Associations Between XPD Lys751Gln Polymorphism and Leukemia: A Meta-Analysis

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Objectives: The aim of the present study was to define the potential relationship of xeroderma pigmentosum group D (XPD) Lys751Gln polymorphisms and the risk of leukemia.

Methods: Comprehensive electronic search in Pubmed, Web of Science, EBSCO, the Cochrane Library and China National Knowledge Infrastructure (CNKI) to find original articles about the association between XPD Lys751Gln polymorphisms and leukemia risk published before March 2017. Literature quality assessment was performed using the Newcastle-Ottawa Scale. Heterogeneity across studies was assessed by I^2 statistics. Random- or fixed-effects models was used to calculate pooled odds ratios (ORs) in the presence or absence of heterogeneity, respectively. Sensitivity analysis was used to assess the influence of individual studies on the pooled estimate. Publication bias was investigated using funnel plots and Egger's regression test. All data analyses were performed using Stata 14.0 and Revman 5.3.

Results: Fourteen studies with a total of 7525 participants (2,757 patients; 4,768 controls) were included in this meta-analysis. We found that XPD Lys751Gln polymorphism significantly increased the risk of developing leukemia in both a dominant [Odds Ratio (OR)] = 1.21, 95%CI [1.10–1.35], $P < 0.001$) and heterozygote (OR = 1.22, 95%CI [1.09–1.36], $P < 0.001$) models. An allele model showed borderline significant increase in leukemia risk (OR = 1.13, 95%CI [1.00–1.27], $P = 0.05$). Subgroup analysis revealed a consistent association for some genetic models in Caucasian populations, adult or chronic groups, and in almost all models of childhood or acute groups.

Conclusion: Our results overall indicate that XPD Lys751Gln polymorphism increases the risk of leukemia, especially in childhood and acute cases.

Keywords: leukemia, XPD, ERCC2, meta-analysis, polymorphism

INTRODUCTION

Leukemia, a common malignant disease of the hematopoietic system (Jiang et al., 2014), can be classified on the basis of speed of disease progression and cell cytogenetics into four common subtypes: acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML) and chronic lymphocytic leukemia (CLL) (Arber et al., 2016). The etiological and

mechanism of leukemogenesis are still unclear, though radiation, smoking, obesity and exposure to chemical carcinogens are considered high risk factors (Larsson and Wolk, 2008; Fircanis et al., 2014; Malagoli et al., 2016; Nikkila et al., 2016). Nevertheless, only a small proportion of people exposed to these risk factors develop leukemia, suggesting that hereditary factors may play critical role in leukemia carcinogenesis (Li et al., 2016; Huang and Ovcharenko, 2017).

Decreased efficiency of DNA repair is considered a crucial event in carcinogenesis (Hoeijmakers, 2001). Recently, a series of studies revealed that reduced DNA repair, leading to chromosomal aberrations and genomic instability, is a major contributor to the pathogenesis of leukemia (Das-Gupta et al., 2000; Esposito and So, 2014). Xeroderma pigmentosum group D (XPD) gene, also known as ERCC2, encodes a $5'$–$3'$ superfamily 2 (SF2) helicase that plays a key role in unwinding the DNA double helix around damaged DNA during nucleotide excision repair (NER) (Kuper et al., 2012; Constantinescu-Aruxandei et al., 2016). Because of the biological significance of XPD, the XPD polymorphism has been extensively studied in different malignant diseases, such as pancreatic (Wu et al., 2017), colorectal (Ni et al., 2014) and gallbladder (Srivastava et al., 2010) cancers.

Several studies revealed inconsistent results on the relationship between the XPD Lys751Gln polymorphism (SNP IDs: rs13181) and leukemia susceptibility. Some studies showed a clear trend of XPD Lys751Gln polymorphism with increased risk of leukemia (Juan et al., 2005; Ganster et al., 2009; Shi et al., 2011; Banescu et al., 2014, 2016), while others displayed decreased risk of leukemia (Ozcan et al., 2011; Douzi et al., 2015), and yet others suggested no association between this polymorphism and leukemia (Seedhouse et al., 2002; Allan et al., 2004; Matullo et al., 2006; Mehta et al., 2006; Pakakasama et al., 2007; Batar et al., 2009; Canalle et al., 2011; Ozdemir et al., 2012; Sorour et al., 2013; Dincer et al., 2015). To evaluate more precisely the potential relationship between XPD Lys751Gln polymorphism and leukemia, we hereby report on a meta-analysis using all available published data.

MATERIALS AND METHODS

Search Strategies

A computerized search of Pubmed, Web of Science, EBSCO, the Cochrane Library and China National Knowledge Infrastructure (CNKI) up to March 2017 was conducted using the following search strategy: ("XPD" or "ERCC2" or "XPD"), and ("polymorphism" or "variant" or "mutation"), and "Leukemia." The search was restricted to English and Chinese written publications. A manual search of references of the retrieved articles and relevant reviews was also conducted. A flowchart of information pertaining to identification, screening, eligibility, and final datasets selected was constructed according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Moher et al., 2009).

Inclusion and Exclusion Criteria

In this report, the studies that investigate the association between XPD Lys751Gln polymorphism and leukemia risk were included. The inclusion criteria were (1) case-control study design; (2) available genotype information of the XPD Lys751Gln polymorphism; (3) evaluation of the XPD gene polymorphism and the risk of leukemia; and (4) the distribution of genotypes among the controls agreeing with Hardy–Weinberg equilibrium (HWE). Major criteria for exclusion were: (1) duplication of earlier publications (for studies using the same sample in different publications, only the most complete information was included following careful examination), (2) unpublished papers, dissertations, conference articles and reviews, (3) family based studies of pedigrees.

Data Extraction

Data from each eligible study were extracted into Excel including country of origin, ethnicity of each study population, age group (adult or childhood), subtypes of leukemia, genotyping method, numbers of cases and controls, numbers of cases and controls in the XPD Lys751Gln genotypes and results of the HWE test.

Study Quality Assessment

The quality of the included studies was assessed by two reviewers according to the Newcastle-Ottawa Scale (NOS) (Stang, 2010), which is used to assess the quality of observational studies. Discrepancies were reported and settled by a third party. Three major aspects of study quality were scored: (1) selection of the study groups (0 ± 4 points); (2) determination of the exposure of interest in the studies (0 ± 3 points); and (3) the quality of the adjustment for confounding variables (0 ± 2 points). A study could be scored as a maximum of one star for each item numbered within the categories of Selection and Exposure, while at most two stars could be allocated to Comparability. A higher score represents improved greater quality of the study methodology. A score equal to or higher than 6 was considered to indicate high study quality.

