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META-ANALYSIS

Xeroderma pigmentosum group D polymorphisms and esophageal cancer susceptibility: A meta-analysis based on case-control studies

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Abstract

AIM: To clarify the effects of the xeroderma pigmentosum group D (XPD) Asp312Asn and Lys751Gln gene polymorphisms on the risk of esophageal cancer (EC).

METHODS: A computerised literature search was conducted to identify the relevant studies from the PUBMED and EMBASE databases, reviews, and reference lists of relevant articles. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the associations between the XPD Asp312Asn and/or Lys751Gln polymorphisms and EC susceptibility. Statistical analyses were performed using the software Stata 12.0. A fixed or random effects model was selected based on a heterogeneity test. Publication bias was estimated using funnel plots and Egger's linear regression method. Subgroup analyses were performed based on histological type and ethnicity.

RESULTS: Thirteen case-control studies with a total of 10 comparisons for the Asp312Asn polymorphism, including 2373 cases and 3175 controls, and 15 comparisons for the Lys751Gln polymorphism, including 3226 cases and 5237 controls, were recruited for the meta-analysis. In terms of the XPD Asp312Asn polymorphism, significantly increased EC risks were identified in the Asp/Asn *vs* Asp/Asp comparison (OR = 1.17, 95%CI: 1.02-1.33, P = 0.03) and in the dominant-model comparison (Asn/Asn+Asp/Asn *vs* Asp/Asp: OR = 1.18, 95%CI: 1.04-1.34, P = 0.01). However, no significant associations were found in the Asn/Asn *vs* Asp/Asp comparison (OR = 1.30, 95%CI: 1.00-1.70, P = 0.05) or in the recessive-model comparison (Asn/Asn *vs* Asp/Asn + Asp/Asp: OR = 1.17, 95%CI: 0.91-1.50, P = 0.22). In terms of the XPD Lys751Gln polymorphism, a significant association with EC susceptibility was found under the recessive model (Gln/Gln *vs* Lys/Gln+Lys/Lys: OR = 1.21, 95%CI: 1.02-1.43, P = 0.03). However, no associations were identified in the other comparisons (co-dominant model: Lys/Gln *vs* Lys/Lys: OR = 1.11, 95%CI: 0.94-1.31, P = 0.20; Gln/Gln *vs* Lys/Lys: OR = 1.31, 95%CI: 0.98-1.75, P = 0.07; dominant model: OR = 1.14, 95%CI: 0.96-1.35, P = 0.14).

CONCLUSION: The results of this meta-analysis suggest that the XPD Asp312Asn and Lys751Gln gene polymorphisms are associated with a significantly increased risk for EC.

Key words: Esophageal cancer; Xeroderma pigmentosum group D; Polymorphism; Meta-analysis

Core tip: To clarify the effects of xeroderma pigmentosum group D (XPD) gene polymorphisms on the risk of esophageal cancer (EC), we performed a meta-analysis of all of the case-control studies that evaluated the association between the genetic polymorphisms of

XPD (Asp312Asn and Lys751Gln) and EC susceptibility. Thirteen case-control studies were recruited in the meta-analysis. For the XPD Asp312Asn polymorphism, significantly increased EC risks were found in the Asp/Asn *vs* Asp/Asp comparison and in the dominant model comparison. For the XPD Lys751Gln polymorphism, a significant association between the XPD Lys751Gln polymorphism and EC susceptibility was found under the recessive model.

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INTRODUCTION

Esophageal cancer (EC) is the sixth most frequently diagnosed cancer and the fifth most common cause of cancer death among males[1]. The major risk factors for EC are not well understood but are thought to include smoking, excessive alcohol consumption, poor nutritional status, low intake of fruits and vegetables, *etc.*[2-5]. Several studies have suggested that the genes involved in the DNA repair system play a crucial role in protecting against mutations, while a decreased DNA repair capacity is viewed as a crucial event in carcinogenesis[6]. The xeroderma pigmentosum group D (XPD) enzyme, an evolutionarily conserved ATP-dependent helicase, plays an important role in the repair of bulky DNA adducts, such as pyrimidine dimers, photoproducts and cross-links[7,8]. Mutations at different sites in the *XPD* gene can give rise to repair and transcription defects, and altered DNA repair capacity can render a higher risk of developing different types of cancer[9-11]. Several single nucleotide polymorphisms (SNPs) have been identified in the *XPD* gene. Among them, Asp312Asn (rs1799793 G>A) and Lys751Gln (rs13181 T>G) are commonly identified and result in amino acid changes.

Currently, there are many molecular epidemiological studies exploring the associations between the genetic polymorphisms of XPD, particularly Asp312Asn and Lys751Gln, and EC susceptibility, but the results remain controversial rather than conclusive. To address the inconsistencies in the findings of these studies, we performed a meta-analysis, based on published case-control studies, to derive a more precise estimation of the association between these two XPD polymorphisms and EC susceptibility.

MATERIALS AND METHODS

Search strategy

We systematically searched PubMed, Embase, previous reviews and the reference lists from identified articles published up to January 1, 2014 for studies related to EC and genetic polymorphisms[12,13]. We used the following search terms: "ERCC2" or "XPD" or "xeroderma pigmentosum group D" or "excision repair cross-complementing group 2" or "DNA repair gene", "polymorphism" or "variant", "esophageal" or "esophagus", and "cancer" or "carcinoma" or "squamous cell" or "adenocarcinoma", of which the exploration was limited to human studies. No language restrictions were imposed, and all of the eligible studies were examined carefully, and their references were checked for other relevant publications. All of the literature findings were independently reviewed by two professional co-workers (Yang R. and Wu Y.) to identify the studies that met the following criteria: (1) case-control study design; (2) evaluating the associations between XPD polymorphisms (Asp312Asn and/or Lys751Gln) and EC susceptibility; and (3) reporting the odds ratio (OR) and the corresponding 95% confidence intervals (CIs), or the size of the sample. Any differences were resolved by consensus. The major excluding criteria included the following: (1) not a case-control study; (2) review publications; or (3) overlapping data.

