RESEARCH ARTICLE

Genetic Association between the XPG Asp1104His Polymorphism and Head and Neck Cancer Susceptibility: Evidence Based on a Meta-Analysis

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Abstract

Background: Previous studies evaluating the association between the xeroderma pigmentosum group G (XPG) Asp1104His polymorphism and head and neck cancer susceptibility have proven controversial. This meta-analysis of the literature was performed to obtain a more precise estimation of the relationship. Materials and Methods: We systematically searched PubMed, Embase and Web of Science with a time limit of Dec 18, 2014. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of any association. Results: We performed a meta-analysis of eight published case-control studies, including 3,621 cases and 5,475 controls. Overall, no significant association was found between the XPG Asp1104His polymorphism and head and neck cancer susceptibility under all genetic models. In the subgroup analysis by ethnicity, the XPG Asp1104His polymorphism had statistically significant association with elevated head and neck cancer risk under CC *vs* GG (OR=1.24, 95% CI=1.00~1.54) and the recessive model (OR=1.22, 95%CI=1.01~1.46) in Asian populations. A similar result was found under CC *vs* GG (OR =1.22, 95%CI =1.01~1.47) in the population based subgroup by source of control. When performed by tumor site, the XPG Asp1104His polymorphism had statistically significant association with elevated laryngeal cancer under all genetic models (CC *vs* GG: OR=1.59, 95% CI=1.16~2.19; GC *vs* GG: OR=1.38, 95%CI=1.10~1.72; dominant model: OR=1.42, 95% CI=1.15~1.74; recessive model: OR=1.36, 95% CI=1.02~1.81). Conclusions: This meta-analysis suggested that the XPG Asp1104His polymorphism is a risk factor for head and neck cancer susceptibility, especially for laryngeal cancer and in Asian populations.

Keywords: *XPG* Asp1104His - polymorphism - head and neck cancer - meta-analysis

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Introduction

Head and neck cancer (HNC), which includes cancers of the oral cavity, pharynx, hypopharynx, and larynx, is one of the most common cancers worldwide (Siegel et al., 2014). It accounts for nearly 3% of all incident malignancies in the United States with an estimated 52, 610 new cases and 11, 500 deaths from HNC in 2012 (Siegel et al., 2012). To date, there are ample evidences indicating that HNC is a complex multifactorial disorder involving genetic factors, lifestyle, tobacco smoke, alcohol consuming, and environmental factors (Shammaa et al., 2008; Liu et al., 2012; Mokhtari., 2012; Smith et al., 2012) and some low penetrant genes have been identified as potential HNC susceptibility genes (Hopkins et al., 2008; Arora et al., 2012).

Among them, an important one is the xeroderma pigmentosum group G (*XPG*) gene, also known as the excision repair cross complementing group 5 (ERCC5) gene, the *XPG* gene is located on chromosome 13q22-q33, encodes a 1186 amino-acid protein that functions as an endonuclease, cutting the DNA at the 3' terminus during the DNA repair process via the amino acids located in the N-terminus of the protein (Emmert et al., 2001; Clarkson, 2003). It is a member of the flap structure-specific endonuclease 1 (FEN1) family and encodes a protein of 1186 amino acids. The primary structure of human *XPG* protein harbors the N- and Inuclease domains that are highly conserved, which together form the nuclease core (Melis et al., 2013). Single nucleotide polymorphisms (SNPs) in *XPG* gene have been discovered in human populations, the Asp1104His polymorphism (rs17655 G>C) is common [minor allele frequency (MAF) >0.05] and regarded as a tagger, which was most frequently investigated for its association with cancer risk.

To date, molecular epidemiological studies have

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investigated the relationship between the *XPG* Asp1104His polymorphism and predisposition to HNC. However, results of these studies are controversial; Therefore, we performed this meta-analysis in order to precisely assess the possible association of the *XPG* Asp1104His with the susceptibility to develop HNC.

