XPD Lys^{751}Gln and Asp^{312}Asn polymorphisms and hepatocellular carcinoma susceptibility: A meta-analysis of 11 case-control studies in an Asian population

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Received August 1, 2014; Accepted March 20, 2015

DOI: 10.3892/etm.2015.2421

Abstract. This meta-analysis was performed to evaluate the association between xeroderma pigmentosum complementary group D (XPD) Lys^{751}Gln and Asp^{312}Asn polymorphisms and susceptibility to hepatocellular carcinoma (HCC). PubMed, Embase, Google Scholar and the Chinese National Knowledge Infrastructure and the Chinese Biomedicine databases were systematically searched to identify relevant studies published up to June 1, 2014. Statistical analyses were performed using Stata version 12.0 software. A total of 11 case-control studies, comprising 2,852 cases and 2,936 controls, were included. The results of the meta-analysis revealed that a significant association between the risk of HCC and variant genotypes of the XPD Lys^{751}Gln and Asp^{312}Asn polymorphisms was evident in the homozygote comparison [Gln/Gln versus Lys/Lys: Odds ratio (OR), 1.831; 95% confidence interval (CI), 1.001-3.349], heterozygote comparison (Lys/Gln versus Lys/Lys: OR, 1.486; 95% CI, 1.044-2.114), dominant model (Gln/Gln + Lys/Gln versus Lys/Lys: OR, 1.540; 95% CI, 1.054-2.249) and allelic contrast (Gln-allele versus Lys-allele: OR, 1.453; 95% CI, 1.032-2.046) for the Lys^{751}Gln polymorphism and the homozygote comparison for the Asp^{312}Asn polymorphism (Asn/Asn versus Asp/Asp: OR, 1.352; 95% CI, 1.010-1.808). By contrast, no significant association was observed in the recessive model for the Lys^{751}Gln polymorphism (Gln/Gln versus Lys/Gln + Lys/Lys: OR, 1.603; 95% CI, 0.924-2.779), or for the heterozygote comparison (Asn/Asp versus Asp/Asp: OR, 1.229; 95% CI, 0.857-1.762), dominant model (Asn/Asn + Asp/Asn versus Asp/Asp: OR, 1.249; 95% CI, 0.910-1.715), recessive model (Asn/Asn versus Asp/Asn + Asp/Asp: OR, 1.250; 95% CI, 0.940-1.663) or allelic contrast (Asn-allele versus Asp-allele: OR, 1.226; 95% CI, 0.965-1.557) for the Asp^{312}Asn polymorphism. The present meta-analysis has indicated that the XPD Lys^{751}Gln polymorphism could be a potential biomarker of HCC susceptibility and that the XPD Lys^{751}Gln and Asp^{312}Asn polymorphisms could be risk factors for HCC susceptibility in an Asian population; however, further large-scale and well-designed studies are required to reach a more precise and comprehensive conclusion.

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Key words: xeroderma pigmentosum complementary group D polymorphisms, hepatocellular carcinoma, Lys^{751}Gln, Asp^{312}Asn, meta-analysis

Introduction

Hepatocellular carcinoma (HCC), as the most common primary cancer of the liver, contributes significantly to rates of cancer-related morbidity and mortality worldwide. The annual estimated incidence of new HCC cases is >0.5 million (1), and the highest incidence rates of HCC (>20/100,000) have been reported in East and Southeast Asian countries. In total, >80% of HCC cases occur in developing countries (2). Thus, the diagnosis, treatment and prevention of HCC represent significant challenges worldwide. It is well established that the development of HCC is a complex biological process, and the precise mechanism underlying the occurrence of HCC is still not completely understood. Multiple risk factors contribute to HCC susceptibility, such as chronic hepatitis B virus (HBV) infection, aflatoxin B1 (AFB1) intake, smoking and an excessive consumption of alcohol (3). In addition to these exogenous factors, genetic polymorphisms play an important role in HCC susceptibility.

Within recent decades, several studies have evaluated and highlighted the association between DNA repair genes and hepatocellular neoplasm susceptibility. Nucleotide excision repair (NER) has been proposed to be the most versatile DNA repair mechanism. Xeroderma pigmentosum complementary group D (XPD), also known as excision repair cross-complementing group 2 (ERCC2), is a gene located at

chromosome 19q13.3 and encodes a type of NER enzyme (4). Several important single nucleotide polymorphisms have been identified in the XPD locus, with high variant frequencies in exon 10 (rs1799793, codon 312 G→A, Asp→Asn) and exon 23 (rs1052559, codon 751 A→C, Lys→Gln) (5). These two polymorphisms have been largely investigated in genetic epidemiological studies, and individuals with these polymorphisms exhibit a higher risk of developing different types of cancer (6-8).

