

XRCC1 Arg280His polymorphism and glioma risk: A meta-analysis involving 1439 cases and 2564 controls

Liang Zhang¹, Yan Wang², Zhiqun Qiu³, Jiaohua Luo⁴,
Ziyuan Zhou⁵, Weiqun Shu⁶

ABSTRACT

Objectives: Previous reports indicated that XRCC1 Arg280His polymorphism might be a possible risk factor for several cancers. Published studies on the association of XRCC1 Arg280His polymorphisms with glioma risk have yielded controversial results. The present study aimed to derive a more precise estimation of the relationship.

Methodology: Meta-analyses assessing the association of XRCC1 Arg280His variation with glioma were conducted and subgroup analyses on ethnicity and source of controls were further performed. Eligible studies for the period up to May 2012 were identified.

Results: A total of four case-control studies comprising 1439 cases and 2564 controls were selected for analysis. The overall data indicated no significant association of XRCC1 Arg280His polymorphism with glioma risk (His vs Arg: OR=1.05; 95%CI=0.88-1.25; His/His vs Arg/Arg: OR=1.42; 95%CI=0.87-2.29; dominant model: OR=1.00; 95%CI=0.82-1.22; recessive model: OR=1.41; 95%CI=0.88-2.25). Likewise, in the subgroup analysis regarding ethnicity and source of controls, no associations were observed.

Conclusion: The results of the present study failed to suggest an association of XRCC1 Arg280His polymorphism with glioma risk. Further large and well-designed studies are needed to confirm this conclusion.

KEY WORDS: XRCC1 Arg280His, Glioma, Malignancy, Susceptibility, Meta-analysis, Polymorphism.

doi: <http://dx.doi.org/10.12669/pjms.291.2694>

How to cite this:

Zhang L, Wang Y, Qiu Z, Luo J, Zhou Z, Shu W. XRCC1 Arg280His polymorphism and glioma risk: A meta-analysis involving 1439 cases and 2564 controls. *Pak J Med Sci* 2013;29(1):37-42. doi: <http://dx.doi.org/10.12669/pjms.291.2694>

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

1. Liang Zhang,
 2. Yan Wang,
Institute of Respiratory Diseases, Xinqiao Hospital,
Third Military Medical University, Chongqing, China.
 3. Zhiqun Qiu,
 4. Jiaohua Luo,
 5. Ziyuan Zhou,
 6. Weiqun Shu,
- 1,3-6: Department of Environmental Hygiene,
College of Preventive Medicine,
Third Military Medical University,
Chongqing, China.

Correspondence:

Weiqun Shu, MD,
Department of Environmental Hygiene,
College of Preventive Medicine,
Third Military Medical University,
Chongqing, China.
E-mail: sydsqw@163.com

- * Received for Publication: July 15, 2012
- * Accepted: October 5, 2012

INTRODUCTION

Glioma is the most common type of primary brain tumor in adults. The general prognosis for patients is very poor, particularly for the elderly patients. The mechanisms of carcinogenesis for glioma are still not fully understood. Evidence suggests that exposure to radiation might be an important risk factor for glioma, which could explain a small proportion of glioma because the exposure is generally rare.¹ However, only a small proportion of individuals exposed to radiation eventually developed glioma, indicating that host genetic factors might play a critical role in the carcinogenesis of glioma.²

Radiation exposure may cause DNA damage as well as cell injury. The consequences to the damaged cells can be disastrous, ranging from

single gene mutations to massive chromosomal breakdown. The gene damage of the cells could result in severe human diseases including tumor.³ Generally, the repairing of various types of DNA damage is important for maintenance of genomic stability and cell survival. In this process, base excision repair pathways may play a predominant role in protecting both nuclear and mitochondrial DNA from radiation damages.⁴ X-ray repair cross-complementing gene 1 (XRCC1) is one of the most important DNA repair genes that play a key role in the process of base excision repair. The XRCC1 gene is located on chromosome 19q13.2-13.3 and is 33 kb in length, containing 17 exons and encoding a 70 kDa protein. A widely studied XRCC1 single nucleotide polymorphism at the codon 280, with a Arg to His change (rs25489), could have a diminished capacity to remove DNA adducts and oxidized DNA damage.⁵ Hence, Arg280His variation has been thought to associate with carcinoma risk.

