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Association between XPD Lys751Gln polymorphism and risk of head and neck cancer: a meta-analysis

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ABSTRACT. Several studies have investigated the association between Lys751Gln polymorphism in the xeroderma pigmentosum group D (*XPD*) gene and risk of head and neck cancer; however, the published results are conflicting. We conducted a meta-analysis that comprised 15 published case-control studies examining the association of head and neck cancer risk with *XPD* Lys751Gln polymorphism in different populations, based on the data identified in Medline up to November 2010. Odds ratios (ORs) with 95% confidence intervals (CI) were used to assess the strength of the association. Overall, significantly elevated head and neck cancer risk was associated with *XPD* Lys751Gln polymorphism when all studies were pooled into the meta-analysis [(Gln/Gln + Lys/Gln) *vs* Lys/Lys: OR = 1.12, 95%CI = 1.03-1.22, P < 0.01, heterogeneity P = 0.11]. In the subgroup analysis by ethnicity, borderline significantly increased risk was found for Europeans [(Gln/Gln + Lys/Gln) *vs* Lys/Lys: OR = 1.11, 95%CI = 1.00-1.23, P < 0.05]. In conclusion, our meta-analysis demonstrated that *XPD* Lys751Gln polymorphism could be a prediction marker for risk of head and neck cancer.

Key words: Polymorphism; Head and neck cancer; Meta-analysis; XPD

INTRODUCTION

Head and neck cancer (HNC) is one of most common cancers worldwide. It constitutes about 5% of all cancers in the US and the incidence is similar in most developed and developing countries. Smoking and alcohol consumption are well-recognized risk factors for HNC. It has been reported that HNC is much more common in smokers Fthan in non-smokers and most common in males over 50 years of age (Kamangar et al., 2006; American Cancer Society, 2007). Specifically, cancers in the mouth and throat are about six times more common in smokers than in non-smokers, increasing to about 15 times if the smokers are also heavy drinkers (Blot et al., 1988; Lichtenstein et al., 2000; Schottenfeld and Fraumeni, 2006). Furthermore, candidate gene association studies also provide cumulative evidence that genetic factors including family history and polymorphisms in genes, such as DNA repair genes, play an important role in the development of HNC.

Many environmental factors, such as radiation, diet, smoking, and endogenous or exogenous estrogens, are associated with DNA damage (Schottenfeld and Fraumeni, 2006). Unrepaired or misrepaired DNA results in gene mutations, chromosomal alterations and genomic instability. Several studies have suggested that genes involved in the DNA repair system play a crucial role in protecting against mutations and patients with certain cancers have reduced DNA repair capacity (Goode et al., 2002). Associations between polymorphisms in several DNA repair genes and risks of multiple cancers have been extensively examined. Of those, xeroderma pigmentosum group D (*XPD*), also known as excision repair cross-complementing group 2 (*ERCC2*), is one of eight nucleotide excision repair (NER) core genes (i.e., *ERCC1*, *XPA*, *XPB*/*ERCC3*, *XPC*, *XPD*/*ERCC2*, *XPE*/*DDB1*, *XPF/ERCC4* and *XPG*/*ERCC5*). The XPD protein is a DNA helicase and an essential part of the TFIIH transcription factor complex. Some studies have suggested that polymorphisms in *XPD* may be associated with reduced DNA repair due to a possible reduction in helicase activity (Schaeffer et al., 1994; Coin et al., 1998; Winkler et al., 2000). One of the common *XPD* polymorphisms is Lys751Gln (rs13181) in exon 23. It has been reported that this amino acid change in exon 23 may lead to loss of an acidic residue and a complete change in the electronic configuration of the amino acid (de Boer and Hoeijmakers, 2000; Pastorelli et al., 2002).

A number of studies have investigated the effect of *XPD* Lys751Gln polymorphism on HNC risk; however, the results remain conflicting rather than conclusive (Sturgis et al., 2000; Rydzanicz et al., 2005; Huang et al., 2005; Kietthubthew et al., 2006; Matullo et al., 2006; Ramachandran et al., 2006; Bau et al., 2007; An et al., 2007; Majumder et al., 2007; Harth et al., 2008; Abbasi et al., 2009; Mitra et al., 2009; Jelonek et al., 2010; Ji et al., 2010; Sliwinski et al., 2011). Therefore, we performed a meta-analysis including 15 published case-control studies to assess the overall relationship between the *XPD* Lys751Gln polymorphism and HNC risk.