To date, molecular epidemiological studies have investigated the effect of these two polymorphisms on the risk of HCC (9-18); however, the results obtained in these studies have been inconsistent, particularly in an Asian population. In addition, the majority of studies have solely examined the effect of XPD polymorphisms, while only a few studies have explored the interaction of XPD with HBV and other environmental factors. Furthermore, the small sample sizes and missing genotypic data have potentially contributed to false-positive or -negative findings. A meta-analysis is a useful method to overcome the disadvantages of individual studies, thereby increasing the statistical power and precision of the effect estimates (19). The aim of the present study, therefore, was to perform a meta-analysis of all eligible studies to evaluate the association between Lys^{751}Gln and Asp^{312}Asn polymorphisms and hepatocellular neoplasm susceptibility, and to further explore the interaction between XPD polymorphisms and HBV.

Materials and methods

Search strategy. All case-control studies of XPD polymorphisms and HCC risk published in either the English or Chinese language up to June 1, 2014 were identified by performing systematic searches in PubMed, Embase, Google Scholar, the Chinese National Knowledge Infrastructure (CNKI) and the Chinese Biomedicine databases. The search terms used included: ('XPD' OR 'ERCC2' OR 'DNA repair gene' OR 'xeroderma pigmentosum group D') AND ('polymorphism' OR 'variation' OR 'variant' OR 'genotype' OR 'genetic') AND ('hepatocellular carcinoma' OR 'HCC' OR 'liver cancer' OR 'liver tumour' OR 'liver neoplasms' OR 'hepatic tumour'). The references of each identified article were also manually searched to identify additional relevant publications. If more than one article was published using the same case series, then only the study with the largest sample size was included.

Inclusion criteria. A study was accepted for inclusion in the meta-analysis if it met the following criteria: i) It assessed the correlation between HCC and the XPD Lys^{751}Gln or Asp^{312}Asn polymorphism in an Asian population; ii) it employed a case-control design; iii) it provided sufficient data regarding the genotypes (Gln/Gln, Lys/Lys, Gln /Lys, Asn/Asn, Asp/Asp and Asn/Asp) to estimate an odds ratio (OR) with a 95% confidence interval (95% CI); and iv) it clearly described the method used to perform the HCC diagnoses and the sources of the cases and controls. When multiple studies containing duplicate or overlapping data were published by the same authors, the most recent study with the largest participant population was selected.

Data extraction. Literature searches and the identification of eligible articles based on the inclusion criteria were conducted in duplicate by two investigators using a standard protocol and data-collection form (20). The original extracted data were confirmed by another two investigators, and any disagreement was resolved by discussion among the four investigators. The following data were independently extracted: Surname of the first author, ethnicity or country, source of controls, genotyping methods, frequency and genotypes of cases and controls, and the Hardy-Weinberg equilibrium (HWE) of the controls.

Statistical analysis. The allelic frequency was initially calculated, and the observed genotype frequencies of the XPD Lys^{751}Gln and Asp^{312}Asn polymorphisms in the control group were assessed for HWE using the χ^2 test in each study. The strength of the association between the XPD Lys^{751}Gln and Asp^{312}Asn polymorphisms and HCC risk was assessed by calculating ORs with 95% CIs. The overall pooled analysis was performed for homozygote comparisons (Gln/Gln versus Lys/Lys and Asn/Asn versus Asp/Asp), heterozygote comparisons (Lys/Gln versus Lys/Lys and Asn/Asp versus Asp/Asp), the dominant model (Gln/Gln + Lys/Gln versus Lys/Lys and Asn/Asn + Asp/Asn versus Asp/Asp), the recessive model (Gln/Gln versus Lys/Gln + Lys/Lys and Asn/Asn versus Asp/Asn + Asp/Asp) and allelic contrasts (Gln-allele versus Lys-allele and Asn-allele versus Asp-allele). The significance of the pooled ORs was determined using the Z-test, and $P<0.05$ was considered to indicate statistical significance. The heterogeneity of the studies was assessed using Cochran's Q-test and the I^2 test (21). If $P>0.1$ or $<50\%$ the study was considered to lack heterogeneity, in which case the pooled OR was calculated for each study using the fixed-effects model. Otherwise, the random-effects model was used (22). To assess the stability of the results, a sensitivity analysis, in which each study in the meta-analysis was systematically deleted to establish the impact of each individual dataset on the overall pooled OR, was conducted. Furthermore, the potential publication bias was evaluated through visual inspection of the symmetry of the Begg's funnel plots. The statistical analysis of the publication bias was conducted using Egger's test. The meta-analysis was performed using Stata software (version 12.0; StataCorp LP, College Station, TX, USA), and all the P-values were two-sided.

