An updated meta-analysis of XRCC4 rs1805377 polymorphism and the risk of cancer based on 23 case-control studies

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Abstract

Background The growing studies reports that the genes participating in repairing of DNA double-strand breaks may be cancer-susceptibility genes. Rs1805377 (A>G) is a functional single nucleotide polymorphism (SNP) in the x-ray cross-complementing group 4 (XRCC4) gene that may be involved in the etiology of cancer. However, no conclusive results can be determined from individually published studies. Thus, we performed a meta-analysis to examine the association between XRCC4 rs1805377 polymorphism and cancer risk.

Methods The potential literatures were searched using three online electronic databases (PubMed, Embase, and Web of Science). The available studies were included according to the inclusion criteria. The pooled analysis were performed to explore the association between XRCC4 rs1805377 locus and the risk of cancer. Additionally, we also performed subgroup analysis and sensitivity analysis.

Results Twenty-three studies were included in our meta-analysis. It contained 9,433 cancer patients and 10,337 healthy controls. The pooled results showed that there was no association between rs1805377 and the risk of cancer. Under the dominant model, the final pooled odds ratios (ORs) was 1.115 (95% confidence intervals: 0.956-1.301; P = 0.165) in a random effects model without the statistical significance. The subgroup analysis by ethnicity and source of controls also didn't find that rs1805377 polymorphism was related to cancer occurrence. In the subgroup by type of cancers, the significant association was only found in gastric antrum adenocarcinoma.

Conclusions our meta-analysis suggested that there was no association between rs1805377 polymorphism and cancer occurrence. It may provide useful information for the relevant studies on the etiology of cancer in future.

Background

Presently, cancer remains one of the leading cause of mortality globally because of an aging population, the prevalence of smoking, a lack of physical inactivity, and other lifestyle factors [1]. It is a cellular abnormality that is initiated by uncontrolled growth caused by an accumulation of damage or mutation in the genetically mediated factors and environmental factors, which causes cells to evade the signal mediated controls of cell growth and dearth [2]. The genetic factor has a greater effect on cancer initiation than the environmental and lifestyle factor [3]. Presently, a number of potential susceptible genes and variations have been examined and identified to participate in cancer occurrence.

For DNA damage repair, the usually known molecular pathways includes sing-strand damage repair, double-strand break repair, and damage reversal [4]. Presently, the evidence finds that the genes participating in repairing of DNA double-strand breaks may be involved in modifying the risk of various cancers [5]. Among them, the gene x-ray cross-complementing group 4 (XRCC4), which is a specific member of nonhomologous end-joining system, functions together with DNA ligase IV and the DNA-dependent protein kinase in the repair of DNA double-strand breaks [6]. This protein exerts its function in both non-homologous end joining and the completion of V(D)J recombination. XRCC4 gene is located on the chromosome 5q14.2 with the full length 276 kb and contains 23 exons. Mutations in XRCC4 gene can cause severe short stature, gonadal failure,

microcephaly, and increased genomic instability [7,8]. Additionally, its mutations also cause primordial dwarfism without causing immunodeficiency [9]. XRCC4 knockdown by lentivirus-mediated shRNA had no significant effect on proliferation of triple-negative breast cancer (TNBC) cells while knockdown of XRCC4 could substantially increase the sensitivity of TNBC cells to ionizing radiation [10]. Moreover, XRCC4 expression might have an influence on results of radiotherapy for patients with esophageal squamous cell carcinoma [11]. Another study suggests that XRCC4 may be an independent prognostic factor for hepatocarcinoma patients, and that decreasing XRCC4 expression may be beneficial for post-operative adjuvant transarterial chemoembolization treatment in hepatocarcinoma [12].

The variation of XRCC4 gene can be involved in the etiology of cancer by influencing the normality of the protein function. Rs1805377 (A>G) is in intron 7, with the potential function of abolishing an acceptor splice site at exon 8 [13]. This polymorphic locus has been reported to be related with the occurrence of different cancers and tumor diffusing capacity [14–16]. However, their results remain inconclusive due to insufficient population size, genetic heterogeneity of samples, and other possible confounding bias.

