Association of XRCC1 rs1799782 and ERCC2 rs13181 Polymorphisms with Glioma Risk: A Systematic Review and Meta-Analysis

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Research article

Keywords: XRCC1, Arg194Trp polymorphism, ERCC2, Lys751Gln polymorphism, gliomas meta-analysis

DOI: https://doi.org/10.21203/rs.3.rs-56338/v1

Abstract

Background

Gliomas are the most common primary tumors of the central nervous system with unclear etiology, however hereditary factors may play important roles in the development of gliomas with mutations and single nucleotide polymorphisms (SNPs) being prominent among the genetic changes. this systematic review and meta-analysis assess the association of *XRCC1* (rs1799782) and *ERCC2* (rs13181) gene polymorphisms and glioma risk.

Methods

This study included articles indexed in the PUBMED and EMBASE databases published during the past 15 years. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. The PICOS model was used to develop the inclusion criteria and search terms. This review was recorded at PROSPERO International prospective register of systematic reviews, ID 196173. The META-MAR V2.7.0 meta-analysis calculator was used for the statistical analysis with p-values < 0.05 being considered statistically significant. Dichotomous data are presented as odds ratios (OR) with a 95% confidence interval (CI). Statistical heterogeneity was measured using the I^2 test and I^2 > 50% were regarded as high heterogeneity. Funnel plots, Begg (BT) and Egger Tests (ET) were used to assess publication bias (p<0.1).

Results

Literature review identified 10 articles on *ERCC2* gene rs13181 variant and 11 on *XRCC1* rs1799782. The meta-analysis identified a risk for gliomas for the TT genotype of the *XRCC1* rs1799782 SNP in Asians (OR: 1.59, 95% CI: 1.3-1.93; p=0.006; I^2 13.1%). *ERCC2* rs13181 polymorphisms identified as risks for gliomas were AC genotypes in Asians (OR: 2.06, 95% CI: 1.75-1.42; p = 0.00057; I^2 91.1%) and Caucasians (OR: 1.16, 95% CI: 1.01-1.31; p = 0.02; I^2 12.2%), and CC genotypes in Caucasians (OR: 2.06, 95% CI: 1.75-1.42; p = 0.0001; I^2 98.9%).

Conclusions

TT genotypes of the *XRCC1* rs1799782 SNP in Asians, AC genotypes of *ERCC2* rs13181 polymorphisms in Asians and Caucasians, and CC genotypes of *ERCC2* rs13181 polymorphisms in Caucasians were associated with increased risk for gliomas that may benefit these patients with early diagnostic and therapeutic strategies.

Background

Gliomas are the most common primary tumors of the central nervous system, representing approximately 80% of all malignant central nervous system tumors. There are four histological subtypes of which astrocytomas are the most prevalent. According to the World Health Organization (WHO) 2010 classification, astrocytomas can be stratified into four grades with grades I and II being low grade or benign and grades III and IV being high grade or malignant. The latter grades are highly aggressive and present a poor prognosis, even when adequately treated with surgical resection, chemotherapy, and radiotherapy [1–5].

Many environmental and lifestyle factors are considered to be associated with increased risk for the development of gliomas, including some occupations, exposure to ionizing radiation, and smoking, among

others. Hereditary factors may also play an important role in the development of gliomas as genetic studies have identified several genes that may be associated with the onset and/or growth of these tumors [5–7].

Among several genetic changes, mutations and polymorphisms stand out and may result in inter-individual differences in susceptibility to diseases and response variations to drugs and environmental factors. Single nucleotide polymorphisms (SNPs) are the simplest and most common form of polymorphism, characterized as the change of a single nitrogenous base at a frequency greater than 1% and is sometimes associated with the insertion or deletion of one or more nucleotides [8].

Multiple genes encode proteins involved in correcting possible DNA errors, including the X-ray repair cross-complementing group 1 (*XRCC1*) and excision repair cross-complementation group 2 (*ERCC2*). *XRCC1* encodes proteins that repair base excisions and single-strand breaks in DNA while the *ERCC2* gene encodes proteins that are involved in transcription-coupled nucleotide excision repair. These represent three of the main mechanisms of DNA repair, preventing mutations that can lead to the development of cancer in different organs. However, the presence of SNPs in these genes can alter or inhibit repair mechanisms, resulting in mutations and increased risks for the development of gliomas [8, 9].

Numerous studies have been published on these genes and their various polymorphisms, but they often contain conflicting results. There is a need for greater understanding of the pathways involved in the regulation of the aberrant growth of glial neoplasms. This need led us to conduct a systematic review of the literature and to perform a meta-analysis regarding *XRCC1* rs1799782 and *ERCC2* rs13181 polymorphisms in effort to determine their association with the risk of healthy individuals developing gliomas.

Methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) standards and used a targeted search to identify and retrieve relevant articles [9]. The Population, Intervention, Comparison, Outcome and Study design (PICOS) model was used for developing the inclusion criteria and search terms. This review was recorded at PROSPERO International prospective register of systematic reviews, ID 196173.

Literature search

The PUBMED and EMBASE databases were searched for case-controls articles published between January 2005 and April 2020 with an association of XRCC1 rs1799782 or ERCC2 rs13181 (intervention) and increased or decreased risk (comparison) of developing gliomas (outcome) in healthy individuals (population). The following search terms and Booleans were used: (“SNP” OR “polymorphism” OR “single nucleotide polymorphism”) AND (“gliomas” OR “glioma” OR “astrocytoma” OR “glioblastoma”) AND (“XRCC1 gene” OR “ERCC2 gene"). The search process included only articles in English.

Selection Criteria

The inclusion criteria were: a) case-control studies, b) articles on the risk of developing gliomas for participants free from the disease, c) studies of human beings, and d) studies on SNPs of the *XRCC1* and *ERCC2* genes. The

exclusion criteria were: a) irrelevant studies, b) repeated publications, c) articles with only abstract being available, d) case reports/case series, e) editorials, f) comments, g) literature reviews, h) polymorphisms in tumors other than gliomas, i) polymorphisms of the *XRCC1* gene other than rs1799782, j) polymorphisms of the *ERCC2* gene other than rs13181, and l) letters to the editor.

To expand the scope of the evaluation, all articles were inspected by two experienced investigators. The data were extracted and compiled by one reviewer using a standardized abstraction form and independently verified by the second reviewer. In the event of any disagreements, the issues were resolved by consulting with two additional reviewers for consensus.

