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Review Article

Association between polymorphisms in XRCC4 gene and glioma risk: a meta-analysis and systematic review

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Abstract: Objective: Increasing evidences have shown that DNA repair molecule related genes can be cancer-risk genes. In recent, polymorphisms in XRCC4, which is a member of DNA repair genes, have been identified contributed to the risk of a variety of cancers, including glioma. Nevertheless, data derived from these studies are inconclusive. Therefore, to obtain a more precise estimation, the present meta-analysis was conducted. Methods: A comprehensive retrieve was conducted to identify all eligible studies concerning XRCC4 polymorphisms and glioma risk. Odds ratios (ORs) correspondence with 95% confidence intervals (CIs) were applied to evaluate the strength of associations. Results: We included seven publications comprising 12 case-control studies including 3,199 cases and 5,340 controls concerning two polymorphisms (rs1805377 and rs3734091) in XRCC4 and glioma risk. Overall, significant association was uncovered for rs1805377 polymorphism and risk of glioma (BB VS. AA: OR=1.372, 95% CI: 1.061-1.775, P=0.016; BB VS. BA+AA: OR=1.346, 95% CI: 1.054-1.721, P=0.017). In addition, we also uncovered an increased risk of glioma for rs3734091 polymorphism (BA VS. AA: OR=1.379, 95% CI: 1.052-1.808, P=0.020). When subgroup analysis was performed by ethnicity, we identified a significantly increased risk for glioma of rs1805377 polymorphism (BB VS. AA: OR=1.363, 95% CI: 1.045-1.778, P=0.022; BB VS. BA+AA: OR=1.333, 95% CI: 1.035-1.716, P=0.026), as well as rs373409 polymorphism in Asian population (BA VS. AA: OR=1.442, 95% CI: 1.085-1.916, P=0.012). Conclusions: Our work suggests that rs1805377 and rs3734091 polymorphisms in XRCC4 might be risk factors of glioma. Nevertheless, future well-designed studies are warranted to explore the molecular mechanisms underlying the biological functions of XRCC4 polymorphisms in glioma development.

Keywords: XRCC4 gene, polymorphisms, glioma risk, DNA repair molecule related genes

Introduction

Glioma is one the most frequent type of intracerebral tumor, which accounts for more than 40% of primary brain tumors [1-3]. Although the etiology of glioma is still unknown, enormous evidences have suggested that exposure to ionizing radiation (IR) and genetic variations are definitely related to an increased risk of glioma [4].

Recently, increasing studies have suggested that DNA repair system plays an essential part in maintaining regular function and the stability of genetic materials in mammalian [5, 6]. If the DNA damage causes, such as diverse exogenous damages (i.e., ultraviolet radiation), reactive oxygen species, and etc., are not repaired in time, subsequently, it may lead to carcinogenesis or apoptosis [7, 8]. Commonly, two dominant pathways (homologous recombination and nonhomologous DNA end joining (NHEJ), are widely reported contributing to the repair process of DNA damage. In addition, recent research indicates that several polymorphisms in the genes of NHEJ pathway, including XRCC4, XRCC5 (also known as Ku80), XRCC7 (also known as Ku70), LIG4 (DNA ligase IV, LIG4), *etc.*, potentially related to the modification of cancer risk.

XRCC4 is located on 5q14.2, and the protein encoded by this gene comprising of 8 exons including 336 amino acid residues. XRCC4 is uncovered to renovate DNA double-strand breaks (DSB) [9], which can interacts with Ku70/Ku80, directly. Previous study suggested that XRCC4 acts as a flexible tether between ligase 4 (its associated protein) and Ku70/Ku80 [10]. Two polymorphisms (rs1805377 and rs37340-