Meta-analysis is a powerful method for quantitatively summarizing the results of different studies [17]. An advantage is increasing the sample size by pooling the relevant studies, which can, to some degree, decrease the occurrence of a false-positive or false-negative association generated by random error. Previous meta-analysis studies have investigated the association between XRCC4 gene polymorphisms and the risk of cancer, but as research progressed, an exhaustive and updated meta-analysis is needed to be conducted [18–20]. Consequently, in our present study, we carried out a meta-analysis of studies examining the association between XRCC4 gene polymorphism and the risk of cancer.

Methods

2.1. Literature search and eligibility of relevant studies

To identify studies eligible for our meta-analysis, three online electronic databases (PubMed, Embase, and Web of Science) were searched (the last update date was February 2019). The following key words were used in the literature search: *XRCC4,* rs1805377, and cancer. The additional potential studies were also screened from the included articles and relevant reviews.

Studies which were included in this meta-analysis met the following inclusion criteria: (1) case-control studies; (2) patients with cancer; (3) available allele or genotype frequencies; (4) of the studies with the same or overlapping data published by the same authors, the most latest ones were selected. Major reasons for exclusion of studies were: (1) without controls; (2) duplicate of earlier publication; (3) no usable genotype frequency data.

2.2. Data extraction

According to the inclusion criteria listed above, two of the authors extracted information from all eligible publications independently. Any disagreement was resolved through discussion until the two authors reached a consensus. We calculated the number of genotypes based on the allele frequencies according to Hardy-

Weinberg equilibrium formula. The following data were included from each study: the first author's last name, publication year, region, ethnicity, type of cancer, source of controls, and numbers of genotype between cases and controls.

2.3. Statistical analysis

Hardy-Weinberg equilibrium was checked in control groups using chi-square goodness-of-fit or exact test before statistical analysis (significant at the 0.05 level). The strength of the association between XRCC4 rs1805377 locus and cancer risk was measured by ratios (ORs) and 95% confidence intervals (CIs). Pooled effect sizes across studies were performed by a random effects model (DerSimonian and Laird method), which evaluates the likely effect size across different populations and takes heterogeneity across studies into account [21].

The pooled ORs were calculated using the allele comparison model, dominant comparison model, and recessive comparison model, which were reported previously [22]. Then the most appropriate genetic model was selected in our pooled analysis to according to the criteria [23,24].

The degree of heterogeneity between studies was measured by Q-statistic. P value >0.05 for the Q-test indicated a lack of heterogeneity and P value <0.05 indicated an existence of heterogeneity [25,26]. The I^2 is the proportion of observed variance in effect sizes attributable to the true differences among studies. A conventional interpretation of I^2 is that it defines bounds for low (<25%), moderate (□50%), and high (>75%) heterogeneity. Subgroup analysis was performed by ethnicity, source of controls, and types of cancer.

Sensitivity analysis was carried out to assess the potential influences of any single study on the pooled effect size. It was performed by omitting each included study to assess the stability of the results.

An estimate of publication bias was performed by visual inspection of a funnel plot, in which the standard error of log (OR) of each study was plotted against its log (OR). An asymmetric plot indicated a possible publication bias, and the degree of asymmetry was tested using Egger's test (P <0.05 was considered to indicate significant publication bias) [27].

All statistical tests were two-sided. The meta-analysis was performed using Stata version 10.0 (Stata Corp., College Station, TX, USA).

Results

There were 23 eligible studies as a result of the searching and screening carried out on the basis of our eligibility criteria [13,28–49]. Subjects involved in these studies are not overlapping. We collected 23 case-control studies, which contained 9,433 patients with cancer (i.e., cases) and 10,337 unaffected participants (i.e., controls). The individuals with the different genetic backgrounds and different types of cancer were included (e.g., East Asian and Caucasian; breast cancer, bladder cancer, renal cell carcinoma, oral cancer, glioma, thyroid cancer, non-small-cell lung cancer, prostate cancer, gastric antrum adenocarcinoma, non-hodgkin lymphoma, pancreatic cancer, hepatocellular carcinoma, and esophageal squamous cell carcinoma). The

main characteristics of the included studies were listed in Table 1. The genotype and allele frequencies of rs1805377 SNP and HWE in controls were showed in Table 2. Of the 23 studies, there were four publications deviated significantly from HWE [31,38,40,47].

