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Systematic review on the association between ERCC1 rs3212986 and ERCC2 rs13181 polymorphisms and glioma risk

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ABSTRACT. Several studies have examined the association between excision repair cross-complementation group 1 (ERCC1) C8092A and ERCC2 Lys751Gln polymorphisms and glioma risk, but the results have been inconclusive. We conducted a meta-analysis of 12 studies to determine the association between ERCC1 rs3212986 and ERCC2 rs13181 genes and glioma susceptibility. We searched for relevant studies in both Chinese and English in PubMed, Web of Science, Cochrane Library, and EMBASE through January 1, 2014, and identified 3939 cases and 5407 controls. The results showed that individuals carrying the ERCC1 rs3212986 AA genotype had higher risk of glioma compared with the CC genotype, with a pooled odds ratio = 1.29, 95% confidence interval = 1.07-1.55. Subgroup analysis showed that the ERCC1 rs3212986 AA genotype was significantly associated with an increased risk of glioma in the Chinese population (odds ratio = 1.37, 95% confidence interval = 1.07-1.55), but no association in Caucasian Chinese. No significant association was observed between ERCC2 rs13181 polymorphisms and glioma risk. The results of our meta-analysis strongly suggested that the ERCC1 rs3212986 polymorphism

was associated with a higher susceptibility to glioma, particularly in the Chinese population. Studies including a larger sample size and more specified information regarding pathological types of glioma are needed to confirm our results.

Key words: ERCC1; ERCC2; Glioma; Polymorphism

INTRODUCTION

Glioma is one of the most common brain tumors, accounting for 70% of all brain tumors. Malignant gliomas are the most common primary brain tumor in adults and is associated with a poor survival rate when compared with other brain tumors (Cobbs, 2013; Omuro and DeAngelis, 2013). Various environmental and lifestyle factors play an important role in the development of glioma, including ionizing radiation, cellular phones, smoking, and diet (Kitahara et al., 2012; Mihailović et al., 2013). Recently, accumulating evidence suggests that inherited risks play a significant role in glioma susceptibility (Fan et al., 2013; Adel Fahmideh et al., 2014; Jin et al., 2014). Genetic studies demonstrated that several genetic factors may be associated with glioma, including the SLC7A7, XRCC1, P53, MTHFR C677T, EGFR, GSTM1, GSTT1, and LIG4 genes (Fan et al., 2013; Wang et al., 2013; He et al., 2013; Xu et al., 2013; Silva et al., 2013).

In normal cells, DNA is continually subjected to a variety of assaults, including ionizing radiation, ultraviolet rays, and genotoxic agents. Thus, efficient DNA repair is required to prevent the propagation of errors and to maintain genomic stability (Kidane et al., 2014). Damage repair involves more than 130 genes and several molecular pathways, including nucleotide excision repair (NER), base-excision repair, homologous recombination, and non-homologous end joining (Kidane et al., 2014). Thus, polymorphisms in DNA repair genes may cause a defect in DNA repair and subsequently influence an individual's susceptibility to carcinogenesis (Higgins et al., 2003). Excision repair cross complementation group 1 (ERCC1) and ERCC2, 2 DNA repair genes whose products are important in the NER, are located on chromosome 19q13.3 (Kidane et al., 2014).

Recently, several studies have focused on the association between ERCC1 C8092A and ERCC2 Lys751Gln polymorphisms and glioma risk; however, the results were inconclusive, which may have been because the studies involved limited sample sizes or ethnic differences. Additionally, no meta-analysis has been conducted to investigate the association between ERCC1 rs3212986 and ERCC2 rs13181 polymorphisms and glioma risk. In this study, we conducted a meta-analysis to investigate whether polymorphisms in ERCC1 rs3212986 and ERCC2 rs13181 genes are risk factors for glioma susceptibility.

MATERIAL AND METHODS

Search strategy

A comprehensive literature search was conducted for this meta-analysis. We searched for relevant studies in both Chinese and English language in the PubMed, Web of Science, Cochrane Library and EMBASE databases through January 1, 2014. Search strategies were conducted using the following terms and their combinations: "glioma" or "brain tumor",

"polymorphism" or "variant", and "ERCC1 C8092A", "ERCC2 Lys751Gln", "rs3212986" or "rs13181". In addition, the reference lists of all selected articles were checked manually to identify additional potential studies.

