RESEARCH ARTICLE

XPD Lys751Gln and Asp312Asn Polymorphisms and Gastric Cancer Susceptibility: A Meta-analysis of Case-control Studies

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Abstract

Background: Published data regarding the association between xeroderma pigmentosum group D (XPD) Lys751Gln and Asp312Asn polymorphisms and gastric cancer susceptibility havew been inconclusive. This meta-analysis was therefore performed toobtain a more precise estimation of any relationship. Materials and Methods: A comprehensive literature search was conducted to identify all case–control studies of Lys751Gln and Asp312Asn polymorphisms and susceptibility to gastric cancer. Summary odds ratios (ORs) and its 95% confidence intervals (95% CIs) were calculated using a random-effects model with the software STATA (version10.0). Results: A total of 12 case-control studies including 3,147 cases and 4,736 controls were included. Overall, no significant associations were found in some models (for Lys751Gln: Lys/Gln vs Lys/Lys: OR=1.144, 95% CI=0.851–1.541, Gln/Gln vs Lys/Lys: OR=1.215, 95% CI = 0.740–1.955, dominant model: OR=1.137, 95% CI=0.818–1.582; recessive model: OR=1.123, 95% CI=0.765–1.650; for Asp312Asn: Asp/Asn vs Asp/Asp: OR=1.180, 95% CI=0.646–2.154, dominant model: OR=1.380, 95% CI = 0.812–2.346), but significantly elevated susceptibility was found for Asp312Asn polymorphism in some models (Asn/Asn vs Asp/Asp: OR=2.045, 95% CI=1.254–3.335, recessive model: OR=1.805, 95% CI =1.219–2.672), for the additive model, the XPD Lys751Gln and Asp312Asn polymorphisms were not significantly associated with gastric cancer susceptibility. In stratified analyses, significantly elevated susceptibility was found for some models in the Chinese population. Conclusion: This meta-analysis suggested the XPD Asp312Asn polymorphism might be a potential biomarker of gastric cancer susceptibility in overall population, while both XPD Lys751Gln and Asp312Asn polymorphisms might be risk factors of gastric cancer susceptibility in Chinese.

Keywords: Meta-analysis - gastric cancer - XPD polymorphisms; Lys751Gln; Asp312Asn

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Introduction

Gastric cancer is one of the most common cancers, a total of 989,600 new stomach cancer cases and 738,000 deaths are estimated to have occurred in 2008, accounting for 8% of the total cases and 10% of total deaths (Bertuccio et al., 2009; Ahmedin et al., 2011). The accurate mechanism that leads to gastric cancer remains to be elucidated. There are multiple risk factors that play a role in the gastric cancer susceptibility, such as unhealthy diet, infectious agents (e.g., Helicobacter pylori) and pre-existing conditions (e.g., pernicious anemia, atrophic gastritis, and intestinal polyps) (Lee et al., 2002). In addition to above exogenous factors, genetic polymorphism also plays an important role in gastric cancer susceptibility. The studies evaluate the association between DNA repair genes and gastric cancer susceptibility has been highly emphasized (Berwick et al., 2000).

Decreased efficiency of DNA repair is viewed as a crucial event in carcinogenesis (Hoeijmakers et al., 2001; Wood et al., 2001). Nucleotide excision repair (NER) is believed to be the most versatile DNA repair mechanism (Jiao et al., 2007). The xeroderma pigmentosum group D (XPD), also called excision repair cross complementing group 2 (ERCC2), is one of the NER enzymes, which is located at chromosome 19q13.3. Several important single nucleotide polymorphisms have been identified in the XPD locus, the high variant frequencies are at exon 10 (rs 1799793, codon 312 G→A, Asp→Asn) and exon 23 (rs 1052559, codon 751 A→C, Lys→Gln) (Shen et al., 1998), the two polymorphisms have been largely investigated in genetic epidemiologic studies and can render a higher risk of developing different types of cancer (Hemminki et al., 2001; Spitz et al., 2001; Hu et al., 2004; Ramos et al., 2004; Shi et al., 2004) .

To date, molecular epidemiological studies have investigated the relationships between the XPD

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polymorphisms and gastric cancer susceptibility. However, results of these studies were controversial, Therefore, we performed this meta-analysis of all eligible studies to evaluate the association between Asp312Asn and Lys751Gln polymorphisms and gastric cancer susceptibility.

