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Original Article

Polymorphisms in the nuclear excision repair gene ERCC2/XPD and susceptibility to cutaneous basal cell carcinoma

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Abstract: Studies have investigated the relationship between XPD Lys751Gln and Asp312Asn genetic variants and risk of cutaneous basal cell carcinoma (BCC). However, the results remain inconclusive. We performed a meta-analysis, using a comprehensive strategy based on the allele model and a model-free approach, to investigate the association of between XPD Lys751Gln and Asp312Asn polymorphisms with BCC risk. For XPD Lys751Gln, no significant BCC risk was found in the allele model (OR = 0.97, 95% CI 0.90-1.04, I^2 = 35.3%, $P_{heterogeneity}$ = 0.125) and with model-free approach (OR_G = 0.95, 95% CI 0.87-1.04, I^2 = 15.9%, $P_{heterogeneity}$ = 0.296). For XPD Asp312Asn, there was also no association between this polymorphism and BCC risk in the allele model (OR = 0.94, 95% CI 0.86-1.03, I^2 = 0, $P_{heterogeneity}$ = 0.650) and with the model-free approach (OR_G = 0.94, 95% CI 0.85-1.05, I^2 = 0, $P_{heterogeneity}$ = 0.603). Therefore, this meta-analysis suggests that the XPD Lys751Gln and Asp312Asn polymorphisms were not associated with BCC risk. Further large and well-designed studies are needed to confirm these findings.

Keywords: XPD/ERCC2, basal cell carcinoma, polymorphism, meta-analysis

Introduction

Basal cell carcinoma (BCC) is the most common neoplasm of the skin and accounts for >75% of all skin cancers [1, 2]. BCC tumors grow slowly and are only locally invasive; however, these cause extensive morbidity through recurrence and tissue destruction [3]. The etiology of BCC involves an interplay between genetic and environmental factors, such as UV radiation that induces mutations in critical genes and provides growth advantage to the affected cells for clonal expansion [4, 5].

DNA repair is the basic mechanism in the function of human cells and stimulated in response to DNA damage. Further, DNA repair is a complex process in maintaining the integrity of the genome, which is made up of a series of DNA repair pathways, including more than 130 genes. In humans, there are at least four DNA repair pathways. One of the four pathways, base excision repair (BER) pathway, is responsible for DNA damage repair in exposure to various endogenous and exogenous carcinogens. This pathway is to eliminate error and damaged bases, and can specifically remove methylated, oxidized, or reduced single base pair alterations [6].

Mutations in nucleotide excision repair (NER) genes are the cause of xeroderma pigmentosum, a genetic syndrome with proneness to BCC of the skin. Single nucleotide polymorphisms (SNPs) may affect the effectiveness of DNA repair and hence influence individual susceptibility to a variety of neoplasms. Polymorphisms in the NER genes Xeroderma pigmentosum groups D (XPD) have also been associated with cancer susceptibility, with particular emphasis on two nonsynonymous polymorphisms: Lys751Gln (A→C; rs13181) in exon 23 and Asp312Asn (G→A; rs1799793) polymorphism in exon 10. Several studies have ana-

