RESEARCH ARTICLE

Association of XRCC1 Arg399Gln Polymorphism with Colorectal Cancer Risk: A HuGE Meta Analysis of 35 Studies

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Abstract

Background: Non-synonymous polymorphisms in XRCC1 hase been shown to reduce effectiveness of DNA repair and be associated with risk of certain cancers. In this study we aimed to clarify any association between XRCC1 Arg399Gln and colorectal cancer (CRC) risk by performing a meta-analysis of published case-control studies. Materials and Methods: PubMed and Google Scholar were searched to explore the association between XRCC1 and CRC. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the association strength. Publication bias was assessed by Egger's and Begg's tests. Results: Up to January 2015, 35 case control studies involving 9,114 CRC cases and 13,948 controls were included in the present meta-analysis. The results showed that the Arg399Gln polymorphism only under an allele genetic model was associated with CRC risk (A vs. G: OR 0.128, 95% CI 0.119-0.138, p<0.001). Also, this meta-analysis suggested that the XRCC1 Arg399Gln polymorphism might associated with susceptibility to CRC in Asians (A *vs* G: OR 0.124, 95% CI 0.112-0.138, p<0.001) and Caucasian (A *vs* G: OR 0.132, 95% CI 0.119-0.146, p<0.001) only under an allele genetic model. Conclusions: This meta-analysis confirms the association between XRCC1 Arg399Gln polymorphism and CRC risk and suggests that the heterogeneity is not strongly modified by ethnicity and deviation from the Hardy-Weinberg equilibrium.

Keywords: Colorectal cancer - XRCC1 - Arg399Gln - polymorphism - meta-analysis.

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Introduction

Colorectal cancer is the leading cause of cancer-related death worldwide. Overall, it ranks as the third most frequent cancer worldwide, and the third and second most frequent cancer in men and women respectively (Magaji et al., 2014). It remains an enormous financial burden on the health care system. Although many new and advanced techniques have been introduced for the management and surveillance of CRC, but local recurrence and distant metastasis are still considered major complications (Mehrabani et al., 2014; Omranipour et al., 2014).

Amongst the known genetic susceptibility to CRC, the x-ray cross-complementig group 1 and 3 (XRCC1 and XRCC3) have been studied most commonly (Gao et al., 2014). The X-ray repair cross-complementing group 1 (XRCC1) protein, which is encoded by the XRCC1 gene, is an important component of the base excision repair (BER) pathway. The XRCC1 gene is located on chromosome 19q13.2-13.3, spans a genetic distance of 33 kb, comprises of 17 exons and encodes a 70-kDa protein consisting of 633 amino acids. XRCC1 has been shown to have a large number of SNPs, and several have been extensively evaluated in cancer epidemiology association investigations because of their relative high frequency in the population (Ladiges et al., 2006). Although there are more than 300 validated polymorphisms in the XRCC1 gene only three of XRCC1 are most studied and lead to amino acid substitutions in XRCC1 at codon 194, codon 280 and codon 399, these non-conservative amino acid changes may alter XRCC1 protein function (li et al., 2014).

The XRCC1 Arg399Gln polymorphism has been the most studied of the XRCC1 variations and one of the most frequently studied SNPs among all DNA repair gene variations. XRCC1 Arg399Gln showed associations in different directions for different cancers (Ladiges et al., 2006). So, the XRCC1 Arg399Gln polymorphism is associated with an increased risk for CRC (Wang et al., 2010; Liu et al., 2013). Other studies found no relationship between this polymorphism and CRC risk. Limited and controversial results were obtained regarding the association between colorectal cancer risk and XRCC1 Arg399Gln polymorphism. To provide a comprehensive and objective assessment of the association between the XRCC1 gene Arg399Gln polymorphism and CRC risk, a meta-analysis of all eligible case-control studies was

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performed.

Materials and Methods

Study identification and selection

A comprehensive literature search was performed using PubMed and Google scholar to identify studies that evaluated the association between XRCC1 Arg399Gln polymorphism and the risk of CRC up to February 1, 2015. The following key words were used: 'Colorectal cancer' or 'Colon cancer, 'X-ray repair cross - complementing group 1' or 'XRCC1', Arg399Gln and 'polymorphism' or 'variant'. The search was restricted to English and Chinese. The reference lists of reviews and retrieved articles were hand searched at the same time. Abstracts or unpublished reports were not considered. If more than one article was published by the same author using the same case series, we selected the study where the most individuals were investigated. The following criteria were used for the study selection: 1) only case- control studies; 2), studies should concern the association between XRCC1 Arg399Gln polymorphism and CRC risk; 3) papers should offer the sample sizes and the genetic distribution or the information that can help infer the results; 4) no overlapping data. If studies had the same or overlapping data, only the largest study should be included in the final analysis.