Quality assesment

The quality of the methodology used in the published reports included in our study was assessed using the Quality Assessment Tool for Quantitative Studies [10]. This tool globally rated the studies as weak, moderate, or strong by evaluating potential selection bias, study design, confounding factors, concealment, data collection methodology, and withdrawal and dropout reports. Component ratings were scored according to the criteria specified in the dictionary accompanying the assessment tool [10]. The global quality assessment rating of each study was determined by evaluating the six component classifications [10]. The studies without any weak ratings and with at least four strong ratings were considered strong. Those with one weak and less than four strong ratings were considered moderate. Finally, those with two or more weak ratings were considered weak.

Data analysis

Statistical analysis was conducted using the META-MAR V2.7.0 meta-analysis calculator and p-values < 0.05 were considered statistically significant. Dichotomous data are presented as odds ratios (OR) with a 95% confidence interval (CI). Statistical heterogeneity was measured using the I^2 test and $I^2 > 50\%$ were regarded as high heterogeneity. Funnel plots, Begg (BT) and Egger Tests (ET) were used to assess publication bias with significance level established at $p < 0.1$.

Results

A total of 933 published articles were identified by searching the PUBMED and EMBASE databases; however, only 160 of the articles met the inclusion criteria. After being evaluated by the two reviewers, 139 studies were excluded and only 21 were included in the systematic review. Ten of the included papers were on *ERCC2* rs13181 and eleven were on *XRCC1* rs1799782 (Fig. 1). All the studies included in our analysis were considered to be of moderate quality according to the evaluation tool (Table 1).

Table 1

Quality assessment of the reports included in the current study.

Study	Component Ratings						Global Rating
	Selection Bias	Study Design	Confounders	Blinding	Data Collection Method	Withdrawals and Dropouts	
Gao K et al.	strong	moderate	strong	moderate	strong	weak	moderate
Hai-Bo Liu et al.	strong	moderate	strong	moderate	strong	weak	moderate
Jiang Li et al.	strong	moderate	strong	moderate	strong	weak	moderate
Wein-ran Pan et al.	strong	moderate	strong	moderate	strong	weak	moderate
Rajaramam et al.	strong	moderate	strong	moderate	strong	weak	moderate
Gaofeng Xu et al.	strong	moderate	strong	moderate	strong	weak	moderate
Xue-Bin Hu et al.	strong	moderate	strong	moderate	strong	weak	moderate
Zhou Lu-Qiu et al.	strong	moderate	strong	moderate	strong	weak	moderate
Custodio AC et al.	strong	moderate	strong	moderate	strong	weak	moderate
Dianhong W et al.	strong	moderate	strong	moderate	strong	weak	moderate
Fan SC et al.	strong	moderate	strong	moderate	strong	weak	moderate
Rajaramam et al.	strong	moderate	strong	moderate	strong	weak	moderate
Caggana et al.	strong	moderate	strong	moderate	strong	weak	moderate
Da-Qing Chen et al.	strong	moderate	strong	moderate	strong	weak	moderate
Gao X et al.	strong	moderate	strong	moderate	strong	weak	moderate
Hui L. et al.	strong	moderate	strong	moderate	strong	weak	moderate
Luo Ke-Qin et al.	strong	moderate	strong	moderate	strong	weak	moderate
Margaret W et al.	strong	moderate	strong	moderate	strong	weak	moderate
Roberta MC et al.	strong	moderate	strong	moderate	strong	weak	moderate

Study	Component Ratings						Global Rating
	Selection Bias	Study Design	Confounders	Blinding	Data Collection Method	Withdrawals and Dropouts	
Rodriguez-Hernandez I et al.	strong	moderate	strong	moderate	strong	weak	moderate
Salnikova LE et al.	strong	moderate	strong	moderate	strong	weak	moderate

Of the eleven articles on *XRCC1* rs1799782, nine were based on Asian populations. Of the studies on *ERCC2* rs13181, five were based on Caucasian populations, four were based on Asian populations, and one was based on both Caucasians and Asians. Only one study was conducted using a Latin-American population (Brazilian) to evaluate the *XRCC1* rs1799782 SNP (Table 2).

Table 2
Summary of characteristics found in the selected studies on *XRCC1* rs1799782.

AUTHORS	YEAR	SPECIMEN STUDIED	(n)	MOLECULAR ANALYSIS	POPULATION	RESULTS
Gao K et al.	2014	Serum	326 × 376	PCR	Asians	No association.
Hai-Bo Liu et al.	2012	Serum	312 × 312	PCR	Asians	Increased risk for glioma in TT genotypes.
Jiang Li et al.	2014	Serum	368 × 346	PCR	Asians	No association.
Wein-ran Pan et al.	2013	Serum	443 × 443	PCR	Asians	Increased risk for glioma in TT genotypes.
Rajaramam et al.	2010	Serum	362 × 495	PCR	Caucasians	Increased risk for gliomas.
Gaofeng Xu et al.	2014	Serum	886 × 886	PCR	Asians	Increased risk for glioma in TT genotypes.
Xue-Bin Hu et al.	2011	Serum	127 × 249	PCR	Asians	Increased risk for gliomas.
Zhou Lu-Qiu et al.	2011	Serum	271 × 289	PCR	Asians	No association.
Custodio AC et al.	2011	Serum	80 × 100	PCR	Caucasians	Increased risk for gliomas. Presence of the 194Trp allele improved survival.
Dianhong W et al.	2012	Serum	624 × 580	PCR	Asians	No association.
Fan SC et al.	2016	Serum	115 × 228	PCR	Asians	Increased risk for gliomas in Trp/Trp, Arg/Trp + Trp/Trp patients.

All the published articles evaluated in our study used serum samples to investigate the peripheral nervous system except one, which used oral mucosa specimens. The method used to detect polymorphisms for all the published studies was polymerase chain reaction (Table 2).

Of the studies on *XRCC1* rs1799782, four reported no relationship with the risk of developing gliomas while the other seven reported an association, especially in the presence of the TT genotype and/or the Trp allele (Table 2). Of the studies on *ERCC2* rs13181, six reported no association with the risk of gliomas, two reported an increased risk, and the other two reported a decreased risk in the presence of the AGC haplotype or C allele (Table 3).

Table 3

Summary of characteristics found in the selected studies on ERCC2 **rs13181**.

