Original Research Article

Prognostic Role of DNA Damage Response Genes Mutations and their Association With the Sensitivity of Olaparib in Prostate Cancer Patients

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Abstract

Objective: Evidence shows that gene mutation is a significant proportion of genetic factors associated with prostate cancer. The DNA damage response (DDR) is a signal cascade network that aims to maintain genomic integrity in cells. This comprehensive study was performed to determine the link between different DNA damage response gene mutations and prostate cancer.

Materials and methods: A systematic literature search was performed using PubMed, Web of Science, and Embase. Papers published up to February 1, 2022 were retrieved. The DDR gene mutations associated with prostate cancer were identified by referring to relevant research and review articles. Data of prostate cancer patients from multiple PCa cohorts were obtained from cBioPortal. The OR or HR and 95% CIs were calculated using both fixed-effects models (FEMs) and random-effects models (REMs).

Results: Seventy-four studies were included in this research, and the frequency of 13 DDR genes was examined. Through the analysis of 33 articles that focused on the risk estimates of DDR genes between normal people and PCa patients, DDR genes were found to be more common in prostate cancer patients (OR = 3.6293 95% CI [2.4992; 5.2705]). Also, patients in the mutated group had a worse OS and DFS outcome than those in the unmutated group ($P < .05$). Of the 13 DDR genes, the frequency of 9 DDR genes in prostate cancer was less than 1%, and despite differences in race, *BRCA2* was the potential gene with the highest frequency (REM Frequency = .0400, 95% CI .0324 - .0541). The findings suggest that mutations in genes such as *ATR, BLM,* and *MLH1* in PCa patients may increase the sensitivity of Olaparib, a PARP inhibitor.

Conclusion: These results demonstrate that mutation in any DDR pathway results in a poor prognosis for PCa patients. Furthermore, mutations in *ATR, BLM,* and *MLH1* or the expression of *POLR2L, PMS1, FANCE,* and other genes significantly influence Olaparib sensitivity, which may be underlying therapeutic targets in the future.

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Introduction

Prostate cancer is the most common malignant tumor with the highest number of confirmed cases and the second-highest number of fatal patients after lung cancer in American males. In the United States, an estimated 268 490 new cases will be diagnosed in 2022, with 34 500 men dying as a result of the disease.[1] Urologists and academics are focusing on how to detect prostate cancer early and provide accurate and effective treatment. The genetic susceptibility of malignant tumors is receiving increasing attention these days. Cancers such as breast, ovarian, colorectal, and kidney cancer have all been linked to genetic factors. Recent data show that approximately 10% of patients with advanced prostate cancer may have a well-characterized tumor suppressor gene mutation.[2] Prostate cancer occurrence may also be linked to genetic factors.[3,4] For instance, studies have shown that high-risk genetic factors cause 8% of prostate cancer.[5] The proportion of prostate cancer variation by germline genetics is about 58% in prostate cancer patients.[6]

So far, genome-wide studies have identified more than 100 common mutations in prostate cancer patients, which account for a significant portion of the genetic factors underlying prostate cancer, including mutations in DNA damage repair genes.[7-10] Genomic DNA is frequently harmed by a variety of internal and external factors such as double-strand breaks. Cells have evolved a well-coordinated signal cascade network called DNA damage response (DDR) to maintain genomic integrity, which senses and transmits damage signals to effector proteins and induces cell responses such as cell cycle arrest, DNA repair pathway activation, and cell death, and many genes are involved, including *BRCA, ATM,* and *CHEK2*.[11] Because cancer cells frequently have specific abnormalities in DNA damage response, several treatment strategies based on this discovery have been concerned and developed, for example, in combination with DNA damage drugs to enhance the ability to kill cancer cells, or as a single drug to treat cancer with DNA damage repair defects. One of the most notable examples is the killing effect of poly ADP ribose polymerase (PARP) inhibitor on *BRCA1* or *BRCA2* deficient tumors, which takes advantage of the defects of DNA repair of cancer cells.[12]

PARP is an enzyme found in our cells which helps damaged cells to repair themselves. As a targeted cancer drug, PARP inhibitors (PARPi) stop the PARP from doing its repair work in cancer cells. Although PARPi such as Olaparib and Rucaparib has been developed for cancer patients with DDR gene mutation, research on the relationship between prostate cancer and DDR genes mutations is still in infancy. Owing to the variability in research design, target genes, and researches involved in this field, there are only a few systematic reviews on the relationship between the frequency of different subtypes of DDR genes mutations and their prognosis in prostate cancer patients,[13,14] and no meta-analysis on the association of different subtypes of DDR gene mutations with prostate cancer risk and frequency. Furthermore, despite a few meta-analyses focusing on the high-incidence mutation genes such as *BRCA1/2*, there are subtle differences in the results.[15,16]

Hence, it is imperative to undertake a comprehensive analysis of the relationship between DDR gene mutations and prostate cancer. We examined several genes associated with PCa DDR, including *ATM, BRCA1, BRCA2, BRIP1, CHEK2, MUTYH, MSH2, MSH6, NBN, PALB2, PMS2, RAD51D,* and *TP53*. The present study has gathered as many original studies as possible for analysis, which can provide more detailed and credible data support for the incidence of prostate cancer in DDR gene mutation carriers and the frequency of DDR genes mutations in PCa patients.[17]

Materials and Methods

Literature Search

We consulted relevant research and review articles for the most commonly identified DDR gene mutations in PCa patients. Furthermore, we deleted the DDR genes that few studies focused on.[18,19] On February 1, 2022, we conducted searches in PubMed, Web of Science, and Embase using the search string (*BRCA1*) OR (*CHEK2*)) OR (*BRCA2*)) OR (*ATM*)) OR (*BARD1*)) OR (*BRIP1*)) OR (*CHEK1*)) OR (*PALB2*)) OR (*RAD51D*)) OR (*RAD51B*)) OR (*RAD51C*)) OR (*NBN*)) OR (*MLH1*)) OR (*MSH2*)) OR (*MSH6*)) OR (*PMS2*)) OR (DDR)) OR (DNA damage response) AND (PCa) OR (prostate cancer)). We were left with 2432 potentially relevant articles after removing duplicates. At least 2 of us (Xinglin Chen, Xu Zhang) independently screened the titles and abstracts of retrieved articles. This meta-analysis was conducted in accordance with the guidelines for systematic reviews and meta-analysis preferred reporting items.[20] In addition, our study was registered with INPLASY, number INPLASY2021120095.

