RESEARCH ARTICLE

Association of XRCC3 Thr241Met Polymorphisms and Gliomas Risk: Evidence from a Meta-analysis

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Abstract

The relationship between the X-ray repair cross-complementing group 3 (XRCC3) Thr241Met polymorphism and gliomas remains inclusive or controversial. For better understanding of the effect of XRCC3 Thr241Met polymorphism on glioma risk, a meta-analysis was performed. All eligible studies were identified through a search of PubMed, Elsevier Science Direct, Excerpta Medica Database (Embase) and Chinese Biomedical Literature Database (CBM) before May 2013. The association between the XRCC3 Thr241Met polymorphism and gliomas risk was conducted by odds ratios (ORs) and 95% confidence intervals (95% CIs). A total of nine case-control studies including 3,533 cases and 4,696 controls were eventually collected. Overall, we found that XRCC3 Thr241Met polymorphism was significantly associated with the risk of gliomas (T vs. C: OR=1.10, 95%CI=1.01-1.20, *P*=0.034; TT vs. CC: OR=1.30, 95%CI=1.03-1.65, *P*=0.027; TT vs. TC/CC: OR=1.29, 95%CI=1.01-1.64, *P*=0.039). In the subgroup analysis based on ethnicity, the significant association was found in Asian under four models (T vs. C: OR=1.17, 95%CI=1.07-1.28, *P*=0.00; TT vs. CC: OR=1.79, 95%CI=1.36-2.36, *P*=0.00; TT vs. TC/CC: OR=1.75, 95%CI=1.32-2.32, *P*=0.00; TT/TC vs. CC: OR=1.11,95% CI=1.02-1.20). This meta-analysis suggested that the XRCC3 Thr241Met polymorphism is a risk factor for gliomas, especially for Asians. Considering the limited sample size and ethnicities included in the meta-analysis, further large scale and well-designed studies are needed to confirm our results.

Keywords: XRCC3 - gliomas - polymorphism - meta-analysis

Asian Pac J Cancer Prev, **14 (7)**, 4243-4247

Introduction

Glioma is the most common tumors of the central nervous system in adults, exhibiting various degrees of differentiation inside the same tumor. Gliomas account for almost 80% of primary malignant brain tumors, and lead to more years of life lost than do any other tumors (Kyritsis et al., 2010). It is associated with median survival of only 12 to 15 months for patients with glioblastoma, the most common type of glioma (Prasad and Haas-Kogan, 2009). What is worse, gliomas occur at the beginning, usually without typical or distinct clinical manifestations. The outcomes for patients are poor in general, especially for older patients. Therefore, it is of great importance to have a good understanding of gliomas, especially to clarify its etiology. Unfortunately, the exact etiology of gliomas remains unclear.

Over the past several decades, researches on the etiology of gliomas has yielded few consistent findings; the exposure to radiation or therapeutic is the only established environmental risk factor for explaining the etiology of gliomas. However, this statement can only explain a small number of gliomas because the exposure to radiation or therapeutic is relatively rare and only a minority of individuals exposed to radiation develop gliomas eventually, suggesting additional genetic factors may play an important role in the development of gliomas (Melin, 2011).

It has been well accepted that DNA damage is an important mechanism in the pathogenesis of multiple cancers including gliomas. If damaged DNA is not repaired, mutations and development of cancer happens. Considering the established relationship between radiation and glioma, a hypothesis that genetic variant of the DNA repair pathway may affect susceptibility to gliomas.

The X-ray repair cross-complementing group 3 (XRCC3) is an important member of DNA repair genes that belongs to a family of genes responsible for repairing DNA double strand breaks or exposure to ionizing radiation (Tebbs et al., 1995). The XRCC3 gene codes for a protein involved in homologous recombinational repair (HRR) for double strand breaks of DNA (DBSs)

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and cross-link repair in mammalian cells. XRCC3 gene has been found polymorphic in the gliomas. Since XRCC3 may have a role in gliomas, any mutations in the XRCC3 affecting the production of XRCC3 may be of candidate risk factors for the development of this disease. However, the Thr241Met substitution is the most thoroughly investigated polymorphism in XRCC3 due to a (C/T) transition at exon7 (XRCC3-18067C/T, rs861539), in this study, we called this SNP in the XRCC3 gene "-18067C/T" for short.