AUTHORS	YEAR	SPECIMEN MATERIAL	(n)	MOLECULAR ANALYSIS	POPULATION	RESULTS
Rajaramam et al.	2010	Serum	362 × 495	PCR	Caucasians	No association.
Caggana et al.	2001	Serum	187 × 171	PCR	Caucasians	No association.
Da-Qing Chen et al.	2012	Serum	393 × 410	PCR	Asians	Increased risk for gliomas. Decreased mortality. Increased QT efficacy.
Gao X et al.	2015	Serum	165 × 330	PCR	Asians	Increased risk for glioma, recessive and co-dominant.
Hui L. et al.	2014	Serum	138 × 204	PCR	Asians	No association.
Luo Ke-Qin et al.	2013	Serum	202 × 68	PCR	Asians	No association.
Margaret W et al.	2005	Oral swab	450 × 500	PCR	Asians + Caucasians	No association.
Roberta MC et al.	2009	Serum	1015 × 1994	PCR	Caucasians	Reduced risk of gliomas in the AGC haplotype.
Rodriguez-Hernandez I et al.	2013	Serum	115 × 200	PCR	Caucasians	Haplotypes containing the C allele decreased the risk of glioblastoma.
Salnikova LE et al.	2013	Serum	284 × 464	PCR	Caucasians	No association.

Five articles reported an increased risk for gliomas for Asian populations in the presence of *XRCC1* rs1799782 and two articles reported an increase in the presence of *ERCC2* rs13181. For Caucasian populations, two articles reported an increased risk for gliomas in the presence of the *XRCC1* rs1799782 SNP and two articles reported a decreased risk in the presence of *ERCC2* rs13181 (Table 2 and Table 3).

The meta-analysis identified an increased risk of gliomas for only the TT genotype of *XRCC1* rs1799782 (OR: 1.61, 95% CI: 1.33–1.94; p = 0.001; I^2: 0%). Considering the population type, only Asians presented with an increased risk (OR: 1.59, 95% CI: 1.3–1.93; p = 0.006; I^2: 13.1%). For *ERCC2* rs13181 polymorphisms, increased risks of gliomas were identified for Asians with AC genotypes (OR: 1.53, 95% CI: 1.2–1.97; p = 0.00057; I^2: 91.1%) and Caucasians with AC genotypes (OR: 1.16, 95% CI: 1.01–1.31; p = 0.02; I^2: 12.2%). For the general population, the CC genotype of ERCC2 rs13181 was also associated with increased risk (OR: 1.83, 95% CI: 1.57–2.13; p < 0.001; I^2: 98%), as well as for Caucasians specifically (OR: 2.06, 95% CI: 1.75–1.42; p < 0.0001; I^2: 98.9%). There was no relationship identified between the GCC and GT genotypes of ERCC2 rs13181 and the risk of glioma development (Fig. 2 through Fig. 7).

Among the genotypes of the polymorphisms that showed an increased risk for glioma development, only in the study in Asians with ERCC2 rs13181 AC was not possible to perform the tests of publication bias due to the small number of studies (< 3). In the other studies, Begg and Egger test did not show publication bias (ERCC2 rs13181 AC in Caucasians BT p = 0.117 / ET p = 0.256; ERCC2 rs13181 CC in Caucasians BT p = 0.602 / ET p = 0.966; XRCC1 rs1799782 TT in Asians BT p = 0.105 / ET p = 0.281. However, when analyzing the Funnel Plot, only the results of the studies of XRCC1 rs1799782 TT in Asians and ERCC2 rs13181 AC in Caucasians showed an asymmetric distribution, denoting no publication bias (Fig. 8).

Discussion

There are four main pathways involved in repairing DNA damage, nucleotide excision repair (NER), base excision repair (BER), double-strand break repair (DSBR), and mismatch repair (MMR). *XRCC1* and *ERCC2* encode proteins that are involved in the BER and NER pathways, respectively, and polymorphisms in these genes may change a cell's DNA repair efficiency. This in turn may be related to the development of several types of cancers, including lung, colorectal, breast, ovary, and thyroid cancers, esophageal carcinoma, and even brain tumors [9–11].

The XRCC group is an important component of the BER system, which is the predominant DNA repair pathway for small errors resulting from oxidation and alkylation damage. The proper functioning of the BER system may prevent the activation of oncogenes or the inactivation of tumor suppression genes and thereby reduce the risk of cancer development. The *XRCC1* gene is located on chromosome 19q13.2-13.2, is 33 kb in size, and consists of 17 exons. The *XRCC1* protein coordinates several protein-protein interactions, including those between DNA ligase III, DNA polymerase, and poly ADP-ribose polymerase, which together play an important role in DNA repair. Numerous studies shown a positive correlation between SNPs of XRCC1 and the risk of developing glial neoplasms, and the most common being Arg194Trp (rs1799782), Arg399Gln (rs25487), and Arg280His (rs25489) [7, 9, 12, 13].

Our current systematic review included eleven published articles on *XRCC1* rs1799782, which contained contradictory findings. For instance, studies by Gao et al. [7], Li et al. [10], Zhou et al. [14] and Wang et al. [15] reported no association between the *XRCC1* rs1799782 SNP and the risk of developing gliomas. However, other studies reported an increased risk, including those by Hu et al. [16] and Rajaraman et al. [17]. Mean while, Liu et al. [18], Xu et al. [9] and Pan et al. [12] reported an increased risk for glioma specific for the TT genotypes in an Asian population. Custodio et al. [20] reported an increased risk for gliomas in Caucasians with the *XRCC1* rs1799782 SNP (Brazilian population), but they also observed improved survival in the presence of the 194Trp allele. Finally, in the study published by Fan et al. [8] there was an increased risk for gliomas in participants that had TT or CT + TT genotypes (Table 2) [14–24].

Due to the discrepancies in the published results, we performed this meta-analysis and found for healthy individuals an increased risk for the development of glial tumors only in Asians with the TT genotype of the *XRCC1* rs1799782 as an association was not observed with the CT and/or CT + TT genotypes. These results were similar to the meta-analyses by Li et al. [21], He et al. [22], and Zhang et al. [23]. However, in none of those studies was the data analysis broken down by observed population type [25–27]. Contrary to our study, a review by Sun et al. [5], reported an increased risk associated with the TT genotype in the general population, but no association when individually analyzed in the Asian and Caucasian populations [28].

Lu et al. [24] reviewed sixteen published papers and reported increased risk only for Asians with TT and TT + CT genotype in their meta-analysis. Xu et al. [25] found an increased risk only in Asians with CT + TT genotype and in both Asians and Caucasians with TT genotype. There are currently also systematic reviews in the literature that include meta-analysis and report a relationship between the *XRCC1* rs1799782 polymorphism and its genotypes with the development of glial tumors [31–33].

The *ERCC2* gene is located on chromosome 19q13.3 and encodes a protein responsible for DNA repair as part of the NER pathway. There are published reports on the relationship between some *ERCC2* SNPs and the risk of systemic tumors with the most studied being *ERCC2* Lys751Gln (rs13181). This polymorphism is characterized by the replacement of thymine (T) by guanine (G) at the locus 751, which changes the enzymatic activity of some encoded proteins, such as helicase, and can be associated with several types of cancers, including gastric, esophageal, hepatocellular carcinoma, non-small cell lung, prostate, skin, and bladder cancers, as well as gliomas [6]. Our current study reviewed and analyzed ten published reports that included five based on Asian populations, four based on Caucasian populations, and one that included both populations and the genotypes studied in these reports were AC, CC, GG, and TG.