Data extraction

We used a standardised data extraction method to extract the data from the included papers[14]. Information was collected from each article, including the first author, year of publication, country, journal, racial descent of the study population, demographics, number of cases and controls for each genotype, genotyping method, histological type and confirmation of diagnosis. While the allele frequencies were not given, they were calculated from the corresponding genotype frequencies of the case and control groups.

Statistical analysis

The ORs were employed to evaluate the associations between the XPD Asp312Asn and/or Lys751Gln polymorphisms and EC susceptibility[15]. For Asp312Asn, the pooled ORs were calculated for a co-dominant model (Asp/Asn *vs* Asp/Asp, Asn/Asn *vs* Asp/Asp), a dominant model (Asn/Asn+Asp/Asn *vs* Asp/Asp), a recessive model (Asn/Asn *vs* Asp/Asn+Asp/Asp) and an additive model [(2Asn/Asn+Asp/Asn) *vs* 2(Asp/Asn+Asn/Asn+Asp/Asp)]. We evaluated the risks of the same four models for the Lys751Gln genotype as well. The χ^2 goodness-of-fit test was used to evaluate whether the genotypes among the control subjects conformed to the Hardy-Weinberg equilibrium (HWE). We applied two models of meta-analysis for any dichotomous outcomes according to the results of heterogeneity tests among the individual studies, using the software Stata 12.0 (Stata Corp., College Station, TX, United States): the fixed-effects model (the Mantel-Haenszel method) and the random-effects model (the DerSimonian and Laird method)[15]. Subgroup analyses were performed based on histological type and ethnicity. The publication bias was investigated with a funnel plot, in which the standard error (SE) of log (OR) for each study was plotted against

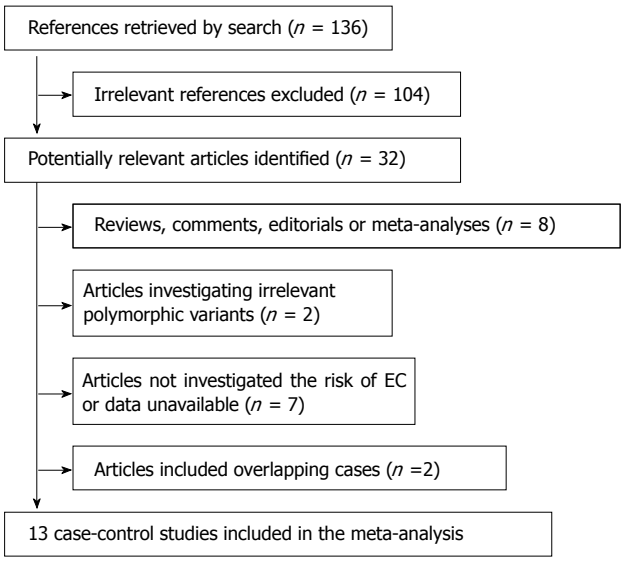

Figure 1 Flow diagram of the study selection process.

the respective log (OR). The funnel plot asymmetry was assessed using Egger's linear regression method[15]. The significance of the intercept was determined by the *t*-test, and $P < 0.05$ was considered statistically significant[16]. All of the statistical tests were performed using Stata version 12.0. All of the *P*-values were two-sided.

RESULTS

Eligible studies

A total of 136 articles were identified by the combined database search (PubMed and Embase) and manual approach (searching the previous studies cited in previous reviews and use of the reference lists from identified articles) of case-control studies, of which 15 case-control studies satisfied the inclusion criteria. After reading the full texts, two studies by Liu *et al*[17] and Huang *et al*[18] were excluded because the subjects had also been included in the studies by Tse *et al*[19] or Huang *et al*[20]. Therefore, 13 case-control studies were eventually included in the meta-analysis[19-31]. Figure 1 presents a flowchart of the retrieved and excluded studies with a specification of reasons. Table 1 shows the characteristics of the included studies. Overall, of the 13 included studies, a total of 10 comparisons, including 2373 cases and 3175 controls, for the Asp312Asn polymorphism, and 15 comparisons, including 3226 cases and 5237 controls, for the Lys751Gln polymorphism were reviewed. The distribution of genotypes in the controls of all of the included studies was in accordance with the HWE.