Inclusion criteria

The inclusion criteria were as follows: 1) studies assessed the association between ERCC1 C8092A and ERCC2 Lys751Gln polymorphisms and glioma risk; 2) studies were case-control studies; and 3) studies reported available genotype frequencies. The exclusion criteria were as follows: 1) studies were dissertations, comments, reviews, or duplicated publications; and 2) studies included no data regarding genotype frequencies.

Data extraction

Information was extracted from the articles independently by 2 researchers, including first author's name, publication year, ethnicity, and genotype distribution in cases and controls. If the article did not provide sufficient data for analysis, the researchers emailed the authors to obtain more detailed data.

Statistical analysis

Analyses were performed using STATA 11.0 (StataCorp., College Station, TX, USA). The association between ERCC1 C8092A and ERCC2 Lys751Gln polymorphisms and glioma risk was estimated based on the odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Between-study heterogeneity was assessed using the I^2 statistic test and the heterogeneity Q statistic test. The following cut-off points indicated different degrees of heterogeneity: I^2 ranging from 0-25% was regarded as no heterogeneity; I^2 ranging from 25-50% was regarded moderate heterogeneity; I^2 ranging from 50-75% was regarded as large heterogeneity; I^2 ranging from 75-100% was regarded as extreme heterogeneity (Higgins et al., 2003). If there was significant between-study heterogeneity ($P \geq 0.10$), the random-effect model was used to calculate the ORs (95%CI); otherwise, a fixed-effect model was used. Publication bias was assessed using funnel plots.

RESULTS

The initial search identified a total of 12 studies examining ERCC1 rs3212986 and ERCC2 rs13181. A total of 12 studies met the inclusion criteria and were selected for analysis (Chen et al., 2000; Caggana et al., 2001; Yang et al., 2005; Wrensch et al., 2005; Liu et al., 2009; McKean-Cowdin et al., 2009; Rajaraman et al., 2010; Chen et al., 2012; Zhang et al., 2012; Luo et al., 2013; Pan et al., 2013; Dong et al., 2014). Among the 12 selected studies, 8 studies reported an association between the ERCC1 C8092A polymorphism and glioma risk, including 3008 glioma cases and 4319 controls (Table 1). Four studies were conducted in Asian populations and 4 were conducted in European populations. Four studies reported an association between the ERCC2 Lys751Gln polymorphism and glioma risk, including 3055 glioma cases and 4262 controls. Four studies were conducted in Asian populations and 4 were conducted in European populations (Table 2).

Table 1. Meta-analysis of the association between ERCC1 rs3212986 and glioma risk.

Study ID	Country	Total cases	Total controls	Cases			Controls			P for HWE	OR(95%CI)	
				CC	CA	AA	CC	CA	AA		CA *vs* CC	AA *vs* CC
Chen (2000)	Caucasian	122	159	73	43	6	81	70	8	0.47	0.68 (0.42-1.12)	0.83 (0.28-2.51)
Wrensch (2005)	Caucasian	393	410	206	144	25	237	184	23	0.09	0.90 (0.68-1.20)	1.25 (0.69-2.27)
Liu (2009)	Caucasian	72	302	208	130	31	219	126	17	0.83	1.09 (0.80-1.48)	1.92 (1.03-3.57)
McKean-Cowdin (2009)	Caucasian	369	362	557	361	59	1087	728	105	0.24	0.97 (0.82-1.14)	1.10 (0.78-1.53)
Chen (2012)	Chinese	977	1920	202	141	50	221	154	35	0.28	1.00 (0.74-1.35)	1.56 (0.97-2.51)
Zhang (2012)	Chinese	443	444	123	98	36	144	105	29	0.14	1.09 (0.76-1.58)	1.45 (0.84-2.51)
Pan (2013)	Chinese	375	444	229	169	45	241	162	41	0.08	0.10 (0.83-1.45)	1.16 (0.73-1.83)
Dong (2014)	Chinese	257	278	33	32	7	137	144	21	0.94	0.92 (0.54-1.58)	1.38 (0.54-3.53)
Pooled results											0.98 (0.89-1.09)	1.29 (1.07-1.55)
P for heterogeneity[a]											0.79	0.76

OR = odds ratio; CI = confidence interval. [a]P < 0.05, it was considered statistically significant.