Similar to the results regarding the XRCC1 polymorphisms, the findings for *ERCC2* rs13181 polymorphisms are highly contradictory. Six reports demonstrate no relationship between *ERCC2* rs13181 polymorphisms and the risk of developing glial tumors. However, the studies by Gao et al. [7] and Chen et al. [29] reported increased risks of gliomas while the reports by McKean-Cowdin [30] and Rodriguez-Hernandez et al. [11] showed a decrease risk in the presence of the AGC haplotype and C allele, respectively.

Based on meta-analysis, the AC genotypes of *ERCC2* rs13181 in Asians and Caucasians and the CC genotypes in Caucasians were associated to an increased risk of gliomas. This result corroborates the findings reported by Qian et al. [6], who reviewed fifteen studies and conducted a meta-analysis [38]. These investigators reported increased risks for the development of glial cell tumors only in Asians with the CC and AC genotypes (Figs. 2 and 3).

In our current review and analysis, the GG and TG genotypes showed no relationship with the development of glial tumors, corroborating the studies by Xin et al. [31] and Zhou et al. [32] (Fig. 2 and Fig. 3). However, contrary results were described in the reviews and meta-analyses by Cui et al. [33] and Jia et al. [34], who found increased risks only in Asian populations and with the TG genotype. On the other hand, Huang et al. [35] found increased risks in the general population for patients with either TG or GG genotypes.

Although the meta-analysis shows the importance of SNPs XRCC1 rs1799782 TT, ERCC2 rs13181 AC and CC in the development of gliomas in certain populations, the high heterogeneity between studies and the presence of publication biases evidenced in some Plot Funnel, show the need for further multicenter studies with larger samples, more uniform methodologies and research with different ethnic groups in order to establish the association of these polymorphisms with the risk of developing gliomas.

The studies presented in our current review and analysis had limitations, which thereby contributed to limitations of our study. These included the fact that most all of them used only one population type, which prevents the extrapolation of the results to other ethnic groups. Furthermore, in most of the studies, the samples were collected from only a single hospital, increasing the potential for selection bias. Finally, in most of the studies the

interactions between genes, environmental factors, and even the loci of the polymorphisms were not considered, which are factors that may influence the risk of developing gliomas.

Conclusion

In the present study, TT genotypes of *XRCC1* rs1799782 in Asians and *ERCC2* rs13181 polymorphisms with AC genotypes in Asians and Caucasians and CC genotypes in Caucasians are associated with increased risk for gliomas that may benefit these patients with early diagnostic and therapeutic strategies.

Abbreviations

XRCC1
X-ray repair cross-complementing group 1; ERCC2:excision repair cross-complementation group 2; SNPs:single nucleotide polymorphisms; PRISMA:Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PICOS:The Population, Intervention, Comparison, Outcome and Study design; OR:odds ratios; CI:confidence interval; WHO:World Health Organization; NER:nucleotide excision repair; BER:base excision repair; DSBR:double-strand break repair; MMR:mismatch repair; T:thymine; G:guanine; BT:Begg Test; ET:Egger Test.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable.

Availability of data and materials

All data generated in this analysis are available from the corresponding

author.

Competing interests

The authors declare that they have no competing interests.

Funding

No funding was obtained for this study.

Author Contributions

CB and BB conceived and designed the study;

FA and EJ provided study materials and tools*;*

RJ, LC, VC , AC, EB, RO, CB BB were responsible for the collection and assembly of data, data analysis, and interpretation;

FC, PV, dos AR, AL was involved in writing the manuscript*;*

CB, BB and LH revised the manuscript.

all authors have read and approved the manuscript

Acknowledgments

The authors thank to Postgraduate Program of the Northeast Network of Biotechnology (RENORBIO), the largest network Program in Brazil for qualification of doctors in Biotechnology.

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36. Legends.