Data Analysis

The combined odds ratios (ORs) and 95% confidence interval (CI) were used to evaluate the strength of the association with the risk of leukemia. Pooled ORs were performed for allelic comparison (a vs. A), dominant (aa + Aa vs. AA), recessive (aa vs. Aa + AA) and codominant (aa vs. AA and Aa vs. AA) models ('a' and 'A' represent the mutant allele and the wild-type allele, respectively). Heterogeneity among the included studies was assessed by I^2 statistic. A random-effects model or fixed-effects model was used to calculate pooled odds ratio (OR) in the presence or absence of heterogeneity, respectively. To detect possible sources of heterogeneity and potential difference among subgroups, meta-regression and subgroup analyses were carried out on stratification of different ethnicity, age group and subtypes of leukemia. The significance of the pooled OR was determined by Z-test, with $p < 0.05$ considered statistically significant. Publication bias was investigated using funnel plots and Egger's regression test. We also conducted

sensitivity analysis to test the robustness of associations by sequentially omitting each of the included studies one at a time. All the data analysis was performed using the software STATA 14.0 (StataCorp, College Station, TX, United States) and Review Manager 5.3 (Cochrane Collaboration, Oxford, United Kingdom).

RESULTS

Literature Search and Study Characteristics

We used several search criteria to include or exclude reported studies on the relationship between XPD polymorphism and leukemia (**Figure 1**). A total of 14 studies (2,757 cases and 4,768 controls) about XPD Lys751Gln polymorphism were included in the final evaluation (**Table 1**). Quality assessment of the individual studies showed that the Newcastle-Ottawa scale

(NOS) score ranged from 6 to 8, indicating that the quality of methodology was generally good (**Table 2**).

Association Between the XPD Lys751Gln Polymorphism and Risk of Leukemia

Since significant heterogeneity was identified in recessive, homozygote and alleles models, random-effects model was used. The other genetic models were analysis by fixed-effects model. Overall, significant increase in leukemia risk was identified in dominant (Gln/Gln + Lys/Gln vs. Lys/Lys: I^2 = 24%, P < 0.001, **Figure 2**) and heterozygote models (Lys/Gln vs. Lys/Lys: I^2 = 0%, P < 0.001, **Figure 3**). No significant association was found in recessive (Gln/Gln vs. Lys/Gln + Lys/Lys: I^2 = 43%, P = 0.560, **Figure 4**) and homozygote (Gln/Gln vs. Lys/Lys: I^2 = 51%, P = 0.29, **Figure 5**) models. In addition, allele model showed a borderline significant increase in leukemia risk (Gln vs. Lys: I^2 = 50%, P = 0.05, **Figure 6**). Moderate heterogeneity (I^2: 43–51%)
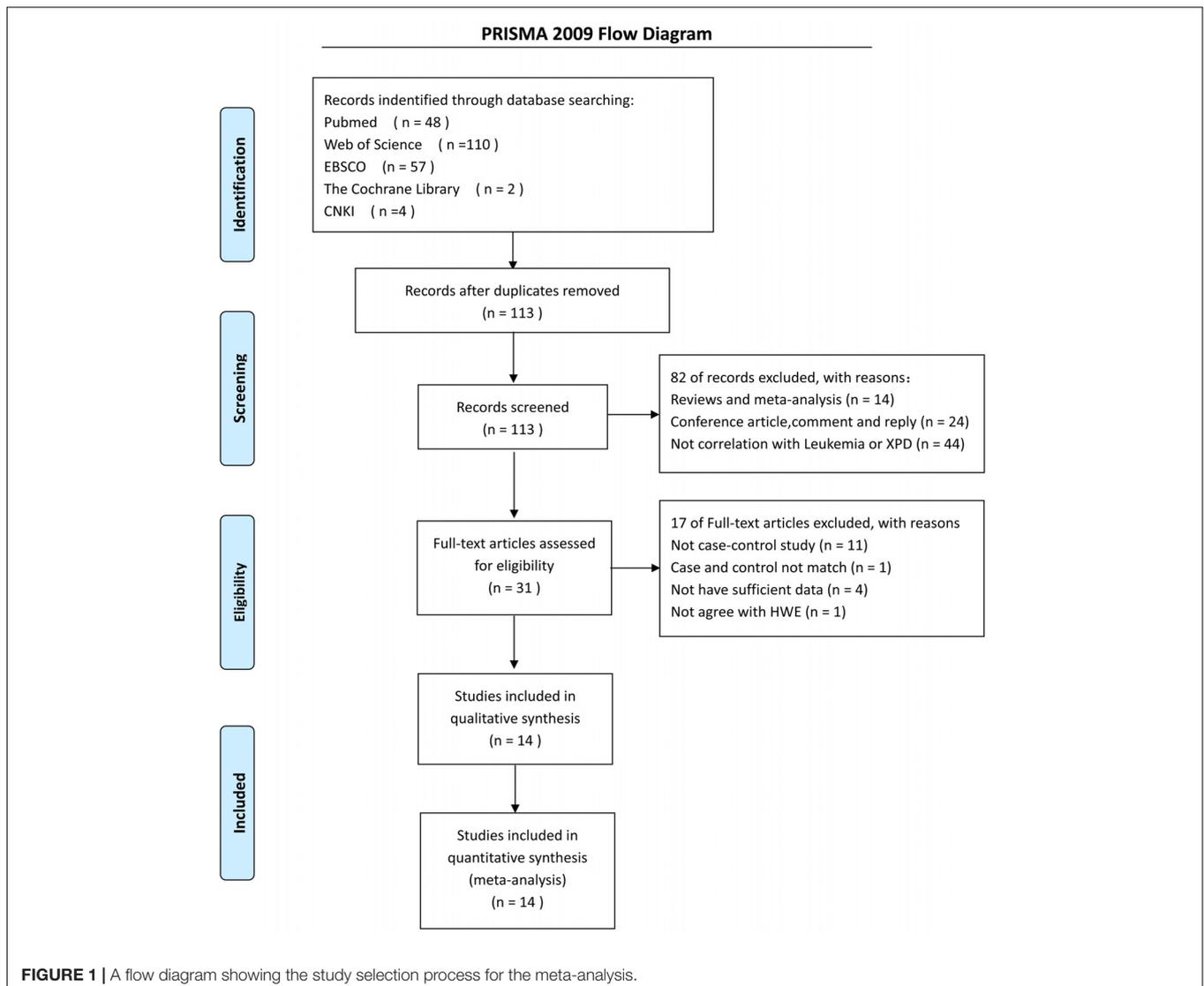

