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Meta-analysis of the relationship between *XRCC3* T241M polymorphism and colorectal cancer susceptibility

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ABSTRACT. Numerous studies have evaluated the relationship between the T241M polymorphism of the X-ray repair cross-complementing group 3 (*XRCC3*) gene and colorectal cancer (CRC) risk. However, the specific relationship remains controversial. We conducted meta-analysis to investigate the relationship between the *XRCC3* T241M polymorphism and CRC risk. The PubMed and Embase databases were searched for relevant studies investigating the relationship between the *XRCC3* T241M polymorphism and CRC risk. The odds ratio (OR) and 95% confidence interval (CI) were used to assess the possible relationship. Thirteen individual case-control studies, including 4720 cases and 6104 controls, were identified and included in this meta-analysis. Meta-analyses revealed no relationship between the *XRCC3* T241M polymorphism and CRC risk (TT *vs* MM: OR = 0.85, 95%CI = 0.63-1.14; TT *vs* MT: OR = 0.87, 95%CI = 0.68-1.10; dominant model: OR = 1.18, 95%CI = 0.92-1.50; recessive model: OR = 0.87, 95%CI = 0.69-1.11). In the further subgroup analysis by ethnicity, we found no direct relationship between the polymorphism and CRC risk in either Asians or Europeans. Our findings demonstrated that

the T241M polymorphism in the *XRCC3* gene may not be a risk factor for CRC development.

Key words: Colorectal cancer; Meta-analysis; Polymorphism; *XRCC3*

INTRODUCTION

Colorectal cancer (CRC) is the commonest malignancy of the gastrointestinal tract worldwide (Parkin et al., 1993). The highest morbidity of CRC occurs in Australia, Europe, and North America. In addition, the morbidity of CRC is rapidly increasing in many countries in Eastern Asia (Jemal et al., 2011). As one of the leading causes of cancer-related mortality, CRC accounts for more than 600,000 deaths every year (Ahlquist et al., 2012). Although numerous studies have been conducted, the pathogenesis of CRC is not fully understood. Epidemiological studies have shown that CRC is influenced by many environmental factors, such as lack of dietary fiber, overweight and obesity, physical inactivity, a short appendix vermiformis, a high-fat diet, smoking, and excessive alcohol consumption (Cakmak et al., 2014). However, most people exposed to these environmental factors never develop CRC. Additionally, many CRC cases develop among individuals have no known risk factors, suggesting that other factors are important in the pathogenesis of CRC. Molecular biology studies have provided strong evidence that genetic factors also play important roles in colorectal carcinogenesis (Peng et al., 2014).

The X-ray repair cross-complementing group 3 (*XRCC3*) belongs to the RAD51 gene family, which codes for a protein that functions in the homologous recombination repair of DNA double-strand breaks, participates in DNA double-strand break/recombination repair, and likely participates in homologous recombination repair (Brenneman et al., 2000). *XRCC3* is localized to human chromosomes 14q32.3. T241M is the most common polymorphism of *XRCC3*, which substitutes a C to T at codon 241 in exon 7 (Matullo et al., 2001). Variants of the T241M polymorphism may affect the function of the encoded protein and consequently alter DNA repair capacity (Mohrenweiser et al., 2003). Therefore, the T241M polymorphism may play a role in colorectal carcinogenesis.

Previous studies have shown that the *XRCC3* T241M polymorphism was associated with an increased risk of head and neck, breast, and bladder cancer (Li et al., 2011; He et al., 2012; Yin et al., 2012). In recent years, several studies have evaluated the relationship between the T241M polymorphism in the *XRCC3* gene and CRC risk. However, the results of these studies are controversial, which may be related to the limitations of individual studies. Meta-analysis is a useful tool for detecting associations that may otherwise remain masked in studies of limited sample size, particularly in those evaluating rare allele frequency polymorphisms. In the present study, therefore, we performed meta-analysis to examine whether the *XRCC3* T241M polymorphism is associated with CRC risk.

