Meta-analysis showing that ERCC1 polymorphism is predictive of osteosarcoma prognosis

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ABSTRACT

To investigate correlations between excision repair cross-complementation group 1 (ERCC1) and 2 (ERCC2) polymorphisms and osteosarcoma prognosis, we conducted a meta-analysis of studies published through October 2016. Studies were identified in the PubMed, ScienceDirect, Springer, and Web of Science databases using preferred reporting items for systematic reviews and meta-analyses (PRISMA). Odds ratios (ORs) or hazard ratios (HRs) and their 95% confidence intervals (CIs) for overall survival (OS), tumor response (TR), and event-free survival (EFS) were estimated. Our meta-analysis included eleven studies in which four SNPs (ERCC1 rs11615 and rs3212986, ERCC2 rs13181 and rs1799793) reportedly associated with osteosarcoma prognosis were investigated. Each of these studies scored > 6 on the Newcastle-Ottawa Scale (NOS). We found that only one SNP, ERCC1 rs11615, correlated with improved OS and TR. The HR of T vs. C for OS was 1.455 (T/C, 95% CI = 1.151–1.839, P = 0.002, I² = 37.80%). The OR of T vs. C for good TR was 0.554 (T/C, 95% CI = 0.437–0.702, P < 0.001, I² = 0%). Few significant outcome was observed in subgroup analyses stratified based on study characteristics with adjustments for potential confounders. Our results suggest that ERCC1 rs11615 CC is associated with a better clinical outcome. This suggests rs11615 may be a useful genetic marker for predicting osteosarcoma prognosis.

INTRODUCTION

Osteosarcoma is one of the most common and aggressive malignant bone tumors, primarily occurring during adolescent growth and in the elderly [1]. Osteosarcoma incidence in adolescents is relatively consistent globally and ranges from 3–4.5 cases per million persons per year [2]. Although osteosarcoma treatment options have improved, patient prognosis remains poor [3]. Multiple genes, including VEGF, GRM4, GSTP1, ABCB1, and key enzymes of the DNA repair system, have been identified as osteosarcoma biomarkers that may predict patient susceptibility and prognosis [4–6].

DNA repair is critical for maintaining DNA stability and integrity, and cell function. The nucleotide excision repair (NER) pathway is responsible for recognizing and excising DNA lesions [7]. Excision repair cross-complementation group 1 (ERCC1) and 2 (ERCC2), located in 19q13.3, are key rate-limiting enzymes in the NER process [8]. ERCC1 and xeroderma pigmentosum group F (XPF) form a heterodimer to catalyze 5′–3′ incisions, while ERCC2 exhibits ATP-dependent DNA helicase activity, inducing apoptosis and basal transcription. Therefore, ERCC polymorphisms may impact DNA repair and cancer development and progression [7, 9]. Several ERCC single nucleotide polymorphisms (SNPs) associated with osteosarcoma prognosis have been reported, including ERCC1 rs11615 (Asn118Asn) and rs3212986, ERCC2 rs13181 and rs1799793] [10–21]. We conducted a systematic review and meta-analysis of ERCC1 and 2 polymorphisms to identify any direct correlations between such polymorphisms and osteosarcoma patient prognosis.
RESULTS

Reference search

The combined search yielded 556 potentially relevant references. References were screened by title, abstract, and full-text (Figure 1). We found 14 studies regarding ERCC polymorphisms, including one meta-analysis and one commentary, both of which were excluded. One study [19] was excluded due to lack of detailed data. Eleven studies met our criteria and were included in the meta-analysis.

Data extraction and reference assessment

Data extracted from the 11 studies are shown in Supplementary Table 1, and primary extracted data are shown in Supplementary Table 2. We encountered several challenges during data extraction. In studies by Yang, et al. and Hao, et al., rs13181 referred to G/A, but was an A/C SNP of ERCC2 according to PubMed dbSNP. Websites of dbSNP of the studied SNPs were provided in Supplementary Table 16. Similarly, in the Hao, et al. study, rs1799793 referred to G/T, but was a G/A SNP of ERCC2 according to PubMed dbSNP. We therefore excluded these rs13181 and rs1799793 studies. Additionally, two rs11615 genotype formats were referred to as T/C and C/T, which was also the case in previous rs11615-related studies, and this issue remains unsettled.