PRISMA 2009 Flow Diagram

Identification

Records indentified through database searching:
Pubmed   (n = 48)
Web of Science   (n =110)
EBSCO   (n = 57)
The Cochrane Library   (n = 2)
CNKI   (n =4)

Records after duplicates removed
(n = 113)

Screening

Records screened
(n = 113)

82 of records excluded, with reasons：
Reviews and meta-analysis (n = 14)
Conference article,comment and reply (n = 24)
Not correlation with Leukemia or XPD (n = 44)

Eligibility

Full-text articles assessed
for eligibility
(n = 31)

17 of Full-text articles excluded, with reasons
Not case-control study (n = 11)
Case and control not match (n = 1)
Not have sufficient data (n = 4)
Not agree with HWE (n = 1)

Included

Studies included in
qualitative synthesis
(n = 14)

Studies included in
quantitative synthesis
(meta-analysis)
(n = 14)

FIGURE 1 | A flow diagram showing the study selection process for the meta-analysis.

TABLE 1 | Main characteristics of datasets included for the XPD Lys751Gln polymorphism and leukemia risk.

Author	Year	Country	Ethnicity	Subtypes	Age group	Genotyping method	Sample size		Genotype (n/frequency)						HWE
							Case	Control	Case			Control			
									Lys/Lys	Lys/Gln	Gln/Gln	Lys/Lys	Lys/Gln	Gln/Gln	
Seedhouse	2002	United Kingdom	Caucasians	AML	Adult	PCR-RFLP	122	73	44 36.07%	59 48.36%	19 15.57%	30 41.10%	32 43.83%	11 15.07%	0.6195
Allan	2004	United Kingdom	Caucasians	AML	Adult	PCR-RFLP	474	696	180 37.97%	216 45.57%	78 16.46%	293 42.10%	299 42.96%	104 14.94%	0.0597
Matullo	2006	European	Caucasians	Unclassified	Adult	TaqMan	169	1094	70 41.42%	79 46.75%	20 11.83%	397 36.29%	504 46.07%	193 17.64%	0.1330
Mehta	2006	United States	Caucasians	AML	Child	TaqMan	313	432	116 37.06%	142 45.37%	55 17.57%	183 42.36%	194 44.91%	55 12.73%	0.7521
			African	AML	Child	TaqMan	38	146	20 52.63%	18 47.37%	0 0%	87 59.59%	52 35.62%	7 4.79%	1.0000
Pakakasama	2007	Thailand	Asia	ALL	Child	PCR-RFLP	108	317	87 80.56%	19 17.59%	2 1.85%	260 82.02%	56 17.67%	1 0.31%	0.4932
Batar	2009	Turkish	Caucasians	ALL	Child	PCR-RFLP	70	75	26 37.14%	33 47.14%	11 15.72%	27 36.00%	35 46.67%	13 17.33%	0.8119
Ganster	2009	Austria	Caucasians	CLL	Adult	PCR-RFLP	444	444	157 35.36%	222 50.00%	65 14.64%	186 41.89%	194 43.69%	64 14.42%	0.2589
Canale	2011	Brazil	Caucasians	ALL	Child	PCR-RFLP	162	223	72 44.44%	78 48.15%	12 7.41%	105 47.09%	101 45.29%	17 7.62%	0.3415
			African	ALL	Child	PCR-RFLP	27	138	16 59.26%	9 33.33%	2 7.41%	91 65.94%	40 28.99%	7 5.07%	0.4134
Ozcan	2011	Turkish	Caucasians	AML	Adult	PCR-RFLP	35	100	18 51.43%	16 45.71%	1 2.86%	41 41.00%	41 41.00%	18 18.00%	0.2049
				ALL	Adult	PCR-RFLP	10	100	4 40.00%	4 40.00%	2 20.00%	41 41.00%	41 41.00%	18 18.00%	
Shi JY	2011	China	Asia	AML	Adult	MALDI-TOF MS	303	554	243 80.20%	58 19.14%	2 0.66%	480 86.64%	70 12.64%	4 0.72%	0.3373
Sorour A	2013	Egypt	Caucasians	AML	Adult	PCR-RFLP	90	60	33 36.67%	45 50.00%	12 13.33%	27 45.00%	30 50.00%	3 5.00%	0.2197
Banescu C	2014	Romania	Caucasians	CML	Adult	PCR-RFLP	156	180	51 32.69%	77 49.36%	28 17.95%	82 45.56%	79 43.89%	19 10.55%	1.0000
Douzi K	2015	Tunisia	Caucasians	ALL	No age limit	PCR-RFLP	85	206	33 38.82%	43 50.59%	9 10.59%	92 44.66%	93 45.15%	21 10.19%	0.8742
				AML		PCR-RFLP	34	206	21 61.77%	11 32.35%	2 5.88%	92 44.66%	93 45.15%	21 10.19%	
				CML		PCR-RFLP	87	206	40 45.98%	46 52.87%	1 1.15%	92 44.66%	93 45.15%	21 10.19%	
Dincer Y	2015	Turkish	Caucasians	ALL	Child	PCR-RFLP	30	30	11 36.67%	12 40.00%	7 23.33%	9 30.00%	17 56.67%	4 13.33%	0.4721

AML, Acute myeloid leukemia; ALL, acute lymphoid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia.
PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; MALDI-TOF MS, matrix assisted laser desorption/ionization time-of-flight mass spectrometry.
HWE P-value in the control group, P > 0.05 indicates that the participants in the control group met the HWE.

TABLE 2 | Quality assessment analysis.