3.1 meta-analysis result

The association between rs1805377 polymorphism and the risk of different cancers was evaluated using the pooled ORs and corresponding 95% CIs under the following genetic models: homozygous codominant, heterozygous codominant, dominant, recessive, and allele contrast (Table 3 and Figure 1). Finally, the dominant model was selected to perform the pooled analysis according to the selection criteria of genetic models. The pooled results showed that no association was observed between rs1805377 polymorphism and the risk of cancer. In the dominant model, the summary OR generated by a random effects model was 1.115 (95% CI, 0.956–1.301; P = 0.165). Results of subgroup analysis by ethnicity showed that the SNP was not associated with the risk of cancer among East Asian and Caucasian (Table 4). Moreover, there was no association between rs1805377 and cancer in subgroup analysis in light of the source of controls (hospital based and population-based). Additionally, we also performed the subgroup analysis by the type of cancer. The results showed that rs1805377 increased the occurrence of gastric antrum adenocarcinoma, but not other cancer types (Table 4).

3.2 Sensitivity analysis

Sensitivity analysis was carried out by removing each included study to assess the influence of every single study. The corresponding pooled ORs were no significant change when removing one study at the time from each meta-analysis, indicating that our results were stable and reliable.

3.3 Publication bias

Funnel plot was performed to assess the publication bias of literature. Funnel plot is shown in Figure 2. Egger's test was used to supply statistical evidence for funnel plot symmetry. The results showed no significant effect of publication bias (P_e = 0.950) (Table 3).

Discussion

Our meta-analysis explored the association between *XRCC4* rs1805377 polymorphism and cancer risk. A total of 23 case-control studies were included, which contained 9,433 cases and 10,337 controls. The pooled results indicated that there was an association, and subgroup analysis by ethnicity, source of controls, and types of cancer further investigated the distribution deviation between cases and controls.

Previously, there were three meta-analyses reported the putative association between rs1805377 and cancer risk [18–20]. Although our meta-analysis seems redundant, there are still some highlights in our present analysis. On the one hand, the newly published studies were included after the previous meta-analyses. A total of 23 studies were included to comprehensively investigate the role of rs1805377 in the occurrence of cancer. It contained various types of cancer (breast cancer, bladder cancer, renal cell carcinoma, oral cancer, glioma, thyroid cancer, non-small-cell lung cancer, prostate cancer, gastric antrum adenocarcinoma, non-

hodgkin lymphoma, pancreatic cancer, hepatocellular carcinoma, and esophageal squamous cell carcinoma). On the other hand, we preformed subgroup analysis by ethnicity, source of controls, and types of cancer to further explore the existing of heterogeneity. Therefore, to some degree, the final results in our meta-analysis is more accurate and comprehensive than the previous meta-analysis.

However, the relatively small sample sizes of some cancers (renal cell carcinoma, non-small-cell lung cancer, gastric antrum adenocarcinoma, non-hodgkin lymphoma, hepatocellular carcinoma, and esophageal squamous cell carcinoma) limited our ability to isolate stable effects for these subgroups. Our meta-analysis found an association between rs1805377 and the risk of gastric antrum adenocarcinoma. Regrettably, the results need to be interpreted cautiously considering that just one study was included. Thus, we cannot obtain the accurate and comprehensive results of the association between rs1805377 and the risk of the above cancers because of the limitation of sample size.

XRCC4 is indispensable for non-homologous end joining, the major pathway for repairing DNA double-strand breaks. Thus, it is generally believed that abnormalities in XRCC4 cause severe combined immunodeficiency [9]. But one patient with the mutations in XRCC4 gene displayed the microcephaly and progressive ataxia but a normal immune response, which suggested that XRCC4 deficiency in human subjects caused a marked neurological phenotype but no overt immunodeficiency [50]. Moreover, the XRCC4 c.482G>A mutation, which affects the last nucleotide of exon 4, induces defective splicing of XRCC4 pre-mRNA mainly resulting in premature protein truncation and most likely loss of XRCC4 function [8]. In addition, genome-wide gene expression analysis revealed age-related impairment of mitosis, telomere and chromosome maintenance and induction of genes associated with DNA repair and non-homologous end-joining, most notably XRCC4 and ligase 4 [51]. Considering the inconsistency of the current results, more effort need to explore the role of XRCC4 mutations in the occurrence of cancer.