Table 1. Details of the enrolled case-control studies

SNP	First author	Year	Ethnicity	Genotyping method	Source of control	Cancer Type	Case			Control			
							PAA	PAB	PBB	HAA	HAB	HBB	P (HWE)
rs1805377	Zhao *et al.*	2013	Asian	TaqMan	H-B	Glioma	179	143	62	195	153	36	Y
	Rajaraman *et al.*	2010	Caucasian	TaqMan	H-B	Glioma	261	71	8	347	115	7	Y
	Su *et al.*	2015	Asian	PCR-RFLP	H-B	Glioma	62	70	30	137	134	53	N
	Liu *et al.*	2007	Asian	TaqMan	H-B	Glioma	382	312	53	379	305	48	Y
rs3734091	Luo *et al.*	2013	Asian	Sequenom Mass ARRAY	H-B	Glioma	262	31	4	369	35	11	N
	Rajaraman *et al.*	2010	Caucasian	TaqMan	H-B	Glioma	326	8	0	436	12	0	Y
	Lin *et al.*	2014	Asian	TaqMan	H-B	Glioma	168	40	34	298	39	21	N
	Gao *et al.*	2014	Asian	Sequenom Mass ARRAY	H-B	Glioma	284	37	5	339	34	3	N

PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism; HWE: Hardy-Weinberg equilibrium; H-B: Hospital based; P-B: Population based. AA, Homozygotes for the common allele; AB, Heterozygotes; BB, Homozygotes for the rare allele.

91) in XRCC4 gene were found contributed to the risk of a variety of cancers, such as pancreatic cancer [11], salivary gland carcinoma [12], and colorectal cancer (CRC) [13], etc. In addition, till now, many studies have investigated the role of two polymorphisms (rs1805377 and rs3734091) in XRCC4 gene and glioma risk. Nevertheless, results arising from these studies were controversial and inconclusive. To conquer the limitations of individual genetic association studies and achieve a more precise estimation of the relationships between XRCC4 polymorphisms and glioma risk, we conducted the present meta-analysis.

Material and methods

Publication search

We searched PubMed, Google, Embase and Wanfang Databases (China) using the following search terms: "x-ray cross complementing group 4 OR XRCC4" AND "polymorphism OR mutation OR variant OR allele OR SNP OR genotype" AND "cancer OR tumor OR carcinoma OR neoplasm OR malignancy" (last retrieve was updated on January 5, 2016). The language of present study was restricted to English or Chinese. We also performed a hand search of the reference lists of original articles to identify additional eligible studies. If publication with overlapping data published by the same team, we will enroll the most complete or recent one.

Inclusion and exclusion criteria

Studies enrolled in the current meta-analysis should refer to the following criteria: 1) assessing the relationship between XRCC4 polymorphisms and glioma risk; 2) case-control or cohort studies; 3) we can obtain sufficient data from the main text or the supporting information (allele and genotype frequencies). Studies should be removed when they were: 1) not case-control or cohort study, such as Comments, Reviews, or case reports; 2) no sufficient data; or 3) date duplicates.

Data extraction

Two reviewers have devoted themselves to data extraction process, and all the consensuses were achieved through discussion. For individual study, the following details should be extracted: name of the first author, ethnicity, year of publication, genotyping method, source of control, hardy weinberg equilibrium (HWE) and genotype frequencies, etc. Diverse ethnic descents were classified to Caucasian and Asian. In addition, for studies comprising participants of different ethnicities, we extract the data individually referring to the specific ethnic group.

Statistical analysis

OR and 95% CI were calculated to measure the strength of the relationship between XRCC4 polymorphisms and glioma risk. *Z*-test was performed to determine the significance of the summary ORs. Five genetic models were applied to assess the associations, including allele contrast B vs. A, homozygote comparison BB vs. AA, heterozygote comparison BA vs. AA, dominant model BA+BB vs. AA, and recessive model BB vs. BA+BB. Stratification analyses were also conducted by genotyping method, ethnicity and HWE status (conform or not conform). X^2-based Q test was applied to check the heterogeneity. Once the *P*-value less than 0.1 for the Q-test indicated the existence of heterogeneity between studies, thus, random-effects model (DerSimonian and Laird method) was adopted to calculate the summary OR estima-