Materials and Methods

Study identification and selection

We searched for studies in the PubMed, Embase, Web of Science, and CNKI (China National Knowledge Infrastructure) electronic databases by using the terms"XPD", "xeroderma pigmentosum group D", "ERCC2", "NER", "polymorphism" and "cancer" or "carcinoma", combined with "gastric cancer"or "stomach cancer" . The search was performed without any restrictions on language and was focused on studies that had been conducted in humans.

Inclusion criteria were defined as follows: (1) The articles evaluating the association between XPD Lys751Gln and Asp312Asn polymorphisms and the risk of gastric cancer; (2) The studies designed as case-control; (3) The sufficient data available to estimate an odds ratio (OR) with its 95% CI.

Data extraction

Information was carefully extracted from all eligible publications independently by two investigators according to the inclusion criteria listed above, discrepancies were adjusted by a third reviewer until consensus was achieved on every item. For each study, the following characteristics were collected: the first author's name, country or region, year of publication, source of publication, method of genotyping, total numbers of cases and controls, and numbers of cases and controls who harbored the XPD Lys751Gln and Asp312Asn polymorphisms.

Statistical analysis

We assessed the strength of association between XPD Lys751Gln and Asp312Asn polymorphisms and gastric cancer susceptibility by using ORs with 95% CIs given or could be calculated in the eligible studies. Although fixed-effect model and random-effects model yielded similar conclusions, we chose to use the random-effects model with Mantel-Haenszel statistics (DerSimonian et al., 1986; Ades et al., 2005), which assumed that the true underlying effect varied among included individuals. Moreover, many investigators also considered the random effects model to be a more natural choice than fixed effects model in medical decision-making contexts. First, the pooled ORs were performed for codominant model (Gln/Gln vs Lys/Lys and Asn/Asn vs Asp/Asp, Lys/Gln vs Lys/Lys and Asp/Asn vs Asp/Asp), dominant model (Gln/Gln+Lys/Gln vs Lys/Lys, Asn/Asn+Asp/Asn vs Asp/Asp), and recessive model (Gln/Gln vs. Lys/Gln+Lys/Lys, Asn/Asn vs. Asp/ Asn+Asp/Asp), respectively. Subgroup analyses were assessed according to ethnicity. Heterogeneity assumptions among studies were checked by the Chi square-test based Q-statistic. A significant Q-statistic ($P < 0.05$) indicated heterogeneity across studies (Cochran., 1954). Meanwhile, we measured the effect of heterogeneity by another measure, $I^2 = 100\% \times (Q - df)/Q$ (Higgins et al., 2002). Publication bias was observed with

