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The polymorphism of XRCC1 and coronary artery disease risk: a meta-analysis

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Abstract. – OBJECTIVE: Coronary artery disease (CAD) is a life-threatening disease and is caused by various factors, with genetic variation being an important risk factor. The association between X-ray repair cross-complementing group 1 (XRCC1) polymorphisms and CAD has been extensively studied with conflicting results. We performed a meta-analysis to investigate the overall association between XRCC1 polymorphisms and CAD risk.

MATERIALS AND METHODS: We searched PubMed and Embase databases until October 19, 2016. The total number and distribution of genotypes, genotyping methods, and ethnicity were extracted. Overall and subgroup analyses were performed.

RESULTS: A total of seven publications involving 1.862 subjects and 1.568 controls were included in this meta-analysis. The Arg399Gln and Arg194Trp polymorphisms of XRCC1 were analyzed. The results indicated that the XRCC1 Arg399Gln homozygous GG genotype showed no association with CAD risk [GG *vs.* GA+AA: odd's ratio (OR) = 0.95, 95% confidence interval (CI) = 0.82-1.11, *p* = 0.53] both in the overall and subgroups evaluation. However, the XRCC1 Arg194Trp homozygous TT genotype was associated with an increased CAD risk [(TT *vs.* TC+CC: OR =1.52, 95%CI = 1.16–2.00, *p*=0.003)]. Subgroup analysis based on ethnicity showed a significant increase in the association of CAD risk and the Arg194Trp gene polymorphism among the Asian population.

CONCLUSIONS: This meta-analysis suggested that TT genotype in the Arg194Trp polymorphism contributes to the CAD susceptibility, particularly in the Asian population.

Key Words
X-ray repair cross-complementing group 1 (XRCC1), Coronary artery disease, Polymorphism, Meta-analysis.

Introduction

Coronary artery disease (CAD) is universally acknowledged as the leading cause of morbidity and mortality, especially in the elderly[1]. Hypertension, smoking, diabetes mellitus, and hypercholesterolemia are identified as risk factors. While the exact cause of CAD is still unknown[2], there is a consensus that CAD results from environmental and genetic factors[3,4]. A large number of CAD susceptible genes have been identified in genome-wide association study (GWAS) and genetic association studies[5-8]. X-ray repair cross-complementing group 1 (XRCC1) is one of the genes identified and studied.

Deoxyribonucleic acid (DNA) damage could cause gene mutations that contribute to CAD pathogenesis[9]. To ameliorate the unrepaired damage, repair mechanisms are deployed to maintain the integrity of the genetic blueprint[10,11]. XRCC1 plays an important role in the base-excision repair (BER) pathway, which is a part of DNA repair. Studies on XRCC1 polymorphisms Arg-399Gln (rs25487) at codon 399 and Arg194Trp (rs199782) at codon 194 suggested a potential association with risk of cancers. The gene conserved site at codon 399 in exon 10 leads to a G→A substitution and the amino acid alteration of arginine (Arg) to glutamine (Gln), whereas codon 194 in exon 6 leads to a C→T substitution and the alteration of Arg to tryptophan (Trp). The 399Gln and 194Trp alleles were significantly associated with a higher level of DNA adducts, chromosomal damage, and prolonged DNA repair, which could affect the BER pathway[12]. The association between XRCC1 polymorphisms and CAD risk had been studied with conflicting

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results reported. Hence, we conducted a meta-analysis to investigate the association between XRCCI and CAD risk.

Materials and Methods

Study Identification and Selection

Studies investigating the association between XRCC1 polymorphisms and CAD risk were searched in Pubmed and Embase databases updated on October 19, 2016 by two authors. The language was limited to English. The search terms used were as follows: "coronary artery disease" in combination with "polymorphism or variant or mutation" and "XRCC1." The inclusion criteria were as follows: (1) studies that evaluated the association between XRCC1 polymorphism and CAD risk; (2) genetic association case-control studies; (3) genotype distributions for cases and controls must be available to estimate an odd's ratio (OR) with 95% confidence interval (CI). Studies were excluded if one of the following were satisfied: (1) genotype frequency was not reported; (2) abstracts, letters, and reviews only; (3) repeated and overlapping data were involved, and the study with the largest participants was included.