Results

Characteristics of the studies. A flow chart of the exclusion/inclusion of the studies in the meta-analysis is presented in Fig. 1. A total of 39 potentially relevant publications up to June 1, 2014 were systematically identified using the PubMed, Embase, Google Scholar and CNKI databases. Of these publications, 23 studies (59.0%) were excluded due to a failure to satisfy the inclusion criteria or to provide sufficient information to determine whether the criteria were satisfied. An additional four publications were excluded for one or more of the following reasons: i) They did not examine the XPD Lys^{751}Gln or Asp^{312}Asn polymorphisms; ii) they did not provide allele frequencies, which were required for OR calculation; iii) they deviated from the HWE; iv) they included a family-based control or lacked a control group. Review articles

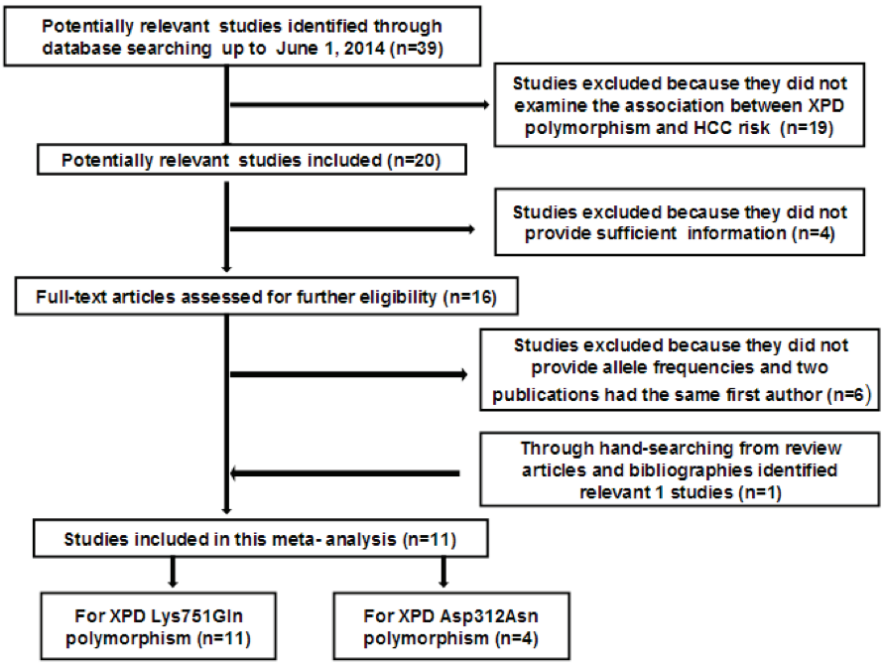

Figure 1. Studies identified with criteria for inclusion and exclusion. XPD, xeroderma pigmentosum complementary group D; HCC, hepatocellular carcinoma.

and bibliographies were manually searched to identify relevant studies. A total of 11 studies (9-18; Yu, unpublished data) were ultimately included in this meta-analysis based on the search strategy and inclusion criteria. Four of the 11 studies examined both the XPD Lys^{751}Gln and Asp^{312}Asn polymorphisms. In total, 11 studies (2,852 HCC cases and 2,936 controls) for the XPD Lys^{751}Gln polymorphism (9-18; Yu, unpublished data) and four studies (1,753 HCC cases and 1,914 controls) for the XPD Asp^{312}Asn polymorphism (11,13,15,17) were retrieved in the final meta-analysis. The characteristics of the included studies are listed in Tables I and II.

Heterogeneity and sensitivity analyses. The statistical heterogeneity of the XPD Lys^{751}Gln and Asp^{312}Asn allelic contrast, homozygote and heterozygote comparisons and dominant and recessive genetic models were analysed for all studies and are shown in Table III. With regard to the heterogeneity of the XPD Lys^{751}Gln and Asp^{312}Asn polymorphisms, no heterogeneity was found among the studies for Asn/Asn versus Asp/Asp and the recessive genetic model comparison (I^2=0%); therefore, fixed-effect models were used to analyse the OR. A random-effect model was used in the pooled analysis of the other studies. Following the test for heterogeneity, a sensitivity analysis was performed to evaluate the stability of the results. The effect of each study on the pooled OR was confirmed by repeating the meta-analysis, while systematically omitting each study, one at a time. The results were not materially altered and confirmed the non-significant association between the XPD Lys^{751}Gln and Asp^{312}Asn polymorphisms and HCC risk.