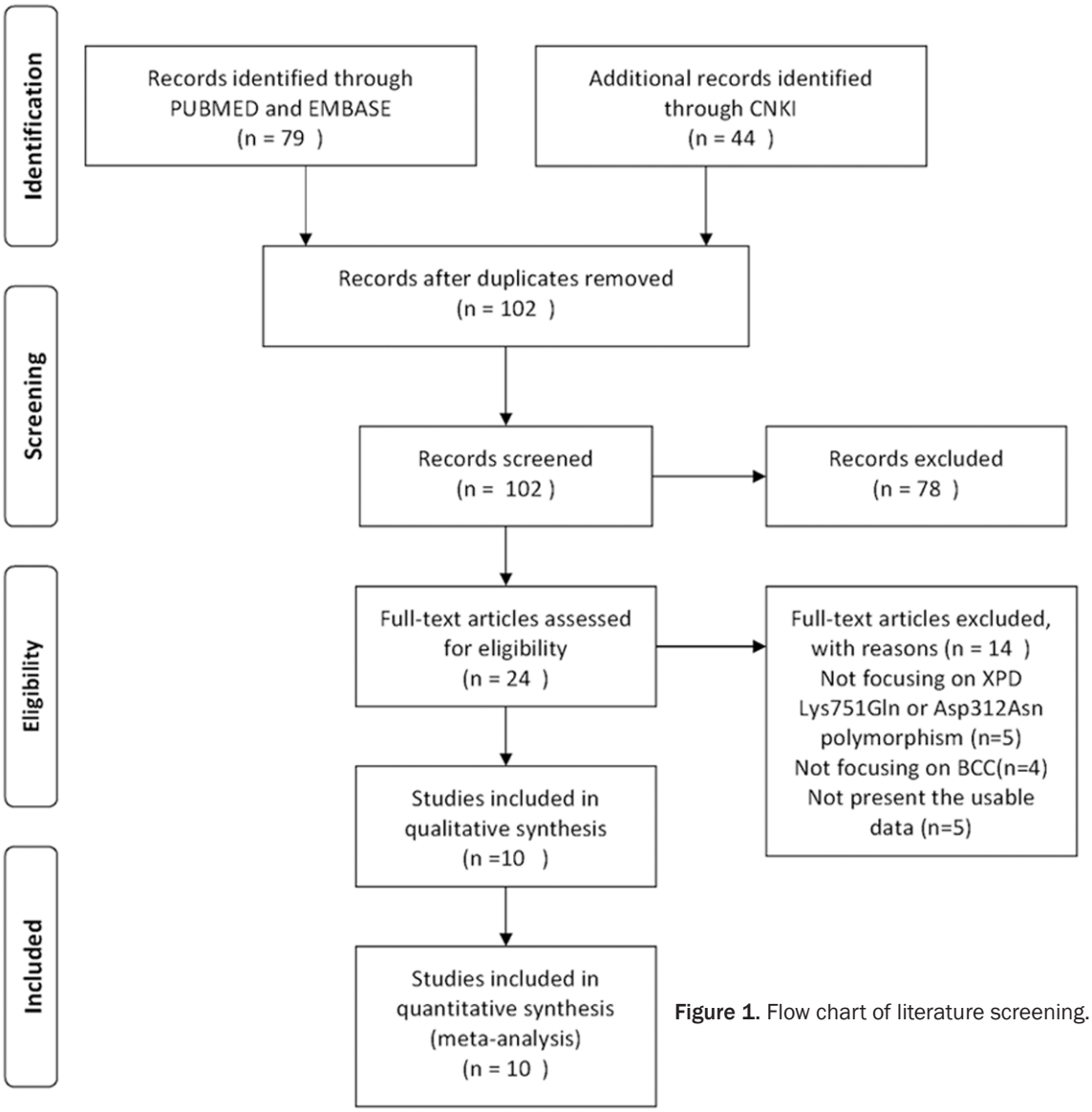

Figure 1. Flow chart of literature screening.

lyzed associations between XPD Lys751Gln and Asp312Asn genetic polymorphism and susceptibility to BCC [7-16]. However, this relationship remains controversial. Therefore, this meta-analysis was performed to evaluate the association between the XPD Lys751Gln and Asp312Asn genetic polymorphism and cutaneous basal cell carcinoma risk.

Materials and methods

Search strategy

To identify all the studies that examined the association of XPD Lys751Gln and Asp312Asn polymorphisms and basal cell carcinoma risk, we searched the PubMed, Embase and China National Knowledge Infrastructure (CNKI) databases without language limitations using the following searching strategies: 1) XPD or ERCC2, 2) polymorphism or variant, and 3) skin cancer or basal cell carcinoma. And the last research was updated on Oct 15, 2014. To explore potentially additional studies, we also examined the references of articles and reviews. Then we downloaded the relevant papers and further screened to identify potentially eligible studies.

