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XPD Polymorphisms and Risk of Hepatocellular Carcinoma and Gastric Cancer: A Meta-Analysis

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Abstract

Background: Cancer is associated with genetic variants of DNA repair genes that alter DNA repair capacity. The aim of this meta-analysis was to evaluate the relations between the rs13181 and rs1799793 XPD gene polymorphisms and risk for hepatocellular carcinoma (HCC) and gastric cancer. **Methods:** Relevant publications were systematically sought from Web of Science, Pubmed, and China Academic Journals Full-text Database. The selection of eligible studies was performed by 2 independent authors. A total of 32 case-control studies were included. Meta-analyses were undertaken in all study participants and each ethnic group. **Results:** The risk of HCC was significantly increased with the XPD rs13181 G allele ($P = 0.028$, pooled odds ratio (OR) = 1.36, 95% confidence interval (CI) = 1.03-1.80) in all study participants. A subgroup analysis by ethnicity showed that the association was significant in Chinese ($P = 0.009$, pooled OR = 1.49, 95% CI = 1.11-2.02), but not in Caucasians ($P = 0.619$, pooled OR = 1.17, 95% CI = 0.64-2.13). Meta-analysis of the XPD rs1799793 polymorphism and HCC showed an association between its variant T allele and increased HCC risk in all study participants ($P = 0.017$, pooled OR = 1.23, 95% CI = 1.04-1.46, all Chinese). Our results showed no associations between the XPD rs13181 G allele and rs1799793 T allele and gastric cancer risk (rs13181: $P = 0.298$, pooled OR = 1.10, 95% CI = 0.92-1.31; rs1799793: $P = 0.068$, pooled OR = 1.31, 95% CI = 0.98-1.74). **Conclusions:** This meta-analysis demonstrated that the XPD rs13181 G allele and rs1799793 T allele have significant associations with HCC and may be risk factors for HCC in the Chinese population. Current evidence indicated that they are not related to gastric cancer risk.

Keywords

hepatocellular carcinoma, gastric cancer, XPD, meta-analysis, polymorphism

Abbreviations

CI, confidence interval; HCC, hepatocellular carcinoma; NER, nucleotide excision repair; OR, odds ratio; XPD, Xeroderma pigmentosum complementation group D

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Introduction

Repair of genetic damage is important for humans to prevent multiple diseases including cancer. A large body of research has repeatedly shown that there is inter-individual variation in capacity for DNA repair and individuals with reduced DNA repair capacity are more vulnerable to developing cancer.[1] Therefore, genetic variants of DNA repair genes that alter DNA repair capacity are considered to have a significant influence on individual predisposition to cancer. The Xeroderma pigmentosum complementation group D (XPD, also known as ERCC2) gene encodes an adenosine triphosphate-dependent DNA helicase mediating DNA unwinding in the 5'-3' direction.[2] The enzyme plays a vital role in the nucleotide excision repair (NER) pathway,[2] which is the major DNA repair pathway for removing bulky DNA lesions caused by environmental

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carcinogens, compounds, and oxidative stress. Researchers have identified several XPD polymorphisms in the coding regions, including a change of lysine to glutamine in codon 751 (Lys751Gln, rs13181) and a transition of aspartic acid to asparagine in codon 312 (Asp312Asn, rs1799793).[3] The Gln allele of XPD rs13181 and the XPD rs1799793 Asn allele have been associated with reduced NER capacity. Since XPD is an important gene for DNA repair, the association between XPD polymorphisms and cancer risk is of particular interest.

Hepatocellular carcinoma (HCC) and gastric cancer are 2 common types of digestive system cancer, which cause severe morbidity and mortality worldwide. Emerging evidence suggests that defects in the DNA repair mechanisms are implicated in the initiation and progression of HCC and gastric cancer.[4,5] Accordingly, a number of studies have evaluated the association of polymorphisms in the DNA repair genes, especially XPD rs13181 and rs1799793, with the risk of HCC and gastric cancer. However, some studies have found associations with increased risk of these cancers, while some others have not. Therefore, the purpose of this study was to systematically evaluate the published studies and offer an updated analysis of the association of XPD rs13181 and rs1799793 polymorphisms with the risk of HCC and gastric cancer.

Methods

Included Studies

We searched Pubmed, Web of Science and China Academic Journals Full-text Database to identify all studies reporting the genotypes of XPD rs13181 and rs1799793 among patients with HCC or gastric cancer. The search terms were XPD or Xeroderma pigmentosum complementation group D; genetic polymorphism or gene; HCC, hepatocellular carcinoma, liver cancer or gastric cancer. Since an online database search might miss relevant published studies, the references of important review articles in the field were also screened. The studies meeting the following criteria were included: a) original case-control studies that assessed the XPD rs13181 and rs1799793 polymorphisms and risk of HCC or gastric cancer; and b) sufficient data were provided for meta-analytic comparison.

Data Extraction and Study Quality Assessment

This process was performed by 2 authors (QZ and YF) using a data-collecting form. The data extracted included year of publication, family name of the first author, ethnicity of the studied sample, region or country where the studied was performed, case group number, control group number, age, variant type of the XPD polymorphisms, methods used for detecting the variant, allele distribution and major findings of the study. In the process of data extraction, any discrepancies between the 2 authors were resolved by mutual consensus. The Newcastle-Ottawa Scale (NOS) is one of the most frequently used method to evaluate the quality of non-randomized studies in meta-analysis, which contains 3 major domains including selection, comparability, and exposure. The quality of each study was assessed using the NOS. Studies with $\geq$5 scores were considered as high quality studies.