Materials and Methods

Search strategy

A systematic and electronic search of the PubMed, EMBASE and Web of Science was performed to identify studies using combinations of the following search terms: "*head and neck cancer*", "*oral cancer*", "*oropharyngeal cancer*", "*hypopharynx cancer*" "laryngeal cancer", "pharyngeal cancer", "cancer", "tumor", "carcinoma", "nucleotide excision repair", "*XPG*", "*ERCC5*", "*polymorphism*", and "*variation*". All of the studies were

Table 1. Characteristics of Case-Control Studies Included in the Meta-Analysis

No. of											
Study	**Year**	**Country**	**Gene test**	**Source**	**Site**	**Case/ Control**	**Case**				
XPG His1104Asp							**GG**	**GC**	**CC**		
Lu B	2014	Asian	MassARRAY Analyzer	HB	Laryngeal	176/176	53	69	54		
Li X	2014	Asian	Sequenom MassARRAY	HB	Laryngeal	211/210	64	79	68		
Wyss AB	2013	Caucasian	Illumina GoldenGate assay	PB	head and neck	915/1066	365		550		
Ma H	2012	Caucasian	ABI7900 sequence detection system	HB	head and neck	1059/1056	648	359	52		
Yuan H	2012	Asian	ABI7900 sequence detection system	HB	head and neck	394/884	108	191	95		
Abbasi R	2009	Caucasian	PCR-RFLP	PB	Laryngeal	248/647	137	103	8		
Wen SX	2006	Asian	PCR-RFLP	HB	head and neck	175/525	55	81	39		
Cui Y	2006	Caucasian	PCR-RFLP	PB	head and neck	443/911	214	194	35		
Study	**Year**	**Country**	**Gene test**	**Source**	**Site**	**Case/ Control**	**Control**			**HWE**	**NOS**
XPG His1104Asp							**GG**	**GC**	**CC**		
Lu B	2014	Asian	MassARRAY Analyzer	HB	Laryngeal	176/176	78	62	36	0	8
Li X	2014	Asian	Sequenom MassARRAY	HB	Laryngeal	211/210	88	73	49	0	8
Wyss AB	2013	Caucasian	Illumina GoldenGate assay	PB	head and neck	915/1066	415		651	-	7
Ma H	2012	Caucasian	ABI7900 sequence detection system	HB	head and neck	1059/1056	654	350	52	0.56	8
Yuan H	2012	Asian	ABI7900 sequence detection system	HB	head and neck	394/884	234	433	217	0.55	9
Abbasi R	2009	Caucasian	PCR-RFLP	PB	Laryngeal	248/647	380	230	37	0.78	8
Wen SX	2006	Asian	PCR-RFLP	HB	head and neck	175/525	129	296	100	0	9
Cui Y	2006	Caucasian	PCR-RFLP	PB	head and neck	443/911	474	357	80	0.28	8

*HB hospital based, PB population based; HWE: Hardy-Weinberg equilibrium; PCR: Polymerase chain reaction; RFLP: Restriction fragment length polymorphism. NOS: Newcastle-Ottawa Scale

published from their earliest entry points to Dec 18, 2014. The search was limited to human studies and performed without any restrictions on language.

Inclusion criteria were defined as follows: (1) Studies that evaluated the association between the *XPG* Asp1104His polymorphism and HNC risk; (2) Case-control studies; (3) Studies with full-text article; (4) Sufficient data for estimating an odds ratio (OR) with 95% confidence interval (CI). (5) When duplicated studies were published by the same author obtained from the same patient sample, only the most complete publication study was included in this meta-analysis. Unpublished reports and abstracts were not considered.

Data extraction and quality assessment

Information was extracted carefully from all eligible publications independently by two investigators according to the inclusion criteria listed above. For conflicting evaluation, an agreement was reached following discussion. Data extracted from the selected articles included the first author's name, year of publication, country of origin, ethnicity, tumor site, genotyping methods, source of control, number of cases and controls. Ethnicities were categorized as Asian and Caucasian. Source of control were categorized as population based and hospital based. Tumor sites were categorized as laryngeal and mixed HNC. We did not define any minimum number of patients to include in our meta-analysis. The methodological quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS) (Stang, 2010) for quality of case control and cohort studies in this meta-analysis, a study awarded 7 or more stars as a high-quality study.

