RESEARCH ARTICLE

Comprehensive Assessment of Associations between ERCC2 Lys751Gln/Asp312Asn Polymorphisms and Risk of Non-Hodgkin Lymphoma

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Abstract

Background: Excision repair crossing-complementing group 2 (ERCC2), also called xeroderma pigmentosum complementary group D (XPD), plays a crucial role in the nucleotide excision repair (NER) pathway. Previous epidemiological studies have reported associations between ERCC2 polymorphisms and non-Hodgkin lymphoma (NHL) risk, but the results have remained controversial. Materials and Methods: We conducted this meta-analysis based on eligible case-control studies to investigate the role of two ERCC2 polymorphisms (Lys751Gln and Asp312Asn) in determining susceptibility to NHL. Ten case-control studies from several electronic databases were included in our study up to August 14, 2014. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using fixed- or random-effects models to estimate the association strength. Results: The combined results based on all studies did not show any association between Lys751Gln/Asp312Asn polymorphisms and NHL risk for all genetic models. Stratified analyses by histological subtype and ethnicity did not indicate any significant association between Lys751Gln polymorphism and NHL risk. However, a significant reduced risk of NHL was found among population-based studies (Lys/Gln versus Lys/Lys: OR=0.87, 95% CI=0.77-0.99, *P*=0.037) but not hospital-based studies. As for Asp312Asn polymorphism, there was no evidence for the association between this polymorphism and the risk of NHL in all subgroup analyses. Conclusions: This meta-analysis suggests that there may be no association between Lys751Gln/Asp312Asn polymorphism and the risk of NHL and its two subtypes, whereas ERCC2 Lys751Gln heterozygote genotype may provide protective effects against the risk of NHL in population-based studies. Therefore, large-scale and well-designed studies are needed to clarify the effects of haplotypes, gene-gene, and gene-environment interactions on these polymorphisms and the risk of NHL and its different histological subtypes in an ethnicity specific population.

Keywords: ERCC2 - XPD - polymorphism - non-Hodgkin lymphoma - meta-analysis

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Introduction

Non-Hodgkin lymphoma (NHL), the most common histologic type of malignant lymphoma, is a complex group of heterogeneous diseases with multiple subtypes, each of which has distinct morphologic, immunophenotypic and clinical manifestations. In the last few decades, the occurrence of NHL has increased steadily. Environmental exposure to some chemicals, ultraviolet light, dietary factors, family history, immune dysfunction, immune stimulation, and viral infection, have all been associated with the risk for NHL, but the results remain inconsistent. In addition to exogenous exposures, individual genetic susceptibility may be important in the pathogenesis of NHL (Chiu et al., 2004; Hartge, 2004; Grulich et al., 2007). Although this would not explain the rising incidence of NHL per se, genetic variants could interact with environmental exposures and thereby contribute to lymphomagenesis.

Environmental factors often cause damage to DNA, and most of these damage, if not removed, can lead to genetic mutagenesis and cell death. Therefore, DNA repair capacity plays a critical role in maintaining the stability and integrity of human genome in general and specialized functions of cell as well as in the prevention of carcinogenesis, and the deficient of those genes in DNA repair pathway can lead to higher susceptibility to multiple cancers (Berwick and Vineis, 2000; Wood et al., 2001). Nucleotide excision repair (NER), one of the major DNA repair pathways in humans, is capable of removing helix-distorting base lesions produced by ultraviolet light and an array of chemical agents, including bulky adducts, oxidative DNA damage, cross links, alkylating damage and thymidine dimmers (De Silva et al., 2000; Friedberg, 2001; Gillet and Scharer, 2006). Excision repair crossing-complementing group 2 (ERCC2), also known as xeroderma pigmentosum complementary group D (XPD), functions in DNA unwinding during NER and basal

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transcription because it possesses single-strand DNA-dependent ATPase and 5'-3' DNA helicase activities (Sung et al., 1993; de Boer and Hoeijmakers, 2000). ERCC2 gene which located at chromosome 19q13.3 comprises 23 exons and spans about 54, 000 base pairs (Weber et al., 1990; Itin et al., 2001). Single nucleotide polymorphisms (SNPs) of this gene are thought to engender structural alterations of NER pathway and influence cancer susceptibility. The most extensively investigated ERCC2 polymorphisms associated with cancer susceptibility comprise a non-synonymous A>C substitution in exon 23 causing a lysine (Lys) to glutamine (Gln) substitution in codon 751 (Lys751Gln, rs13181) and a non-synonymous G>A substitution in exon 10 leading to an aspartic acid (Asp) to asparagine (Asn) substitution in codon 312 (Asp312Asn, rs1799793) (Benhamou and Sarasin, 2002).

