

Comprehensive Analysis of the Expression and Prognosis for RAD51 Family in Human Breast Cancer

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Purpose: The RAD51 family of genes, including RAD51 and the five RAD51-like paralogs (RAD51B, RAD51C, RAD51D, XRCC2, and XRCC3), are known to be crucially associated with DNA damage repair pathway. Increasing evidence indicated that RAD51 family members were implicated in breast cancer tumorigenesis. However, their biological roles and prognostic values in breast cancer have yet to be clarified.

Methods: In this study, by using the OncoPrint and GEPIA databases, we explored the transcriptional levels of RAD51 family members in breast cancer. Besides, the associations between RAD51 family expression and clinical features were evaluated by using the UALCAN database and Kaplan–Meier (KM) Plotter. We also analyzed the mutations of the RAD51 family and differentially altered genes from the cBioPortal database.

Results: We found that RAD51 mRNA was significantly elevated in breast cancer samples than in normal tissues, while XRCC2 mRNA was downregulated. Besides, a remarkable correlation was detected between the expression of RAD51/RAD51B/XRCC2 genes and the breast cancer stage. Survival analysis utilizing the KM Plotter indicated that high RAD51 and XRCC3 mRNA was associated with a poor prognosis. Conversely, RFS data suggested that high levels of RAD51B/RAD51C/RAD51D/XRCC2 were associated with a favorable prognosis. Moreover, a high genetic variation rate of RAD51C (7%) was detected in breast cancer patients.

Conclusion: Conclusively, we implied that RAD51 and XRCC3 might be potential targets for precision therapy in breast cancer and the RAD51B/RAD51C/RAD51D/XRCC2 genes have significant values for breast cancer prognosis.

Keywords: RAD51, breast, cancer, expression, gene, prognosis

Introduction

According to the latest statistics on the GLOBOCAN 2018 estimates of cancer incidence, breast cancer is the most commonly diagnosed cancer among female.¹ Although the advances in breast cancer detection programs and the development of systemic therapies have resulted in a 38% decrease in breast cancer death rate, disease recurrence and metastasis are common with a high mortality rate.² Discovering the new diagnostic biomarkers and therapeutic targets are arduous challenges for the optimal management of breast cancer.

The DNA damage repair pathways are invoked to maintain genomic stability after induction and detection of DNA damage.³ The double-strand breaks (DSBs) are one of the most cytotoxic DNA lesions, which could be repaired by two major pathways: homologous recombination (HR) and nonhomologous end-joining (NHEJ) repair. Compared to NHEJ, HR uses a homologous DNA template to provide an error-free and versatile alternative for DSB repair.⁴ RAD51 is a homolog of RecA of *Escherichia coli* and functions as an essential factor to catalyze strand invasion into the homologous DNA template to restore broken DNA.⁵ RAD51 recruitment at broken DNA sites depends on the BRCA2, RAD51 family, and RAD52 proteins,

which interacts directly with RAD51 to catalyze the invasion of ssDNA. The RAD51 family of proteins, including RAD51 and the five RAD51 paralogs (*RAD51B*, *RAD51C*, *RAD51D*, *XRCC2*, *XRCC3*), have been identified in human cells.⁶

Alterations in HR-related genes are associated with accumulated unrepaired DSBs and contribute to tumorigenesis. Previous studies have identified that the alterations of RAD51 may be involved in the development of hereditary breast cancer.⁷ Besides, RAD51C has been implicated as a tumor suppressor. RAD51C mutations were identified in FA and breast and ovarian cancer patients.⁸ A three-stage genome-wide association study (GWAS) of breast cancer underscored that RAD51B mutation was associated with breast cancer.⁹ However, the biological role of RAD51 family members in breast cancer remains unclear. A detailed understanding of biological and molecular roles would help develop new biomarkers and novel treatment options for breast cancer.

Herein, by using the online databases, we explored the transcriptional levels of RAD51 family members in breast cancer. Then, we evaluated the associations between RAD51 family expression with individual cancer stage or survival rate in breast cancer progression and prognosis. Furthermore, we also analyzed the predicted functions and pathways of the mutations in the RAD51 family and their related frequently altered genes.

Materials and Methods

OncoPrint Database Analysis

OncoPrint is a cancer microarray database, which is designed to facilitate the discovery from powerful genome-wide expression analysis. To date, OncoPrint contains 715 datasets, as well as 86,733 normal and pan-cancer samples.¹⁰ The mRNA levels of RAD51 family members were studied in breast cancer. A fold change of 2 and a *p*-value of 0.01 were set as the significance thresholds. The Student's *t*-test was used to evaluate the difference of RAD51 family members in breast cancer.

GEPIA Database Analysis

GEPIA (<http://gepia.cancer-pku.cn/>) is a newly developed web-based tool for analyzing the RNA sequencing expression data of 9736 tumors and 8587 normal samples from the TCGA and the GTEx data.¹¹ GEPIA provides key interactive and customizable functions such as differential gene expression analysis, profiling plotting, patient survival analysis, correlation analysis, similar gene detection, and dimensionality reduction analysis.¹¹ Using the GEPIA dataset, we analyzed the expression of the RAD51 family among multiple cancers. Besides, we compared mRNA expression of the RAD51 family between different cancer stages.

Kaplan–Meier Plotter

Kaplan–Meier plotter databases (<http://kmplot.com/analysis/>) were assigned to explore mRNA expression of the RAD51 family and its relationship with prognosis. The Kaplan Meier plotter is capable to assess the effect of 54k genes on survival in breast cancer (n=7830).¹² Its database sources include GEO, EGA, and TCGA. A *p*-value<0.05 was considered significant.