MATERIAL AND METHODS

Eligibility of relevant studies

The PubMed and Embase databases were searched (the last search was updated in

October 1, 2014) to identify all relevant publications regarding the association between the *XRCC3* T241M polymorphism and CRC risk. The following search terms were used: 'Colorectal cancer/ CRC', 'X-ray repair cross-complementing group 3/*XRCC3*, 'T241M', and 'gene polymorphism' for relevant citations. There was no language limitation. All searched studies were retrieved, and their references were checked for other relevant publications. If sequential or multiple publications from the same data were identified, the publication reporting data from the largest or most recent study was included. Publications met the following inclusion criteria: (1) estimated the association between the *XRCC3* T241M polymorphism and CRC risk, (2) used case-control designs, and (3) provided enough information to determine the frequency of alleles and genotypes in cases and controls. Major exclusion criteria were: (1) case reports, letters, reviews, meta-analysis, and editorial articles, (2) studies that were based on incomplete data and those with no usable data reported, and (3) duplicated studies.

Data extraction

Two independent investigators extracted the original data according to the inclusion criteria and exclusion criteria to ensure the accuracy of the retrieved information. The following characteristics were collected from the eligible studies: first author, year of publication, area, number of cases and controls, genotype frequencies in cases and controls, and evidence of Hardy-Weinberg equilibrium (HWE) in controls. For conflicting evaluations, an agreement was reached following discussion.

Statistical analysis

We assessed HWE in the controls for each study using a chi-square test, and $P < 0.05$ was considered to indicate significant disequilibrium. The pooled odds ratio (OR) with corresponding 95% confidence interval (95%CI) was calculated to assess the strength of the association between the *XRCC3* T241M polymorphism and CRC risk under homozygote comparison (TT *vs* MM), heterozygote comparison (TT *vs* MT), a dominant model (MM + MT *vs* TT), and a recessive model (TT + MT *vs* MM) between groups. Between-study heterogeneity was estimated using the I^2 test. I^2 ranges from 0-100% and represents the proportion of inter-study variability that can be attributed to heterogeneity rather than to chance. I^2 values of 25, 50, and 75% were defined as low, moderate, and high estimates, respectively. $I^2 > 50\%$ indicated heterogeneity across studies, and the random effects model was used for meta-analysis; otherwise, the fixed effects model was used. Subgroup analyses were performed by ethnicity and sample sizes. Sensitivity analysis was performed by removing the studies not in HWE. Funnel plot asymmetry was assessed by Begg's test to estimate potential publication bias ($P < 0.05$ indicated statistical significance). Meta-analysis was performed using the STATA package version 12.0 (Stata Corporation, College Station, TX, USA).

RESULTS

Characteristics of retrieved studies

By searching the databases, 73 abstracts were identified according to the search

criteria. Base on the inclusion criteria, 13 case-control studies with full-text were included in this meta-analysis (Krupa and Blasiak, 2004; Jin et al., 2005; Moreno et al., 2006; Skjelbred et al., 2006; Yeh et al., 2007; Improta et al., 2008; Pardini et al., 2008; Curtin et al., 2009; Canbay et al., 2011; Gil et al., 2012; Zhao et al., 2012; Mucha et al., 2013; Moghtit et al., 2014). The flow chart outlining the criteria used for study selection is shown in Figure 1. The 13 case-control studies selected included a total of 4720 CRC cases and 6104 healthy controls. The publication year of the included studies ranged from 2005-2014. All articles were written in English. The source of controls was mainly based on healthy populations. Among the 13 case-control studies, there were 8 studies of Caucasians (Krupa and Blasiak, 2004; Skjelbred et al., 2006; Improta et al., 2008; Pardini et al., 2008; Curtin et al., 2009; Canbay et al., 2011; Gil et al., 2012; Mucha et al., 2013) and 5 studies of Asians (Jin et al., 2005; Moreno et al., 2006; Yeh et al., 2007; Zhao et al., 2012; Moghtit et al., 2014). Nine studies were consistent with HWE for the genotype distribution of the controls (Moreno et al., 2006; Skjelbred et al., 2006; Yeh et al., 2007; Improta et al., 2008; Pardini et al., 2008; Curtin et al., 2009; Gil et al., 2012; Mucha et al., 2013; Moghtit et al., 2014), while 4 were not (Krupa and Blasiak, 2004; Jin et al., 2005; Canbay et al., 2011; Zhao et al., 2012). The baseline characteristics and methodological quality of all studies included are summarized in Table 1. The genotype distribution and risk allele frequency are summarized in Table 2.

