD51 polymorphisms, rs1801320 (G>C) and rs1801321 (G>T), increase BC risk and RT resistance. Four studies reported that RAD51 may be a predictive and/or prognostic biomarker for BC development and therapeutic responses.

Conclusion: RAD51 overexpression correlates with BC development and radio-resistance. Downregulation radiosensitises tumour cells. RAD51 may serve as a predictive biomarker and represent a promising therapeutic target. RAD51 polymorphisms may influence RT response and BC risk. However, verification is needed.

Keywords: RAD51 Protein, Breast Neoplasms, Radiation Tolerance, Biomarkers, Tumour, Homologous Recombination

Background

Breast cancer (BC) is the most prevalent malignancy among women and a major cause of mortality (1). Each year, more than 1.5 million women worldwide are diagnosed with BC. It is a form of metastatic cancer capable of disseminating to several organs, including the bones, lungs, liver, and brain, thereby leaving it incurable. Early diagnosis of cancer results in an improved prognosis and elevated survival rates (2). Environmental, genetic (BRCA1/BRCA2), and lifestyle factors may influence the onset of BC.

Approximately 20% to 30% of BC cases may be affected by modifiable factors (3).

Treatment for BC often includes radiotherapy (RT), chemotherapy (CT), and hormonal therapy based on tumour stage, grade, and molecular subtype (4). RT kills malignant cells locally using high-energy photons or particles. Adjuvant radiation is used after mastectomy or lumpectomy to reduce cancer recurrence (5, 6). Cancer patients may react differently to RT. This diversity reflects the multiple genes and their interactions that influence radiation damage response. (7). The presence of radio-resistance remains a

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significant barrier to improving treatment outcomes, leading to failure of RT, metastasis, recurrent tumours, and a negative prognosis. This challenge persists despite advancements in radiotherapy methods and the implementation of new treatment strategies (8). Radio-resistance may manifest via several mechanisms, mostly due to the tumour's heterogeneity and the surrounding microenvironment, as well as multiple gene modifications. One such alteration is the presence of the DNA-dependent recombinase RAD51 (9). DNA repair protein RAD51, also known as radiation-sensitive protein 51, participates in the cellular response to damaged DNA and is crucial for the repair of double-strand breaks (DSBs) by homologous recombination repair (HRR) (10). RAD51's interactions with proteins like p53, BRCA1, and BRCA2 suggest its possible role as a tumour suppressor. In contrast, certain tumours and cell lines exhibit increased RAD51 levels (11). RAD51 in BC has been focused on its expression level, which is linked favourably to lymph node metastases (12) as well as tumour size and grade. Since RAD51 is overexpressed in tumour cells, treatment resistance to RT and CT is facilitated by higher RAD51 levels. As a result, RAD51 is a very intriguing target for the treatment of resistant malignancies (13, 14). The common single-nucleotide polymorphisms (SNPs) in the RAD51 gene, such as 135 G>C (rs1801320), have been shown to impact the ability of DNA repair and may have a role in the development of BC (15, 16). Therefore, this systematic review aims to synthesise existing translational evidence on RAD51's role as a predictive biomarker and therapeutic target in breast cancer, particularly in the context of radiotherapy resistance.

Main text

Literature Search and Study Selection

A comprehensive literature search was performed across PubMed, Scopus, Google Scholar, and IASJ databases to locate pertinent studies published from 2014 to 2024, following the PICO criteria (17). Combining keywords and Boolean operators created the search approach. For instance, PubMed searched for ("RAD51" AND "breast cancer" AND ("radiotherapy" OR "radioresistance" OR "radiosensitivity")). Searches ended on October 22, 2024. Language

or research design filters were not employed. Repetitive data were eliminated utilising EndNote software, and further studies were discovered manually by reviewing reference lists. The review followed PRISMA 2020 guidelines (18) and was registered in PROSPERO (CRD42024569928). Although clinical investigations were prioritised in pre-registration, mechanistic and translational studies were needed to clarify biological observations and improve translational relevance during screening. This deviation was deemed essential because of the restricted access to solely clinical evidence concerning RAD51-mediated radioresistance. The selection of studies was conducted via a two-phase screening process. In the first phase, two reviewers executed a separate screening of the titles and abstracts. In the second phase, a thorough evaluation of full-text articles was conducted to determine their eligibility. Disagreements were addressed through dialogue or by seeking the input of a third reviewer. Studies that fulfilled the designated criteria included clinical, translational, and experimental research evaluating RAD51 concerning BC susceptibility, biomarkers of RT responses or toxicities, or its potential as a therapeutic target (19). Articles, reviews, case reports, and research not in English or not focused on RAD51 or BC were omitted from consideration.

Characteristics of Included Studies

Through database searches, 216 records were found at first. After screening, 25 papers met the requirements for inclusion, as shown in Figure 1. The research used in this study was done in different countries and was published between 2014 and 2024. The study designs encompassed experimental (n = 15), cohort (n = 6), and a hybrid of clinical-experimental methodologies (n = 4). The total number of BC patients across all clinical studies exceeded 4000. Most of them received radiation therapy. There were three main groups of studies: therapeutic modulation of RAD51 (n = 17), RAD51 polymorphisms (n = 6), and predictive/prognostic biomarker assessment (n = 4). Tables 2–4 show all of the important details of the studies that are included.

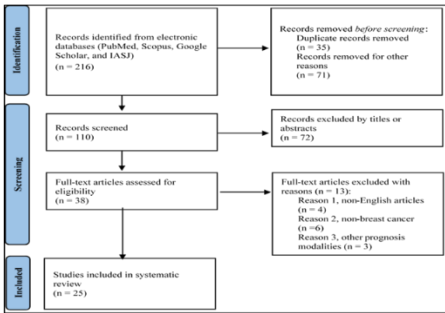


Figure 1. PRISMA flow diagram of study selection

Table 1 demonstrates an in-depth evaluation of quality across recognised domains. The methodological quality of the clinical studies was moderate. Many studies had good outcome assessment and eligibility criteria, but a retrospective design, limited sample size, and insufficient adjustment for confounding variables

were major concerns. Domain-based evaluation categorised 22% of studies as low bias, 67% as moderate bias, and 11% as high bias. All studies had low outcome assessment bias (100%), low selective reporting bias (67%), and moderate 33%.