Although several epidemiological studies have assessed the relationship between these polymorphisms and the risk of NHL (Shen et al., 2006; Smedby et al., 2006; Song et al., 2008; Baris et al., 2009; Worrillow et al., 2009; Yang et al., 2009; El-Din et al., 2013; Kim et al., 2014), the results remain inconsistent across these studies due to limitations in individual studies. Hence, we performed a meta-analysis with subgroup analysis from all eligible studies to examine the association between these two ERCC2 polymorphisms and the risk of NHL.

Materials and Methods

Search strategy

All relevant studies on the association between ERCC2 polymorphisms and NHL risk published up to August 14, 2014 were identified through literature searches using PubMed and EMBASE with the following terms and keywords: ("excision repair crossing-complementing group 2" OR "ERCC2" OR "xeroderma pigmentosum complementary group D" OR "XPD") and ("polymorphism" OR "variation" OR "mutation") and "lymphoma". The references cited in all studies were also reviewed to identify additional published articles which were missed by the searching.

Inclusion criteria

Studies which met the following criteria were included in our meta-analysis: (1) a case-control study evaluating at lease one of these two ERCC2 polymorphisms; (2) studies with full-text articles; (3) no overlapping data; (4) the distribution of genotypes in the controls was consistent with Hardy-Weinberg equilibrium (HWE); (5) sufficient data for estimating an odds ratio (OR) with 95% confidence interval (95% CI).

Data extraction

Information was carefully extracted from all the eligible studies independently by three researchers according to the inclusion criteria listed above and reached a consensus on all of the eligibility items. The following data were collected from each study: first author, publication year, country of origin, ethnicity, source of control (population-based or hospital-based controls), subtype of NHL, genotyping method, total numbers of cases and controls, numbers of cases and controls for each genotype, and result of the Hardy-Weinberg equilibrium test. Different racial descents were categorized as Caucasians and Asians. We did not define any minimum number of patients for inclusion in our meta-analysis.

Statistical analysis

A chi-square test was applied to detect whether the genotype distribution of the control population reported conformed to HWE (P<0.05 was considered significant). The strength of association between these two ERCC2 polymorphisms (Lys751Gln and Asp312Asn) and NHL risk was measured by the combined OR corresponding to the 95% confidence interval (95% CI). The risks (ORs) of NHL associated with ERCC2 polymorphisms were estimated for each study. The pooled ORs were performed for additive model (a allele versus A allele, a was for the minor allele and A was for the major allele), codominant model (aa versus AA, Aa versus AA), dominant model (aa+Aa versus AA), recessive model (aa versus Aa+AA) respectively. Heterogeneity assumption was assessed by a chi-square-based Q test (Cochran, 1954), and the proportion of the total variation due to heterogeneity was quantified by calculating I^2 statistics (Higgins et al., 2003). If the P value of the Q test was greater than 0.05 which indicated a lack of heterogeneity among studies, the Mantel-Haenszel method-based fixed-effects model was used to calculate the pooled OR (Mantel and Haenszel, 1959). Otherwise, the DerSimonian and Laird method-based random-effects model was applied (DerSimonian and Laird, 1986). Subgroup analyses were performed by ethnicity, source of controls and histological subtype. Moreover, one-way sensitivity analysis was mainly performed by excluding a single study each time to assess the stability of the results. Publication bias was evaluated with funnel plot, in which the standard error of log (OR) of each study was plotted against its log (OR). Funnel plot asymmetry was further assessed by the method of Egger's linear regression test (P<0.05 was considered a significant publication bias) (Egger et al., 1997). All of the statistical analyses were carried by STATA version 11.0 (Stata, College Station, TX, USA).

