EBioMedicine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Research Paper

Association Between Twelve Polymorphisms in Five X-ray Repair Cross-complementing Genes and the Risk of Urological Neoplasms: A Systematic Review and Meta-Analysis

Meng Zhang [1], Wanzhen Li [1], Zongyao Hao, Jun Zhou, Li Zhang *, Chaozhao Liang *

Department of Urology, The First Affiliated Hospital of Anhui Medical University, Hefei, China
Institute of Urology, Anhui Medical University, Hefei, China
Graduate School of Anhui Medical University, Hefei, China

ARTICLE INFO

Article history:
Received 3 January 2017
Received in revised form 7 March 2017
Accepted 7 March 2017
Available online xxxx

Keywords:
XRCC
Polymorphism
Urological neoplasm
Risk
Meta-analysis

ABSTRACT

Polymorphisms in X-ray repair cross-complementing (*XRCC*) genes have been implicated in altering the risk of various urological cancers. However, the results of reported studies are controversial. To ascertain whether polymorphisms in *XRCC* genes are associated with the risk of urological neoplasms, we conducted present updated meta-analysis and systematic review. Summary odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were used to estimate the association. Finally, 54 publications comprising 129 case-control studies for twelve polymorphisms in five *XRCC* genes were enrolled. We identified that *XRCC1*-rs25489 polymorphism was associated with an increased risk of urological neoplasms in heterozygote and dominant models. Moreover, in the subgroup analysis by cancer type, we found that *XRCC1*-rs25489 polymorphism was associated with an increased risk of bladder cancer (BC) in heterozygote model. Although overall analyses suggested a null result for *XRCC1*-rs25487 polymorphism, in the stratified analysis by ethnicity, an increased risk of urological neoplasms for Asians in allelic and homozygote models was identified. While for other polymorphisms in *XRCC* genes, no significant association was uncovered. To sum up, our results indicated that *XRCC1*-rs25489 polymorphism is a risk factor for urological neoplasms, particularly for BC. Further studies with large sample size are needed to validate these findings.

1. Introduction

Deoxyribonucleic acid (DNA) in a normal cell is capable of withstanding internal and external damage to prevent the damage or death of the cell (Alli et al., 2009; Orlow et al., 2008). The direct reversal, base excision, nucleotide excision in the main DNA repair pathways of human beings' function as restoring lost gene information and maintaining DNA integrity (Rajaraman et al., 2010). Some research studies have already showed that polymorphisms in DNA-repair genes are an integral part of cancer risk, apart from environmental factors, diet, intake of non-steroidal and anti-inflammatory drugs, and endogenous factors (Spitz et al., 2003). At the cellular level, checkpoints activated by the DNA-repair genes can regulate the cell cycle and transcription to make the choice of the damage or the apoptosis (Vispe et al., 2000). In addition, DNA repair-gene is also critical in defending the cellular genome from the risk of environmental factors (Hoeijmakers, 2001). Therefore, making certain of the genetic mechanisms of DNA repair system might take an insight into the pathogenesis of relevant cancers. X-ray repair cross-complementing (*XRCC*) genes are members of the family of DNA repair system (Dizdaroglu, 2015), which are polymorphic with several non-synonymous polymorphisms, such as Arg194Trp (rs1799782), Arg280His (rs25489), Arg399Gln (rs25487) in *XRCC1*, Arg188His (rs3218536) polymorphisms in *XRCC2*, IVS6-14 (rs1799796) and Thr241Met (rs861539) polymorphisms in *XRCC3*, rs1805377, rs6869366 and rs28360071 polymorphisms in *XRCC4* and rs7003908 in *XRCC7*. To date, plenty of evidences have indicated that more than one hundred proteins encoded by *XRCC* genes are implicated in four DNA repair pathways, including nucleotide excision repair (NER), base excision repair (BER), double-strand break repair (DSBR) and mismatch repair (MMR), working as tumor suppressors or oncogenes for the sake of participating in tumorigenesis through posting expression regulation of homologous target genes (Liesegang, 2001). Recently, studies have highlighted the ambivalent association between polymorphisms in *XRCC* genes and risk of urological neoplasms. In the study conducted by Agalliu et al. (2010), they have proved that there was no significant association between *XRCC1* polymorphisms