Statistical analysis

Pooled Odds ratios (ORs) with 95% confidence intervals (CIs) were used to evaluate the association between the *XPG* Asp1104His polymorphism and susceptibility to HNC. Although fixed-effects model and random-effects model yielded similar conclusions, many investigators considered that the random-effects model was a more natural choice than fixed-effects model in medical decision-making contexts (DerSimonian and Laird, 1986; Ades et al., 2005). So we chose to use the random-effects model with Mantel-Haenszel statistics (Mantel and Haenszel, 1959; Laird and Ware, 1982), which assumed that the true underlying effect varied among included studies. First, the pooled ORs were performed for co-dominant model (CC *vs* GG and GC *vs* GG), the dominant model (CC+GC *vs* GG), and the recessive model (CC *vs* GC+GG), respectively. For subgroup analysis, ethnicity, source of control, and tumor sites were analyzed statistically. Heterogeneity among the studies was assessed using the chi-square-based Q statistic (P<0.05 for the Q test indicates significant heterogeneity) (Cochran, 1954). We also quantified the effect of heterogeneity using the I2 statistic (Higgins and Thompson, 2002). Venice criteria (Ioannidis et al., 2008) for I^2 test: 'I^2 <25% represents no heterogeneity, I^2=25~50% represents moderate heterogeneity, I^2=50~75% represents significant heterogeneity, I^2>75% represents extreme heterogeneity. Finally, potential publication bias was evaluated through Begg's test and Egger's test by visual analysis of the funnel plot (Begg and Mazumdar, 1994; Egger et al., 1997), P< 0.05 was considered statistically significant publication bias. Hardy-Weinberg equilibrium in controls was calculated in our meta-analysis. The chi-squared goodness-of-fit test was used to test deviation from Hardy-Weinberg equilibrium (HWE; P<0.05 was considered significant). Meta-analysis was performed using the STATA statistical software (version 10.0). All the P values were two-sided.

Results

Study characteristics

The flow chart of study selection in summarized in Figure 1. The search strategy retrieved 193 potentially relevant studies. According to the inclusion criteria, as summarized in Table 1, a total of 8 eligible studies (Cui et al., 2006; Wen et al., 2006; Abbasi et al., 2009; Ma et al., 2012; Yuan et al., 2012; Wyss et al., 2013; Li et al., 2014; Lu et al., 2014) including 3, 621 cases and 5, 475 controls were included in the meta-analysis. All of the cases were histologically confirmed. The controls were primarily healthy population. In those included studies, four studies (Wen et al., 2006; Yuan et al., 2012; Li et al., 2014; Lu et al., 2014) were performed in Asians and four

Table 2. Main Results of Pooled Odds Ratios (OR) with Confidence Interval (CI) in the Meta-Analysis in Overall Population

Polymorphism	Genetic model	Genetic type	Heterogeneity test			OR (95% CI)	P1	Begg's test		Egger's test	
			Q	I^2 (%)	PH			Z	P2	t	P3
XPG His1104Asp	Codominant model	CC vs GG	15.2	60.50%	0.02	1.11 (0.94~1.31)	0.24	0.3	0.76	0.3	0.78
		GC vs GG	13.71	56.30%	0.03	1.09 (0.98~1.21)	0.12	0.9	0.37	0.46	0.67
	Dominant model	CC+GC vs GG	16.47	63.60%	0.01	1.10 (0.99~1.22)	0.07	0.9	0.37	0.91	0.41
	Recessive model	CC vs GC+GG	12.2	42.60%	0.09	1.03 (0.92~1.16)	0.57	1.11	0.27	0.59	0.58

*PH value for heterogeneity; Po value for OR; Pb value for Begg's test; Pe value for Egger's test; OR: Odds ratio; CI: Confidence interval

Table 3. Main Results of Pooled Odds Ratios (OR) with Confidence Interval (CI) in the Meta-Analysis by Ethnicity, Source of Controls and Tumor Site