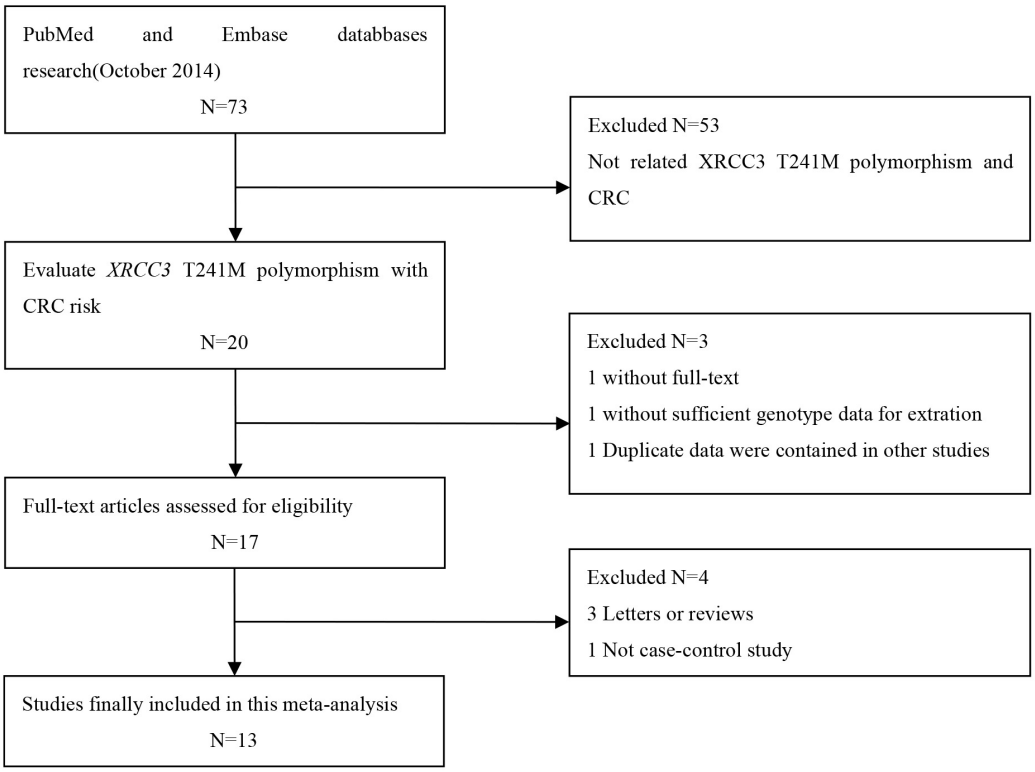

Figure 1. Detailed process of identifying eligible studies.

Table 1. Characteristics of eligible studies.

