

RESEARCH ARTICLE

Genetic Association between ERCC5 rs17655 Polymorphism and Colorectal Cancer Risk: Evidence Based on a Meta-analysis

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Abstract

Background: Previous studies evaluating the association between the excision repair cross complementing group 5 (ERCC5) gene rs17655 polymorphism and colorectal cancer susceptibility generated controversial results. To generate large-scale evidence on whether the ERCC5 rs17655 polymorphism might indeed be associated with colorectal cancer susceptibility, the present meta-analysis was performed. **Materials and Methods:** Data were collected from PubMed, Embase and Web of Science, with the last report up to Apr 03, 2015. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of any association. **Results:** A total of nine studies including 5,102 cases and 6,326 controls based on the search criteria were included and significant associations were found between ERCC5 rs17655 polymorphism CG vs GG overall (OR = 1.29, 95% CI = 1.18~1.40) and in the dominant model (OR=1.23, 95% CI = 1.13~1.33). On subgroup analysis by ethnicity and source of controls, the ERCC5 rs17655 polymorphism was found to correlate with the pathogenesis of colorectal cancer among Asians and Caucasians and with hospital-based populations. **Conclusions:** This meta-analysis suggests that the ERCC5 rs17655 polymorphism might contribute to genetic susceptibility to colorectal cancer.

Keywords: ERCC5 - rs17655 polymorphism - meta-analysis - colorectal cancer

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Introduction

Cancer has developed to be one of the most common and severe diseases that leads to high mortality worldwide in recent decades. Colorectal cancer (CRC) is the third most common malignancy and the fourth most common cause of cancer-related death in the world (Siegel et al., 2014). The incidence of CRC is increasing each year (Center et al., 2009; Ferlay et al., 2010). Generally, CRC is considered as a multifactorial disease caused by the interaction of both environmental and genetic factors (Hagggar and Boushey, 2009; Rawson et al., 2011). Evidence from epidemiological studies has suggested that a wide range of environmental factors are involved in the etiology of CRC, such as diet, increasing age, and related aspects of lifestyle (Dahm et al., 2010; Ogino et al., 2010). Genetic susceptibility to this disease may result from inherited mutations in genes involved in carcinogen metabolism and DNA repair (Shields and Harris, 2000; Goode et al., 2002).

Single nucleotide polymorphisms (SNPs) are the most common sources of human genetic variation, and they may contribute to an individual's susceptibility to cancer (Zhang et al. 2013). A recent study has revealed that approximately 35% of CRC cases can be attributed to inherited genetic (Markowitz and Bertagnolli, 2009).

Then, investigating the effects of genetic variants on CRC risk may help better understand the association between genetic variants and cancer risk.

Excision repair cross-complementing group 5 (ERCC5 or xeroderma pigmentosum group G, XPG), one of the functional genes in the base excision repair (NER) pathway, is located on chromosome 13q22-q33, consisting of 15 exons and 14 introns (Emmert et al., 2001). ERCC5 is a member of the flap structure-specific endonuclease 1 (FEN1) family and encodes a protein of 1186 amino acids. It has reported that a defective ERCC5 plays a pivotal role in the initiation of carcinogenesis and leads to DNA repair defects, genomic instability, and failure of gene transcription modulation (Cheng et al., 2002; Koeppl et al., 2004; Bartolucci et al., 2009). SNPs in ERCC5 gene have been discovered in human populations, a polymorphism at codon 1104, resulting in the amino acid change of His1104Asp (rs17655, G>C), is common and regarded as a tagger, which was most frequently investigated for its association with cancer risk.

To date, rs17655 polymorphism in the ERCC5 gene has been found to be involved in the pathogenesis of CRC. However, the results from different laboratories are conflicting. Therefore, we performed a quantitative synthesis of the evidence on the association of ERCC5 rs17655 polymorphism with the developing risk of CRC.