Quantitative synthesis. The main results of this pooled analysis are listed in Table III. The association between XPD polymorphism and HCC risk is shown in the form of forest plots in Figs. 2 and 3. For the overall analysis, a significant association between the risk of HCC and the variant genotypes of the XPD Lys^{751}Gln polymorphism was found in the homozygote comparison (Gln/Gln versus Lys/Lys: OR, 1.831; 95% CI, 1.001-3.349), heterozygote comparison (Lys/Gln versus Lys/Lys: OR, 1.486; 95% CI, 1.044-2.114), dominant model (Gln/Gln + Lys/Gln versus Lys/Lys: OR, 1.540; 95% CI, 1.054-2.249) and allelic contrast (Gln-allele versus Lys-allele: OR, 1.453; 95% CI, 1.032-2.046). By contrast, no significant association was found in the recessive model (Gln/Gln versus Lys/Gln + Lys/Lys: OR, 1.603; 95% CI, 0.924-2.779).

For the overall analysis, no significant association between the risk of HCC and the variant genotypes of the XPD Asp^{312}Asn polymorphism was found in the heterozygote comparison (Asn/Asp versus Asp/Asp: OR, 1.229; 95% CI, 0.857-1.762), dominant model (Asn/Asn + Asp/Asn versus Asp/Asp: OR, 1.249; 95% CI, 0.910-1.715), recessive model (Asn/Asn versus Asp/Asn + Asp/Asp: OR, 1.250; 95% CI, 0.940-1.663) or allelic contrast (Asn-allele versus Asp-allele: OR, 1.226; 95% CI, 0.965-1.557). By contrast, a significant association was found in the homozygote comparison (Asn/Asn versus Asp/Asp: OR, 1.352; 95% CI, 1.010-1.808).

Publication bias. Begg's funnel plots and Egger's test were used to assess the publication bias for the reported comparisons of the XPD Lys^{751}Gln and Asp^{312}Asn genotypes and HCC. As shown in Fig. 4, no obvious asymmetry in the comparison models was revealed for the XPD Lys^{751}Gln and Asp^{312}Asn polymorphisms by Begg's funnel plot. In addition, Egger's test was used to provide statistical evidence of the funnel plot symmetry. These results similarly did not show any evidence of publication bias (t=-0.38 and P=0.715 for Lys/Gln versus Lys/Lys; t=-0.13 and P=0.897 for the dominant model of XPD Lys^{751}Gln; t=-1.53 and P=0.170 for the recessive model of XPD Lys^{751}Gln; t=-0.59 and P=0.569 for Gln-allele versus Lys-allele; t=-1.59 and P=0.358 for Asn/Asn versus Asp/Asp;

Table I. Baseline characteristics and methodological quality of the included studies investigating Lys^{751}Gln polymorphism.

First author, year (ref.)	Ethnicity (country)	Source of controls	Genotyping method	Cases/controls, n/n	No. of cases			No. of controls			P-HWE
					Lys/Lys	Lys/Glyn	Gln/Gln	Lys/Lys	Lys/Glyn	Gln/Gln	
Xu, 2004 (6)	Asian (China)	PB	PCR-RFLP	71/136	57	13	1	125	10	1	0.1348843
Chen, 2005 (7)	Asian (China)	HB	PCR-RFLP	570/381	496	72	2	322	55	4	0.3457913
Xie, 2007 (8)	Asian (China)	HB	PCR-RFLP	429/480	393	36	0	404	76	0	0.0596231
Su, 2008 (9)	Asian (China)	HB	PCR-RFLP	100/111	76	23	1	98	11	2	0.0244717
Zeng, 2009 (10)	Asian (China)	HB	TaqMan-PCR	300/312	263	32	5	270	39	3	0.2438713
Cui, 2010 (11)	Asian (China)	HB	PCR-RFLP	94/111	69	24	1	97	14	0	0.4782435
Long, 2009 (12)	Asian (China)	HB	TaqMan-PCR	618/712	272	222	124	464	187	61	1.361×10^{-9}
Yu, 2012[a]	Asian (China)	PB	PCR-RFLP	76/80	32	26	18	54	20	6	0.0503993
Hu, 2012 (13)	Asian (China)	PB	PCR-RFLP	124/129	98	26	0	119	10	0	0.6469693
Guo, 2012 (14)	Asian (China)	HB	PCR-CTPP	410/410	190	183	37	233	159	18	0.1576467
Gulnaz, 2013 (15)	Asian (Pakistan)	HB	PCR-RFLP	60/74	25	29	6	30	29	15	0.1161690

[a]Unpublished data. PB, population-based; HB, hospital-based; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; CTPP, confronting two-pair primers; HWE, Hardy-Weinberg equilibrium.

Table II. Baseline characteristics and methodological quality of the included studies investigating XPD Asp^{312}Asn polymorphism.