Data extraction

Necessary information was carefully extracted from all the eligible studies independently by 2 investigators according to the inclusion criteria. The following data were collected from each study: first author, publication year, country, racial descent (categorized as Asian, Caucasian, or mixed descent), numbers of cases and controls, genotype frequency of cases and controls, and the result of Hardy- Weinberg equilibrium test. If a consensus was not reached, another author was consulted to resolve the dispute; then, a final decision was made by the majority of the votes. We did not define any minimum number of patients for inclusion in our meta-analysis.

Statistical methods

The strength of associations between XRCC1 Arg399Gln polymorphism and CRC risk were evaluated by crude ORs together with their corresponding 95%CIs. Also, the pooled ORs and 95%CIs for XRCC1 Arg399Gln polymorphism was calculated by homozygous model

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

Author	Country	Case	Control	Genotypes			Alleles		Genotypes			Alleles		HWE
				GG	GA	AA	G	A	GG	GA	AA	G	A	
Poomphakwaen	Thailand	230	230	102	101	27	305	155	126	97	7	349	111	0.0213
Zhang	China	247	300	131	91	25	353	141	142	132	26	416	184	0.5478
Gil	Poland	133	100	52	67	14	171	95	37	51	12	125	75	0.3789
Przybylowska	Poland	152	170	41	69	40	151	149	61	79	30	201	139	0.6146
Procopciuc	Thailand	150	162	42	80	28	164	136	88	64	10	240	84	0.7161
Parveen Khan	Kashmir	120	146	34	80	6	148	92	50	62	34	162	130	0.0899
Nissar	Kashmir	130	150	63	37	30	163	97	75	30	45	180	120	0
Li	China	451	630	207	215	29	629	273	298	280	52	876	384	0.2206
Zhao	China	485	970	239	188	59	666	306	556	354	60	1466	474	0.7158
Muniz-Mendoza	Mexico	103	103	48	48	7	144	62	65	47	8	177	63	0.8992
Yin	Japan	685	776	356	275	54	987	383	436	299	41	1171	381	0.2638
Engin	Turkey	96	108	47	37	12	131	61	50	49	9	149	67	0.5316
Gsur	Austria	85	1663	35	31	19	101	69	667	763	233	2097	1229	0.5322
Canbay	Turkey	79	247	63	16	0	142	16	202	43	2	447	47	0.8616
Zhu	China	250	213	121	112	17	354	146	94	102	17	290	136	0.1376
Brevik	USA	305	360	120	144	41	384	226	136	181	43	453	267	0.1416
Jelonek	Poland	113	295	35	49	29	119	107	124	142	29	390	200	0.2031
Wang	India	302	291	124	138	40	386	218	139	113	39	391	191	0.0417
Huang	China	120	150	63	46	11	172	68	76	64	10	216	84	0.476
Curtin	USA	1582	1950	679	725	178	2083	1081	826	872	252	2524	1376	0.3585
Improta	Italy	109	121	46	54	9	146	72	53	61	7	167	75	0.0495
Sliwinski	Poland	100	100	47	37	16	131	69	39	45	16	123	77	0.619
Song	China	207	255	92	74	12	258	98	52	108	20	212	148	0.0013
Kasahara	Japan	68	121	42	23	3	107	29	62	48	11	172	70	0.698
Pardini	Czech	530	532	229	233	68	691	369	219	240	73	678	386	0.5758
Jin	China	202	616	109	72	21	290	114	337	222	57	896	336	0.0231
Stern	Singapore	294	1120	167	112	15	446	142	607	428	85	1642	598	0.4292
Yeh	Taiwan	718	729	407	260	51	1074	362	384	291	54	1059	399	0.9116
Martinez-Balibrea	Spain	70	82	30	33	7	93	47	39	32	11	110	54	0.2915
Ren	China	178	180	92	74	12	258	98	52	108	20	212	148	0.0013
Moreno	Spain	355	322	154	160	41	468	242	137	145	40	419	225	0.8647
Skjelbred	Norway	157	399	63	70	24	196	118	148	187	64	483	315	0.7015
Hong	Korea	209	209	112	88	9	312	106	136	64	9	336	82	0.6747
Krupa and Blasiak	Poland	51	100	23	19	9	65	37	39	45	16	123	77	0.619
Abdel-Rahman	Egypt	48	48	22	21	5	65	31	37	9	2	83	13	0.1674