Study included	Year	Area	Race	Cases/Controls	Genotypes for cases			Genotypes for controls			HWE test
					MM	MT	TT	MM	MT	TT	
Jin et al.	2005	China	Asian	140/280	1	15	124	1	11	268	0.03
Skjelbred et al.	2006	Norway	Caucasian	157/399	20	73	64	60	201	138	0.34
Moreno et al.	2006	Spain	Asian	361/316	51	170	140	47	158	111	0.45
Yeh et al.	2007	China	Asian	721/734	1	60	660	2	74	658	0.96
Improta et al.	2008	Italy	Caucasian	109/121	26	43	40	8	46	67	0.98
Pardini et al.	2008	Czech	Caucasian	532/532	65	264	203	63	250	219	0.51
Curtin et al.	2009	USA	Caucasian	1581/1948	208	702	671	277	911	760	0.88
Canbay et al.	2011	Turkey	Caucasian	79/247	11	45	23	27	146	74	0.00
Krupa et al.	2004	Poland	Caucasian	100/100	9	55	36	3	47	50	0.04
Zhao et al.	2012	China	Asian	485/970	38	89	357	43	81	846	0.00
Gil et al.	2012	Poland	Caucasian	132/100	12	65	55	13	36	51	0.11
Mucha et al.	2013	Poland	Caucasian	194/209	25	72	97	25	104	80	0.32
Moghtit et al.	2014	Algeria	African	129/148	16	68	45	21	72	55	0.74

Table 2. Meta-analysis results.

Subgroup	*Genetic model*	*Sample size*		*Type of model*	*Test of heterogeneity*		*Test of association*		*Test of publication bias*	
		Case	*Control*		I^2	*P*	*OR*	*95% CI*	*z*	*P*
Overall	*TT vs MM*	*4720*	*6104*	*Random*	*64.8%*	*0.00*	*0.85*	*0.63-1.14*	*0.73*	*0.46*
	TT vs MT			*Random*	*81.1%*	*0.00*	*0.87*	*0.68-1.10*	*0.73*	*0.46*
	Dominant model			*Random*	*84.0%*	*0.00*	*1.18*	*0.92-1.50*	*0.73*	*0.46*
	Recessive model			*Random*	*52.3%*	*0.01*	*0.87*	*0.69-1.11*	*0.73*	*0.46*
Asian	*TT vs MM*	*1707*	*2300*	*Random*	*62.2%*	*0.05*	*0.78*	*0.38-1.59*	*1.04*	*0.30*
	TT vs MT			*Random*	*91.3%*	*0.00*	*0.69*	*0.35-1.35*	*1.04*	*0.30*
	Dominant model			*Random*	*92.0%*	*0.00*	*1.42*	*0.74-2.75*	*1.04*	*0.30*
	Recessive model			*Fixed*	*41.3%*	*0.16*	*0.79*	*0.58-1.07*	*1.04*	*0.30*
Caucasian	*TT vs MM*	*2884*	*3656*	*Random*	*69.3%*	*0.00*	*0.84*	*0.58-1.23*	*0.00*	*1.00*
	TT vs MT			*Random*	*65.0%*	*0.01*	*0.98*	*0.78-1.22*	*0.00*	*1.00*
	Dominant model			*Random*	*72.9%*	*0.00*	*1.07*	*0.84-1.37*	*0.00*	*1.00*
	Recessive model			*Random*	*60.6%*	*0.01*	*0.87*	*0.64-1.18*	*0.00*	*1.00*
Sample size	*TT vs MM*	*3837*	*4899*	*Random*	*65.8%*	*0.01*	*0.97*	*0.70-1.34*	*0.00*	*1.00*
> 500	*TT vs MT*			*Random*	*87.9%*	*0.00*	*0.94*	*0.68-1.31*	*0.00*	*1.00*
	Dominant model			*Random*	*89.8%*	*0.00*	*1.05*	*0.75-1.46*	*0.00*	*1.00*
	Recessive model			*Fixed*	*42.6%*	*0.12*	*1.01*	*0.87-1.16*	*0.00*	*1.00*
Consistent	*TT vs MM*	*3916*	*4507*	*Random*	*55.9%*	*0.02*	*1.00*	*0.75-1.33*	*0.34*	*0.73*
with HWE	*TT vs MT*			*Random*	*55.3%*	*0.02*	*1.06*	*0.89-1.26*	*0.34*	*0.73*
	Dominant model			*Random*	*64.1%*	*0.00*	*0.97*	*0.80-1.16*	*0.34*	*0.73*
	Recessive model			*Fixed*	*45.4%*	*0.07*	*1.03*	*0.89-1.18*	*0.34*	*0.73*