Table 1: Simplified risk-of-bias assessment for included cohort studies

Author, Year	Selection bias	Outcome assessment bias	Selective reporting bias	Overall risk
Goričar et al., 2022 (20)	Low	Low	Low	Low
Söderlund et al., 2015 (21)	Low	Low	Low	Low
Ragudo et al., 2020 (22)	Moderate	Low	Moderate	Moderate
Qureshi et al., 2015 (23)	Moderate	Low	Low	Moderate
Smolarz et al., 2019 (24)	Moderate	Low	Moderate	Moderate
Al Zoubi et al., 2017 (25)	High	Low	Moderate	Moderate–High
Gasparini et al., 2014 (26)	Moderate	Low	Low	Moderate
Wiegman et al., 2014 (27)	Moderate	Low	Low	Moderate
Turdo et al., 2022 (28)	Moderate	Low	Low	Moderate

Risk of bias was assessed using a simplified domain-based framework evaluating selection bias, outcome assessment bias, and selective reporting, owing to the variability in study designs.

Therapeutic Modulation of RAD51 to Overcome Radioresistance

By altering DNA repair pathways, RAD51 targeting can boost BC's sensitivity to radiation, according to 17 studies. Table 2 illustrates the various ways in which the interventions affected RAD51 expression, stability, and function. Numerous studies have shown that suppressing RAD51 increases radiosensitivity and decreases HRR. Metformin, valproate, HPTA, melatonin, and Huaier extract reduce RAD51 levels, making BC cells more susceptible to RT and CT (29, 30, 31, 32, 33). The suppression of RAD51-associated protein 1 (RAD51AP1) reduced RAD51 activity and tumour cell survival (34). A different mechanistic group studied the ubiquitin–proteasome pathway, which stabilises RAD51. Perifosine treatment, ubiquitin-specific protease 7

(USP7), and ubiquitin C-terminal hydrolase L3 (UCHL3) suppression increased RAD51 ubiquitination and degradation, decreasing HRR and increasing radiosensitivity (35, 36, 37). RAD51-foci formation was impeded by Cyclin D1 inhibition, compromising DNA repair (38). In contrast, various studies have demonstrated that the stabilisation and overexpression of RAD51 enhance radioresistance. Studies indicate that pathways involving β 1-integrin, DNA damage binding protein 2 (DDB2), and Myc/Sam68 can either enhance or inhibit RAD51 degradation, resulting in improved DNA repair and reduced sensitivity to radiation (28, 39, 40). The association of RAD51 overexpression with resistance to PARP inhibitors underscores its significance in treatment resistance (41). The data indicate that RAD51 appears to play a crucial role in regulating responses to radiation. While therapeutic approaches that sustain RAD51 could lead to treatment resistance, those that decrease or degrade it increase radiosensitivity.

Table 2: Characteristics of selected studies regarding RAD51 and therapeutic targets in breast cancer.

Author, Year	Country	Study design	Type of BC studied	Method used	Treatment/Exposure	Statistical method	Therapeutic target	RAD51 expression	Main conclusion
Ahmed et al., 2018 (39)	United States	Experimental	Human BC cell lines	Western blot	IR	Student's t-test	β 1-integrin	High	Elevated β 1-integrin levels may increase tumour cell radioresistance by decreasing RAD51 breakdown via the RING1-mediated proteasomal pathway.

Choi <i>et al.</i> , 2020 (42)	Korea	Experimental	Human TNBC cell lines	Western blot	PBT	Student's t-test, ANOVA	CHK1	Low	Low CHK1 levels improved PBT efficacy in the treatment of TNBC by direct inhibition of RAD51
Vogt <i>et al.</i> , 2024 (35)	Germany	Experimental	Human TNBC cell lines	IF	RT	Student's t-test.	USP7	Low	Suppressing USP7 activity, in vivo and in vitro, resulted in reduced levels of RAD51. Thus, targeting USP7 may be a viable approach to counteract the resistance of BC to RT.
Choi <i>et al.</i> , 2019 (38)	Korea	Experimental	Human BC cell lines	IF	PBT	Student t-test, ANOVA	Cyclin D1	Low	Cyclin D1 disruption prevented protons from establishing RAD51 foci in BC cells, improving PBT.
Jia <i>et al.</i> , 2017 (43)	China	Experimental	Human BC cell lines	Western blot	RT, CT	Student's t-test	R-O2-SWCNTs	Low	By lowering RAD51 expression, R-O2-FA-CHI SWCNTs dramatically increased BC cell sensitivity to chemotherapy and radiation.
Liu <i>et al.</i> , 2021 (29)	China	Experimental	BC cell lines, animal models	Western blot	IR	Student's t-test	VPA	Low	VPA suppressed RAD51 to radiosensitize BC cells. RAD51 excess was connected to BC carcinogenesis and poor prognosis.
Luo <i>et al.</i> , 2016 (36)	China	Experimental	Human BC cell lines	Western blot	IR, CT	Student's t-test, ANOVA	UCLH3	High	By upregulating RAD51, UCLH3 overexpression in BC cell lines confers resistance to RT and CT. UCLH3 is a novel therapeutic target for therapy-resistant BC.
Song <i>et al.</i> , 2019 (37)	United States	Experimental	TNBC cell lines, animal models	IF	IR	Student's t-test, Chi-square	Perifosine	Low	Perifosine suppresses UCLH3 activity. By ubiquitinating HR-inhibiting RAD51, it makes TNBC cells more sensitive to CT and radiation.
Ding <i>et al.</i> , 2016 (30)	China	Experimental	Human BC cell lines	Western blot	IR	Student's t-test, linear regression	<i>Trametes robiniophila</i> Murr (Huaier)	Low	Huaier can enhance the sensitivity of BC cells to radiation and disrupt the HR pathway of DNA repair by reducing the expression of RAD51.
Alonso-González <i>et al.</i> , 2015 (31)	Spain	Experimental	Human BC cell lines	Real-time PCR	IR	Student's t-test, ANOVA	Melatonin	Low	Human BC cells treated with melatonin and radiation are more sensitive to RT because it down-regulates DSB repair proteins such as RAD51.
Wiegman <i>et al.</i> , 2014 (27)	Australia	Experimental	Human BC cell lines, animal models	IHC, Western blot	NR	Chi-square, Student's t-test	RAD51	High	RAD51 is overexpressed during BC progression and metastasis. Suppressing RAD51 prevented cancer spread in vitro and tumour growth in vivo. RAD51 may be a metastatic TNBC biomarker and therapy target.
Liu <i>et al.</i> , 2017 (41)	China	Experimental	Human TNBC cell lines, animal models	Western blot	RT	ANOVA, Tukey or Sidak test	PARPi	High	BRCA1-mutant and BRCA1-wild-type TNBCs resist PARP inhibition. Targeting RAD51 may improve PARPi treatment, as increasing RAD51 expression can overcome resistance.
Lee <i>et al.</i> , 2019 (32)	Korea	Experimental	Human TNBC cell lines, animal models	IF, Western blot	IR, CT	ANOVA, post hoc test	Metformin	Low	RAD51 downregulation by metformin increases the anticancer effects of chemo- and radiotherapy in vitro and in vivo, making it a new TNBC treatment target.
Turdo <i>et al.</i> , 2022 (28)	Italy	Experimental	Human BC cell lines,	IF, IHC, Western blot	RT	Student's t-test	Myc, Sam68, and RAD51	High	High Myc levels in BCSCs promote Sam68 and RAD51 expression in vivo and in vitro following RT. BC biomarkers Myc, Sam68, and RAD51