(AA *vs* GG), heterozygous model (GA *vs* GG), dominant genetic model (AA *vs* GA+GG) and recessive model (GA+AA *vs* GG). HWE was evaluated for control subjects of each study, using the goodness-of-fit χ^2 test, and $P < 0.05$ was considered representative of deviation from HWE. Heterogeneity was quantified with the I^2 statistic, a value that indicates what proportion of the total variation across studies is beyond chance. Specifically, 0 % indicates no observed heterogeneity, and larger values show increasing heterogeneity. When P value of the heterogeneity test was ≥0.05, the fixed-effects model, based on the Mantel-Haenszel method was used, which assumes the same homogeneity of effect size across all studies. Otherwise, the random effects model, based on the DerSimonian and Laird method, was more appropriate, which tends to provide wider 95%CIs as the results of the constituent studies differ among themselves. Subgroup analyses were also performed by ethnicity. To assess the effects of individual studies on CRC risk, sensitivity analysis was performed by excluding each study at a time individually and recalculating the ORs and 95%CIs. Visual inspection of Begg's funnel plots was performed for assessment of publication bias. An asymmetric plot suggested possible bias, in which case Egger's test was used. All the analysis was performed using the Comprehensive Meta-Analysis software, version 2.2 (Biostat, Englewood, New Jersey).

Results

Thirty five studies were included based on the search criteria for CRC susceptibility related to the XRCC1 Arg399Gln polymorphisms (Abdel-Rahman et al., 2000; Krupa et al., 2004; Hong et al., 2005; Skjelbred et al., 2006; Ren et al; Moreno et al., 2006; Jin et al., 2007; Stern et al., 2007; Yeh et al., 2007; Martinez-Balibrea et al., 2008; Pardini et al., 2008; Kasahara et al., 2008;

Table 2. Results of Meta-analysis for XRCC1 Arg399Gln Polymorphism and the Risk of Colorectal Cancer

	Test of association 95% CI				Test of heterogeneity	
	OR	Lower	Upper	p value	I^2	p value
A *vs* G						
Overall	0.128	0.119	0.138	<0.001	72.00	<0.001
Asian	0.124	0.112	0.138	<0.001	0.897	<0.001
Caucasian	0.132	0.119	0.146	<0.001	66.64	<0.001
GA *vs* GG						
Overall	1.022	0.916	1.140	0.703	64.90	<0.001
Asian	1.023	0.857	1.221	0.805	78.25	<0.001
Caucasian	0.977	0.892	1.070	0.613	<0.001	0.897
AA *vs* GG						
Overall	1.112	0.917	1.347	0.281	68.85	<0.001
Asian	1.016	0.737	1.400	0.922	78.74	<0.001
Caucasian	1.054	0.920	1.207	0.448	49.14	0.010
AA *vs* GA+GG						
Overall	1.100	0.929	1.303	0.268	63.53	<0.001
Asian	1.067	0.922	1.403	0.672	69.15	<0.001
Caucasian	1.031	0.901	1.181	0.656	73.32	<0.001
GA+AA *vs* GG						
OverallS	1.041	0.942	1.152	0.430	63.12	<0.001
Asian	1.046	0.891	1.227	0.583	76.27	<0.001
Caucasian	0.984	0.903	1.072	0.707	68.21	<0.001