Number	Author	Selection	Exposure	Comparability	Total score
1	Seedhouse C	4	2	2	8
2	Allan JM	3	2	1	6
3	Matullo G	4	2	1	7
4	Mehta PA	3	2	1	6
5	Pakakasama S	3	2	1	6
6	Batar B	4	2	2	8
7	Ganster C	4	2	2	8
8	Canalle R	4	2	1	7
9	Ozcan Ali	4	2	1	7
10	Shi JY	3	2	1	6
11	Sorour A	4	2	1	7
12	Banescu C	4	2	2	8
13	Douzi K	3	2	2	7
14	Dincer Y	4	2	2	8
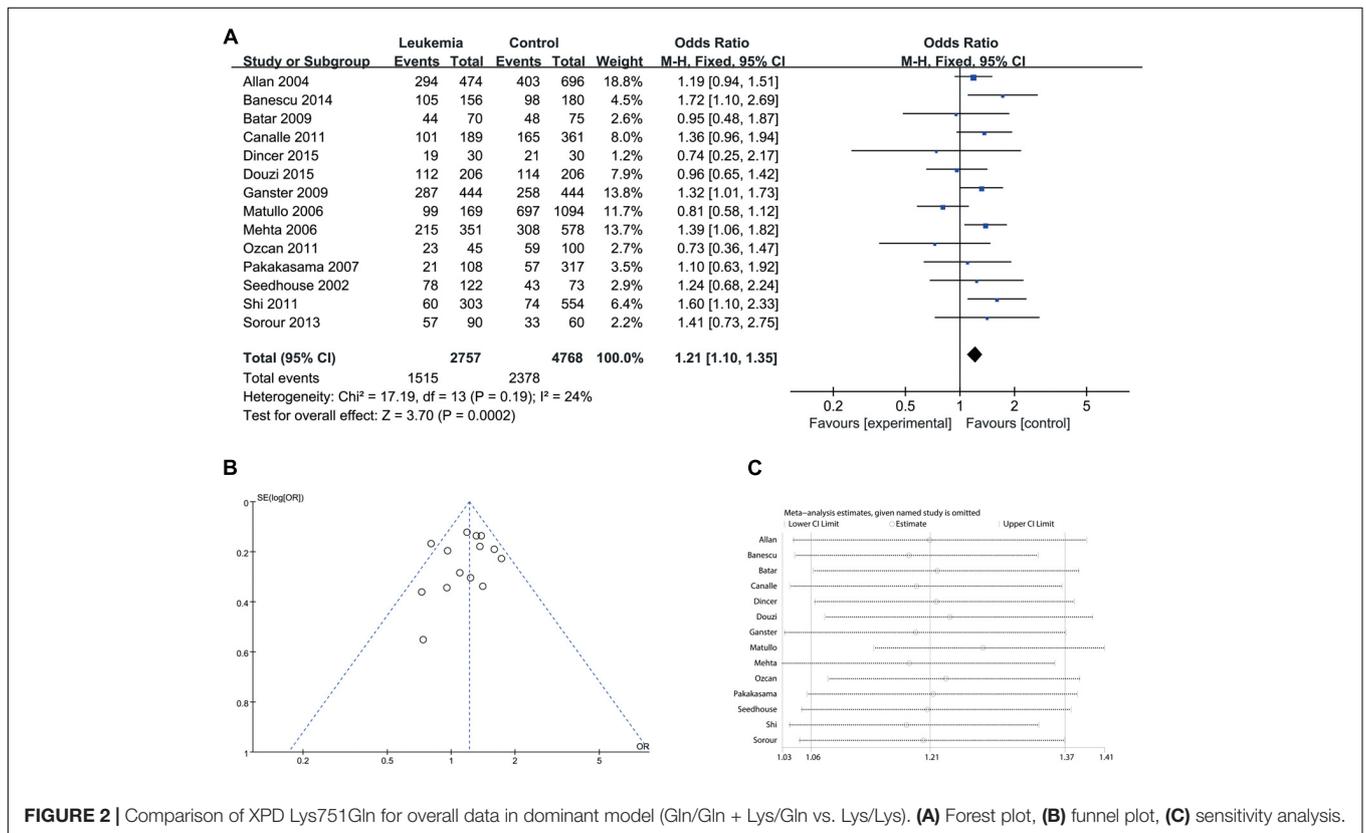
FIGURE 2 | Comparison of XPD Lys751Gln for overall data in dominant model (Gln/Gln + Lys/Gln vs. Lys/Lys). **(A)** Forest plot, **(B)** funnel plot, **(C)** sensitivity analysis.

was found in the no-association model group. To explore the source of this heterogeneity, a meta-regression analysis was conducted. The results revealed that the heterogeneity was not associated with ethnicity, age, clinical subtype or detection method ($p > 0.05$ in all genetic models). We further explored the source of heterogeneity by removing one study each time. The results showed that the Matullo's study was one of the central sources of heterogeneity (its inclusion increased heterogeneity by 12–24%). No publication bias was found in any of the models. Sensitivity analysis suggested that with

exception of the allele model, the results were stable and reliable.

Association Between the XPD Lys751Gln Polymorphism and Risk of Leukemia by Ethnicity