Data Extraction

Two reviewers independently checked all relevant studies and reached a consensus on all items. Author, year of publication, ethnicity, genotyping methods, total number and distribution of genotypes, case definition (by coronary angiography as having ≥50% luminal stenosis), and source of controls were extracted.

Statistical Analysis

Hardy-Weinberg equilibrium (HWE) was tested using Pearson's χ^2-test (p<0.05 indicates deviation from HWE). The strength of the association between XRCC1 polymorphisms at codon 399 and codon 194 and CAD risk were assessed by OR with the corresponding 95% CI. Heterogeneity was assessed by a χ^2-based Q statistic, with p<0.10 considered to be statistically significant. The recessive genetic model was used to evaluate the pooled OR of each polymorphism (GG *vs*. AG+AA for codon 399 and TT *vs*. TC+CC for codon 194). Dominant genetic models (GG+AG *vs.* AA and TT+TC *vs.* CC), codominant models (GG *vs*. AA and TT *vs.* CC), and allele models (G *vs.* A and T *vs.* C) were also used to assess the association of each genotype with the risk of CAD. OR was calculated using a random-effects or fixed-effects model according to the heterogeneity. For a p<0.10, the pooled OR was calculated using random-effects model; otherwise, a fixed-effects model was used. Z-test was performed to evaluate the significance of the pooled OR, and p< 0.05 was considered to be statistically significant. Subgroup analyses were performed for accordance with HWE, case definition, and ethnic group. Publication bias was analyzed using Begg's funnel plots and Egger's test. Sensitivity was analyzed to identify the potential influence of the individual data set to the pooled OR. Revman 5.0 software (Review Manager, Version 5.0, the Nordic Cochrane Centre, the Cochrane Collaboration, Copenhagen, 2008) and STATA 12.0 software (Statistical Software, Release 12.0, College Station, TX: Stata Corp LP, American, 2009) were used for all statistical tests.

Results

Characteristics of Included Studies

A total of 43 articles were identified after an initial search of the Pubmed and Embase databases (Figure 1). Eight studies evaluating the association between XRCC1 polymorphisms and CAD risk were included in the meta-analysis[13-20]. One study was excluded because it evaluated the rs3213245 single nucleotide polymorphisms (SNP) in XRCC1 and CAD[20]. A total of 1.862 subjects and 1.568 controls were included in the data analysis from six studies related to codon 399 and four studies related to codon 194. Genotypes in the control groups were tested for accordance with HWE; one study on codon 399 and two studies on codon 194 deviated from HWE. The characteristics of each case-control study are summarized in Table I, and genotype and allele distributions are listed in Table II.

Quantitative Synthesis

To select the most suitable calculation model for the XRCC1 Arg399Gln polymorphism, we analyzed the heterogeneity of GG *vs.* AG+AA in all six studies. The χ^2 value was 6.39 with 5 degrees of freedom (p=0.27); hence, we choose the fixed-effects model to synthesize the data. Overall OR was 0.95 (95% CI = 0.82-1.11), and

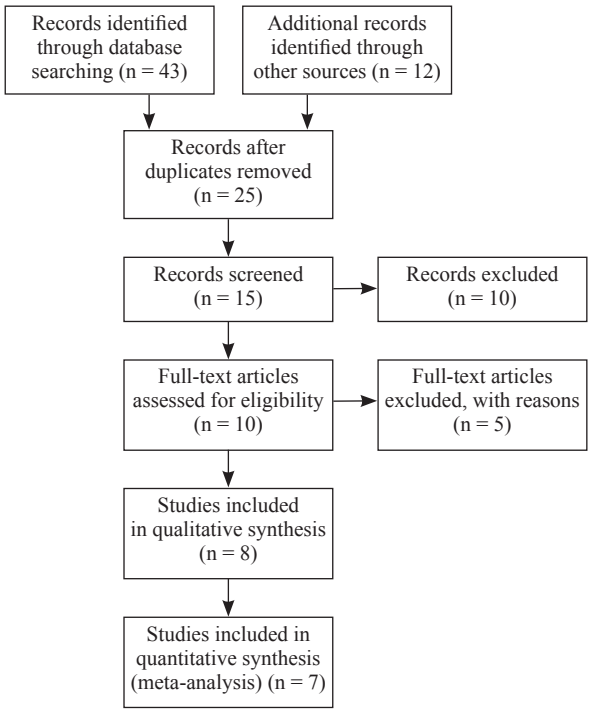

Figure 1. The flow diagram of included and excluded studies.

overall effect Z value was 0.64 (p=0.53) for the GG *vs.* GA +AA model, which showed no association with CAD risk. Also, the *I*-square value, which is another index of heterogeneity, was 22%, suggesting an absence of heterogeneity. Subgroups analyses were performed for ethnicity, case definition, and accordance with HWE (Figure 2); all results showed no association with CAD risk. A summary of other genetic comparisons is listed in Table III.

