

Associations of NQO1 C609T and NQO1 C465T polymorphisms with acute leukemia risk: a PRISMA-compliant meta-analysis

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Objective: The NAD(P)H:quinone oxidoreductase (NQO1) C609T and C465T polymorphisms have been widely thought to be associated with the risk of acute leukemia (AL) in recent years, but the correlations are still unclear. A meta-analysis is generally acknowledged as one of the best methods for secondary research, and so it was applied in this study with the aim of elucidating how the NQO1 C609T and C465T polymorphisms are related to the risk of AL.

Methods: Relevant studies were searched in the PubMed, EMBASE, CNKI, and Wanfang databases, and the obtained data were analyzed using Stata (version 12.1). The allele-contrast model was applied, and odds ratios (ORs) with 95% confidence intervals (CIs) were used to evaluate relationship strengths. Meta-regression was used to identify sources of heterogeneity, and subgroup analyses were conducted. Publication bias was analyzed using funnel plots, with the trim-and-fill method used to analyze the effect of publication bias on pooled results. In addition, sensitivity analysis, the fail-safe number method, and cumulative analysis by publication year were performed to measure the stability of the obtained results.

Results: This meta-analysis included 28 relevant studies involving 5,953 patients and 8,667 controls. Overall, the C609T polymorphism was associated with the risk of acute lymphoblastic leukemia (ALL; OR =1.18, 95% CI =1.00–1.39, $P=0.05$). Meanwhile, race was found to be a potential source of heterogeneity for the relationship between the C609T polymorphism and acute myeloid leukemia (AML) risk, and the subgroup analysis identified the C609T polymorphism as a risk factor for AML in Asians (OR =1.34, 95% CI =1.03–1.74, $P=0.03$). The number of studies about C465T polymorphism was too small to pool the data.

Conclusion: There are increased risks of ALL in all subjects and of AML in Asians for carriers of the NQO1 C609T polymorphism. Further studies are needed to verify the associations of the C465T polymorphism with the risk of AL.

Keywords: NQO1, polymorphism, AML, ALL

Introduction

Leukemia is a clonal disorder of hematopoietic cells that is mostly associated with genetic mutation along with a diversity of chromosomal and molecular changes.¹ It is one of top ten malignant tumors in China, and the number of leukemia patients has increased markedly in recent years.² Acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) are the most common types of acute leukemia (AL) in both adults and children. Although there are well-documented studies of the clinical and biological aspects of leukemia, little is known about the predisposing factors of leukemia.³ Smoking, obesity, and exposure to radiation and chemical carcinogens are putative or actual risk factors for AL. However, AL only develops in a small proportion

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of individuals who have been exposed to these environmental and lifestyle risk factors, and so the genetic background may also be a possible etiology in AL.⁴

NAD(P)H:quinone oxidoreductase (NQO1), which was originally called DT-diaphorase, is a flavoenzyme that can detoxify quinines derived from the oxidation of phenolic metabolites of benzene by catalyzing two or four electron reductions of these substrates. It can protect cells against oxidative damage by preventing redox cycling and the generation of free radicals.⁵ Single-nucleotide polymorphisms (SNPs) are the most common type of variant in the human genome.⁶ A widely researched SNP in NQO1 is C609T. A C/T change at nucleotide 609 causes a proline-to-serine substitution and therefore destabilizes and inactivates the enzyme. Individuals with TT genotype completely lack NQO1 activity, and CT genotype carriers present about threefold decreased enzyme activity compared with wild-type carriers.⁷ The frequency of the NQO1 C609T polymorphism exhibits ethnic variation. The prevalence of the homozygous variant genotype (TT) was ~20% in Asian populations and 4% in Caucasians.⁸ Another common SNP was C465T: a C/T change at nucleotide 465. This SNP can also diminish the activity of NQO1.⁹ So the ability to detoxify carcinogens is reduced when these two polymorphisms are present, which may increase the probability of malignant changes in susceptible individuals.¹⁰ These observations support the hypothesis that the TT genotypes for C609T or C465T polymorphisms are likely to be related to the high risk of AL.