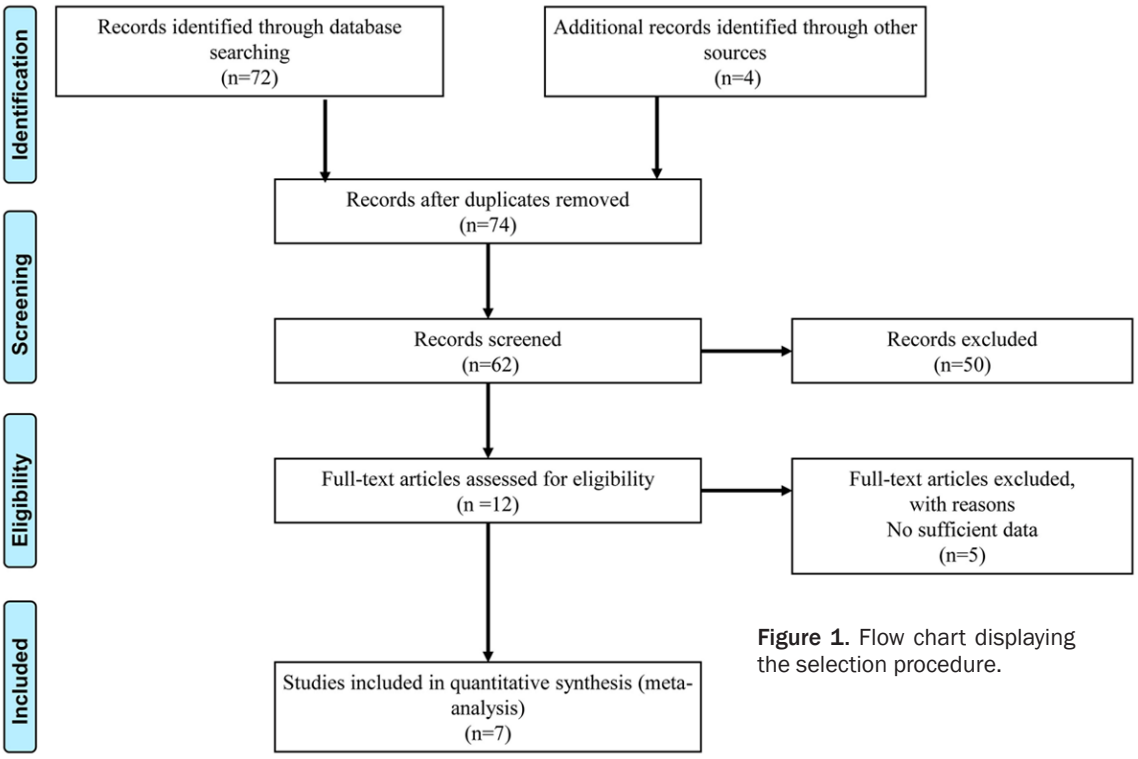

Figure 1. Flow chart displaying the selection procedure.

tion; otherwise, the fixed-effects model will be preferred [14, 15]. In addition, subgroup analyses were conducted by ethnicity, genotyping method and source of control to investigate the causes of heterogeneity. The publication bias was assessed by Begg's funnel plot and egger's test. Sensitivity analysis was performed to investigate the effects of separate study on the overall pooled ORs. All the statistical analyses were conducted by Stata 12.0 software (version 12.0; Stata Corp LP, TX, USA).

Results

Eligible studies

A total of seven studies that met the eligibility criteria were eventually involved in quantitative synthesis for systematic review (**Table 1** and **Figure 1**) [16-22]. For XRCC4 rs1805377 polymorphism, there are four studies with 1,633 cases and 1,909 controls that met the inclusion criteria. Of these studies, three were of Asian, and one was Caucasian. For XRCC4 rs3734091 polymorphism, there are also four case-control studies with 1,199 cases and 1,597 controls met the eligibility criteria, and three of these studies emphasizing on Asians and one in Caucasian. In addition, control groups of all eligible studies were hospital-based (H-B). Genotyping methods used in the eligible studies including TaqMan, MassArray and polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). In addition, there are four case-control studies deviated from HWE [17-19, 21].