In the past ten years, several molecular epidemiological studies have investigated the association between XRCC3 -18067C/T polymorphism and gliomas susceptibility, but the results were inconsistent or controversial. The inconsistency of these studies may caused by small sample size, different population background and study design and so on. In order to derive a more precise estimation of the association between XRCC3 -18067C/T polymorphism and the risk of gliomas, we carried out a meta-analysis of all eligible case-control studies in this article.

Materials and Methods

Search strategy

We conducted an extensive search to identify all currently available studies on the association between the XRCC3 Thr241Met polymorphisms and gliomas risk. All the eligible studies were identified through a search of PubMed, Excerpta Medica Database (Embase) and Chinese Biomedical Literature Database (CBM) before May 2013 by using the terms as follows: ("XRCC3" or "X-ray cross complementing group 3") in combination with ("polymorphism" or "polymorphisms" or "variant" or "mutation") in combination with ("gliomas" or "glioblastoma") for all publications. There were no limitations to the language of publication. Additional studies were identified by a hand search of the references of original studies. Review articles were also examined to find additional eligible studies.

Inclusion and exclusion criteria

The following inclusion criteria were used for literature selection: (1) a case-control design; (2) Articles evaluating the association between the XRCC3 Thr241Met polymorphism and gliomas risk; (3) The study was published in English or Chinese; (4) The article had to provide sufficient data to estimate an odds ratio (OR) and 95% confidence interval (95%CI). The following exclusion criteria were used for excluding studies: (1) studies contained duplicate data; (2) Only recruited the latest study if more than one studies from the same group occurred; (3) Case reports.

Data extraction

Data were carefully extracted by two authors independently. If encountered the conflicting evaluations, an agreement was reached following a discussion; if could not reached agreement, another author was consulted to resolve the debate. The following information were extracted with the inclusion criteria mentioned above: (1) The name of first author; (2) Year of publication; (3) Country of origin; (4) Ethnicity of the population; (5) Genotyping methods; (6) Source of the control group; (7) The sample size of cases and controls. Different ethnicities were categorized as Asian, Caucasians or Mixed. The results were reviewed by a third author and the disagreement was resolved by carried a discussion.

Statistical analysis

The possible association between the XRCC3 Thr241Met polymorphisms and gliomas risk was evaluated by OR and 95%CI according to allele contrast (T vs. C), homozygote (TT vs. CC), heterozygote (TC vs. CC), recessive (TT vs. TC/ CC), and dominant (TT/ TC vs. CC) models. A Chi-square based Q statistic test was performed to assess heterogeneity. If the result of the heterogeneity test $P < 0.10$, between-study heterogeneity was considered existed, ORs were pooled by random-effects model (DerSimonian and Laird method) (DerSimonian and Laird, 1986). Otherwise, the fixed-effects model (the Mantel-Haenszel method) was used (Mantel and Haenszel, 1959). In addition, the effect of heterogeneity was quantified also by using I^2 value (Higgins and Thompson, 2002). If obvious heterogeneity was existed (I^2 value >50 % or $P < 0.10$), the overall estimate of risk was calculated by the random-effects model; When obvious heterogeneity was absent (I^2 value <50 % or P >0.10), the fixed-effects model was used. We did logistic meta-regression analyses to explore sources of between-study heterogeneity. We examined the following study characteristics: ethnicity, source of controls and the sample size of study.

The Hardy-Weinberg equilibrium (HWE) of controls was tested by using a professional web-based program (http://ihg2.helmholtz-muenchen.de/cgibin/ hw/hwa1.pl), if the P>0.05 suggests the controls was followed HWE balance. Sensitivity analysis was used to test the stability of pooled studies by sequential omission of individual studies. When the Hardy–Weinberg equilibrium (HWE) disequilibrium existed (P<0.05 was considered statistically significant), the sensitivity analysis was also conducted. Publication bias was assessed by Egger's test (P<0.05 was considered representative of statistically significant publication bias) (Egger et al., 1997). Publication bias was also test by visual observation of funnel plot (Begg and Mazumdar, 1994). Statistical analysis was undertaken using the program STATA Software (version 9.0, Stata Corp) in the meta-analysis.