Selection criteria

Studies were selected according to the following inclusion criteria: (1) information on the association of BCC risk with XPD Lys751Gln or

Table 1. Characteristics of studies included in this meta-analysis

Author	Year	Country	Ethnicity	Source of control	Genotyping methods	Sample size (case/control)	Case			Control			P_{HWE}
XPD Lys 751 Gln							AA	AC	CC	AA	AC	CC	
Dybdah1	1999	Denmark	Caucasian	PB	PCR-RFLP	40/40	21	17	2	17	16	7	0.354
Vogel	2001	Denmark	Caucasian	HB	PCR-RFLP	71/117	24	35	12	44	61	12	0.169
Yin	2003	Denmark	Caucasian	PB	PCR-RFLP	20/20	10	9	1	8	8	4	0.456
Festa	2005	Sweden	Caucasian	PB	pyrosequencing	197/561	69	94	34	194	282	85	0.289
Han	2005	USA	Caucasian	PB	Taqman	286/844	98	141	47	295	415	134	0.551
Lovatt	2005	UK	Caucasian	HB	PCR-RFLP	509/379	217	218	74	149	177	53	0.970
Vogel	2005	Denmark	Caucasian	PB	Taqman	318/322	131	147	40	118	157	47	0.654
Thirumaran	2006	Hungary	Caucasian	HB	Taqman	529/533	174	269	86	179	262	92	0.817
Applebaum	2007	USA	Caucasian	PB	Taqman	854/753	395	349	110	322	338	93	0.768
SUAREZ-MARTINEZ	2007	Puerto Rico	Caucasian	PB	PCR-RFLP	8/178	1	5	2	93	83	2	<0.001
XPD Asp 312 Asn							GG	GA	AA	GG	GA	AA	
Vogel	2001	Denmark	Caucasian	HB	PCR-RFLP	68/105	29	25	14	46	39	20	0.033
Han	2005	USA	Caucasian	PB	Taqman	285/836	104	149	32	342	373	121	0.240
Lovatt	2005	UK	Caucasian	HB	PCR-RFLP	509/379	224	219	66	151	163	65	0.070
Vogel	2005	Denmark	Caucasian	PB	Taqman	318/321	136	149	33	142	135	44	0.194
Applebaum	2007	USA	Caucasian	PB	Taqman	782/728	347	341	94	301	343	84	0.356

PB, Population-based; HB, Hospital-based; PCR-RFLP: Polymerase Chain Reaction-restriction Fragment Length Polymorphism; HWE: Hardy-Weinberg Equilibrium.

Asp312Asn polymorphism; (2) case–control studies; and (3) sufficient genotype data to calculate the odds ratios (ORs) with 95% confidence intervals (CIs). Studies were excluded if one of the following existed: (1) data unavailable for calculating genotype or allele frequencies; (2) no control population.

Data extraction

According to the inclusion criteria, two reviewers extracted eligible studies independently, and disagreement between the two reviewers was settled by discussing with the third reviewer. For each study, we recorded the first author, year of publication, country of origin, ethnicity, source of control, the method of genotyping, sample size and genotype distributions in cases and controls.

Statistical analysis

ORs and corresponding 95% CIs were used to evaluate the possible association between XPD Lys751Gln and Asp312Asn polymorphisms and BCC risk. A novel method to calculate the generalized odds ratio (OR_G) based on a genetic model-free approach was also performed [17]. The heterogeneity among different studies was assessed by chi-square-based Q-tests (considered significant for P<0.10). And the value of I^2 was used to quantify the effect of heterogeneity. Both fixed-effects model with Mantel-Haenszel method and random-effects model with the method of Dersimonian & Laird were used to combine the data. Hardy-Weinberg equilibrium was examined by chi-square goodness-of-fit test (P>0.05) using gene frequencies of the healthy individuals. Relative influence of each study on the pooled estimate was assessed by omitting one study at a time for sensitivity analysis. The evaluation of potential publication bias was performed using the Begg's funnel plots and Egger's test (P<0.05 was regarded as representative of statistical significance). Statistical analyses were done in ORGGASMA and STATA 12.0 (STATA Corp., College Station, TX, USA).