Meta-analysis

***XPD* Asp312Asn:** Table 2 indicates the associations between the *XPD* Asp312Asn polymorphism and EC susceptibility. Significantly increased risks were found in the Asp/Asn *vs* Asp/Asp comparison (OR = 1.17, 95%CI: 1.02-1.33, $P = 0.03$, Table 2) and in the dominant model comparison (Asn/Asn + Asp/Asn *vs* Asp/Asp: OR = 1.18, 95%CI: 1.04-1.34, $P = 0.01$, Figure 2, Table 2). However, no significant associations were found in the Asn/Asn *vs* Asp/Asp comparison (OR = 1.30, 95%CI: 1.00-1.70, $P = 0.05$, Table 2) or in the recessive model comparison (Asn/Asn *vs* Asp/Asn + Asp/Asp: OR = 1.17, 95%CI: 0.91-1.50, $P = 0.22$, Table 2). In the subgroup analysis according to cancer type [esophageal squamous cell carcinoma (ESCC) or esophageal adenocarcinoma (EADC)], significant associations between the *XPD* Asp312Asn polymorphism and EC susceptibility were detected in the EADC subgroup in the co-dominant model (Asp/Asn *vs* Asp/Asp: OR = 1.26, 95%CI: 1.03-1.53, $P = 0.02$; Asn/Asn *vs* Asp/Asp: OR = 1.40, 95%CI: 1.04-1.89, $P = 0.03$, Table 2) and the dominant model (OR = 1.29, 95%CI: 1.07-1.55, $P = 0.01$, Figure 2, Table 2). Further analysis by ethnicity revealed significant associations of the *XPD* Asp312Asn polymorphism with EC susceptibility in non-Chinese populations in the Asp/Asn *vs* Asp/Asp comparison (OR = 1.23, 95%CI: 1.03-1.47, $P = 0.02$, Table 2) and in the dominant model comparison (OR = 1.24, 95%CI: 1.05-1.47, $P = 0.01$, Table 2, Figure 3), but the same associations were not seen in Chinese populations. Finally, for the additive model (Table 2), individuals carrying the 312Asn allele were not significantly associated with an increased risk for EC (OR = 1.10, 95%CI: 1.00-1.21, $P = 0.06$).

***XPD* Lys751Gln:** Table 3 lists the overall results of the meta-analysis for the associations between the *XPD* Lys751Gln polymorphism and EC susceptibility. There was a significant association with EC susceptibility for the recessive model comparison (Gln/Gln *vs* Lys/Gln + Lys/Lys: OR = 1.21, 95%CI: 1.02-1.43, $P = 0.03$, Figure 4, Table 3). However, such associations were not found in the other comparisons (co-dominant model: Lys/Gln *vs* Lys/Lys: OR = 1.11, 95%CI: 0.94-1.31, $P = 0.20$; Gln/Gln *vs* Lys/Lys: OR = 1.31, 95%CI: 0.98-1.75, $P = 0.07$; dominant model: OR = 1.14, 95%CI: 0.96-1.35, $P = 0.14$. Table 3). In the stratified analysis based on cancer type (ESCC or EADC), we observed an OR of 1.44 (95%CI: 1.01-2.06, $P = 0.05$, Table 3) for ESCC risk and an OR of 1.26 (95%CI: 1.02-1.56, $P = 0.03$, Table 3) for EADC risk, when comparing the Gln/Gln type to the wild type Lys/Lys (Table 3). When stratified by ethnicity, statistically significantly elevated risks were found in Chinese populations in the Gln/Gln *vs* Lys/Lys comparison (OR = 2.49, 95%CI: 1.44-4.29, $P = 0.001$, Table 3) and in the recessive model comparison (OR = 2.37, 95%CI: 1.38-4.10, $P = 0.002$, Figure 5, Table 3), but the same associations were not identified in non-Chinese populations. Finally, for the additive model (Table 3), individuals carrying the 751Gln allele were not significantly associated with an increased risk for EC (OR = 1.10, 95%CI: 0.99-1.22, $P = 0.10$, Table 3).

Heterogeneity and sensitivity analysis

There was moderate heterogeneity among the studies that described the *XPD* Asp312Asn polymorphism (co-dominant model: Asp/Asn *vs* Asp/Asp, $P = 0.97$; Asn/Asn *vs*

Table 1 Characteristics of the studies included in the meta-analysis

Ref.	Country	Ethnicity	Control source	Cancer type	Genotype distribution (case/control)						*P* for HWE	
					Asp312Asn			Lys751Gln				
					Asp/Asp	Asp/Asn	Asn/Asn	Lys/Lys	Lys/Gln	Gln/Gln	Asp312Asn	Lys751Gln
Xing *et al*[21] 2002	China	Chinese	PB	ESCC	381/461	49/62	3/1	367/451	63/70	3/3	0.47	0.87
Xing *et al*[22] 2003	China	Chinese	PB	ESCC	286/338	38/45	1/0	278/331	44/49	3/3	0.22	0.43
Yu *et al*[23]2004	China	Chinese	HB	ESCC	121/136	14/16	0/0	108/133	16/17	11/2	0.49	0.11
Casson *et al*[24] 2005	Canada	Caucasian	HB	EADC	-	-	-	31/34	21/46	4/15	-	0.93
Ye *et al*[25]2006	Sweden	Swedish	PB	EADC	31/176	51/237	14/57	27/198	51/203	18/71	0.09	0.11
				ESCC	30/176	41/237	10/57	23/198	44/203	14/71	0.09	0.11
Sobti *et al*[26] 2007	India	Indian	HB	ESCC	-	-	-	52/63	61/77	7/20	-	0.64
Doecke *et al*[27] 2008	Australia	Mixed	PB	EADC	-	-	-	108/575	123/588	32/174	-	0.22
Ferguson *et al*[28] 2008	Ireland	Caucasian	PB	EADC	-	-	-	80/91	94/121	34/35	-	0.61
Tse *et al*[19] 2008	United States	Mixed	HB	EADC	117/199	150/206	43/49	104/193	159/208	49/52	0.69	0.72
Pan *et al*[29] 2009	United States	Caucasian	HB	ESCC	16/201	20/185	1/48	17/187	18/216	3/53	0.58	0.43
				EADC	137/201	163/185	43/48	137/187	153/216	56/53	0.58	0.43
Zhai *et al*[30] 2009	China	Chinese	HB	ESCC	-	-	-	167/148	31/51	2/1	-	0.12
Huang *et al*[29] 2012	China	Chinese	HB	ESCC	171/298	42/60	0/0	150/274	55/79	8/5	0.08	0.80
Li *et al*[31] 2013	China	Chinese	PB	ESCC	342/351	56/47	2/2	283/321	105/73	12/6	0.75	0.43

PB: Population-based study; HB: Hospital-based study; ESCC: Esophageal squamous cell carcinoma; EADC: Esophageal adenocarcinoma; HWE: Hardy-Weinberg equilibrium.