Meta-analysis results

A summary of the meta-analysis findings regarding the association between the *XRCC3* T241M polymorphism and CRC risk is shown in Table 2 and Figures 2 and 3. Overall, we found no significant association between the *XRCC3* T241M polymorphism and CRC in the total analysis (TT *vs* MM: OR = 0.85, 95%CI = 0.63-1.14; TT *vs* MT: OR = 0.87, 95%CI = 0.68-1.10; dominant model: OR = 1.18, 95%CI = 0.92-1.50; recessive model: OR = 0.87, 95%CI = 0.69-1.11).

Subgroup analysis

When stratified according to ethnicity, we detected no significant association in Asians

(TT *vs* MM: OR = 0.78, 95%CI = 0.38-1.59; TT *vs* MT: OR = 0.69, 95%CI = 0.35-1.35; dominant model: OR = 1.42, 95%CI = 0.74-2.75; recessive model: OR= 0.79, 95%CI = 0.58-1.07) and in Caucasians (TT *vs* MM: OR = 0.84, 95%CI = 0.58-1.23; TT *vs* MT: OR = 0.98, 95%CI = 0.78-1.22; dominant model: OR = 1.07, 95%CI = 0.84-1.37; recessive model: OR = 0.87, 95%CI = 0.64-1.18). In stratified analysis by sample size (subjects > 500), we detected no significant association between the T241M polymorphism and CRC (TT *vs* MM: OR = 0.97, 95%CI = 0.70-1.34; TT *vs* MT: OR = 0.94, 95%CI = 0.68-1.31; dominant model: OR = 1.05, 95%CI = 0.75-1.46; recessive model: OR = 1.01, 95%CI = 0.87-1.16).