Results

Characteristics of the studies

Figure 1 showed the process of identifying eligible studies. 123 publications were identified from the initial keywords search. After review, 113 were excluded. Overall, 10 articles met our inclusion criteria. There were 10 studies with 2832 cases and 3747 controls for the XPD Lys751Gln polymorphism, and 5 studies with 1962 cases and 2369 controls for the XPD Asp312Asn polymorphism. **Table 1** summarized the characteristics of the studies included in the meta-analysis. The genotype distribu-

Table 2. Meta-analysis of the XPD Lys 751 Gln and Asp 312 Asn polymorphisms and cutaneous basal cell carcinoma risk

Study characteristics		Case/controls	Genetic model	OR (95% CI)	I^2 (%)	P for heterogeneity
XPD Lys 751 Gln						
Total (N = 10)		2832/3747	Allele Model	0.97 (0.90-1.04)	35.3	0.125
			OR_G	0.95 (0.87-1.04)	15.9	0.296
Source of control	PB (N = 7)	1723/2718	Allele Model	0.96 (0.87-1.05)	51.5	0.054
			OR_G	0.94 (0.84-1.05)	34.0	0.169
	HB (N = 3)	1109/1029	Allele Model	0.99 (0.88-1.12)	0	0.506
			OR_G	0.98 (0.85-1.14)	0	0.508
Sample size	≥500 (N = 6)	2693/3392	Allele Model	0.96 (0.89-1.04)	0	0.864
			OR_G	0.95 (0.87-1.04)	0	0.840
	<500 (N = 4)	139/355	Allele Model	1.07 (0.78-1.46)	74.1	0.009
			OR_G	1.06 (0.48-2.33)	64.7	0.037
HWE	YES (N = 9)	2824/3569	Allele Model	0.96 (0.89-1.04)	0	0.593
			OR_G	0.95 (0.87-1.04)	0	0.687
	NO (N = 1)	8/178	Allele Model	3.98 (1.44-10.99)	--	--
			OR_G	8.60 (1.26-58.49)	--	--
XPD Asp 312 Asn						
Total (N=5)		1962/2369	Allele Model	0.94(0.86-1.03)	0	0.650
			OR_G	0.94 (0.85-1.05)	0	0.603
Source of control	PB (N = 3)	1385/1885	Allele Model	0.97 (0.87-1.08)	0	0.807
			OR_G	0.98 (0.86-1.10)	0	0.628
	HB (N = 2)	577/484	Allele Model	0.87 (0.73-1.04)	0	0.337
			OR_G	0.86 (0.70-1.06)	0	0.382
Sample size	≥500 (N = 4)	1894/2264	Allele Model	0.94 (0.86-1.03)	0	0.533
			OR_G	0.94 (0.84-1.05)	0	0.470
	<500 (N = 1)	68/105	Allele Model	1.06 (0.68-1.65)	--	--
			OR_G	1.06 (0.63-1.77)	--	--
HWE	YES (N = 4)	1894/2264	Allele Model	0.94 (0.86-1.03)	0	0.533
			OR_G	0.94 (0.84-1.05)	0	0.470
	NO (N = 1)	68/105	Allele Model	1.06 (0.68-1.65)	--	--

OR_G: The Generalized Odds Ratio.

tions in the controls of all studies were consistent with HWE except for two studies [8, 16].