Published investigations on the association of XRCC1 Arg280His polymorphism with glioma have yielded inconclusive results. In the present study, we carried out a quantitative meta-analysis that increased statistical power to derive a more precise estimation of the relationship.

METHODOLOGY

1: Literature search strategy: We carried out a search in the Medline, EMBASE, OVID, Sciencedirect, and Chinese National Knowledge Infrastructure (CNKI) without a language limitation, covering all papers published up to May 2012, with a combination of the following keywords: *XRCC1, Arg280His, glioma, brain, neoplasm, cancer, variation and polymorphism*. All searched studies were retrieved and the bibliographies were checked for other relevant publications. Review articles and bibliographies of other relevant studies identified were hand searched to find additional eligible studies.

2: Inclusion criteria: The following criteria were used for the literature selection: first, studies should concern the association of XRCC1 Arg280His polymorphism with glioma risk; second, studies must be observational studies (Case-control or cohort); third, papers must offer the size of the sample, odds ratios (ORs) and their 95% confidence intervals (CIs), the genetic distribution or the information that can help infer the results. After rigorous searching, we reviewed all papers in accordance with the criteria defined above for further analysis.

3: Data extraction: Data were carefully extracted from all eligible publications independently by two of the authors according to the inclusion criteria mentioned above. For conflicting evaluations, an agreement was reached following a discussion. If a consensus could not be reached, another author was consulted to resolve the dispute and then a final decision was made by the majority of the votes. Extracted information was entered into a database.

4: Statistical analysis: The OR of XRCC1 Arg280His polymorphism and glioma risk was estimated for each study. The pooled ORs were assessed for the genetic comparisons of allelic contrast (His vs Arg), homozygote comparison (His/His vs Arg/Arg), dominant model (His/His+His/Arg vs Arg/Arg) and recessive model (His/His vs His/Arg+Arg/Arg), respectively. For detection of any possible sample size biases, the OR and its 95% confidence interval (CI) to each study was plotted against the number of participants respectively. A Chi-square based Q statistic test was performed to assess heterogeneity. If the result of the Q-test was $P > 0.1$, ORs were pooled according to the fixed-effect model (Mantel-Haenszel); otherwise, the random-effect model (DerSimonian and Laird) was used. The significance of the pooled ORs was determined by Z-test. The Hardy-Weinberg equilibrium (HWE) was assessed by Fisher's exact test. Publication bias was assessed by visual inspection of funnel plots⁶, in which the standard error of log (OR) of each study was plotted against its log (OR). An asymmetric plot indicates a possible publication bias. The symmetry of the funnel plot was further evaluated by Egger's linear regression test.⁷ Statistical analysis was undertaken using the program STATA 11.0 software (Stata Corporation, Texas).

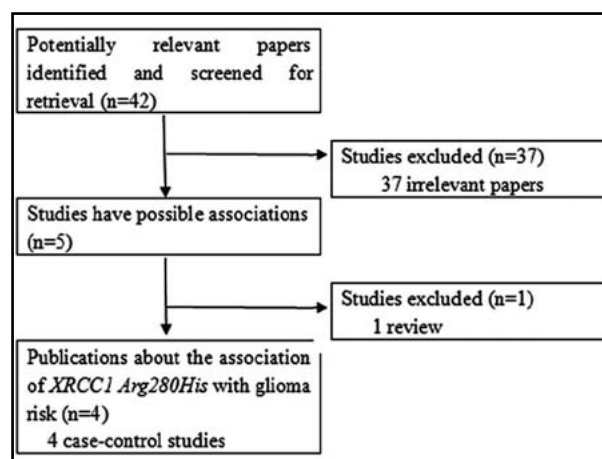


Fig.1: The flow diagram of included/excluded studies.