* Corresponding authors at: Department of Urology, The First Affiliated Hospital of Anhui Medical University, Hefei, China.
E-mail addresses: lzhang@ahmu.edu.cn (L. Zhang), liang_chaozhao@ahmu.edu.cn (C. Liang).
[1] These authors contributed equally to the work.

http://dx.doi.org/10.1016/j.ebiom.2017.03.009

(rs1799782, rs25487, rs25489 and rs915927) and prostate cancer (PCa) risk. Consistent with Agalliu et al.'s conclusion, Lavender et al. (2010) also confirmed that no significant influence of *XRCC1*-rs25487 polymorphism on PCa risk was identified for African population. While in another population-based case-control dataset, Lan et al. (2006) suggested that *XRCC1*-rs25487 polymorphism was significantly associated with the development of PCa. Both Matullo (2005) and Nowacka-Zawisza et al. (2015) have not revealed a significant association between *XRCC2*-rs3218536 polymorphism and urological neoplasms risk in their work, respectively. As for polymorphisms in *XRCC3* gene, Wu et al. (2006) indicated that there was no association between *XRCC3*-rs861539 polymorphism and bladder cancer (BC) risk, while Narter et al. (2009) reported the conflicting results that there was a 4.87-fold protective role of *XRCC3* T allele against BC. In 2011, Mandal et al. (2011) conducted a case-control study comprising 192 PCa cases and 224 age-matched healthy controls and obtained a conclusion that *XRCC4* promoter-1394 (rs6869366) heterozygote was associated with a lower risk of PCa, a result inconsistent with Chang et al.'s (2008) work. In addition, Mandal et al. (2010) provided a strong supportive evidence that common sequence variants genotype of *XRCC7* gene might increase the risk of PCa.

As mentioned above, although many studies have conducted to investigate the associations between one or multiple polymorphism (s) and the risk of urological neoplasms, but there results were not consistent or even contradictory, which was partially due to the heterogeneity within cancer subtypes, the diverse ethnicities of patient cohorts and the small sample sizes. Therefore, we conducted the current updated meta-analysis and systematic review at the aim of precisely determines the association between genetic variants in five *XRCC* genes and the susceptibility to urological neoplasms.

2. Materials and Methods

2.1. Literature Search

We conducted a systematic literature search on PubMed, Medline, Google Scholar and Web of Science to retrieve all eligible publications on the association between polymorphisms in all *XRCC* genes and the risk of all urological cancer types (up to December 27, 2016) with the following keywords: (*XRCC1-9* OR X-Ray Repair Cross Complementing 1-9) AND (polymorphism OR mutation OR variation OR SNP OR genotype) AND (carcinoma OR cancer OR neoplasm OR adenocarcinoma OR tumor OR malignancy) (Supplementary Table 1). The language of enrolled studies was restricted to English. Moreover, we identified additional articles by screening the references of enrolled eligible articles and Reviews. We would contact authors for critical data not mentioned in the eligible articles. If data or datasets were published in several articles, the publication with largest sample sizes was selected. However, after carefully screening, twelve polymorphisms in five *XRCC* genes were left for further investigation, and the cancer types were restricted to PCa, BC and renal cell carcinoma (RCC).

2.2. Inclusion Criteria and Exclusion Criteria

Publications satisfied the following inclusion criteria would be enrolled: (1) case-control studies that evaluated the association between polymorphisms in *XRCC* genes and urological neoplasms risk; (2) publications focusing on population genetic polymorphisms (3) articles with sufficient genotype data to assess ORs and the corresponding 95%CIs; (4) the control subjects satisfied Hardy-Weinberg equilibrium (HWE). The major exclusion criteria were: (1) case-only studies, case reports, or Reviews; (2) studies without raw data for the *XRCC* genotype (or contacted the corresponding author also cannot obtain the necessary original data): (3) studies that compared the *XRCC* variants in precancerous lesions and other cancers.