In these 11 studies, we were able to examine tumor response (TR), overall survival (OS), and event-free survival (EFS). TR was categorized as either good (GTR) or poor (PTR). GTR was defined as the extent of tumor necrosis > 90% in histology or response (complete response (CR) and partial response (PR)) as per Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Tumor necrosis < 90% or non-response (stable disease (SD) and progressive disease (PD)) as per RECIST criteria was defined as PTR. If the histological findings and RECIST criteria showed good homogeneity, subgroup analysis would be performed if necessary. RECIST criteria was employed to assess TR only in the studies by Yang, et al. and Liu, et al. Primary and adjusted PTR were only available in the study by Carolina, et al. Therefore, we used crude ORs from other studies so that this study could be included. OS was usually obtained from diagnosis until death by any cause or last follow-up. EFS was usually defined as the period before first relapse and after tumor diagnosis.

Newcastle-Ottawa Scale (NOS) assessments are shown in Table 1. With the aim of evaluating studies more precisely, we added additional clauses to some items. All studies received scores ≥ 6.

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**Figure 1: PRISMA 2009 flow diagram.**
Statistical analysis

Statistical analysis was performed after study assessment and primary data extraction. This study included 1834 osteosarcoma cases. We were unable to merge OS/TR/EFS data extracted from the study by Hattinger, et al. into the pooled analysis, and these data were therefore excluded. Hattinger, et al. found that ERCC1 rs11615 and rs3212986 were not associated with osteosarcoma EFS. Meta-analysis results are shown in Supplementary Table 3, and rs11615 subgroup analysis outcomes are shown in Supplementary Table 4.

Overall survival

For ERCC1 rs11615, no correlation was observed in the pooled outcomes, but high heterogeneity was detected, which may have resulted from the unclear genotype designations discussed above. We observed a strong positive correlation between the C allele and OS in the T/C subgroup. The hazard ratio (HR) of the T vs. C OS model was 1.455 (T/C, 95%CI = 1.151–1.839, P = 0.002, I² = 37.80%). For the ERCC2 rs1799793 G allele and the rs13181 A allele, we observed slightly positive OS trends, but these were not significant. In rs3212986, no significant outcome was observed. OS forest plot for rs11615 subgroup analysis is shown in Figure 2, forest plots for other SNPs are available in Supplementary Figures 4–6.

Tumor response

For ERCC1 rs11615, the C allele was more significant in the T/C subgroup than overall outcomes. The odds ratio (OR) for CC vs. TT was 2.659 (95%CI = 1.554–4.548, P < 0.001, I² = 0.00%). The C/T subgroup showed no significance. For the ERCC2 SNPs, rs1799793 and rs13181, no significance was observed before sensitivity analysis. The rs1799793 A allele might have a better TR than the G allele, and the rs13181 C allele had a better TR than the A allele. No significance was found in rs3212986. GTR forest plot for rs11615 is shown in Figure 3, is revised as forest plots for other SNPs are available in Supplementary Figures 1–3. Differences between PTR and GTR outcomes were not significant.

Event-free survival

All models for the four SNPs about EFS information included ≤ 3 studies. High heterogeneity was observed and could not be eliminated, and no significant outcome differences were found before or after sensitivity analysis.

Subgroup analysis

OS and TR subgroup analyses were performed according to the indexes TR evaluation method, HWE, race, treatment and adjustment of confounding factors of tumor-related variables. From subgroup analyses, no significant difference was observed from overall

Figure 2: Forest plot of rs11615 OS (TC+CC vs. TT).
outcomes. We observed that two assessments for TR, histological assessment and RECIST criteria, could be seen as in a good homogeneity. In subgroup analysis of race, only study by Biason, et al. was included in Caucasian subgroup, thus power of this estimation was limited and further study was needed. Results of subgroup analysis were available in Supplementary Tables 5–13.

Heterogeneity

No models exhibited high heterogeneity and most of the heterogeneity could be eliminated. In 12+22 vs. 11 and 1 vs. 2, heterogeneity likely stemmed from crude ORs merged with adjusted ORs, or from unclear genotype formats like ERCC1 rs11615. However heterogeneity was mainly concentrated in several studies, especially that of Sun, et al. We were unable to determine why these studies provided such large heterogeneity. Sensitivity analyses for the rs11615 OS is shown in Figure 4, plots for other SNPs are available in Supplementary Figures 10–12.

Publication bias

Begg’s tests did not show significance for any SNPs with any outcomes, and Egger’s test found significance for TR only in some models (Figure 5 and Supplementary Figures 7–9). This may have been because TR was not estimated in some studies, and thus sample size was reduced.

DISCUSSION

ERCCs are key enzymes of the NER system, which monitors and repairs DNA damage caused by endogenous and exogenous factors, and are vital in maintaining genome stability and cellular functions [25]. Some of ERCC polymorphisms negatively impact NER system function, promoting tumor development and progression [26]. We conducted an updated systematic review and meta-analysis to investigate associations between ERCC1 and 2 polymorphisms and osteosarcoma prognosis. Of the four SNPs studied, only ERCC1 rs11615 was associated with improved patient OS and TR. No significant outcomes were associated with ERCC2 rs13181 or rs1799793, or ERCC1 rs3212986.