UALCAN Analysis

UALCAN is a comprehensive web resource to provide easy access to publicly available cancer OMICS data (TCGA, MET500, and CPTAC). This web server provides analyses of gene expression in various tumor subgroups such as gender, cancer stages, tumor grade, and other clinicopathological features. Herein, we use the UALCAN database to analyze relative expression of the RAD51 gene family based on sample types, patients' races, major tumor classes, TP53 mutations.¹³

cBioportal Analysis

cBioportal analysis is an open-access resource that can be used to interactively explore multiple, methylomic, and multi-omic cancer genomic datasets. The portal can convert molecular profiling data into easy-to-understand genetic, epigenetic, mRNA expression, and proteomic events, which can also provide graphic descriptions of gene-level data from multiple platforms, survival analysis, network visualization, etc. We used cBioportal to analyze RAD51 family mutations and their co-expressed genes in the TCGA breast invasive carcinoma sample (TCGA, PanCancer Atlas).

Functional and Pathway Enrichment Analysis

Genes significantly related to RAD51 family mutations screened from cBioportal databases were analyzed in the Database for Annotation, Visualization, and Integrated Discovery (DAVID 6.8) (<https://david.ncifcrf.gov/>) to perform the Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses.¹⁴ Gene ontology analyses focus on three domains: biological processes (BP), cellular components (CC), and molecular functions (MF). A *p*-value<0.05 was considered significant.

Statistical Analysis

Statistical analyses were conducted using Prism 9 (GraphPad Software). Differences were calculated using Student’s unpaired *t*-test. *P*-values less than 0.05 were considered statistically significant.

Results

Transcriptional Levels of RAD51 Family in Patients with Breast Cancer

By using Oncomine databases, we analyzed the expression of RAD51 family genes in cancer compared with normal samples. The results in Figure 1 showed that in five datasets and eleven analysis, the mRNA of RAD51 was significantly elevated in patients with breast cancer. However, the expression of XRCC2 was remarkably down-regulated in 1 dataset and 8 analyses. No trend of increased or decreased mRNA expression of RAD51B/RAD51C/RAD51D/XRCC3 was detected in breast cancer samples compared with normal samples. In the TCGA breast cancer dataset, compared with normal samples, the fold change of

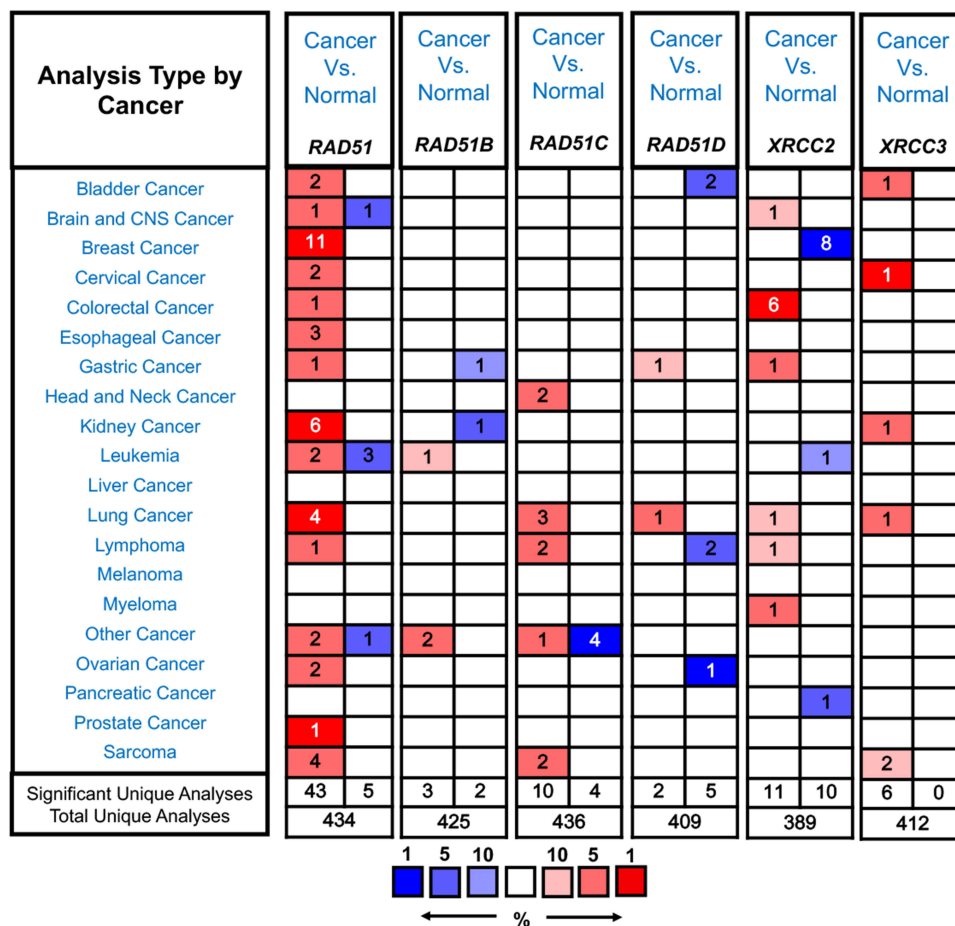


Figure 1 The transcription levels of RAD51 family in various types of cancer diseases. Oncomine dataset analysis showed the number of datasets with significant mRNA up-regulation (red) or down-regulation (blue) of RAD51 family members. The fold change cutoff was 2, and the *p* value cutoff was 0.01. Gene rank: 10%, data type: mRNA.

RAD51 overexpression in invasive ductal carcinoma was 6.407 ($p=1.74E-44$), and the fold change in invasive lobular breast cancer was 3.588 ($p=4.41E-14$). The dataset of Turashvili Breast demonstrated increased expression of RAD51 mRNA, and the fold change in invasive ductal breast carcinoma was 3.118 ($p=0.005$). In Richardson Breast's dataset, RAD51 was also up-regulated in ductal breast carcinoma with a fold change of 3.228 ($p=7.75E-6$). Ma Breast's dataset indicated that RAD51 overexpression was detected in ductal breast carcinoma in situ epithelia, with a fold change of 2.406 ($p=0.002$). In addition, Gluck Breast's study showed that RAD51 has a fold change of 4.441 in invasive breast cancer compared with normal samples ($p=0.003$).