MATERIAL AND METHODS

Search strategy

The PubMed database was searched with the terms “head and neck cancer”, “oral cancer”, “oropharyngeal cancer”, “laryngeal cancer”, “pharyngeal cancer”, “XPD”, “excision

repair cross-complementing group 2", and "polymorphism" (last search update February 2011). We also used the PubMed option "Related Articles" to identify additional studies on the same topic. Reference lists in retrieved articles were also screened. All selected studies should fulfill the following two criteria: a) case-control studies on *XPD* Lys751Gln polymorphism and HNC risk; b) sufficient published data for estimating an odds ratio (OR) with 95% confidence interval (CI). We selected the largest or most recent publication (Little et al., 2002) if multiple publications reported on the same or overlapping data.

Data extraction

The following information was extracted from each included publication: the first author's name, publication data, sources of controls, racial descent of the study population (categorized as Asian or European), genotyping method and number of cases and controls with different genotypes, and P value for Hardy-Weinberg equilibrium (HWE).

Statistical analysis

Crude ORs with 95% CIs were computed to assess the strength of relationship between the *XPD* Lys751Gln polymorphism and HNC risk. The pooled ORs were performed for the allele contrast (Gln *vs* Lys), co-dominant model (Gln/Gln *vs* Lys/Lys, Lys/Gln *vs* Lys/Lys), dominant model [(Gln/Gln + Lys) / Gln *vs* Lys/Lys], and recessive model [Gln/Gln *vs* (Lys/Lys + Lys/Gln)], respectively. In addition, we conducted the stratification analysis in Asians and Europeans. Heterogeneity assumption was assessed by the chi-square based Q-test (Lau et al., 1997). The pooled OR estimation of each study was calculated by the random-effects model (the DerSimonian and Laird method) when $P < 0.10$; otherwise, the fixed-effects model (the Mantel-Haenszel method) was used (DerSimonian and Laird, 1986). The potential publication bias was estimated by Egger's linear regression test by visual inspection of the Funnel plot (Egger et al., 1997). Statistical analysis was performed using the Statistical Analysis System software (v.9.1.3; SAS Institute, Cary, NC) and Review Manage (v.4.2; Oxford, England), using two-sided P values.

RESULTS

Study characteristic

A total of 15 eligible case-control studies on the association between *XPD* Lys751Gln polymorphism and HNC risk were included for this meta-analysis (Sturgis et al., 2000; Rydzanicz et al., 2005; Huang et al., 2005; Kietthubthew et al., 2006; Matullo et al., 2006; Ramachandran et al., 2006; Bau et al., 2007; An et al., 2007; Majumder et al., 2007; Harth et al., 2008; Abbasi et al., 2009; Mitra et al., 2009; Jelonek et al., 2010; Ji et al., 2010; Sliwinski et al., 2011). Table 1 presents the main characteristics of these studies. There were 9 studies of European populations and 6 studies of Asians. Diverse genotyping methods included PCR-RFLP and TaqMan. All studies indicated that the distribution of genotypes in the controls was consistent with HWE except two (Abbasi et al., 2009; Jelonek et al., 2010).

Table 1. Characteristics of case-control studies on *XPD* Lys751Gln included in the meta-analysis.

First author	Racial descent	Source of controls	Case	Control	Genotype distribution						Genotying type	P for HWE†
					Case			Control				
					Lys/Lys	Lys/Gln	Gln/Gln	Lys/Lys	Lys/Gln	Gln/Gln		
Sturgis, 2000	Europeans	Healthy controls	189	496	75	83	31	218	221	57	PCR-RFLP	0.93
Rydzanicz, 2005	Europeans	Healthy controls	172	143	69	73	30	54	64	25	PCR-RFLP	0.43
Huang, 2005	Europeans	Healthy controls	544	775	240	235	69	345	325	105	TaqMan-PCR	0.04
Kietthubthew, 2006	Asians	Hospital controls	105	164	83	21	1	126	36	2	PCR-RFLP	0.75
Matullo, 2006	Europeans	Healthy controls	82	1094	34	39	9	397	504	193	TaqMan-PCR	0.13
Ramachandran, 2006	Asians	Healthy controls	110	110	49	46	15	71	31	8	PCR-RFLP	0.09
Bau, 2007	Asians	Healthy controls	154	105	134	18	2	89	15	1	PCR-RFLP	0.68
Jiaze, 2007	Europeans	Hospital controls	829	854	330	394	105	358	386	110	PCR-RFLP	0.71
Majumder, 2007	Asians	Hospital controls	309	388	158	125	26	190	158	40	PCR-RFLP	0.40
Harth, 2008	Europeans	Healthy controls	312	300	111	154	47	108	149	43	PCR-RFLP	0.46
Abbasi, 2009	Europeans	Healthy controls	246	644	95	117	34	250	280	114	PCR-RFLP	0.02
Mitra, 2009	Asians	Healthy controls	385	275	88	148	39	163	179	43	PCR-RFLP	0.56
Jelonek, 2010	Europeans	Healthy controls	103	110	29	52	22	38	60	12	PCR-RFLP	0.10
Ji, 2010	Asians	Hospital controls	267	348	232	32	3	298	48	2	PCR-SBE	0.96
Tomasz, 2010	Europeans	Healthy controls	265	280	93	155	17	106	151	23	PCR-RFLP	<0.01

†HWE in control.