Meta-Analysis Methods

All the meta-analyses were performed using the STATA software. Between-study heterogeneity was evaluated with the I^2 statistic. I^2 values > 50% suggest high heterogeneity.[6] As an effect measure, a pooled odds ratio (OR) and its 95% confidence interval (CI) were calculated to evaluate the association between the XPD polymorphisms and risk of HCC or gastric cancer. Random- or fixed-effects models were used for the calculation. A pooled OR > 1 indicates an increased risk. The Z-test was used to test the significance of the pooled OR. We used funnel plots to graphically evaluate publication bias and conducted the Egger test to quantify funnel plots' asymmetry.[7] The significant results of meta-analyses were verified using trial sequential analysis (TSA) and false positive report probability (FPRP) test.[8]

Results

Study Characteristics

Figure 1 shows the literature inclusion and exclusion process using a flow diagram. We identified 329 studies meeting the search criteria in total. One hundred forty-two duplicates were removed after screening the titles. One hundred forty-six irrelevant studies that did not meet the inclusion criteria were excluded after carefully evaluating the abstracts. These steps left 41 articles for full-text evaluation. In the end, 32 studies were included in the meta-analyses: 15 studies evaluated the association between XPD polymorphisms and HCC risk,[9-23] and 19 studies examined the relation of XPD polymorphisms with gastric cancer risk.[16,23-40] The basic information of the included studies was shown in Tables 1 and 2. Regarding study origin, China was the most common country. The other countries were mainly from Europe and Asia, including Poland, Italy, Sweden, Spain, Turkey, India and Pakistan. Allele distribution of the XPD polymorphisms was shown in Supplemental Tables 1 and 2.

Meta-Analyses Results

After conducting a meta-analysis of 13 eligible studies, we found that the variant G allele of XPD rs13181 polymorphism was significantly associated with an increased risk of HCC (P = 0.028, pooled OR = 1.36, 95% CI = 1.03-1.80; Figure 2). A subgroup analysis by ethnicity showed that this significant association only existed in Chinese (P = 0.009, pooled OR = 1.49, 95% CI = 1.11-2.02) but not in Caucasians (P = 0.619, pooled OR = 1.17, 95% CI = 0.64-2.13). Moreover, a pooled analysis of XPD rs1799793 polymorphism showed an increased risk of HCC with the T allele (P = 0.017, pooled OR = 1.23, 95% CI = 1.04-1.46; Figure 3). All of the eligible

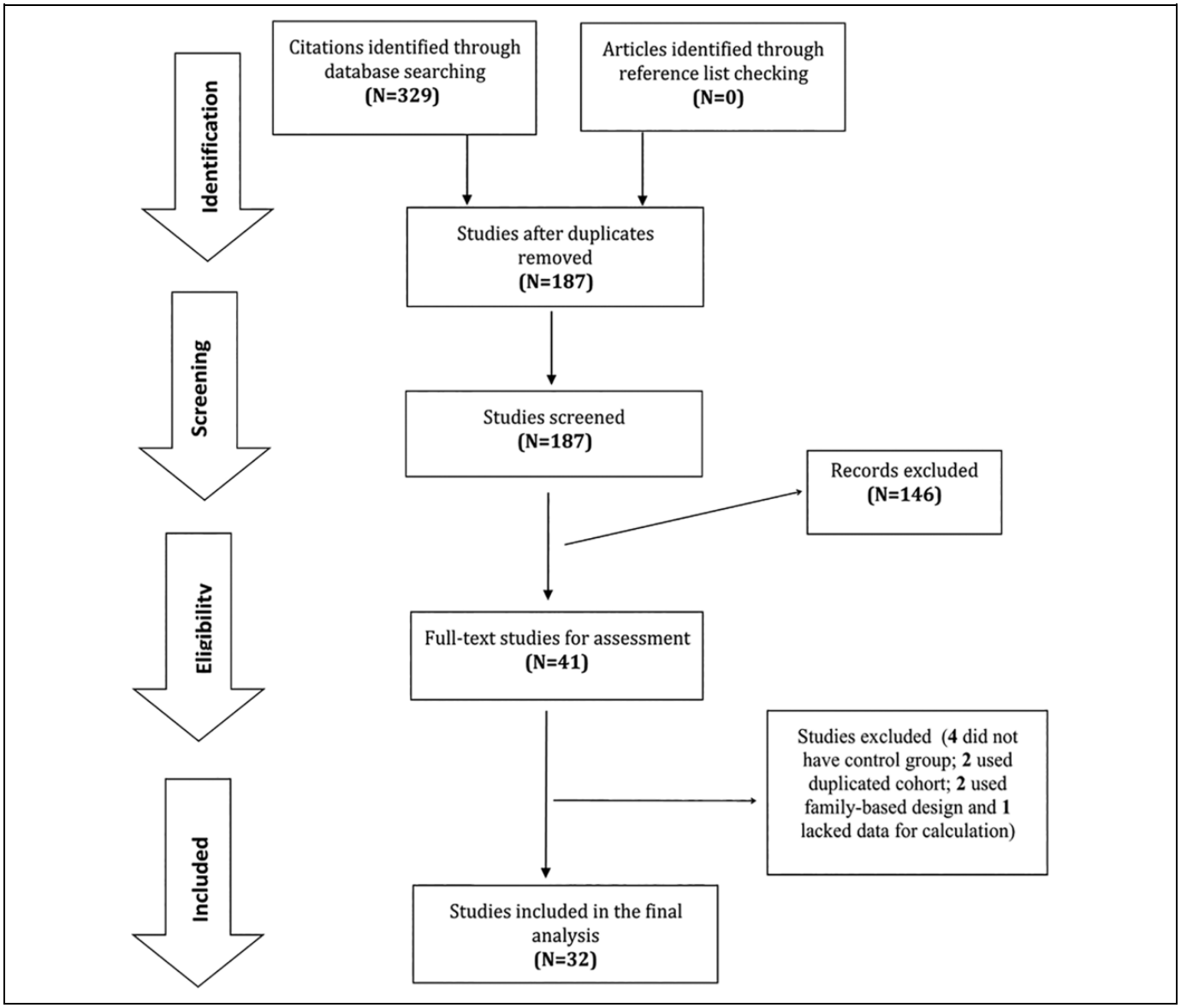

Figure 1. Flow diagram for identification of studies.

studies for XPD rs1799793 were done in Chinese HCC patients and controls.

