Association between XRCC1 single-nucleotide polymorphisms and susceptibility to nasopharyngeal carcinoma
An update meta-analysis
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Abstract
Background: Many studies have investigated polymorphisms of X-ray repair cross-complementing protein 1 (XRCC1) and risk of nasopharyngeal carcinoma (NPC), but the results are somewhat contradictory in different studies. There is an urgent need to keep in step with the relevant observational studies to more comprehensively understand the effects of XRCC1 variants on the NPC risk.

Methods: A systematic literature search accompanied with meta-analysis was carried out to obtain a detailed evaluation on the association between XRCC1 polymorphisms and NPC risk.

Results: Meta-analyses showed that there was no statistically significant association observed between Arg194Trp/Arg280His variants in the XRCC1 gene and NPC risk with all genetic models, when relatively larger samples were pooled into the update meta-analysis. The reassessment suggested NPC risk was significantly increased with Arg399Gln polymorphism. The significant association was identified in homozygous, recessive, and allelic models, more than previously reported.

Conclusion: We confirmed that Arg399Gln polymorphism of XRCC1 gene is a potential predictor for susceptibility to NPC, especially for Asians. More studies are required to evaluate the association in different populations.

Abbreviations: A = wild type, AA = wild homozygote, B = variant type, BA = heterozygote, BB = variant homozygote, CI = confidence interval, CNKI = Chinese National Knowledge Infrastructure, EBV = Epstein–Barr virus, HWE = Hardy–Weinberg equilibrium, NPC = nasopharyngeal carcinoma, OR = odds ratio, XRCC1 = X-ray repair cross-complementing protein 1.

Keywords: meta-analysis, nasopharyngeal carcinoma, polymorphism, XRCC1

1. Introduction
Nasopharyngeal carcinoma (NPC) is a malignant tumor of the nasopharynx with an unusual geographical distribution, especially occurs within economically developing countries.\(^{[1,2]}\) The high incidence are mainly found in North Africa, Southeast Asia, and the arctic region. It has been reported that about 86,700 new cases of NPC and 50,800 deaths occurred in 2012.\(^{[1]}\) NPC is an epithelial cancer whose etiology is associated with several factors, including Epstein–Barr virus (EBV) infection, genetics, and environmental exposures to chemical carcinogens.\(^{[3]}\) The difference of clinical response and outcome on NPC suggests the inter-individual variation might play a more important role in NPC susceptibility,\(^{[4]}\) especially the ability of DNA damage repair.\(^{[5,6]}\)

Damage to cellular DNA relates to the development of cancer.\(^{[7]}\) Cells have evolved several systems to detect DNA damage and repair damaged DNA, since mutations arise each time DNA is replicated. Genetic polymorphisms in DNA repair genes may account for some of the observed differences in development of different cancers,\(^{[8]}\) including NPC. Therefore, polymorphisms in DNA repair genes may be an explanation for susceptibility of some cancer.\(^{[9]}\) The X-ray repair cross-complementing group 1 (XRCC1) gene plays an important role in DNA-damage processing.\(^{[10]}\) XRCC1 functions as a scaffold to be recruited to sites of damaged DNA and facilitated in various DNA repair pathways.\(^{[11]}\) Three functional polymorphisms in XRCC1, including Arg194Trp, Arg280His, and Arg399Gln, are most commonly studied.\(^{[12]}\) Many studies have investigated the association between XRCC1 polymorphisms and clinical outcomes in cancer patients. They revealed that individual susceptibility of cancer treatment and survival of patients was different due to genetic polymorphisms in XRCC1, including head and neck cancer,\(^{[13]}\) cervical carcinoma,\(^{[14]}\) and non-small-cell lung cancer.\(^{[15]}\) Meta-analyses have also revealed significant associations between various polymorphisms in XRCC1 and cancer risk, such as the lung,\(^{[16]}\) breast,\(^{[17]}\) stomach,\(^{[18]}\) esophageal cancer,\(^{[19]}\) and NPC.\(^{[20]}\)