Zhao <i>et al.</i> , 2019 (40)	China	Experimental	animal models Human TNBC cell lines	Western blot, IF	NR	Student's t-test	DDB2	High	are promising targets since treating them together reduces tumour growth. By stabilising RAD51 and inhibiting its ubiquitination, high DDB2 levels in TNBC cells increase resistance to RT and PARPi. DDB2 is a possible TNBC treatment target.
Bridges <i>et al.</i> , 2020 (34)	Georgia	Experimental	Human BC cell lines, animal models	Western blot	IR, CT	Student's t-test, ANOVA	RAD51A P1	Low	RAD51AP1 knockdown increased CT and radiation response by preventing RAD51 and BCSC self-renewal, proving that RAD51AP1 is necessary for BC formation and spread.
Cai <i>et al.</i> , 2023 (33)	China	Experimental	Human BC cell lines, animal models	IF, IHC, Western blot	IR	Student's t-test, post hoc test	HPTA	Low	Administration of HPTA is a potent radiosensitizer that significantly improves the effectiveness of RT in the treatment of BC, in vitro and in vivo, by reducing the activity of RAD51.

BC=breast cancer, TNBC=triple-negative breast cancer, IF=immunofluorescence, IHC=immunohistochemistry, PBT =proton beam therapy, IR=ionizing radiation, RT=radiotherapy, CT=chemotherapy, CHK1= checkpoint kinase 1, USP7=ubiquitin specific protease 7, R-O2-SWCNTs=tombarthite-modified-single-walled carbon nanotubes, VPA=valproate, UCHL3=ubiquitin C-terminal hydrolase L3, PARPi= Poly ADP-ribose polymerase inhibitors inhibitor, DDB2=DNA damage binding protein 2, RAD51AP1=RAD51-associated protein 1, HPTA =2-hexyl-4-pentynoic acid, RING1=E3 ubiquitin-protein ligase, BRCA1= breast cancer gene 1, BCSCs =breast cancer stem cell

RAD51 Polymorphisms and Clinical Outcomes
Six cohort studies looked at the link between *RAD51* polymorphisms and the risk of BC, as well as how different groups of patients responded to RT (Table 3). Studies focused the most on the variants rs1801320 (G>C) and rs1801321 (G>T), which were both linked to a higher risk of BC and radioresistance. In particular, the heterozygous genotype (GC) of rs1801320 has been linked to a higher risk of getting BC and a lower response to RT in several studies (20, 22, 23). Likewise, the rs1801321 was related to BC vulnerability and radiation resistance (20, 25). Other SNPs of *RAD51*, like rs2619679 and rs5030789, have been linked to BC and resistance to treatment. This shows how important *RAD51* genetic variability is in the disease's progression (24). In addition, the rs12593359 (T>G) polymorphism was linked to tumour recurrence and radiotoxicity in patients with HER2-positive BC (21). Most polymorphisms

occur in the regulatory region of *RAD51*, enhancing its promoter activity, leading to *RAD51* overexpression, unregulated HRR, and genomic instability, which are associated with resistance to RT (16). Various studies yielded various results. A study found that the rs1801320 polymorphism was linked to higher radiosensitivity and a lower chance of local recurrence (21). This is different from other studies that found higher resistance. Several factors in the reviewed studies explain the disparities. For instance, sample sizes, ethnicities, treatments (radiation vs. control groups), and study methodologies varied. This variation may affect how *RAD51* polymorphisms repair DNA and how they work in practice. The findings indicate that *RAD51* polymorphisms contribute to individual variations in BC risk and the efficacy of RT responses. Nonetheless, the clinical applicability of these findings is constrained by the variability of the evidence.

Table 3: Characteristics of selected studies related to *RAD51* polymorphisms in breast cancer patients.

Authors, Year	Country	Sample size	Study design	Type of BC studied	Method used	Treatment	Statistical method	<i>RAD51</i> SNP	Main conclusion
Goričar <i>et al.</i> , 2022 (20)	Slovenia	101	Cohort study	HER2-positive BC patients	PCR-SNP	RT	Chi-square, odds ratio	rs1801320 (G>C), rs1801321 (G>T), rs12593359(T>G)	<i>RAD51</i> polymorphisms may cause RT side effects in HER2-positive BC patients. They were linked to new primary tumours.