As shown in Table 3, a pooled evaluation of 18 eligible studies did not show statistically significant association between the XPD rs13181 G allele and gastric cancer risk (P = 0.298, pooled OR = 1.10, 95% CI = 0.92-1.31; Figure 4). In addition, our results did not support any significant association of the XPD rs1799793 T allele with gastric cancer (P = 0.068, pooled OR = 1.31, 95% CI = 0.98-1.74). Subgroup analysis of ethnicity did not show any significant results for the rs13181 G allele and rs1799793 T allele.

Heterogeneity and Meta-Regression

Heterogeneity among studies that evaluated the XPD rs13181 G allele and HCC was very high (P = 0.000, I^2 = 90.5%). Therefore, we performed a meta-regression analysis to explore the factors associating with the heterogeneity. Sample size, ethnicity, source of control subjects (hospital-based or population-based) and year of publication were assessed in the meta-regression analysis. However, the results showed that these variables did not explain the heterogeneity (sample size: P = 0.173, ethnicity: P = 0.382, source of control subjects: P = 0.083, year of publication: P = 0.351).

TSA and FPRP Analysis

TSA analysis was performed using the TSA software (0.9.5.10 Beta version, Copenhagen, Denmark). For XPD rs13181 and HCC risk, the cumulative Z curve did not cross the the traditional boundary (Figure 5A), indicating that further relevant studies are needed to confirm the present findings. With respect

Table 1. Basic Information of the Included Studies for HCC.

Author	Country	Year	Ethnicity	Cases	Controls	Age, years	Source of controls	Virus infection Cases	Controls	Genotyping Method	Significant test for association	NOS
rs13181												
Chen	China	2005	Chinese	570	381	52	PB	HBsAg (+): 100%; anti-HCV (+): not reported	HBsAg (+): 100%; anti-HCV (+): not reported	5' nuclease PCR assays	NS	8
Xie	China	2007	Chinese	429	480	49	PB	HBsAg (+): 75.6%; anti-HCV (+): not reported	HBsAg (+): 38.8%; anti-HCV (+): not reported	PCR-RFLP	P = 0.001	6
Zeng	China	2009	Chinese	300	312	49	HB	HBsAg (+): 66%; anti-HCV (+): not reported	HBsAg (+): 19.2%; anti-HCV (+): not reported	TaqMan PCR genotyping	NS	7
Long	China	2009	Chinese	618	712	Unknown	HB	HBsAg (+): 72.8%; anti-HCV (+): 18.4%	HBsAg (+): 71.3%; anti-HCV (+): 18%	TaqMan PCR genotyping	P < 0.001	7
Cui	China	2010	Chinese	94	111	50	HB	HBsAg (+): not reported; anti-HCV (+): not reported	HBsAg (+): not reported; anti-HCV (+): not reported	PCR-RFLP	P = 0.011	6
Guo	China	2012	Chinese	410	410	52	HB	HBsAg (+): 36.5%; anti-HCV (+): 5.1%	HBsAg (+): 8.6%; anti-HCV (+): 0.9%	Sequenom MassARRAY	P < 0.05	7
Jiang	China	2012	Chinese	76	80	Unknown	PB	HBsAg (+): not reported; anti-HCV (+): not reported	HBsAg (+): not reported; anti-HCV (+): not reported	PCR-RFLP	P = 0.002	7
Gulnaz	Pakistan	2013	South Asian	50	74	Unknown	PB	HBsAg (+): 22%; anti-HCV (+): 54%	HBsAg (+): 0; anti-HCV (+): 0	PCR-RFLP	P = 0.61	8
Wu	China	2014	Chinese	218	277	52	HB	HBsAg (+): 52.3%; anti-HCV (+): 7.4%	HBsAg (+): 7.2%; anti-HCV (+): 1.1%	Sequenom MassARRAY	P = 0.005	8
Yao	China	2014	Chinese	1486	1996	Unknown	HB	HBsAg (+): 72.9%; anti-HCV (+): 18.6%	HBsAg (+): 70.5%; anti-HCV (+): 17.8%	TaqMan PCR genotyping	P < 0.001	7
Zhao	China	2014	Chinese	102	102	45	HB	HBsAg (+): 84.3%; anti-HCV (+): not reported	HBsAg (+): 23.5%; anti-HCV (+): not reported	DHPLC	P = 0.070	6
Krupa	Poland	2017	Caucasian	65	50	68	HB	HBsAg (+): not reported; anti-HCV (+): not reported	HBsAg (+): 100%; anti-HCV (+): not reported	TaqMan PCR genotyping	P = 0.021	7
Balkan	Turkey	2020	Caucasian	40	40	50	HB	HBsAg (+): not reported; anti-HCV (+): not reported	HBsAg (+): not reported; anti-HCV (+): not reported	LightSNiP typing assay	NS	6
rs1799793												
Xie	China	2007	Chinese	425	480	49	PB	HBsAg (+): 75.6%; anti-HCV (+): not reported	HBsAg (+): 38.8%; anti-HCV (+): not reported	PCR-RFLP	NS	6
Zeng	China	2009	Chinese	300	312	49	HB	HBsAg (+): 66%; anti-HCV (+): not reported	HBsAg (+): 19.2%; anti-HCV (+): not reported	TaqMan PCR genotyping	P < 0.001	7
Long	China	2009	Chinese	618	712	Unknown	HB	HBsAg (+): 72.8%; anti-HCV (+): 18.4%	HBsAg (+): 71.3%; anti-HCV (+): 18%	TaqMan PCR genotyping	NS	7
Yuan	China	2012	Chinese	254	251	52	PB	HBsAg (+): 80.6%; anti-HCV (+): not reported	HBsAg (+): 77.6%; anti-HCV (+): not reported	PCR experiments	NS	8
Guo	China	2012	Chinese	410	410	52	HB	HBsAg (+): 36.5%; anti-HCV (+): 5.1%	HBsAg (+): 8.6%; anti-HCV (+): 0.9%	Sequenom MassARRAY	NS	7
Wu	China	2014	Chinese	218	277	52	HB	HBsAg (+): 52.3%; anti-HCV (+): 7.4%	HBsAg (+): 7.2%; anti-HCV (+): 1.1%	Sequenom MassARRAY	NS	8

DHPLC, denaturing high performance liquid chromatography; HB, hospital-based; NOS, Newcastle-Ottawa scale; NS, not significant; PB, population-based; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism.