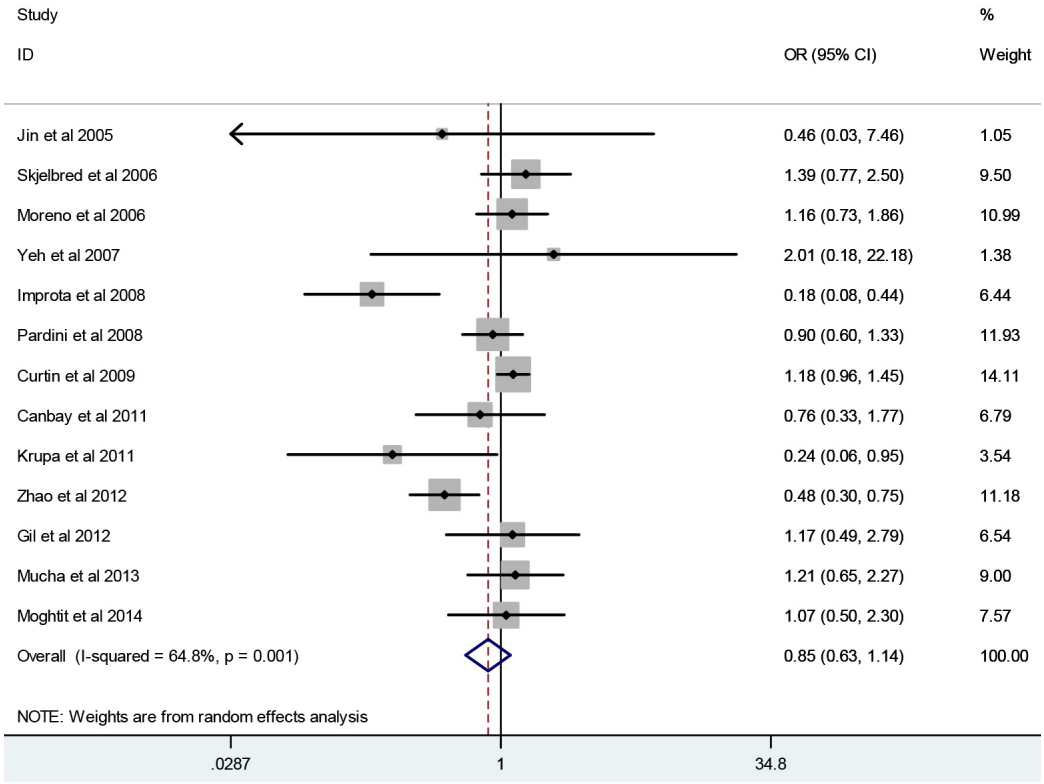

Figure 2. Association between the *XRCC3* T241M polymorphism and CRC risk (TT *vs* MM): total analysis.

Sensitivity analysis and publication bias

Sensitivity analysis was performed by omission of non-HWE studies and the results were not altered, indicating that the results of this meta-analysis were statistically significant (Table 2). Publication bias of the literature was assessed by Begg's funnel plot (Figure 4 and Table 2). The funnel plot was used to measure the asymmetry of the funnel plot. The results of the Begg's funnel plot test are shown in Table 2. The results revealed no publication bias (all P > 0.05).

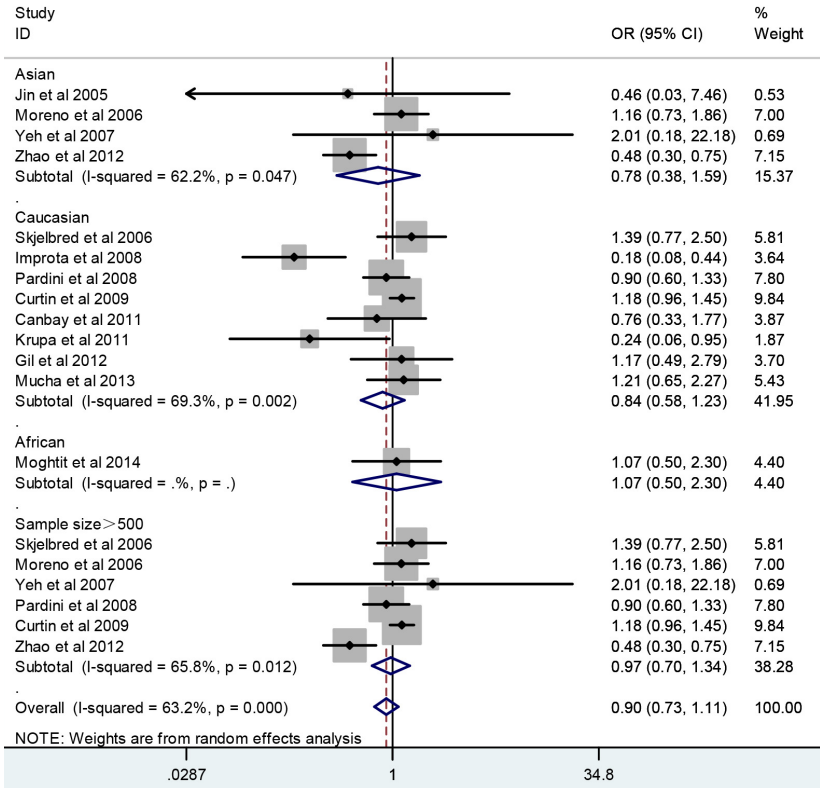

Figure 3. Association between the *XRCC3* T241M polymorphism and CRC risk (TT *vs* MM): subgroup analysis by ethnicity and sample sizes > 500.