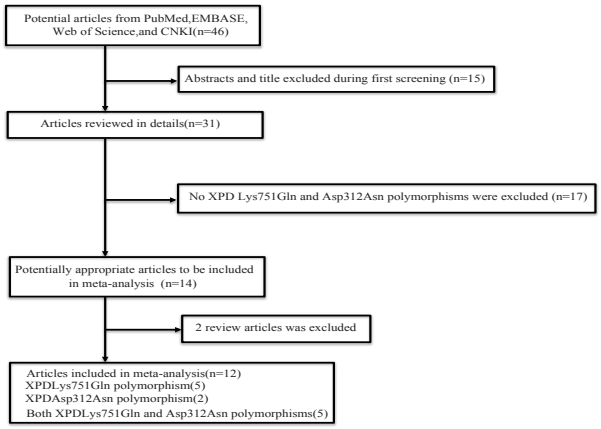

Figure 1. Study Selection Process for the Meta-analysis

Table 1. Main Characteristics of All Studies Included in the Meta-analysis

First author	Year	Area	Ethnicity	Single nucleotide polymorphism studied	Genotyping method	Control source	No. of cases	No. of Control
Engin AB	2011	Turkey	Non-China	Rs(1052559)Lys751Gln	PCR–RFLP	HB	106	116
Chen Z	2011	China	China	Rs(1052559)Lys751Gln	PCR–RFLP	HB	208	339
Palli D	2010	Italy	Non-China	Rs(1052559)Lys751Gln	PCR	PB	295	546
Canbay E	2010	Turkey	Non-China	Rs(1052559)Lys751Gln	PCR–RFLP	HB	40	247
Long XD	2010	China	China	Rs(1052559)Lys751Gln	TaqMan-PCR	HB	361	616
Zhang CZ	2009	China	China	Rs(1052559)Lys751Gln	PCR–RFLP	HB	207	212
Ruzzo A	2007	Italy	Non-China	Rs(1052559)Lys751Gln	PCR-RFLP	HB	89	94
Ye W	2006	Sweden	Non-China	Rs(1052559)Lys751Gln	PCR-SSCP	PB	126	303
Huang WY	2005	Poland	Non-China	Rs(1052559)Lys751Gln	PCR-SpectroDesigner Software	PB	279	381
Yi Lou	2006	China	China	Rs(1052559)Lys751Gln	PCR-RFLP	HB	238	200
Yuan T	2011	China	China	Rs(1799793)Asp312Asn	PCR and DNA sequenced	HB	190	180
Chen Z	2011	China	China	Rs(1799793)Asp312Asn	PCR–RFLP	HB	208	339
Zhang CZ	2009	China	China	Rs(1799793)Asp312Asn	PCR–RFLP	HB	207	212
Ruzzo A	2007	Italy	Non-China	Rs(1799793)Asp312Asn	PCR-RFLP	HB	69	121
Ye W	2006	Sweden	Non-China	Rs(1799793)Asp312Asn	PCR-SSCP	PB	126	470
Deng Sl	2010	China	China	Rs(1799793)Asp312Asn	ABI Analyzer	HB	160	160
Yi Lou	2006	China	China	Rs(1799793)Asp312Asn	PCR-RFLP	HB	238	200

HB, hospital based; PB, population based; PCR, Polymerase chain reaction; RFLP, Restriction fragment length polymorphism; SSCP, Single Strand Conformation Polymorphism

Table 2. Distribution of the Frequencies of XPD Lys751Gln and Asp312Asn Polymorphisms and Gastric Cancer

Lys751Gln First author	Year	Ethnicity	HWE	Genotype					
				Case n (%)			Control n (%)		
				Lys/Lys	Lys/Gln	Gln/Gln	Lys/Lys	Lys/Gln	Gln/Gln
Engin AB	2011	Non-China	0.006	30(28.30)	56(52.83)	20(18.87)	40(34.48)	43(37.07)	33(28.45)
Chen Z	2011	China	0.698	166(79.81)	40(19.233)	2(0.96)	282(83.19)	55(16.22)	2(0.59)
Palli D	2010	Non-China	0.099	90(30.51)	157(53.22)	48(16.27)	177(32.42)	284(52.01)	85(15.57)
Canbay E	2010	Non-China	0.922	14(35.00)	18(45.00)	8(20.00)	102(41.30)	114(46.15)	31(12.55)
Long XD	2010	China	0	139(38.50)	151(41.83)	71(19.67)	400(64.94)	164(26.62)	52(8.44)
Zhang CZ	2009	China	0.44	166(80.19)	39(18.84)	2(0.97)	172(81.13)	39(18.40)	1(0.47)
Ruzzo A	2007	Non-China	0.181	29(32.58)	44(49.44)	16(17.98)	25(26.60)	53(56.38)	16(17.02)
Ye W	2006	Non-China	0.299	49(38.89)	61(48.41)	16(12.70)	99(32.67)	156(51.49)	48(15.84)
Huang WY	2005	Non-China	0.028	107(38.35)	126(45.16)	46(16.49)	145(38.06)	163(42.78)	73(19.16)
Yi Lou	2006	China	0.378	205(86.13)	30(12.61)	3(1.26)	164(82.00)	33(16.50)	3(1.50)
Asp312Asn				Genotype					
				Case n (%)			Control n (%)		
				Asp/Asp	Asp/Asn	Asn/Asn	Asp/Asp	Asp/Asn	Asn/Asn
Yuan T	2011	China	0	156(82.11)	18(9.47)	16(8.42)	133(73.89)	35(19.44)	12(6.67)
Chen Z	2011	China	0.165	75(36.06)	118(56.73)	15(7.21)	220(64.90)	111(32.74)	8(2.36)
Zhang CZ	2009	China	0.636	75(36.23)	117(56.52)	15(7.25)	132(62.26)	72(33.96)	8(3.77)
Ruzzo A	2007	Non-China	0.061	23(33.33)	26(37.68)	20(28.99)	41(33.86)	67(55.37)	13(10.74)
Ye W	2006	Non-China	0.093	41(32.54)	69(54.76)	16(12.70)	176(37.45)	237(50.43)	57(12.13)
Deng Sl	2010	China	0	132(82.50)	15(9.38)	13(8.13)	118(73.75)	31(19.38)	11(6.88)
Yi Lou	2006	China	0.019	189(79.41)	39(16.39)	10(4.20)	176(88.00)	21(10.50)	3(1.50)

HWE Hardy–Weinberg equilibrium (>0.05 was considered representative of agreement with HWE in the controls)

the funnel plot and Egger's linear regression test (Egger et al., 1997).