Results

Extraction process and study characteristics

A total of 10 articles were retrieved based on the search criteria for risks of NHL related to ERCC2 polymorphisms (Shen et al., 2006; Smedby et al., 2006; Shen et al., 2007; Song et al., 2008; Baris et al., 2009; Worrillow et al., 2009; Yang et al., 2009; El-Din et al., 2013; Fabisiewicz et al., 2013; Kim et al., 2014). We identified 9 articles for Lys751Gln polymorphism (3, 067 cases and 4, 491 controls) and 7 articles for Asp312Asn polymorphism (2, 462 cases and 2, 822 controls). Our initial search and the process of study selection were summarized in Figure 1. The distribution of genotypes among controls was consistent with HWE in all studies. The main characteristics of included studies are shown in Table 1. Of these eligible studies, some provided genotype data for specific histological subtypes of NHL, such as

diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL). Among them, three studies (Shen et al., 2006; Shen et al., 2007; Worrillow et al., 2009) focused on both DLBCL and FL, the studies by EI-Din et al. (2013) and Kim et al. (2014) on DLBCL, and that by Smedby et al. (Smedby et al., 2006) on FL. Distributions of the genotypes and alleles of the included polymorphisms for individual studies are provided in Table 2. Most of the cases were confirmed histologically or pathologically.

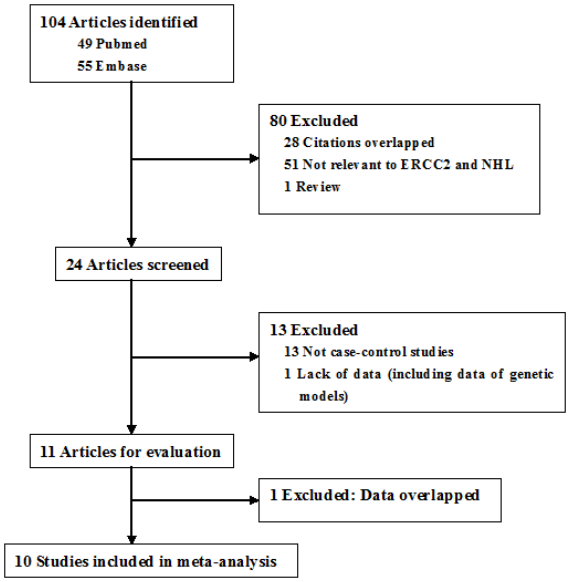

Figure 1. Flow Diagram of Included Studies for this Meta-Analysis

Meta-analysis result

The results of meta-analysis for polymorphisms in the ERCC2 gene were listed in Table 3. For Lys751Gln polymorphism, no significant association was found between this polymorphism and the risk of NHL when all studies were pooled into the meta-analysis (Gln/Gln versus Lys/Lys: OR=0.96, 95% CI=0.76-1.20, *P*=0.703; Lys/Gln versus Lys/Lys: OR=0.90, 95% CI=0.78-1.02, *P*=0.108; recessive model: OR=1.02, 95% CI=0.82-1.26, *P*=0.883; dominant model: OR=0.91, 95% CI=0.80-1.04, *P*=0.171; additive model: OR=0.95, 95% CI=0.86-1.05, *P*=0.325; Figure 2). In terms of subgroup analyses by ethnicity, no significant association between Lys751Gln polymorphism and the risk of NHL was found among Caucasians or Asians. When stratified by source of control, we found a significant reduced risk of NHL in population-based studies (Lys/Gln versus Lys/Lys: OR=0.87, 95% CI=0.77-0.99, *P*=0.037; Figure 3) but not in hospital-based studies. Also, we found that there was no statistically significant link between Lys751Gln polymorphism and the risk of either NHL histological subtypes (DLBCL or FL).

As for Asp312Asn polymorphism, the combined results based on all studies did not show any association between Asp312Asn polymorphism and NHL risk for all genetic models (Table 3). Furthermore, there was