Several polymorphisms in XRCC1 have been reported to undertake crucial functions in NPC risk. Cho et al first reported
high-risk genotypes of XRCC1 for developing NPC.\cite{20} Subsequent studies had shown inconsistent conclusions.\cite{21-27} Most of published studies were conducted with the high NPC incidence regions in Asia, except for North Africa.\cite{23} Although previous 2 studies performed pooling analyses regarding the association of XRCC1 Arg194Trp, Arg280His, and Arg399Gln with NPC risk,\cite{19,28} However, several published studies with additional origin were not included in these meta-analyses.\cite{29-32} Importantly, the previous meta-analyses on XRCC1 from case–control studies conducted different conclusions. Hence, the association of XRCC1 polymorphisms remains unknown before reevaluating the susceptibility effects. Herein, we summarize the data from more reliable studies to perform a meta-analysis to reevaluate the effect of XRCC1 variants (Arg194Trp, Arg280His, and Arg399Gln) on NPC risk.

2. Methods

2.1. Identification of eligible studies

A comprehensive literature search was performed by 2 independent investigators. The database of reference included PubMed, Web of Science, Chinese National Knowledge Infrastructure (CNKI), Wanfang, and Weipu. The published references in English or Chinese were both considered, and last search was updated on January 1, 2018. The key terms were used during searching: “XRCC1,” “Polymorphism,” and “Nasopharyngeal carcinoma.” After filtering duplicate publications, we retrieved all eligible studies and checked for the case–control studies of NPC with at least one of the 3 SNPs, Arg194Trp, Arg280His, and Arg399Gln.

2.2. Inclusion and exclusion criteria

The inclusion criteria were made to select eligible studies. The following factors were mainly considered: case–control studies, focus on XRCC1 polymorphisms and NPC, odds ratio (OR) and 95% confidence interval (CI) with clear genotype, and studies focusing on human beings.

In contrast, the exclusion criteria were used to filter out ineligible studies. A few criteria were included as follows: duplicate publication of an article, only case population reported, studies on family pedigrees, not cancer research, not experiment, and no genotype data.

2.3. Data extraction

According to the inclusion and exclusion criteria, we carried out the data extraction carefully and independently by 2 investigators. These contents were collected from each study: author name, publication year, country and ethnicity of origin, study design, the criteria of NPC, control source, genotyping methods, sample sizes of cases, and controls. Ethnicity was categorized as “African” and “Asian.” The extracted data from 2 authors were compared to reach to consensus on all the data.

2.4. Quality assessment

We established a set of predetermined criteria to score the included studies (Table S1, http://links.lww.com/MD/C391), with a few modification from the previous studies.\cite{13-31} Two reviewers (YQ and ZY) independently evaluated the qualities of these studies. The main parts of these criteria for quality score of studies comprised the following aspects: diagnosed criteria of cases, collected criteria of healthy controls, population size, quality methods of controls, and Hardy–Weinberg equilibrium (HWE). Finally, an overall quality score was generated within a certain range from 0 to 10. Higher score means better quality for quality assessment. Studies gained more than 3 points were regarded as eligible studies. Disagreements on the inclusion or exclusion were resolved by corresponding author.

2.5. Statistical analysis

The deviation of genotypes among controls was evaluated by HWE, $P < .05$ in a Chi-squared test was considered a departure from HWE. The extent of association with XRCC1 polymorphisms was assessed by ORs and 95% CIs. The significance of association was performed by Z-test with $P < .05$. The genetic models used for meta-analysis were dominant model: BB+BA versus AA; recessive model: BB versus BA+AA; homozygous model: BB versus AA; heterozygous model: BA versus AA; and allelic model: B versus A, respectively (where BB=variant homozygote, BA=heterozygote, AA= wild homozygote, B= variant type, A= wild type).

The heterogeneity analysis used a $Q$ statistic and I$^2$ statistic, respectively.\cite{36,37} Significant inconsistency was satisfied with either $P > .10$ or $I^2 > 50\%$. A fixed-effect model was selected if there was not heterogeneous, otherwise a random-effect model was used.

Sensitivity analysis was used to investigate the stability of outcomes. We deleted any study one by one with all genetic models and recalculated the association. No significant change of the meta-analysis was thought to be stable and reliable results. Finally, publication bias was used to examine the stability of the meta-analysis by Begg funnel plot\cite{38} and Egger regression test\cite{39} with all genetic models. These statistical analyses were all conducted by using Stata SE 12.0.