Table-I: Characteristics of studies included in the meta-analysis.

First Author	Publication Year	No. of Cases (male/female)	No. of Controls (male/female)	Type of controls	Median (or mean) age, (range) year (Cases/Controls)	Racial decent	Country
Kiuru	2008	426 (259/167)	1560 (705/855)	Healthy controls (age-, sex-, geographical area-matched; PB)	48.2(NA)/63(NA)	Caucasian	Four countries in Europe
Rajaraman	2010	362 (198/164)	495 (228/267)	Non-cancer controls (age-, race-, sex-, hospital-, residence-matched; HB)	51.2(18-90)/49.2(18-90)	Caucasian	USA
Hu	2011	127 (87/40)	249 (166/83)	Non-cancer controls (age-, sex-matched; HB)	49.5(NA)/48.9(NA)	Asian	China
Zhou	2011	271 (168/103)	289 (180/109)	Healthy controls (age-matched; PB)	47.8(NA)/46.9(NA)	Asian	China

NA: not available; PB: population-based; HB: hospital-based

RESULTS

1: Study characteristics: Relevant publications were retrieved and screened originally. As shown in Fig.1, a total of forty-two publications were identified, of which thirty-seven irrelevant papers were excluded. Thus, five publications were preliminary eligible, of which one review article⁸ was discarded. Consequently, four case-control studies were included for data extraction and analysis.⁹⁻¹²

All the selected publications were written in English. The relevant information was listed in Table-I. According to this table, the first author and the number and characteristics of cases and controls for each study as well as other necessary information were presented. There were two groups of Caucasians^{9,10} and two of Asians^{11,12} in the present meta-analysis.

The distributions of XRCC1 Arg280His genotypes as well as the genotyping methods of the included studies were presented in Table-II. The genetic distributions of the control groups in all studies were consistent with HWE, except for one study.¹²

2: Test of heterogeneity: As shown in Table-III, we analyzed the heterogeneities for the four genetic comparisons, respectively. No evident heterogeneities for the overall data were shown in the four genetic models (allelic contrast: $P=0.191$ for Q-test; homozygote comparison: $P=0.705$ for Q-test; dominant model: $P=0.423$ for Q-test; recessive model: $P=0.719$ for Q-test). Additionally, *I*-square value is another index for the heterogeneity test¹³, with value less than 25% indicating low, 25% to

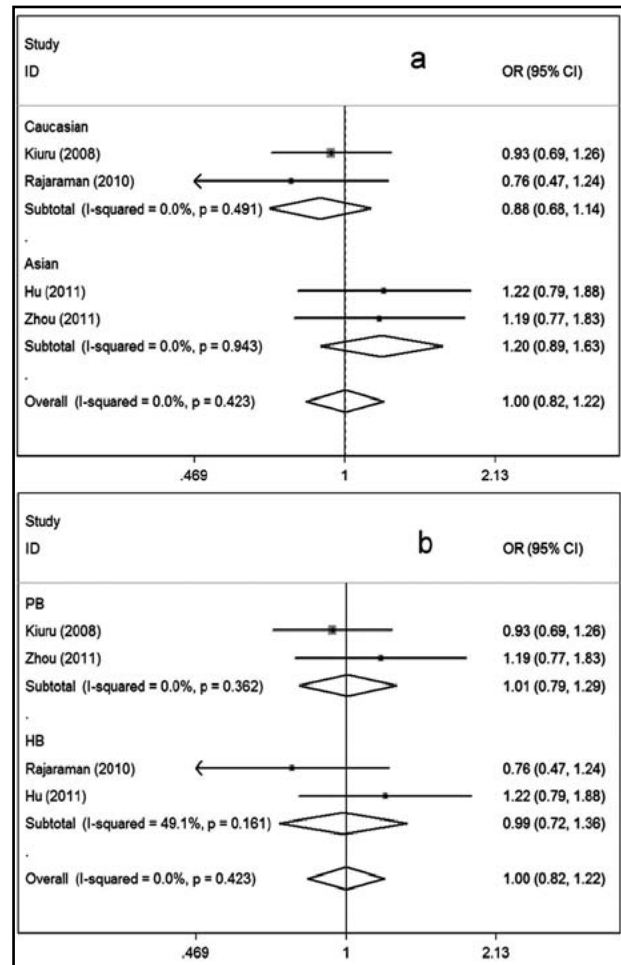


Fig.2: Meta-analysis for the association of glioma risk with XRCC1 Arg280His polymorphism. (His/His+His/Arg vs Arg/Arg); (a) Stratified by ethnicity; (b) Stratified by source of control.