Quantitative synthesis

As shown in **Table 2**, pooled analysis did not yield a significant association between XPD Lys751Gln polymorphism and overall basal cell carcinoma risk (**Figure 2**, allele model: OR = 0.97, 95% CI 0.90-1.04, I^2 = 35.3%, $P_{heterogeneity}$ = 0.125 and model-free: OR_G = 0.95, 95% CI 0.87-1.04, I^2 = 15.9%, $P_{heterogeneity}$ = 0.296). Next, we performed stratification analysis for the association between the XPD Lys751Gln polymorphism variant genotypes by source of control, sample size, and HWE, no significant association was found (**Table 2**).

Similarly, for XPD Asp312Asn polymorphism, no significant association was found in overall comparison (**Figure 3**, allele model: OR = 0.94, 95% CI 0.86-1.03, I^2 = 0, $P_{heterogeneity}$ = 0.650 and model-free: OR_G = 0.94, 95% CI 0.85-1.05, I^2 = 0, $P_{heterogeneity}$ = 0.603) and stratification analysis by source of control, sample size, and HWE (**Table 2**).

Sensitive analysis

The influence of each study on the overall meta-analysis estimate was assessed by eliminating one study at a time, respectively. The OR was not significantly influenced by omitting any single study (**Figure 4**).

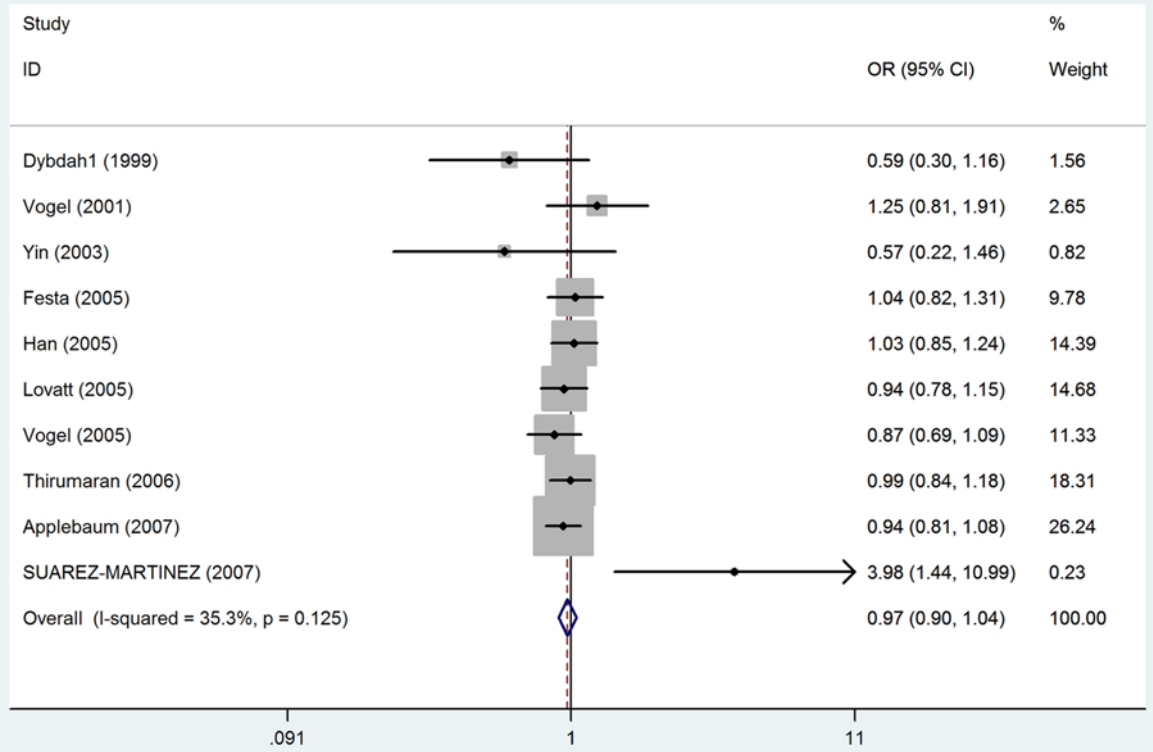

Figure 2. Forest plot of cutaneous basal cell carcinoma associated with XPD Lys751Gln polymorphism under an allelic genetic model.