Results

Study characteristics

On the basis of the search criteria, a total of eleven publications met our inclusion criteria. Of these articles, two was excluded because on (Goode et al., 2002) is a review and the other is a repeated article (Zhou et al., 2009). At last, a total of nine studies were included in this meta-analysis (Wang et al., 2004; Kiuru et al., 2008; Liu et al., 2009; Zhou et al., 2009; Rajaraman et al., 2010; Custodio et al., 2012; Liu et al., 2012; Luo et al., 2013; Pan et al., 2013), all of these publications were written in English. The study characteristics of the included in

Table 1. General Characteristics of Studies Included in the Meta-analysis

First Author	Year	Country	Ethnicity	Method of Genotyping	Source of Control	Sample size (case /control)	HWE of Control
Ke-Qin Luo	2013	China	Asia	MassARRAY	HB	297/414	Yes
Wei-Ran Pan	2013	China	Asia	MassARRAY	HB	443/443	Yes
Li-E Wang	2004	America	Caucasians	PCR- RFLP	PB	309/342	Yes
AC Custodio	2012	Brasil	Mixed	PCR- RFLP	PB	80/100	Yes
Hai-bo Liu	2012	China	Asia	MassARRAY	HB	443/443	Yes
Keke Zhou	2009	China	Asia	TaqMan	HB	760/708	Yes
Anne Kiuru	2008	Finland	Caucasians	PCR- RFLP	PB	701/1560	Yes
Rajaraman	2010	America	Caucasians	TaqMan	HB	350/479	Yes
Yanhong Liu	2009	America	Caucasians	MassARRAY	PB	369/360	Yes

PCR-RFLP, PCR-restriction fragment length polymorphism; HWE, Hardy-Weinberg equilibrium; HB, hospital based; PB, population based

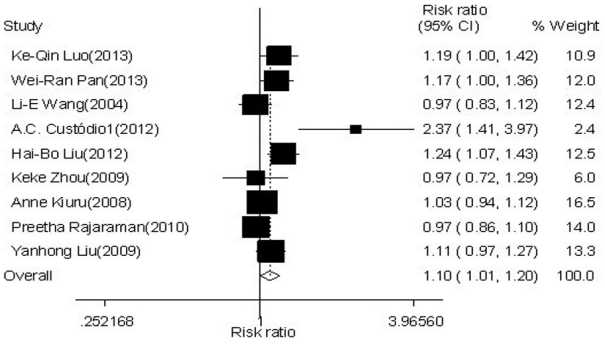

Figure 1. The Forest Plot Describing the Meta-analysis with a Random-effect under Allelic Model for the Association Between XRCC3 Thr241 Met Polymorphism and Gliomas Risk (T vs. C)

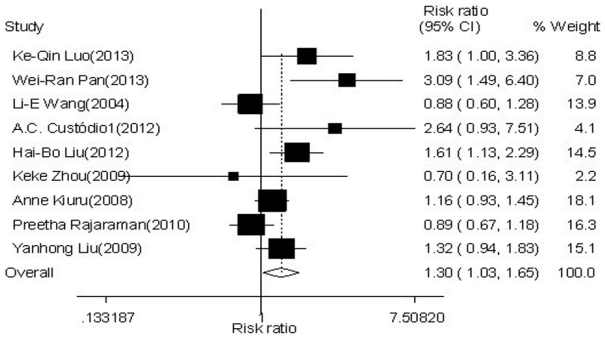

Figure 2. The Forest Plot Describing the Meta-analysis with a Random-effect under Homozygote Model for the Association Between XRCC3 Thr241 Met Polymorphism and Gliomas Risk (TT vs. CC)