Meta-analyses

Results of the present meta-analysis were demonstrated in **Table 2**. Significant association was uncovered for rs1805377 polymorphism and an increased risk of glioma (BB VS. AA: OR=1.372, 95% CI: 1.061-1.775, P=0.016, **Figure 2**; BB VS. BA+AA: OR=1.346, 95% CI: 1.054-1.721, P=0.017). In addition, we also uncovered an increased risk of glioma for rs3734091 polymorphism (BA VS. AA: OR=1.379, 95% CI: 1.052-1.808, P=0.020, **Figure 3**).

Subgroup analysis

When subgroup analysis was performed by ethnicity, we probed significant increased risk of rs1805377 polymorphism for glioma in Asian population (BB VS. AA: OR=1.363, 95% CI: 1.045-1.778, P=0.022; BB VS. BA+AA: OR=1.333, 95% CI: 1.035-1.716, P=0.026). In addition, we further probed the relationship of rs1805377 polymorphism and the risk to can-

Table 2. Results of the meta-analysis

SNP	Comparison	Subgroup	N	*P*H	*P*Z	Random	Fixed
rs1805377	B VS. A	Overall	4	0.246	0.119	1.092 (0.957-1.247)	1.090 (0.978-1.214)
	B VS. A	Asian	3	0.266	0.057	1.128 (0.983-1.296)	1.120 (0.997-1.258)
	B VS. A	TaqMan	3	0.133	0.195	1.080 (0.905-1.290)	1.081 (0.961-1.216)
	B VS. A	Y	3	0.133	0.195	1.080 (0.905-1.290)	1.081 (0.961-1.216)
	BA VS. AA	Overall	4	0.616	0.907	0.992 (0.858-1.147)	0.991 (0.858-1.146)
	BA VS. AA	Asian	3	0.858	0.671	1.035 (0.882-1.216)	1.036 (0.882-1.216)
	BA VS. AA	TaqMan	3	0.544	0.707	0.971 (0.832-1.134)	0.971 (0.832-1.133)
	BA VS. AA	Y	3	0.544	0.707	0.971 (0.832-1.134)	0.971 (0.832-1.133)
	BA+BB VS. AA	Overall	4	0.474	0.518	1.047 (0.912-1.201)	1.046 (0.912-1.201)
	BA+BB VS. AA	Asian	3	0.664	0.255	1.092 (0.938-1.272)	1.092 (0.938-1.272)
	BA+BB VS. AA	TaqMan	3	0.355	0.714	1.028 (0.884-1.195)	1.028 (0.887-1.191)
	BA+BB VS. AA	Y	3	0.355	0.714	1.028 (0.884-1.195)	1.028 (0.887-1.191)
	BB VS. AA	Overall	4	0.381	0.016	1.370 (1.053-1.781)	1.372 (1.061-1.775)
	BB VS. AA	Asian	3	0.220	0.022	1.365 (0.979-1.902)	1.363 (1.045-1.778)
	BB VS. AA	TaqMan	3	0.231	0.022	1.425 (0.972-2.088)	1.410 (1.052-1.890)
	BB VS. AA	Y	3	0.231	0.022	1.425 (0.972-2.088)	1.410 (1.052-1.890)