Söderlund <i>et al.</i> 2015 (21)	Sweden	306	Cohort study	Early BC patients	IHC	RT	Chi-square, Cox's regression	135G>C (rs1801320)	<i>RAD51</i> 135G>C polymorphism in BC patients who were G homozygotes exhibited high sensitivity to RT with a decreased risk of local recurrences. The <i>RAD51</i> C/C genotype was identified as a separate and significant risk factor for the development of BC. Passive smokers with the <i>RAD51</i> G/C genotype had a substantially elevated risk of BC. The <i>RAD51</i> G/C genotype does not seem to elevate the risk of BC. The heterozygous genotype (GC) of the <i>RAD51</i> 135 G/C polymorphism was associated with a greater risk of BC and radiation resistance. This genotype may independently predict BC risk in Pakistan.
Ragudo <i>et al.</i> , 2020 (22)	Philippines	120	Cohort study	BC patients	PCR-RFLP	NR	Odds ratio	135G>C (rs1801320)	DNA repair genes, such as <i>RAD51</i> , and their variations, such as 4719A/T (rs2619679) and 4601A/G (rs5030789), may have a role in the development of breast cancer and resistance to therapy.
Qureshi <i>et al.</i> , 2015 (23)	Pakistan	306	Cohort study	BC patients	PCR-RFLP	RT	Chi-square, odds ratios	135G>C (rs1801320)	In an Italian population, a correlation was found between their susceptibility to BC and the 5'-UTR polymorphisms of HRR genes (<i>RAD51</i> and <i>XRCC3</i>), which enhanced the risk of radioresistance.
Smolarz <i>et al.</i> , 2019 (24)	Poland	600	Cohort study	BC patients	Real-time PCR	untreated	Chi-square, odds ratios	4719A/T (rs2619679), 4601A/G (rs5030789)	
Al Zoubi <i>et al.</i> , 2017 (25)	Italy	39	Cohort study	BC patients	DNA sequencing	IR	Chi-square	G172T (rs1801321)	

SNP=single nucleotide polymorphism, HER2= human epidermal growth factor receptor 2, PCR = polymerase chain reaction, RFLP = restriction fragment length polymorphism

RAD51 as a Predictive and Prognostic Biomarker
Four studies assessed the significance of *RAD51* as a predictive and prognostic biomarker in BC through a combination of clinical and experimental settings. The results consistently demonstrate a robust correlation between *RAD51* expression levels, tumour behaviour, and treatment response efficacy, as illustrated in Table 4. Several studies have linked high levels of *RAD51* to tumour growth, spread, and resistance to radiation therapy. This suggests that HRR is more active and DNA repair is more effective (27, 28, 44). This increase is a major cause of genomic instability and helps tumours survive longer when they are being treated. This increase makes it a

better sign of aggressive disease and bad treatment outcomes (15). On the other hand, lowering *RAD51* levels has been shown to make tumour cells more sensitive to radiation and slow the tumour's growth in both in vivo and in vitro models (26). The findings indicate that *RAD51* significantly influences therapy efficacy, with reduced *RAD51* expression potentially indicating a favourable outcome. Overall, the results indicate that *RAD51* is a useful biomarker for predicting and prognosing BC. The expression indicates the aggressiveness of a tumour and its responsiveness to treatment. This study demonstrates its potential utility in treatment planning.

Table 4: Characteristics of selected studies of *RAD51* in breast cancer prediction and prognosis.

Authors , Year	Country	Sample size	Study design	Type of BC studied	Method used	Treatment	Statistical method	Predictive/prognostic biomarker	<i>RAD51</i> expression	Main conclusion
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Gasparini <i>et al.</i> , 2014 (26)	United States	365	Cohort, experimental study	TNBC patients, human BC cell lines	cDNA Microarray	IR	Student's t-test	RAD51 inhibitor (miR-155)	Low	In vitro and in vivo settings, upregulation of miR-155 in breast cancer cells increased the susceptibility to radiation therapy by lowering RAD51 levels.
Marsden <i>et al.</i> , 2016 (44)	United States	NR	Experimental study	Human BC cell lines	IF	IR	NR	RAD51 G151D	High	Human breast cancer cells that expressed the RAD51 G151D variant had higher homology-directed repair levels, which gave them resistance to IR. RAD51 is upregulated throughout the development and metastasis of BC.
Wiegman <i>et al.</i> , 2014 (27)	Australia	235 BC patients, 4 BC cell lines, female mice	Cohort, experimental study	BC patients, BC cell lines, animal models	IHC, Western blot	NR	Student's t-test, Chi-square	RAD51	High	Suppression of RAD51 hindered the spread of cancer cells and decreased the size of the initial tumour in vitro and in vivo. RAD51 serves as a potential prognostic biomarker and target for therapy in metastatic TNBC.
Turdo <i>et al.</i> , 2022 (28)	Italy	211 BC patients, 2 BC cell lines, 105 female mice	Cohort, experimental study	BC patients, BC cell lines, animal models	IF, IHC, Western blot	RT	Student's t-test	Myc, Sam68, RAD51	High	After RT, BCSCs with high Myc levels upregulate Sam68 and RAD51 in vivo and vitro. By targeting Sam68 and RAD51, tumour development may be reduced, making Myc, Sam68, and RAD51 attractive BC biomarkers and targetable nominees.

NR= not reported, cDNA= complementary DNA, miR-155=microRNA 155

Limitations and Future Directions

Several limitations must be acknowledged. First, in preclinical and translational experimental studies, methodologies and outcome definitions varied; hence, formal standardised tools for bias assessment were not used. We used a domain-based evaluation strategy to provide consistent assessment across varied study designs, but such an approach may limit comparability with standardised appraisal tools. Second, the variety of study designs, patient demographics, outcome evaluations, and experimental frameworks initially prevented quantitative synthesis and meta-analysis. Third, retrospective clinical research may reduce causality. The integrative synthesis provides a complete and biologically coherent view of radiation response and resistance molecular variables. Genetic association studies linked to radiation-based treatment should include additional cancer types and patients and have sufficient statistical power, given poor RAD51 reporting and sample sizes.