Conclusion

Our study found no association between the rs1805377 in *XRCC4* gene and the risk of cancer. The studies containing different types of cancer need to validate the findings of this meta-analysis and to ascertain the epigenetic mechanisms and environmental influences that contribute to the risk of cancer.

Abbreviations

SNP: single nucleotide polymorphism; *XRCC4:* x-ray cross-complementing group 4; *HWE:* Hardy-Weinberg equilibrium; *ORs:* Odds ratios; *CIs:* confidence interval.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

XYZ and JY conceived and designed the study. XYZ, XHW and BJW were responsible for collection of data, performing statistical analyses, and manuscript preparation. JY were responsible for reviewing the data. All authors contributed to drafting the manuscript, and all read and approved the final version.

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Tables

Table 1. Baseline characteristics of qualified studies in this meta-analysis.

Author	Year	Region	Ethnicity	Controls source	Type of cancer	Case/control
Fu	2003	Taiwan	Asian	hospital-based	breast cancer	254/379
García-Closas	2006	USA	Caucasian	population-based	breast cancer	1898/1514
Figueroa	2007	Spain	Caucasian	hospital-based	bladder cancer	1150/1149
Margulis	2008	USA	Caucasian	hospital-based	renal cell carcinoma	326/335
Tseng	2008	Taiwan	Asian	hospital-based	oral Cancer	636/636
Liu	2008	China	Asian	hospital-based	glioma	771/752
Chiu	2008	Taiwan	Asian	hospital-based	oral Cancer	318/318
Siraj	2008	Saudi Arabia	Asian	population-based	papillary thyroid cancer	223/229
Tseng	2009	Taiwan	Asian	hospital-based	non-small-cell lung cancer	152/162
Leudeke	2009	Germany	Caucasian	hospital-based	prostate cancer	512/539
Long	2010	China	Asian	hospital-based	gastric antrum adenocarcinoma	361/616
Gomes	2010	Portugal	Caucasian	hospital-based	thyroid cancer	109/217
Shen	2010	USA and Australia	Caucasian	population-based	non-hodgkin lymphoma	1946/1808
Rajaraman	2010	USA	Caucasian	hospital-based	glioma, meningioma and acoustic neuroma	565/495
Mandal	2011	India	Asian	hospital-based	prostate cancer	192/224
Mittal	2012	India	Asian	hospital-based	urothelial bladder cancer	211/244
Zhao	2013	China	Asian	hospital-based	glioma	384/384
Ding	2015	China	Asian	hospital-based	pancreatic cancer	206/412
Shen	2015	China	Asian	hospital-based	pancreatic cancer	248/496
Su	2015	China	Asian	hospital-based	glioma	162/324
Jiao	2016	China	Asian	hospital-based	glioma	317/352
Makkoch	2016	Thailand	Asian	hospital-based	hepatocellular carcinoma	121/107
Yang	2016	China	Asian	hospital-based	esophageal squamous cell carcinoma	189/189

Table 2. Distribution of genotype and allele frequencies of the *XRCC4* rs1805377 polymorphism.