Polymor phism	Subgroup (N)	Genetic type	Heterogeneity test			OR (95% CI)	P1	Begg's test		Egger's test	
Asp148Glu			Q	I^2 (%)	PH			Z	P2	t	P3
Race	Asian (4)	CC vs GG	11.27	73.40%	0.01	1.24 (1.00~1.54)	0.05	1.7	0.09	6.05	0.28
		GC vs GG	11.62	74.20%	0.01	1.03 (0.85~1.24)	0.77	1.02	0.31	3.85	0.51
		CC+GC vs GG	15.65	80.80%	0	1.11 (0.93~1.32)	0.24	1.02	0.31	5.69	0.43
		CC vs GC+GG	5.67	47.10%	0.13	1.22 (1.01~1.46)	0.04	1.7	0.09	5.03	0.05
	Caucasian (4)	CC vs GG	1.39	0.00%	0.5	0.93 (0.71~1.22)	0.58	1.04	0.3	-2.62	0
		GC vs GG	1.51	0.00%	0.47	1.12 (0.98~1.28)	0.09	1.04	0.3	3.27	0.24
		CC+GC vs GG	0.81	0.00%	0.68	1.10 (0.99~1.22)	0.17	0	1	2.11	0.37
		CC vs GC+GG	2.03	0.00%	0.57	0.93 (0.80~1.08)	0.37	1.7	0.09	-1.12	0.26
Source	HB (5)	CC vs GG	12.05	66.80%	0.02	1.19 (0.98~1.43)	0.08	1.71	0.09	6.25	0.16
		GC vs GG	11.63	65.60%	0.02	1.03 (0.90~1.17)	0.64	0.73	0.46	0.96	0.7
		CC+GC vs GG	15.94	74.90%	0	1.07 (0.95~1.21)	0.28	0.73	0.46	2.04	0.5
		CC vs GC+GG	6.45	38.00%	0.17	1.17 (0.99~1.39)	0.07	2.2	0.03	4.65	0.08
	PB (3)	CC vs GG	1.1	9.10%	0.29	0.86 (0.59~1.25)	0.43	0	1	-2.61	-
		GC vs GG	0.03	0.00%	0.87	1.22 (1.01~1.47)	0.04	0	1	0.94	-
		CC+GC vs GG	0	0.00%	0.97	1.16 (0.97~1.39)	0.11	0	1	-0.19	-
		CC vs GC+GG	1.92	42.60%	0.09	0.92 (0.79~1.09)	0.33	1.04	0.3	-1.46	0.25
Site	Laryngeal (3)	CC vs GG	7.78	74.30%	0.02	1.59 (1.16~2.19)	0	0	1	-7.91	0.25
		GC vs GG	1.04	0.00%	0.6	1.38 (1.10~1.72)	0.01	1.04	0.3	2.71	0.09
		CC+GC vs GG	3.86	48.20%	0.15	1.42 (1.15~1.74)	0	1.04	0.3	6.52	0.02
		CC vs GC+GG	6.51	69.30%	0.04	1.36 (1.02~1.81)	0.04	0	1	-6.12	0.21
	Mixed (5)	CC vs GG	0.1	0.00%	0.99	0.96 (0.79~1.18)	0.7	0.34	0.73	-0.22	0.81
		GC vs GG	7.23	58.50%	0.07	1.02 (0.90~1.15)	0.8	1.02	0.31	-3.7	0.27
		CC+GC vs GG	5.03	40.40%	0.17	1.01 (0.90~1.34)	0.84	1.02	0.31	-3.22	0.26
		CC vs GC+GG	1.3	0.00%	0.86	0.98 (0.86~1.12)	0.78	0.73	0.46	0.57	0.52

*N for numbers of studies; PH value for heterogeneity; Po value for OR; Pb value for Begg's test; Pe value for Egger's test; OR: Odds ratio; CI: Confidence interval