Table-II: Distribution of XRCC1 Arg280His genotypes among glioma cases and controls included in the meta-analysis.

First Author	Year	Genotyping method	Cases			Controls			HWE (control)
			His/His	Arg/His	Arg/Arg	His/His	Arg/His	Arg/Arg	
Kiuru	2008	PCR-RFLP	1	67	633	4	157	1399	Yes
Rajaraman	2010	TaqMan	0	28	312	1	48	417	Yes
Hu	2011	PCR-CTPP	27	28	72	38	58	153	No
Zhou	2011	TaqMan	8	45	218	5	44	240	Yes

PCR-RFLP: Polymerase Chain Reaction–Restriction Fragment Length Polymorphism;
 PCR-CTPP: polymerase chain reaction with confronting two -pair primers.

50% indicating moderate, and greater than 50% indicating high heterogeneity. The *I*-square values were 36.8%, 0.0%, 0.0% and 0.0% for the overall data of the allelic contrast, homozygote comparison, dominant and recessive models, respectively, confirming the absence of the heterogeneities between the studies. Thus, the fixed-effect model was used in this model.

3: Meta-analysis results: The main results of the meta-analysis are listed in Table-III. For the overall data including 1439 cases and 2564 controls, no significant associations of XRCC1 Arg280His polymorphism with glioma risk were found in the four genetic models (His vs Arg: OR=1.05; 95%CI=0.88-1.25; His/His vs Arg/Arg: OR=1.42; 95%CI=0.87-2.29; His/His+His/Arg vs Arg/Arg: OR=1.00; 95%CI=0.82-1.22; His/His vs His/Arg+Arg/Arg: OR=1.41; 95%CI=0.88-2.25), indicating that XRCC1 Arg280His polymorphism might not have an association with glioma risk.

In subgroup analysis according to ethnicity, no association was presented in either the Asian subgroup or the Caucasian subgroup. Similarly, when the data were divided by source of controls, no associations were shown in either the population-based subgroup or the hospital-based subgroup (Fig.2).

4: Sensitivity analysis: To test the stability of the overall results, we carried out the one-way sensitivity analysis.¹⁴ The statistical significance of the results was not changed when any single study was omitted (data not shown), indicating the robustness of the results.

5: Bias diagnostics: Funnel plots were created for assessment of possible publication biases (Fig.3a). Then, Egger's linear regression tests were used to assess the symmetries of the plots. The funnel plots appeared to be symmetrical for the overall data indicated by the Egger's tests (allelic contrast: $t = -0.33$, $P > 0.05$, homozygote comparison: $t = -1.90$, $P > 0.05$; dominant model: $t = 0.19$, $P > 0.05$; recessive

model: $t = -1.90$, $P > 0.05$) (Fig.3b), indicating that the publication bias was not evident.

DISCUSSION

For the overall data, XRCC1 Arg280His polymorphism has little association with glioma risk. Likewise, in the subgroups regarding ethnicity and source of controls, no associations could be observed.