Meta-analysis

The main results of this meta-analysis and the heterogeneity test are shown in Table 2. Overall, we found a significant association of *XPD* Lys751Gln polymorphism with HNC risk for the dominant comparison [(Gln/Gln + Lys/Gln) *vs* Lys/Lys: OR = 1.12, 95%CI = 1.03-1.22, P = 0.01, heterogeneity P = 0.11, Figure 1] and borderline significantly increased risk was found in heterozygote comparison (Lys/Gln *vs* Lys/Lys: OR = 1.08, 95%CI = 0.99-1.19, P = 0.08, heterogeneity P = 0.47, Figure 2). However, such associations were not found in other comparisons [Gln *vs* Lys: OR = 1.04, 95%CI = 0.93-1.15, P = 0.51, heterogeneity P = 0.006; Gln/Gln *vs* Lys/Lys: OR = 1.06, 95%CI = 0.92-1.22, P = 0.45, heterogeneity P = 0.12; Gln/Gln *vs* (Lys/Lys + Lys/Gln): OR = 0.98, 95%CI = 0.86-1.12, P = 0.75, heterogeneity P = 0.16]. In the stratified analysis by ethnicity, we only found a borderline association of *XPD* Lys751Gln polymorphism with HNC risk in European populations [(Gln/Gln + Lys/Gln) *vs* Lys/Lys: OR = 1.11, 95%CI = 1.00-1.23, P = 0.05, heterogeneity P = 0.62), but not in Asian populations. Sensitivity analysis was carried out by limiting the meta-analysis to those studies fulfilling HWE and the results in any genetic model were not materially altered (data not shown).

Table 2. Summary ORs and 95%CI of *XPD* Lys751Gln polymorphism and HNC risk.

Contrast	Racial descent	OR	95%CI	P*
Gln *vs* Lys	Total	1.04	0.93-1.15	<0.01†
	Asian	1.02	0.75-1.40	<0.01†
	European	1.02	0.95-1.10	0.38
Gln/Gln *vs* Lys/Lys	Total	1.06	0.92-1.22	0.12
	Asian	1.31	0.95-1.82	0.21
	European	1.00	0.86-1.17	0.19
Lys/Gln *vs* Lys/Lys	Total	1.08	0.99-1.19	0.47
	Asian	1.13	0.84-1.52	0.04†
	European	1.06	0.96-1.19	0.99
(Gln/Gln + Lys/Gln) *vs* Lys/Lys	Total	1.12	1.03-1.22	0.11
	Asian	1.15	0.84-1.57	0.01†
	European	1.11	1.00-1.23	0.62
Gln/Gln *vs* (Lys/Lys + Lys/Gln)	Total	0.98	0.86-1.12	0.16
	Asian	1.16	0.85-1.58	0.53
	European	0.96	0.78-1.18	0.09†

*Test for heterogeneity. †Estimates for random effects model.

Publication bias

Funnel plot and Egger's test were performed to estimate the publication bias of literatures. The shapes of the funnel plots in all genetic models did not reveal any evidence of obvious asymmetry. Figure 3 shows the shape of the funnel plots of the dominant model (Gln/Gln + Lys/Gln *vs* Lys/Lys) in all populations and the result was further supported by Egger's tests [P = 0.31 for (Gln/Gln + Lys/Gln) *vs* Lys/Lys].

