

## RESEARCH ARTICLE

# Association Between XPD Asp312Asn Polymorphism and Esophageal Cancer Susceptibility: A Meta-analysis

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### Abstract

**Objective:** To investigate the association between xeroderma pigmentosum group D (XPD) Asp312Asn polymorphism and esophageal cancer (EC) susceptibility by meta-analysis. **Methods:** We searched PubMed up to April 9th, 2012, to identify relevant papers, and 8 published case-control studies including 2165 EC patients and 3141 healthy controls were yielded. Odds ratios (ORs) with relevant 95% confidence intervals (CIs) were applied to assess the association between XPD Asp312Asn polymorphism and EC susceptibility with the Comprehensive Meta-Analysis software, version 2.2. **Results:** Overall, the meta-analysis results suggested the XPD Asp312Asn polymorphism to be significantly associated with EC susceptibility [(Asn/Asn+Asp/Asn) vs. Asp/Asp: OR=1.20, 95% CI=1.05-1.36, p=0.01; and Asp/Asn vs. Asp/Asp: OR= 1.15, 95% CI =1.01-1.31, p=0.04]. In the subgroup analysis by ethnicity and cancer type, significantly associations were found for Caucasian populations [(Asn/Asn+Asp/Asn) vs. Asp/Asp: OR=1.26, 95% CI=1.08-1.47, p<0.001; Asp/Asn vs. Asp/Asp: OR=1.19, 95% CI=1.02-1.40, p=0.03] and esophageal squamous cell carcinoma [(Asn/Asn+Asp/Asn) vs. Asp/Asp: OR=1.19, 95% CI=1.01-1.41, p=0.04]. There was no heterogeneity and no publication bias existed. **Conclusions:** This meta-analysis shows that the XPD Asp312Asn polymorphism may be a risk factor for developing EC, especially for Caucasian populations and esophageal squamous cell carcinoma.

**Keywords:** XPD - excision repair - polymorphism - esophageal cancer - susceptibility - meta-analysis

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### Introduction

Esophageal cancer (EC) is one of the most common malignant diseases in an area that stretches from the Caucasian mountains to northern China, it is ranked as the eighth most common malignancy and the sixth most common cancer mortality worldwide (Umar et al., 2008). According to histopathology, EC can be major classified into esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EADC), higher incidence rate of EAC occurs in Western countries, while ESCC appears more oftenly in oriental countries (Brown et al., 2008; Szumilo, 2009; Zheng et al., 2010). Up to now, the cause and pathogenesis for EC are still unknown, several lifestyle risk factors including exposed to tobacco, alcohol, obesity, and dietary factors have been identified (Vaughan et al., 1995; Mayne et al., 2001). Molecular researches provide genetic alteration is a novel risk factor of EC, that make individual more sensitive to carcinogen exposure (Lea et al., 2007). The genetic alteration s include aberrant cell cycle control, DNA repair, cellular enzymes, growth factor receptors, and nuclear receptors (Xu, 2009). Decreased efficiency of DNA repair is

considered as a crucial role in carcinogenesis, as such defects accelerate genetic instability and the rate of genetic change (Hoeijmakers, 2001; Wood et al., 2001). The xeroderma pigmentosum group D (XPD) enzyme plays an important role in the repair of bulky DNA adducts, such as pyrimidine dimers, photoproducts and cross-links (Hoeijmakers, 2001).

The XPD gene now also named excision repair cross-complementing group 2 (ERCC2) gene, that maps to chromosome 19q13.3 and is composed of 23 exons. The XPD enzyme is 761 amino acids in length, has fuction of nucleotide excision repair pathway. Mutations in the XPD gene can result in three different disorders: xeroderma pigmentosum, trichothiodystrophy, and Cockayne syndrome (Cleaver et al., 1999). Several single-nucleotide polymorphisms (SNPs) have been identified in the XPD gene, Asp312Asn (rs1799793) and Lys751Gln (rs13181) are commonly found and result in amino acid changes (Shen et al., 1998). Currently, there are many molecular epidemiological studies have explored the association between XPD Asp312Asn and and Lys751Gln polymorphism and EC susceptibility. Two meta-analyses focused on XPD Lys751Gln polymorphism and EC risk

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suggested that it may be associated with increased risk of EADC (Yuan et al., 2011), or may be a potential biomarker of EC susceptibility in Chinese populations (Ding et al., 2012). However, XPD Asp312Asn polymorphism and EC susceptibility of the relevant studies are still controversial rather than conclusive. Therefore, we performed this meta-analysis of eight published eligible studies, follow the proposed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Moher et al., 2009) guidelines, to derive a more precise estimation of the XPD Asp312Asn polymorphism and EC susceptibility

## Materials and Methods

### Literatures search

Initially we identified relevant studies which tested the association between XPD Asp312Asn polymorphism and EC susceptibility by searching the PubMed (up to April 9<sup>th</sup>, 2012), using the following search terms: (“ERCC2” or “XPD” or “xeroderma pigmentosum group D” or “excision repair cross-complementing group 2” or “DNA repair gene”) and (“esophageal” or “esophagus”). No restrictions were imposed, and the bibliographies of the included studies were checked for other relevant publications.