the meta-analysis were presented in Table 1. In total, nine case-control studies that examined the association between XRCC3 Thr241Met polymorphism and gliomas risk consisted of 3533 gliomas patients and 4696 controls. There were four studies of Asians (Zhou et al., 2009; Liu et al., 2012; Luo et al., 2013; Pan et al., 2013), four studies of Caucasians (Wang et al., 2004; Kiuru et al., 2008; Liu et al., 2009; Rajaraman et al., 2010) and one mixed (Custodio et al., 2012) in present meta-analysis. The genotypes distribution in the controls of all the studies included in the meta-analysis were consistent with HWE (all $P>0.05$).

Quantitative synthesis of data

The main results of the meta-analysis were listed in Table 2. We found that XRCC3 Thr241Met polymorphism

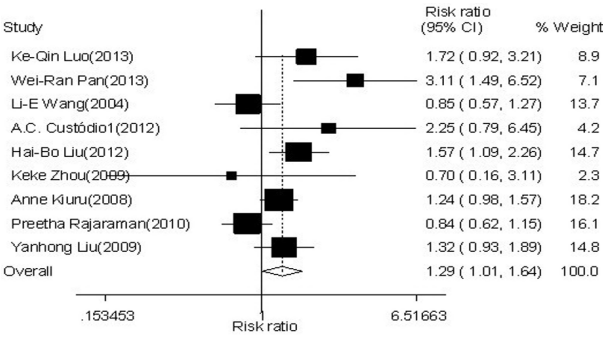

Figure 3. The Forest Plot Describing the Meta-analysis with a Random-effect under Recessive Model for the Association Between XRCC3 Thr241 Met Polymorphism and Gliomas Risk (TT vs. TC/ CC)

was significant associated with gliomas risk in overall population (T vs. C: OR=1.10, 95%CI=1.01-1.20, P=0.034, Figure 1; TT vs. CC: OR=1.30, 95%CI=1.03-1.65, P=0.027, Figure 2; TT vs. TC/CC: OR=1.29, 95%CI=1.01-1.64, P=0.039, Figure 3), while there no association between Thr241Met polymorphism and gliomas risk in the dominant models (TT/TC vs.CC: OR=1.06, 95%CI=0.99-1.13, P=0.088, Figure not shown) and heterozygote model (TC vs. TT: OR=1.04, 95%CI=0.98-1.09, P=0.228, Figure not shown).

In the sub-group analysis according to ethnicity, the results suggested that XRCC3 Thr241Met polymorphism was not associated with gliomas risk in Caucasians population (Table 2). However, the significant association was found in Asian (Table 2) under the four models below (Table 2).

Heterogeneity analysis and sensitive analysis

There was significant heterogeneity for all of the genetic models in overall population. To examine the source of heterogeneity, we assessed the dominant model (TT/TC vs. CC) by ethnicity (Caucasian or Asian), source of control (Hospital-based or Population-based), genotyping methods (PCR-RFLP or TaqMan or MassARRAY) and sample size (≤400 subjects or >400 subjects). As a result, ethnicity (P=0.007) but not sample size ($P>0.05$), genotyping methods ($P>0.05$) or source of control ($P>0.05$) was found to contribute to substantial heterogeneity. Sensitivity analysis was used to evaluate the stability of the overall results by sequential omission of individual studies. In this meta-analysis, the result

Table 2. Results of Meta-analysis for XRCC3 Thr241Met Polymorphism and Gliomas Risk