Table 2 Results of the meta-analysis for the xeroderma pigmentosum group D Asp312Asn polymorphism and esophageal cancer susceptibility

Study group	Co-dominant model						Dominant model			Recessive model			Additive model		
	Asp/Asn *vs* Asp/Asp			Asn/Asn *vs* Asp/Asp			Asn/Asn + Asp/Asn *vs* Asp/Asp			Asn/Asn *vs* Asp/Asn + Asp/Asp			(2Asn/Asn + Asp/Asn) *vs* 2(Asp/Asn + Asn/Asn + Asp/Asp)		
	OR (95%CI)	*P*	Ph	OR (95%CI)	*P*	Ph	OR (95%CI)	*P*	Ph	OR (95%CI)	*P*	Ph	OR (95%CI)	*P*	Ph
Total	1.17 (1.02, 1.33)	0.03	0.97	1.30 (1.00, 1.70)	0.05	0.75	1.18 (1.04, 1.34)	0.01	0.98	1.17 (0.91, 1.50)	0.22	0.71	1.10 (1.00, 1.21)	0.06	1.00
Cancer type															
ESCC	1.09 (0.91, 1.31)	0.35	0.95	0.99 (0.54, 1.79)	0.96	0.48	1.09 (0.91, 1.30)	0.35	0.99	0.93 (0.53, 1.63)	0.79	0.40	1.06 (0.90, 1.24)	0.49	0.99
EADC	1.26 (1.03, 1.53)	0.02	0.97	1.40 (1.04, 1.89)	0.03	0.93	1.29 (1.07, 1.55)	0.01	0.99	1.24 (0.94, 1.64)	0.13	0.90	1.12 (0.99, 1.28)	0.07	0.98
Ethnicity															
Chinese	1.08 (0.88, 1.33)	0.45	0.88	2.08 (0.57, 7.60)	0.27	0.66	1.10 (0.90, 1.35)	0.36	0.93	2.06 (0.57, 7.51)	0.27	0.65	1.10 (0.91, 1.33)	0.34	0.98
Non-Chinese	1.23 (1.03, 1.47)	0.02	0.95	1.27 (0.97, 1.67)	0.08	0.54	1.24 (1.05, 1.47)	0.01	0.93	1.14 (0.89, 1.47)	0.31	0.53	1.10 (0.98, 1.23)	0.11	0.92

ESCC: Esophageal squamous cell carcinoma; EADC: Esophageal adenocarcinoma; Ph: *P* value of the *Q*-test for heterogeneity.

Asp/Asp, $P = 0.75$; dominant model: $P = 0.98$; recessive model: $P = 0.71$; additive model: $P = 1.00$), but this was not observed in the Lys751Gln polymorphism (co-dominant model: Lys/Gln *vs* Lys/Lys, $P = 0.01$; Gln/Gln *vs* Lys/Lys, $P = 0.03$; dominant model: $P = 0.001$; recessive model: $P = 0.11$; additive model: $P = 0.02$). The details are shown in Tables 2 and 3.

A sensitivity analysis was carried out by individually omitting each study included in the meta-analysis, and the subsequent results of each genetic model were not materially altered (data not shown), indicating that the results were statistically robust.

Publication bias

Begg's funnel plot and Egger's test were performed to assess any possible publication bias. The shape of the funnel plots did not reveal any obvious asymmetry. We have presented the funnel plots of *XPD* Asp312Asn for the dominant model (Asn/Asn + Asp/Asn *vs* Asp/Asp) and *XPD* Lys751Gln for the recessive model (Gln/Gln *vs* Lys/Gln + Lys/Lys) in Figure 6. The statistical evidence from the results of Egger's test confirmed the funnel