Study Selection

The following modified PICOS were used to guide study eligibility screening: (1) participants: human adult subjects (age >18) with DDR gene mutations; (2) intervention: none; (3) comparisons: prostate cancer patients vs the general

population, prostate cancer patients with DDR gene mutations vs those without DDR gene mutations; (4) outcomes: frequency (number of DDR gene mutation carriers among prostate cancer patients), ratio (with or without DDR genes between prostate cancer patients); (5) study design: observational studies; (6) only prostate cancer were included, other cancers and other prostate diseases were excluded. DDR gene mutations included in our analysis were pathogenic, deleterious (frameshift insertion, deletion, nonsense mutation, or known pathogenic splice-site alteration), truncation, or assumed loss of function (in the pedigree analysis). Studies without explicit mention of clinical significance but with data on the specific nucleotide change were included if the variants were defined as pathogenic in ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/), a public archive of relationships among sequence variation and human phenotype. We also excluded editorials, letters, commentaries, conference abstracts, and review papers, as well as publications reporting on prostate diseases other than prostate cancer, studies with duplicate participants, and studies with insufficient data to allow calculations.

Data Extraction

Four reviewers (Xinglin Chen, Xiaohan Ren, Xu Zhang, and Yuang Wei) independently screened article titles and abstracts for eligibility to reduce bias and improve reliability. Data were extracted using a predeveloped worksheet: author; publication date; study design; mutation type; study location; population; description of cases and, as applicable, controls (eg, number, recruitment method, matching, etc.); age and gender of subjects; estimates of risk, frequency, or survival with corresponding 95% confidence intervals (95% CI) or relevant data to calculate such. If more information was required, the authors were contacted. Disagreement was resolved by consensus.

Quality Assessment

Four reviewers (Xinglin Chen, Xiaohan Ren, Xu Zhang, Guangyao Li) independently assessed the quality of studies using the Newcastle-Ottawa Scale (NOS), which consists of 8 items covering 3 domains: study group selection, exposure and outcome determination, and group comparability. The ratings are based on a five-star scale, with a maximum score of 9. Studies with 1 to 3 stars are considered low quality, studies with 4 to 6 stars are considered moderate quality, and studies with 7 to 9 stars are considered high quality.

Outcome Measures

We examined several genes associated with PCa DDR, including *ATM, BRCA1, BRCA2, BRIP1, CHEK2, MUTYH, MSH2, MSH6, NBN, PALB2, PMS2, RAD51D,* and *TP53*. The mutation frequency of each gene in prostate cancer patients were measured, and the frequency and 95% CI were calculated directly from the data presented in this article.

Open-Access Data Acquisition

cBioPortal (cBio Cancer Genomics Portal, https://www.cbioportal.org/) was used to obtain data of the expression, mutation, and survival data of patients from multiple PCa cohorts. As a public resource project, the cBioProtal integrated multidimensional cancer genomics data from over 5000 tumor samples from 20 cancer studies, which could assist researchers in exploring genomic information in cancers intuitively.[17] The drug sensitivity data were obtained from the website of the Genomics of Drug Sensitivity in Cancer (GDSC) project, which is the l most comprehensive open-access resource for drug sensitivity in cancer cells and molecular markers of drug response.[18]

Data Synthesis and Analysis

All statistical analyses were performed in the R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org) and RevMan v.5.0 software (Cochrane Collaboration, Oxford, UK). Fixed effects models (FEMs) and random effects models (REMs) were both fitted to determine which model types were best suited to the data. Heterogeneity was assessed by the Q test and the I2 statistic. Statistical significance was set at a P-value <.05. Publication bias was assessed using funnel plots for direct comparisons with 10 or more studies. Sensitivity analysis was performed to assess the influence of individual studies on the summary effect estimate.

Results

Search Results

The database search yielded 2208 PubMed results, 104 Cochrane results, 4350 Embase results. We discarded 4094 duplicates and removed 1596 studies based on title and abstract screening. Additionally, 177 studies were systematic reviews or case reports, 374 studies did not provide indicators related to exposure outcomes, and 312 studies focused on the related mechanism of the DDR gene. We were unable to obtain the full text of 35 articles despite efforts to contact the investigators in 74 of included studies.[21-94] The frequency of DDR genes assessment was the main objective of the study. Figure 1 summarizes the study selection procedure and search results.

Description of Studies

The included studies were published between 1973 and 2021. A total of 74 studies were included in the meta-analysis. According to the DDR gene Classification of outline, we

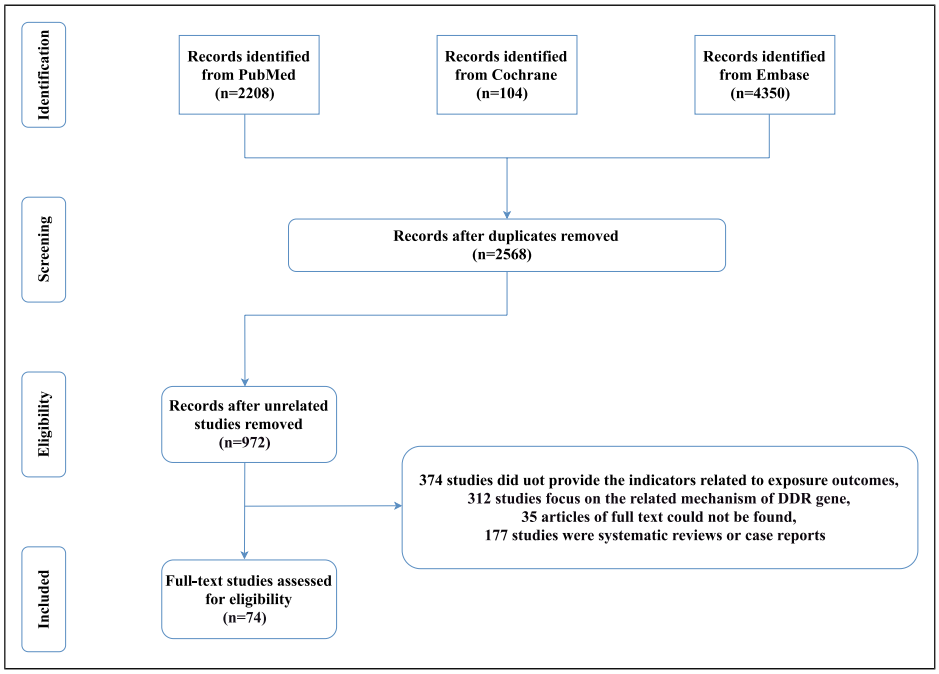

Figure 1. Flow diagram of literature search strategy for the meta-analysis.