Besides, compared with normal tissues, a remarkable down-regulation of XRCC2 mRNA was identified in breast cancer tissues. The results from Curtis Breast's dataset unfolded that there was a fold change of -2.732 in XRCC2 mRNA expression in 1556 invasive ductal breast cancer tissues compared with 144 breast normal tissues ($p=1.93E-85$). XRCC2 expression was decreased in 148 invasive lobular breast cancer tissues by a fold change of -2.546 ($p=5.95E-51$). For 90 samples with invasive ductal and lobular breast cancer, the fold change of XRCC2 was -2.665 ($p=7.06E-39$). The conclusion is that by analyzing the Oncomine database, compared with normal samples, RAD51 is up-regulated in breast cancer, while XRCC2 is significantly down-regulated. Furthermore, GEPIA, the online tool sourced from TCGA and GTEx, was used to investigate the expression of RAD51 family genes in multiple cancers. Consistent with results from the Oncomine analysis, GEPIA heatmap and box plots both revealed that RAD51 was highly expressed in breast cancer samples compared with normal tissues (Figure S1). However, no significant differences in other RAD51 family genes were detected in breast cancer tissues (Figure S1B–G).

The Relationship between the mRNA Levels of RAD51 family and the Clinical Features of Patients with Breast Cancer

To analyze the clinical features related to gene expression of the RAD51 family, we use the UALCAN database to integrate various clinical factors of breast cancer (Figure 2). The box plots depict the expression of RAD51/RAD51B/RAD51C/RAD51D/XRCC2/XRCC3 genes based on the patients' races, breast cancer subclasses, and TP53 status. The results demonstrated that among patients of different races, RAD51 maintained the lowest transcriptional levels in Caucasians (Figure S2). Among the three breast cancer subtypes, RAD51 and XRCC2 have the lowest expression in the luminal subtypes and the highest expression in TNBC (Figure 2A and E). RAD51B and XRCC3 have the highest expression in TNBC, while RAD51D is expressed lowest in HER2-positive breast cancer (Figure 2B and D).

Besides, we investigated the association between the expression of RAD51 family genes and TP53 status. RAD51/XRCC2/XRCC3 genes maintain higher expression in TP53-mutant breast cancer (Figure 2G, K and L). However, the levels of RAD51B and RAD51D genes were higher in TP53-nonmutated breast cancer patients than in TP53-mutated patients (Figure 2H and J). Next, we analyzed the relationship between the mRNA expression of different RAD51 family members and the cancer stages of breast cancer patients through GEPIA (Figure 3). The genes of RAD51/RAD51B/XRCC2 significantly varied, whereas RAD51C/RAD51D/XRCC3 genes did not differ. Conclusively, the above results indicate that the mRNA levels of RAD51/RAD51B/XRCC2 genes are significantly associated with the stages of breast cancer.

The Prognostic Values of RAD51 Family in Breast Cancer

To evaluate the prognostic value of RAD51 family genes in breast cancer, we interrogated the Kaplan-Meier (KM) plotter to investigate whether the expression of RAD51 family genes was related to patients' survival. The results from the KM plot and Log rank test uncovered that high RAD51 mRNA expression was associated with relatively poor OS (Overall Survival) and RFS (Relapse Free Survival) in breast cancer (Figure 4A and G). For OS analysis, RAD51B/RAD51C/RAD51D/XRCC2 genes were not significantly correlated with OS, while high XRCC3 mRNA expression was associated with low OS (Figure 4B–F). Interestingly, further analysis of the RFS data indicated that high expression of RAD51B/RAD51C/RAD51D/XRCC2 was associated with a favorable prognosis. However, no association between XRCC3 expression and RFS was detected in breast cancer (Figure 4H–L). Therefore, highly expressed RAD51 and XRCC3 expression may be poor prognostic factors for breast cancer. The increase in RAD51B/RAD51C/RAD51D/XRCC2 may be related to a better recurrence-free rate.