A 2014 meta-analysis of the association between ERCC polymorphisms and osteosarcoma prognosis [27] appears to have had several limitations [28]. The analysis did not provide NOS assessments or HWE test outcomes, and sensitivity analysis and publication bias tests were not performed as well. Additionally, crude ORs/HRs were used in primary outcomes, rather than adjusted ORs/HRs. Finally, two rs11615 genotype formats, T/C or C/T, were not in accordance in included studies, and might have lead to unclear estimations. Based on the recent studies, we attempted to more precisely clarify associations of the tested ERCC polymorphisms with osteosarcoma prognosis.

Metastasis and TR are two of the most important osteosarcoma patient prognosis predictors [29], and current
osteosarcoma therapies include surgery and primary and adjuvant chemotherapy. Success of the first-line methotrexate, doxorubicin/adriamycin, and cisplatin (MAP) chemotherapy regimen is limited by osteosarcoma heterogeneity [30] and tumor resistance to platinum-based cisplatin. Cisplatin is a widely-used first-line anti-cancer chemotherapeutic. Platinum agents adduct to DNA, leading to cell death. Platinum resistance is generally defined by tumor recurrence within one month after the last drug administration [31]. Cisplatin resistance may result from increased DNA repair capacity, changes in cisplatin cellular accumulation, and drug inactivation. High-level ERCC1 may remove the platinum-DNA adduct, leading to cisplatin resistance through increased DNA repair capacity. Some ERCC1 SNPs were confirmed as potential cisplatin resistance biomarkers [31]. ERCC SNPs and expression variations may alter DNA repair, thus impacting cell sensitivity to platinum agents [32]. ERCC1 mRNA increased by 6-fold in human ovarian cancer cells exposed to cisplatin, possibly due to increased expression of transactivating factors and c-Jun phosphorylation [33]. Nucleotides -415 to -220 and -220 to -110, upstream of the ERCC1 initiation site, are critical to cisplatin-induced ERCC1 overexpression and promoter activity, respectively [34].

Figure 4: Sensitivity analysis of rs11615 OS (TC+CC vs. TT).

Figure 5: Funnel plot for publication bias estimation, rs11615 OS (TC+CC vs. TT).
found that Hsp90 inhibitors were able to induce cisplatin resistance in human cancer cell lines, which suggests a potential role for these inhibitors in reversing cisplatin resistance. Moreover, it has been suggested that Hsp90 may be a target for reversing cisplatin resistance.

These findings suggest that ERCC1 is a target for reversing cisplatin resistance. UCN-01 (7-hydroxylstaurosporine) is a protein kinase C (PKC) inhibitor that inhibits the ERCC1/xeroderma pigmentosum group A (XPA) interaction, and may reduce ERCC1-induced cisplatin resistance. However, UCN-01 was not fully developed with the specific aim of reversing cisplatin resistance, and remains in Phase I clinical trials [35–36].

These findings suggest that ERCC1 is an attractive target for reversing cisplatin resistance. UCN-01 (7-hydroxylstaurosporine) is a protein kinase C (PKC) inhibitor that inhibits the ERCC1/xeroderma pigmentosum group A (XPA) interaction, and may reduce ERCC1-induced cisplatin resistance. However, UCN-01 was not fully developed with the specific aim of reversing cisplatin resistance, and remains in Phase I clinical trials [35–36]. Li, et al. observed that siRNA-mediated ERCC1 inhibition promoted cisplatin sensitivity and apoptosis in gastric cancer [37].

This study also demonstrates the importance of understanding the role of ERCC1 in the context of cisplatin resistance. By targeting ERCC1, we may be able to reverse this resistance and improve treatment outcomes. However, further research is needed to fully understand the mechanisms underlying this process and to develop effective therapeutic strategies.
sensitivity analysis. Further studies are needed to identify the value of these two SNPs in targeted therapies and prognosis prediction.