	BB VS. BA+AA	Overall	4	0.307	0.017	1.346 (1.02-1.777)	1.346 (1.054-1.721)
	BB VS. BA+AA	Asian	3	0.174	0.026	1.330 (0.948-1.866)	1.333 (1.035-1.716)
	BB VS. BA+AA	TaqMan	3	0.205	0.017	1.429 (0.969-2.109)	1.412 (1.063-1.875)
	BB VS. BA+AA	Y	3	0.205	0.017	1.429 (0.969-2.109)	1.412 (1.063-1.875)
rs3734091	B VS. A	Overall	4	0.007	0.202	1.355 (0.849-2.161)	1.526 (1.238-1.882)
	B VS. A	Asian	3	0.005	0.154	1.459 (0.868-2.454)	1.576 (1.270-1.955)
	B VS. A	Sequenom	2	0.229	0.391	1.143 (0.794-1.646)	1.141 (0.844-1.542)
	B VS. A	TaqMan	2	0.057	0.320	1.567 (0.647-3.798)	2.026 (1.508-2.721)
	B VS. A	N	3	0.005	0.154	1.459 (0.868-2.454)	1.576 (1.270-1.955)
	BA VS. AA	Overall	4	0.498	0.020	1.383 (1.054-1.814)	1.379 (1.052-1.808)
	BA VS. AA	Asian	3	0.500	0.012	1.444 (1.086-1.919)	1.442 (1.085-1.916)
	BA VS. AA	Sequenom	2	0.911	0.179	1.274 (0.895-1.814)	1.274 (0.895-1.814)
	BA VS. AA	TaqMan	2	0.173	0.042	1.419 (0.729-2.762)	1.547 (1.015-2.356)
	BA VS. AA	N	3	0.500	0.012	1.444 (1.086-1.919)	1.442 (1.085-1.916)
	BA+BB VS. AA	Overall	4	0.071	0.097	1.396 (0.942-2.069)	1.483 (1.166-1.887)
	BA+BB VS. AA	Asian	3	0.057	0.067	1.495 (0.972-2.299)	1.544 (1.202-1.983)
	BA+BB VS. AA	Sequenom	2	0.487	0.269	1.204 (0.865-1.677)	1.205 (0.866-1.676)
	BA+BB VS. AA	TaqMan	2	0.074	0.325	1.539 (0.652-3.633)	1.890 (1.326-2.694)
	BA+BB VS. AA	N	3	0.057	0.067	1.495 (0.972-2.299)	1.544 (1.202-1.983)
	BB VS. AA	Overall	3	0.032	0.458	1.518 (0.504-4.577)	1.941 (1.221-3.084)
	BB VS. AA	Asian	3	0.032	0.458	1.518 (0.504-4.577)	1.941 (1.221-3.084)
	BB VS. AA	Sequenom	2	0.150	0.719	0.940 (0.25-3.531)	0.855 (0.365-2.003)
	BB VS. AA	TaqMan	1	1.000	0.000	2.872 (1.615-5.108)	2.872 (1.615-5.108)
	BB VS. AA	N	3	0.032	0.458	1.518 (0.504-4.577)	1.941 (1.221-3.084)
	BB VS. BA+AA	Overall	3	0.041	0.491	1.450 (0.504-4.177)	1.823 (1.150-2.891)
	BB VS. BA+AA	Asian	3	0.041	0.491	1.450 (0.504-4.177)	1.823 (1.150-2.891)
	BB VS. BA+AA	Sequenom	2	0.151	0.678	0.918 (0.246-3.427)	0.835 (0.357-1.955)
	BB VS. BA+AA	TaqMan	1	1.000	0.001	2.623 (1.482-4.642)	2.623 (1.482-4.642)
	BB VS. BA+AA	N	3	0.041	0.491	1.450 (0.504-4.177)	1.823 (1.150-2.891)

PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism; HWE: Hardy-Weinberg equilibrium; *P*H: *P* value of the heterogeneity test; *P*z: *P* value of the Z test. Y: Study conform to HWE; N: Study do not conform to HWE; B: Mutated allele; A: Wild allele.

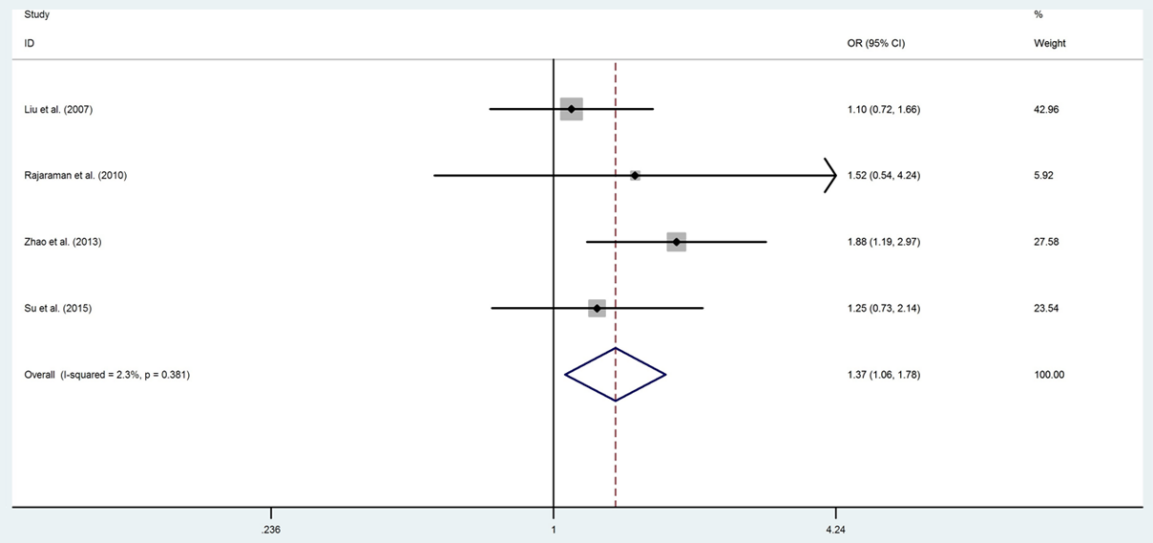

Figure 2. OR estimates with the corresponding 95% CI for the association of XRCC4 rs1805377 polymorphism with overall glioma risk (BB VS. AA); the sizes of the squares represent the weighting of included studies. Note: Weights are from random effect analysis. Abbreviations: OR, odds ratio.

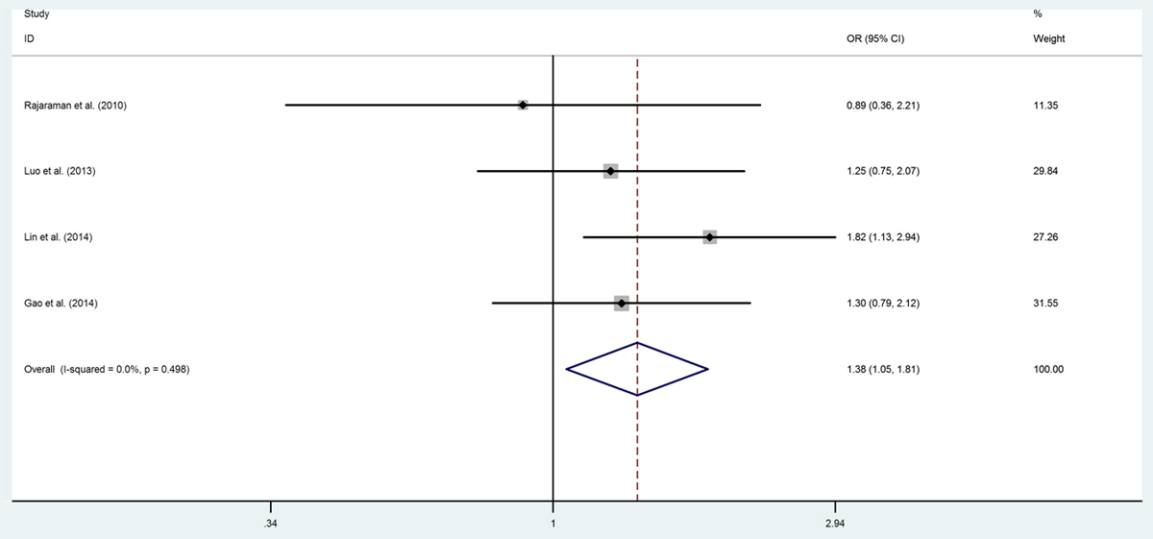

Figure 3. OR estimates with the corresponding 95% CI for the association of XRCC4 rs3734091 polymorphism with overall glioma risk (BA VS. AA); the sizes of the squares represent the weighting of included studies. Note: Weights are from random effect analysis. Abbreviations: OR, odds ratio.

cer in accordance with TaqMan and HWE status. Besides, similar association was acquired from our analysis when stratified by TaqMan (**Table 2**).

For rs373409 polymorphism, in subgroup analysis by ethnicity, we uncovered an increased risk of glioma in Asian population (BA VS. AA: OR=1.442, 95% CI: 1.085-1.916, P=0.012). When the stratified analysis was conducted by genotyping method, we identified a significant association of TaqMan method (**Table 2**). In addition, as for the subgroup analysis by HWE status, there also existed significant association (**Table 2**).