Table 2. Meta-analysis of the association between ERCC2 rs13181 and glioma risk.

Study ID	Country	Total cases	Total controls	Cases			Controls			P for HWE	OR (95%CI)	
				GG	GT	TT	GG	GT	TT		CT *vs* GG	TT *vs* GG
Caggana (2001)	Caucasian	148	148	23	63	62	23	76	49	0.46	0.83 (0.43-1.62)	1.27 (0.64-2.52)
Wrensch (2005)	Caucasian	365	432	57	169	139	55	213	164	0.27	0.77 (0.50-1.17)	0.82 (0.53-1.26)
Yang (2005)	Chinese	135	44	0	32	103	0	3	41	0.81	-	-
Liu (2009)	Chinese	367	362	56	172	139	45	156	161	0.45	0.89 (0.57-1.39)	0.69 (0.44-1.09)
McKean-Cowdin (2009)	Caucasian	999	1970	143	480	376	256	891	823	0.54	0.96 (0.76-1.22)	0.82 (0.64-1.04)
Rajaraman (2010)	Caucasian	351	481	52	171	128	66	215	200	0.50	1.01 (0.67-1.53)	0.81 (0.53-1.24)
Chen (2012)	Chinese	393	410	139	198	56	175	186	49	0.97	1.34 (0.99-1.81)	1.44 (0.92-2.24)
Luo (2013)	Chinese	297	415	230	58	9	343	62	10	0.03	1.40 (0.94-2.07)	1.34 (0.54-3.35)
Pooled results											1.04 (0.91-1.19)	0.89 (0.76-1.04)
P for heterogeneity[a]											0.22	0.22

OR = odds ratio; CI = confidence interval. [a]P < 0.05, it was considered statistically significant.

In these studies, in terms of ERCC1 rs3212986, the genetic distributions of polymorphisms in the studies were in accordance with Hardy Weinberg equilibrium (P > 0.05). The population in a study examining ERCC2 rs13181 was not in Hardy Weinberg equilibrium (P < 0.05).

The results of the meta-analysis examining the association between ERCC1 rs3212986 and ERCC2 rs13181 and the risk of glioma are shown in Tables 1 and 2. There was no significant heterogeneity between studies in all comparisons, and thus a fixed-effect model was used to calculate the pooled OR (95%CI). We found that individuals carrying the ERCC1 rs3212986 AA genotype had a higher risk of glioma compared with individuals carrying the CC genotype, with pooled OR (95%CI) of 1.29 (1.07-1.55). However, no significant association was observed between the ERCC1 rs3212986 CA genotype and glioma risk. We did not observe a significant association between ERCC2 rs13181 polymorphisms and glioma risk.

Subgroup analysis showed that the ERCC1 rs3212986 AA genotype was significantly associated with an increased risk of glioma in a Chinese population (OR = 1.37, 95%CI = 1.07-1.55) (Figure 1), but no association in Caucasian Chinese. However, we did not observe a significant association between the ERCC2 rs13181 polymorphism and glioma risk in different genetic models according to stratified analysis.