### Study selection

Two authors independently evaluated the eligibility of all studies retrieved from the database according to the following criteria: (1) case-control study design; (2) investigated the association between XPD Asp312Asn polymorphism and EC susceptibility; (3) diagnosis of ESCC and EAC were either histologically, pathologically or cytologically confirmed; (4) the odds ratios (OR) and the corresponding 95% confidence intervals (CIs), or the number of events that can calculate them reported. Disagreements were resolved by discussion.

### Data extraction

Two authors independently extracted data from all eligible publications as follow: first author’s last name, year of publication, site of origin, characteristics of cancer cases, source of controls, matching criteria, number of cases and controls, number of different genotypes in cases and controls, Hardy-Weinberg equilibrium (HWE), and minor allele frequency in controls. When study included subjects of more than one cancer types, genotype data was extracted separately for subgroup analysis. Any disagreements were resolved by consensus.

### Statistical analysis

We computed a pooled OR and 95% CI for the risk allele by using the Comprehensive Meta-Analysis software, version 2.2 (Biostat, Englewood, New Jersey) (Borenstein et al., 2005) to generate forest plots, so as to determine whether there was a statistical association between cases and controls and to assess heterogeneity of the included studies. HWE was tested by chi-square test at a significant level of  $p < 0.05$ . Heterogeneity was evaluated by using the Cochran’s Q statistic (Higgins et al., 2002) and the  $I^2$  statistic,  $I^2$  statistic yields results ranged

from 0 to 100% ( $I^2=0-25%$ , no heterogeneity;  $I^2=25-50%$ , moderate heterogeneity;  $I^2=50-75%$ , large heterogeneity; and  $I^2=75-100%$ , extreme heterogeneity) (Higgins et al., 2003). If heterogeneity existed, the random effects model was used, otherwise, the fixed effects model was used. In addition, we investigated the influence of a single study to the overall risk estimate by removal each study in turn, and to test the robustness of the main results, subgroup analysis was also conducted if significant heterogeneity is identified. If possible, potential publication bias was assessed by visual inspection of the funnel plots and the Egger weighted regression method ( $P < 0.05$  was considered representative of statistical significance) (Egger et al., 1997).

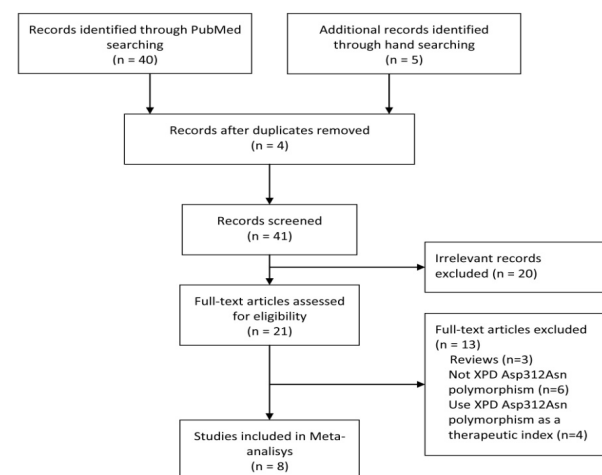
## Results

### Study identification

Of the 45 records found initially, 8 case-control studies were included for this meta-analysis (Xing et al., 2002; Xing et al., 2003; Yu et al., 2004; Ye et al., 2006; Liu et al., 2007; Tse et al., 2008; Pan et al., 2009; Huang et al., 2012). A detailed flowchart of the selection process was showed in Figure 1.