First author, year (ref.)	Ethnicity (country)	Source of controls	Genotyping method	Cases/controls, n/n	No. of cases			No. of controls			P-HWE
					Asp/Asp	Asp/Asn	Asn/Asn	Asp/Asp	Asp/Asn	Asn/Asn	
Xie, 2007 (8)	Asian (China)	HB	PCR-RFLP	425/480	404	21	0	445	35	0	0.4071126
Zeng, 2009 (10)	Asian (China)	HB	PCR-RFLP	300/312	204	92	4	252	54	6	0.1330516
Long, 2009 (12)	Asian (China)	HB	TaqMan-PCR	618/712	364	190	64	453	200	59	3.851×10^{-7}
Guo, 2012 (14)	Asian (China)	HB	PCR-CTPP	410/410	260	107	43	282	96	32	2.548×10^{-7}

HB, hospital-based; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; CTPP, confronting two-pair primers; HWE, Hardy-Weinberg equilibrium.

Table III. Heterogeneity and sensitivity analyses and the quantitative synthesis of this meta-analysis.

A, XPD Lys[751]Gln genetic comparison

Comparison	OR (95% CI)	Z (P-value)	Heterogeneity P-value	Heterogeneity I^2	Analysis model
Gln-allele vs. Lys-allele	1.453 (1.032-2.046)	2.14 (0.033)	<0.001	0.879	Random
Gln/Gln vs. Lys/Lys	1.831 (1.001-3.349)	1.96 (0.050)	0.007	0.621	Random
Lys/Gln vs. Lys/Lys	1.486 (1.044-2.114)	2.20 (0.028)	<0.001	0.824	Random
Gln/Gln + Lys/Gln vs. Lys/Lys (dominant)	1.540 (1.054-2.249)	2.23 (0.026)	<0.001	0.864	Random
Gln/Gln vs. Lys/Gln + Lys/Lys (recessive)	1.603 (0.924-2.779)	1.68 (0.093)	0.018	0.568	Random

B, XPD Asp312Asn genetic comparison

Comparison	OR (95% CI)	Z (P-value)	Heterogeneity P-value	Heterogeneity I^2	Analysis model
Asn-allele vs. Asp-allele	1.226 (0.965-1.557)	1.67 (0.095)	0.040	0.639	Random
Asn/Asn vs. Asp/Asp	1.352 (1.010-1.808)	2.03 (0.042)	0.716	<0.001	Fixed
Asn/Asp vs. Asp/Asp	1.229 (0.857-1.762)	1.12 (0.262)	0.006	0.757	Random
Asn/Asn + Asp/Asn vs. Asp/Asp (dominant)	1.249 (0.910-1.715)	1.37 (0.169)	0.013	0.723	Random
Asn/Asn vs. Asp/Asn + Asp/Asp (recessive)	1.250 (0.940-1.663)	1.54 (0.125)	0.515	<0.001	Fixed

XPD, xeroderma pigmentosum complementary group D; OR, odds ratio; CI, confidence interval.

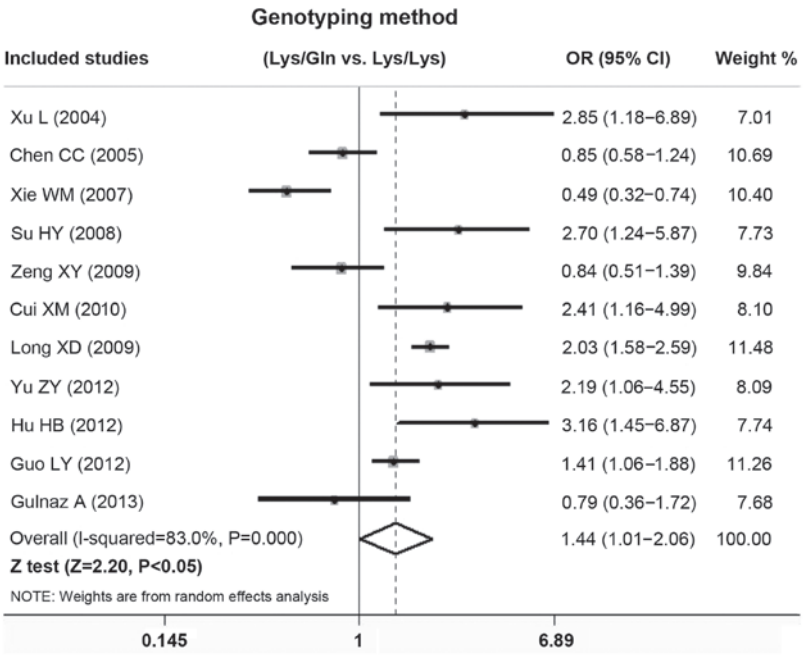

Figure 2. Forest plot of hepatocellular carcinoma risk associated with xeroderma pigmentosum complementary group D Lys[751]Gln polymorphism under the heterozygote comparison (Lys/Gln versus Lys/Lys). The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95% CI. OR, odds ratio; CI, confidence interval.

t=-0.27 and P=0.813 for Asn/Asp versus Asp/Asp; t=-0.35 and P=0.761 for the dominant model of XPD Asp[312]Asn; t=-0.89 and P=0.538 for the recessive model of Lys[751]Gln; t=-0.44 and P=0.700 for Asn-allele versus Asp-allele).