2.6. Ethical approval

As this article is a meta-analysis of the previous works of literature, in which informed consent has already been obtained by the previous clinical researcher, hence approval of the ethics committee was not required.

3. Results

3.1. Literature search and characteristics of studies

The selection of eligible studies is summarized in Figure 1. A total of 78 publications were relevant to the search term. Among these publications, 16 duplicates and 45 articles were firstly excluded according to improper title and abstract. After reviewing the full text of the remaining literature, we excluded 6 studies, including meeting report, meta-analysis, and not about NPC. Finally, a total of 11 eligible studies were included in meta-analysis of XRCC1 polymorphisms and NPC risk.

The characteristics of each study are summarized in Table 1. Among them, 5 studies on XRCC1 Arg194Trp contained 1428 patients and 1519 controls, and 5 studies on XRCC1 Arg280His contained 1416 patients and 1343 controls, and 10 studies on XRCC1 Arg399Gln contained 2143 patients and 2269 controls. The distribution of genotype within controls conformed with HWE, except for 1 study\cite{29} on XRCC1 Arg194Trp and XRCC1 Arg399Gln.

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3.2. Significant association between XRCC1 Arg399Gln polymorphism and NPC susceptibility

The meta-analysis displayed that no significant association was found between XRCC1 Arg194Trp and NPC risk. In heterogeneity analysis with all genetic models, heterogeneity of studies was to a significant extent. Therefore, a random-effect model should be used in the subsequent meta-analysis. The results are summarized in Table 2. There was no significant association in any genetic model, such as dominant model (OR = 1.24, 95% CI 0.78–1.98, \( P = .369 \)), recessive model (OR = 1.21, 95% CI 0.49–2.96, \( P = .682 \)), homozygous model (OR = 1.33, 95% CI 0.45–3.94, \( P = .602 \)), and heterozygous model (OR = 1.23, 95% CI 0.85–1.79, \( P = .369 \)).

| Study ID | Year | Country | Ethnicity | Case | Control | HWE | Quality |
|----------|------|---------|-----------|------|---------|-----|---------|
| The Arg194Trp polymorphism of XRCC1 gene | | | | | | | |
| Cao Y 2006 China | Arg/Arg | Arg/Trp | Trp/Trp | Arg/Arg | Arg/Trp | Trp/Trp |
| Yang ZH 2007 China | Arg/Arg | Arg/Trp | Trp/Trp | Arg/Arg | Arg/Trp | Trp/Trp |
| Lautriti N 2011 North African | Arg/Arg | Arg/Trp | Trp/Trp | Arg/Arg | Arg/Trp | Trp/Trp |
| Zhu QJ 2014 China | Arg/Arg | Arg/Trp | Trp/Trp | Arg/Arg | Arg/Trp | Trp/Trp |
| Dai Q 2007 China | Arg/Arg | Arg/Trp | Trp/Trp | Arg/Arg | Arg/Trp | Trp/Trp |
| The Arg280His polymorphism of XRCC1 gene | | | | | | | |
| Cho EY 2003 China | Arg/Arg | Arg/Trp | Trp/Trp | Arg/Arg | Arg/Trp | Trp/Trp |
| Yang ZH 2007 China | Arg/Arg | Arg/Trp | Trp/Trp | Arg/Arg | Arg/Trp | Trp/Trp |
| Lautriti N 2011 North African | Arg/Arg | Arg/Trp | Trp/Trp | Arg/Arg | Arg/Trp | Trp/Trp |
| Visuvanathan S 2014 Malaysia | Arg/Arg | Arg/Trp | Trp/Trp | Arg/Arg | Arg/Trp | Trp/Trp |
| Dai Q 2007 China | Arg/Arg | Arg/Trp | Trp/Trp | Arg/Arg | Arg/Trp | Trp/Trp |
| The Arg399Gln polymorphism of XRCC1 gene | | | | | | | |
| Cho EY 2003 China | Arg/Arg | Arg/Gln | Gln/Gln | Arg/Arg | Arg/Gln | Gln/Gln |
| Cao Y 2006 China | Arg/Arg | Arg/Gln | Gln/Gln | Arg/Arg | Arg/Gln | Gln/Gln |
| Yang ZH 2007 China | Arg/Arg | Arg/Gln | Gln/Gln | Arg/Arg | Arg/Gln | Gln/Gln |
| Lautriti N 2011 North African | Arg/Arg | Arg/Gln | Gln/Gln | Arg/Arg | Arg/Gln | Gln/Gln |
| Visuvanathan S 2014 Malaysia | Arg/Arg | Arg/Gln | Gln/Gln | Arg/Arg | Arg/Gln | Gln/Gln |
| Zhu QJ 2014 China | Arg/Arg | Arg/Gln | Gln/Gln | Arg/Arg | Arg/Gln | Gln/Gln |
| Guo JY 2016 China | Arg/Arg | Arg/Gln | Gln/Gln | Arg/Arg | Arg/Gln | Gln/Gln |
| Singh SA 2016 India | Arg/Arg | Arg/Gln | Gln/Gln | Arg/Arg | Arg/Gln | Gln/Gln |