	Genotype distribution							Allele frequency			
	Cases, n			Controls, n				Cases, %		Controls, %	
Author	AA	AG	GG	AA	AG	GG	P_{HWE}	A	G	A	G
Fu	14	102	135	24	159	196	0.2698	0.26	0.74	0.27	0.73
García-Closas	1231	285	20	964	239	10	0.2494	0.89	0.11	0.89	0.11
Figueroa	13	232	841	12	168	852	0.2574	0.12	0.88	0.09	0.91
Margulis	12	82	229	13	58	262	**0.0001**	0.16	0.84	0.13	0.87
Tseng	173	127	18	167	130	21	0.5210	0.74	0.26	0.73	0.27
Liu	382	312	53	379	305	48	0.1985	0.72	0.28	0.73	0.27
Chiu	173	127	18	167	130	21	0.5210	0.74	0.26	0.73	0.27
Siraj	2	13	33	12	88	127	0.5168	0.18	0.82	0.25	0.75
Tseng	83	48	19	83	59	9	0.7266	0.71	0.29	0.75	0.25
Leudeke	8	107	422	8	89	410	0.2200	0.11	0.89	0.10	0.90
Long	96	173	92	340	205	71	**<0.0001**	0.51	0.49	0.72	0.28
Gomes	1	15	93	6	45	166	0.1793	0.08	0.92	0.13	0.87
Shen	29	253	795	33	229	831	**0.0007**	0.14	0.86	0.13	0.87
Rajaraman	10	103	413	7	115	347	0.4665	0.12	0.88	0.14	0.86
Mandal	131	55	6	149	65	10	0.4000	0.83	0.17	0.81	0.19
Mittal	140	70	1	156	79	9	0.7969	0.83	0.17	0.80	0.20
Zhao	179	143	62	195	153	36	0.4537	0.65	0.35	0.71	0.29
Ding	74	95	37	159	184	69	0.2079	0.59	0.41	0.61	0.39
Shen	92	112	44	201	216	79	0.1043	0.60	0.40	0.62	0.38
Su	62	70	30	137	134	53	**0.0413**	0.60	0.40	0.63	0.37
Jiao	173	121	22	197	132	23	0.8884	0.74	0.26	0.75	0.25
Makkoch	60	66	12	55	42	10	0.6322	0.67	0.33	0.71	0.29
Yang	95	80	14	88	83	18	0.8052	0.71	0.29	0.69	0.31

Abbreviation: P_{HWE} represents the *P* value of Hardy-Weinberg equilibrium test in the genotype distribution of controls.

Table 3. Summarized ORs with 95% CIs for the association of *XRCC4* rs1805377 polymorphism with cancer.

Polymorphism	Genetic model	n	Statistical model	OR	95% CI	p_z	I^2(%)	p_h	p_e
Rs1805377									
	Allele contrast	23	Random	1.064	0.943-1.202	0.313	61.1	<0.0001	0.949
	Homozygous codominant	23	Random	1.202	0.943-1.532	0.137	64.9	<0.0001	0.044
	Heterozygous codominant	23	Random	1.107	0.963-1.272	0.155	59.0	<0.0001	0.717
	Dominant	23	Random	1.115	0.956-1.301	0.165	69.5	<0.0001	0.950
	Recessive	23	Random	1.110	0.935-1.319	0.233	70.5	<0.0001	0.371

Note: n, the number of studies; p_z, *P* value for association test; p_h, *p* value for heterogeneity test; p_e, *p* value for publication bias test.

Table 4. Stratified analysis of the association of *XRCC4* polymorphisms with cancer under dominant model.

Subgroup analysis	Rs1805377					
	n	OR	95% CI	p_z	I^2(%)	p_h
Overall	23	1.115	0.956-1.301	0.165	69.5	<0.0001
Ethnicity						
East Asians	16	1.139	0.940-1.380	0.185	77.8	<0.0001
Caucasians	7	0.983	0.836-1.157	0.837	0.0	0.945
Source of controls						
Hospital-based	20	1.125	0.943-1.341	0.191	72.5	<0.0001
Population-based	3	0.981	0.824-1.169	0.832	0.0	0.796
Type of cancer						
Breast cancer	2	0.971	0.811-1.164	0.752	0.0	0.623
Bladder cancer	2	0.913	0.645-1.292	0.606	0.0	0.864
Renal cell carcinoma	1	1.053	0.473-2.343	0.900	-	-
Oral cancer	2	0.927	0.744-1.156	0.500	0.0	1.000
Glioma	5	1.077	0.941-1.233	0.280	0.0	0.863
Thyroid cancer	2	1.728	0.499-5.987	0.388	0.0	0.512
Non-small-cell lung cancer	1	0.985	0.626-1.552	0.949	-	-
Prostate cancer	2	0.944	0.646-1.380	0.766	0.0	0.803
Gastric antrum adenocarcinoma	1	3.401	2.564-4.510	<0.001	-	-
Non-hodgkin lymphoma	1	1.125	0.678-1.866	0.648	-	-
Pancreatic cancer	2	1.140	0.903-1.438	0.271	0.0	0.900
Hepatocellular carcinoma	1	1.375	0.828-2.283	0.218	-	-
Esophageal squamous cell carcinoma	1	0.862	0.576-1.291	0.471	-	-

Note: n, the number of studies; p_z, p value for association test; p_h, p value for heterogeneity test.