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Materials and Methods

Literature sources and search strategies

This meta-analysis was performed by searching PubMed, EMBASE, and Web of Science databases, with a time limit of Apr 03, 2015. The following key terms were used: “*excision repair cross-complementing group 5*”, “*ERCC5*”, “*XPG*”, “*xeroderma pigmentosum group G*”, “*NER*”, “*polymorphism*”, combined with “*colon cancer*”, “*rectal cancer*”, or “*colorectal cancer*”. There was no language limitation in the search of databases. All of the searched studies were retrieved, and the bibliographies were checked for other relevant publications. Review articles and bibliographies of other relevant studies identified were searched by hand in order to find additional eligible studies. If more than one article was published using the same study population, only the study with largest sample size was selected.

Inclusion criteria

The following inclusion criteria were used to identify eligible articles. (1) Sufficient genotype data were presented to allow calculation of the odds ratios (ORs). (2) Studies designed as case-controls; (3) Study clearly described the diagnosis of CRC and the sources of the cases and controls.

Data extraction and methodological ^{overall} assessment.

Information was extracted carefully from all eligible publications independently by two investigators according to the inclusion criteria listed above. For conflicting evaluation, an agreement was reached following discussion. The following information was extracted from each study: first author, publication year, ethnicity (country), source of controls, number of cases and controls, and the genotype frequencies of the cases and controls. Ethnicities were categorized as Asian and Caucasian. Source of control were categorized as hospital based, population based and family based. We did not define any minimum number of patients to include in our meta-analysis. Methodological quality was evaluated separately by two authors using the Newcastle-Ottawa Scale (NOS) criteria (Stang, 2010). The NOS criteria is based on three aspects: (1) subject selection: 0~4; (2) comparability of subject: 0~2; (3) clinical outcome: 0~3. NOS scores range from 0 to 9 with scores ≥ 7 indicating good quality.

Statistical analysis

The pooled odds ratio (OR) and 95 %CI were used to assess the association between ERCC5 rs17655 polymorphism and CRC risk for each case-control study. Heterogeneity among studies was estimated with the Cochran's Q statistic and I^2 tests (Zintzaras and Ioannidis, 2005a). If the Q test showed a $P < 0.05$ or I^2 test exhibited $> 50\%$, indicating significant heterogeneity, the random effects model was used. Otherwise, the fixed effects model was used (Zintzaras and Ioannidis, 2005b). We explored potential sources of heterogeneity using subgroup analyses, and the subgroup analyses were done by ethnicity and source of control. The pooled ORs

were performed for co-dominant model (CC vs GG and CG vs GG), the dominant model (CC+CG vs GG), and the recessive model (CC vs CG+GG), respectively. The significance of the pooled ORs was determined by Z test. The Hardy-Weinberg equilibrium (HWE) was assessed by Fisher's exact test. Publication bias was assessed by visual inspection of funnel plots (Munafa et al., 2004), in which the standard error of log (OR) of each study was plotted against its log (OR). An asymmetric plot indicates a possible publication bias. Publication bias may be absent if the plot resembles a symmetrical inverted funnel in which smaller, less precise, and more numerous studies have increasingly large variation in the estimates of their effect size (Sutton et al., 2000). Thus, publication bias was further investigated using Begg's funnel plot and Egger's regression test (Begg and Mazumdar, 1994; Egger et al., 1997) ($p < 0.05$ was considered to be statistically significant). All statistical analyses were performed using STATA statistical software (version 10.0). Two-sided p values less than 0.05 were considered statistically significant.