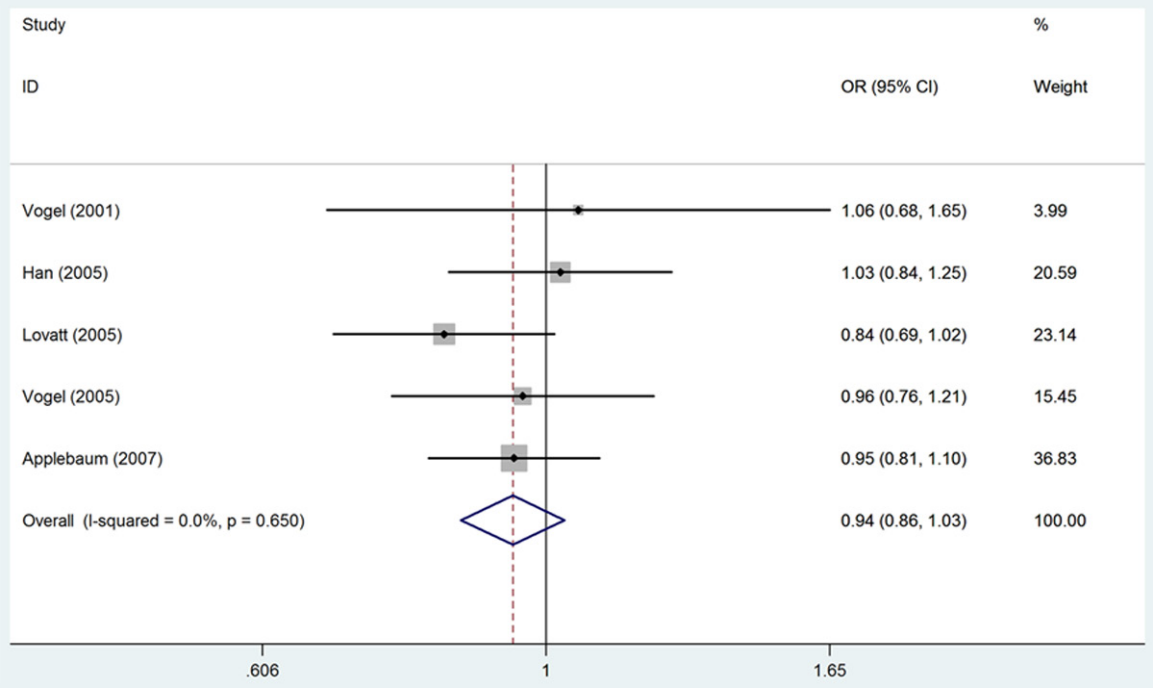

Figure 3. Forest plot of cutaneous basal cell carcinoma associated with XPD Asp312Asn polymorphism under an allelic genetic model.