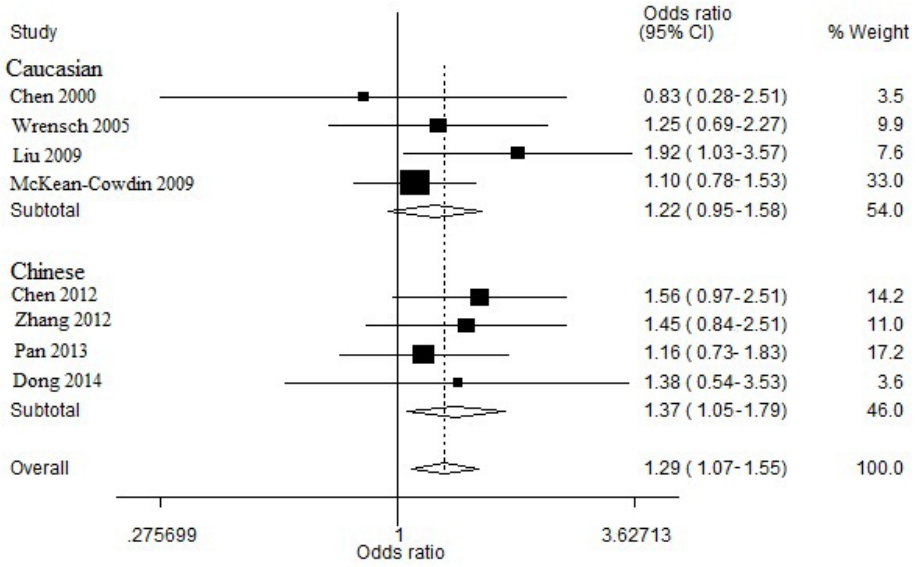

Figure 1. Subgroup analysis for association between ERCC1 rs3212986 AA and risk of glioma.

Funnel plots were used to evaluate publication bias. In this study, the shapes of the funnel plots for the ERCC1 rs3212986 and ERCC2 rs13181 polymorphisms showed a symmetric distribution, suggesting no publication bias in this meta-analysis (Figures 2 and 3).

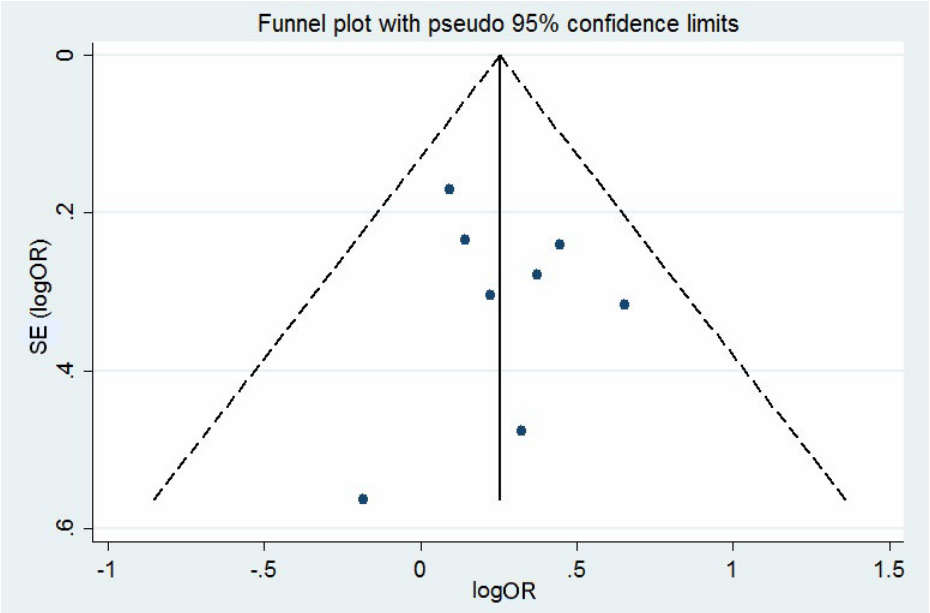

Figure 2. Funnel plots of the association between ERCC1 rs3212986 polymorphism and risk of glioma.