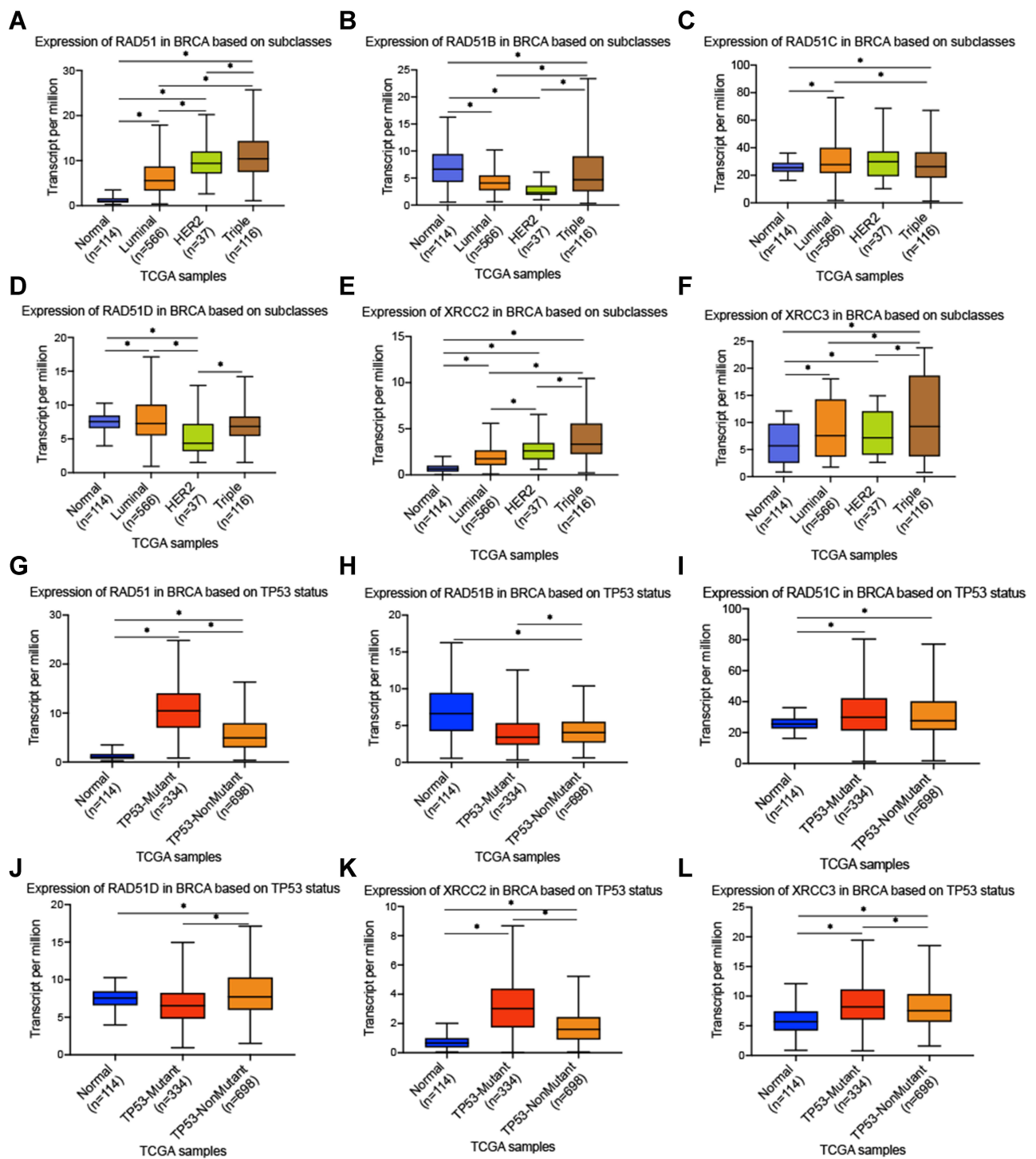


Figure 2 The expression of RAD51 family and its association with the clinical features of breast cancer patients. The box plots depicted the expression of genes, including RAD51, RAD51B, RAD51C, RAD51D, XRCC2, and XRCC3 according to subclasses (A–F) and TP53 status of breast cancer (G–L), respectively, in UALCAN database. * $p < 0.05$.

Genetic Alterations of RAD51 Family and Their Associations with the Prognosis of Breast Cancer

The loss of genetic stability is a key molecular and pathophysiologic step in cancer development. Based on this, we investigated the RAD51 family alterations by using the cBioPortal database. The differential degrees of genetic

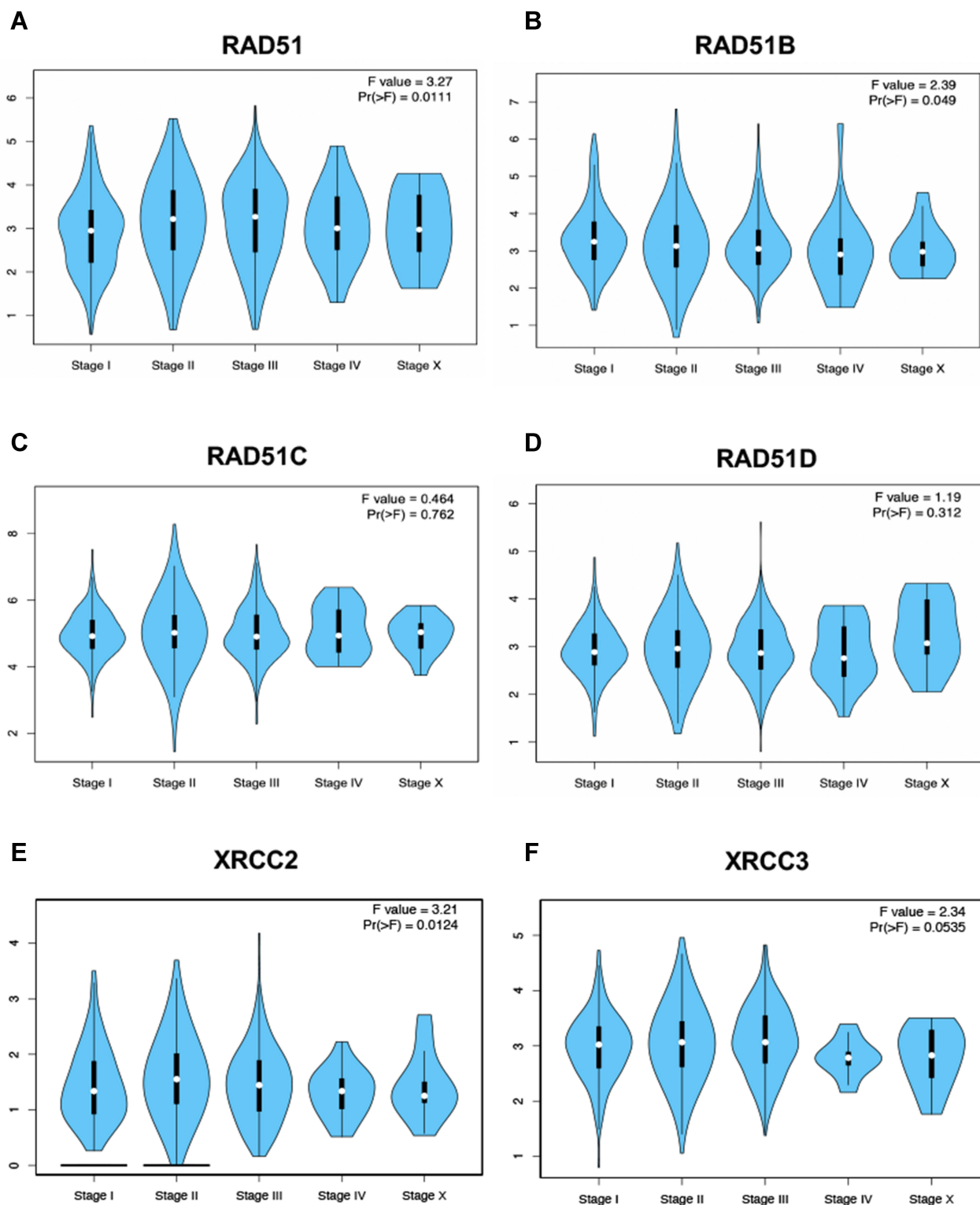


Figure 3 The correlation between RAD51 family gene expression and tumor pathological stage in breast cancer patients. The mRNA levels of RAD51/RAD51B/XRCC2 genes were significantly correlated with the stages of breast cancer (**A** and **B–E**), while expression of other members (RAD51C/RAD51D/XRCC3) were not correlated with cancer stages (**C** and **D–F**).