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

Author	Year	Ethnicity	Region	Cancer Types	SNPs studied	Genotyping	Design	Cases/Controls	MAF	HWE
Smedby	2006	Caucasian	Denmark, Sweden	FL	312	MassArray	PB	428/602	0.353	0.075
Shen	2006	Caucasian	USA	FL, DLBCL	751, 312	Real-time PCR	PB	456/530, 445/534	0.368, 0.354	0.375, 0.557
Shen	2007	Caucasian	Australia	FL, DLBCL	751, 312	TagMan	PB	542/478, 554/501	0.340, 0.314	0.720, 0.606
Song	2008	Asian	China	NHL	751, 312	PCR-RFLP	HB	309/305, 307/303	0.062, 0.068	0.075, 0.142
Baris	2009	Caucasian	Turkey	NHL	751, 312	PCR-RFLP	HB	33/52, 33/52	0.423, 0.452	0.336, 0.728
Worrillow	2009	Caucasian	England	FL, DLBCL	751, 312	TaqMan	PB	700/779, 614/730	0.380, 0.338	0.405, 0.483
Yang	2009	Asian	China	NHL	751	MassArray	HB	72/354	0.073	0.944
EI-Din	2013	Caucasian	Egypt	DLBCL	751, 312	PCR-RFLP	HB	81/100, 81/100	0.390, 0.400	0.611, 0.405
Fabisiewicz	2013	Caucasian	Poland	NHL	751	TaqMan	HB	181/193	0.443	0.086
Kim	2014	Asian	Korea	DLBCL	751	PCR-RFLP	PB	693/1700	0.056	0.907

Abbreviations: RFLP, restriction fragment length polymorphism; TaqMan, real-time TaqMan analysis; MassARRAY: genotyping was performed using the Sequenom MassARRAY iPLEXTMplatform; NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; PB, population-based; HB, hospital-based; HWE, Hardy-Weinberg equilibrium

Table 2. Characteristics of Studies Included in the Meta-Analysis and their Genotype Distributions of ERCC2 Polymorphisms

Polymorphism	First author	Year	Ethnicity	Design	Sample size (case/control)		Case			Control			HWE in control	MAF
							Aa	aa	aa	AA	Aa	aa		
Lys751Gln	Shen	2006	Caucasian	PB	456	530	203	189	64	207	256	67	0.375	0.368
	Shen	2007	Caucasian	PB	542	478	239	229	74	210	211	57	0.72	0.34
	Song	2008	Asian	HB	309	305	261	43	5	270	32	3	0.075	0.062
	Baris	2009	Caucasian	HB	33	52	12	19	2	19	22	11	0.336	0.423
	Worrillow	2009	Caucasian	PB	700	779	286	329	85	294	378	107	0.405	0.38
	Yang	2009	Asian	HB	72	354	64	7	1	304	48	2	0.944	0.073
	EI-Din	2013	Caucasian	HB	81	100	25	40	16	36	50	14	0.611	0.39
	Fabisiewicz	2013	Caucasian	HB	181	193	57	94	30	54	107	32	0.086	0.443
	Kim	2014	Asian	PB	693	1700	622	65	6	1516	179	5	0.907	0.056
Asp312Asn	Smedby	2006	Caucasian	PB	428	602	167	211	50	262	255	85	0.075	0.353
	Shen	2006	Caucasian	PB	445	534	199	189	57	226	238	70	0.557	0.354
	Shen	2007	Caucasian	PB	554	501	272	210	72	238	211	52	0.606	0.314
	Song	2008	Asian	HB	307	303	256	47	4	265	35	3	0.142	0.068
	Baris	2009	Caucasian	HB	33	52	13	16	4	15	27	10	0.728	0.452
	Worrillow	2009	Caucasian	PB	614	730	270	265	79	316	335	79	0.483	0.338
	EI-Din	2013	Caucasian	HB	81	100	30	37	14	38	44	18	0.405	0.4

Abbreviations: HWE, Hardy-Weinberg equilibrium; HB, hospital-based; MAF, minor allele frequency; A, the major allele; a, the minor allele

Table 3. Results of Meta-Analysis for Lys751Gln and Asp312Asn Polymorphisms and the Risk of NHL and its Subtypes