For the XRCC1 Arg194Trp polymorphism, we analyzed the heterogeneity of TT *vs.* TC+CC in all four studies. The χ^2 value was 1.74 with 3 degrees of freedom (p=0.63) in a fixed-effects model. Additionally, the *I*-square value was 0%, suggesting an absence of heterogeneity. Thus, we choose the fixed-effects model for data analysis. The pooled OR was 1.47 (1.13-1.93), and the effect Z value was 2.83 (p=0.005). Subgroup analysis of TT *vs.* TC+CC based on ethnicity showed an OR of 1.52 (95% CI = 1.16-2.00, p=0.003) in the Asian population. Both results suggested an increased CAD risk with the TT genotype. In accordance with the HWE subgroup analysis, no association was found between the XRCC1 Arg194Trp gene polymorphism and CAD (Figure 3). Genetic comparisons are summarized in Table III.

Table I. Characteristics of case-control studies included in the present meta-analysis.

Genotype	Author	Year	Country	Ethnicity	Case	Control	Genotyping method	HWE	Coronary angiography	Stenosis
rs25487 (codon399)	Bazo	2011	Brazil	Latin	117	52	PCR-RFLP	Yes	Yes	>20%
	Gokkusu	2013	Turkey	Unknown	197	135	PCR-RFLP	Yes	Yes	≥50%
	Guven	2007	Turkey	Turkish	147	48	PCR-RFLP	No	Yes	≥50%
	Hameed	2016	Pakistan	Mixed	99	106	PCR-RFLP	Yes	Not mentioned	Not mentioned
	Narne	2013	India	Asian	160	121	PCR-RFLP	Yes	Yes	≥50%
	Yu	2014	China	Asian	1142	1106	PCR-LDR	Yes	Yes	≥50%
rs1799782 (codon194)	Bazo	2011	Brazil	Latin	46	39	PCR-RFLP	Yes	Yes	>20%
	Hameed	2016	Pakistan	Mixed	99	106	PCR-RFLP	Yes	Not mentioned	Not mentioned
	Pahlavanneshan	2015	Iran	Asian	203	203	PCR-RFLP	No	Yes	Not mentioned
	Yu	2014	China	Asian	1142	1106	PCR-LDR	No	Yes	≥50%

PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism. HEW: Hardy-Weinberg equilibrium. PCR-LDR: polymerase chain reaction-ligase detection reaction.

Table II. Distributions of CRCC1 genotype and allele among CAD patients and controls.

Genotype	Author	Year	Case			Control			Case		Control		Case	Control
			AA	AG	GG	AA	AG	GG	A	G	A	G		
rs25487 (codon399)	Bazo	2011	25	76	16	20	28	4	126	108	68	36	117	52
	Gokkusu	2013	169	27	1	119	16	0	365	29	254	16	197	135
	Guven	2007	50	76	21	12	33	3	176	118	57	39	147	48
	Hameed	2016	31	28	40	23	30	53	90	108	76	136	99	106
	Narne	2013	52	84	24	58	49	14	188	132	165	77	160	121
	Yu	2014	80	437	625	60	419	627	597	1687	539	1673	1142	1106
rs1799782 (codon194)	Bazo	2011	40	6	0	28	10	1	86	6	66	12	46	39
	Hameed	2016	94	3	2	99	4	3	191	7	202	10	99	106
	Pahlavanneshan	2015	155	44	4	182	18	3	354	52	382	24	203	203
	Yu	2014	517	486	139	483	531	92	1520	764	1497	715	1142	1106

Sensitivity Analysis and Publication Bias

Sensitivity analysis was assessed to evaluate the stability of the individual data to the pooled OR (GG *vs.* AG+AA and TT *vs.* TC+CC). After sequentially excluding each study, the results suggested stable meta-analysis both in XRCC1 Arg399Gln and Arg194Trp SNPs.