Figures

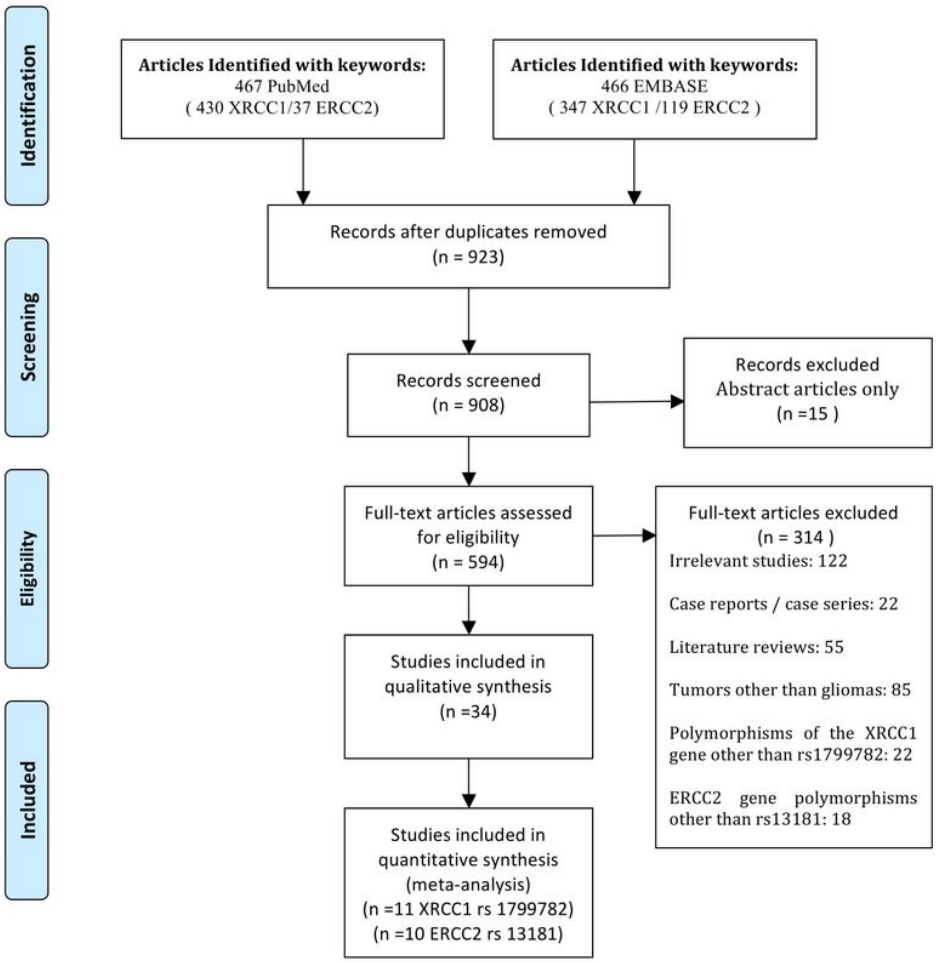

Figure 1

Flow diagram illustrating the search strategy

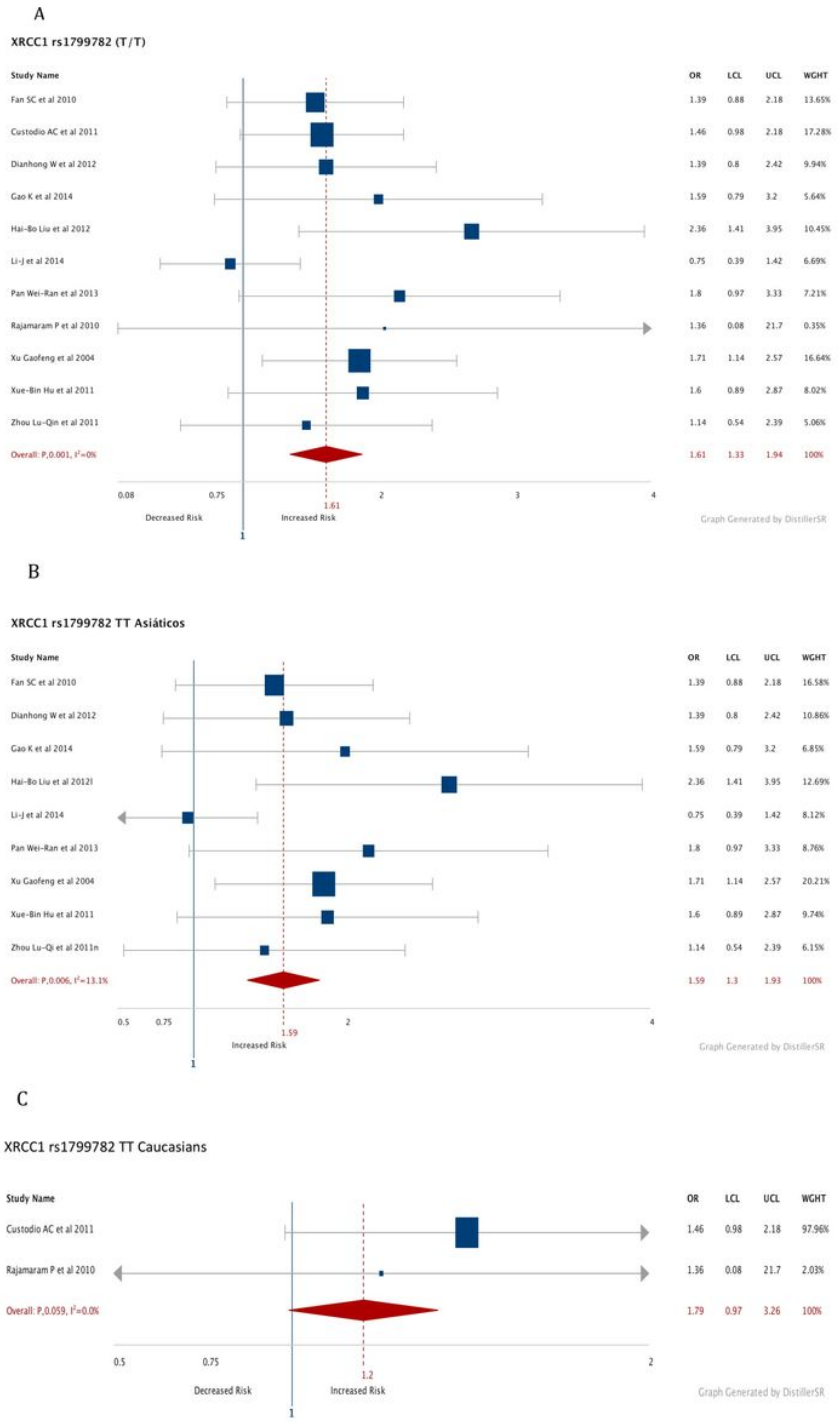

Figure 2

Forest plots. ORs with 95% CI for XRCC1 rs1799782 TT and the risk of glioma.Legend: (A) General population. (B) Asian population. (C) Caucasian population.