Results

Characteristics of eligible study

We retrieved and screened the publications relevant to the keywords originally. The detailed characteristics of the included studies are listed in Table 1. A total of nine articles (Figure 1) were collected according to the search criteria (Pardini et al., 2008; Joshi et al., 2009; Canbay et al., 2011; Gil et al., 2012; Liu et al., 2012; Du et al., 2014; Steck et al., 2014; Paszkowska-Szczur et al., 2015; Sun et al., 2015). One publication (Steck et al., 2014) contained two case-control data was considered to two separate studies, therefore, 10 articles including 5,102 cases and 6,326 controls were used for this meta-analysis. The controls were primarily healthy population. All of the cases were pathologically confirmed. In terms of ethnicity, there were three groups of Asians (Liu et al., 2012; Du et al., 2014; Sun et al., 2015), six groups of Caucasians (Pardini et al., 2008; Joshi et al., 2009; Canbay et al., 2011; Gil et al., 2012; Steck et al., 2014; Paszkowska-Szczur et al., 2015). In terms of source of control, there were six groups of hospital based (Pardini et al., 2008; Canbay et al., 2011; Liu et al., 2012; Du et al., 2014; Paszkowska-Szczur et al., 2015; Sun et al., 2015), three groups of population based (Gil et al., 2012; Steck et al., 2014), one group of family based (Joshi et al., 2009). Studies with control not in Hardy-Weinberg equilibrium (HWE) were also considered for meta-analysis, but they were excluded in the sensitivity analysis (Minelli et al., 2008).

Quantitative data synthesis

The main results of our meta-analysis under four distinct genetic models were listed in Table 2 and Table 3. Overall, significant associations were found between the ERCC5 rs17655 polymorphism and CRC susceptibility for CG vs GG (OR = 1.29, 95% CI = 1.18~1.40, $p = 0.10$ for heterogeneity, Figure 2A) and the dominant model (OR = 1.22, 95% CI = 1.13~1.33, $p = 0.24$ for heterogeneity, Figure 2B). But no significant association was found

Table 1. Characteristics of Case-Control Studies Included in the Meta-Analysis

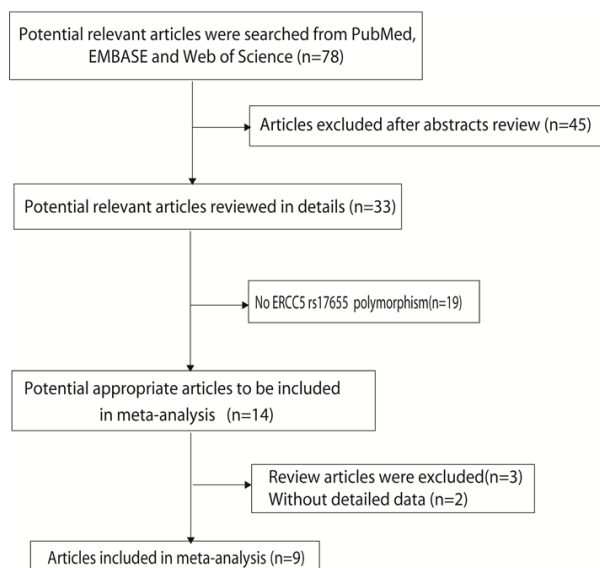
Study	Race	Gene test	Source	Site	No. of Case/Control	Case			Control			HWE	NOS
						GG	CG	CC	GG	CG	CC		
Paszkowska-Szczur K 2014	Caucasian	TaqMan assays	HB	rs17655	733/1358	429	272	32	869	404	85	0	8
Sun K 2014	Asian	PCR-RFLP	HB	rs17655	890/910	216	476	198	227	497	186	0	9
Du H 2014	Asian	TaqMan assay	HB	rs17655	878/884	286	459	133	355	405	124	0.62	7
Steck SE 2014	Caucasian	MassARRAY system	PB	rs17655	224/317	65	120	39	100	151	66	0.52	8
Steck SE 2014	Caucasian	MassARRAY system	PB	rs17655	298/532	183	100	15	335	170	27	0.37	8
Liu D 2012	Asian	PCR-RFLP	HB	rs17655	1028/1085	233	603	192	329	537	219	1	8
Gil J 2012	Caucasian	PCR-RFLP	PB	rs17655	132/100	86	35	11	64	31	5	0.62	9
Canbay E 2011	Caucasian	PCR-RFLP	HB	rs17655	79/247	43	34	2	148	83	16	0.35	8
Joshi AD 2009	Caucasian	TaqMan assay	FB	rs17655	308/361	183	125		213	148		-	7
Pardini B 2008	Caucasian	TaqMan assay	HB	rs17655	532/532	334	177	21	356	153	23	0.21	8