Table 2. Basic Information of the Included Studies for Gastric Cancer.

Author	Country	Year	Ethnicity	Cases	Controls	Age, years	Source of controls	Genotyping Method	Significant test for association	NOS
rs13181										
Huang	Poland	2005	Caucasian	279	381	Unknown	PB	MALDI-TOF/hME multiplex assay	NS	7
Ye	Sweden	2006	Caucasian	126	472	66	PB	PCR-RFLP	NS	8
Lou	China	2006	Chinese	238	200	Unknown	HB	PCR-RFLP	NS	6
Zhou	China	2007	Chinese	253	612	60	PB	PCR-RFLP	NS	7
Ruzzo	Italy	2007	Caucasian	89	94	67	HB	PCR-RFLP	NS	8
Capellá	Spain	2008	Caucasian	245	1058	Unknown	PB	LightCycler™ assay	$P < 0.05$	6
Canbay	Turkey	2010	Caucasian	40	247	60	PB	PCR-RFLP	NS	7
Long	China	2010	Chinese	361	616	Unknown	HB	TaqMan PCR assay	<0.001	6
Palli	Italy	2010	Caucasian	295	546	69	PB	TaqMan PCR assay	NS	8
Chen	China	2011	Chinese	208	339	Unknown	PB	PCR-RFLP	NS	7
Engin	Turkey	2011	Caucasian	106	116	60	HB	PCR-RFLP	NS	6
Jiang	China	2012	Chinese	98	80	Unknown	PB	PCR-RFLP	0.038	6
He	China	2013	Chinese	1125	1196	59	PB	TaqMan PCR assay	NS	8
Guo	China	2014	Chinese	98	80	52	HB	PCR-RFLP	NS	8
Ji	China	2015	Chinese	121	363	51	HB	PCR-RFLP	NS	7
He	China	2018	Chinese	1141	1173	56	PB	TaqMan PCR assay	NS	7
Nissar	India	2018	Indian	180	200	61	HB	PCR-RFLP	NS	8
Balkan	Turkey	2020	Caucasian	40	40	50	HB	LightSNiP typing assay	NS	6
rs1799793										
Ye	Sweden	2006	Caucasian	126	470	66	PB	PCR-SSCP	NS	8
Lou	China	2006	Chinese	238	200	Unknown	HB	PCR-RFLP	$P = 0.041$	6
Zhou	China	2007	Chinese	253	612	60	PB	PCR-RFLP	NS	7
Ruzzo	Italy	2007	Caucasian	89	121	67	HB	PCR-RFLP	NS	8
Capellá	Spain	2008	Caucasian	244	1028	Unknown	PB	LightCycler™ assay	$P < 0.05$	6
Chen	China	2011	Chinese	208	339	Unknown	PB	PCR-RFLP	$P < 0.01$	7
Yuan	China	2011	Chinese	190	180	56	PB	Sequencing	NS	8
Ji	China	2015	Chinese	121	363	51	HB	PCR-RFLP	$P < 0.05$	7

HB, hospital-based; NOS, Newcastle-Ottawa scale; NS, not significant; PB, population-based; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism.

to XPD rs1799793 and HCC risk, the cumulative Z curve crossed the traditional boundary, suggesting that the meta-analysis results were stable (Figure 5B). In addition, the FPRP values were calculated for these polymorphisms. With the assumption of a prior probability of 0.1, the FPRP values were noteworthy for XPD rs1799793 (<0.2) but not XPD rs13181 (>0.2), consistent with the results of TSA analysis.

Publication Bias

Visual evaluation of the funnel plots indicated no publication bias for studies evaluated the association between XPD polymorphisms and risk of HCC and gastric cancer (Supplemental Figures 1 and 2), because there was no significant asymmetry in these plots. Moreover, the P values of Egger test were > 0.05, suggesting the absence of publication bias.

Discussion

DNA repair capacity is critical to the maintenance of genomic stability and has long been suggested as a potential candidate modifying susceptibility to cancer. This meta-analysis was intended to evaluate 2 important polymorphisms of the DNA repair gene XPD, including rs13181 and rs1799793 and their contribution to the risk of HCC and gastric cancer. The main findings were that the variant G allele of XPD rs13181 and the variant T allele of XPD rs1799793 were associated with increased risk of HCC in Chinese populations (rs13181 G, OR = 1.49; rs1799793 T, OR = 1.23).

XPD is a key member of the human TFIIH complex. It is involved in basal transcription and the NER pathway. During NER, XPD participates in the DNA unwinding, which is one of the main NER steps.[2] Genetic defects in the XPD gene can lead to various human diseases including xeroderma pigmentosum, Cockayne syndrome and cancer through alterations of DNA repair capacity.[41] The XPD gene consists of 23 exons and several polymorphisms have been identified. The XPD rs13181 polymorphism (Lys751Gln) is one of the commonly identified genetic variant leading to amino acid substitution. It causes a non-synonymous substitution of lysine by glutamine in codon 751 (exon 23), which results in decreased DNA repair capacity.[23] An early meta-analysis performed by Peng and colleagues suggested that XPD rs13181 was associated with a statistically significant increased HCC risk.[42] Conversely,