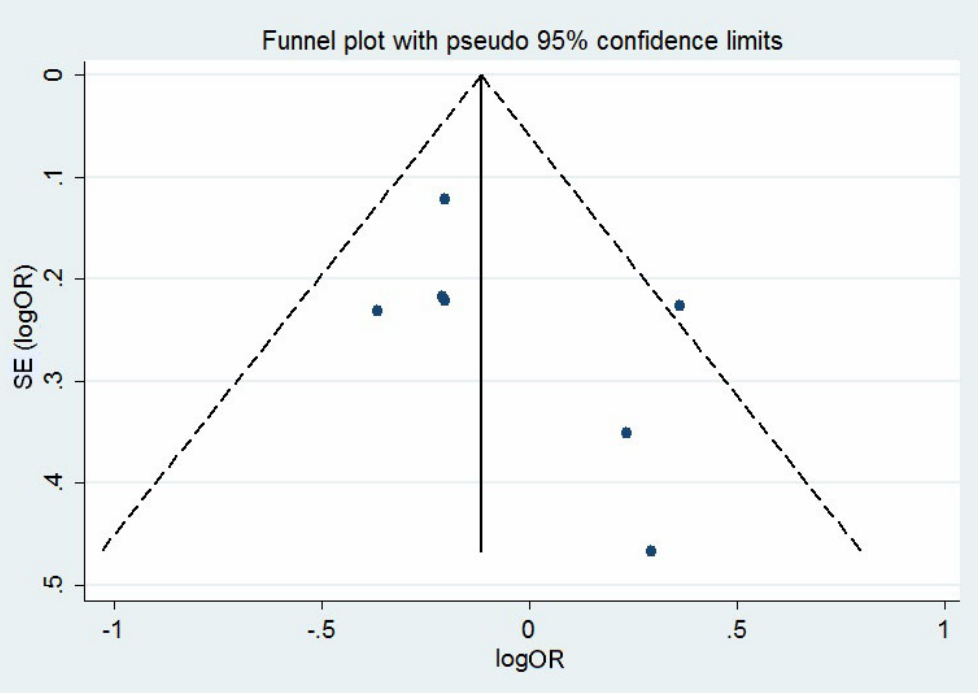

Figure 3. Funnel plots of the association between ERCC2 rs13181 polymorphism and risk of glioma.

DISCUSSION

In humans, damage to DNA has been implicated in many cancers, and this process occurs throughout the life cycle of many organisms and is caused by both exogenous and endogenous factors. Exogenous or endogenous factors are required for efficient DNA repair to restore genomic integrity, and involves over 100 DNA repair genes in 5 major DNA damage repair pathways (Jeggo, 1998; Khanna and Jackson, 2001). Several recent studies have indicated that single nucleotide polymorphisms in DNA repair genes are associated with the risk of glioma (Feng et al., 2013; Wang et al., 2014).

NER is an important mechanism of the DNA repair pathway and is important for maintaining genomic integrity by removing DNA interstrand crosslinks (Neumann et al., 2005; Wu et al., 2005). The ERCC1 and ERCC2 genes are 2 important rate-limiting enzymes involving in the NER process. Polymorphisms in the ERCC2 gene are thought to reduce helicase activity, resulting in a lower DNA repair capacity of the NER pathway and influencing cancer susceptibility (Zhang et al., 2010; Pérez-Mayoral et al., 2013). ERCC1 is a subunit of the NER complex that interacts with xeroderma pigmentosum group A, xeroderma pigmentosum group X, and/or replication protein A, guiding the 5'-cleavage activity in the NER pathway (Sijbers et al., 1996; Volker et al., 2001). Cells from ERCC1-deficient mice consistently present a high mutation frequency, increased level of genomic instability, and decreased probability of S-phase-dependent illegitimate chromosome exchange as well as a response adopted by rodent cells to prevent the accumulation of DNA double-strand breaks. Therefore, potentially func-

tional ERCC1 and ERCC2 single nucleotide polymorphisms may affect cellular DNA repair capacity and the development of glioma.

This meta-analysis demonstrated that the ERCC1 rs3212986 AA genotype was significantly associated with glioma risk compared with the CC genotype (AA *vs* CC: OR = 1.29, 95%CI = 1.07-1.55). When stratified by ethnicity, a significant association was only observed in the Asian population, but not in the Caucasian population, suggesting that the contribution of the ERCC1 rs3212986 polymorphism varies in different populations.

We used the heterogeneity Q statistic test and the I^2 statistic to assess the heterogeneity between studies. We did not find significant heterogeneity in the ERCC2 Lys751Gln and ERCC2 rs13181 polymorphisms. When the studies were stratified according to ethnicity, significant heterogeneity was not observed between the Chinese and Caucasian populations.

There were several limitations to our study. First, only 12 eligible studies were included in this meta-analysis. Therefore, in the subgroup analyses by ethnicity, the number of cases and controls was relatively small, which may have resulted in low statistical power for identifying the association. Second, the genetic susceptibility to cancer is complex because of interactions between genes and environmental factors. However, we could not assess gene-environment interactions because insufficient data in most studies.

In conclusion, our meta-analysis strongly suggested that the ERCC1 rs3212986 polymorphism was associated with a higher susceptibility to glioma, particularly in the Chinese population. However, no significant association was found between the ERCC2 rs13181 polymorphism and glioma risk. Studies including a larger sample size and more specified information in pathological types of glioma are needed to confirm our results.

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