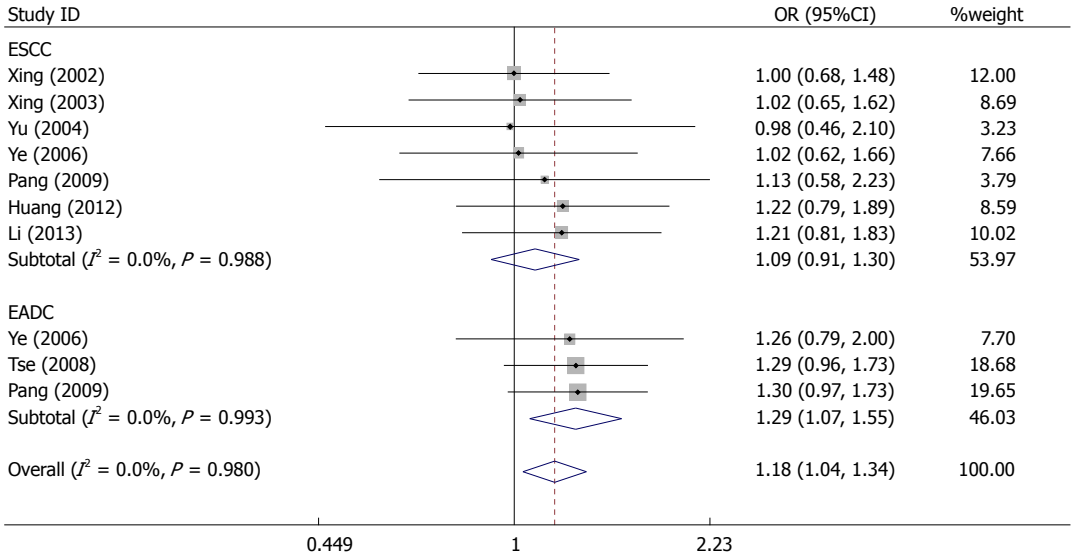

Figure 2 Forest plot for the xeroderma pigmentosum group D Asp312Asn polymorphism when stratified by cancer type in a dominant model comparison. Dominant model: Asn/Asn + Asp/Asn *vs* Asp/Asp; ESCC: Esophageal squamous cell carcinoma; EADC: Esophageal adenocarcinoma.

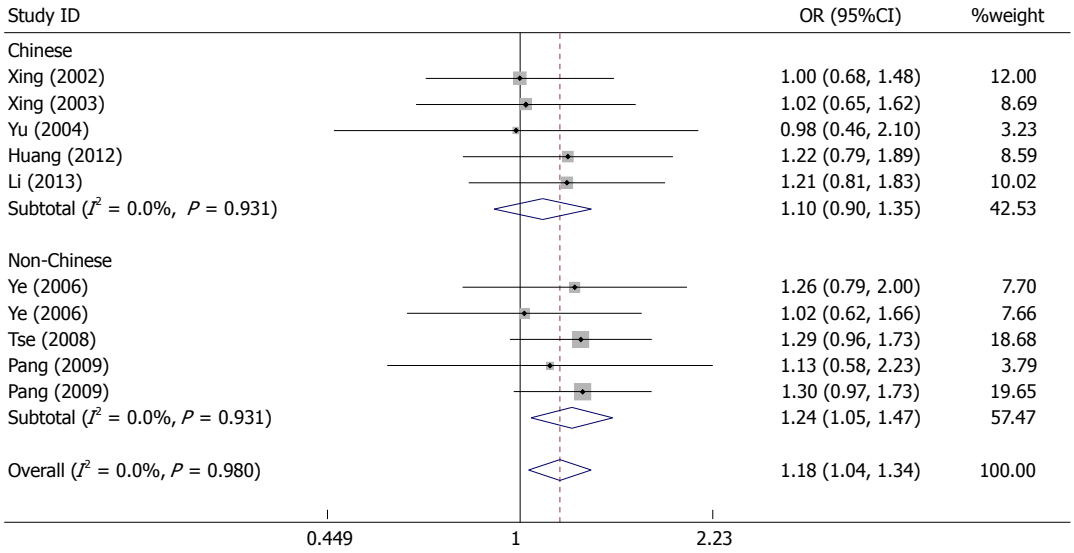

Figure 3 Forest plot for the xeroderma pigmentosum group D Asp312Asn polymorphism when stratified by ethnicity in a dominant model comparison. Dominant model: Asn/Asn + Asp/Asn *vs* Asp/Asp; ESCC: Esophageal squamous cell carcinoma; EADC: Esophageal adenocarcinoma.

plot symmetry (*XPD* Asp312Asn: P = 0.31 for Asp/Asn *vs* Asp/Asp, P = 0.77 for Asn/Asn *vs* Asp/Asp, P = 0.06 for the dominant model, P = 0.89 for the recessive model, and P = 0.11 for the additive model; *XPD* Lys751Gln: P = 0.38 for Lys/Gln *vs* Lys/Lys, P = 0.99 for Gln/Gln *vs* Lys/Lys, P = 0.40 for the dominant model, P = 0.86 for the recessive model, and P = 0.69 for the additive model).

DISCUSSION

DNA repair enzyme gene polymorphisms that are capable of altering the function or efficiency of damaged DNA repair can lead to genetic instability and carcinogenesis[32]. A small proportion of published studies have explored the relationship between XPD polymorphisms and EC risk and have yielded inconsistent results[17-31]. In order to derive a more precise estimation of the relationship, we performed a meta-analysis of 13 case-control studies, including 10 comparisons for the Asp312Asn polymorphism (2373 cases and 3175 controls) and 15 comparisons for the Lys751Gln polymorphism (3226 cases and 5237 controls).

In the case of the XPD Asp312Asn polymorphism, our results indicated that individuals carrying the variant heterozygous Asp/Asn showed an increased risk for EC compared to those with the wild-type homozygous Asp/Asp (OR = 1.17, 95%CI: 1.02-1.33). Similarly, a significant association between the XPD Asp312Asn polymorphism and EC was found under the dominant model (OR

Table 3 Results of the meta-analysis for the xeroderma pigmentosum group D Lys751Gln polymorphism and esophageal cancer susceptibility