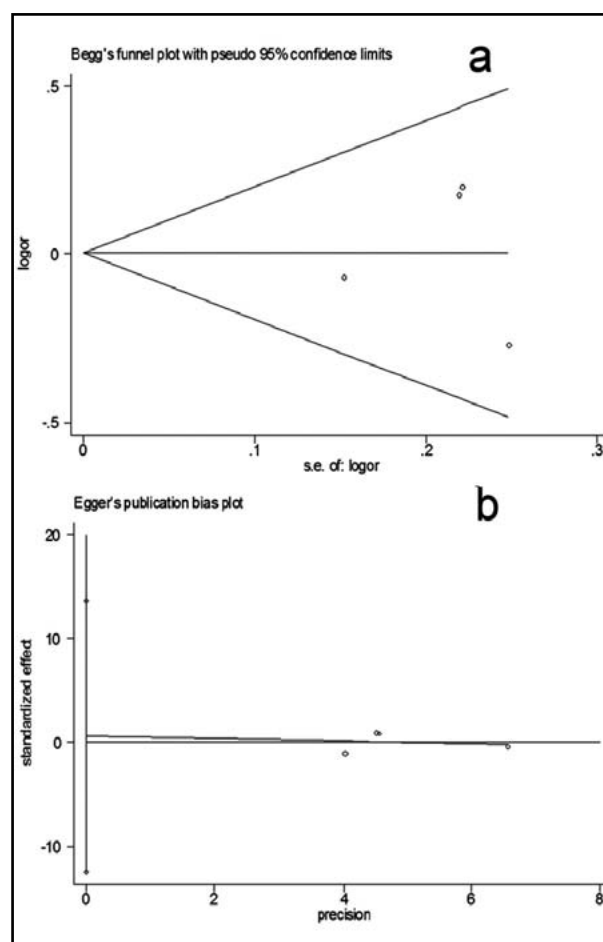


Fig.3: Publication bias test for the overall data (His/His+His/Arg vs Arg/Arg). (a) Funnel plot; (b) Egger's linear regression test.

Table-III: Main results of the pooled data in the meta-analysis.

	No. (cases/ controls)	His allele vs Arg allele			His/His vs Arg/Arg			(His/His + His/Arg) vs Arg/Arg			His/His vs (His/Arg + Arg/Arg)		
		OR (95% CI)	P	P (Q-test)	OR (95% CI)	P	P (Q-test)	OR (95% CI)	P	P (Q-test)	OR (95% CI)	P	P (Q-test)
Total	1439/ 2564	1.05 (0.88-1.25)	0.595	0.191	1.42 (0.87-2.29)	0.157	0.705 (0.82-1.22)	1.00	0.988	0.423	1.41 (0.88-2.25)	0.152	0.719
<i>Ethnicity</i>													
Caucasian	1041/ 2026	0.88 (0.69-1.12)	0.298	0.475	0.52 (0.08-3.16)	0.474	0.913 (0.68-1.14)	0.88	0.339	0.491	0.52 (0.09-3.19)	0.482	0.920
Asian	398/538	1.27 (0.99-1.63)	0.064	0.844	1.56 (0.94-2.59)	0.086	0.811 (0.89-1.63)	1.20	0.234	0.943	1.54 (0.94-2.52)	0.084	0.825
<i>Source of controls</i>													
PB	972/1849	1.03 (0.81-1.29)	0.833	0.250	1.34 (0.51-3.50)	0.552	0.356 (0.79-1.29)	1.01	0.936	0.362	1.32 (0.51-3.46)	0.586	0.367
HB	467/715	1.08 (0.83-1.41)	0.568	0.068	1.44 (0.83-2.51)	0.197	0.462 (0.72-1.36)	0.99	0.937	0.161	1.44 (0.84-2.46)	0.186	0.472

PB: population-based; HB: hospital-based

Considering the possible effects of ethnic variation and source of controls on the results, we further conducted subgroup analyses. Evidence indicates the potential effects of ethnic-specific variation and different socioeconomic classes on glioma.¹⁵ However, in the subgroup analysis according to ethnicity, significant associations were shown among neither Asians nor Caucasians, implying little effects of the ethnic variation of XRCC1 Arg280His polymorphism on glioma risk. Notably, the results should be interpreted with care because the limited number of the included studies containing small sample sizes might result in insufficient statistical power to evaluate a minor effect. Hence, future investigations regarding different ethnicities with large sample sizes are needed to address this issue.