assessed 207655 participants. The DDR gene Classification of outline included base excision repair (BER), Fanconi anemia (FA) pathway, Checkpoint factors, homologous recombination (HR), mismatch excision repair (MMR), nucleotide excision repair (NER), non-homologous end-joining (NHEJ), and translesion DNA synthesis (TLS). In our meta-analysis, we looked at the frequency of 13 DDR genes in prostate cancer gene cells, including *ATM, BRCA1, BRCA2, BRIP1, CHEK2, MUTYH, MSH2, MSH6, NBN, PALB2, PMS2, RAD51D,* and *TP53*. 27 studies assessed the frequency of *ATM*, 28 studies evaluated *BRCA1*, 38 studies evaluated *BRCA2*, 6 studies assessed *BRIP1*, 21 studies assessed *CHEK2*, 14 studies assessed *MSH2*, 14 studies assessed *MSH6*, 6 studies assessed *MUTYH*, 9 studies assessed *NBN*, 13 studies assessed *PALB2*, 10 studies assessed *PMS2*, 5 studies assessed *RAD51D*, and 6 studies assessed *TP53*.

The Frequency of Main DNA Damage Response Gene in Prostate Cancer Patients

BRCA2 gene had the highest possibility of occurrence (REM Frequency = .0400, 95% CI .0299 - .0513), whereas *BRIP1* gene had the lowest possibility of occurrence (REM Frequency = .0016, 95% CI .000 - .0046) in PCA patients. The overall results are shown in Figure 2. Furthermore, the mutation frequency of *CHEK2, ATM,* and *MUTYH* in prostate cancer patients was greater than 1%.

We conducted a subgroup analysis of the study and evaluated the frequency of DDR genes in different country PCa patients in order to investigate the causes of heterogeneity; the detailed information is provided below.

The frequency of ATM *gene in prostate cancer patients.* In articles that explored patients with *ATM* gene mutation, 12 studies focused on American PCa patients, and the frequency was .0126, heterogeneity estimates were reduced when participants were selected from the USA (I^2 = 51%) (Figure 3A), *ATM* gene mutations occurred in prostate cancer for all different races. Sensitivity analyses demonstrated that the the removal of Momozawa study influenced the observed pooled effect size (Figure 5A). The funnel chart revealed a publication bias (Figure 4A).

The frequency of BRCA1 *gene in prostate cancer patients.* The BRCA1 studies demonstrated that the frequency of *BRCA1* genes in prostate cancer patients in the USA was .0070 (95CI .0029 to .0123). Heterogeneity reduced when we conducted subgroup analysis and decreased for the USA subgroup (I^2 = 57%), for all different races, *BRCA1* gene mutations occurred in prostate cancer (Figure 3B). Sensitivity analyses demonstrated that the removal of any of the studies had no material effect on the observed pooled effect size (Figure 5B). The funnel chart showed little publication bias (Figure 4B).

The frequency of BRCA2 *gene in prostate cancer patients.* *BRCA2* gene mutations are also *common* in prostate cancer patients; the results showed that the frequency of *BRCA2* gene in prostate cancer patients in the USA and UK was .041 and .0393, respectively; *BRCA2* gene mutations occur in prostate cancer patients of all different races. Heterogeneity remained high for the USA subgroup (I^2 = 89%) and UK subgroup (I2= 85%) (Figure 3C). Sensitivity