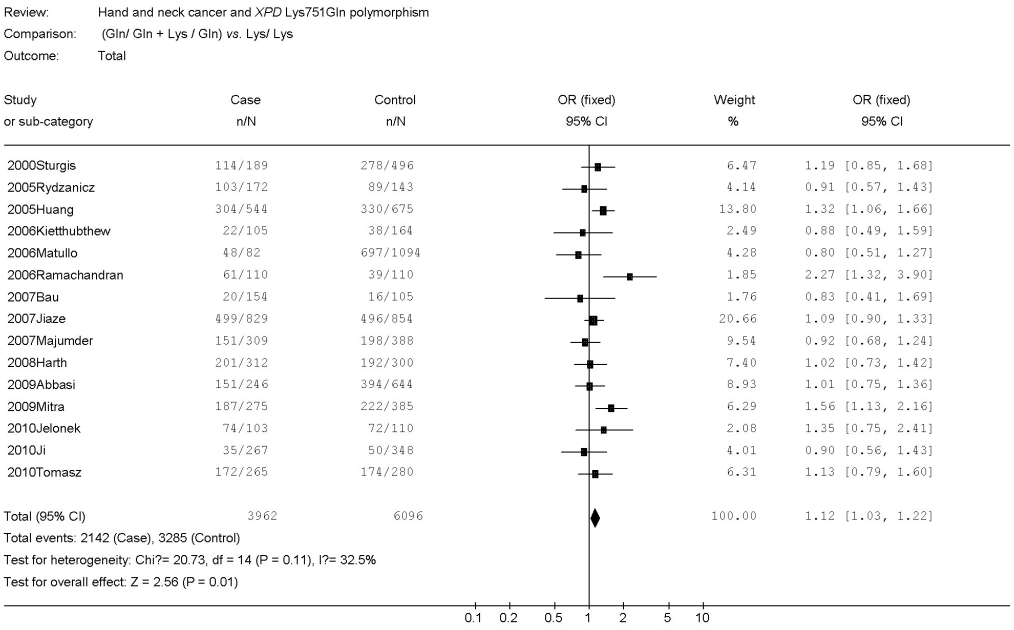

Figure 1. ORs of HNC cancer associated with *XPD* Lys751Gln polymorphism for the Gln/Gln + Lys/Gln genotype compared with the Lys/Lys genotype.

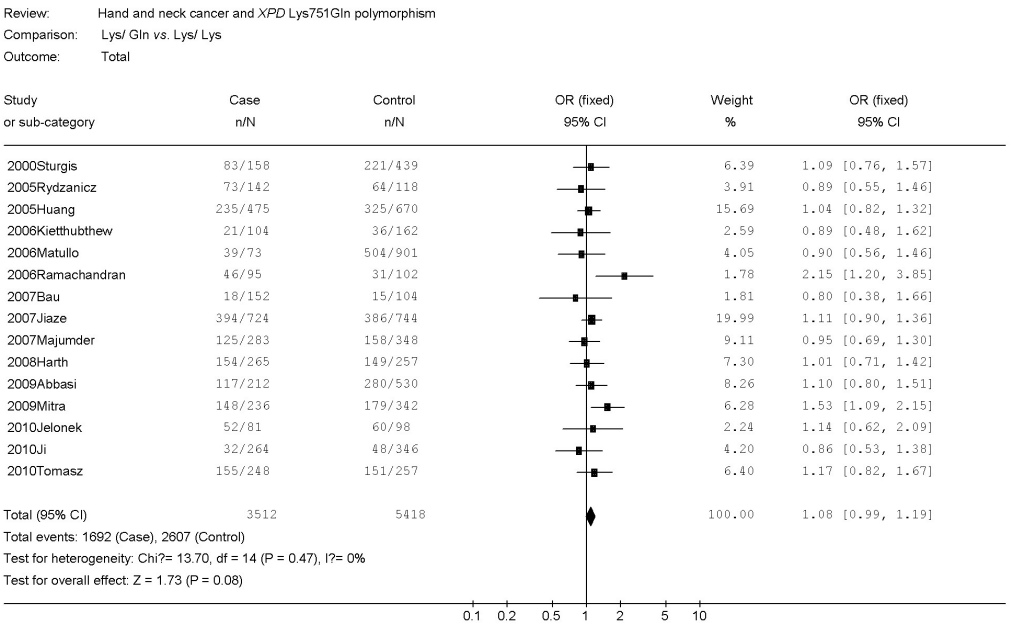

Figure 2. OR of HNC cancer associated with *XPD* Lys751Gln polymorphism for the Lys/Gln genotype compared with the Lys/Lys genotype in total.