Overall Synthesis and Translational Implications

The human RAD51 protein seems to be crucial as a recombinase in the HRR of the DSBs, which can occur due to DNA replication stress or various

environmental influences, including CT, RT, and alkylating agents (10). RAD51 constructs helical nucleoprotein filaments on DNA through ATP utilisation and promotes the exchange of strands among homologous sequences (45). The disruption of RAD51 can lead to impaired HR and genomic instability, frequently observed in cancer cases like BC (46).

This review presents a comprehensive synthesis of clinical, translational, and experimental evidence, illustrating that RAD51 functions as a molecular convergence point connecting DNA repair capacity, tumour progression, and treatment resistance. In the studies reviewed, a clear trend is observed: the modulation of RAD51 expression has a direct impact on radiosensitivity, establishing it as both a potential biomarker and a target for therapy.

The evidence suggests that lowering RAD51 makes cells more sensitive to radiation through different pathways. Multiple experimental studies have shown that drugs like metformin, valproate, and HPTA accelerate the breakdown of RAD51 through ubiquitin–proteasome pathways. This makes RAD51 less available and slows down HRR efficiency (29, 32, 33). This process leads to unrepaired DNA damage and makes BC cells

sensitive to RT and CT (47). Complementary mechanisms include stopping RAD51 from being transcribed and stopping RAD51-foci formation, which makes DNA repair less effective and improves treatment (34, 38, 43). These results point to the idea that blocking RAD51 is a biologically active way to overcome radioresistance, indicating that more RAD51 diminishes the efficacy of treatments, highlighting its significance in two distinct aspects. Increased RAD51 levels enhance the efficiency of HRR, allowing tumour cells to rapidly repair IR-induced DNA damage. The noted overexpression could be linked to stabilisation pathways that prevent ubiquitination, possibly influenced by DDB2, or it might result from sharp gene expression triggered by DNA damage signalling (27, 28, 36, 40, 41). Further, β 1-integrin signalling plays a vital role in preserving RAD51 stability and improving cellular radioresistance (39). This dual behaviour exemplifies the "RAD51 paradox," as it maintains genomic integrity under normal physiological conditions while also promoting tumour survival under therapeutic stress. This reveals that RAD51 is not merely a passive biomarker; it actively influences the treatment efficacy.

Genetic diversity and the dynamics of RAD51's expression profoundly affect its functional impact (45). Several cohort studies (20, 23, 25) have found that polymorphisms such as rs1801320 (G>C) and rs1801321 (G>T) are connected to a higher risk of BC and how well RT works. Even so, the results were not the same, as certain genotypes showed more susceptibility to radiation in different trials (21, 22). The disparities found are probably because the study populations were of people of different races, had different sample sizes, and had different levels of RT exposure. A major translational problem is that it is challenging to use *RAD51* polymorphisms as clinical markers. This shows how badly we need standardisation and full validation projects right now. The research shows that genetic differences in *RAD51* affect how well people repair DNA and respond to treatment. This suggests that *RAD51* variations may be important in the field of precision oncology.

More studies support the prognostic and predictive value of RAD51. They show that higher levels of RAD51 expression are linked to tumour growth, metastasis, and poor treatment outcomes (27, 28, 44, 48, 49). Higher RAD51-mediated HRR activity helps cells survive after DNA damage, making them resistant to RT and CT. Instead, blocking RAD51, either directly or through regulatory molecules like miR-155, slows the growth of tumours and makes them more sensitive to radiation in vitro and in vivo models (26). These results point to RAD51 expression levels as a sign of tumour progression and

treatment efficacy. This makes it an important clinical biomarker.

Putting these results together gives us a clear idea: RAD51 controls how well DNA is repaired. When RAD51 is dysfunctional, it causes genomic instability and tumorigenesis (50). When it is hyperactive, it makes DNA repair easier and makes treatment less effective (51). This duality explains the clinical and experimental results in terms of how they work, which supports RAD51 targeting in treatment methods. These findings are significant for clinical applications. RAD51 expression and activity may be used to identify the benefit from RT or combination treatments. Second, targeting RAD51 for therapeutic purposes, either directly or through its regulatory pathways, may help overcome radioresistance (26). Third, using RAD51 manipulation along with PARP inhibitors may make therapy more effective by taking advantage of problems in the DNA repair system (4).

Conclusion

This systematic review shows RAD51's importance for BC growth, DNA repair, and the effectiveness of RT. When RAD51 levels are high, tumours grow faster, and treatment is harder. Downregulation makes cells more sensitive to radiation. This biomarker could be useful to predict BC and a target for treatment-resistant cases. Variations in *RAD51*, especially rs1801320 and rs1801321, may affect the RT response and BC risk. However, confirmation is needed. More clinical studies are needed to confirm that RAD51 expression and genetic variants can be used to predict patients and improve RT protocols.

List of Abbreviations

BC: Breast Cancer
 BCSCs: Breast Cancer Stem Cells
 BRCA1: Breast Cancer Gene 1
 BRCA2: Breast Cancer Gene 2
 cDNA: Complementary DNA
 CHK1: Checkpoint Kinase 1
 CT: Chemotherapy
 DDB2: DNA Damage Binding Protein 2
 DSBs: Double-Strand Breaks
 HER2: Human Epidermal Growth Factor Receptor 2
 HPTA: 2-Hexyl-4-Pentynoic Acid
 HRR: Homologous Recombination Repair
 Huaier: *Trametes robiniophila* Murr
 IASJ: Iraqi Academic Scientific Journals
 IF: Immunofluorescence
 IHC: Immunohistochemistry
 IR: Ionising Radiation
 miR-155: MicroRNA-155
 PARPi: Poly ADP-Ribose Polymerase Inhibitor
 PBT: Proton Beam Therapy
 PCR: Polymerase Chain Reaction

PICO: Population, Intervention, Comparison, Outcomes
 PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
 PROSPERO: International Prospective Register of Systematic Reviews
 RAD51: DNA Repair Recombinase RAD51
 RAD51AP1: RAD51-Associated Protein 1
 RFLP: Restriction Fragment Length Polymorphism
 RING1: E3 Ubiquitin-Protein Ligase
 R-O2-SWCNTs: Tombarthite-Modified Single-Walled Carbon Nanotubes
 RT: Radiotherapy
 SNP: Single Nucleotide Polymorphism
 TNBC: Triple-Negative Breast Cancer
 UCHL3: Ubiquitin C-Terminal Hydrolase L3
 USP7: Ubiquitin-Specific Protease 7
 VPA: Valproate

Declarations

Ethics approval and consent to participate
 Not applicable (systematic review).