(Cui et al., 2006; Abbasi et al., 2009; Ma et al., 2012; Wyss et al., 2013) were conducted in Caucasians. Five studies (Wen et al., 2006; Ma et al., 2012; Yuan et al., 2012; Li et al., 2014; Lu et al., 2014) were hospital-based, three studies (Cui et al., 2006; Abbasi et al., 2009; Wyss et al., 2013) were population-based. Three studies (Abbasi et al., 2009; Li et al., 2014; Lu et al., 2014) was performed on laryngeal cancer, five studies (Cui et al., 2006; Wen et al., 2006; Ma et al., 2012; Yuan et al., 2012; Wyss et al., 2013) on mixed cancers. Consequently, we performed subgroup analysis by stratification of ethnicity, source of controls and cancer type. Details of subjects in these studies were outlined in Table 1. Studies with control not in Hardy-Weinberg equilibrium (HWE) were also considered for meta-analysis, but they were excluded in the sensitivity analysis (Minelli et al., 2008).

Main meta-analysis results

The main results of our meta-analysis under four distinct genetic models were listed in Table 2and Table 3. Overall, the *XPG* Asp1104His polymorphism had no association with increased HNC risk under all four genetic models (CC *vs* GG: OR=1.11, 95% CI=0.94~1.31, *P*=0.02, Figuer 2A; GC *vs* GG: OR=1.09, 95% CI=0.98~1.21,

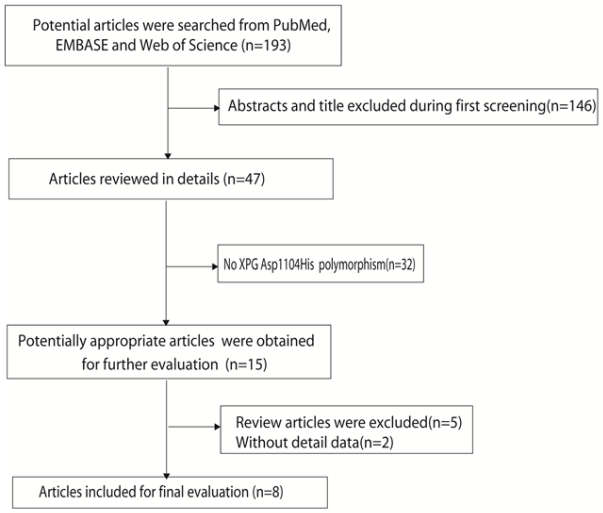

Figure 1. Study Selection Process for the Meta-Analysis

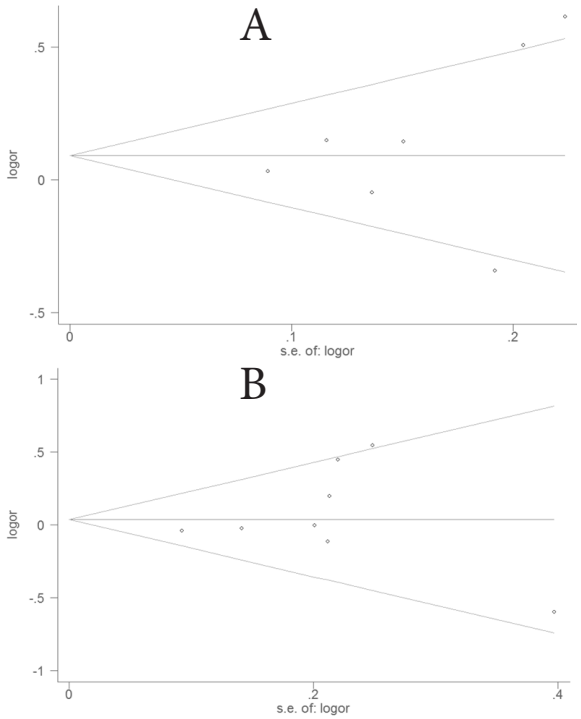

Figure 3. Publication Bias in Studies of the Relation between the XPG Asp1104His polymorphism and HNC Susceptibility Under the Dominant Model and the Recessive Model. A funnel plot with pseudo-95% confidence limits (dashed lines) was used

P=0.03, Figuer 2B; dominant model: OR=1.10, 95% CI=0.99~1.22; *P*=0.01, Figuer 2C; recessive model: OR=1.03, 95% CI=0.92~1.16, *P*=0.09, Figuer 2D).