*HB: hospital based; PB: population based; FB: family based; HWE: Hardy-Weinberg equilibrium; PCR: Polymerase chain reaction; RFLP: Restriction fragment length polymorphism; NOS: Newcastle-Ottawa Scale

Table 2. Summary Odds Ratios Relations Between the ERCC5 rs17655 Polymorphism and Colorectal Cancer Susceptibility

Polymorphism	Genetic model	Genetic type	Heterogeneity test			OR (95% CI)	P1	Begg's test		Egger's test	
			Q	I ² (%)	PH			Z	P2	t	P3
rs17655	Codominant model	CC vs GG	8.07	0.90%	0.43	1.11 (0.98~1.27)	0.11	0.73	0.47	-1.5	0.18
		CG vs GG	13.33	40.00%	0.1	1.29 (1.18~1.40)	0	1.15	0.25	-1.25	0.25
	Dominant model	CC+CG vs GG	11.58	22.20%	0.24	1.22 (1.13~1.33)	0	0.89	0.37	-1.68	0.13
	Recessive model	CC vs CG+GG	8.71	8.10%	0.37	0.97 (0.86~1.09)	0.56	0.1	0.92	-0.85	0.42

PH value for heterogeneity; P1 value for OR; P2 value for Begg's test; P3 value for Egger's test; OR: Odds ratio; CI: Confidence interval

**Figure 1. Study Selection Process for the Meta-Analysis**

for CC vs GG (OR=1.11, 95% CI =0.98~1.27, $p=0.43$ for heterogeneity, Figure 2C) and the recessive model (OR=0.97, 95% CI =0.86~1.09, $p=0.37$ for heterogeneity, Figure 2D).

To comprehensively evaluate the effect of ERCC5 rs17655 polymorphism on the pathogenesis of CRC, we also carried out subgroup analysis based on ethnicity and source of control. Ethnicity-stratified analysis indicated that ERCC5 rs17655 polymorphism was correlated with the pathogenesis of CRC among both Asians and Caucasians in the majority of subgroups. Furthermore, the results of stratified analyses based on source of control revealed that ERCC5 rs17655 polymorphism was closely linked to the pathogenesis of CRC in the majority in hospital based subgroup, but neither in population based nor family subgroups.

Heterogeneity and sensitivity analysis

We observed no substantial heterogeneity in the meta-analysis ($P>0.05$; Table 2). To check the stability of the