In the subgroup analyses stratified by source of controls, significant increased glioma risk was not also observed in either the population-based subgroup or the hospital-based subgroup. Since hospital-based controls might not be always truly representative of the general population, any selection bias might exist. However, the data of the present study indicated that the influence of the possible selection bias on the overall results was not evident. Noticeably, use of proper control participants with rigorous matching criteria and large sample sizes in future studies is important for reducing such possible selection biases.

Several limitations might be included in the present meta-analysis. First, in this meta-analysis, the primary articles only provided data about

Caucasians and Asians. Other ethnicities such as African should be noted in the future studies. Second, subgroup analyses regarding age, gender, histological types, radiation exposure and other factors have not been performed in the present study because relevant data were insufficient for further analysis. Third, only studies written in English were searched. Thus, some selection biases might exist. Therefore, the results should be interpreted with caution. However, the sensitivity analysis and publication bias analysis indicated the stability and credibility of the present meta-analysis.

In summary, the data of the present meta-analysis failed to suggest an association between XRCC1 Arg280His polymorphism and glioma risk. Further investigations with larger sample sizes and rigorous matching criteria in view of confounding factors are needed to confirm the associations.

REFERENCES

1. Prasad G, Haas-Kogan DA. Radiation-induced gliomas. *Expert Rev Neurother.* 2009;9(10):1511-1517.
2. Montelli Tde C, Peracoli MT, Rogatto SR, Kaneno R, do Prado CH, Rocha Pde M. Genetic and modifying factors that determine the risk of brain tumors. *Cent Nerv Syst Agents Med Chem.* 2011;11(1):8-30.
3. Li GM. A special issue on DNA damage response and genome stability. *Cell Biosci.* 2012;2(1):4.
4. Blaisdell JO, Harrison L, Wallace SS. Base excision repair processing of radiation-induced clustered DNA lesions. *Radiat Prot Dosimetry.* 2001;97(1):25-31.
5. Ginsberg G, Angle K, Guyton K, Sonawane B. Polymorphism in the DNA repair enzyme XRCC1: utility of current database and implications for human health risk assessment. *Mutat Res.* 2011;727(1-2):1-15.

6. Munafo MR, Clark TG, Flint J. Assessing publication bias in genetic association studies: evidence from a recent meta-analysis. *Psychiatry Res.* 2004;129(1):39-44.
7. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 1997;315(7109):629-634.
8. Goode EL, Ulrich CM, Potter JD. Polymorphisms in DNA repair genes and associations with cancer risk. *Cancer Epidemiol Biomarkers Prev.* 2002;11(12):1513-1530.
9. Kiuru A, Lindholm C, Heinavaara S, Ilus T, Jokinen P, Haapasalo H, et al. XRCC1 and XRCC3 variants and risk of glioma and meningioma. *J Neurooncol.* 2008;88(2):135-142.
10. Rajaraman P, Hutchinson A, Wichner S, Black PM, Fine HA, Loeffler JS, et al. DNA repair gene polymorphisms and risk of adult meningioma, glioma, and acoustic neuroma. *Neuro Oncol.* 2010;12(1):37-48.
11. Zhou LQ, Ma Z, Shi XF, Yin XL, Huang KX, Jiu ZS, et al. Polymorphisms of DNA repair gene XRCC1 and risk of glioma: a case-control study in Southern China. *Asian Pac J Cancer Prev.* 2011;12(10):2547-2550.
12. Hu XB, Feng Z, Fan YC, Xiong ZY, Huang QW. Polymorphisms in DNA repair gene XRCC1 and increased genetic susceptibility to glioma. *Asian Pac J Cancer Prev.* 2011;12(11):2981-2984.
13. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327(7414):557-560.
14. Tobias A. Assessing the influence of a single study in the meta-analysis estimate. *Stata Techn Bull.* 1999;8:15-17.
15. Curry WT Jr., Barker FG, 2nd. Racial, ethnic and socioeconomic disparities in the treatment of brain tumors. *J Neurooncol.* 2009;93(1):25-39.