alterations among RAD51 family genes are shown in [Figure 5A](#). RAD51C showed the highest genetic variation rate (7%), and amplification was the predominant form of gene variation in the RAD51 family. The genetic alteration rates of RAD51, RAD51B, RAD51D, XRCC2, and XRCC3 were 1.2%, 2.2%, 2.1%, 1.1%, and 1.1% in breast cancer samples,

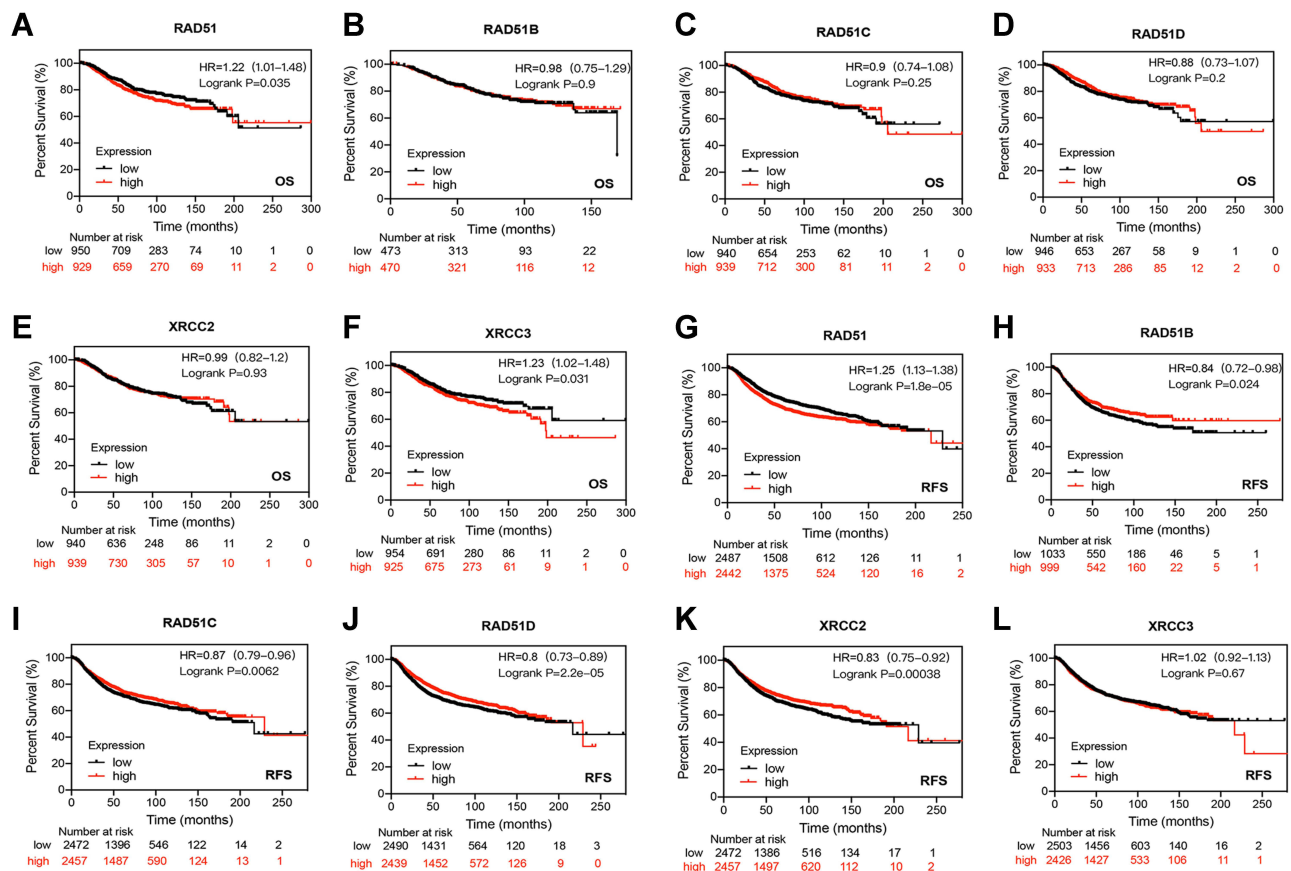


Figure 4 Prognostic features of RAD51 family genes expression in breast cancer patients. The Kaplan-Meier curve of OS (A–F) and RFS (G–L) based on RAD51 family gene expression in breast cancer patients in Kaplan-Meier plotter database.

respectively (Figure 5A). As described in Figure 5B–D, among the PAM50 subtypes of breast cancer, HER2-positive breast cancer had the highest mutation frequency, followed by luminal B and Basal subtypes, while luminal A and normal-like subtype have the lowest mutation frequency of RAD51 family members. Besides, we analyzed the KM curves of the prognostic role of the RAD51 family alterations in breast cancer. The results indicated that there was no significant association between RAD51 family genetic alterations and overall survival (Figure 5E).