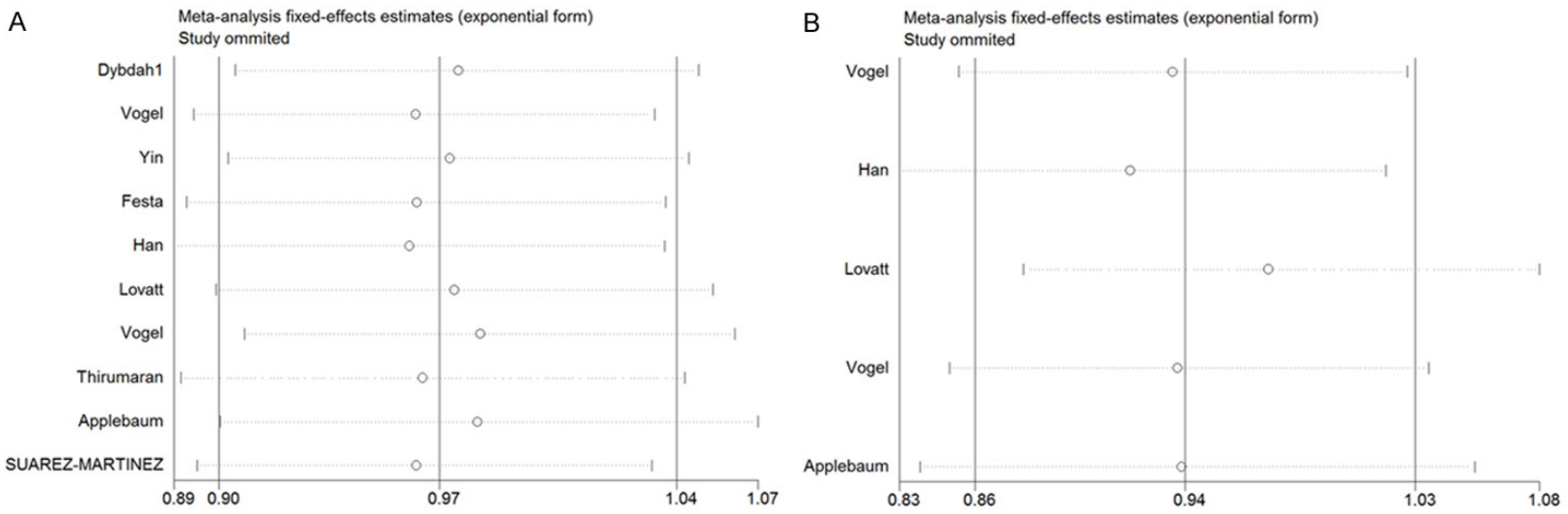

Figure 4. Sensitivity analysis: examining the influence of individual studies to pooled odds ratios (OR). A. XPD Lys751Gln polymorphism in allele model. B. XPD Asp312Asn polymorphism in allele model.