Test of heterogeneity and publication bias

As most of the analyses had no heterogeneity, the summary ORs estimate of these models were calculated by the fixed-effects model. While a few *P*-value of heterogeneity were less

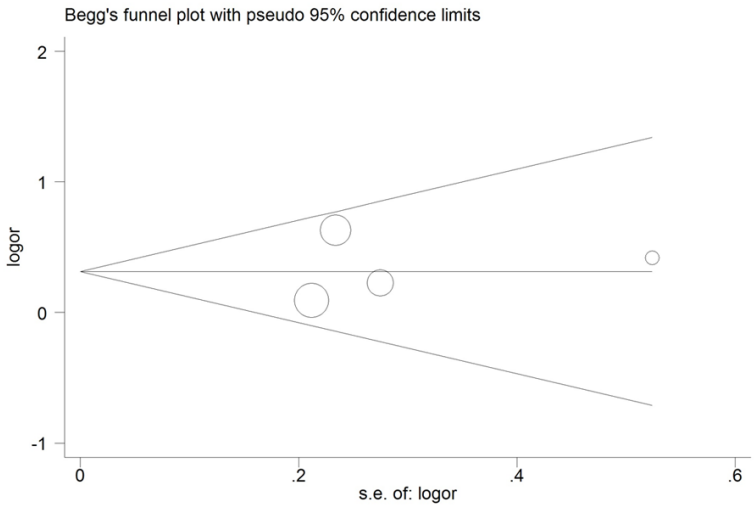

Figure 4. Publication bias in studies of the association between the XRCC4 rs1805377 polymorphism and glioma susceptibility assessed by Begg's funnel plot and Egger's test (BB VS. AA). Abbreviations: Log (OR), the natural logarithm of the odds ratio; SE, standard error.

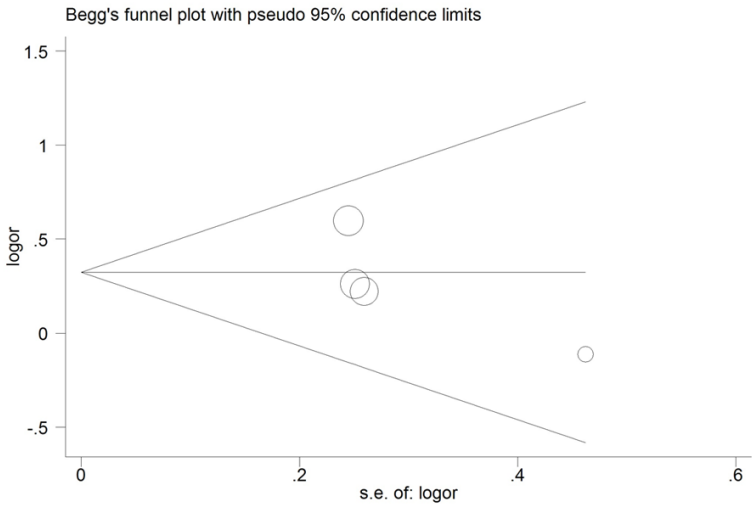

Figure 5. Publication bias in studies of the association between the XRCC4 rs373409 polymorphism and glioma susceptibility assessed by Begg's funnel plot and Egger's test (BA VS. AA). Abbreviations: Log (OR), the natural logarithm of the odds ratio; SE, standard error.

than 0.1 in overall or subgroups analyses, the random-effects model was used (Data are shown in **Table 2**).

Sensitivity analysis and publication bias

We performed sensitivity analysis by sequential omission of each study in all the five contrasts and no significant influence was identified. Then, publication bias was accessed by Egger's linear regression test and Begg's funnel plot. All the graphical funnel plots seemed to be symmetrical (rs1805377: BB VS. AA, **Figure 4** & rs373409: BA VS. AA, **Figure 5**) and Egger's test also demonstrated that no significant publication bias was uncovered for all evaluations (rs1805377: BB VS. AA, P>|t|= 0.830; rs373409: BA VS. AA, P>|t|= 0.295). In addition, the quality of these enrolled case-control studies was evaluated by Newcastle-Ottawa Scale (NOS) (**Table 3**).