Results

Characteristics of studies

A total of 12 eligible including studies involving 3147 cases and 4736 controls met the inclusion criteria were included in the pooled analyses (Huang et al., 2005; Ye et al., 2006; Yi et al., 2006; Ruzzo et al., 2007; Zhang et al., 2009; Canbay et al., 2010; Deng et al., 2010; Long et al., 2010; Palli et al., 2010; Chen et al., 2011; Engin et al., 2011; Yuan et al., 2011). The study selection process is shown in Figure 1. The characteristics of selected studies were summarized in Table 1. Almost all of the cases were histologically confirmed. The controls were primarily healthy populations. There were six groups of Chinese, six groups of non-Chinese. All polymorphisms in the control subjects were calculated in Hardy–Weinberg equilibrium. Table 2 list all of the details abstracted from included studies. Studies with control not in Hardy-Weinberg equilibrium (HWE) were also considered for the meta-analysis, but they were excluded in the sensitivity analysis. All statistical analyses were performed using STATA statistical software (version 10.0).

Quantitative synthesis

XPD Lys751Gln: The studies that evaluated the association between XPD Lys751Gln polymorphism and gastric cancer susceptibility analyzed a total of 1949 cases and 3054 controls. As shown in Table 3, overall, no significant associations were found between Lys751Gln

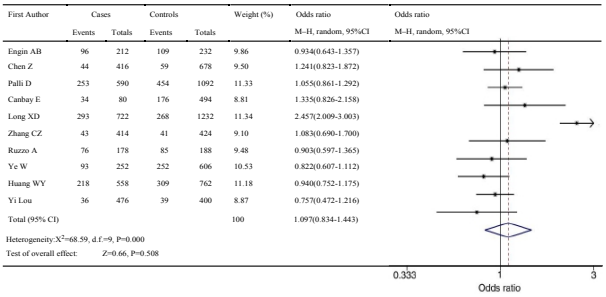

Figure 2. Overall Meta-analysis for XPD Lys751Gln Allele in the Additive Model in Gastric Cancer Risk

polymorphism and gastric cancer susceptibility when all studies pooled into the meta-analysis (Lys/Gln vs Lys/Lys: OR=1.144, 95% CI=0.851–1.541, P=0.000 for heterogeneity; Gln/Gln vs Lys/Lys: OR=1.215, 95% CI=0.740-1.955, P=0.000 for heterogeneity; dominant model: OR=1.137, 95% CI=0.818–1.582, P=0.000 for heterogeneity; recessive model: OR=1.123, 95% CI=0.765–1.650, P=0.001 for heterogeneity). Similarly, no significant association was found for the additive model (OR=1.097, 95% CI=0.834–1.443, Figure 2). In stratified analyses, statistically significantly elevated susceptibility was found for Gln/Gln vs Lys/Lys (OR=2.526, 95% CI=1.167–5.468) and recessive model (OR=2.449, 95% CI=1.730–3.522) in the Chinese population, but in the non-Chinese population, there was no evidence for the association (Table 3).

XPD Asp312Asn: The studies that evaluated the association between XPD Lys751Gln polymorphism and gastric cancer susceptibility analyzed a total of 1198 cases and 1682 controls. As shown in the Table

Table 3. Results of Meta-analysis for XPD Lys751Gln and Asp312Asn Polymorphisms and Gastric Cancer