In Caucasian populations, a significant increase in leukemia risk was found in heterozygote model (Lys/Gln vs. Lys/Lys: $I^2 = 0\%$, $P = 0.02$) and dominant models (Gln/Gln + Lys/Gln vs. Lys/Lys:
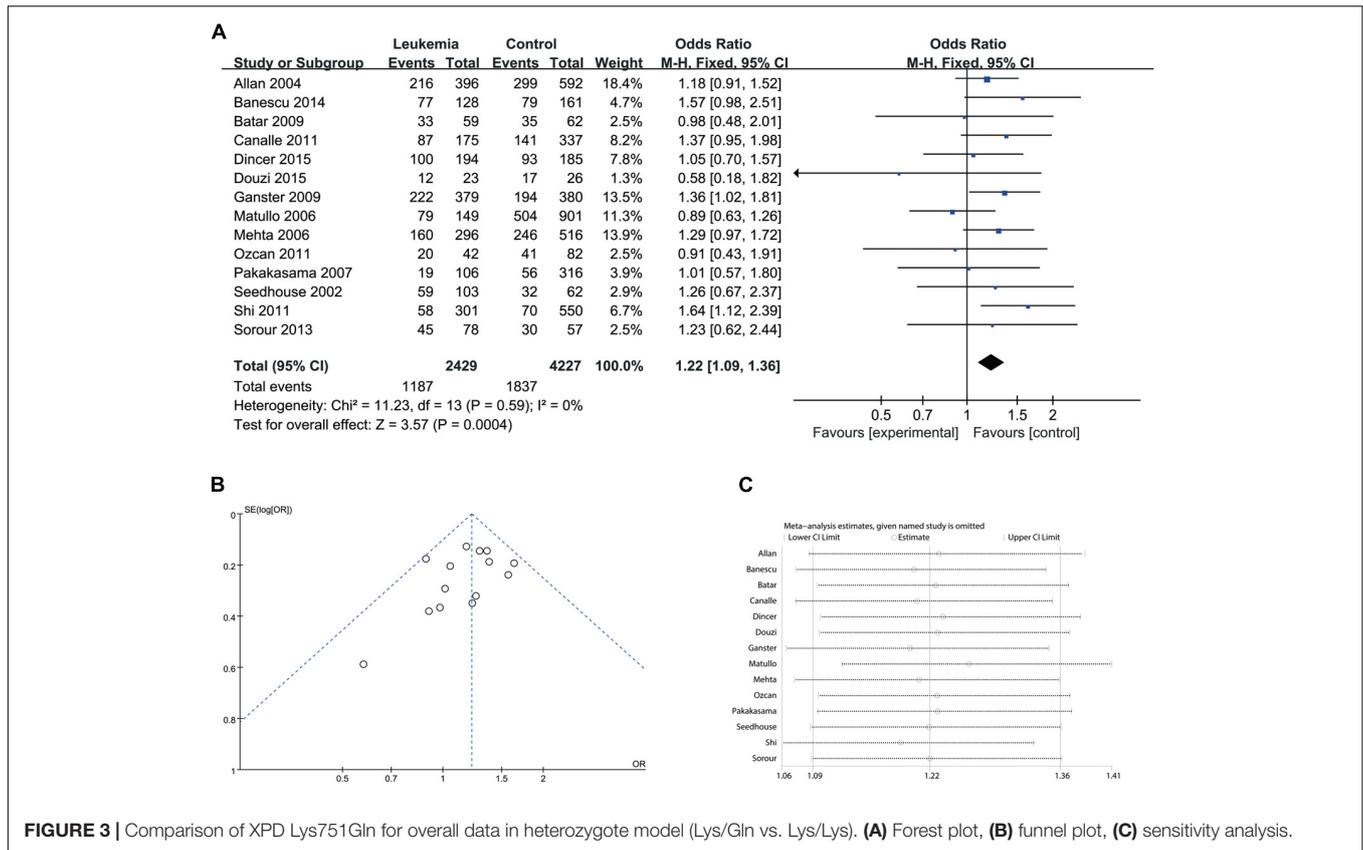
FIGURE 3 | Comparison of XPD Lys751Gln for overall data in heterozygote model (Lys/Gln vs. Lys/Lys). (A) Forest plot, (B) funnel plot, (C) sensitivity analysis.
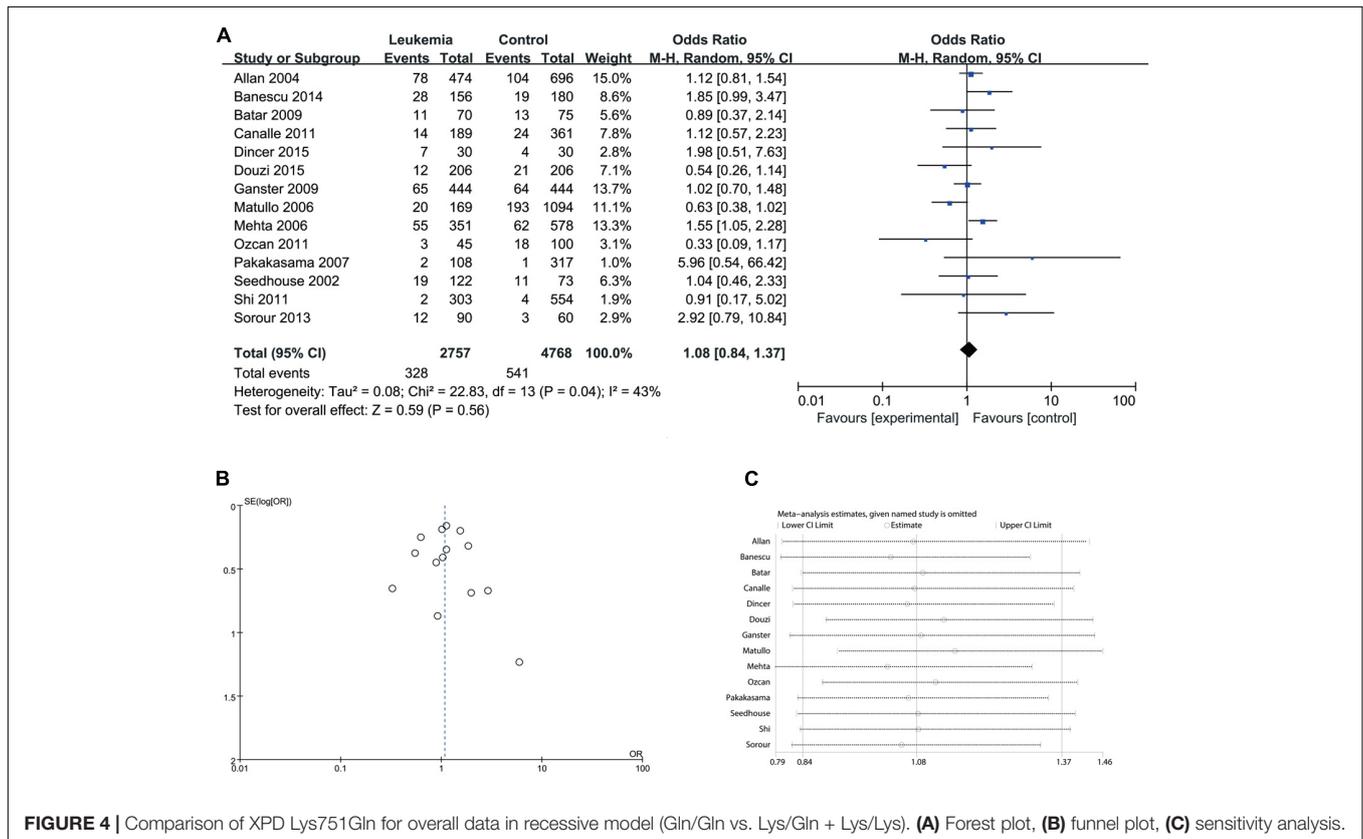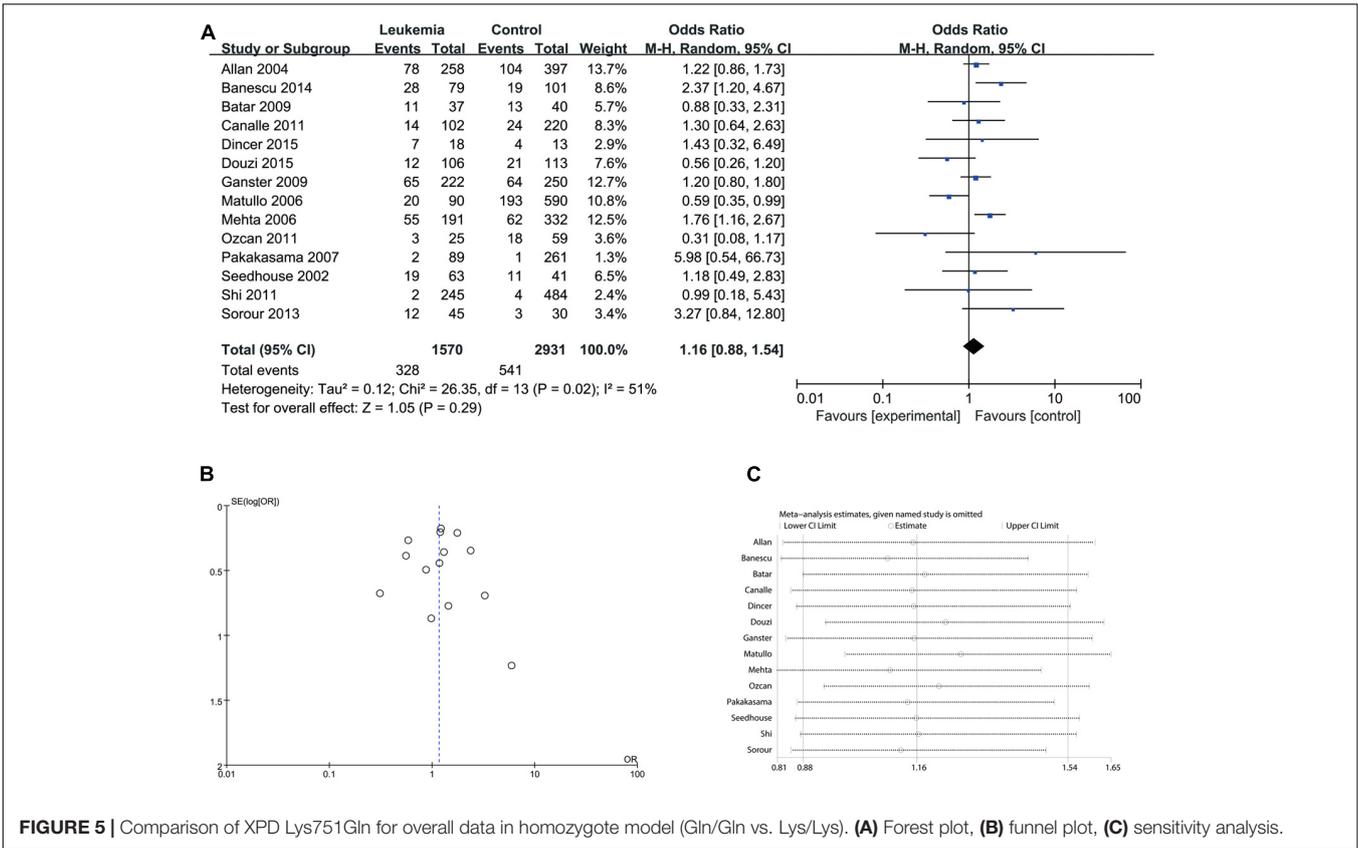