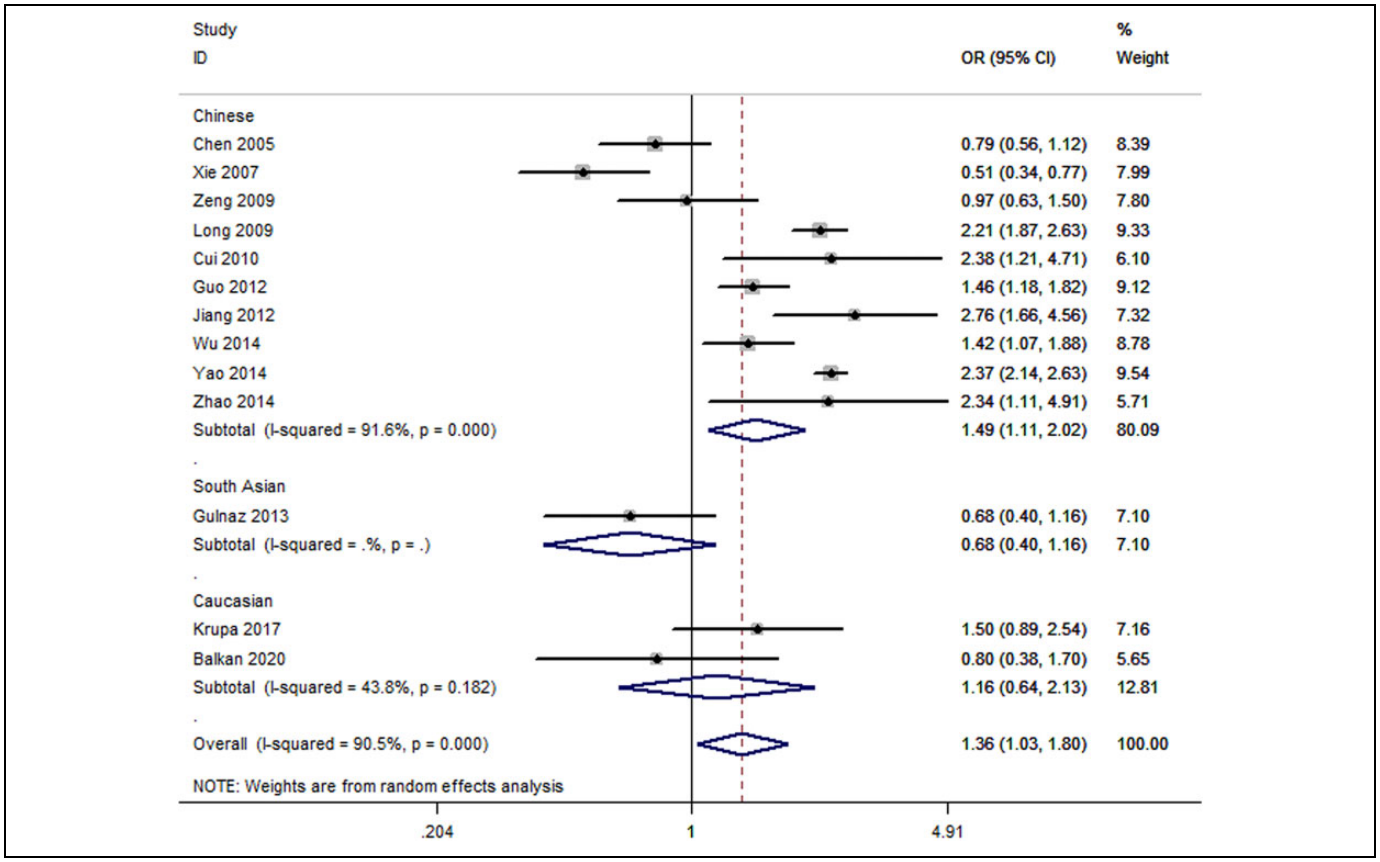

Figure 2. Forest plot of HCC risk related to the G allele of XPD rs13181 polymorphism.