In the subgroup analysis by ethnicity, the *XPG* Asp1104His polymorphism had statistically significant association with elevated HNC risk under CC *vs* GG (OR=1.24, 95% CI=1.00~1.54) and the recessive model (OR=1.22, 95% CI=1.01~1.46) in Asian population.

In the subgroup analysis by source of control, the *XPG* Asp1104His polymorphism had statistically significant association with elevated HNC risk under CC *vs* GG (OR=1.22, 95% CI=1.01~1.47) in the population based

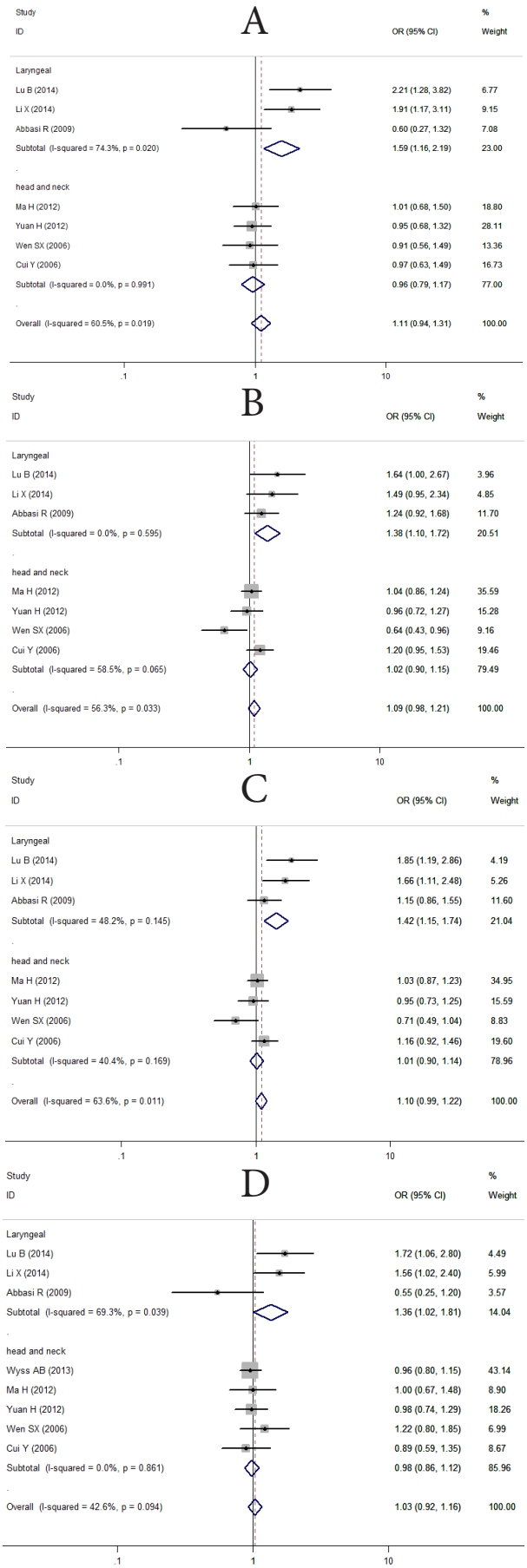

Figure 2. Odds ratios (ORs) for associations between the XPG Asp1104His polymorphism and HNC susceptibility.

subgroup.

In the subgroup analysis by cancer type, the *XPG* Asp1104His polymorphism had statistically significant association with elevated laryngeal cancer under all genetic models (CC *vs* GG: OR=1.59, 95% CI=1.16~2.19, Figuer 2A; GC *vs* GG: OR=1.38, 95% CI=1.10~1.72, Figuer 2B; dominant model: OR=1.42, 95% CI=1.15~1.74, Figuer 2C; recessive model: OR=1.36, 95% CI=1.02~1.81, Figuer 2D).