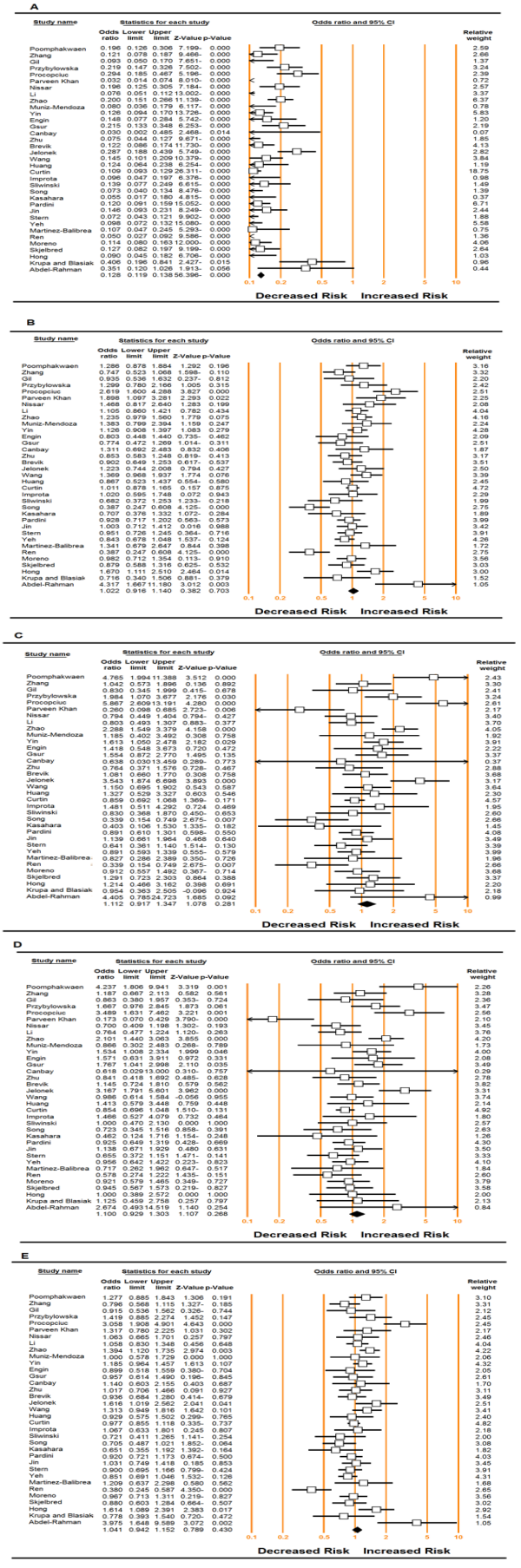

Figure 1. Forest Plots Showing the Association of the XRCC1 Arg399Gln Polymorphism with Risk of CRC (A: A *vs* G; B: GA *vs* GG; C: AA *vs* GG; D: AA *vs* GA+GG; E: GA+AA *vs* GG)

Song et al., 2008; Sliwinski et al., 2008; Improta et al., 2008; Curtin et al., 2009; Brevik et al., 2010; Jelonek et al., 2010; Wang et al., 2010; Canbay et al., 2011; Engin et al., 2011; Gsur et al., 2011; Huang et al., 2011; Zhu et al., 2011; Muniz-Mendoza et al., 2012; Yin et al., 2012; Zhao et al., 2012; Gil et al., 2013; Khan et al., 2013; Li et al., 2013; Przybylowska et al., 2013; Procopciuc et al., 2013; Nissar et al., 2014; Poomphakwaen et al., 2014; Zhang et al., 2014). Study characteristics were summarized in Table 1. There were 18 studies of subjects of Asian descent, 15 studies of subjects of Caucasian descent and 2 studies of subjects of African descent and Mexican (Table 1).

Meta-analysis results

Table 2 listed the main results of the meta-analysis for XRCC1 Arg399Gln polymorphism. The overall analysis investigating the allele model (OR=0.128 CI 90% 0.119-0138 p=0.00) showed significant association between XRCC1 Arg399Gln polymorphism and increased CRC risk, although no evidence of associations was detected in the additive (OR=1.022 CI 90% 0.916-1.140 p=0.703), recessive (OR=1.112 CI 90% 0.917-1.347 p=0.281) and dominant (OR=1.100 CI 90% 0.929-1.303 p=0.268), and (OR=1.041 CI 90% 0.942-1.152 p=0.430) models. Next, stratified analyses by ethnicity were performed between XRCC1 Arg399Gln polymorphism and CRC risk. A significant association between XRCC1 Arg399Gln polymorphism and CRC susceptibility was found in Asian and Caucasian populations only in the allele model (Asians: OR=0.124 95% CI 0.112-0.138, p=0.00; Caucasians: OR=0.132 95% CI 0.119-0.146 p=0.00), (Table 2).