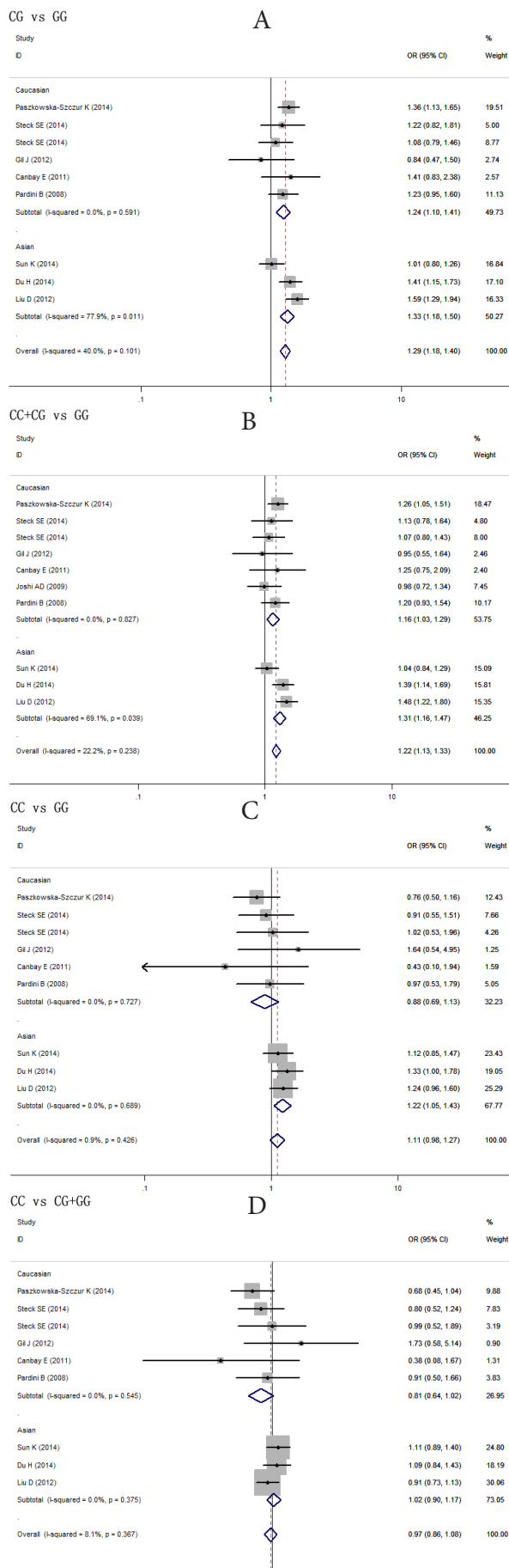


Figure 2. Odds Ratios (ORs) for Associations between the ERCC5 rs17655 Polymorphism and CRC Susceptibility

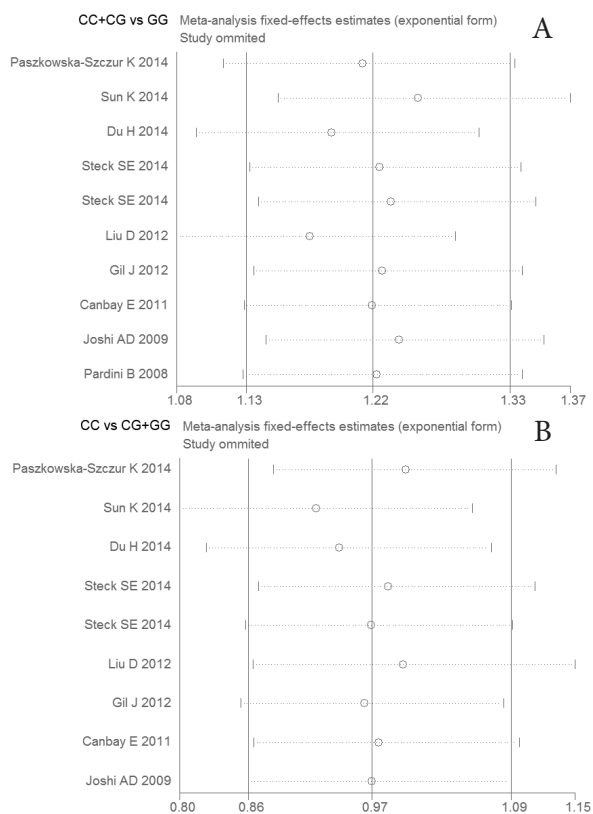


Figure 3. Sensitivity Analysis Using the One-Study Remove Approach in the Dominant Model and the Recessive Model