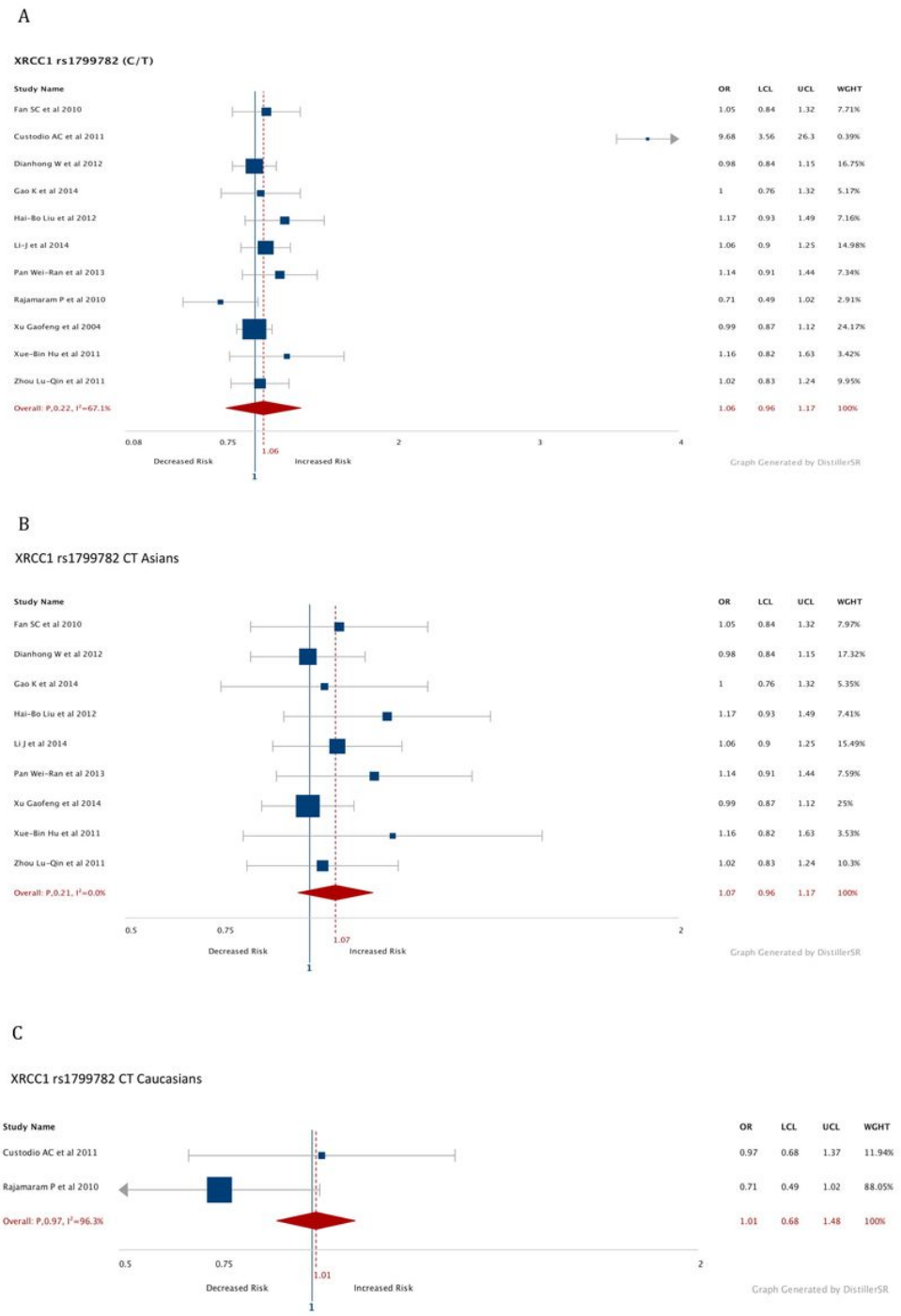

Figure 3

Forest plots. ORs with 95% CI for XRCC1 rs1799782 CT and the risk of glioma. Legend: (A) General population. (B) Asian population. (C) Caucasian population.

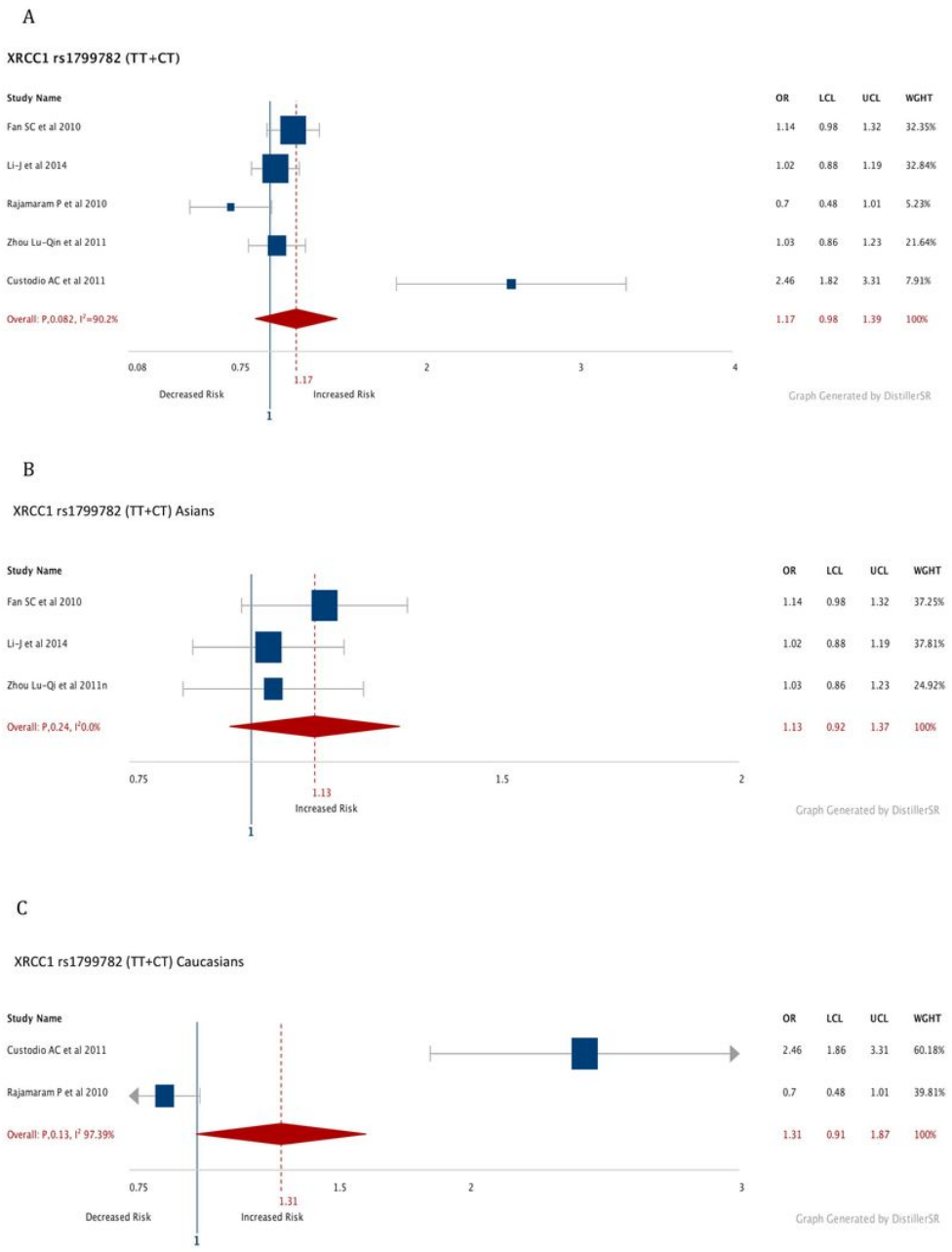

Figure 4

Forest plots. ORs with 95% CI for XRCC1 rs1799782 TT+CT and the risk of glioma. Legend: (A) General population. (B) Asian population. (C) Caucasian population.