Analysis of Gene Ontology and KEGG pathways of RAD51 Family Alterations and Their Co-Expressed Genes in Breast Cancer

The functions of RAD51 family members and the genes that were significantly associated with RAD51 family alterations can be predicted by analyzing GO and KEGG in DAVID 6.8. GO enrichment analysis predicted gene functions based on three aspects: biological processes, cellular components, and molecular functions. The co-expressed genes significantly associated with RAD51 family alterations were screened out through calculating the Spearman correlation coefficients respectively (Spearman correlation >0.6 or <-0.6 , p value < 0.05). The 255 co-expressed genes were enrolled into DAVID 6.8. The RAD51 family alterations were mainly associated with the BP terms GO:0051301 (cell division), GO:0007067 (mitotic nuclear division), GO:0007062 (sister chromatid cohesion), GO:0006260 (DNA replication), and GO:0000082 (G1/S transition of mitotic cell cycle) (Figure 6A). In addition, we found that MF such as GO:0005515 (protein binding), GO:0005524 (ATP binding), GO:0008017 (microtubule binding), GO:0003777 (microtubule motor activity), and GO:0019901 (protein kinase binding) were remarkably regulated by the RAD51 family alterations in breast cancer (Figure 6B). Besides, RAD51 family mutations are also significantly related to CC, including GO:0005654

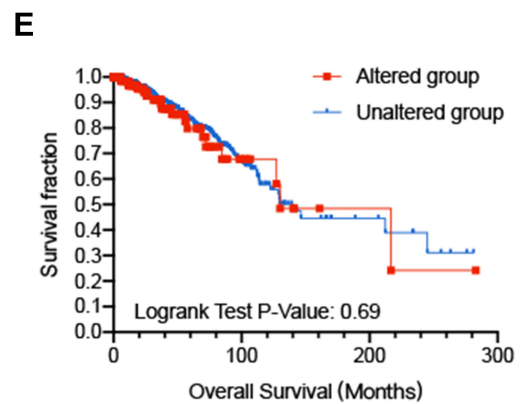
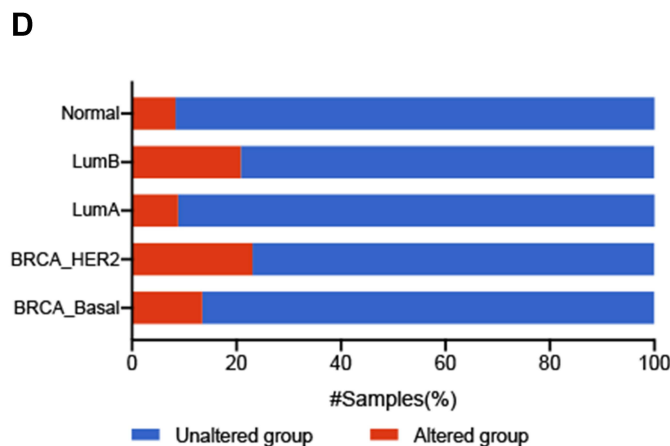
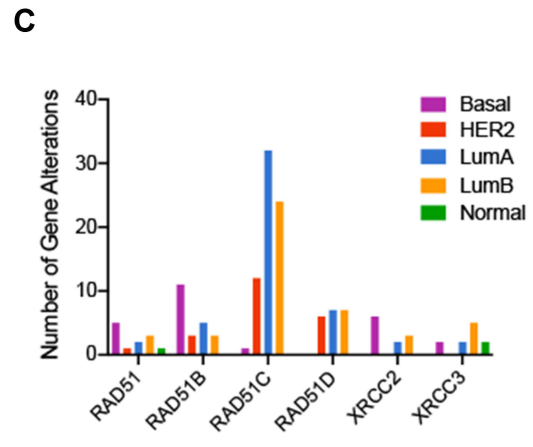
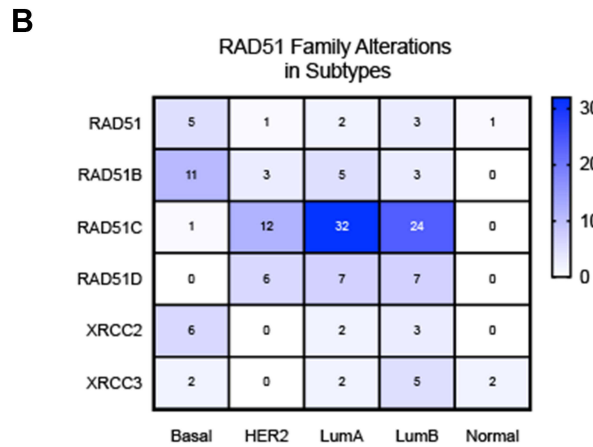
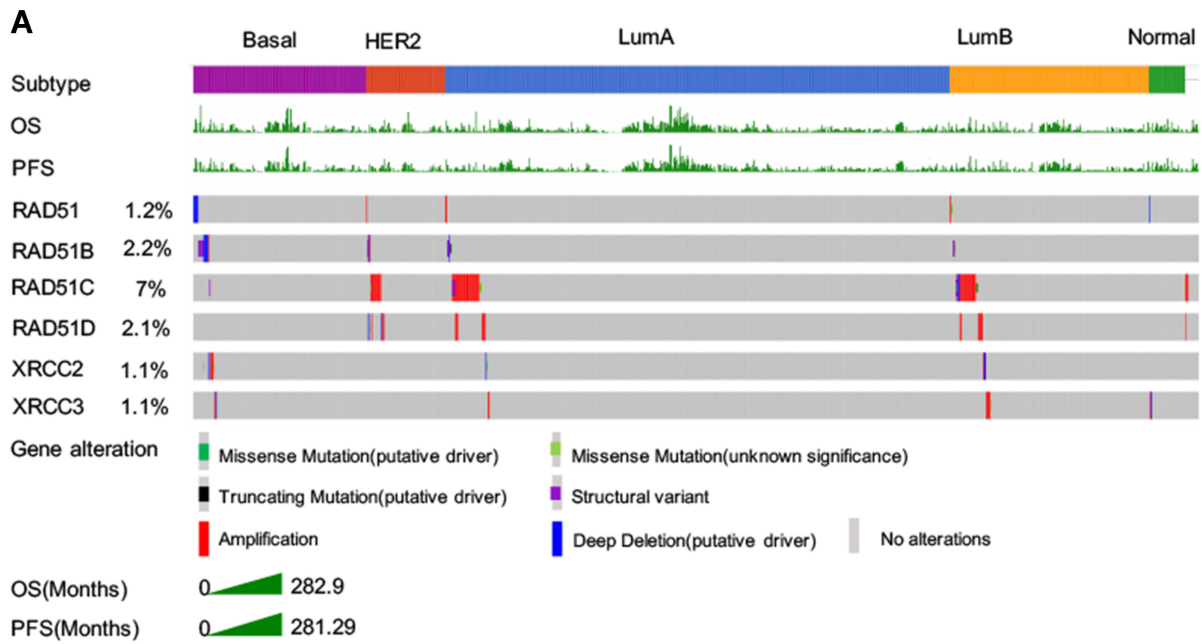


Figure 5 The genetic alterations of RAD51 family members and their association with OS in breast cancer patients. The schematic diagrams (A) depicted the proportions and types of genetic alterations in breast cancer and its related subtypes, respectively. The number of RAD51 family alterations (B and C) in different breast cancer subtypes. The proportions of altered and unaltered samples (D) in different breast cancer subtypes. The relationship between RAD51 family gene alterations and OS (E) in breast cancer.