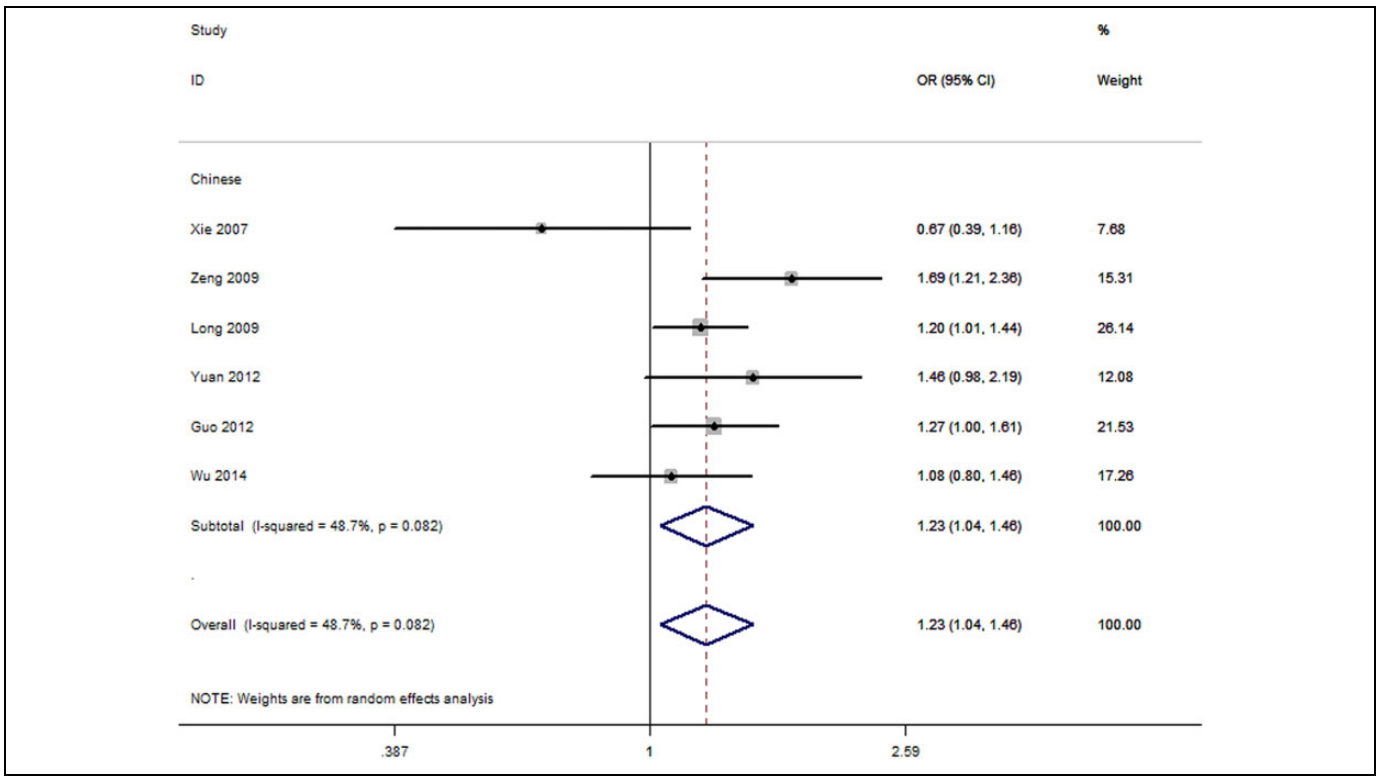

Figure 3. Forest plot of HCC risk related to the T allele of XPD rs1799793 polymorphism.

Table 3. The Results for the Meta-Analyses Evaluating HCC and Gastric Carcinoma.

			Test of association		Test of heterogeneity	
Polymorphism	Population	Number of studies	OR (95% CI)	P value	I^2	P value
HCC						
rs13181 G vs T	Overall	13	1.36 (1.03-1.80)	0.028	90.5	0.000
	Chinese	10	1.49 (1.11-2.02)	0.009	91.6	0.000
	Caucasian	2	1.17 (0.64-2.13)	0.619	43.8	0.182
	Population-based	4	0.92 (0.47-1.80)	0.815	89.2	0.000
	Hospital-based	9	1.66 (1.32-2.09)	0.000	81.4	0.000
	Sample size (≥500)	6	1.24 (0.83-1.86)	0.293	95.0	0.000
	Sample size (<500)	7	1.50 (1.04-2.18)	0.030	69.9	0.003
rs1799793 T vs C	Overall	6	1.23 (1.04-1.46)	0.017	48.7	0.082
	Chinese	6	1.23 (1.04-1.46)	0.017	48.7	0.082
	Population-based	2	1.01 (0.47-2.18)	0.973	80.3	0.024
	Hospital-based	4	1.26 (1.09-1.47)	0.002	29.1	0.237
	Sample size (≥500)	5	1.27 (1.03-1.55)	0.023	54.9	0.065
	Sample size (<500)	1	1.08 (0.80-1.46)	0.608	NA	NA
Gastric cancer						
rs13181 G vs T	Overall	18	1.10 (0.92-1.31)	0.298	82.3	0.000
	Chinese	9	1.28 (0.92-1.79)	0.150	89.2	0.000
	Caucasian	8	1.00 (0.90-1.10)	0.933	0	0.454
	Indian	1	0.89 (0.65-1.23)	0.481	NA	NA
	Population-based	10	1.03 (0.92-1.14)	0.648	30.9	0.161
	Hospital-based	8	1.11 (0.72-1.69)	0.639	89.0	0.000
	Sample size (≥500)	9	1.10 (0.86-1.40)	0.452	88.7	0.000
	Sample size (<500)	9	1.10 (0.84-1.45)	0.494	67.4	0.002
rs1799793 T vs C	Overall	8	1.31 (0.98-1.74)	0.068	83.8	0.000
	Chinese	5	1.41 (0.91-2.18)	0.123	85.8	0.000
	Caucasian	3	1.12 (0.88-1.42)	0.367	53.1	0.119
	Population-based	5	1.13 (0.76-1.69)	0.541	88.6	0.000
	Hospital-based	3	1.66 (1.33-2.06)	0.000	0	0.697
	Sample size (≥500)	4	1.24 (0.78-1.95)	0.361	90.3	0.000
	Sample size (<500)	4	1.39 (0.95-2.02)	0.091	73.1	0.011

CI, confidence interval; HCC, hepatocellular carcinoma; OR, odds ratio.

Wang *et al* found no significant association between XPD rs13181 and risk for HCC.[43] These early meta-analyses were done before 2015 and were limited by a small sample size. For example, the Wang *et al*'s meta-analysis only involved 4 studies.[43] A lack of statistical power could affect pooled analyses and influence the results.

Compared with them, this meta-analysis increased the statistical power and performed comprehensive subgroup analyses. Thirteen studies were included in this meta-analysis for evaluating XPD rs13181 and HCC risk. We concluded that the variant G allele of XPD rs13181 was associated with increased HCC risk in the Chinese ethnic group but not in Caucasians. It is not surprising that XPD rs13181 did not have associations with HCC in all ethnic groups. The genotype distribution of XPD rs13181 changes by geographical distance. The variant G allele frequency in Chinese was lower than that of Caucasians (14.8% vs 31.9%). Another reason is that, for Chinese, chronic infection with hepatitis B virus is the predominant risk factor of HCC, whereas hepatitis C virus infection is the most common infection that causes chronic liver disease including HCC in Caucasians. Low statistical power may also influence the results of subgroup analysis for Caucasians, because Caucasian studies used small sample sizes (105 cases and 90 control subjects). In this study, the XPD rs13181 association was also evaluated in different subgroup analyses considering covariates such as source of the control group. Hospital-based studies showed significant association between XPD rs13181 and HCC. With respect to XPD rs1799793, this meta-analysis found that it was associated with increased HCC risk in Chinese, which was consistent with an early meta-analysis by Yang *et al*[44] but contrasted with the results of Peng *et al*'s meta-analysis.[42]