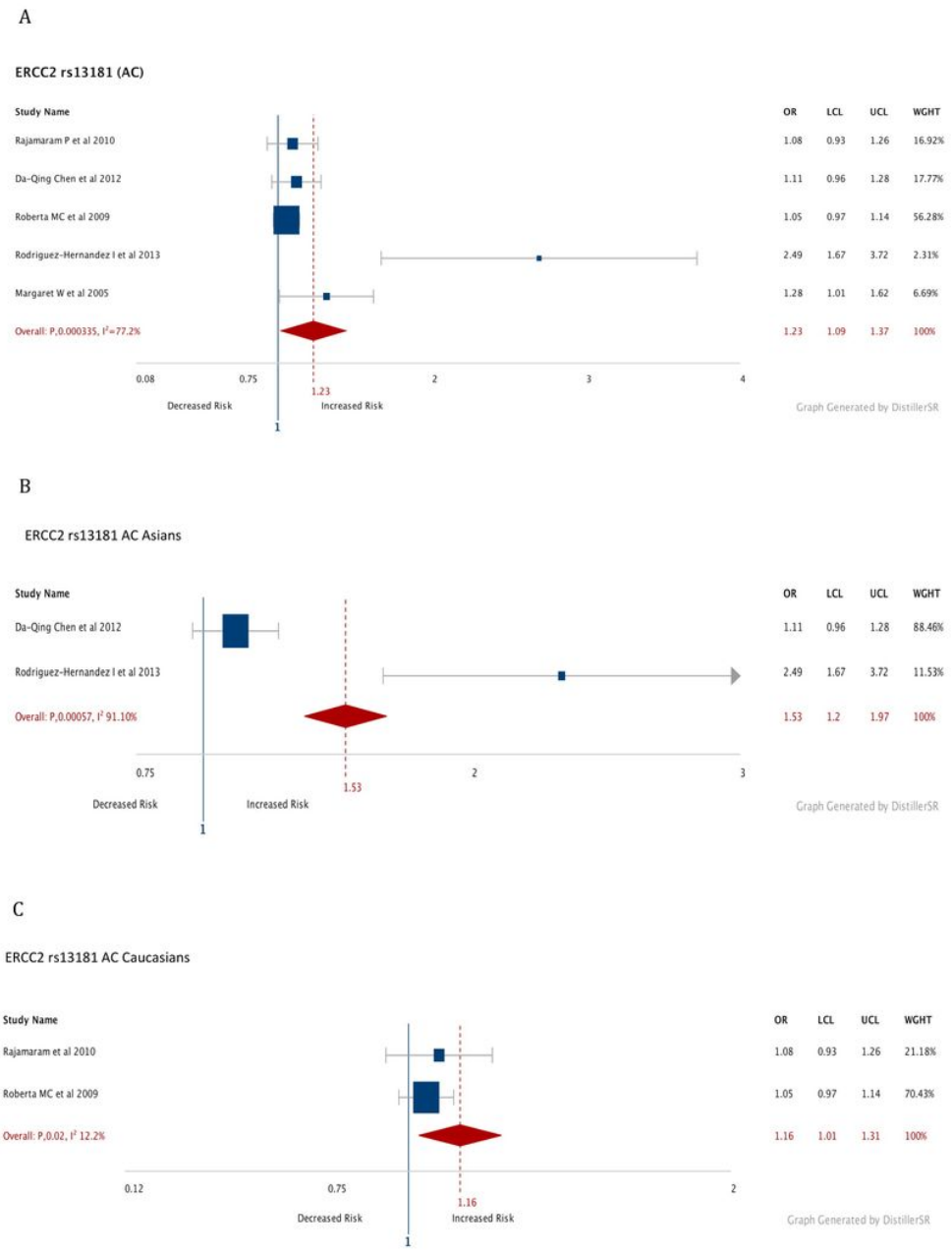

Figure 5

Forest plots. ORs with 95% CI for ERCC2 rs13181 AC and the risk of glioma. Legend: (A) General population. (B) Asian population. (C) Caucasian population.

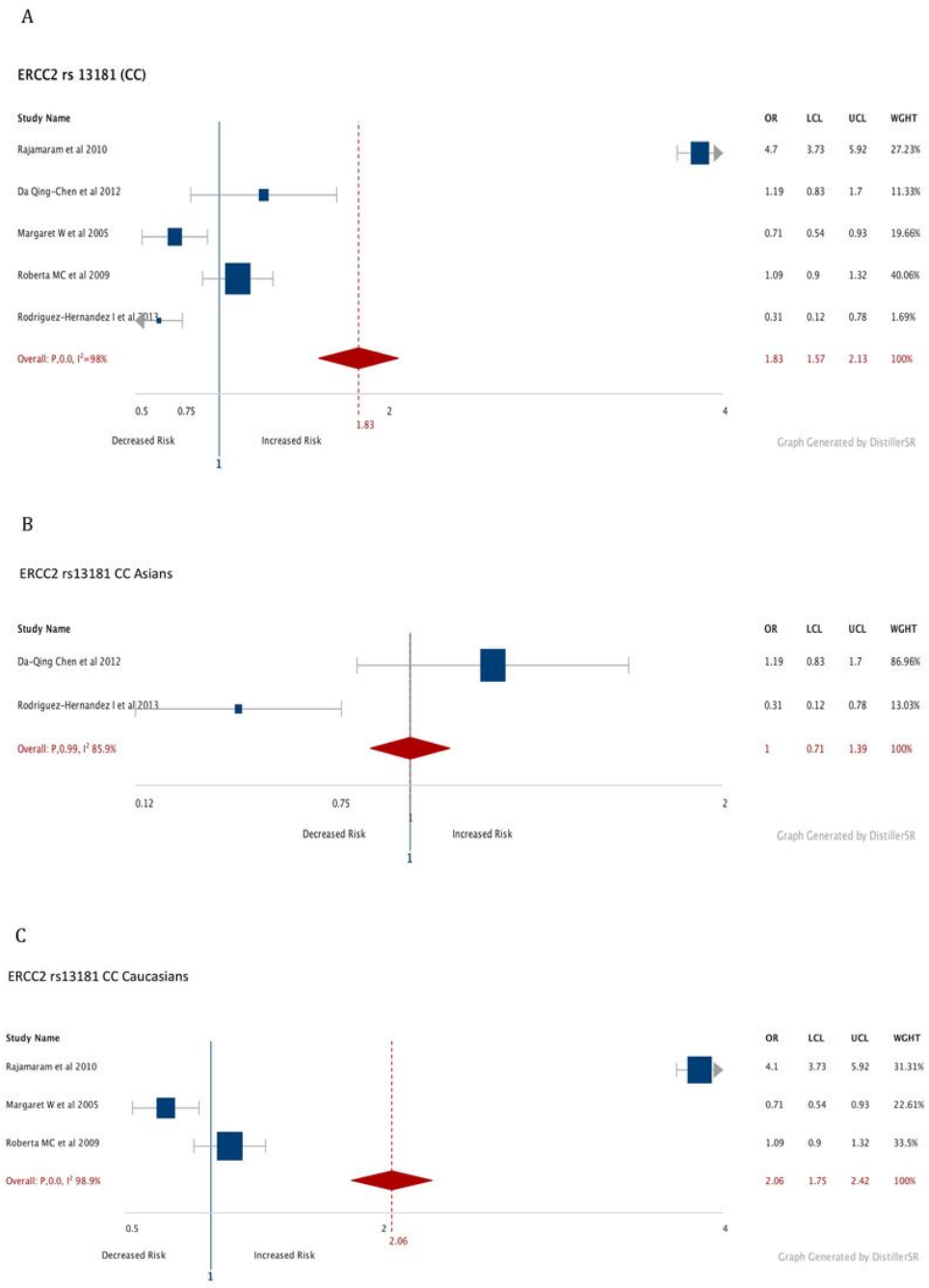

Figure 6

Forest plots. ORs with 95% CI for ERCC2 rs13181 CC and the risk of glioma. Legend: (A) General population. (B) Asian population. (C) Caucasian population.