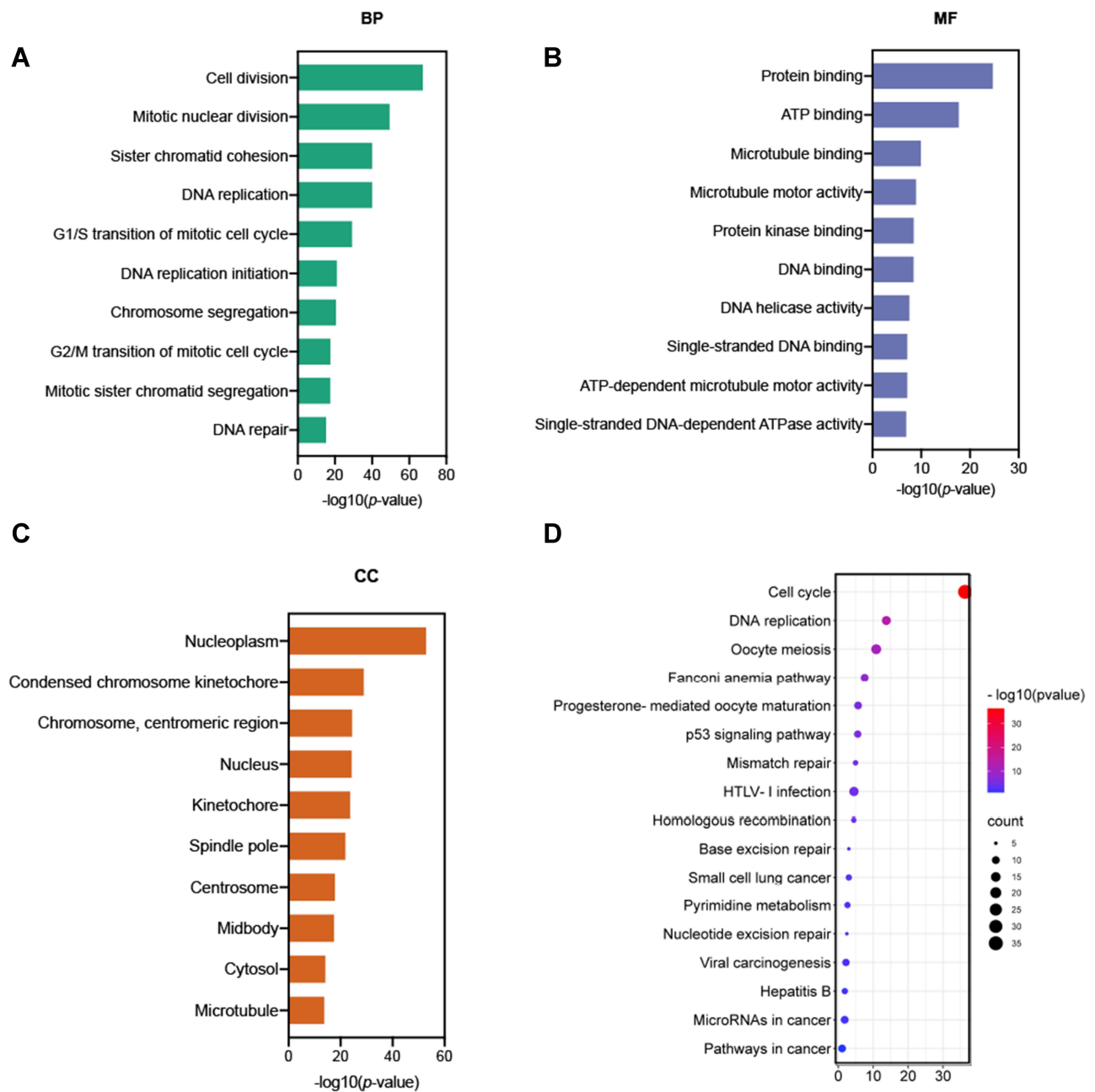


Figure 6 Gene ontology and KEGG analysis of RAD51 family alterations and their co-expressed genes in breast cancer. The analysis predicted gene functions based on three aspects: biological processes (**A**), cellular components (**B**), and molecular functions (**C**). KEGG pathway enrichment bubble plot (**D**) defined the pathways related to the functions of genes significantly associated with RAD51 family mutations.

(nucleoplasm), GO:0000777 (condensed chromosome kinetochore), GO:0000775 (chromosome, centromeric region), GO:0005634 (nucleus), and GO:0000776 (kinetochore) (**Figure 6C**).

KEGG analysis can define the pathways related to the functions of genes significantly associated with RAD51 family mutations. 17 pathways were detected through KEGG analysis (**Figure 6D**). Among these pathways, hsa04110 (Cell cycle), hsa03030 (DNA replication), hsa04114 (Oocyte meiosis), hsa03460 (Fanconi anemia pathway), and hsa04914 (Progesterone-mediated oocyte maturation) were greatly associated with the functions of RAD51 family in breast cancer (**Figure 6D**).