Study group	Co-dominant model						Dominant model			Recessive model			Additive model		
	Lys/Gln *vs* Lys/Lys			Gln/Gln *vs* Lys/Lys			Gln/Gln + LysGln *vs* Lys/Lys			Gln/Gln *vs* Lys/Gln + Lys/Lys			(2Gln/Gln + Lys/Gln) *vs* 2(Lys/Gln + Gln/Gln + Lys/Lys)		
	OR (95%CI)	*P*	Ph	OR (95%CI)	*P*	Ph	OR (95%CI)	*P*	Ph	OR (95%CI)	*P*	Ph	OR (95%CI)	*P*	Ph
Total	1.11 (0.94, 1.31)	0.20	0.01	1.31 (0.98, 1.75)	0.07	0.03	1.14 (0.96, 1.35)	0.14	0.001	1.21 (1.02, 1.43)	0.03	0.11	1.10 (0.99, 1.22)	0.10	0.02
Cancer type															
ESCC	1.13 (0.89, 1.42)	0.31	0.03	1.44 (1.01, 2.06)	0.05	0.06	1.16 (0.91, 1.49)	0.23	0.01	1.26 (0.90, 1.77)	0.17	0.08	1.13 (0.94, 1.36)	0.21	0.02
EADC	1.09 (0.85, 1.40)	0.51	0.02	1.26 (1.02, 1.56)	0.03	0.05	1.11 (0.85, 1.44)	0.45	0.01	1.19 (0.98, 1.45)	0.08	0.25	1.07 (0.98, 1.18)	0.13	0.22
Ethnicity															
Chinese	1.10 (0.82, 1.47)	0.53	0.02	2.49 (1.44, 4.29)	0.001	0.64	1.18 (0.88, 1.60)	0.27	0.01	2.37 (1.38, 4.10)	0.002	0.65	1.21 (0.94, 1.56)	0.15	0.02
Non-Chinese	1.12 (0.91, 1.38)	0.30	0.03	1.13 (0.82, 1.56)	0.45	0.02	1.11 (0.89, 1.39)	0.35	0.01	1.12 (0.93, 1.34)	0.23	0.14	1.06 (0.98, 1.15)	0.16	0.27

ESCC: Esophageal squamous cell carcinoma; EADC: Esophageal adenocarcinoma; Ph: *P* value of the *Q*-test for heterogeneity.

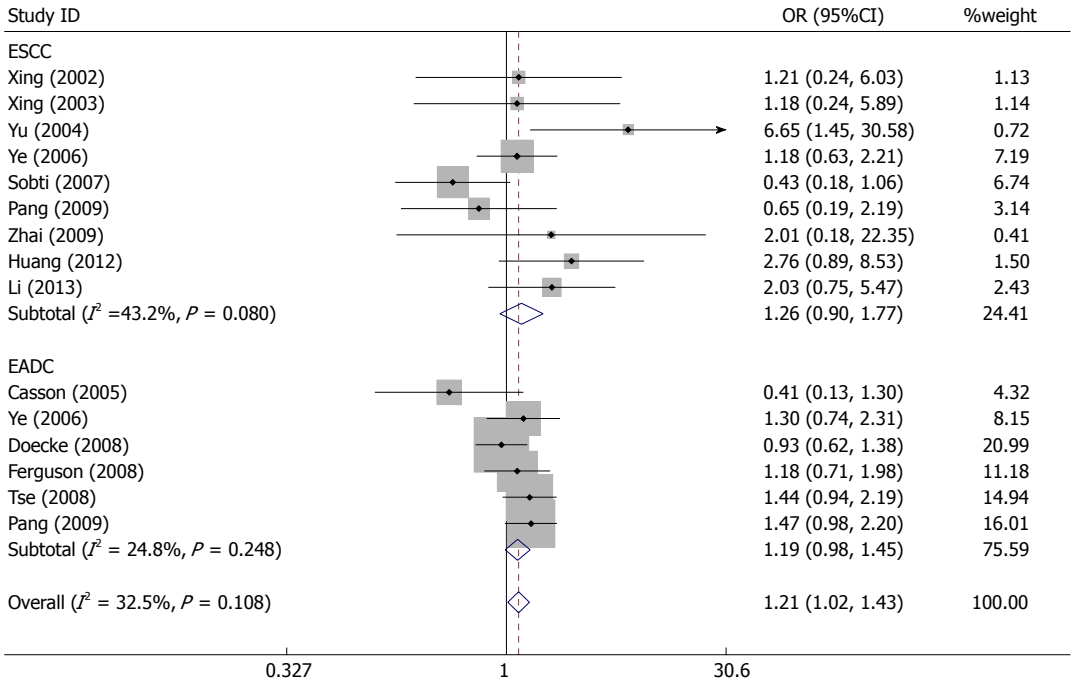

Figure 4 Forest plot for the xeroderma pigmentosum group D Lys751Gln polymorphism when stratified by cancer type in a recessive model comparison. Recessive model: Gln/Gln *vs* Lys/Gln+Lys/Lys; ESCC: Esophageal squamous cell carcinoma; EADC: Esophageal adenocarcinoma.

= 1.18, 95%CI: 1.04-1.34). After stratifying based on cancer type, an association was found in both the co-dominant model and the dominant model for EADC (Asp/Asn *vs* Asp/Asp: OR = 1.26, 95%CI: 1.03-1.53; Asn/Asn *vs* Asp/Asp: OR = 1.40, 95%CI: 1.04-1.89; dominant model: OR = 1.29, 95%CI: 1.07-1.55) but not for ESCC. This was opposite to the results of the meta-analysis performed by Duan *et al*[33], which showed a borderline association with the dominant model for ESCC but not for EADC. Our meta-analysis excluded the study by Liu *et al*[17], because the subjects had also been included in the study by Tse *et al*[19], but this exclusion was not performed by Duan *et al*[33]. In addition, our meta-analysis included a new study by Li *et al*[31]. Therefore, the present meta-analysis provides more reliable evidence in regards to the importance of the XPD Asp312Asn polymorphism in relation to EC. When stratified by ethnicity, a significant association was found in non-Chinese populations for the Asp/Asn *vs* Asp/Asp comparison (OR = 1.23, 95%CI: 1.03-1.47) and under the dominant model (OR = 1.24, 95%CI: 1.05-1.47), but the same association was not observed in Chinese populations, indicating that ethnic differences in the genetic background and the environment they live in may play a possible role in EC susceptibility. Therefore, the same *XPD* Asp312Asn polymorphism plays different roles in EC susceptibility among Chinese and non-Chinese populations, because cancer is a complicated multifactorial disease, and different genetic backgrounds may contribute to the discrepancy[34].