Comparison	Population	N	Sample size		Test of association			Mode	Test of heterogeneity		
			Case	Control	OR	95% CI	*P*		χ^2	*P*	I^2
T vs. C	Overall	9	7504	10179	1.1	1.01-1.20	0.034	R	21.68	0.006	63.1
	Asian	4	3886	4016	1.17	1.07-1.28	0	F	2.28	0.516	0
	Caucasians	4	3458	5479	1.02	0.96-1.08	0.508	F	2.73	0.436	0
TT vs. CC	Overall	9	2384	2969	1.3	1.03-1.65	0.027	R	21.02	0.007	61.9
	Asian	4	1380	1418	1.79	1.36-2.36	0	F	4.03	0.259	25.5
	Caucasians	4	942	1460	1.07	0.93-1.23	0.352	F	4.7	0.195	36.2
TC vs. CC	Overall	9	3380	4424	1.04	0.98-1.09	0.228	F	10.64	0.223	24.8
	Asian	4	1825	1936	1.07	0.98-1.17	0.135	F	0.95	0.814	0
	Caucasians	4	1484	2393	1	0.94-1.06	0.896	F	1.26	0.738	0
TT vs. TC/CC	Overall	9	3752	4849	1.29	1.01-1.64	0.039	R	19.68	0.012	59.3
	Asian	4	1943	2008	1.75	1.32-2.32	0	F	4.12	0.249	27.1
	Caucasians	4	1729	2741	1.06	0.84-1.33	0.63	R	6.25	0.1	52
TT/TC vs. CC	Overall	9	3752	4849	1.06	0.99-1.13	0.088	R	15.65	0.048	48.9
	Asian	4	1943	2008	1.11	1.02-1.20	0.013	F	1.46	0.692	0
	Caucasians	4	1729	2741	1	0.96-1.06	0.855	F	1.12	0.772	0

OR, odds ratio; CI, confidence interval; F, fixed effects model; R, random effects model

of sensitive analysis shows that any single study could not influence the overall results qualitatively, indicating robustness and reliability of our results.

Publication bias

Funnel plot were used to assess the possible publication bias, and Egger's test were used to provide statistical evidence of symmetries of the plots. As a result, the shape of the funnel plot did not suggest any evidence of obvious asymmetry (Figure not shown). Similarly, the results revealed the absence of publication bias (allelic model: Egger's Test *P*=0.454; homozygote model: Egger's Test *P*=0.229; heterozygote model: Egger's Test *P*=0.503; recessive model: Egger's test *P*=0.098; dominant model: Egger's test *P*=0.634).

Discussion

Small genetic association studies have different study designs, various methodology, insufficient power and different population background, and could inevitably increase the risk that chance could be responsible for their conclusions. However, meta-analysis is a good statistic method which has the advantage of reducing random error and achieving precise estimates for potential genetic associations by combining data from all eligible studies. No meta-analysis evaluating on the association between the XRCC3 Thr241Met polymorphisms and gliomas risk has been performed, and our meta-analysis is the first one on this association. Consequently, nine individual case-control studies with 8,229 subjects (3,533 gliomas patients and 4,696 controls) were included in our meta-analysis.

Up to now, numerous studies have investigated on the XRCC3 Thr241Met polymorphism with cancers risk, including lung, breast, colorectal, bladder, pancreatic, thyroid, prostate cancer and so on. Several meta-analyses have been performed on XRCC3 Thr241Met polymorphism and cancers risk, such as colorectal cancer, lung cancer, bladder cancer, and breast cancer. Our study was performed to investigate the association between XRCC3 Thr241Met polymorphism and gliomas. Previous meta-analysis which focused on relationship between XRCC3 Thr241Met polymorphism with cancers risk showed different results. Generally, elevated r risk of XRCC3 Thr241Met polymorphism has been found in breast cancer, bladder cancer, colorectal cancer and deceased risk of this polymorphism found only in skin cancer (He et al., 2013). No significant association was found in other cancers such as lung cancer, head and neck cancer, melanoma, leukemia, gastric cancer, ovarian cancer or prostate cancer (He et al., 2013). This phenomenon indicates that the XRCC3 Thr241Met polymorphism exerts different effect on various types of cancers. So that it is necessary for us to get a better understanding of XRCC3 Thr241Met polymorphism on gliomas risk, especially when inclusive and controversial findings still exists. Our meta-analysis showed XRCC3 Thr241Met polymorphism was significant associated with gliomas risk (T vs. C: OR=1.10, 95%CI=1.01-1.20, *P*=0.034, Figure 1; TT vs. CC: OR=1.30, 95%CI=1.03-1.65, *P*=0.027, Figure 2; TT vs. TC/CC: OR=1.29, 95%CI=1.01-1.64, *P*=0.039, Figure 3). Subgroup analysis based on ethnicity indicated that XRCC3 Thr241Met polymorphism was a risk factor for glioma not in Caucasians but in Asians (T vs. C: OR=1.17, 95%CI=1.07-1.28, *P*=0.000; TT vs. CC: OR=1.79, 95%CI=1.36-2.36, *P*=0.000; TT vs. TC/CC: OR=1.75, 95%CI=1.32-2.32, *P*=0.000; TT/TC vs. CC: OR=1.11, 95% CI=1.02-1.20, *P*=0.013)