Gene-HBV interaction. In this meta-analysis, four of the studies (9,11,12,15) analysed the gene-HBV interaction. Subgroup analyses were performed based on whether or not the patients had chronic HBV infection, The main results of this

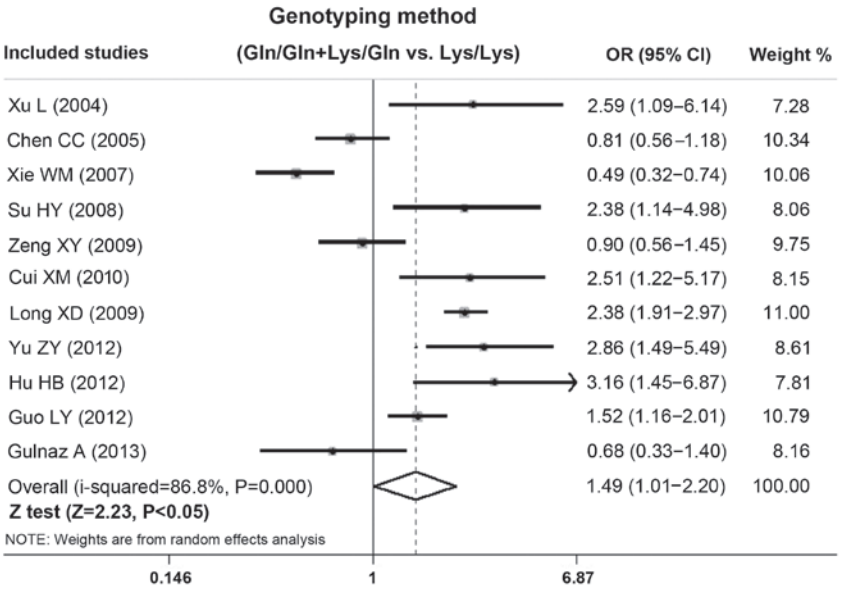

Figure 3. Forest plot of hepatocellular carcinoma risk associated with xeroderma pigmentosum complementary group D Lys[751]Gln polymorphism under the dominant model (Gln/Gln + Lys/Gln versus Lys/Lys) for different types of HCC. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95% CI. OR, odds ratio; CI, confidence interval.

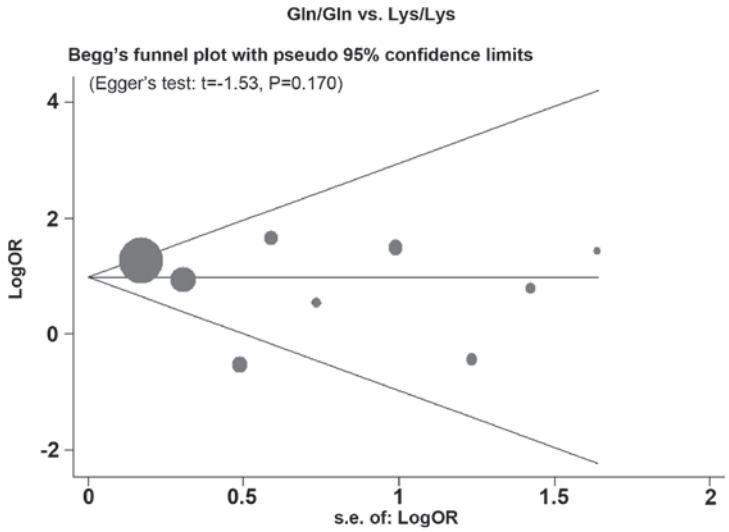

Figure 4. Begg's funnel plot for publication bias test (Gln/Gln versus Lys/Lys). Each point represents in independent study for the indicated association. The horizontal line represents the mean effect size. SE, standard error; OR, odds ratio.

pooled analysis are shown in Table IV and Figs. 5 and 6, and the associations between XPD Lys[751]Gln polymorphism/HBV status and HCC risk are presented in the form of forest plots. No significant associations were found in the HBV^+ and HBV^- subgroups.

Discussion

Worldwide statistics indicate that liver cancer is notably more common among men compared with women. In men, it is the second leading cause of cancer death worldwide and in less developed countries. An estimated 782,500 new liver cancer cases and 745,500 deaths occurred worldwide during 2012, with China alone accounting for ~50% of cases (23).