Figures

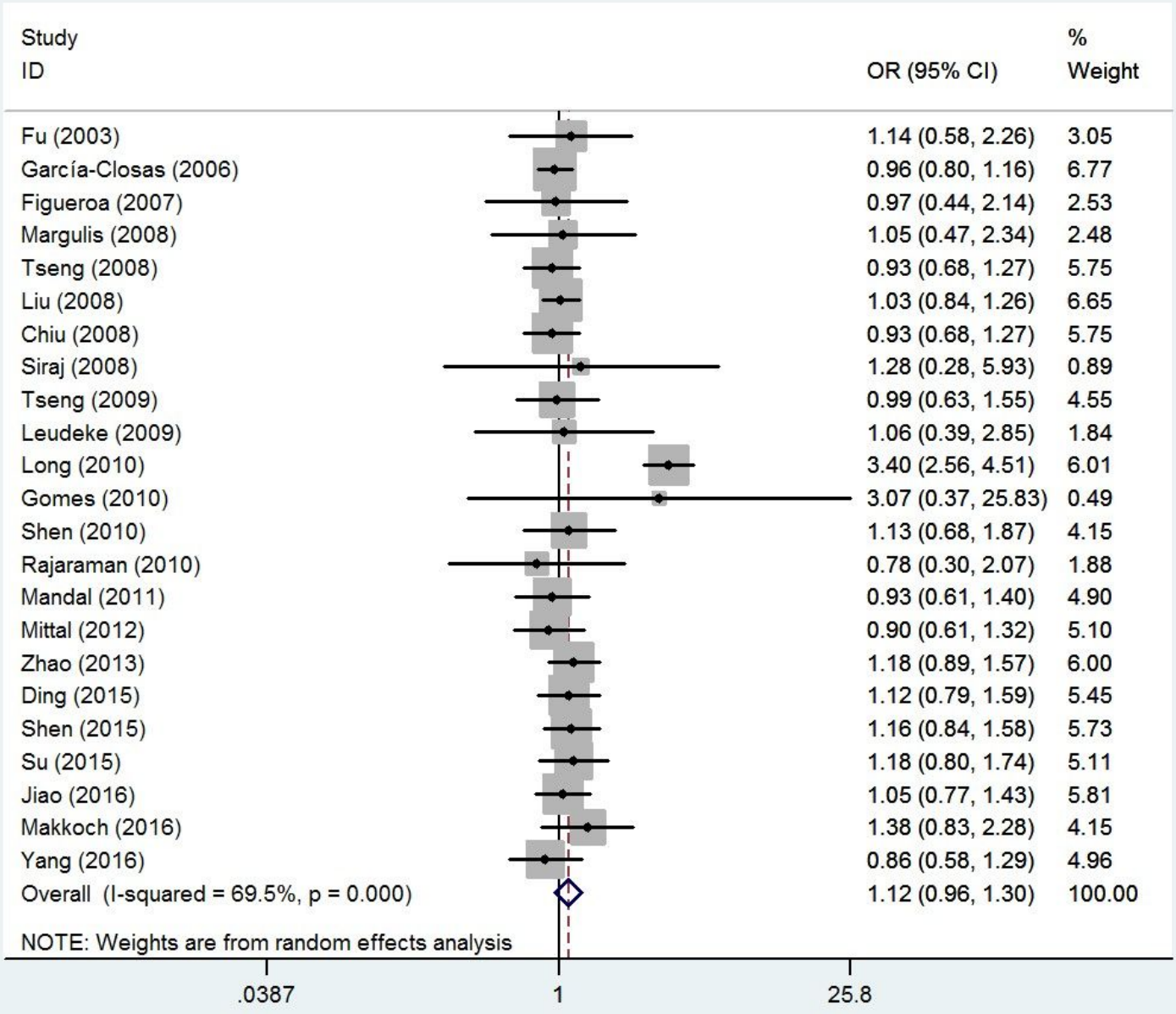

Figure 1

Forest plot of the association between the rs1805377 polymorphism of XRCC4 and cancer in the dominant genetic model (GG + GA vs. AA).