HWE = Hardy–Weinberg equilibrium, XRCC1 = X-ray repair cross-complementing protein 1.
Forest-plot-illustrated meta-analysis of XRCC1 Arg280His and NPC under allelic model (OR = 1.19, 95% CI 0.79–1.79, \( P = .408 \)) is given in Figure 2.

The meta-analysis also indicated that no significant association was found between XRCC1 Arg280His and NPC risk in any genetic model. Heterogeneity analysis suggested that there was significant heterogeneity in both overall and Asian subgroup with all genetic models. The detailed meta-analysis results under the random-effect model are summarized in Table 2. No significance was detected under the genetic models, including dominant model (OR = 0.97, 95% CI 0.74–1.28, \( P = .837 \)), recessive model (OR = 0.86, 95% CI 0.45–1.63, \( P = .645 \)), homozygous model (OR = 0.84, 95% CI 0.46–1.66, \( P = .682 \)), heterozygous model (OR = 0.99, 95% CI 0.75–1.31, \( P = .933 \)), and allelic model (OR = 0.98, 95% CI 0.83–1.16, \( P = .812 \)). Forest-plot-illustrated meta-analysis of XRCC1 Arg280His and NPC under allelic model is given in Figure 3.

The meta-analysis revealed that significant association was found between XRCC1 Arg399Gln and NPC risk in 3 genetic models. Significant heterogeneity was only observed in the dominant model and heterozygote model, so that the random-effect model was used in those models. No significant association between XRCC1 Arg399Gln and NPC was detected in overall and Asian subgroup under both dominant and heterozygote model (Table 2). In contrast, the fixed-effect model of meta-analysis was selected to be used in the other 3 genetic models. The results of significant association are presented in Table 2, including recessive model (OR = 1.27, 95% CI 1.02–1.60, \( P = .035 \)), homozygote model (OR = 1.34, 95% CI 1.07–1.70, \( P = .013 \)), and allele model (OR = 1.13, 95% CI 1.03–1.24, \( P = .012 \)). Forest-plot-illustrated meta-analysis of XRCC1 Arg399Gln and NPC under allelic model is given in Figure 4. Subgroup analysis was considered in Asian population due to 1 study in other subgroup. The significant association was

### Table 2

Summary of meta-analysis for three X-ray repair cross-complementing protein 1 polymorphisms and nasopharyngeal carcinoma risk in both overall and Asian subgroup with five genetic models.