Consent for Publication

All authors gave consent for publication of the work under the Creative Commons Attribution-Non-Commercial 4.0 license.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare no competing interests.

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Authors' contributions

AHS and MAAH: Conceptualisation, Writing-review, Literature search & Screening, Drafting-manuscript.

TNK: Data validation, Disagreements resolving, Revision- manuscript.

All authors read and approved the final manuscript.

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References

1. Hameed BH, Al-Rayahi IA, Muhsin SS. Evaluation of Preoperative CA15-3 Level and

its Relationship with Clinico-Pathological Characteristics in Primary Breast Cancer Patients. *Journal of Techniques*. 2022 Jun 30;4(2):21-6.

<https://doi.org/10.51173/jt.v4i2.480>

2. Hameedi BH, Sultan AS, MAHDI A. Updating of PD-1, PDL-1 and CD8+ in Benign and Malignant Breast Cancer in Iraqi Women. *International Journal of Drug Delivery Technology*. 2022;12(4):1849-52.

<https://doi.org/10.25258/ijddt.12.4.60>

3. Shawq AH, Globe IH, Hussaini M. Comparison of some models of spatial regression using simulation. *Journal of Techniques*. 2023 Jun 30; 5(2):197-205.

<https://doi.org/10.51173/jt.v5i2.598>

4. Huang X, Song C, Zhang J, Zhu L, Tang H. Circular RNAs in breast cancer diagnosis, treatment and prognosis. *Oncology Research*. 2023 Dec 28;32(2):241.

<https://doi.org/10.32604/or.2023.046582>

5. Inalegwu A, Cuypers B, Claesen J, Janssen A, Coolkens A, Baatout S, Laukens K, De Vos WH, Quintens R. Fractionated irradiation of MCF7 breast cancer cells rewires a gene regulatory circuit towards a treatment-resistant stemness phenotype. *Molecular Oncology*. 2022 Oct;16(19):3410-35.

<https://doi.org/10.1002/1878-0261.13226>

6. Naji L, Zwyea S, Raheem A. Measurement of the radiation level dose to patient from fluoroscopy device during cardiac catheterization. *Journal of Techniques*. 2020 Mar 31;2(1):35-41.

<https://doi.org/10.51173/jt.v2i1.165>

7. Shah C, Al-Hilli Z, Vicini F. Advances in breast cancer radiotherapy: implications for current and future practice. *JCO Oncology Practice*. 2021 Dec;17(12):697-706.

<https://doi.org/10.1200/OP.21.00635>

8. Chandra RA, Keane FK, Voncken FE, Thomas CR. Contemporary radiotherapy: present and future. *The Lancet*. 2021 Jul 10;398(10295):171-84.

[https://doi.org/10.1016/S0140-6736\(21\)00233-6](https://doi.org/10.1016/S0140-6736(21)00233-6)

9. Wu Y, Song Y, Wang R, Wang T. Molecular mechanisms of tumor resistance to radiotherapy. *Molecular Cancer*. 2023 Jun 15;22(1):96. <https://doi.org/10.1186/s12943-023-01801-2>

10. Wassing IE, Esashi F. RAD51: Beyond the break. In *Seminars in Cell & Developmental Biology* 2021 May 1 (Vol. 113, pp. 38-46). Academic Press.

<https://doi.org/10.1016/j.semcdb.2020.08.010>

11. Wang Z, Jia R, Wang L, Yang Q, Hu X, Fu Q, Zhang X, Li W, Ren Y. The emerging roles of Rad51 in cancer and its potential as a therapeutic target. *Frontiers in Oncology*. 2022