The heterogeneity plays an important role when performing meta-analysis and finding the source of heterogeneity is very important for the final result of meta-analysis. Because the inconsistent findings included in our meta-analysis among different studies were probably attributed to different genetic backgrounds, environmental exposures, methodology and sample size. In the current study, obvious heterogeneity between-study was found in the overall population. The heterogeneity cannot be explained by several possible source of heterogeneity such as source of control (Hospital-based or Population-based), genotyping methods (PCR-RFLP or TaqMan or MassARRAY) or sample size (≤400 subjects or >400 subjects). By conduct the meta-regression, we found the ethnicity was the major source of the high heterogeneity

in our meta-analysis, which could be explained by the race-specific effect of XRCC3 Thr241Met polymorphism on the susceptibility to glioma. Because different countries may have different genetic backgrounds and environmental exposures. However, the ethnicity did not explain all heterogeneity in this meta-analysis and other sources need further investigating. It is possible that other limitations of recruited studies may partially contribute to the observed heterogeneity. For this reason, we conducted analyses using the random effects model. Another important aspect which may have a negative effect on our meta-analysis is the publication bias. In our meta-analysis, Funnel plot and Egger's test were used to test the publication bias of the included studies. Both the shape of funnel plot and statistical results show no obvious publication bias, this suggests that the publication bias have little effect on the results in our study and the results of our meta-analysis are relatively stable.

Although comprehensive analysis was conducted to show the association between XRCC3 Thr241Met polymorphism and risk of gliomas, there are still some limitations should point out. First, the primary studies in the present meta-analysis mainly provided data towards Asians and Caucasians. Given that the race-specific association probably exist, other ethnicities including Africans, mixed and others should be researched in future studies. Second, only four of nine included studies used controls that were population-based (Wang et al., 2004; Kiuru et al., 2008; Liu et al., 2009; Custodio et al., 2012). Other articles used hospital-based controls, which may not be representative of the general population (Zhou et al., 2009; Rajaraman et al., 2010; Liu et al., 2012; Luo et al., 2013; Pan et al., 2013). Third, subgroup analyses according to age, gender, radiation exposure, histological types and other elements haven't been performed in the study because no sufficient relevant data available in the primary studies. Fourth, the number of articles and the number of samples included in the meta-analysis were relatively small. So, more studies with larger sample size and providing detailed information should be performed to assess the effect of XRCC3 Thr241 Met polymorphism on gliomas risk.

In spite of the shortages above, our meta-analysis also had several advantages as follows: First, a meta-analysis of the association of XRCC3 Thr241 Met polymorphism on gliomas risk is statistically more powerful than any other single study. Second, strict searching strategy which combination computer-assisted with manual search make the eligible studies included as much as possible. Third, the quality of case-control studies included in the meta-analysis was met our inclusion criteria and was satisfactory, and the sensitivity analysis and publication bias analysis indicated the stability and credibility of the meta-analysis, which leads to a more convincing result. More important, the process of literature selection, data extraction and data analysis in the meta-analysis was well designed and conducted.

In summary, this meta-analysis systematically analyzed the association between XRCC3 Thr241Met polymorphism and the risk of gliomas. The pooled results suggest that the XRCC3 Thr241 Met polymorphism was a risk factor for gliomas, especially for Asians. Considering the limited sample size and ethnicities included in the meta-analysis, further large scaled and well-designed studies are needed to confirm our results.

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