HCC is the most frequently occurring primary cancer of the liver and the fifth most common solid tumour worldwide. Between 500,000 and 1,000,000 new cases of HCC are believed to occur each year, and HCC is estimated to cause 600,000 mortalities globally each year (1). One characteristic of HCC is the dysregulation of cell growth. HCC has a complex, multistep and heterogeneous malignant tumourigenesis. The pathogenesis of HCC involves a host of genetic and environmental factors and the modulation of molecular signalling pathways that have been implicated in the malignant transformation of hepatocytes and tumour progression (24).

XPD is a DNA repair gene that is also known as ERCC2 (25). XPD plays a key role in NER, a process that is crucial in the elimination of specific DNA cross-links, ultraviolet photo-lesions and bulky chemical adducts (26,27). XPD is a DNA-dependent ATPase/helicase that is associated with the transcription factor IIH complex and acts to perform

Table IV. Quantitative synthesis of subgroup analyses concerning gene-HBV interaction for the XPD Lys^{751}Gln polymorphism.

Subgroup	Comparison	Studies (n)	OR (95% CI)
Total	Gln/Gln + Lys/Gln vs. Lys/Lys (dominant)	11	1.540 (1.054-2.249)
HBV^{+}	Gln/Gln + Lys/Gln vs. Lys/Lys (dominant)	4	1.549 (0.527-4.554)
HBV^{-}	Gln/Gln + Lys/Gln vs. Lys/Lys (dominant)	4	1.058 (0.457-2.432)

HBV, hepatitis B virus; XPD, xeroderma pigmentosum complementary group D; OR, odds ratio; CI, confidence interval.

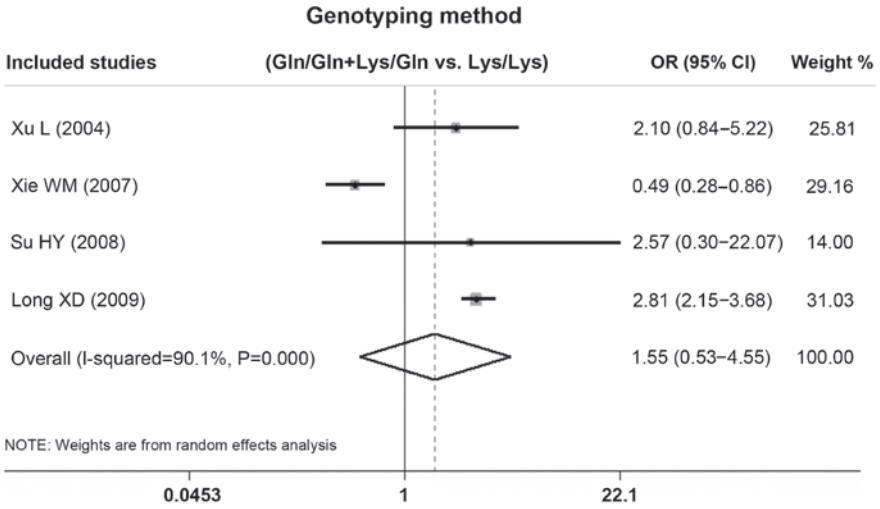

Figure 5. Forest plot of hepatocellular carcinoma risk associated with the xeroderma pigmentosum complementary group D Lys^{751}Gln polymorphism-positive hepatitis B virus infection interaction in the dominant model (Gln/Gln + Lys/Gln vs. Lys/Lys). The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95% CI. OR, odds ratio; CI, confidence interval.

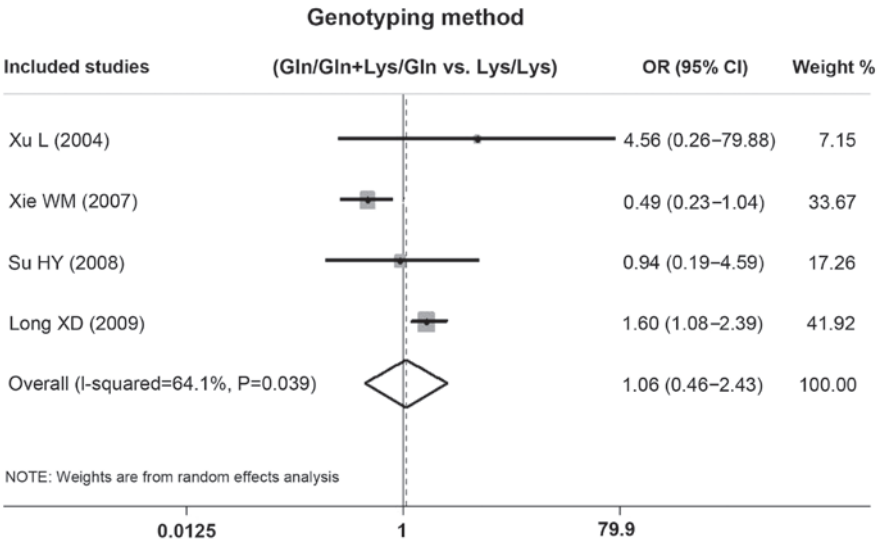

Figure 6. Forest plot of hepatocellular carcinoma risk associated with the xeroderma pigmentosum complementary group D Lys^{751}Gln polymorphism-negative hepatitis B virus infection interaction in the dominant model (Gln/Gln + Lys/Gln vs. Lys/Lys). The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95% CI. OR, odds ratio; CI, confidence interval.