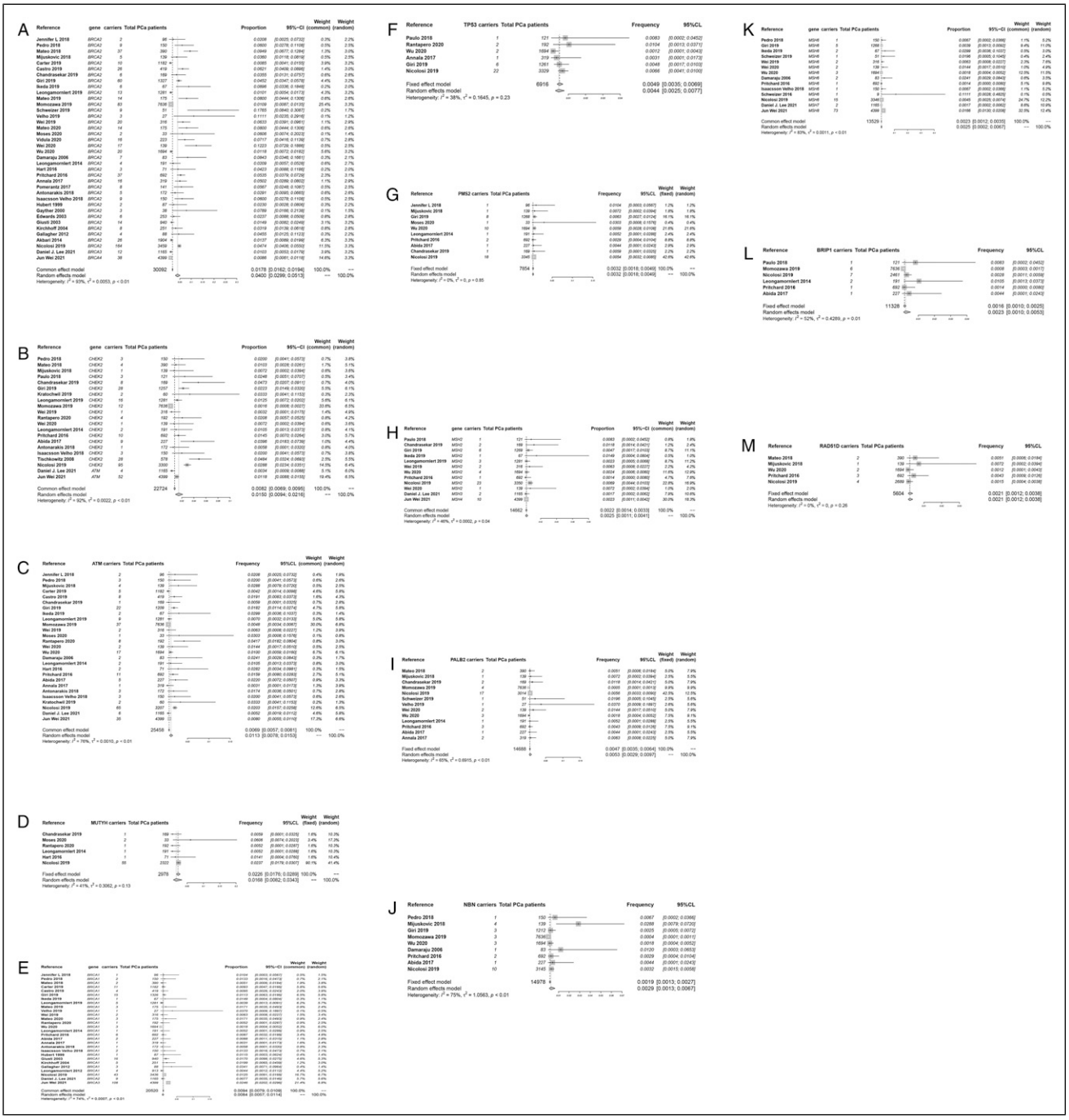

Figure 2. Forest plots of the DDR genes mutation rate in patients with prostate cancer (A) BRCA2 (B) CHEK2 (C) ATM (D) MUTYH (E) BRCA1 (F) TP53 (G) PMS2 (H) MSH2 (I) PALB2 (J) NBN (K) MSH6 (L) BRIP1 (M) RAD51D.

analyses demonstrated that the removal of the Momozawa study influenced the observed pooled effect size (Figure 5C). The funnel chart revealed a publication bias (Figure 4C).

The frequency of CHEK2 gene in prostate cancer patients. The subgroup analysis revealed that the frequency of CHEK2 gene mutations in prostate cancer patients in the USA was .0253, and heterogeneity was modestly reduced ($I^2 = 67\%$) across all races (Figure 3D). Sensitivity analyses demonstrated that the removal of the Momozawa study influenced the observed pooled effect size (Figure 5D). The funnel chart showed a publication bias (Figure 4D).

The frequency of MSH2 gene in prostate cancer patients. The frequency of MSH2 genes in prostate cancer patients varied by country, ranging from .0022 to .0083.

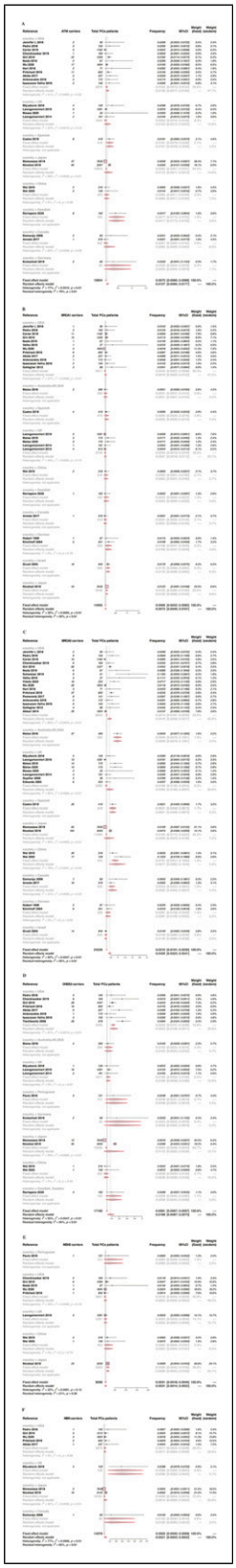

Figure 3. Forest plots of the 6 DNA damage response genes mutation rate in patients with prostate cancer regarding each country (A) ATM (B) BRCA1 (C) BRCA2 (D) CHEK2 (E) MSH2 (F) NBN.

Subgroup analysis showed that heterogeneity was decreased in the USA subgroup (I^2 = 36%), China subgroup (I^2 = 0%) (Figure 3E). Sensitivity analyses demonstrated that removing Nicolosi's study reduced the observed frequency to .0020 (Figure 5E). The funnel chart demonstrated that there is no publication bias (Figure 4E).

The frequency of NBN gene in prostate cancer patients. The subgroup analysis revealed that the frequency of NBN genes in prostate cancer patients from the USA was .0017, and heterogeneity decreased when subgroup analysis was performed (I^2 = 0%), and NBN genes mutations were widely observed across all races (Figure 3F). Sensitivity analyses revealed that when the Momozawa study was removed, the observed frequency increased to .0017 (Figure 5F). The funnel chart demonstrated that there is no publication bias (Figure 4F).

The Risk Estimates of DNA Damage Response Genes Between Normal People and PCa Patients

A total of 33 articles compared the risk estimates of DDR genes in healthy subjects and PCa patients; DDR genes are more likely to be found in prostate patients than in healthy subjects (OR = 3.6293 95% CI [2.4992; 5.2705]). Subgroup analysis revealed that the BRCA2 subgroup exhibited high heterogeneity; however, when BRCA2 related research was excluded, the heterogeneity decreased from 74% to 0%. Subgroups analyses also revealed that the incidence of BRCA2 in prostate cancer patients was significantly higher than in healthy subjects (OR = 6.4010 95% CI [2.6177; 15.6524]) (Figure 6A). The funnel chart demonstrates that the results had a certain publication bias (Figure 6C). Sensitivity analyses demonstrated that the removal of any studies had no significant effect on the observed pooled effect size (Figure 6B).

The Association of DNA Damage Response With Patient Survival

As of October 2020, cBioportal had a total of 22 PCa cohorts, 3 of which are TCGA cohorts (TCGA, Cell 2015; TCGA, Firehose Legacy; TCGA, PanCancer Atlas). Finally, with the exception of TCGA Cell 2015 and PanCancer Atlas, we included 20 PCa cohorts in our survival analysis. The findings showed that patients in the mutated group had a worse prognosis (OS and DFS) than those in the unmutated group in multiple DDR pathways (Figure 7A, Base Excision Repair; Figure 7B, Checkpoints factor; Figure 7C, Fanconi anemia pathway; Figure 7D, Homologous recombination; Figure 7E, Homologous