Sensitivity analysis

In the sensitivity analysis, the influence of each study on the pooled OR was examined by repeating the meta-analysis while omitting each study, one at a time. This procedure confirmed the stability of the overall results.

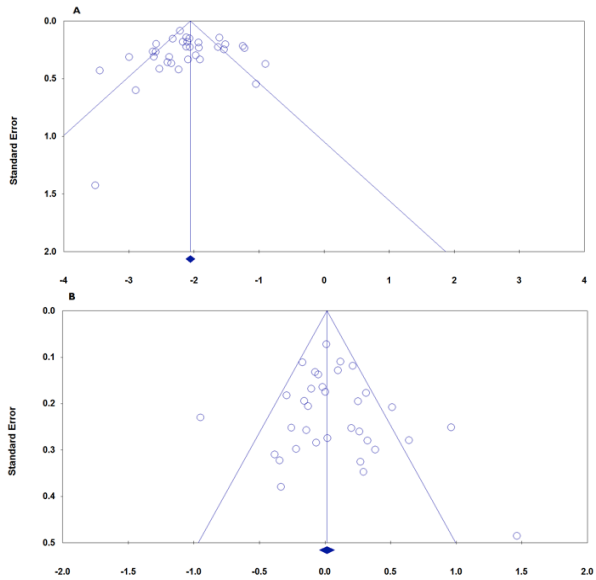

Figure 2. Funnel Plot for Publication BBias in the Meta-analysis Investigating the Association of the XRCC1 Arg399Gln Polymorphism with Risk of CRC, (A: A *vs* G and B: GA *vs* GG)

In addition, when excluding 5 study in Asian population that did not follow Hardy-Weinberg equilibrium, the estimated pooled OR still did not significantly change at all (data not shown).

Publication bias

Both Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures. All these five genetic models for XRCC1 Arg399Gln polymorphism showed consistent results, indicating no publication biases. The shapes of the funnel plot did not indicate any evidence of obvious asymmetry in genetic models model (Figure 4), and the Egger's test suggested the absence of publication bias (A *vs* G: p=0.379; GA *vs* GG: p=0.346; AA *vs* GG: p=0.324; AA *vs* GA+GG: p=0.329; GA+AA *vs* GG: p=0.283).

Discussion

XRCC1 plays an important role in the DNA damage repair pathway for the processing of small base lesions (Improta et al., 2008). To date more than 300 single nucleotide polymorphisms (SNPs) have been identified and described in the XRCC1 gene, only three SNPs have been exten¬sively studied, which are 194(Arg to Trp), 280(Arg to His), and 399 (Arg toGln). The XRCC1 polymorphisms have been implicated in the risk of various cancers such as esophageal, gastric, lung, breast and other types of cancer (li et al., 2014). The relationship between the XRCC1 Arg399Gln polymorphisms and CRC risk has been examined in some case--control studies, but the results of these studies were contradictory and inconclusive.

The contradictory findings among case-control studies might be attributed to different sample size, source of controls, genotyping method and matching criteria of subjects, and so on. In addition, the potential gene-gene and gene-environment interactions may also play vital roles in the pathogenesis of CRC. Single study especially the one with relatively sample size may have not enough statistical power to identify a mild genetic association and introduce random errors. Inversely, meta-analysis by pooling all available data from eligible publications takes the advantage of achieving a more precise estimation for potential genetic associations (Guo et al., 2012). The advantages of this meta-analysis are that it is the most complete and the information from the eligible studies is utilized as much as possible through genetic model and stratified analysis. To help resolve the conflicting results this meta-analysis of published studies was conducted using a larger sample size. In this meta-analysis, it was focused on XRCC1 genetic polymorphism and provides the most comprehensive assessment of its association with CRC risk, by critically reviewing 35 studies on XRCC1 Arg399Gln polymorphism (a total of 9,114 cases and 13,948 controls).

Five meta-analyses previously have estimated the association between XRCC1 Arg399Gln polymorphism and CRC susceptibility (Liu et al., 2010; Wang et al., 2010; Wu et al., 2013; Zeng et al., 2013; Qin et al., 2015). However, the association remains not fully understood

because of inconsistent results across independent studies. Compared with the previous meta-analyses, our meta-analysis involved a remarkably larger number of studies (35 studies) and provided a more comprehensive and reliable conclusion. We have found that the Arg399Gln polymorphism led to an increased risk in allele comparison (Table 2), which was in consistent with a previous meta-analysis among Chinese (Qin et al., 2015).