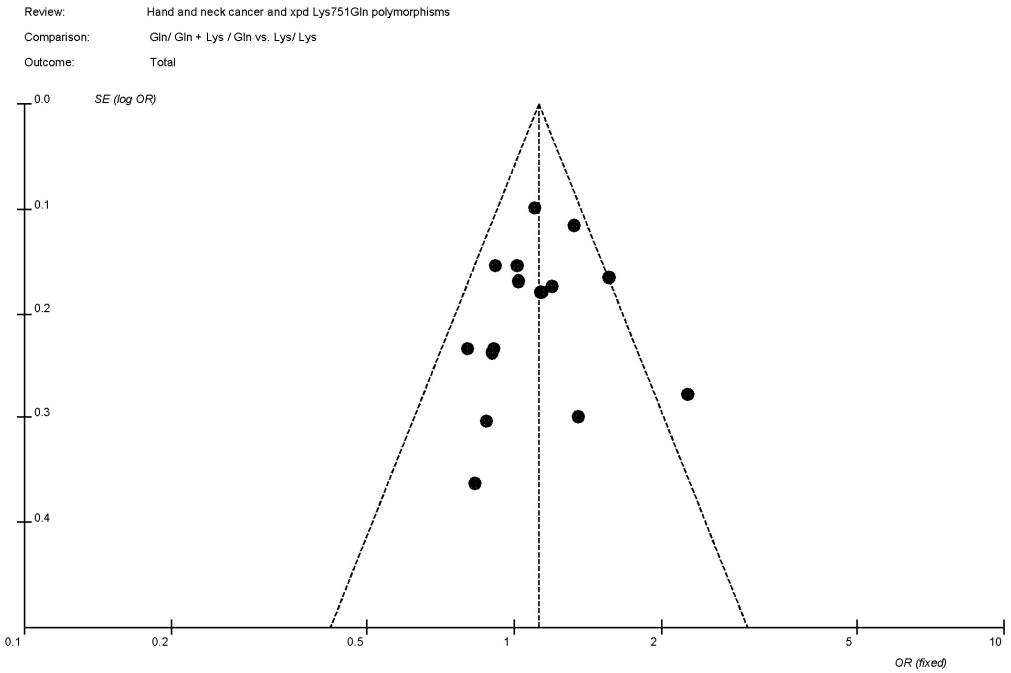

Figure 3. Funnel plot analysis to detect publication bias. Each point represents a separate study for the indicated association.

DISCUSSION

XPD gene maps to chromosome 19q13.3 and is composed of 23 exons. Its protein consists of 761 amino acids in length (Flejter et al., 1992) and is involved in transcription-coupled NER by acting as an integral member of the basal transcription factor BTF2/TFIIH complex (Schaeffer et al., 1994; Winkler et al., 2000). The *XPD* product has an ATP-dependent DNA helicase activity and belongs to the RAD3/XPD subfamily of helicases. Mutations in the XPD gene can result in three different disorders: xeroderma pigmentosum, trichothiodystrophy, and Cockayne syndrome (de Boer and Hoeijmakers, 2000). Correlation of its polymorphisms and cancer risk has been studied, but the results remain controversial.

Sturgis et al. (2000) reported that 13181CC was associated with a borderline increased risk (adjusted OR = 1.55; 95%CI = 0.96-2.52) of SCCHN and it was higher in older subjects (OR = 2.22; 95%CI = 1.03-4.80) and current drinkers (OR = 2.59; 95%CI = 1.25-5.34). Mitra et al. (2009) found statistically significant increased SCCHN risk in individuals with the variant genotypes of rs13181: (OR = 1.680, 95%CI 1.014 to 2.784), (OR = 1.531, 95%CI 1.092 to 2.149) and (OR = 1.560, 95%CI 1.128 to 2.158). The others came to a different conclusion. Huang et al. (2005) found that *XPD*751 was not associated with HNC risk (OR = 1.10; 95%CI, 0.83-1.45). We pooled the results of the 15 eligible case-control studies in this meta-analysis and found a significant association of *XPD* Lys751Gln polymorphism with HNC risk in total populations. In the subgroup analysis based on ethnicities, borderline associations were found

under the dominant model, suggesting that *XPD* Lys751Gln polymorphism play similar roles in Europeans.

There are some limitations that should be addressed. First, these results were based on unadjusted estimates, and the lack of original data from the eligible studies limited the evaluation of the effects of the gene-gene and gene-environment interactions in HNC development. Second, the sample size is still relatively small. Thus, we did not have enough statistical power to find the real relationship between *XPD* polymorphism and HNC risk. Finally, it is well known that each gene has only a moderate effect on HNC development. The combinations of certain genotypes may be more discriminating as risk factors than a single locus.

In conclusion, despite these limitations, we found *XPD* Lys751Gln polymorphism may contribute to HNC susceptibility in the pooled population. Large-scale case-control and population-based association studies are warranted to validate the risk identified in the current meta-analysis and investigate the potential gene-gene and gene-environment interactions on HNC risk.

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Conflict of interest

None declared.

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