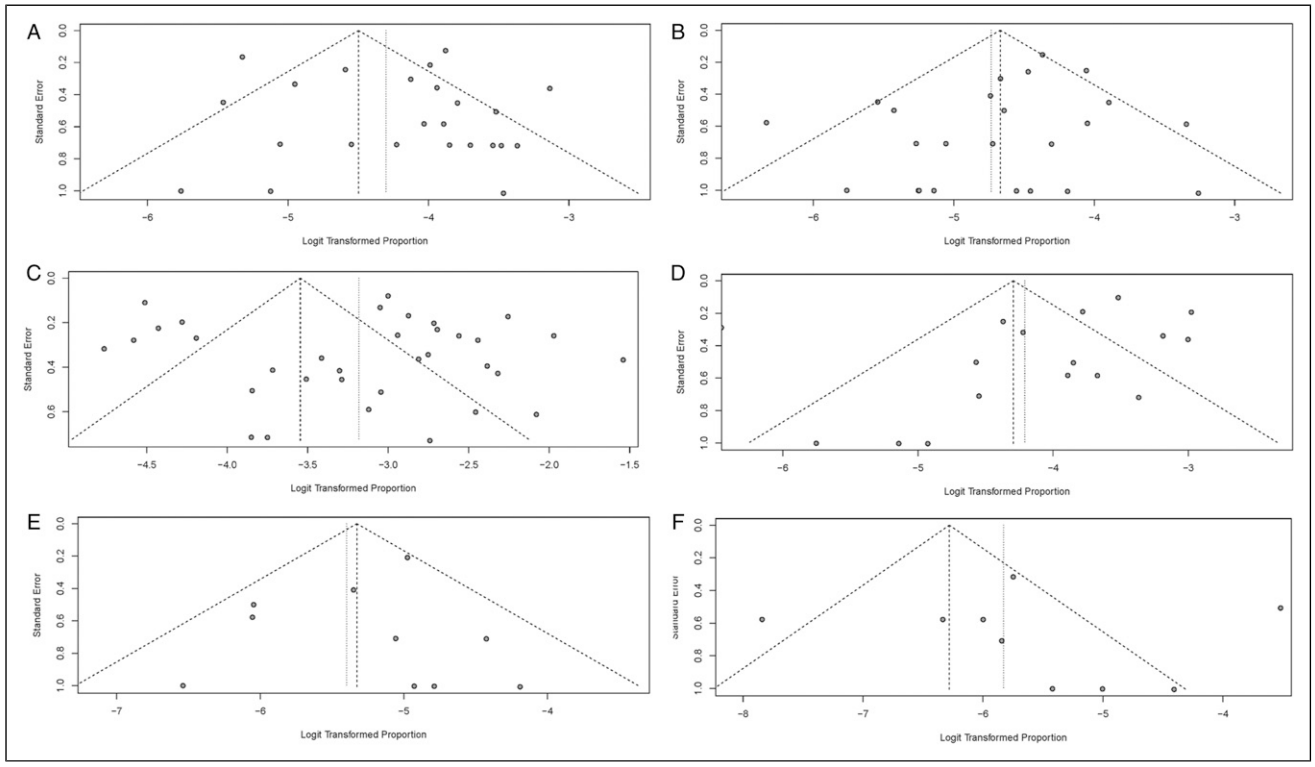

Figure 4. Funnel plots of effect estimates on DNA damage response genes mutation rate in patients with prostate cancer (A) ATM (B) BRCA1 (C) BRCA2 (D) CHEK2 (E) MSH2 (F) NBN.

recombination repair; Figure 7F, Mismatch Repair; Figure 7G, Nucleotide Excision Repair; Figure 7H, Non-homologous End-joining; Figure 7I, Translesion DNA synthesis factor).

The Association of DNA Damage Response Genes With Olaparib Sensitivity

We first investigated the IC50 difference of Olaparib in multiple cancer tissues (Figure 8A) and the relationship between some DDR genes and Olaparib sensitivity by interacting with the website. The findings revealed that the mutation population of ATR, BLM, and MLH1 appears more sensitive to Olaparib (Figure 8B). Moreover, unlike POLR2L, tumor cells with high expression of PMS1, FANCE, WRN, RAD54L2, HMGB1, and DNTT are resistant to Olaparib (Figure 8C).

The Association of DNA Damage Response Genes With Rucaparib Sensitivity

Similarly, the IC50 overview of Rucaparib in multiple cancer tissues was shown in Figure 9A. We found that mutation population of MLL2 appears more sensitive to Rucaparib (Figure 9B).

Discussion

Despite the high long-term survival of localized prostate cancer, the therapeutic effect of metastatic prostate cancer is still insufficient, even following combined treatment. Recent evidence shows that DDR-related gene mutation is tightly associated with PCa progression, particularly in metastatic castration-resistant prostate cancer (mCRPC).[95] Currently, approximately 20-25% of mCRPC patients have germline or somatic DDR gene mutations, and this defect has been shown to influence PCa cell sensitivity to PARP.[96] As a result, it is highly imperative to investigate the underlying relationship between DDR genes and PCa patient prognosis.

We systematically investigated the role of DDR genes in PCa progression and prognosis using integrated meta and bioinformatics analysis. In our analysis, we found that DDR gene mutations, particularly BRCA1, were more common in tumor patients than in healthy males and that patients with DDR gene mutations had poorer OS. Moreover, some DDR genes were linked to the sensitivity of Olaparib, a PARP inhibitor approved for treating advanced ovarian cancer patients with BRCA gene deficiency. In addition, Olaparib is now approved for homologous recombination repair mutated mCRPC as well.[97]

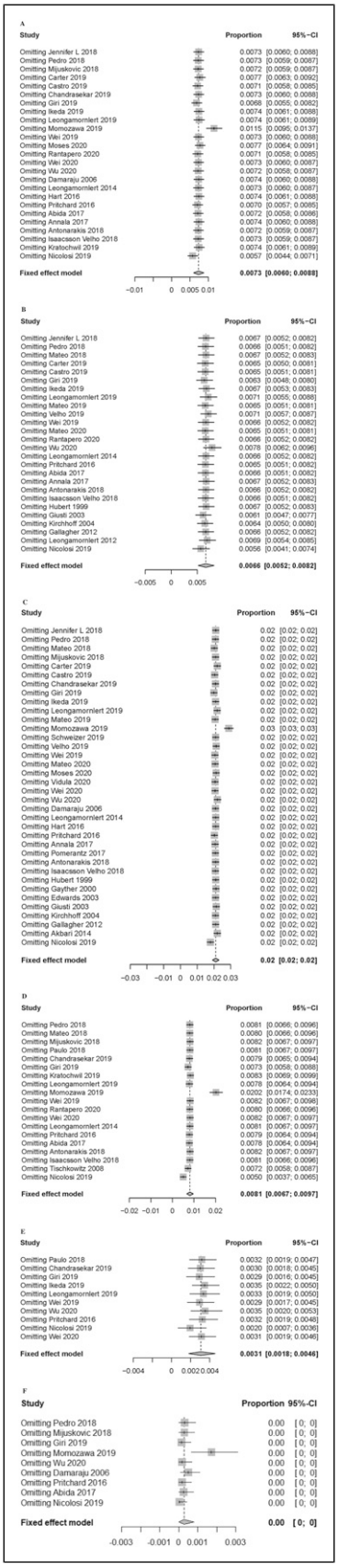

Figure 5. Forest plots of the key factors in each analysis rate (A) ATM (B) BRCA1 (C) BRCA2 (D) CHEK2 (E) MSH2 (F) NBN.