Heterogeneity and sensitivity analysis

As showed in Table2 and Table 3, there was statistically heterogeneity among these studies in overall comparisons (P<0.05), in the stratified analysis by ethnicity, source of control and tumor site, heterogeneity was also found in Asian, hospital based population and laryngeal cancer, but not found in some models in Caucasian, population based population.

Publication bias

Begg's funnel plot and Egger's test were performed to assess the potential publication bias in the available literature. The shape of funnel plots did not reveal any evidence of funnel plot asymmetry under the dominant model (Figuer 3A) and the recessive model (Figuer 3B). Egger's test also showed that there was no statistical significance for the evaluation of publication bias (CC *vs* GG: P=0.78, GC *vs* GG: P=0.67, dominant model: P=0.41, recessive model: P=0.58).

Discussion

DNA repair mechanisms play a critical role in the protection of cells from DNA damage and in the maintenance of genomic integrity. The nucleotide excision repair (NER) pathway is the primary mechanism for removal of bulky adducts from DNA, and thus is an important part of the cellular defense against a large variety of structural unrelated DNA lesions; The NER pathway includes several steps: The first step for NER pathway involves damage recognition by a complex of bound proteins, including *XPC*); The next step involves unwinding of the DNA by a complex including XPD and removal of the damaged single-stranded nucleotide fragment by molecules including *XPG*, ERCC1, and XPF (Tse et al., 2008; Machado et al., 2014; McCullough et al., 2014).

XPG is a NER pathway gene with an important role in the repair of DNA damage induced by exposure to environmental and biological mutagens or normal cellular metabolism. The *XPG* deficiency leads to DNA repair incapability, genomic instability, gene transcription. Abnormality, and facilitates cancer development (Cheng et al., 2002), Single nucleotide polymorphism (SNP) is the most common genetic variant in the genome; subtle functional alterations in SNPs may result in significant biological outcomes (Bernig and Chanock, 2006). Several genetic association studies have connected *XPG* Asp1104His polymorphism with HNC risk in the recent decade. However, the results contradict each other. To shed light on the association between the *XPG* Asp1104His polymorphism and HNC risk, we performed a meta-analysis involving eight case-control studies (9, 096 subjects). The summary OR of all case-control studies suggested no overall association for all genetic models adopted. Subgroup analyses were performed according to ethnicity and source of control, the results revealed the *XPG* Asp1104His polymorphism had statistically significant association with elevated HNC risk in Asian population and in the population based subgroup. The relationship between the *XPG* Asp1104His polymorphism and HNC susceptibility might be affected by the tumor sites. Accordingly, we also performed stratified analysis in the laryngeal cancer group, the result of this subgroup analysis showed a significant association between the *XPG* Asp1104His polymorphism and the risk of laryngeal cancer under all genetic models.

Although we have put considerable efforts and resources into testing possible association between the *XPG* Asp1104His polymorphism and HNC risk, there are still some limitations inherited from the published studies. First, a common limitation of meta-analysis was heterogeneity, heterogeneity was often caused by variation in the environmental and genetic background of study participants, which was unavoidable when combing many studies, and we found evidence of study heterogeneity in our study, presumably because of the ethnicity, source of control and tumor site. Second, the controls were not uniformly defined. Some studies used a healthy population as the reference group, whereas others selected hospital patients without organic breast cancer as the reference group. Therefore, non-differential misclassification bias is possible because these studies may have included the control groups who have different risks of developing breast cancer. Third, the overall outcomes were based on unadjusted estimates, while a more precise evaluation should be adjusted by other co-variants including tobacco use, alcohol consumption, viral infection, and environment factors if individual data were available.

In conclusion, our meta-analysis suggested that the *XPG* Asp1104His polymorphism was a risk factor for HNC susceptibility, especially in laryngeal cancer and in Asian population. However, further studies with large sample sizes are needed to investigate the association between the *XPG* Asp1104His polymorphisms and HNC susceptibility.

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