Genetic model	n	Recessive model			Dominant model			Homozygote			Heterozygote			Additive model		
Lys751Gln		Gln/Gln *vs.* Lys/Gln+Lys/Lys			Gln/Gln+Lys/Gln *vs.* Arg/Arg			Gln/Gln *vs.* Lys/Lys			Lys/Gln *vs.* Lys/Lys			Gln *vs.* Lys		
		OR(95%CI)	P_h	I^2(%)	OR(95%CI)	P_h	I^2(%)	OR(95%CI)	P_h	I^2(%)	OR(95%CI)	Ph	I^2(%)	OR(95%CI)	P_h	I^2(%)
Total	9(3067/4491)	1.05(0.88-1.25)	0.268	19.7	0.92(0.83-1.03)	0.598	0	0.99(0.82-1.19)	0.296	16.5	0.90(0.80-1.01)	0.569	0	0.97(0.89-1.05)	0.531	0
Ethnicity																
Caucasian	6(1993/2132)	1.01(0.85-1.21)	0.299	17.7	0.90(0.79-1.02)	0.736	0	0.95(0.78-1.15)	0.395	3.4	0.88(0.77-1.01)	0.671	0	0.95(0.87-1.04)	0.585	0
Asian	3(1074/2359)	2.32(0.97-5.51)	0.829	0	1.02(0.81-1.29)	0.254	27.1	2.33(0.98-5.53)	0.857	0	0.97(0.76-1.23)	0.215	34.8	1.08(0.87-1.34)	0.327	10.5
Source of control																
PB	4(2391/3487)	1.05(0.86-1.27)	0.181	38.5	0.90(0.79-1.01)	0.66	0	0.98(0.80-1.21)	0.171	40.1	0.87(0.77-0.99)	0.649	0	0.95(0.87-1.04)	0.668	0
HB	5(676/1004)	1.04(0.70-1.55)	0.277	21.5	1.06(0.82-1.37)	0.482	0	1.04(0.67-1.61)	0.344	10.8	1.05(0.80-1.37)	0.47	0	1.04(0.86-1.26)	0.316	15.5
Histology																
FL	3(523/1787)	1.06(0.80-1.42)	0.36	2	0.88(0.72-1.08)	0.41	0	0.97(0.72-1.33)	0.364	1.1	0.86(0.69-1.06)	0.424	0	0.95(0.82-1.10)	0.368	0
DLBCL	5(1054/3587)	1.19(0.67-2.13)	0.003	75.3	0.87(0.74-1.02)	0.162	38.8	1.15(0.61-2.16)	0.002	76.8	0.85(0.71-1.00)	0.416	0	0.95(0.76-1.19)	0.019	66

Asp312Asn	n	Asn/Asn *vs.* Asp/Asn+Arg/Arg			Asn/Asn+Asp/Asn *vs.* Arg/Arg			Asn/Asn *vs.* Asp/Asp			Asp/Asn *vs.* Asp/Asp			Asn *vs.* Asp		
		OR(95%CI)	P_h	I^2(%)	OR(95%CI)	P_h	I^2(%)	OR(95%CI)	P_h	I^2(%)	OR(95%CI)	P_h	I^2(%)	OR(95%CI)	P_h	I^2(%)
Total	7(2462/2822)	1.04(0.88-1.24)	0.543	0	1.01(0.90-1.13)	0.424	0	1.04(0.87-1.25)	0.788	0	1.00(0.89-1.13)	0.217	27.7	1.02(0.93-1.11)	0.681	0
Ethnicity																
Caucasian	6(2155/2519)	1.04(0.87-1.24)	0.426	0	0.99(0.88-1.11)	0.552	0	1.04(0.86-1.25)	0.695	0	0.98(0.86-1.11)	0.28	20.4	1.00(0.92-1.09)	0.835	0
Asian	1(307/303)	1.32(0.29-5.95)	-	-	1.39(0.88-2.19)	-	-	1.38(0.31-6.23)	-	-	1.39(0.87-2.22)	-	-	1.36(0.89-2.07)	-	-
Source of control																
PB	4(2041/2367)	1.06(0.89-1.27)	0.264	24.6	1.00(0.88-1.12)	0.395	0	1.06(0.87-1.28)	0.648	0	0.98(0.86-1.11)	0.128	47.2	1.01(0.93-1.11)	0.861	0
HB	3(421/455)	0.89(0.49-1.61)	0.689	0	1.14(0.82-1.60)	0.292	18.8	0.88(0.46-1.67)	0.534	0	1.17(0.82-1.66)	0.41	0	1.06(0.81-1.39)	0.212	35.6
Histology																
FL	3(825/1833)	1.07(0.83-1.38)	0.108	55.1	1.06(0.89-1.25)	0.183	41.2	1.11(0.85-1.45)	0.39	0	1.01(0.73-1.39)	0.044	68.1	1.05(0.93-1.19)	0.588	0
DLBCL	3(483/1331)	1.06(0.77-1.47)	0.812	0	0.97(0.78-1.20)	0.883	0	1.04(0.74-1.47)	0.932	0	0.95(0.76-1.19)	0.746	0	0.99(0.85-1.16)	0.997	0