Gastric cancer is the third most common cancer worldwide. The established risk factors for gastric cancer included family history, *Helicobacter pylori* (H. pylori) infection, diet and smoking, but they were not enough to explain the risk of developing gastric cancer. For example, gastric cancer occurs only in a minority of H. pylori-infected subjects although high rates of H. pylori infection were reported in the general population.[45] Genetic variations in the DNA repair gene such as the XPD rs13181 and rs1799793 polymorphisms were postulated to have an impact on the risk of gastric cancer. In a hospital-

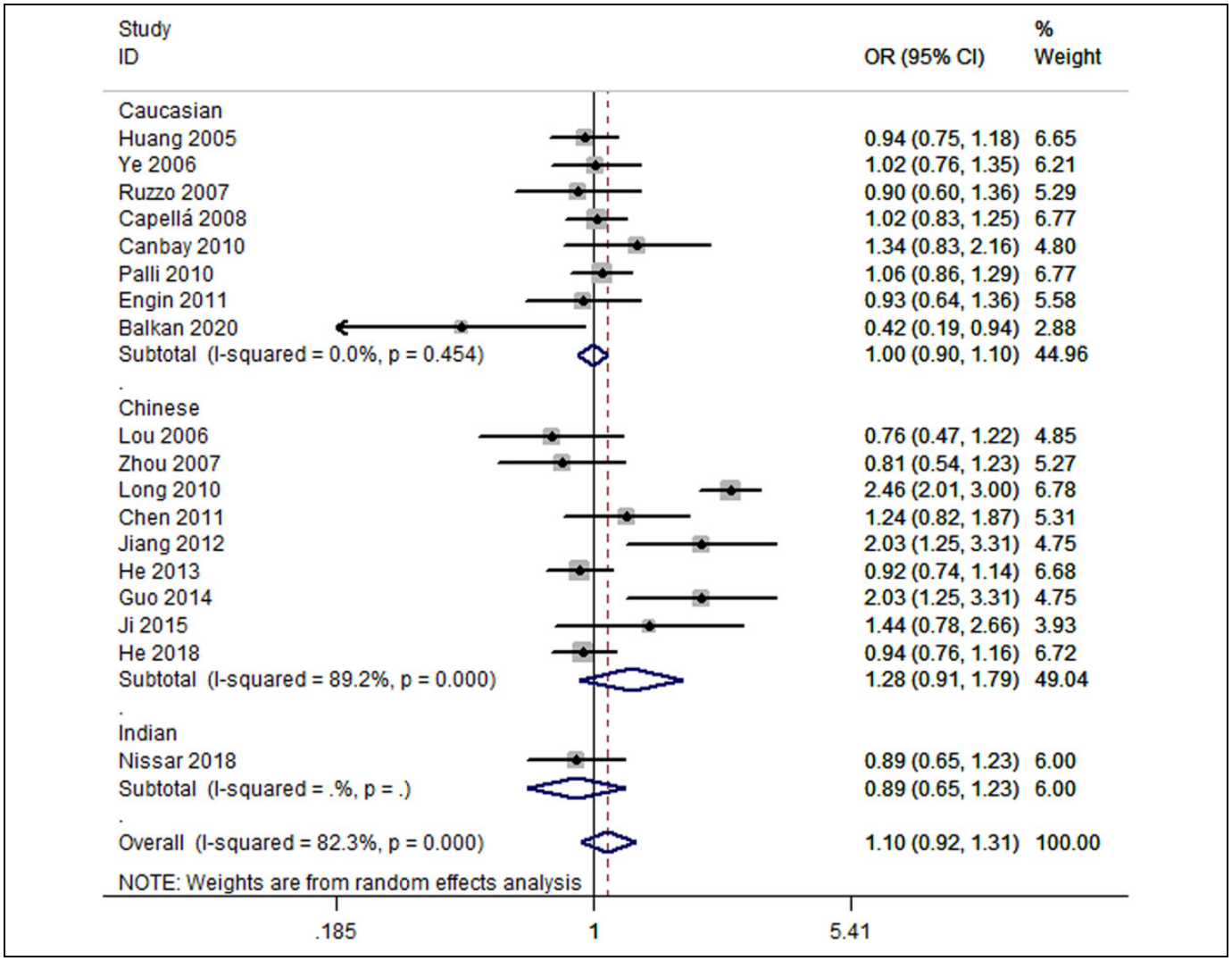

Figure 4. Forest plot showing no association between the XPD rs13181 G allele and gastric cancer risk.

based case-control study with 361 cases and 616 control subjects, Long *et al* observed that the XPD rs13181 G allele was associated with increased risk of gastric cancer in a southern Chinese population.[31] Jiang *et al* also reported a positive association between the XPD rs13181 polymorphism and gastric cancer.[16] With respect to the XPD rs1799793 polymorphism, the study by Lou *et al* showed increased gastric cancer risk associated with individuals who carried at least 1 variant T allele.[26] Ji *et al* found the T allele contributed to gastric carcinogenesis.[38] However, other Chinese studies reported no association between the XPD rs13181 and rs1799793 polymorphisms and gastric cancer, including Zhou *et al*, Chen *et al*, and He *et al*.[27,33,36] In addition, most Caucasian studies did not indicate any relationship between these XPD polymorphisms and gastric cancer. Thus, published studies yielded contradictory results. Several meta-analyses were performed to evaluate the published evidence in an early period. In 2012, Xue *et al*'s meta-analysis noted associations between the XPD rs13181 and rs1799793 polymorphisms and gastric cancer only in Chinese but not in Caucasians.[46] The results of Yin *et al*'s meta-analysis suggested a role of XPD rs1799793 in gastric cancer risk but did not find significant associations for XPD rs13181.[47] In line with Yin *et al*'s results, Du *et al* suggested a null effect of XPD rs13181 in the pathogenesis of gastric cancer.[48] Compared with these meta-analyses, we included 18 studies for XPD rs13181 and 8 studies for XPD rs1799793. It is worth mentioning that we included new evidence such as articles published in 2020. Our results showed no associations between the 2 XPD polymorphisms and gastric cancer in the overall analysis, Chinese and Caucasians.