Lys751Gln Study group	Lys/Gln vs. Lys/Lys		Gln/Gln vs. Lys/Lys		Dominant model		Recessive model	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Total	1.144(0.851-1.541)	0	1.215(0.740-1.995)	0	1.137(0.818-1.582)	0	1.123(0.765-1.650)	0.001
Ethnicity								
China	1.284(0.699-2.360)	0	2.526(1.167-5.468)	0.239	1.331(0.678-2.612)	0	2.449(1.730-3.522)	0.562
Non-China	1.034(0.852-1.255)	0.368	0.940(0.737-1.199)	0.558	1.003(0.844-1.192)	0.525	0.921(0.728-1.143)	0.386
Asp312Asn Study group	Asp/Asn vs. Asp/Asp		Asn/Asn vs. Asp/Asp		Dominant model		Recessive model	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Total	1.180(0.646-2.154)	0	2.045(1.254-3.335)	0.036	1.380(0.812-2.346)	0	1.805(1.219-2.672)	0.148
Ethnicity								
China	1.277(0.571-2.855)	0	2.233(1.139-4.379)	0.031	1.482(0.722-3.044)	0	1.807(1.212-2.694)	0.425
Non-China	0.989(0.561-1.743)	0.151	1.727(0.776-3.842)	0.136	1.170(0.827-1.656)	0.618	1.839(0.586-5.571)	0.019

P value of Q test for heterogeneity

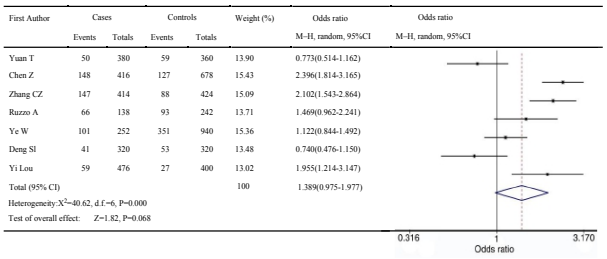

Figure 3. Overall Meta-analysis for XPD Asp312Asn Allele in the Additive Model in Gastric Cancer Risk

3, overall, no significant associations were found for some models between Lys751Gln polymorphism and gastric cancer susceptibility when studies pooled into the meta-analysis (Asp/Asn vs Asp/Asp: OR=1.180, 95% CI=0.646–2.154, P=0.000 for heterogeneity; dominant model: OR=1.380, 95% CI=0.812–2.346, P=0.000 for heterogeneity). Similarly, no significant association was found for the additive model (OR=1.389, 95% CI=0.975–1.977, Figure3). But statistically significantly elevated susceptibility was found for Asn/Asn vs Asp/Asp (OR=2.045, 95% CI=1.254–3.335, P=0.036 for heterogeneity) and for the recessive model (OR=1.805, 95% CI=1.219–2.672, P=0.148 for heterogeneity); In stratified analyses, statistically significantly elevated susceptibility was found for Asn/Asn vs Asp/Asp (OR=2.233, 95% CI=1.139–4.379) and recessive model (OR=1.807, 95% CI=1.212–2.694) in the Chinese population, but in the non-Chinese population, there was no evidence for the association (Table 3).

Heterogeneity and sensitivity analysis: Sensitivity analysis was performed Sensitivity analysis was performed according to heterogeneity.We found heterogeneity for the XPD Lys751Gln and Asp312Asn polymorphisms in overall population, in the stratified analysis by ethnicity, no heterogeneity was found in no-Chinese population. (Table 2)

Publication bias test: We performed Begg's funnel plot and Egger's test to assess the publication bias of literatures. There was no evidence of publication bias in XPD Lys751Gln (Begg's test P = 0.858, Egger's test P = 0.789) and Asp312Asn polymorphisms (Begg's test P = 0.548, Egger's test P = 0.565) (Figure4).

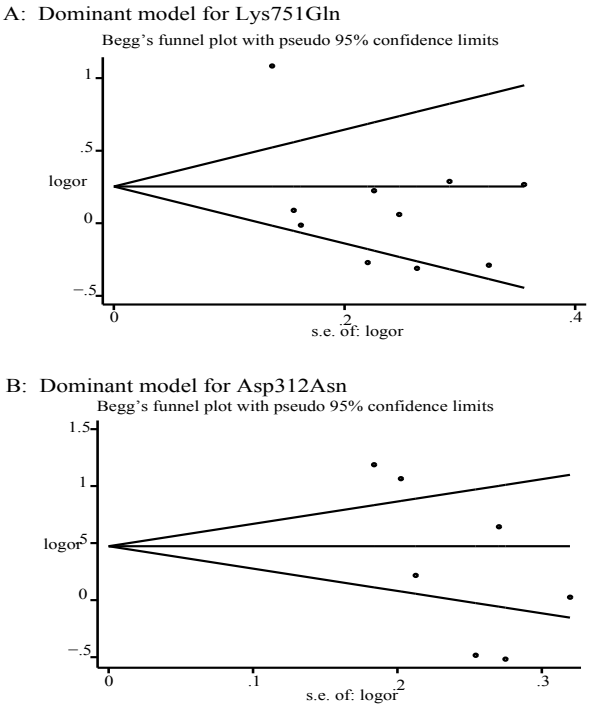

Figure 4. Funnel Plot Analysis for Odds Ratios of Dominant Model for Lys751Gln and Asp312Asn in Overall Studies