Discussion

The Dysregulation of RAD51 family genes has been reported in multiple cancers. Although the role of RAD51 family members in the tumorigenesis and progression of various cancers has been partially investigated, further bioinformatics analysis of breast cancer has yet to be carried out. Our study is the first to explore the mRNA expression, mutations, and prognostic values of different RAD51 family members in breast cancer. We expect that our research will contribute to develop novel diagnostic biomarkers and improve treatment options for breast cancer patients.

RAD51, as the key enzyme for homologous recombination, was elevated in a wide range of different tumor cell lines compared with normal controls by using immunofluorescence staining.^{15,16} In addition, Maacke et al indicated that RAD51 overexpression was detected in 66% of human pancreatic adenocarcinoma samples. The perturbation of RAD51 level was associated with the malignant characteristics of pancreatic cancer.¹⁷ The overexpression of RAD51 was related to the histological grade of breast cancer and contributed to the pathogenesis of breast cancer.¹⁸ In our research, we found that RAD51 mRNA expression was increased in breast cancer, and related to breast cancer staging. Highly expressed RAD51 led to a decrease in OS and RFS, which was consistent with the role of RAD51 as an oncogene in breast cancer. Previous data disclosed that wild-type TP53 could transcriptionally inhibit RAD51 to repress the HR process. The TP53 mutants led to impaired RAD51 repression, thereby inducing malignant transformation.^{19,20} Interestingly, we detected that the RAD51 gene maintained higher expression in TP53-mutant breast cancer compared with TP53 wild-type cancer, which might be related to the impaired RAD51 inhibition caused by the TP53 mutants.

RAD51B, as a human RAD51 homolog, was mapped to human chromosome 14q23-q24.2 and has been shown to play a role in maintaining chromosome integrity and sensing DNA damage.²¹ Deleterious variants of RAD51B have been involved in breast and ovarian cancer predisposition.²² In lung cancer, the univariate analysis identified that RAD51B overexpression was correlated with a better prognosis, while RAD51B mRNA expression was increased in gastric cancer compared to that of matched normal tissues. A high level of RAD51B protein was correlated with advanced gastric cancer staging and poor overall survival.^{23,24} However, the prognostic role of RAD51B in breast cancer remains to be investigated. To our knowledge, our study is the first to explore the correlation between RAD51B and the prognosis of breast cancer. We suggest that high levels of RAD51B may predict a preferable prognosis for breast cancer patients. Recent literature reported that RAD51C was considered to be a new breast cancer susceptibility gene in patients with breast and ovarian cancer.⁸ Kuznetsov et al provided the first evidence that RAD51C functioned as a TP53-dependent tumor suppressor gene through conditional knockout experiments in mice.²⁵ Our research has presented consistent results that RAD51C might exert a tumor suppressor effect in breast cancer. Also, RAD51C displayed the highest genetic variation rate of 7%. Current researches on RAD51D mainly focus on its role as a susceptibility gene.⁶ As far as we know, there is still a lack of research focusing on its related clinical features and prognosis in breast cancer. Our analysis of the RFS data indicated that a high level of RAD51D was associated with a favorable prognosis.

XRCC2 can form a complex with other RAD51 paralogs (RAD51B, RAD51C, RAD51D) to facilitate the HR repair process. Researches on the role of XRCC2 expression and its association with numerous types of cancer are limited.²⁶ The loss of XRCC2 led to tumorigenesis in the brain, which suggested that XRCC2 might act as a tumor suppressor.²⁶ Bashir et al confirmed that the expression of XRCC2 was downregulated in breast cancer samples compared with normal breast tissues. Decreased expression of XRCC2 was associated with lymph node and metastasis status.²⁷ However, in colorectal cancer, Xu reported that a high XRCC2 level was assessed in primary colorectal cancer tissues, and XRCC2 expression was related to TNM stage.²⁸ Our findings raised the possibility that XRCC2 might be a tumor suppressor in breast cancer. By using OncoPrint analysis, XRCC2 expression was significantly down-regulated in breast cancer. Moreover, high levels of XRCC2 were related to reduced RFS. XRCC3, one of the DNA repair genes, has been of considerable interest as a candidate susceptibility gene for various neoplasms.^{6,29} In addition, XRCC3-deficient cells were more sensitive to DNA damaging agents by inhibition of HR and increases in chromosomal instability.^{30,31} In our study, high XRCC3 expression was related to poor OS data, suggesting that XRCC3 might have an oncogenic role rather than a tumor suppressor role in breast cancer.

Conclusions

In conclusion, we systematically analyzed the transcriptional profile, molecular functions, prognostic value, and genetic alterations of RAD51 family genes in breast cancer, which provides a thorough understanding of the RAD51 family. Our findings indicated that high RAD51 and XRCC3 mRNA levels might play oncogenic roles in breast cancer. Additionally, we suggested that RAD51B/RAD51C/RAD51D/XRCC2 could be the potential prognostic factors for the improvement of breast cancer survival. Our research might provide clues and directions to develop the biomarkers or therapeutic targets of RAD51 family members in breast cancer. However, this study has some limitations. Firstly, all analyzed data originated from different online databases, which might lead to background heterogeneity. Secondly, we did not perform experiments to verify the results obtained from bioinformatics analysis. Further prospective experiments should be conducted to verify our results and explore underlying molecular mechanisms.

Abbreviations

BP, biological processes; CC, cellular components; DSBs, double-strand breaks; GO, gene ontology; GO, gene ontology; GWAS, genome-wide association study; HR, homologous recombination; KM, Kaplan–Meier; KEGG, Kyoto Encyclopedia of Genes and Genomes; MF, molecular functions; NHEJ, nonhomologous end-joining; OS, overall survival; RFS, relapse free survival.

Data Sharing Statement

All data generated during this study are included in this published article. The datasets generated in the current study are available in the OncoPrint, UALCAN, GEPIA, Kaplan–Meier (KM) Plotter, cBioPortal databases.

Ethics Statement

This study was approved by the Academic Committee of Soochow University and conducted according to the principles expressed in the Declaration of Helsinki. All the data were retrieved from online databases and written informed consent had already been obtained.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declared that they have no conflicts of interest to this work.

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