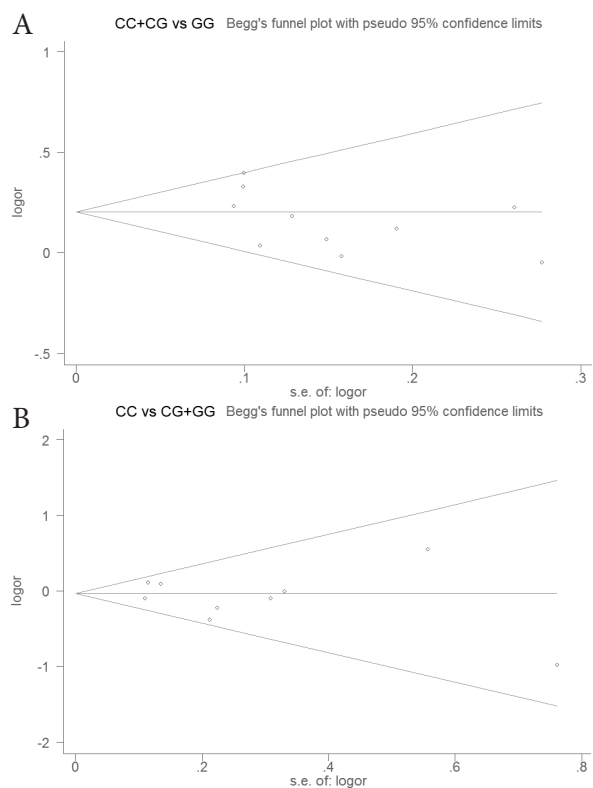


Figure 4. Publication Bias in Studies of the Relation between the ERCC5 rs17655 Polymorphism and CRC Susceptibility in the Dominant Model and the Recessive Model. A funnel plot with pseudo-95% confidence limits (dashed lines) was used

Table 3. Main Results of Pooled Odds Ratios (OR) with Confidence Interval (CI) in the Meta-Analysis by Ethnicity, and Source of Control

Polymorphism Subgroup(N)		Genetic type	Heterogeneity test			OR (95% CI)	P1	Begg's test		Egger's test	
rs17655			Q	I ² (%)	PH			Z	P2	t	P3
Race	Caucasian(7)	CC vs GG	2.82	0.00%	0.73	0.88 (0.69~1.13)	0.32	0.75	0.45	0.32	0.75
		CG vs GG	3.71	0.00%	0.59	1.24 (1.10~1.40)	0	1.13	0.26	-1.26	0.23
		CC+CG vs GG	2.85	0.00%	0.83	1.16 (1.03~1.29)	0.01	1.2	0.23	-1.09	0.18
		CC vs CG+GG	4.03	0.00%	0.55	0.81 (0.64~1.02)	0.08	0.75	0.45	0.51	0.68
	Asian (3)	CC vs GG	0.75	0.00%	0.69	1.22 (1.05~1.43)	0.01	0	1	3.5	0.77
		CG vs GG	9.04	77.90%	0.01	1.33 (1.18~1.50)	0	1.04	0.3	-39.02	0.14
		CC+CG vs GG	6.48	69.10%	0.04	1.31 (1.16~1.47)	0	0	1	-32.65	0.13
		CC vs CG+GG	1.96	0.00%	0.38	1.02 (0.90~1.17)	0.73	0	1	5.62	0.6
Source of control	HB(6)	CC vs GG	6.85	27.00%	0.23	1.13(0.98~1.30)	0.1	1.13	0.26	-1.92	0.1
		CG vs GG	9.47	47.20%	0.09	1.33(1.21~1.46)	0	0.75	0.45	-0.56	0.83
		CC+CG vs GG	6.89	27.40%	0.23	1.28(1.17~1.40)	0	0	1	-0.81	0.71
		CC vs CG+GG	6.9	27.50%	0.23	0.97(0.86~1.10)	0.65	0.75	0.45	-1.52	0.18
	PB(3)	CC vs GG	0.9	0.00%	0.64	1.01(0.70~1.47)	0.95	1.04	0.3	1.9	0.06
		CG vs GG	1.1	0.00%	0.58	1.08(0.87~1.35)	0.49	0	1	-1.48	0.59
		CC+CG vs GG	0.26	0.00%	0.88	1.07(0.86~1.32)	0.54	0	1	-0.78	0.56
		CC vs CG+GG	1.71	0.00%	0.43	0.92(0.66~1.30)	0.65	1.04	0.3	2.27	0.04
FB(1)	CC+CG vs GG	0	-	-	0.98(0.72~1.34)	0.91					

*N for numbers of studies; PH value for heterogeneity; P1 value for OR; P2 value for Begg's test; P3 value for Egger's test; OR: Odds ratio; CI: Confidence interval

combined effects, sensitivity analysis was performed by sequentially deleting each of the included studies and recalculating the ORs. Such a leave-one-out sensitivity analysis indicated that no single study influenced the pooled ORs qualitatively in the dominant model (Figure 3A), the recessive model (Figure 3B) and other models (not showed). Hence, results of the sensitivity analysis suggest that the data in this meta-analysis are relatively stable.