Our study had limitations. First, numerous factors were involved in tumor prognosis. Single SNPs are unlikely to be major factors affecting tumor prognosis. Gene-environment and gene-gene interactions, and the combined effects of multiple SNPs in several genes are more effective outcome predictors than single SNPs alone [77–78]. However, we found no relevant gene interaction data in the included studies. Second, primary data was not available in some models. Thus, adjusted ORs were merged with crude ORs, and heterogeneity under such circumstances was high. We were unable to determine the sources of heterogeneity for some studies, such as that of Sun et al. In addition, in ERCC1 rs11615, discrepancies between T/C and C/T remain unsettled [31]. While rs11615 T/C was correct according to PubMed dbSNP, we could not confirm this with high confidence from our study. rs11615 might reduce levels of ERCC1 mRNA [31], but it was unclear that which allele switched the mRNA levels. In our analysis, T/C and C/T study outcomes were obviously contradictory, with high heterogeneity. We performed a subgroup analysis based on T/C and C/T to reduce heterogeneity, but our sample size was somewhat limited. Further analyses are necessary to rectify this confusing issue.

In conclusion, our meta-analysis indicated that ERCC1 rs11615 is associated with improved osteosarcoma prognosis. Additional studies with larger sample sizes are needed to more precisely estimate the correlation between ERCC polymorphisms and osteosarcoma prognosis.

MATERIALS AND METHODS

We conducted this meta-analysis based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [22]. PRISMA checklist was available in Supplementary Table 15.

Literature search strategy

We comprehensively searched for potential references from the PubMed, ScienceDirect, Springer, and Web of Science databases using key words such as “ERCC,” “osteosarcoma,” “outcome,” etc. through October, 2016. Our detailed literature search strategy is provided in the Supplementary Table 14.

Study selection

Studies included in our analysis met the following criteria: (1) studies were limited to the published research concerning osteosarcoma prognosis and ERCC polymorphisms; (2) patients in the original studies must have been diagnosed with osteosarcoma via imaging, pathology, or the latest clinical diagnostic criteria, and genotyping was performed using valid molecular techniques; and (3) detailed patient data and the number of participants with distinct genotypes were published in the studies so that the adjusted or crude OR/HR value could be calculated. If the same or overlapping data appeared in multiple studies, the study with the largest sample size or most recent publication date was included in the meta-analysis.

Data extraction

Data were extracted by two investigators independently and double-checked by a third investigator. Inconsistent data were addressed by open discussion and consensus was achieved via input from a senior investigator.

Reference quality assessment

Two investigators conducted literature quality assessments of the included studies according to the NOS developed for case-control studies [23], and the star system was employed. The NOS included three domains: case and control selection, comparability, and exposure, eight items with nine stars in total. It was considered as a high quality (or low-bias risk) study if total stars achieved six to nine. Four to five stars would be considered as having intermediate-bias risk and one to three stars may have high-bias risk.

Statistical analysis

Stata 11.0 software was used to perform this meta-analysis. A Hardy-Weinberg equilibrium (HWE) test was performed using extracted data, and \( P < 0.05 \) was considered a significant imbalance. Adjusted HRs/ORs from confounders (age, metastasis, etc.) in every model were used in our meta-analysis; otherwise, crude HRs/ORs calculated by Revman 5.3 software or given were used. Pooled data had low heterogeneity if \( P > 0.1 \) and \( I^2 < 50\% \). In these cases, a fixed effects model was used; otherwise, a random effects model was used. Statistical analysis of pooled data was performed using models as follows: 12 versus 11, 22 versus 11, 12 versus 22, 12+22 versus 11, 1 versus 2 (1 represented the wild allele and 2 represented the mutated allele).

Tumor-related indexes, including TR, OS, and EFS, were assessed if the number of studies containing usable data was greater than 3. Statistical analyses were two-sided and \( P < 0.05 \) was considered significant. Z-score was evaluated by the \( P \) value of two-sided \( u \)-test for overall effect estimation.

Subgroup analysis

Subgroup analyses were conducted based on study characteristics, to investigate sources of heterogeneity and potential correlations. As per the Savage, et al. study [2], the
following variables were assessed in subgroup analyses: TR evaluation method, HWE, race, treatment and adjustment of confounding factors of tumor-related variables.

**Heterogeneity and sensitivity analyses**

Sensitivity analysis was performed to investigate sources of heterogeneity and estimate the impacts of excluded studies on pooled outcomes. We also performed sensitivity analyses by excluding one study at a time to explore whether results were strongly influenced by a specific study. If the I² value decreased (or even reached 0%), the removed study was considered a source of heterogeneity. Meta-analysis outcomes before and after the study was removed were then compared. If heterogeneity could not be eliminated, maximum or minimum extremes were excluded to achieve a more conservative estimation. Sensitivity analysis was not performed when the number of studies was < 3.

**Publication bias**

Egger’s linear regression and Begg’s rank correlation tests were performed to evaluate potential publication bias [24]. \( P < 0.05 \) designated a significant publication bias. Funnel plots were used to visually evaluate publication bias.

**CONFLICTS OF INTEREST**

None.

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