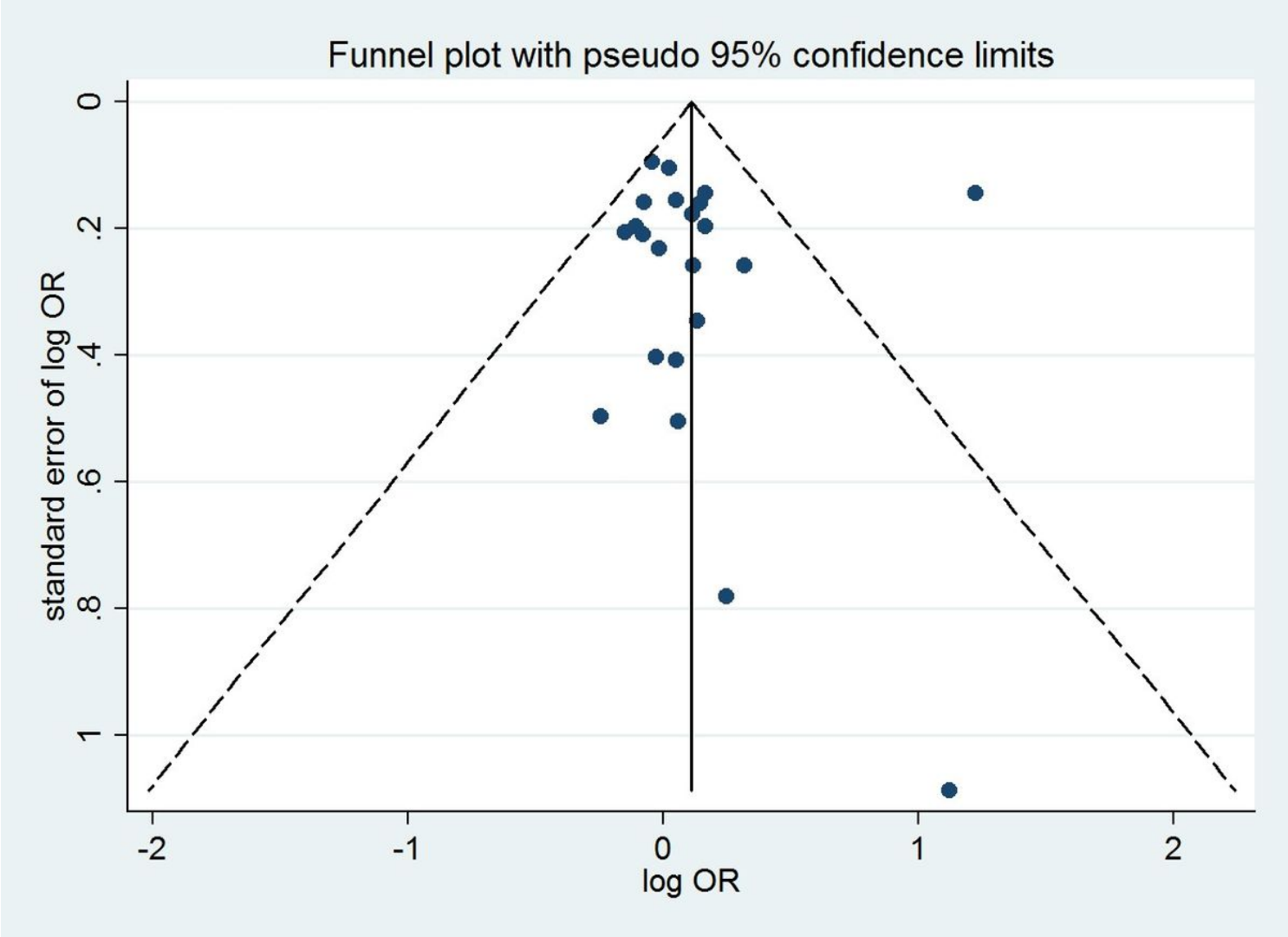

Figure 2

Funnel plot analysis depicting publication bias in the association between the rs1805377 polymorphism of XRCC4 and cancer.

Supplementary Files

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- PRISMAIPDchecklist.docx