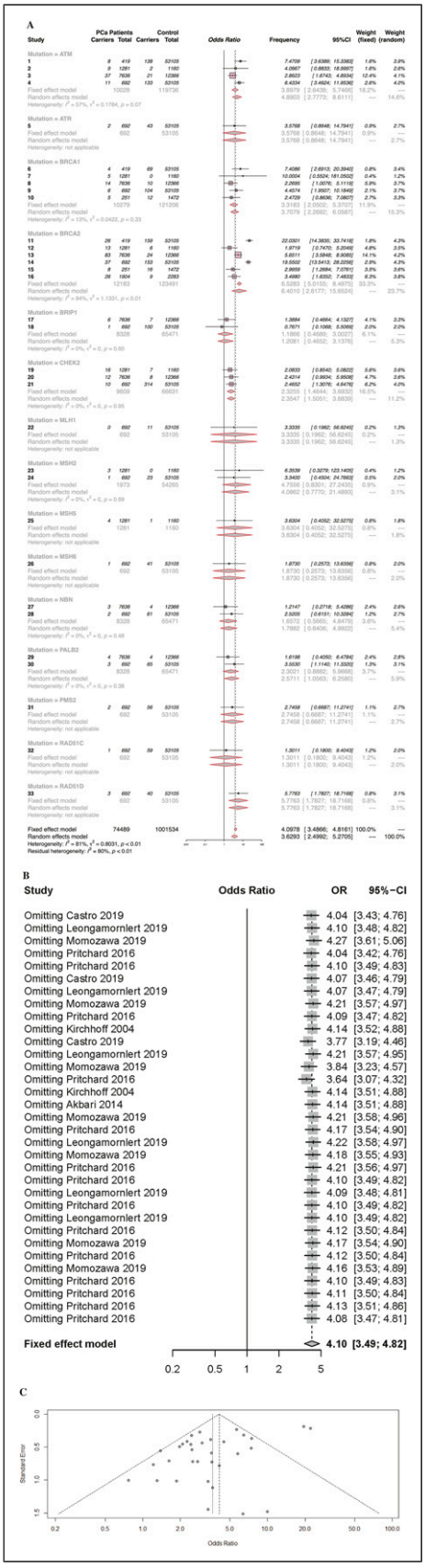

Figure 6. (A) Forest plots of the DNA damage response genes mutation rate between patients with prostate cancer and normal population (B) Forest plots performed the Key factors (C) Funnel plots performed effect estimates of each study.