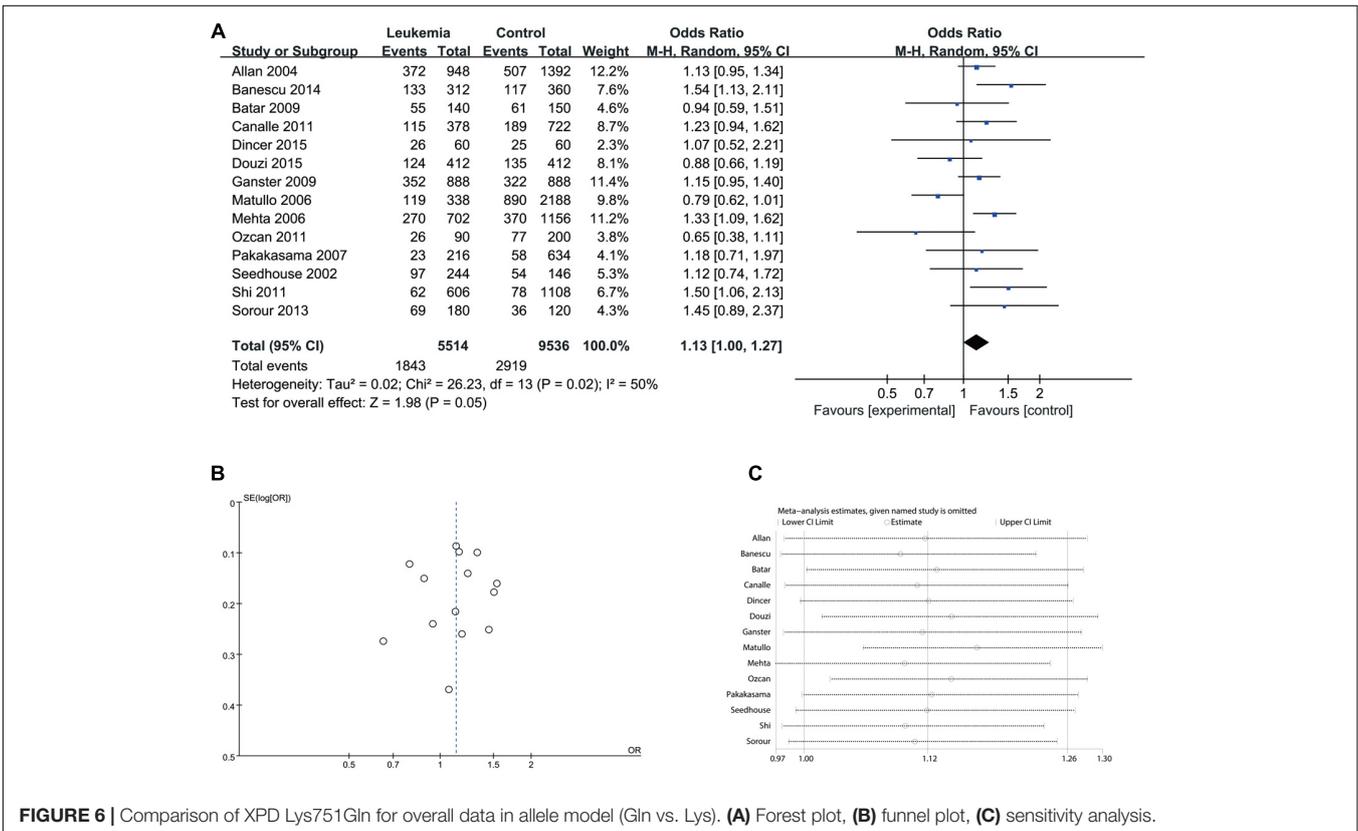FIGURE 4 | Comparison of XPD Lys751Gln for overall data in recessive model (Gln/Gln vs. Lys/Gln + Lys/Lys). (A) Forest plot, (B) funnel plot, (C) sensitivity analysis.