- Jul 7;12:935593.
<https://doi.org/10.3389/fonc.2022.935593>
12. Wang YY, Cheng KH, Hung AC, Lo S, Chen PY, Wu YC, Hou MF, Yuan SS. Differential impact of cytoplasmic vs. nuclear RAD51 expression on breast cancer progression and patient prognosis. *International Journal of Oncology*. 2023 Dec 7;64(2):12.
<https://doi.org/10.3892/ijco.2023.5600>
13. Matos-Rodrigues G, Guirouilh-Barbat J, Martini E, Lopez BS. Homologous recombination, cancer and the 'RAD51 paradox'. *NAR Cancer*. 2021 Jun 1;3(2):zcab016.
<https://doi.org/10.1093/narcan/zcab016>
14. Demeyer A, Benhelli-Mokrani H, Chénais B, Weigel P, Fleury F. Inhibiting homologous recombination by targeting RAD51 protein. *Biochimica et Biophysica Acta (BBA)-Reviews on Cancer*. 2021 Dec 1;1876(2):188597.
<https://doi.org/10.1016/j.bbcan.2021.188597>
15. Tambuwala M, Bakshi H. RAD51-UTR haplotype genetic polymorphisms and susceptibility to breast cancer in women from Jordanian population. *Experimental Oncology*. 2021 Jun 30;43(2):149-54.
<https://doi.org/10.32471/exp-oncology.2312-8852.vol-43-no-2.16338>
16. Abbas HS, Mahdi AA, Tektook NK. The Genetic Polymorphisms of DNA Repair Gene RAD51 and Their Role as a Predictive Biomarker for Breast Cancer Risk and Response to Radiotherapy in Iraqi Women. *Asian Pacific Journal of Cancer Prevention*. 2026 Jan 22;27(1):345-51.
<https://doi.org/10.31557/APJCP.2026.27.1.345>
17. Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, Thomas J. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *The Cochrane Database of Systematic Reviews*. 2019 Oct 3;2019(10):ED000142.
<https://doi.org/10.1002/14651858.ED000142>
18. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021 Mar 29;372.
<https://doi.org/10.1136/bmj.n71>
19. Telli ML, Gradishar WJ, Ward JH. NCCN guidelines updates: breast cancer. *Journal of the National Comprehensive Cancer Network*. 2019 May 1;17(5.5):552-5.
<https://doi.org/10.6004/jnccn.2019.5006>
20. Goričar K, Dugar F, Dolžan V, Marinko T. NBN, RAD51 and XRCC3 polymorphisms as potential predictive biomarkers of adjuvant radiotherapy toxicity in early HER2-positive breast cancer. *Cancers*. 2022 Sep 8;14(18):4365.
<https://doi.org/10.3390/cancers14184365>
21. Söderlund Leifler K, Askliid A, Fornander T, Stenmark Askmalin M. The RAD51 135G> C polymorphism is related to the effect of adjuvant therapy in early breast cancer. *Journal of Cancer Research and Clinical Oncology*. 2015 May;141(5):797-804.
<https://doi.org/10.1007/s00432-014-1859-0>
22. Ragudo GP, Pureza BS, Rimando DA, Manrique MR, Ortin TS, Notarte KI, Albano PM. RAD51 135G> C Single Nucleotide Polymorphism and Risk of Breast Cancer in Selected Filipino Cases. *Philippine Journal of Science*. 2020 Dec 1;149(4).
<https://doi.org/10.56899/149.04.19>
23. Qureshi Z, Mahjabeen I, Baig RM, Kayani MA. Correlation between selected XRCC2, XRCC3 and RAD51 gene polymorphisms and primary breast cancer in women in Pakistan. *Asian Pac J Cancer Prev*. 2014 Jan 1;15(23):10225-9.
<https://doi.org/10.7314/APJCP.2014.15.23.10225>
24. Smolarz B, Michalska MM, Samulak D, Romanowicz H, Wójcik L. Polymorphism of DNA repair genes in breast cancer. *Oncotarget*. 2019 Jan 11;10(4):527.
<https://doi.org/10.18632/oncotarget.26568>
25. Zoubi MS, Zavaglia K, Mazanti C, Hamad MA, Batayneh KA, Aljabali AA, Bevilacqua G. Polymorphisms and mutations in GSTP1, RAD51, XRCC1 and XRCC3 genes in breast cancer patients. *The International Journal of Biological Markers*. 2017 Jul;32(3):337-43.
<https://doi.org/10.5301/ijbm.5000258>
26. Gasparini P, Lovat F, Fassan M, Casadei L, Cascione L, Jacob NK, Carasi S, Palmieri D, Costinean S, Shapiro CL, Huebner K. Protective role of miR-155 in breast cancer through RAD51 targeting impairs homologous recombination after irradiation. *Proceedings of the National Academy of Sciences*. 2014 Mar 25;111(12):4536-41.
<https://doi.org/10.1073/pnas.1402604111>
27. Wiegman AP, Al-Ejeh F, Chee N, Yap PY, Gorski JJ, Da Silva L, Bolderson E, Chenevix-Trench G, Anderson R, Simpson PT, Lakhani SR. Rad51 supports triple negative breast cancer metastasis. *Oncotarget*. 2014 Apr 27;5(10):3261.
<https://doi.org/10.18632/oncotarget.1923>
28. Turdo A, Gaggianesi M, Di Franco S, Veschi V, D'Accardo C, Porcelli G, Lo Iacono M, Pillitteri I, Verona F, Militello G, Zippo A. Effective targeting of breast cancer stem cells by combined inhibition of Sam68 and Rad51. *Oncogene*. 2022 Apr 8;41(15):2196-209.
<https://doi.org/10.1038/s41388-022-02239-4>
29. Liu G, Lim D, Cai Z, Ding W, Tian Z, Dong C, Zhang F, Guo G, Wang X, Zhou P, Feng Z. The