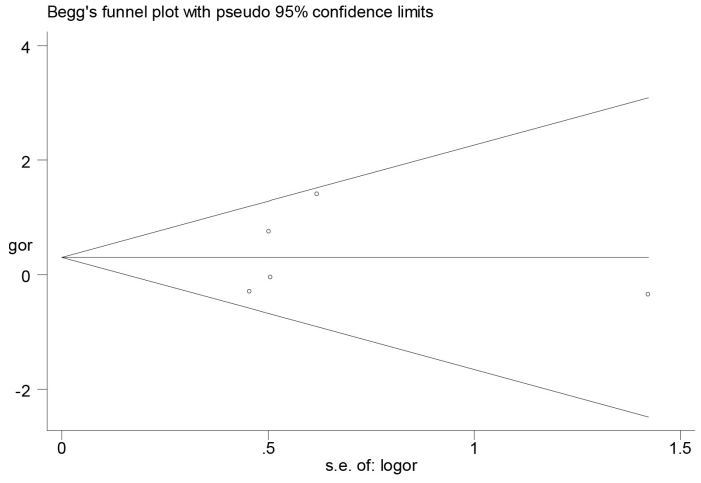

Figure 4. Publication bias for the association between the *XRCC3* T241M polymorphism and CRC risk (TT *vs* MM).

DISCUSSION

CRC is a multifactorial disease with a pathogenesis that is not fully understood. Accumulated evidence has indicated that CRC is determined by a complex interaction between environmental and genetic factors. The DNA repair system is important for maintaining the stability of the normal genomic function of cells. *XRCC3* is the major gene involved in the restoration phase of DNA damage. Recently, numerous studies have examined the association between the *XRCC3* T241M polymorphism and CRC. However, the results are inconsistent, likely because these studies were single case-control studies including small sample sizes (Moghtit et al., 2014). To clarify these inconsistent findings, we conducted this meta-analysis to obtain more reliable results by combining a larger number eligible studies, increasing the sample size, and conducting subgroup analysis.

The current meta-analysis, which included 4720 patients and 6104 controls, explored the association between the *XRCC3* T241M polymorphism and CRC risk. The results of the present meta-analysis revealed that the *XRCC3* T241M polymorphism is not associated with an increased or decreased risk of CRC. Furthermore, we performed ethnicity-specific subgroup analysis. Subgroup analysis results showed that the *XRCC3* T241M polymorphism was not associated with CRC risk both in Asians and in Caucasians. There was only one study of Africans, and thus further studies examining Africans should be conducted (Moghtit et al., 2014). Stratification by sample size (> 500) for subgroup analysis revealed no significant association, indicating there was no small-study bias in our meta-analysis. Deviation of allelic distributions from HWE may have contributed to between-study heterogeneity. Sensitivity analysis conducted by limiting this meta-analysis to those studies that were consistent with HWE revealed our results were reliable. There was no evidence of publication bias in this meta-analysis (all $P > 0.05$).

The results of the present meta-analysis revealed that the *XRCC3* T241M polymorphism is not associated with the risk of CRC. The function of the *XRCC3* T241M polymorphism with CRC may be affected by gene-gene and gene-environment interactions. A previous study showed that the *XRCC1* Arg399Gln and *XRCC3* T241M polymorphisms synergistically increased the risk of CRC (Zhao et al., 2012). However, in contrast to many genetic polymorphisms, the *XRCC3* T241M polymorphism was not associated with environmental factors such as alcohol drinking and cigarette smoking (Goode et al., 2002; Skjelbred et al., 2006). Further studies of gene-gene and gene-environment interaction should be conducted.

There were several limitations to this meta-analysis. First, because of incomplete raw data, some relevant studies could not be included in our analysis. Second, our results were based on unadjusted estimates, and a more precise analysis should be conducted if raw data from each individual study were available. This would allow for adjustment by other co-variants, including age, gender, environmental factors, and other lifestyle factors. Third, we only included articles written in English, which may have eliminated other articles.

In conclusion, the T241M polymorphism in the *XRCC3* gene may not contribute to the risk of CRC. Further studies should be performed to validate these results.

Conflicts of interest

The authors declare no conflict of interest.

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