P_h, *P* values for heterogeneity from Q test. I^2, the percentage of variability in OR attributable to heterogeneity. Random-effects model was used when *P* value for heterogeneity test <0.05; otherwise, fixed-model was used

Figure 3. Forest plot of ORs with 95% CI for ERCC2 Lys751Gln Polymorphism and the Risk of NHL in Subgroup Analyses By Source of Control (Fixed Effects) Under Heterozygote Model (Lys/Gln Versus Lys/Lys). The center of each square represents the OR, the area of the square is the number of sample and thus the weight used in the meta-analysis, and the horizontal line indicates the 95%CI

Figure 2. Forest Plots of ORs with 95% CI for ERCC2 Lys751Gln polymorphism and the risk of NHL observed in subgroup analyses by ethnicity (fixed effects). The center of each square represents the OR, the area of the square is the number of sample and thus the weight used in the meta-analysis, and the horizontal line indicates the 95%CI. **a)** Recessive model. **b)** Dominant model. **c)** Additive model

no evidence for the association between this polymorphism and the risk of NHL in subgroup analyses based on the ethnicity, source of controls and histological subtypes (Table 3).

Test of heterogeneity and sensitivity analyses

The results of heterogeneity test showed that there was no significant heterogeneity for both Lys751Gln and Asp312Asn polymorphisms in the overall comparisons (Table 3). Moreover, influence analysis was performed to assess the influence of each individual study on the pooled ORs by sequential omission of individual studies, and the results suggested that no individual study significantly influence the pooled ORs.

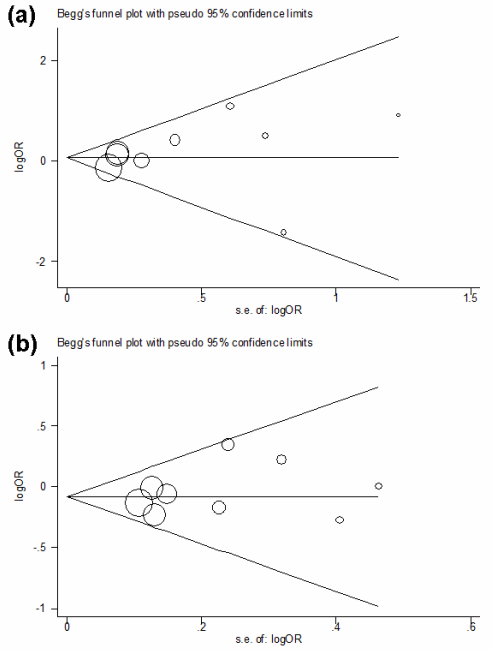

Figure 4. Begg's Funnel Plots of Lys751Gln Polymorphism and the Risk of NHL for Publication Bias Test. Each point represents a separate study for the indicated association. Log (OR), natural logarithm of OR. Horizontal line, mean effect size. (a) Recessive model. (b) Dominant model.

Publication bias

Both Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures. All these two genetic polymorphisms showed consistent results, indicating no evidence of publication bias in the meta-analysis. Take Lys751Gln polymorphism as an example. The shapes of the funnel plot did not indicate any evidence of obvious asymmetry in both recessive model and dominant model (Figure 4), and the Egger's test suggested the absence of publication bias (P=0.287 for Gln/Gln versus Lys/Lys, P=0.282 for Lys/Gln versus Lys/Lys, P=0.462 for recessive model, P=0.284 for dominant model, and P=0.423 for additive model).