Publication bias was assessed by Begg's funnel plots and Egger's test using STATA 12.0 software. The shape of the funnel plots appeared symmetrical in the GG *vs.* AG+AA comparison model of the XRCC1 Arg399Gln polymorphism, suggesting the absence of publication bias (Figure 4). The Egger's test was performed to provide statistical evidence of funnel plot asymmetry. The *p*-value was 0.817 for codon 399, indicating an absence of publication bias. From the four articles regarding Arg194Trp, the shape of the funnel plots appeared symmetrical in the TT *vs.* TC+CC model, and the Egger's test *p*-value was 0.122, showing no publication bias.

Discussion

CAD is caused by a combination of genetic and environmental factors. Differences in individual susceptibility to CAD exist when exposed to the same environment[21]. Gene variants may play a vital function in the pathogenesis of CAD, especially in the young generation[22]; hence, increasing numbers of studies regarding SNP and the pathogenesis of CAD are published every year[23,24]. GWAS is a crucial method to identify susceptible genes for CAD, and many candidate genes have been identified in different ethnic populations to date. Mutations in the CDKN2A/2B/ANRIL gene cluster, PHACTR1, NHGRI, and KCNE2 were thought to be CAD genetic risk factor[25]. Numerous studies on XRCC1 polymorphisms have found that SNPs are associated with CAD risk. Four of the included studies[16-19] suggested a significant association between XRCC1 polymorphisms and CAD, whereas other papers showed no association[13-15]. Hence, we performed this meta-analysis to comprehensively assess the association of XRCC1 and CAD.

The meta-analysis involved seven articles (six reports related to codon 399 and four studies related to codon 194) involving 1.862 subjects and 1.568 controls. Overall, there was no association between the XRCC1 Arg399Gln polymorphism and risk of CAD. Subgroup analysis was performed based on ethnicity, case definition, and