### Study characteristics

Table 1 presents major characteristics of the 8 studies. All the studies’ informations were available. The subjects form 135 to 433 in case group while 152 to 524 in control group, comprising 2165 cases and 3141 controls. Four studies were conducted in China (Xing et al., 2002; Xing et al., 2003; Yu et al., 2004; Huang et al., 2012), three in the USA (Liu et al., 2007; Tse et al., 2008; Pan et al., 2009), and one in Sweden (Ye et al., 2006). In terms of source of control, all had a well matched, two was form hospital-based (HB) (Yu et al., 2004; Huang et al., 2012), and 6 were population-based (PB) (Xing et al., 2002; Xing et al., 2003; Ye et al., 2006; Liu et al., 2007; Tse et al., 2008; Pan et al., 2009). The cancer type of 4 were ESCC (Xing et al., 2002; Xing et al., 2003; Yu et al., 2004; Huang et al., 2012), two were EADC (Liu et al., 2007; Tse et al., 2008), and 2 were both (Ye et al., 2006; Pan et al., 2009). The genotyping methods including PCR-RFLP (5 studies) (Xing et al., 2003; Yu et al., 2004; Ye et al., 2006; Liu et



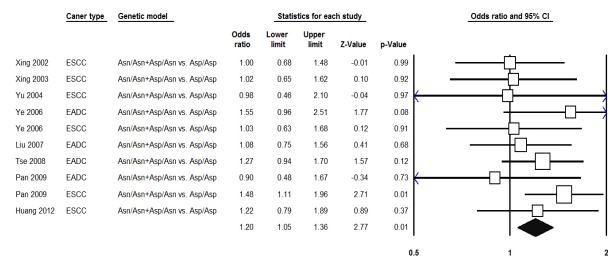
**Figure 1. Flow Diagram of the Study Selection Process**

**Table 1. Characteristics of Case-control Studies on XPD Asp312Asn Polymorphism and Esophageal Cancer Susceptibility Included in the Meta-analysis**

Reference	Country	Ethnicity	Control source	Sample size			Cancer type	Genotype distribution						Genotyping method	p for HWE
								Case			Control				
								Asp/Asp	Asp/Asn	Asn/Asn	Asp/Asp	Asp/Asn	Asn/Asn		
Xing 2002	China	Asia	PB	433	524	ESCC	381	49	3	461	62	1	PCR	0.47	
Xing 2003	China	Asia	PB	325	383	ESCC	286	38	1	338	45	0	PCR-RFLP	0.22	
Yu 2004	China	Asia	HB	135	152	ESCC	121	14	0	136	16	0	PCR-RFLP	0.49	
Ye 2006	Sweden	Caucasian	PB	96	472	EADC	31	51	14	176	237	57	PCR-RFLP	0.09	
				81		ESCC	30	41	10						
Liu 2007	USA	Caucasian	PB	183	336	EADC	75	92	16	144	160	32	PCR-RFLP	0.19	
Tse 2008	USA	Caucasian	PB	312	454	EADC	117	150	43	199	206	49	Taqman	0.69	
Pan 2009	USA	Caucasian	PB	44	462	EADC	16	20	1	201	185	48	Taqman	0.58	
				343		ESCC	137	163	43	201	185	48			
Huang 2012	China	Asia	HB	213	358	ESCC	171	42	0	298	60	0	PCR-RFLP	0.08	