Discussion

ERCC2 is an enzyme in the NER pathway that removes certain DNA cross-links, ultraviolet light photo-lesions, and bulky chemical adducts (Sung et al., 1993). Mutations in this gene can completely prevent DNA opening and dual incision and modify overall capacity to repair DNA damage (Evans et al., 1997). Asp312Asn and Lys751Gln polymorphisms are the two most widely investigated ERCC2 polymorphisms associated with increased DNA adduct levels and with low DNA repair capacity (Lunn et al., 2000), which suggests that these two SNPs may contribute to carcinogenesis and can be regarded as risk factors for cancer development. Recently, many systematic reviews and meta-analyses have been performed to examine the association of ERCC2 polymorphisms with various cancers (Duan et al., 2012; Yin et al., 2013; Huang et al., 2014; Li et al., 2014; Liu et al., 2014; Xin et al., 2014; Yan et al., 2014; Zhu et al., 2014) except for NHL. What's more, epidemiological studies investigating the association of ERCC2 polymorphisms with NHL risk in populations of different ethnic origin have been published, but the results remain inconclusive (Shen et al., 2006; Smedby et al., 2006; Shen et al., 2007; Song et al., 2008; Baris et al., 2009; Worrillow et al., 2009; Yang et al., 2009; El-Din et al., 2013; Fabisiewicz et al., 2013; Kim et al., 2014). The individual studies might have been underpowered to detect the overall effect of polymorphisms on the susceptibility to NHL, and our meta-analysis enhances the statistical power.

To the best of our knowledge, this is the first meta-analysis undertaken so far of the largest and most comprehensive assessment for the relationship between the ERCC2 polymorphisms and the risk of NHL and its two subtypes. In the present study, no significant association was found under any genetic model in the overall analysis. Furthermore, stratified analyses by ethnicity demonstrated that both Lys751Gln and Asp312Asn polymorphism were not associated with the risk of NHL among Caucasians or Asians, respectively. Similarly, the studies for Caucasian population (Smedby et al., 2006; Shen et al., 2007; Baris et al., 2009; Worrillow et al., 2009; Fabisiewicz et al., 2013) and Asian population (Song et al., 2008; Yang et al., 2009; Kim et al., 2014) did not find any statistically significant association between these two polymorphisms and the risk of NHL, which agreed with our conclusion. However, considering only three and one studies of Asian population were included in this meta-analysis regarding Lys751Gln and Asp312Asn polymorphism respectively, our results related to the Asian ethnicity should be treated as preliminary. Therefore, further confirmation of existing findings is still needed in future studies.

Stratified analysis by histological subtype showed that there was no statistically significant link between these two polymorphisms and the risk of DLBCL or FL. The study by Shen et al. (2006) and Worrillow et al (2009) reported that ERCC2 751 Gln allele was associated with a decreased risk of DLBCL, which was not in accordance with our results. The possibility of inconsistent results is that studies with small sample sizes may be underpowered for detecting a small but real association. In our meta-analysis, only three studies were available for some specific subtypes, and they had limited sample size, and hence the results may be capricious and should be interpreted with caution. Larger studies are needed to clarify whether these two polymorphisms could not truly affect different histological subtype and whether the associations between these two polymorphisms and different histological subtype are the same in the different ethnicities. Moreover, the inconsistency may be explained by differences in population background, source of controls and also by chance.

When stratified by the source of controls, our results suggested that only individuals who carried ERCC2 Lys751Gln heterozygote genotype might have a significantly decreased risk of NHL among the population-based studies but not the hospital-based studies. The reason may be that hospital-based studies have some bias. Because these controls may suffer certain begin disease which have different risks of developing malignancy and

may not be very representative of the general population. Thus, the use of a proper and representative cancer-free control subjects is very important in reducing biases in such case-control studies.

Some limitations of our meta-analysis merit consideration. First, the number of published studies was not sufficiently large for a comprehensive analysis, especially for stratified analyses within subgroups by ethnicity and histological subtype. Furthermore, not having sufficient available data limited our further evaluation of analyses stratified by histological subtype among different population. Thus, our results should be interpreted with caution. Second, lacking the original data for the included studies limited our further evaluation of potential interactions among gene-gene, gene-environment, or even different polymorphism loci of the same gene, which all may affect the risk of NHL and its subtypes. Third, our meta-analysis was based on single-factor estimates without adjustment for other risk factors such as gender, age, dietary factors, environmental factors and other variables, which might have caused serious confounding bias.

In conclusion, our meta-analysis suggests that either Lys751Gln or Asp312Asn polymorphism might be not associated with the risk of NHL and its two subtypes. However, ERCC2 Lys751Gln heterozygote genotype might provide protective effects against the risk of NHL among the population-based studies but not the hospital-based studies. Therefore, large-scale and well-designed studies are needed to clarify the effects of haplotypes, gene-gene, and gene-environment interactions on these polymorphisms and the risk of NHL and its different histological subtypes in an ethnicity specific population.

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