Publication bias

Begg's funnel plot and Egger's linear regression test were performed to assess the publication bias of included studies. The funnel plots for publication bias showed symmetry for the dominant model and the recessive model (Figure 4A, Figure 4B). Meanwhile, results of Begg's test and Egger's linear regression method indicated that there was no obvious publication bias ($P>0.05$, Table 2).

Discussion

Development of malignant tumors results from multistep accumulation of genetic and epigenetic

alterations in cells, and the presence of genomic instability has a substantial effect in accelerating the carcinogenic processes. Dysfunction of DNA repair systems may make a significant contribution (Masutani et al., 2003). CRC is a common and complex multifactorial disease in which environmental and host-related factors interact (Bordignon et al., 2012; Petraki et al., 2012; Wang et al., 2013). Data has indicated an association of the descent productivity of DNA repair and the increased susceptibility of colorectal cancer (Jiricny and Marra, 2003). It is widely recognized that mismatch repair pathway is an etiological factor of individual risk to colorectal cancer (Peltomaki, 2003). NER is a crucial DNA repair mechanism, which counteracts the consequences of mutagenic exposure of cell. XPF and ERCC5 are both central players in the NER pathway, and they are involved in incision 5' and 3', respectively, to the DNA lesion.

Since the identification of ERCC5 rs17655 polymorphism, an increasing number of studies suggested that ERCC5 rs17655 polymorphism may play important roles in CRC development. Epidemiological studies of ERCC5 rs17655 polymorphism, if large and unbiased, can provide insight into the *in vivo* relationship between the

gene and CRC risk. However, these studies have resulted in apparently contradicting findings.

Meta-analysis has been recognized as an effective method to solve a wide variety of clinical questions by summarizing and reviewing the previously published quantitative research. By using meta-analysis, CTLA-4 rs231775 (Wang et al., 2015), IRS-1 rs1801278 (Li et al., 2014), hOGG1 Ser326Cys (Zhang et al., 2014) polymorphisms have been proved associated with bladder cancer susceptibility.

In the present meta-analysis, we attempted to identify whether ERCC5 rs17655 polymorphism was a causative factor for the pathogenesis of CRC. A total of 11,428 subjects were included, the results showed that the ERCC5 rs17655 polymorphism was a risk factor for CRC in overall population, furthermore, in the subgroups by ethnicity and by source of control, ERCC5 rs17655 polymorphism was correlated with the pathogenesis of CRC among Asians, Caucasians and hospital based population.

Our meta-analysis has a number of limitations that should be addressed. First, the small sample size does not possess sufficient statistical significance to evaluate the relationship between ERCC5 rs17655 and the risk of CRC with great certainty, especially in the family based subgroup (only one article). Since the small number of studies may constrain the general applicability of our findings, the cognitive function of our meta-analysis should be regarded as preliminary. ^{overall} Second, the controls included in our analysis were selected variously either from populations or hospitals. Therefore, misclassification bias was possible because these studies may have included control groups who have different risks of developing GI cancers. Third, OR value was obtained with a failure to take account of important confounding factors. More accurate OR should be corrected by age, lifestyle, gender, and other environmental risk factors, after adjusting for covariates that might help explain the association between ERCC5 rs17655 polymorphism and susceptibility to CRC.

In summary, this meta-analysis provided reliable evidence that the ERCC5 rs17655 polymorphism was a risk factor for CRC. However, due to the limitations acknowledged above, research based on a larger sample size and more detailed data is needed in order to achieve a more significant and representative statistical analysis.

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