Present meta-analysis results were not consistent with a previous meta-analysis (81-86) on XRCC1 Arg399Gln polymorphism with CRC risk. Liu et al. (Liu et al., 2010) included 22 case-control studies with a total of 6,291 CRC cases and 10,289 controls concerning the XRCC1 Arg399Gln polymorphism. Their results suggested that XRCC1 Arg399Gln polymorphism was not associated with increased CRC risk and by ethnicity. In a meta-analysis, Qin et al retrieved 11 case- control studies with a total of 3194 CRC cases and 4472 controls in the Chinese Han population. They have not found a significant association between the XRCC1 Arg399Gln polymorphism and CRC risk in the population (Qin et al., 2015). Our results are inconsistent with the meta-analysis performed by Zeng et al., which 26 case-control studies with 6,979 cases and 11,470 controls were pooled in the meta-analysis. They have suggested that the XRCC1 Arg399Gln polymorphism was significantly associated with increased risk of CRC in among high quality studies and in Asians, but not in Caucasians (Zeng et al 2013). Lu et al, in a meta-analysis suggests that there is an obvious association between the XRCC1 Arg399Gln polymorphism and increased risk of CRC in East Asians (Lu et al., 2013). Wu et al, in an update meta-analysis suggested that the XRCC1 Arg399Gln polymorphism was significantly associated with increased CRC (Wu et al., 2014).

Three polymorphisms in XRCC1 (Arg194Trp, Arg280His and Arg399Gln) have been frequently examined in the studies on cancer susceptibility. Liu et al. (Liu et al., 2013) included 22 case-control studies with a total of 6,291 CRC cases and 10,289 controls concerning the XRCC1 Arg399Gln polymorphism, 14 studies with a total of 4,814 CRC cases and 8,357 controls for Arg194Trp, seven studies with a total of 3,505 CRC cases and 4,636 controls for Arg280His.Their results suggested that these three SNPs evaluated are not associated with risk of CRC.

The statistically significant association between the XRCC1 Arg399Gln polymorphism and CRC risk was observed among studies with high quality and in all ethnicity. Sensitivity analyses by sequential omission of any individual studies not identified the significant association. Obviously, in all genetic models there were potential to moderate level heterogeneity. When we deleted 5 Asian studies which were not according to HWE any more, the heterogeneity of all genetic models was not decreased. Since the subjects came from different populations that perhaps have genetic heterogeneity, subgroup analyses were conducted on ethnicity. However, we found that ethnicity might not be the source of heterogeneity (Table 2). This further indicated that ethnicity and deviations from HWE might not be one source of heterogeneity. Other factors such as the sample sizes, diversity in study designs, inclusion criteria, and genotyping methods might be source of heterogeneity (Salanti et al., 2005).

Compared with two previous meta-analyses, our meta-analysis involved a remarkably larger number of studies and provided a more comprehensive and reliable conclusion. However, there are still some limitations in this meta-analysis. First, our meta-analysis included only studies with accessible full-text articles in English. Therefore, missing some otherwise eligible studies that were reported in other languages could lead to publication bias in the results. Second, lacking the original data for the included studies limited our further evaluation of potential interactions among gene-gene, gene-environment, or even different polymorphism loci of the same gene, which all may affect cancer risk. The joint effect between XRCC1 Arg399Gln and other repair genes genotypes on the risk of cancer was not addressed in the present study. However, the lack of individual data from the included studies limited the further evaluation of other potential interactions, as in other genes and environment factors. For instance, only two studies have reported the combined effect of XRCC1 Arg399Gln and other repair genes genotypes on the risk of cancer (Krupa et al., 2004; Kasahara et al., 2008; wang et al., 2010). Third, due to the lack of detailed data in the primary articles, our results were based on single-factor estimates without adjustment for other risk factors such as age, gender, environmental factors and other variables, which might have caused serious confounding bias.

In summary, the meta-analysis suggested that the XRCC1 Arg399Gln polymorphism was significantly associated with increased CRC, and the G allele probably acts as an important CRC risk factor.

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