- valproate mediates radio-bidirectional regulation through RFWD3-dependent ubiquitination on Rad51. *Frontiers in Oncology*. 2021 Mar 25;11:646256. <https://doi.org/10.3389/fonc.2021.646256>
30. Ding X, Yang Q, Kong X, Haffty BG, Gao S, Moran MS. Radiosensitization effect of Huaier on breast cancer cells. *Oncology Reports*. 2016 May 1;35(5):2843-50. <https://doi.org/10.3892/or.2016.4630>
31. Alonso-González C, González A, Martínez-Campa C, Gómez-Arozamena J, Cos S. Melatonin sensitizes human breast cancer cells to ionizing radiation by downregulating proteins involved in double-strand DNA break repair. *Journal of Pineal Research*. 2015 Mar;58(2):189-97. <https://doi.org/10.1111/jpi.12205>
32. Lee JO, Kang MJ, Byun WS, Kim SA, Seo IH, Han JA, Moon JW, Kim JH, Kim SJ, Lee EJ, In Park S. Metformin overcomes resistance to cisplatin in triple-negative breast cancer (TNBC) cells by targeting RAD51. *Breast Cancer Research*. 2019 Oct 22;21(1):115. <https://doi.org/10.1186/s13058-019-1204-2>
33. Cai Z, Lim D, Jia B, Liu G, Ding W, Wang Z, Tian Z, Peng J, Zhang F, Dong C, Feng Z. Hexyl-pentynoic acid serves as a novel radiosensitizer for breast cancer by inhibiting UCHL3-dependent Rad51 deubiquitination. *Radiation Medicine and Protection*. 2023 Dec 1;4(4):204-13. <https://doi.org/10.1016/j.radmp.2023.10.003>
34. Bridges AE, Ramachandran S, Pathania R, Parwal U, Lester A, Rajpurohit P, Morera DS, Patel N, Singh N, Korkaya H, Manicassamy S. RAD51AP1 deficiency reduces tumor growth by targeting stem cell self-renewal. *Cancer Research*. 2020 Sep 15;80(18):3855-66. <https://doi.org/10.1158/0008-5472.CAN-19-3713>
35. Vogt M, Classen S, Krause AK, Peter NJ, Petersen C, Rothkamm K, Borgmann K, Meyer F. USP7 Deregulation Impairs S Phase Specific DNA Repair after Irradiation in Breast Cancer Cells. *Biomedicines*. 2024 Mar 29;12(4):762. <https://doi.org/10.3390/biomedicines12040762>
36. Luo K, Li L, Li Y, Wu C, Yin Y, Chen Y, Deng M, Nowsheen S, Yuan J, Lou Z. A phosphorylation–deubiquitination cascade regulates the BRCA2–RAD51 axis in homologous recombination. *Genes & Development*. 2016 Dec 1;30(23):2581-95. <https://doi.org/10.1101/gad.289439.116>
37. Song Z, Tu X, Zhou Q, Huang J, Chen Y, Liu J, Lee S, Kim W, Nowsheen S, Luo K, Yuan J. A novel UCHL3 inhibitor, perifosine, enhances PARP inhibitor cytotoxicity through inhibition of homologous recombination-mediated DNA double strand break repair. *Cell Death & Disease*. 2019 May 21;10(6):398. <https://doi.org/10.1038/s41419-019-1628-8>
38. Choi C, Park S, Cho WK, Choi DH. Cyclin D1 is associated with radiosensitivity of triple-negative breast cancer cells to proton beam irradiation. *International Journal of Molecular Sciences*. 2019 Oct 7;20(19):4943. <https://doi.org/10.3390/ijms20194943>
39. Ahmed KM, Pandita RK, Singh DK, Hunt CR, Pandita TK. β 1-integrin impacts Rad51 stability and DNA double-strand break repair by homologous recombination. *Molecular and Cellular Biology*. 2018 May 1;38(9):e00672-17. <https://doi.org/10.1128/MCB.00672-17>
40. Zhao L, Si CS, Yu Y, Lu JW, Zhuang Y. Depletion of DNA damage binding protein 2 sensitizes triple-negative breast cancer cells to poly ADP-ribose polymerase inhibition by destabilizing Rad51. *Cancer Science*. 2019 Nov;110(11):3543-52. <https://doi.org/10.1111/cas.14201>
41. Liu Y, Burness ML, Martin-Trevino R, Guy J, Bai S, Harouaka R, Brooks MD, Shang L, Fox A, Luther TK, Davis A. RAD51 mediates resistance of cancer stem cells to PARP inhibition in triple-negative breast cancer. *Clinical Cancer Research*. 2017 Jan 15;23(2):514-22. <https://doi.org/10.1158/1078-0432.CCR-15-1348>
42. Choi C, Cho WK, Park S, Shin SW, Park W, Kim H, Choi DH. Checkpoint kinase 1 (CHK1) inhibition enhances the sensitivity of triple-negative breast cancer cells to proton irradiation via Rad51 downregulation. *International Journal of Molecular Sciences*. 2020 Apr 13;21(8):2691. <https://doi.org/10.3390/ijms21082691>
43. Jia Y, Weng Z, Wang C, Zhu M, Lu Y, Ding L, Wang Y, Cheng X, Lin Q, Wu K. Increased chemosensitivity and radiosensitivity of human breast cancer cell lines treated with novel functionalized single-walled carbon nanotubes. *Oncology Letters*. 2017 Jan;13(1):206-14. <https://doi.org/10.3892/ol.2016.5402>
44. Marsden CG, Jensen RB, Zagelbaum J, Rothenberg E, Morrical SW, Wallace SS, Sweasy JB. The tumor-associated variant RAD51 G151D induces a hyper-recombination phenotype. *PLoS Genetics*. 2016 Aug 11;12(8):e1006208. <https://doi.org/10.1371/journal.pgen.1006208>
45. Grundy MK, Buckanovich RJ, Bernstein KA. Regulation and pharmacological targeting of RAD51 in cancer. *NAR Cancer*. 2020 Sep 1;2(3):zcaa024. <https://doi.org/10.1093/narcan/zcaa024>
46. Cortesi L, Piombino C, Toss A. Germline mutations in other homologous recombination repair-related genes than BRCA1/2: predictive

- or prognostic factors?. Journal of Personalized Medicine. 2021 Mar 28;11(4):245. <https://doi.org/10.3390/jpm11040245>
47. Rivero Belenchón I, Congregado Ruiz CB, Saez C, Osman García I, Medina López RA. Parp inhibitors and radiotherapy: a new combination for prostate cancer (systematic review). International Journal of Molecular Sciences. 2023 Aug 19;24(16):12978. <https://doi.org/10.3390/ijms241612978>
48. Laurini E, Marson D, Fermeiglia A, Aulic S, Fermeiglia M, Pricl S. Role of Rad51 and DNA repair in cancer: A molecular perspective. Pharmacology & Therapeutics. 2020 Apr 1;208:107492. <https://doi.org/10.1016/j.pharmthera.2020.107492>
49. Feng Y, Wang D, Xiong L, Zhen G, Tan J. Predictive value of RAD51 on the survival and drug responsiveness of ovarian cancer. Cancer Cell International. 2021 May 5;21(1):249. <https://doi.org/10.1186/s12935-021-01953-5>
50. Abbas HS, Mohammed AA. The appraisal of fetuin-a role in the development of metabolic syndrome in the obese individuals. Biochemical & Cellular Archives. 2021 Apr 2;21. <https://connectjournals.com/03896.2021.21.223>
51. Creeden JF, Nanavaty NS, Einloth KR, Gillman CE, Stanbery L, Hamouda DM, Dworkin L, Nemunaitis J. Homologous recombination proficiency in ovarian and breast cancer patients. BMC Cancer. 2021 Oct 28;21(1):1154. <https://doi.org/10.1186/s12885-021-08863-9>