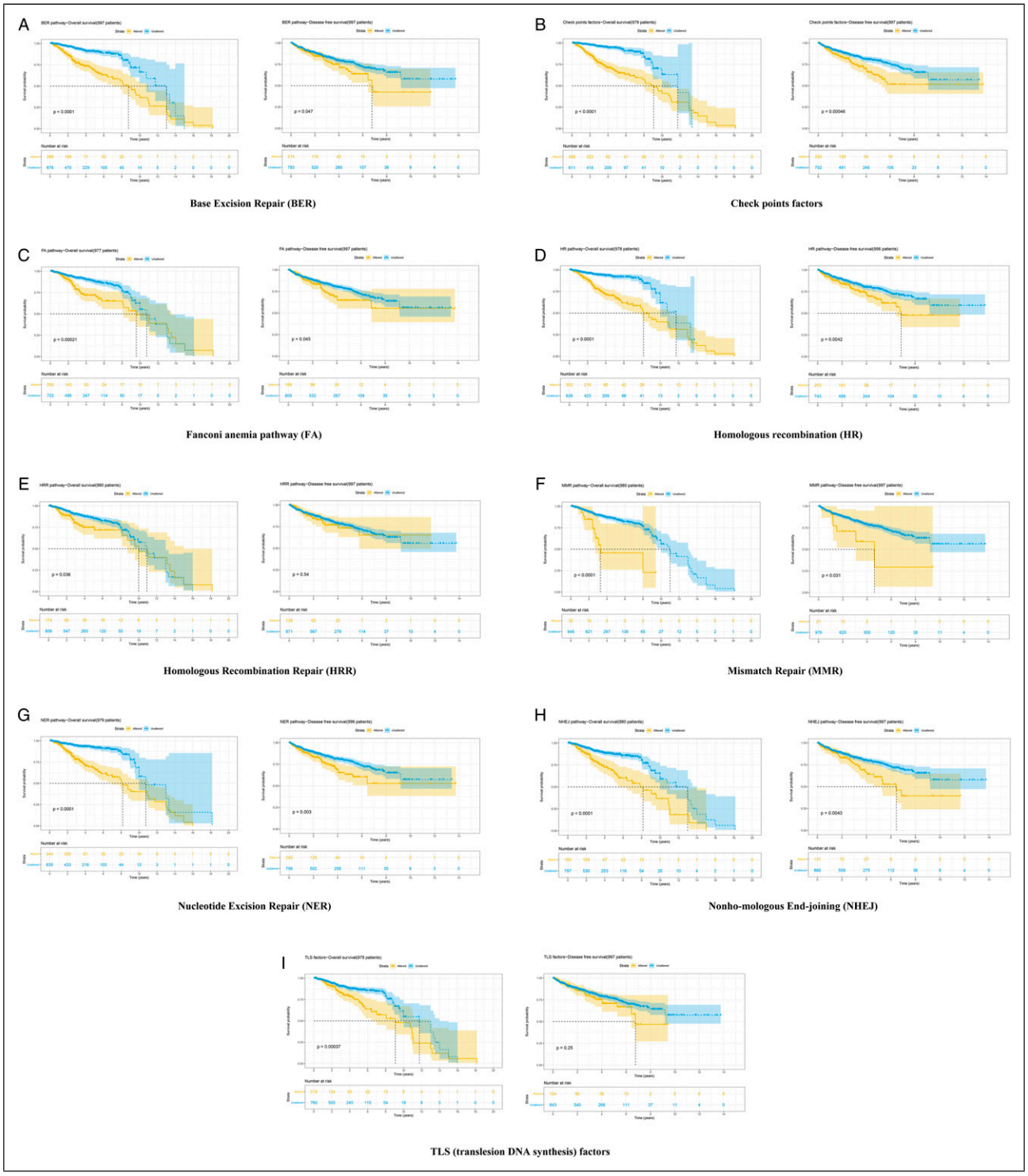

Figure 7. Kaplan-Meier curves showing that the patients with DNA damage response mutations may have a worse prognosis (A) BER pathway (B) Checkpoint factors (C) FA pathway (D) HR pathway (E) HRR pathway (F) MMR pathway (G) NER pathway (H) NHEJ pathway (I) TLS pathway.

Findings from the present investigation revealed that the frequency of mutations in BRCA2 was the highest of any DDR genes, accounting for approximately 3.98% of all mutations. We hypothesize that the prevalence of BRCA2 mutations in the population is unknown; meanwhile, when compared to healthy males, PCa patients may have a sixfold increase in BRCA2 mutation frequency. This result corroborates the findings of a large body of research on DDR

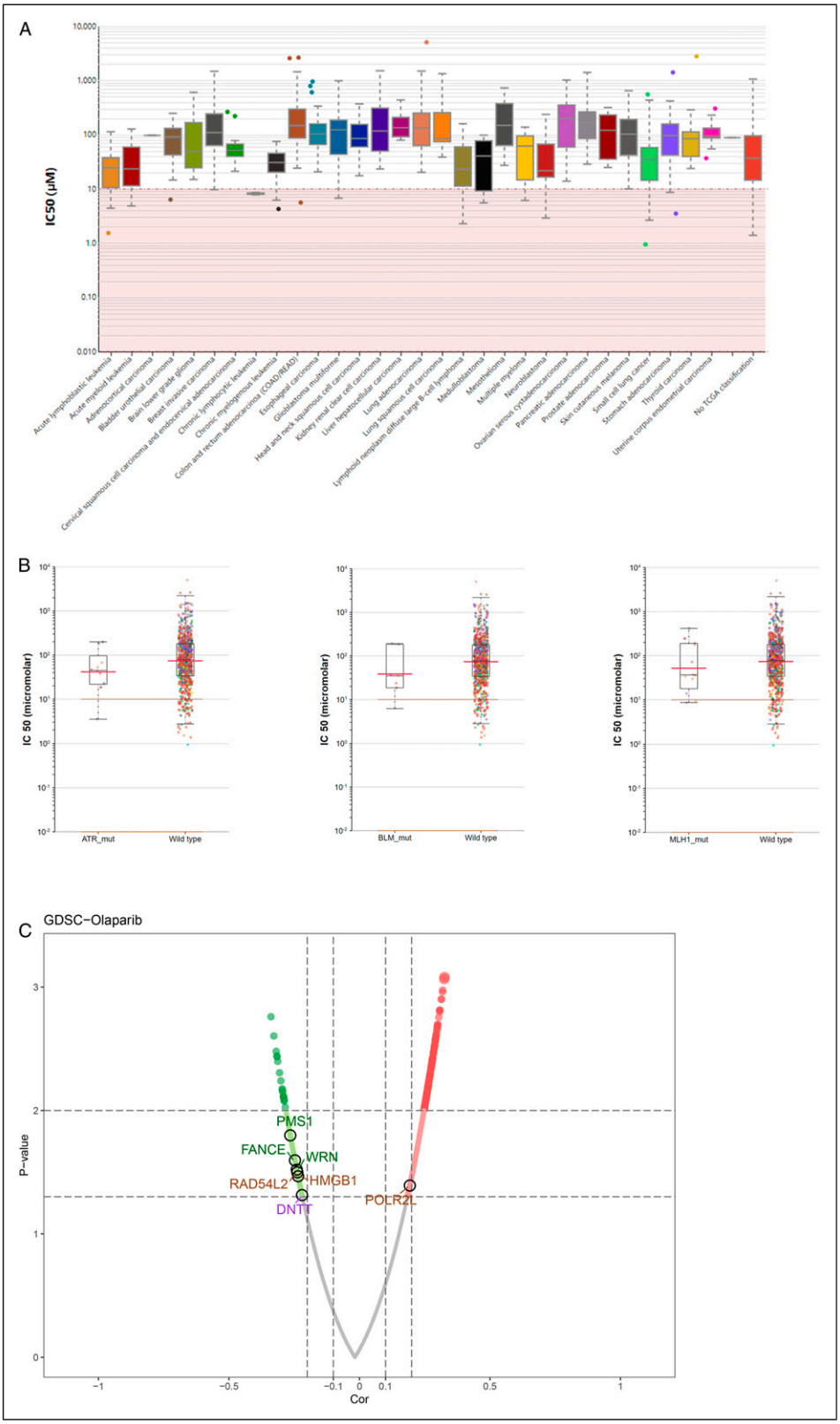

Figure 8. (A) The IC50 of Olaparib in multiple cancers (B) The mutations of ATR, BLM, and MLH1 could improve the sensitivity of patients to Olaparib (C) The volcano plot of the association between gene expression with Olaparib sensibility. The blue dot could decrease the sensibility of Olaparib and the red dot could increase the sensibility of Olaparib.