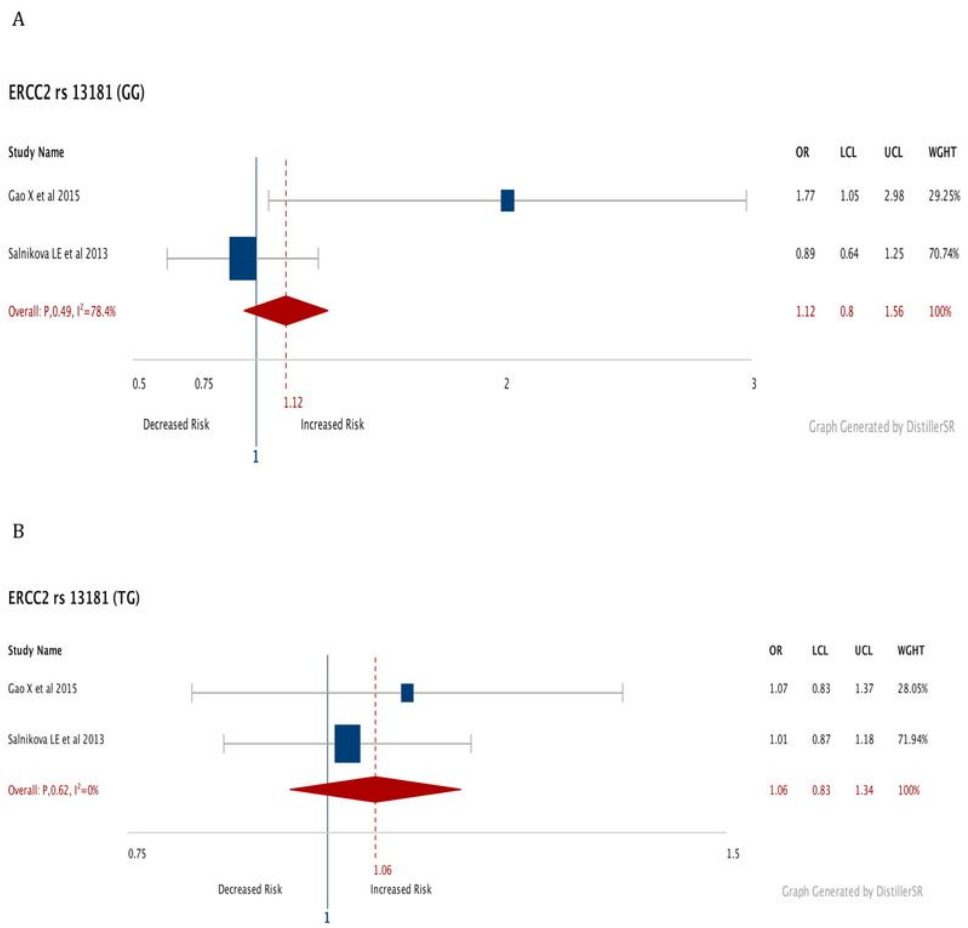

Figure 7

Forest plots. ORs with 95% CI for ERCC2 rs13181 and the risk of glioma. Legend: (A) GG genotype. (B) GT genotype.

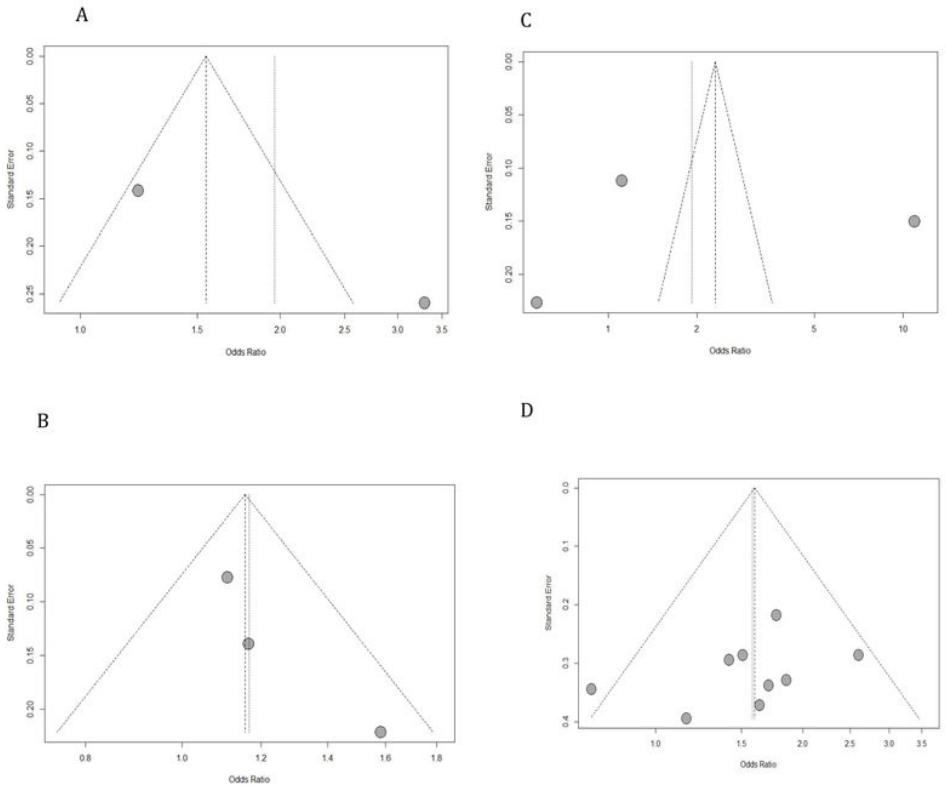

Figure 8

Funnel Plots analysis: (A) ERCC2 rs13181 AC Asians. (B) ERCC2 rs13181 AC Caucasians. (C) ERCC2 rs13181 CC Caucasians. (D) XRCC1 rs1799782 TT Asians.

Supplementary Files

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- PRISMA2009checklist.doc