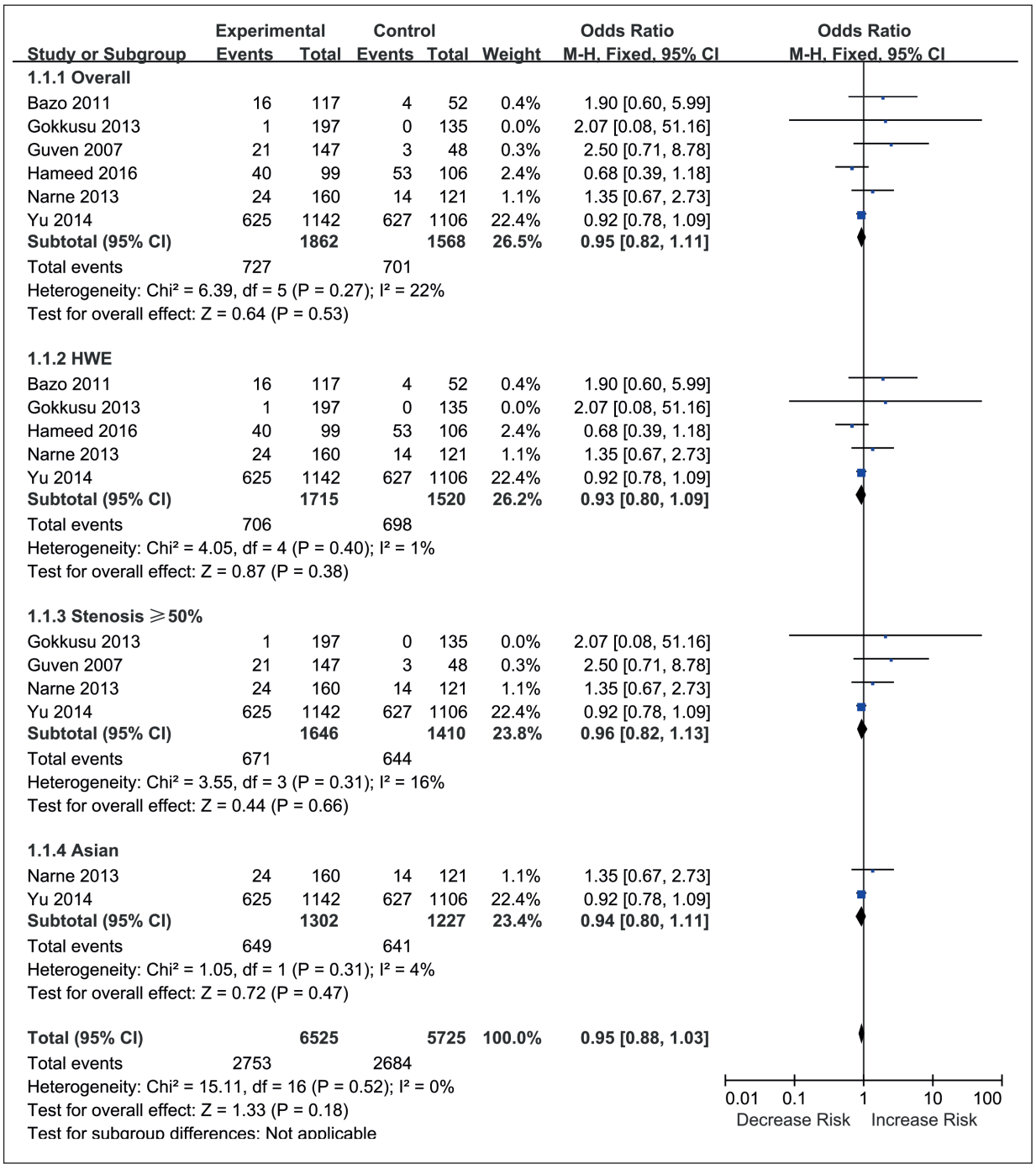

Figure 2. Meta-analysis for the association between XRCC1 Arg399Gln polymorphism and CAD risk (GG vs. AG+AA, fixed-effects model).

accordance with HWE. Ethnicity has been shown to be an important factor in the pathogenesis of CAD, and SNPs can be used to distinguish among different ethnic populations. Also, case definition can influence the result of the meta-analysis. In this study, five studies demonstrated accordance with HWE analysis, with no association between XRCC1 Arg399Gln polymorphism and CAD risk shown. Cases were defined as having ≥50% luminal stenosis after angiography in four studies[13, 15-17], and the assessment showed the absence of an association between XRCC1

Table III. Summary of results from different comparative genetic models.

rs25487 (codon399)	No.	GG vs. AG+AA		GG+AG vs. AA		GG vs. AA		G vs. A	
		OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p
Total	6	0.95 [0.82-1.11]	0.53	1.08 [0.69-1.68]	0.74	1.15 [0.66-2.00]	0.62	1.08 [0.83-1.04]	0.58
By HWE	5	0.93 [0.80-1.09]	0.38	1.18 [0.72-1.94]	0.52	1.11 [0.60-2.04]	0.74	1.10 [0.81-1.50]	0.54
By stenosis ≥50%	4	0.96 [0.82-1.13]	0.66	1.05 [0.63-1.74]	0.85	1.20 [0.62-2.29]	0.59	1.10 [0.83-1.46]	0.50
Asian	2	0.94 [0.80-1.11]	0.47	1.19 [0.48-2.92]	0.71	1.12 [0.45-2.80]	0.80	1.14 [0.70-1.86]	0.60
rs1799782 (codon194)	**No.**	**TT vs. TC+CC**		**TT+TC vs. CC**		**TT vs. CC**		**T vs. C**	
		OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p
Total	4	1.47 [1.13-1.93]	0.005	1.03 [0.50-2.11]	0.94	1.37 [1.03-1.81]	0.03	1.04 [0.58-1.88]	0.89
By HWE	2	0.57 [0.12-2.74]	0.48	0.52 [0.23-1.17]	0.12	0.53 [0.11-2.49]	0.42	0.54 [0.27-1.10]	0.09
Asian	2	1.52 [1.16-2.00]	0.003	1.53 [0.55-4.29]	0.42	1.42 [1.06-1.89]	0.02	1.51 [0.69-3.29]	0.30

Arg399Gln polymorphism and CAD risk. For the ethnicity analysis, which included only two Asian studies, no association appeared to be modified. More studies are needed for further validation of the association between the XRCC1 Arg399Gln polymorphism and CAD risk, especially for different ethnicities, such as Caucasian, Latin, and African populations.