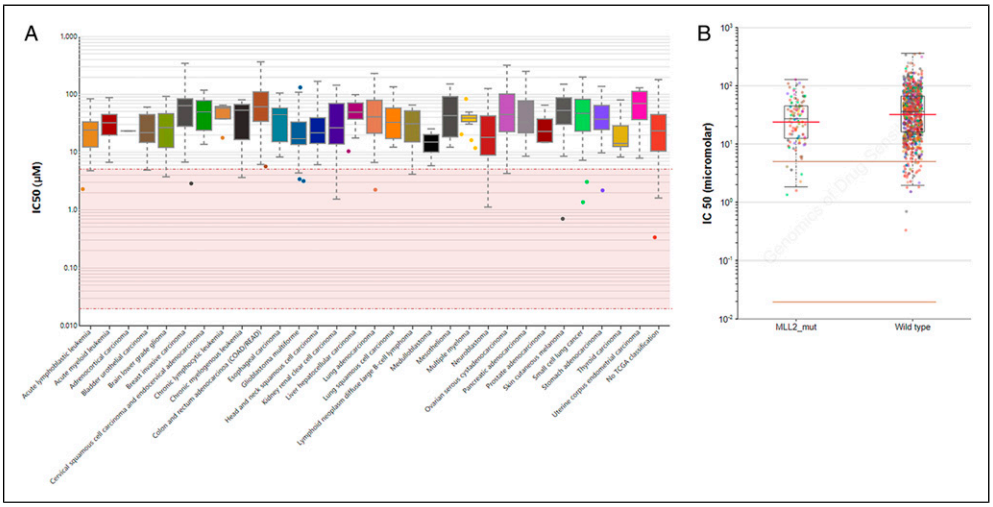

Figure 9. (A) The IC50 of rucaparib in multiple cancers (B) The mutations of MLL2 could improve the sensitivity of patients to Olaparib.

genes. For example, Lecarpentier and colleagues demonstrated that BRCA1/2 mutation could increase the risk of breast and prostate cancer in men based on the genotyping data from 1989 males with a BRCA1/2 mutation. Furthermore, Patel and colleagues analyzed a large sample data of 6333 patients and found that specific BRCA2 mutations may be associated with a higher risk of PCa status.[98] Another multicenter study conducted by Bancroft and colleagues found that people with BRCA1/2 mutation have a higher risk of developing PCa in 2481 male cohorts and that this germline mutation could be a useful marker for disease screening.[99] It should be noted that the BRCA2 mutation in PCa patients was also closely related to the sensitivity of platinum chemotherapy and PARP inhibitors, which may be an underlying therapeutic target in PCa.[100] Aside from BRCA1/2, other DDR genes with high mutation rates in the PCa cohort included ATM, CHEK2, and RAD51D. Southey and colleagues concluded that the CHEK2 mutation serves as reliable evidence for PCa risk in African men based on clinical analysis of 22 301 cases and 22 320 controls.[101] Furthermore, in another meta-analysis, researchers assessed the radiation toxicity of PCa using 8 toxicity scores and found that the ATM rs1801516 SNP may be associated with increased toxicity reaction induced by radiation.[102]

We investigated the impact of mutations in the DDR pathway on PCa prognosis, including OS and DFS, using data from the cBioportal website. To the best of our knowledge, this is the first study that comprehensively examined the role of DDR mutation in PCa survival. Nearly all DDR pathway mutations were associated with a poor prognosis. In contrast to normal cells, cancer cells share the trait of genome instability caused by DDR defects. Meanwhile, men with genome instability, particularly shorter telomere lengths in somatic cells, appeared to have a poor prognosis and were more likely to develop PCa.[103] Activation of cancer signaling is thought to increase DNA damage through increased genome instability and cancer progression.[104] In the ATM knockout mice model, Liyanage and colleagues demonstrated that tumor tissue developed in mice had an increased copy of chromosome 15, where the c-Myc is located.[105] Indeed, c-Myc has been implicated in the development and progression of PCa, and these studies established a link between the DDR gene and c-Myc.[106] Undeniably, some DDR genes were rarely found in PCa patients, as such, few studies focused on them. However, based on our findings, any DDR pathway mutation could significantly worsen the prognosis of PCa patients. Subsequently, in clinical practice, it is critical to pay close attention to the disease status of PCa patients with DDR genes mutations.

Two members of the PARP family, PARP1 and PARP2, are known to be the key enzymes in repairing DNA single-strand breaks via the BER pathway. Olaparib, as a PARP inhibitor, can causing strong killing effects in HR-deficient cells by simultaneously blocking these 2 molecules, but not in cells with a normal HR system.[107] Our findings suggest that some DDR genes such as POLR2L, PMS1, FANCE, WRN, and others, may influence Olaparib sensitivity in PCa patients. Similarly, our findings also suggest that the DDR gene MLL2 may influence Rucaparib sensitivity in PCa patients. Patients with different levels of expression of these genes may have different sensitivity to Olaparib or Rucaparib, which could be useful for individualized treatment.

Our study has some limitations despite the high-quality data and rigorous analysis process. First, our meta-analysis had a level of heterogeneity that was not significantly reduced after subgroup analysis. Second, the cBioportal only provides data on patient survival in the DDR mutation and wild groups. If clinical information such as TNM classification, age, and so on had been made public and available, the conclusions would have become more believable. Finally, due to a lack of data, the prognosis analysis of a single DDR gene was not completed, which may have resulted in latent bias.

Conclusion

Following the analysis of large sample data from multiple studies, the highest frequency of BRCA2 mutation was found in the PCa cohort. The mutation of ATM, BRCA1, BRCA2, CHEK2 and RAD51D genes was more common in PCa patients than in healthy males. Furthermore, it should be noted that mutations in any DDR pathway have been linked to a poor prognosis in PCa patients. Intriguingly, we discovered that the expression of POLR2L, PMS1, FANCE, WRN, and other genes was closely related to Olaparib sensitivity, suggesting that these genes may be underlying therapeutic targets in clinical practice.

Appendix

Key of Definitions for Abbreviations

DDR	DNA damage response
ATM	ataxia telangiectasia-mutated gene
BRCA1	breast cancer gene 1
BRCA2	breast cancer gene 2
BRIP1	BRCA1 interacting protein C-terminal helicase 1
CHEK2	checkpoint kinase 2
MUTYH	MutY DNA glycosylase
MSH2	MutS homologue 2
MSH6	MutS homologue 6
NBN	nibrin
PALB2	partner and localizer of BRCA2
PMS2	PMS1 homolog 2
RAD51D	RAD51 paralog D
TP53	tumor protein 53
BER	base excision repair
CHEK	checkpoints factor
FA	fanconi anemia pathway
HR	homologous recombination
HRR	homologous recombination repair
MR	mismatch repair
NER	nucleotide excision repair
NHEJ	nonho-mologous end-joining
TLS	translesion DNA synthesis factor

Authors Contribution

DZ, XX and YW collected the data and performed the meta-analysis. XX and DZ wrote the manuscript. All authors contributed to the article and approved the submitted version.

Declaration of Conflicting Interests

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Ethics Approval and Consent to Participate

Ethical Approval is not applicable for this article.

Consent for Publication

Yes

Availability of Data and Materials

Yes

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