**Table 2. Summary ORs and 95% CI of XPD Asp312Asn Polymorphism and Esophageal Cancer Susceptibility**

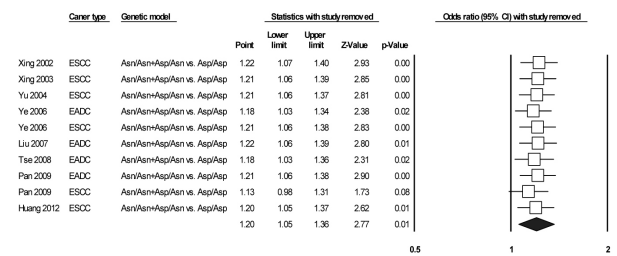
Group and subgroups	No. of trails	Asn/Asn vs. Asp/Asp				Asp/Asn vs. Asp/Asp				(Asn/Asn+Asp/Asn) vs. Asp/Asp				Asn/Asn vs. (Asp/Asp+Asp/Asn)			
		Heterogeneity		Meta-analysis		Heterogeneity		Meta-analysis		Heterogeneity		Meta-analysis		Heterogeneity		Meta-analysis	
		I <sup>2</sup>	p	OR (95%CI)	p'	I <sup>2</sup>	p	OR (95%CI)	P'	I <sup>2</sup>	p	OR (95%CI)	P'	I <sup>2</sup>	p	OR (95%CI)	P'
Total	10	0	0.66	1.27(0.99-1.64)	0.06	0	0.97	1.15(1.01-1.31)	0.04	0	0.70	1.20(1.05-1.36)	0.01	0	0.60	1.17(0.93-1.49)	0.18
Ethnicity																	
Asia	4	0	0.99	3.60(0.57-22.92)	0.17	0	0.83	1.06(0.84-1.34)	0.63	0	0.91	1.06(0.84-1.34)	0.61	0	0.99	3.61(0.57-23.00)	0.17
Caucasian	6	0	0.58	1.25(0.97-1.21)	0.09	0	0.93	1.19(1.02-1.40)	0.03	0	0.49	1.26(1.08-1.47)	<0.001	0	0.54	1.15(0.91-1.46)	0.24
Control source																	
HB	2	NA				0	0.58	1.19(0.81-1.73)	0.38	0	0.63	1.16(0.79-1.69)	0.45	NA			
PB	8	0	0.66	1.27(0.99-1.64)	0.06	0	0.92	1.14(0.99-1.32)	0.06	0	0.52	1.20(1.05-1.38)	0.01	0	0.60	1.17(0.93-1.49)	0.18
Cancer type																	
ESCC	0	0	0.68	1.29(0.87-1.91)	0.20	0	0.80	1.12(0.94-1.33)	0.21	0	0.54	1.19(1.01-1.41)	0.04	0	0.67	1.23(0.85-1.77)	0.27
EADC	4	14.29	0.32	1.26(0.90-1.75)	0.18	0	0.95	1.19(0.97-1.46)	0.09	0	0.50	1.21(0.99-1.47)	0.06	22.80	0.27	1.14(0.84-1.55)	0.41
Genotyping method																	
PCR	1	0	1.00	3.63(0.38-35.04)	0.27	0	1.00	0.98(0.66-1.45)	0.91	0	1.00	1.00(0.68-1.48)	0.99	0	1.00	3.65(0.38-35.20)	0.26
PCR-RFLP	6	0	0.77	1.13(0.76-1.70)	0.55	0	0.97	1.09(0.90-1.32)	0.38	0	0.81	1.14(0.95-1.38)	0.17	0	0.80	1.07(0.74-1.56)	0.72
Taqman	3	24.83	0.26	1.34(0.97-1.86)	0.08	0	0.96	1.27(1.04-1.57)	0.02	8.4	0.34	1.32(1.08-1.60)	0.01	38.37	0.20	1.22(0.90-1.66)	0.19

**Figure 2. ORs of Esophageal Cancer Susceptibility Associated with XPD Asp312Asn Polymorphism for the (Asn/Asn + Asp/Asn) vs. Asp/Asp Model. ESCC, Esophageal Squamous Cell Carcinoma; EADC, Esophageal Adenocarcinoma**

al., 2007; Huang et al., 2012), TaqMan (2 studies) (Tse et al., 2008; Pan et al., 2009), and PCR (one study) (Xing et al., 2002). The genotype distributions in the controls of all 8 studies were in accordance with HWE.

#### Meta-analyses

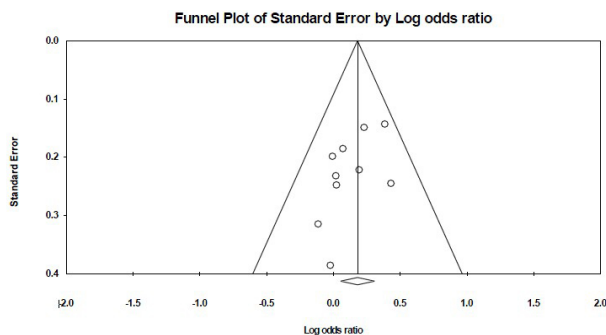
Table 2 showed the main results and the heterogeneity test of meta-analyses in the total population. Overall, there was no substantial heterogeneity existed that all the genetic models used the fixed-effect models. We found a significant association of XPD Asp312Asn polymorphism with EC susceptibility for the dominant comparison [(Asn/Asn+Asp/Asn) vs. Asp/Asp: OR=1.20, 95%CI=1.05-1.36, p=0.01, Figure 2] and borderline significantly increased risk was found in heterozygote comparison (Asp/Asn vs. Asp/Asp: OR= 1.15, 95%CI =1.01-1.31, p=0.04).

**Figure 3. Sensitivity Analysis Through Omitting one Study Each Time to Reflect the Influence of the Individual Dataset to the Pooled ORs in (Asn/Asn + Asp/Asn) vs. Asp/Asp Model. ESCC, Esophageal Squamous Cell Carcinoma; EADC, Esophageal Adenocarcinoma**

However, such associations were not found in other comparisons [Asn/Asn vs. Asp/Asp: OR=1.27, 95%CI =0.99-1.64, p= 0.06; Asn/Asn vs. (Asp/Asp+Asp/Asn): OR=1.17, 95%CI=0.93-1.49, p=0.18].