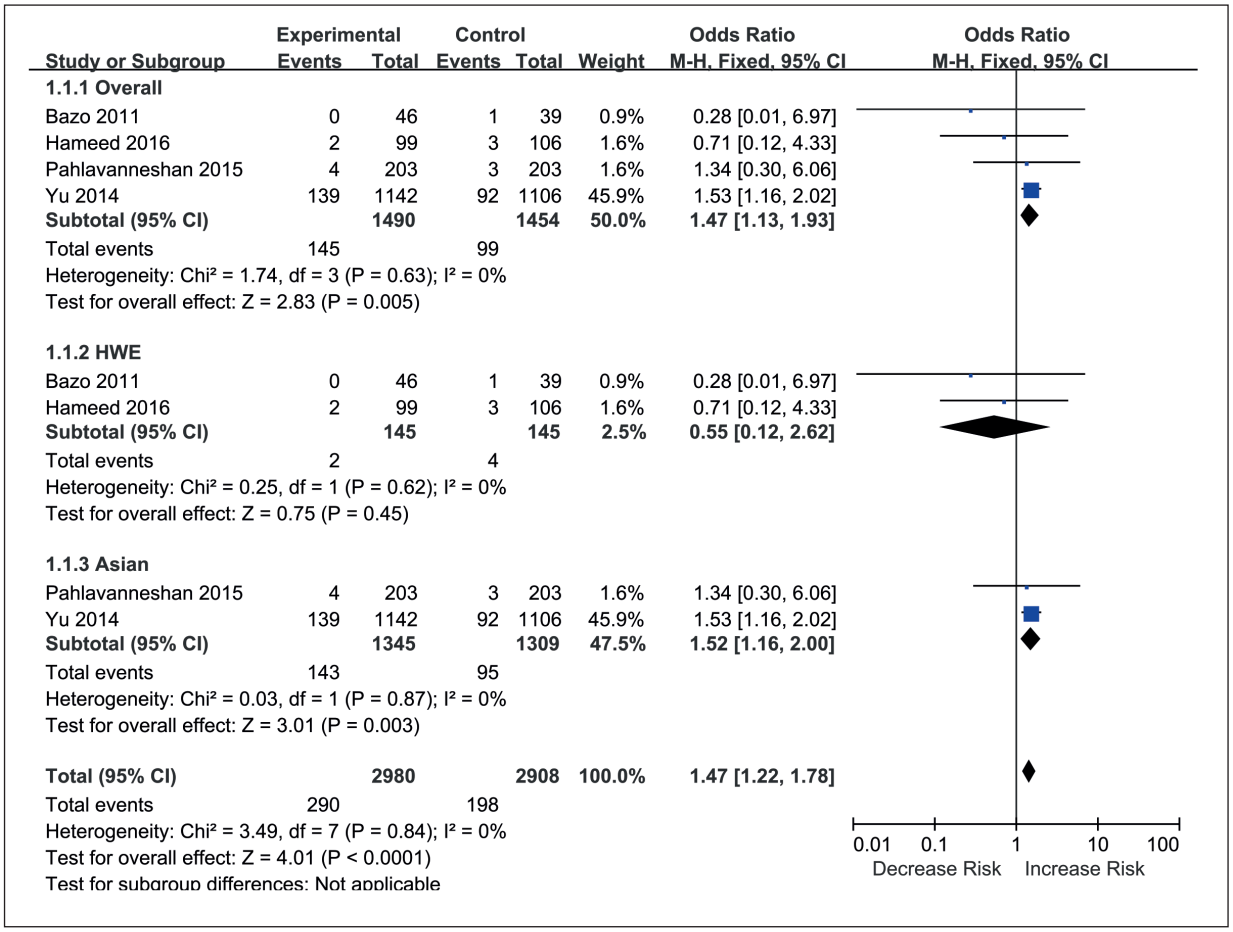

Figure 3. Meta-analysis for the association between XRCC1 Arg194Trp polymorphism and CAD risk (TT vs. TC+CC fixed- effects model).