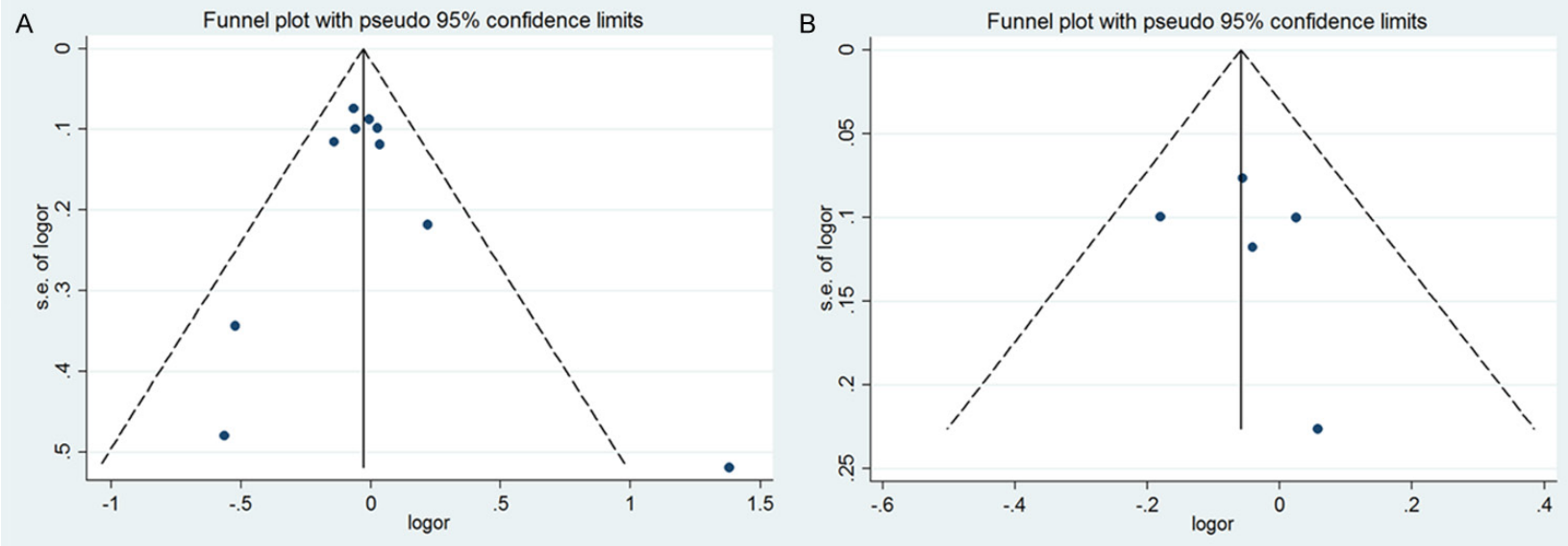

Figure 5. Begg's funnel plot for publication bias test. Each point represents a separate study for the indicated association. A. Funnel plot for allele model of XPD Lys751Gln polymorphism. B. Funnel plot for allele model of XPD Asp312Asn polymorphism.

Publication bias

Begg's funnel plot and Egger's test were performed to assess publication bias among the literatures. As shown in **Figure 5**, there was no evidence of publication bias for XPD Lys751Gln in allele model (Begg's test $P = 0.858$; Egger's test $P = 0.621$) and XPD Asp312Asn in allele model (Begg's test $P = 0.462$; Egger's test $P = 0.625$).

Discussion

DNA in most cells is regularly damaged by endogenous and exogenous mutagens. Unrepaired damage can result in apoptosis or it may lead to unregulated cell growth and cancer [18]. Because of the importance of maintaining genomic integrity in the general and specialized functions of cells as well as in the prevention of carcinogenesis, genes coding for DNA repair molecules have been proposed as candidate cancer-susceptibility genes [19-21]. At least four pathways of DNA repair operate on specific types of damaged DNA, and each pathway involves numerous molecules. DNA base excision repair (BER) operates on small lesions such as oxidized or reduced bases, fragmented or nonbulky adducts, or those produced by methylating agents [22]. The functional significance of these XPD variants has not yet been elucidated, but some of the variants may be associated with a reduced repair capacity and increased cancer susceptibility. Most of the epidemiologic studies on cancer reported to date have focused on SNPs in codons 312 and 751, because of their high frequencies [23].

To our knowledge, the current meta-analysis is the largest one to investigate the association between XPD Lys751Gln and Asp312Asn polymorphisms and BCC risk. Pooled analysis for the XPD Lys751Gln polymorphism contained 10 studies with a total of 2832 cases and 3747 controls; meanwhile, pooled analysis for the XPD Asp312Asn polymorphism encompassed 5 studies with 1962 cases and 2369 controls. The meta-analysis observed no significant association between XPD Lys751Gln and Asp312Asn polymorphisms and BCC risk in the overall population and in the subgroup analysis by source of control, sample size, and HWE.

At present, the majority of meta-analyses of genetic association studies are usually conducted by comparing genotype frequencies between cases and controls under various genetic models. However, these genetic models are not independent, and a priori knowledge or biological justification for model selection is seldom available [24, 25]. But in our study, the model-free approach was used. The application of OR_G might overcome the drawbacks of multiple model testing or erroneous model specification and make the interpretation of the results easier [17].

The current study has some inevitable limitations that should be acknowledged. First, XPD polymorphisms may interact with other known and unknown risk factors which should be considered. Second, our results were based on an unadjusted estimated, a more precise analysis would have been conducted if more detailed individual data were available. Third, the selected studies may have more subject to bias and artifact than prospective studies.

In summary, we concluded that the XPD Lys751Gln and Asp312Asn polymorphisms were not associated with cutaneous basal cell carcinoma risk. However, future well designed large studies, particularly stratified by gene-gene and gene-environment interactions might be necessary to clarify the possible role of the XPD Lys751Gln and Asp312Asn polymorphisms in the susceptibility to BCC.

Disclosure of conflict of interest

None.

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