FIGURE 5 | Comparison of XPD Lys751Gln for overall data in homozygote model (Gln/Gln vs. Lys/Lys). **(A)** Forest plot, **(B)** funnel plot, **(C)** sensitivity analysis.

FIGURE 6 | Comparison of XPD Lys751Gln for overall data in allele model (Gln vs. Lys). **(A)** Forest plot, **(B)** funnel plot, **(C)** sensitivity analysis.

TABLE 3 | Summary of pooled OR in different ethnicities.

Genetic model	Age group	Pooled OR (95% CI)	Heterogeneity		Test for overall effect		Statistical model
			P	I^2	Z	P	
Gln vs. Lys	Caucasians	1.08 [0.95–1.21]	0.04	47%	1.18	0.24	Random-effects model
	African	1.16 [0.74–1.82]	0.66	0%	0.63	0.53	Fixed-effects model
	Asian	1.39 [1.05–1.86]	0.45	0%	2.26	0.02	Fixed-effects model
GlnGln vs. LysLys	Caucasians	1.16 [0.87–1.56]	0.01	55%	1.00	0.32	Random-effects model
	African	0.85 [0.21–3.38]	0.29	12%	0.23	0.82	Fixed-effects model
	Asian	1.77 [0.48–6.52]	0.23	30%	0.86	0.39	Fixed-effects model
LysGln vs. LysLys	Caucasians	1.15 [1.02–1.30]	0.77	0%	2.34	0.02	Fixed-effects model
	African	1.41 [0.81–2.48]	0.78	0%	1.20	0.23	Fixed-effects model
	Asian	1.35 [0.86–2.14]	0.17	46%	1.30	0.19	Random-effects model
GlnGln + LysGln vs. LysLys	Caucasians	1.15 [1.02–1.28]	0.31	14%	2.39	0.02	Fixed-effects model
	African	1.33 [0.77–2.30]	1.00	0%	1.02	0.31	Fixed-effects model
	Asian	1.42 [1.04–1.94]	0.27	17%	2.24	0.03	Fixed-effects model
GlnGln vs. LysGln + LysLys	Caucasians	1.04 [0.81–1.33]	0.05	44%	0.32	0.75	Random-effects model
	African	0.75 [0.19–2.93]	0.26	22%	0.41	0.68	Fixed-effects model
	Asian	1.67 [0.46–6.14]	0.21	36%	0.78	0.44	Fixed-effects model

TABLE 4 | Summary of pooled OR in different age groups.

Genetic model	Age group	Pooled OR (95% CI)	Heterogeneity		Test for overall effect		Statistical model
			P	I^2	Z	P	
Gln vs. Lys	Adult	1.13 [0.95–1.35]	0.006	65%	1.37	0.17	Random-effects model
	Childhood	1.24 [1.08–1.43]	0.74	0%	2.97	0.003	Fixed-effects model
GlnGln vs. LysLys	Adult	1.13 [0.77–1.66]	0.02	58%	0.64	0.52	Random-effects model
	Childhood	1.54 [1.11–2.13]	0.54	0%	1.08	0.28	Fixed-effects model
LysGln vs. LysLys	Adult	1.24 [1.08–1.42]	0.36	9%	3.06	0.002	Fixed-effects model
	Childhood	1.21 [1.01–1.45]	0.77	0%	2.05	0.04	Fixed-effects model
GlnGln+LysGln vs. LysLys	Adult	1.22 [1.01–1.48]	0.07	46%	2.04	0.04	Random-effects model
	Childhood	1.28 [1.06–1.54]	0.65	0%	2.57	0.01	Fixed-effects model
GlnGln vs. LysGln + LysLys	Adult	1.03 [0.76–1.41]	0.07	47%	0.19	0.85	Random-effects model
	Childhood	1.40 [1.04–1.90]	0.51	0%	2.19	0.03	Fixed-effects model

$I^2 = 14\%$, $P = 0.02$). No significant association was found in recessive (Gln/Gln vs. Lys/Gln + Lys/Lys: $I^2 = 44\%$, $P = 0.75$), homozygote (Gln/Gln vs. Lys/Lys: $I^2 = 55\%$, $P = 0.32$) and allele models (Gln vs. Lys: $I^2 = 47\%$, $P = 0.24$) (**Table 3**). In African and Asian populations, subgroup analysis was unreliable as only two studies were available.

Association Between the XPD Lys751Gln Polymorphism and Risk of Leukemia by Age

In subgroup analysis by age group, one study was excluded as it lacked data on patients' age (Douzi et al., 2015). Significant associations were consistently found in some genetic models of adult group (GlnGln + LysGln vs. LysLys: $I^2 = 46.0\%$, $P = 0.04$; LysGln vs. LysLys: $I^2 = 9\%$, $P = 0.002$), and in almost all models of childhood group (Gln vs. Lys: $I^2 = 0\%$, $P = 0.003$; GlnGln + LysGln vs. LysLys: $I^2 = 0\%$, $P = 0.01$; GlnGln vs. LysGln + LysLys: $I^2 = 0\%$, $P = 0.03$; GlnGln vs. LysLys: $I^2 = 0\%$, $P = 0.009$; LysGln vs. LysLys: $I^2 = 0\%$, $P = 0.04$).

Moderate to higher heterogeneity (I^2: 46–65%) was found in the no-association models of the adult group (**Table 4**).