In the case of the *XPD* Lys751Gln polymorphism, our meta-analysis showed that there was a significant association with EC susceptibility under the reces-

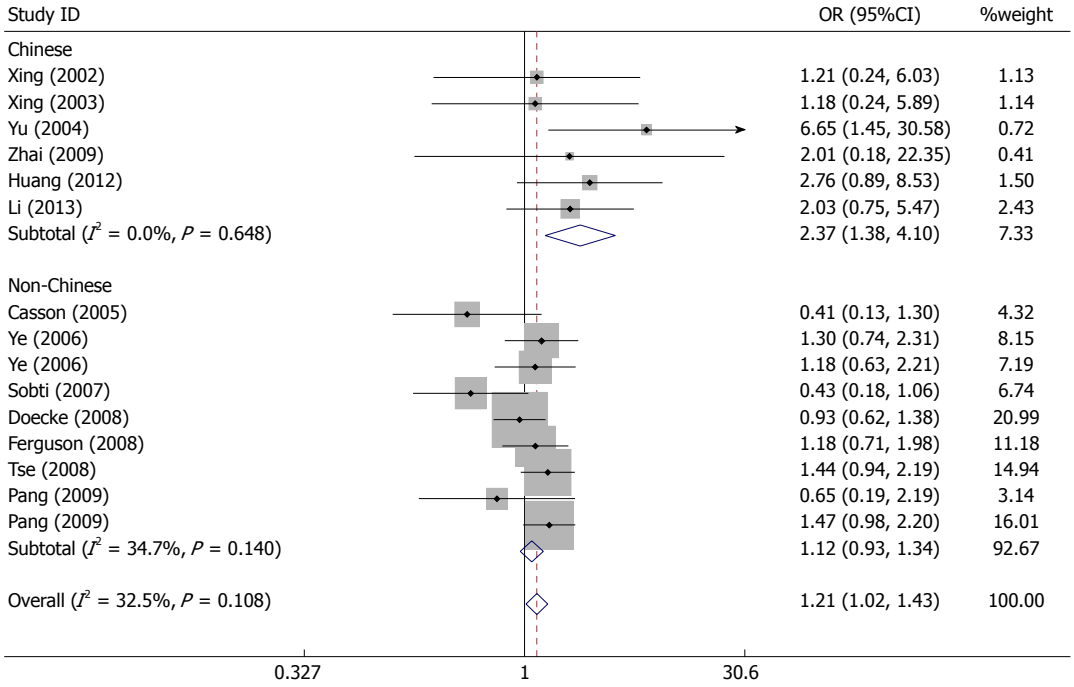

Figure 5 Forest plot for the xeroderma pigmentosum group D Lys751Gln polymorphism when stratified by ethnicity in a recessive model comparison. Recessive model: Gln/Gln *vs* Lys/Gln+Lys/Lys; ESCC: Esophageal squamous cell carcinoma; EADC: Esophageal adenocarcinoma.

sive model (OR = 1.21, 95%CI: 1.02-1.43). Our results were inconsistent with two previously published meta-analyses by Ding *et al*[35] and by Yuan *et al*[36], both of which showed a lack of association between the *XPD* Lys751Gln polymorphism and EC in total populations. Our meta-analysis included a larger number of studies and more EC cases when compared with these two earlier studies. Therefore, the present meta-analysis provides more reliable evidence about the importance of the *XPD* Lys751Gln polymorphism in terms of EC. In the analysis stratified according to histological type, a positive association was observed between the *XPD* Lys751Gln polymorphism and an elevated susceptibility to both ESCC and EADC (ESCC: OR = 1.44, 95%CI: 1.01-2.06; EADC: OR = 1.26, 95%CI: 1.02-1.56), when comparing the Gln/Gln type to the wild type Lys/Lys. When stratified by ethnicity, a significant association was found in Chinese populations for the Gln/Gln *vs* Lys/Lys comparison (OR = 2.49, 95%CI: 1.44-4.29) and under the recessive model (OR = 2.37, 95%CI: 1.38-4.10), suggesting that the *XPD* Lys751Gln polymorphism plays a greater role in Chinese populations. It is worth noting that this observation is opposite to that seen in the XPD Asp312Asn polymorphism.

The associations between the *XPD* Asp312Asn polymorphism and EC susceptibility have been researched in very few studies. Only one study by Huang *et al*[20] reported that *XPD* Asp312Asn was associated with a borderline decrease for the risk of ESCC in the Han and Uygur populations. The majority of the studies[19,21-23,25,29,31] reported that there were no statistically significant associations between the *XPD* Asp312Asn polymorphism and the risk for EC, which is opposite to the results of our meta-analysis, which shows a significant association between the *XPD* Asp312Asn polymorphism and EC susceptibility. A reason may be that the sample sizes of those studies were too small to explore the subtle association between the *XPD* Asp312Asn polymorphism and EC susceptibility, but the pool of ORs generated from 10 comparisons significantly increases the statistical power.