Discussion

XPD plays a key role in NER, which is crucial in the elimination of certain DNA cross-links, ultraviolet (UV) photo-lesions, and bulky chemical adducts (Cleaver., 2000; Au et al., 2004; Vodicka et al., 2004), XPD is a DNA-dependent ATPase/helicase that is associated with the TFIIH transcription factor complex and plays an important role in NER pathway. XPD participates in the opening of the DNA helix to allow the excision of the DNA fragment containing the damaged base (Benhamou et al., 2002; Manuguerra et al., 2006). To date, a number of epidemiological studies have been conducted to evaluate the role of polymorphism Lys751Gln and Asp312Asn on gastric cancer susceptibility, but the results remained controversial. In order to derive a more precise estimation of the relationship, we performed this meta-analysis of 12

studies, including 3147 cases and 4736 controls

H. pylori is a Gram-negative bacterium and mainly persists in the human gastric mucosa, especially gastric antrum mucosa(Montecucco et al., 2001) . One study(Chen et al., 2011) indicated that compared to the H. pylori negative cases, the individuals infected with H. pylori are more susceptible to gastric cancer (OR is 6.81 and 3.31 in Lys/Gln vs Lys/Lys, 9.27 and 6.05 in Gln/Gln vs Lys/Lys, respectively. However, larger studies are needed to confirm this relationship. The discrepancies across these studies might occur because of the relatively small sample size in the studies or because of environmental risk factors. The current knowledge of gastric carcinogenesis indicated a multifactorial and multistep process that involves various genetic alterations and biological pathways. Thus, it is unlikely that risk factors of gastric cancer work in isolation from each other. And the same polymorphism might play different roles in cancer susceptibility, because cancer is a complicated multi-genetic disease, and different genetic backgrounds may contribute to the discrepancy (Chen et al., 2002).

There was an moderate heterogeneity of studies for the XPD Lys751Gln and Asp312Asn polymorphisms in the overall population, but when we stratified the studies into different ethnic subgroups, the heterogeneity disappeared in non-Chinese population. These results suggested that the heterogeneity might be partly due to environmental risk and lacking of sufficient data in the Chinese population, large studies should be needed and subgroup in Chinese population be performed, such as according to H. pylori infection and other factors.

Some limitations of our meta-analysis should be considered in interpreting the results. First, a common limitation of meta-analysis was study heterogeneity. Heterogeneity was often caused by variantions in the environmental and genetic backgrounds of study participants, which was unavoidable when combing many studies, we found evidence of study heterogeneity in our study, presumably because the number of included studies was small, the frequency of demographic variables for cases and controls in one study did not match for age, sex, histology type and so on. Second, the controls were not uniformly defined. Some studies used a healthy population as the reference group, whereas others selected hospital patients without organic gastric cancer as the reference group, therefore, non-differential misclassification bias was possible because these studies might have included the control groups who had different risks of developing gastric cancer. Third, our results were based on single-factor estimates without adjustment for other risk factors including H. pylori infection, cigarette smoking status, red meat and poultry intake, and other lifestyle. Finally, the XPD gene might influence gastric cancer susceptibility with other genes, but we did not conduct the gene-gene interactions analysis in our study.

In conclusion, our meta-analysis suggested XPD Asp312Asn polymorphisms might be a potential biomarker of gastric cancer susceptibility in overall population, both XPD Lys751Gln and Asp312Asn polymorphism might be a potential biomarker of gastric cancer susceptibility in Chinese population. However, large and well designed epidemiological studies are necessary to combine genetic factors together with other potential risk factors in order to validate the exact relationship of XPD Lys751Gln and Asp312Asn polymorphism on gastric cancer susceptibility.

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The author(s) declare that they have no competing interests.

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