Association Between the XPD Lys751Gln Polymorphism and Risk of Leukemia by Subtype

In subgroup analysis by leukemia subtypes, one study was excluded as it lacked such data (Matullo et al., 2006). Significant associations were found in almost all genetic models of acute leukemia (Gln vs. Lys: $I^2 = 12\%$, $P < 0.001$; GlnGln + LysGln vs. LysLys: $I^2 = 0\%$, $P < 0.001$; GlnGln vs. LysLys: $I^2 = 14\%$, $P = 0.02$; LysGln vs. LysLys: $I^2 = 0\%$, $P = 0.003$), and in some models of chronic disease (GlnGln + LysGln vs. LysLys: $I^2 = 34\%$, $P = 0.009$; LysGln vs. LysLys: $I^2 = 0\%$, $P < 0.001$) (**Table 5**).

DISCUSSION

The NER pathway is a highly conserved DNA repair mechanism that removes bulky intra-strand adducts created by agents

TABLE 5 | Summary of pooled OR in different leukemia subtype.

Genetic model	Subtype	Pooled OR (95% CI)	Heterogeneity		Test for overall effect		Statistical model
			P	I^2	Z	P	
Gln vs. Lys	Acute	1.17 [1.07–1.29]	0.33	12%	3.37	0.0007	Fixed-effects model
	Chronic	1.14 [0.83–1.57]	0.03	72%	0.80	0.42	Random-effects model
GlnGln vs. LysLys	Acute	1.29 [1.04–1.59]	0.32	14%	2.35	0.02	Fixed-effects model
	Chronic	1.08 [0.40–2.88]	0.01	78%	0.15	0.88	Random-effects model
LysGln vs. LysLys	Acute	1.22 [1.07–1.39]	0.76	0%	2.99	0.003	Fixed-effects model
	Chronic	1.36 [1.09–1.69]	0.67	0%	2.70	0.007	Fixed-effects model
GlnGln + LysGln vs. LysLys	Acute	1.24 [1.09–1.40]	0.63	0%	3.38	0.0007	Fixed-effects model
	Chronic	1.32 [1.07–1.63]	0.22	34%	2.60	0.009	Fixed-effects model
GlnGln vs. LysGln + LysLys	Acute	1.19 [0.98–1.45]	0.35	10%	1.72	0.09	Fixed-effects model
	Chronic	0.94 [0.39–2.28]	0.02	76%	0.13	0.90	Random-effects model

such as UV radiation and certain chemicals, including several commonly used chemotherapy agents (Scharer, 2013). Genetic polymorphism in DNA repair genes may cause variation in DNA repair capacity, which in turn can lead to cumulative genotoxic damage and increased susceptibility to cancer (Douzi et al., 2015). As an important component of NER, XPD is an evolutionarily conserved ATP-dependent DNA helicase that plays an essential role in DNA repair (Kim et al., 2016). Several studies suggested an increased risk of cancer in individuals with polymorphism in XPD or other NER pathway genes (Paszkowska-Szczur et al., 2013; He et al., 2016). Moreover, several molecular epidemiological studies have found an association between XPD polymorphism and leukemia risk in diverse populations. However, the results were inconsistent and even contradictory. We therefore conducted a meta-analysis to globally evaluate the potential relationship between XPD polymorphism and leukemia.

Our results indicate that XPD Lys751Gln polymorphism significantly increase overall leukemia risk in dominant and heterozygote models, but not in allele model or homozygote model. The results suggest that heterozygous mutations but not homozygote mutations of XPD (Lys/Gln) may increase the genetic susceptibility of leukemia. This may be the result of a higher rates of heterozygous vs. homozygous mutations (the ratio between heterozygous and homozygous mutations is 2.27 ∼ 56 in control and 1.71 ∼ 29 in leukemia). Subgroup analysis by ethnicity showed the same result in Caucasian population. The exact mechanism for association between different tumors susceptibility and XPD Lys751Gln polymorphism is currently unknown. XPD is a $5'-3'$ superfamily 2 DNA helicase that opens damaged DNA for bulky lesion repair in NER. The interaction of C-terminal domain of XPD with the p44 helicase activator protein are critical for both helicase activity and stability of the TFIIH complex, which is essential for RNA polymerase (RNAP) II-mediated transcription initiation and the NER (Liu et al., 2008). The XPD C-terminal Lys751Gln polymorphism may alter the structure of the C-terminal domain, hence blocking critical interaction with p44 and destructive TFIIH conformation, which subsequently reduce DNA repair activity (Lunn et al., 2000; Fan et al., 2008; Monaco et al., 2009).

Furthermore, by stratifying the data by age and subtype of disease, we found that XPD Lys751Gln polymorphism significantly increased leukemia risk in almost all models of childhood and acute disease. The occurrence and development of leukemia appeared to be regulated by genetic and environmental factors. In children with acute leukemia, malignancy manifests with a short latency period, thus does not have enough exposure time to allow the initiation of a long carcinogenic process. Unlike children, adults usually develop cancer because of the cumulative effect of environmental exposure during his/her life (Brisson et al., 2015). Thus, we speculate that genetic polymorphism is more important for childhood and acute leukemia.

Compared to previous reports (Liu et al., 2014; Wu et al., 2014), the present study has the following advantages: (1) it analyzed the association between XPD Lys751Gln polymorphism and acute leukemia, but also it association with chronic leukemia; (2) A total of 14 studies (2,757 cases and 4,768 controls) were compiled in our research, thus increasing the statistical power of the analysis. (3) Strict literature inclusion and exclusion criteria were enforced, the Ozdemir's study was excluded from our analysis due to lack of discerning information between ALL and Burkitt lymphoma patients. However, our research also has some limitations: (1) The number of original studies included in the meta-analysis are relatively small, especially in the subgroup analysis. Future studies on ethnicity, age and subtype of leukemia are needed to further corroborate our findings. (2) Heterogeneity, which can greatly affect conclusions of meta-analysis, was high in some models. Our result showed that moderate or higher heterogeneity was found in some models, which showed no association with leukemia risk. The Matullo's study was a major source of this heterogeneity, probably due to the significant differences in number of cases and controls.

CONCLUSION

Our meta-analysis demonstrates that XPD Lys751Gln polymorphism significantly increases overall leukemia risk in dominant and heterozygote models, and that this polymorphism

is significant associated with almost all genetic models of childhood and acute leukemia.

AUTHOR CONTRIBUTIONS

XH and Y-BD designed this study. XL, YC, and JS searched databases and collected the full-text papers. MW and BZ extracted and analyzed the data and wrote the manuscript. EZ, YL, XH, and Y-BD reviewed the manuscript.

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