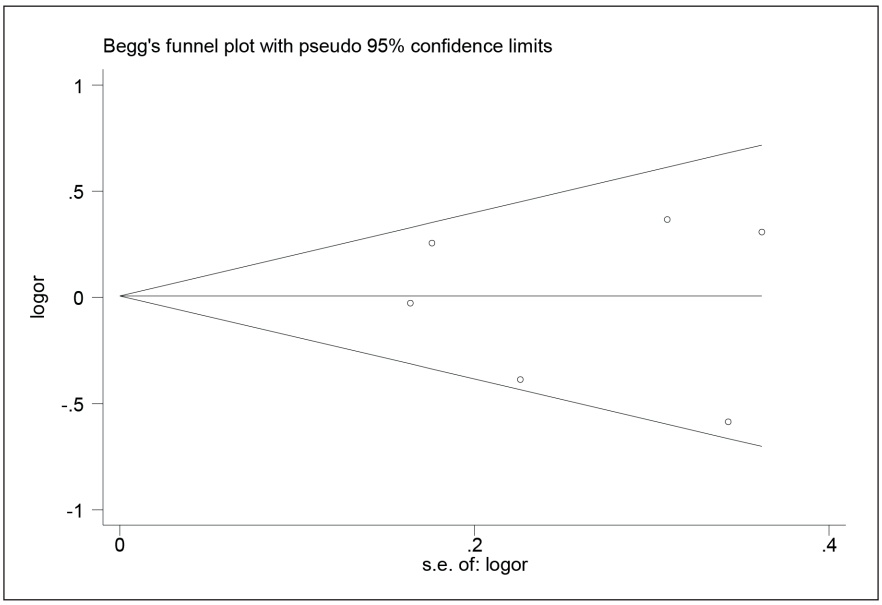

Figure 4. Begg's funnel plot for publication bias in selection of studies on XRCC1 Arg399Gln polymorphism (GG vs. AG+AA).

For the XRCC1 Arg194Trp polymorphism, four studies involving 1.490 cases and 1.454 controls were analyzed. In this meta-analysis, the TT genotype showed increased risk for CAD in the overall and ethnic evaluations, and no association was found by HWE analysis. Additional studies including multi-center and multi-ethnic data are needed to further assess the association of XRCC1 Arg194Trp polymorphism and CAD risk.

Heterogeneity was a key factor in determining the reliability of results in the meta-analysis. Significant heterogeneity was absence for overall comparisons in both recessive genetic models, indicating homogeneity of the included studies for the XRCC1 Arg399Gln and Arg194Trp SNPs.

Publication bias is another important factor to evaluate the reliability of results, and publication bias along with the study quality is vital for conducting a meta-analysis. Publication bias was analyzed using Begg's funnel plots and Egger's test in our study. No significant publication bias was detected, indicating the reliability of our results. Sensitivity analysis suggested similar results. Furthermore, selection bias was diminished by strict inclusion and exclusion criteria.

While this is an up-to-date meta-analysis, some limitations are present. Firstly, as we only searched selected databases in this meta-analysis, publication restriction may exist. It is possible that some unpublished studies with unidentified null results were excluded in these databases. Secondly, the included studies only consisted of Asian, Turkish, and Latin populations; the results may not be applicable to other ethnic populations. Hence, more studies are warranted, especially for different ethnicities. Thirdly, our search only included studies published in English. Nevertheless, the advantages of this meta-analysis include the comprehensive assessment of XRCC1 polymorphisms and CAD risk, which could strengthen the power to evaluate associations compared with a single study. Also, the methodological issues, such as heterogeneity, publication bias, and sensitivity analysis were investigated in this study.

Conclusions

Till date, this is the first meta-analysis to investigate the association of XRCC1 polymorphisms (codon 399 and codon 194) and CAD risk. Our results indicated that the XRCC1 Arg399Gln polymorphism was not associated with CAD risk, whereas the XRCC1 Arg194Trp TT genotype could increase CAD risk in the overall and Asian populations. The results suggest that the XRCC1 Arg194Trp polymorphism could be a susceptibility marker for CAD. Further case-control investigations are required to validate our data.

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Authors contribution

Shujin Guo, Yutian Zhou, Wenyuan Liu contribute equally to the study design, data collection and analysis. Qiunan Zuo and Xiaohui Li contribute to the statistical analysis. Shujin Guo writes and revises the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest for this article.

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