|          | BB + BA vs AA | BB vs BA + AA | BB vs AA | BA vs AA | B vs A |
|----------|---------------|---------------|----------|----------|--------|
|          | N             | OR (95% CI)   | \( P \)  | OR (95% CI) | \( P \) | OR (95% CI) | \( P \) | OR (95% CI) | \( P \) |
| Arg194Trp|                |               |          |          |        |          |       |          |       |
| Asian    | 4             | 1.21 (0.67–2.20) | .522     | 1.05 (0.41–2.72) | .107 | 1.14 (0.35–3.70) | .823 | 1.22 (0.72–2.06) | .450 | 1.15 (0.70–1.88) | .585 |
| Overall  | 5             | 1.24 (0.78–1.98) | .369     | 1.21 (0.49–2.96) | .682 | 1.33 (0.45–3.94) | .602 | 1.23 (0.82–1.86) | .312 | 1.19 (0.79–1.79) | .408 |
| Arg280Gln|                |               |          |          |        |          |       |          |       |                  |       |
| Asian    | 4             | 0.91 (0.64–1.29) | .599     | 0.73 (0.29–1.82) | .500 | 0.73 (0.29–1.83) | .505 | 0.93 (0.65–1.34) | .698 | 0.89 (0.72–1.11) | .308 |
| Overall  | 5             | 0.97 (0.74–1.28) | .837     | 0.86 (0.45–1.63) | .645 | 0.84 (0.46–1.66) | .682 | 0.99 (0.75–1.31) | .933 | 0.98 (0.83–1.16) | .812 |
| Arg399Gln|                |               |          |          |        |          |       |          |       |                  |       |
| Asian    | 9             | 1.12 (0.91–1.38) | .282     | 1.29 (1.00–1.67) | .052 | 1.36 (1.04–1.77) | .025 | 1.09 (0.88–1.35) | .419 | 1.11 (1.00–1.24) | .048 |
| Overall  | 10            | 1.14 (0.95–1.36) | .158     | 1.27 (1.02–1.60) | .035 | 1.34 (1.07–1.69) | .013 | 1.11 (0.92–1.32) | .268 | 1.13 (1.03–1.24) | .012 |

Statistical significance \( P < .05 \) are given in bold.

A = wild type, AA = wild homozygote, B = variant type, BA = heterozygote, BB = variant homozygote, CI = confidence interval, N = number of case-control studies, OR = odds ratio.

Figure 2. Forest plots showed no significant association between X-ray repair cross-complementing protein 1 Arg194Trp and nasopharyngeal carcinoma risk under the allelic genetic model. CI = confidence interval, OR = odds ratio.
repetitively identified in homozygous model (OR = 1.36, 95% CI 1.04–1.77, $P = .025$) and allelic model (OR = 1.11, 95% CI 1.00–1.24, $P = .048$), while under the recessive model, the $P$-value showed a slightly significance (OR = 1.29, 95% CI 1.00–1.67, $P = .052$) (Table 2).

3.3. Sensitivity analysis indicating stable and reliable results
To further assess the stability of meta-analysis outcomes, sensitivity analysis was conducted through the sequential omitting of each study and recalculating of the association.
Arg280His polymorphisms and NPC risk when relatively larger evidence for the association between XRCC1 Arg194Trp and allelic models. Additionally, our reassessment suggested no polymorphism and NPC risk was identified in homozygous model, but not in the other 4 genetic models. The most important conclusion in the previous meta-analyses was that association between XRCC1 Arg399Gln with NPC in homozygous model, but not in the other 4 genetic models. Another meta-analysis study indicated the association between XRCC1 Arg399Gln with NPC in homozygous model, as well as marginally significant association in recessive model. The result contradicts ours due to in part to less number of study, 5 studies in previous meta-analyses. However, we reported the association in 3 genetic models by using 10 studies. Therefore, more studies used in meta-analysis showed stronger ability to detect the association. We noticed that the study with significant departure from HWE in the control groups had an impact on the strength of conclusion in the previous meta-analyses. Likewise, Yang et al also detected a significant deleterious effect under homozygous model through the meta-analysis. However, studies conducted in Chinese, Taiwanese, Malaysian, and North African population did not reported such association. These outcomes indicated the complexity of susceptibility gene for NPC and the related complications. Thus it is beneficial to make the meta-analysis to be updated along with latest study to provide more stable and reliable conclusions.

In conclusion, we demonstrated that Arg194Trp and Arg280His polymorphisms of XRCC1 gene are not significantly associated with NPC risk. The association between XRCC1 Arg399Gln and NPC risk was significant in homozygous, recessive, and allelic genetic models. However, the significant association should be further reevaluate by the meta-analysis with more study and larger population to validate our findings.

Author contributions
J.L. and Q.Y. conceived the study and designed the experiments. Q.Y. and Y.Z. collected identified the eligible studies. Y.H.W. and Y.W. performed the meta-analysis. J.L. and Q.Y. were mainly involved in preparation of manuscript. All authors provided input during the writing of the manuscript. All authors reviewed and approved the final manuscript.

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