Many epidemiological studies have also investigated the association between the *XPD* Lys751Gln polymorphism and EC susceptibility. Xing *et al*[21], Pan *et al*[29] and Ferguson *et al*[28] reported that the Lys751Gln polymorphism in the XPD gene did not influence the risk for ESCC and/or EADC. However, Yu *et al*[23], Huang *et al*[20], Li *et al*[31], Ye *et al*[25] and Tse *et al*[19] revealed a contradictory result, which suggested an increased risk for ESCC and/or EADC in association with the *XPD* Lys751Gln polymorphism. A more interesting finding revealed by Zhai *et al*[30] and Casson *et al*[24] suggested an inverse association, which indicated that the *XPD* Lys751Gln polymorphism is a protective factor rather than a risk factor for ESCC or EADC. The differences in risk observed in different studies could be partially attributable to the small sample sizes and inappropriate study design. More importantly, the interaction with other polymorphisms and/or particular environmental exposures may also influence the genetic effects of a single polymorphism[35].

There are some limitations to our meta-analysis that should be acknowledged. First, though it is known that the *XPD* gene has more polymorphisms than just Asp312Asn and Lys751Gln, we focused our meta-analysis on the two most studied polymorphisms due to limited research on other polymorphisms. Second, the studies investigating genetic associations should be based on a

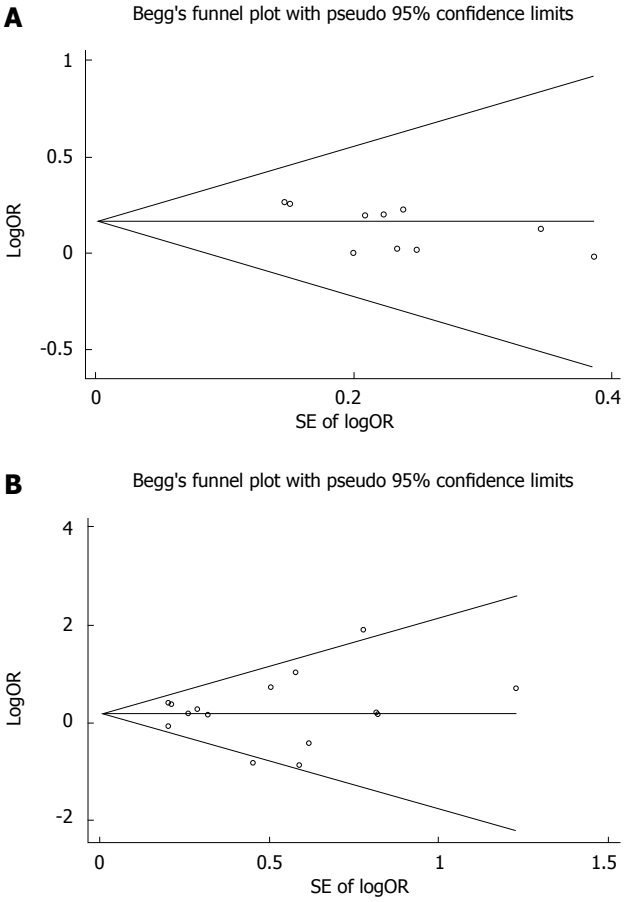

Figure 6 Funnel plots showing the associations between the xeroderma pigmentosum group D polymorphisms and esophageal cancer susceptibility. Each point represents a separate study for the indicated association. A: Funnel plot of *XPD* Asp312Asn for the dominant model (Asn/Asn+Asp/Asn *vs* Asp/Asp); B: Funnel plot of *XPD* Lys751Gln for the recessive model (Gln/Gln *vs* Lys/Gln+Lys/Lys).

large sample size, similar study designs and standardised case and control definitions. Third, the *XPD* gene polymorphisms may influence EC susceptibility in concert with other genes, but we did not have enough data to conduct any gene-gene interaction analyses. Finally, our results were based on single-factor evaluations without adjustment for other risk factors, including BMI, tobacco, alcohol, environmental factors, or lifestyle.

In conclusion, this meta-analysis showed that the *XPD* Asp312Asn polymorphism may contribute to EC susceptibility, particularly in non-Chinese populations. In addition, the analysis showed that the *XPD* Lys751Gln polymorphism may also contribute to EC susceptibility, particularly in Chinese individuals. Large, well-designed case-control studies are recommended in order to further enrich the present findings. Future studies should focus on gene-gene and gene-environment interactions to further shed light on the genetics of EC.

COMMENTS

Background

A small proportion of the published studies have explored the relationship between xeroderma pigmentosum group D (XPD) polymorphisms and esophageal cancer (EC) risk and have yielded inconsistent results. In order to derive a more precise estimation of this relationship, we performed a meta-analysis of all of the case-control studies that evaluated the association between the genetic polymorphisms of XPD (Asp312Asn and Lys751Gln) and EC susceptibility.

Research frontiers

The XPD enzyme plays an important role in the repair of bulky DNA adducts. Mutations at different sites in the XPD gene may render a higher risk for developing EC. However, the evidence is insufficient given the small sample size.

Innovations and breakthroughs

This meta-analysis suggested that the XPD Asp312Asn and Lys751Gln gene polymorphisms are both associated with a significantly increased risk for EC.

Applications

This study provided a potential biomarker to identify high-risk individuals for esophageal cancer.

Terminology

XPD is an evolutionarily conserved ATP-dependent helicase that plays an important role in the repair of bulky DNA adducts, such as pyrimidine dimers, photoproducts and cross-links.

Peer review

The authors clarify the effects of the XPD Asp312Asn and Lys751Gln gene polymorphisms on the risks of esophageal cancer. This is a "delicious" paper.

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