a pivotal function in the NER pathway. XPD is involved in the opening of the DNA duplex, which is necessary for the excision of the fragment of DNA containing the damaged base (28,29).

Numerous meta-analyses have been performed to investigate the association between XPD polymorphism and the risk of different types of cancer, e.g., prostate (30-32), lung (33-35), gastric (8,36), breast (7,37,38), head and neck (39,40) and

oesophageal (41,42). In addition, several studies investigating XPD polymorphisms and HCC susceptibility have been reported. Due to differences in district, ethnicity and genotyping method, as well as an insufficient sample size, however, the association between XPD polymorphism and HCC risk remains conflicting and contradictory. Furthermore, few meta-analyses have investigated the association between the XPD Lys^{751}Gln and Asp^{312}Asn polymorphisms and HCC risk, indicating the necessity for a meta-analysis to provide a quantitative approach for combining different results. To derive a more precise estimation of the association, we performed a meta-analysis of 11 studies, including 2,852 cases and 2,936 controls.

To the best of our knowledge, this study has been the first meta-analysis to investigate the association between the Lys^{751}Gln and Asp^{312}Asn polymorphisms and HCC risk among Asians. The meta-analysis included 2,852 cases and 2,936 controls from 11 case-control studies. A comparison of the pooled ORs revealed a significantly increased risk in the homozygote comparisons (Gln/Gln versus Lys/Lys and Asn/Asn versus Asp/Asp), heterozygote comparison (Lys/Gln versus Lys/Lys), the dominant model (Gln/Gln + Lys/Gln versus Lys/Lys) and allelic contrast (Gln-allele versus Lys-allele). These results indicated that the XPD Lys^{751}Gln and Asp^{312}Asn polymorphisms could increase the risk of HCC.

It is well established that chronic HBV infection plays a specific role in the development of HCC. The present meta-analysis further explored this interaction between HBV and HCC. The results showed that no significantly increased risks were associated with the XPD Lys^{751}Gln gene polymorphisms and HCC risk in the HBV^{+} and HBV^{-} subgroups; however, only a small number of studies have examined the association between the XPD Lys^{751}Gln polymorphism and HCC risk in HBV^{+} and HBV^{-} patients. Furthermore, the P-value of the Q-test for heterogeneity was significant. Considering the limited number of studies and P-value of the Q-test for heterogeneity in this meta-analysis, the present results should be interpreted with caution.

A number of limitations to this meta-analysis should be considered in the interpretation of the results. First, a common limitation of meta-analyses is study heterogeneity. Heterogeneity is often caused by variations in the environmental and genetic backgrounds of the study participants, which is unavoidable when assessing several studies. Evidence of study heterogeneity was found in the present meta-analysis, presumably due to the fact that the number of included studies was small, and the frequency of the demographic variables for the cases and controls in one study was not matched in age, gender or histological type, among other factors. A second limitation was that the control groups were selected from different populations. In certain studies, the controls were healthy individuals, while in other studies the reference group was selected from hospital patients without organic gastric cancer; thus, there was a possibility of non-differential misclassification bias, since these studies may have included control groups with different risks of developing HCC. Thirdly, the present results were based on single-factor estimates without adjustment for other risk factors, including AFB1 intake, excessive consumption of alcohol and other lifestyle factors. Finally, the XPD gene could influence HCC susceptibility through interaction with other genes; however, no gene-gene interaction analyses were performed in this study.

In conclusion, the present meta-analysis provides limited evidence to support the association of XPD Lys^{751}Gln and Asp^{312}Asn polymorphisms with HCC risk. No significantly increased risks were found to be associated with the XPD Lys^{751}Gln gene polymorphism and HCC risk between the HBV^{+} and HBV^{-} subgroups. Large-scale studies with consideration for gene-gene/gene-environment interactions should be performed to further investigate the findings of the present study.

Acknowledgements

This study was supported by the National Natural Science Foundation of China (no. 81260675) and Guangxi Natural Science Foundation (no. 2013GXNSFAA019154) and the Project of Outstanding Young Teachers' Training in Higher Education Institutions of Guangxi.

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