Discussion

During the past decades, investigations have proved that single nucleotide polymorphisms (SNPs) may be taken responsibility of inter individual discrepancies in risk to a variety of cancers. And recently, increasing number of studies have identified that gene polymorphisms in DNA repair pathways play an essential role in tumorigenesis process. Of them, XRCC4, a member of NHEJ pathway, has been widely studied on account of its association with diverse cancer types, such as bladder cancer, pancreatic cancer, and glioma and etc.

In the study conducted by Custódio *et al.* [23], they acquired the evidence that XRCC4 G1394T polymorphism is associated with glioma risk. Then, Youle *et al.* [24] validated their results, suggesting that XRCC4 polymorphisms in the DNA repair pathways play an important role in glioma risk in a Chinese population. However, in Luo *et al.*'s [21] study, they enrolled 297 cases and 458 cancer-free controls and obtained a negative association. As these discoveries are inconclusive, we firstly performed the present meta-analysis concerning the association between

Table 3. Methodological quality of the included studies according to the Newcastle-Ottawa scale

Polymorphism	Author	Ethnicity	Adequacy of case definition	Representativeness of the cases	Selection of controls	Definition of controls	Comparability cases/controls	Ascertainment of exposure	Same method of ascertainment	Non-response rate
rs1805377	Zhao *et al.*	Asian	*	*	*	*	**	*	*	*
	Rajaraman *et al.*	Asian	*	*	*	*	**	*	*	*
	Su *et al.*	Caucasian	*	*	*	*	**	*	*	*
	Liu *et al.*	Asian	*	*	*	*	**	*	*	*
rs3734091	Luo *et al.*	Asian	*	*	*	*	**	*	*	*
	Rajaraman *et al.*	Asian	*	*	*	*	**	*	*	*
	Lin *et al.*	Caucasian	*	*	*	*	**	*	*	*
	Gao *et al.*	Caucasian	*	*	*	*	**	*	*	*

This table identifies 'high' quality choices with a 'star'. A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability. *, Yes; NA, not applicable. (http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm).

polymorphisms in XRCC4 and glioma risk. Our work presents a significant association between the two polymorphisms (rs1805377 and rs3734091) in XRCC4 and glioma risk. In the stratification analysis by ethnicity, an increased risk was uncovered for both polymorphisms in Asian population. Besides, our data also suggested genotyping method and HWE status can affect the pooled results for the two polymorphisms.

In this present meta-analysis, we observed the heterogeneity of between-studies heterogeneity between XRCC4 rs1805377 and XRCC4 rs373409 polymorphisms and cancer risk, absolutely meta-regression analysis indicating that HWE status was conduce to substantial heterogeneity among the meta-analysis for XRCC4 two polymorphisms. Methodological problems could be reflected by Deviation of HWE status, such as the errors of genotyping, the bias of population stratification or selection. The results of overall cancer and some subgroup analyses could be verified for XRCC4, if we excluded these studies, evidencing that our statistical analysis was not fully strong. Hence, there may be not existed significant in glioma cancer although the results were different.

Several drawbacks of the present work should also be noted. Firstly, relative small number of studies enrolled in the meta-analysis would be a restriction, potentially contributing to the limitation of conclusions. Secondly, the ethnicities of these enrolled studies were dominated by Asian, and only two of them were Caucasian. However, no African data was available. Therefore, subgroup analysis by ethnicity cannot be conducted. Thirdly, because the lack of original data, such as eating habits, living environment, drinking and virus carrier status, our results were based on unadjusted estimates. Despite these limitations, our meta-analysis also have several advantages. Firstly, the retrieved studies were up to date and half of them were published in 2013 or 2014. Secondly, the quality of enrolled case-control studies was satisfactory and met our inclusion criteria. Thirdly, our study focus on the most extensively studied polymorphisms of XRCC4.

In summary, our data suggests that XRCC4 polymorphisms (rs1805377 and rs3734091) may be risk factors for glioma. Considering the limitations presented above, future well-designed studies with larger sample size are warranted to verify our findings.

Disclosure of conflict of interest

None.

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