2.3. Data Extraction

Our investigators extracted the data from each study. All the case-control studies satisfied the inclusion criteria and consensus for any controversy was achieved. The data from the eligible articles was composed of the first author's name, year of publication, ethnicity, source of controls, cancer type and numbers of cases and controls in the *XRCC1*, *XRCC2*, *XRCC3*, *XRCC4*, *XRCC7* genotypes. Ethnicity was categorized as "Caucasian", "Asian", and "Mixed". The cancer type was categorized as PCa and BC. With the regard to the sources of controls, all eligible case-control studies were defined as either population-based or hospital-based.

2.4. Statistical Analysis

The strength of association between the polymorphisms in *XRCC* genes and the risk of urological neoplasms were evaluated using summary ORs and the corresponding 95%CIs in allelic (B vs. A), recessive (BB vs. BA + AA), dominant (BA + BB vs. AA), homozygous (BB vs. AA), and heterozygous (BA vs. AA) models (A: wild allele; B: mutated allele). The *P* values of our study were adjusted by Bonferroni correction method to compensate for that increased by testing each individual hypothesis at a significance level of **a/m** (**a**: the desired overall alpha level; **m**: the number of the hypothesis), and the Bonferroni correction rejects the null hypothesis with the value of *P* less than **a/m** ($P_A = P_Z * 60 < 0.05$, was considered as statistical significant) (Bonferroni, 1935). The Cochrane's Q-statistic test was used to assess the heterogeneity between studies (Davey Smith and Egger, 1997), and the inconsistency was quantified with the I^2 statistic. The substantial heterogeneity was considered significant when $I^2 > 50\%$ or $P_Q \leq 0.1$, then, a random effects model (DerSimonian-Laird method) was used; otherwise, the fixed-effects model (Mantel-Haenszel method) was applied (Mantel and Haenszel, 1959). When it came to the comparison among studies, we performed subgroup analyses categorized by cancer type, ethnicity, HWE and the source of control. Last but not least, we also conducted sensitivity analysis to assess stability of the results by omitting one study each time to exclude studies. HWE was estimated by the asymptotic test using the "sampsi command" in the Stata 12.0 software (version 12.0; State Corporation, College Station, Texas, USA), and deviation was considered when $P < 0.05$. The potential publication bias of the eligible studies was evaluated by Begg's funnel plots (Begg and Mazumdar, 1995) graphically and Egger's linear regression test (Seagroatt and Stratton, 1998) quantitatively. Moreover, the trim and fill algorithm which trim off the asymmetric outlying part of the funnel and estimate the true center of the funnel further provide effective and relatively powerful tests for evaluating the existence of such publication bias (Sue and Richard, 2000). The data was analyzed using the Stata 12.0 software (version 12.0; State Corporation, College Station, Texas, USA).

2.5. Linkage Disequilibrium (LD) Analysis Across Populations

Data were extracted from the 1000 genomes Project (http://hapmap.ncbi.nlm.nih.gov/cgi-perl/gbrowse/hapmap3r2_B36/) comprising the polymorphisms in *XRCC1*, *XRCC3* and *XRCC4* evaluated in present study. Briefly, populations enrolled in the project including CHB (Han Chinese in Beijing, China), CEU (Utah residents with Northern and Western European ancestry from the CEPH collection), JPT (Japanese in Tokyo, Japan) and YRI (Yoruba in Ibadan, Nigeria). Then, Haploview software was applied to conduct analyses and LD was assessed by r^2 statistics in each of the above-mentioned populations.

3. Results

3.1. Main Characteristics of the Enrolled Studies

Table 1 showed the characteristics of all the eligible studies and genotype frequency distributions of twelve polymorphisms in five

Please cite this article as: Zhang, M., et al., Association Between Twelve Polymorphisms in Five X-ray Repair Cross-complementing Genes and the Risk of Urological Neoplasms: A Sy..., EBioMedicine (2017), http://dx.doi.org/10.1016/j.ebiom.2017.03.009