Some limitations of this meta-analysis need to be addressed. Firstly, we only calculated crude ORs and 95% CIs. Although some selected publications reported adjusted ORs, there was considerable heterogeneity in the methods they used. So we did not combine these adjusted ORs in this meta-analysis. Secondly, the control group of some studies did not include healthy individuals but hepatitis patients. Thirdly, we did not perform subgroup analysis according to virus status, because only a few

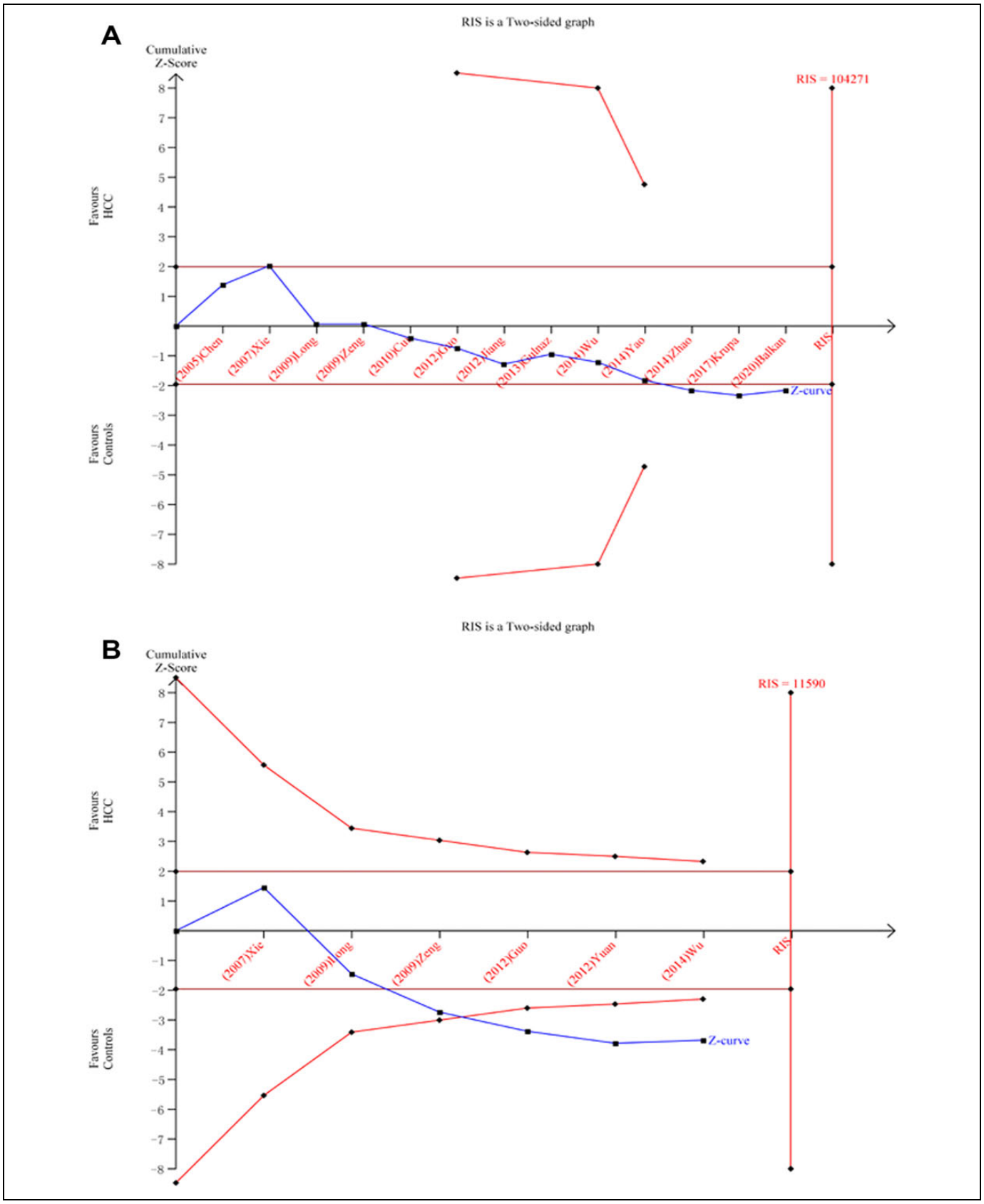

Figure 5. Trial sequential analyses of the association of the XPD rs13181 and rs1799793 polymorphisms with HCC risk. (A) XPD rs13181; (B) XPD rs1799793.

studies provided detailed information on HBV and HCV infection. Fourthly, significant between-study heterogeneity was observed. Meta-regression analysis did not identify the exact contributor to heterogeneity, but the amount of heterogeneity was reduced in subgroup analysis. Future studies may needed to pay more attention to study design to decrease the impact of potential covariates on effect sizes.

Conclusions

In summary, this is the most up-to-date meta-analysis that evaluated the association between the XPD rs13181 and rs1799793 polymorphisms and risk for HCC and gastric cancer. These polymorphisms were associated with increased risk of HCC in the overall analysis and Chinese. No association between them and gastric cancer was identified.

Authors' Note

The need for ethics approval by an institutional board review was waived as this article does not directly involve human participants. QZ, YF, and KL contributed conception and design of the work; QZ and YF performed database search and data extraction. QZ, YF, LW, and YD conducted the statistical analyses; QZ wrote the draft of the manuscript. LW and JC made critical revisions to the manuscript. JC and KL revised the final manuscript. All authors read and approved the submitted version.

Ethical Statement

Ethical permission is not necessary, because this is a meta-analysis Consent is not necessary, because this is a meta-analysis

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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