#### Subgroup and sensitivity analyses

In the stratified analysis by ethnicity, we only found a weak association of XPD Asp312Asn polymorphism with EC susceptibility in Caucasian populations [(Asn/Asn+Asp/Asn) vs. Asp/Asp: OR=1.26, 95%CI =1.08-1.47, p<0.001; Asp/Asn vs. Asp/Asp: OR=1.19, 95%CI =1.02-1.40, p=0.03], but not in Asian populations. The similar association was also found in genotyping method of Taqman [(Asn/Asn+Asp/Asn) vs. Asp/Asp: OR=1.32, 95%CI =1.08-1.60, p=0.01; Asp/Asn vs. Asp/Asp: OR =1.27, 95%CI =1.04-1.57, p=0.02]. When stratified



**Figure 4. Funnel Plot Analysis to Detect Publication Bias for or the (Asn/Asn + Asp/Asn) vs. Asp/Asp Genotype.** Each point represents a separate study for the indicated association

by control source and cancer type, we only detected a significant association for the dominant comparison of population-based [(Asn/Asn+Asp/Asn) vs. Asp/Asp: OR=1.20, 95%CI= 1.05-1.38,  $p=0.01$ ] and ESCC [(Asn/Asn+Asp/Asn) vs. Asp/Asp: OR=1.19, 95%CI= 1.01-1.41,  $p=0.04$ ]. The pooled ORs along with their 95% CIs are presented in detail in Table 2.

Sensitivity analysis was carried out by omitting each study included in the meta-analysis each turn and the results in any genetic model were not materially altered (Figure 3 showed the result for the dominant model), that indicated the results were statistically robust.

#### Publication bias

Funnel plot and the Egger's test were performed to assess possible publication bias. The funnel plot for the dominant genetic model (Asn/Asn+Asp/Asn) vs. Asp/Asp showed that no publication bias was detected (Figure 4), this was also confirmed by the results of Egger's test [for Asn/Asn vs. Asp/Asp:  $p=0.83$ ; for Asp/Asn vs. Asp/Asp:  $p=0.26$ ; for (Asn/Asn+Asp/Asn) vs. Asp/Asp:  $p=0.09$ ; and for Asn/Asn vs. (Asp/Asp+Asp/Asn):  $p=0.83$ ]

## Discussion

Currently, genetic susceptibility to cancer has absorbed growing attention to the study of gene polymorphisms involved in carcinogenesis. The XPD gene has been mapped to chromosome 19q13.3 and it is composed of 23 exons, and the XPD protein is involved in transcription-coupled nucleotide excision repair and is an integral member of the basal transcription factor BTF2/TFIIH complex. The Asp to Asn change at position 312 of XPD changes the electronic configuration of amino acid and alters the interaction between XPD protein and its helicase activator (Coin et al., 1998). To date, a lot of epidemiological studies have been performed to explore the role of XPD Asp312Asn polymorphism on EC susceptibility, but the results remain controversial. In order to obtain a more precise estimation of association, we pooled the results of the 8 eligible case-control studies in this meta-analysis, including 2165 cases and 3141 controls.

The results showed that for the XPD Asp312Asn polymorphism, individuals carrying the variant homozygote Asn/Asn had an increased risk to EC

susceptibility in total populations. In the subgroup analysis based on ethnicities, a significant associations were found under the dominant model, suggesting that XPD Asp312Asn polymorphism play similar roles in Caucasian populations, that indicated ethnic difference in genetic background and the environment they lived in may play a possible role of EC susceptibility. When stratified by cancer type, a borderline associations was also found under the dominant model for ESCC, but not for EADC, worthy of note, this was reversed compared to XPD Lys751Gln polymorphism (Yuan et al., 2011).

There are some limitations in our meta-analysis should be addressed. Firstly, some studies on this association were adjusted by some conventional risk factors such as tobacco, alcohol, and lifestyle, however, our results were based on unadjusted estimates, and lack of original data from the eligible studies limited the evaluation of the effects of the gene-gene and gene-environment interactions in EC development. Secondly, this meta-analysis based on a rather limited number of studies, and the sample size was still relatively small, thus we did not obtain enough evidence to detect the real association between XPD Asp/Asn polymorphism and EC susceptibility. Finally, it is well known that each gene has only a moderate effect on EC development, so the XPD gene may influence susceptibility of EC with other genes, but we did not have enough data to conduct this interactions analysis. In spite of these limitations, no heterogeneity and publication bias were detected, and a large number of subjects still significantly guarantee the statistical power of this meta-analysis.

In conclusion, our meta-analysis suggested that XPD Asp312Asn polymorphism may contribute to EC susceptibility, especially to ESCC susceptibility. In addition, well designed large-scale case-control studies are suggested in order to further enrich the present findings.

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