It is possibly more meaningful to analyze the effects of genotype–environment interactions on chronic leukemia, and the genetic background may play a more important role in the etiology of AL. Since 2000, the NQO1 C609T and NQO1 C465T polymorphisms have been widely thought to be associated with the risk of AL, but the correlations are still unclear, possibly due to insufficient studies with complete data, diverse study designs and methods, differences in race and geography, and publication bias.

A meta-analysis of published case–control studies was therefore undertaken to precisely evaluate whether the NQO1 C609T and NQO1 C465T polymorphisms are associated with the risk of AL. Potential sources of heterogeneity, subgroups, stability of results, and publication bias were carefully analyzed in this study.

Methods

This meta-analysis was designed and written according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Search strategy

The medical literature on associations between the AL risk and the NQO1 C609T and NQO1 C465T polymorphisms that was published before February 2016 was searched in the PubMed, EMBASE, CNKI, and Wanfang electronic databases. The following combination of keywords was used: [AL OR (acute leukemia) OR (AML) OR (acute myeloid leukemia) OR (acute myelocytic leukemia) OR (acute myeloblastic leukemia) OR (ALL) OR (acute lymphocytic leukemia) OR (acute lymphoblastic leukemia)] AND [NQO1 OR (quinone reductase 1) OR (quinone oxidoreductase 1)] AND [polymorphism OR allele OR variant OR variation OR genotype]. The research subjects were limited to humans, and the language was limited to English or Chinese. The references in identified publications were also browsed in order to identify any other relevant studies.

Eligibility criteria

The following inclusion criteria were applied to the studies: 1) must focus on associations of the NQO1 C609T and NQO1 C465T polymorphisms with the AL risk; 2) must have a case–control design; and 3) the reported genotype distribution data must be sufficient to allow the odds ratios (ORs) with 95% confidence intervals (CIs) to be calculated. Studies involving larger samples or published more recently were selected in cases of repeated studies or overlapping data. If the reported data were incomplete, the corresponding author was contacted to obtain complete data.

Data extraction

The following details were extracted from all eligible studies: first author, publication year, race of included subjects, sample sizes of cases and controls, age group, genotyping method, source of controls, mutational location in NQO1, quality score, and results of the Hardy–Weinberg equilibrium (HWE) test for the controls.

Quality assessment

The quality of the included studies was assessed using the quality scoring criteria employed in a previous meta-analysis.¹¹ The representativeness of cases, source of controls, genotyping examination (whether or not genotyping was performed under a blinded condition), the association assessment method, and the HWE test for controls were included as quality assessment indicators. The quality score was calculated by summing the scores for all of these indicators, with the total score ranging from 0 to 10 points. Studies with a score of <6 points were considered to be of low quality.

Statistical analysis

An allele-contrast model was used to investigate the associations of the NQO1 C609T and NQO1 C465T polymorphisms with the risk of AL, and relationship strengths were assessed by ORs with 95% CIs. The statistical random-effects model was used to evaluate different underlying influences and consider variations within or among studies, which provided the advantages of accommodating diversity among studies and offering more conservative evaluations.

Heterogeneity among the studies was analyzed by the chi-square test based on the Q statistic, with significant heterogeneity considered to be present when the P -value was <0.1 . The heterogeneity was quantified by the I^2 value, with a value $>50\%$ indicating higher heterogeneity among the studies. The potential sources of heterogeneity were explored by meta-regression based on the following covariates: race, age, and source of controls. A subgroup analysis was also performed using these covariates.

The publication bias was analyzed by using funnel plots, where an asymmetric funnel plot indicates the presence of such bias. The symmetry of a funnel plot was quantified using Egger's linear regression test, where a P -value of <0.05 was considered to indicate significant asymmetry and significant publication bias existence. Then the trim-and-fill method was used to assess the effect of publication bias on pooled results.

A cumulative analysis by publication year was performed to observe the trend of pooled results over time. The influence analysis of single study was applied to assess the robustness of the obtained results. Meanwhile, sensitivity analyses were also applied to studies of low quality or that did not conform to HWE to evaluate the effect of these studies on the overall results. In addition, the fail-safe number of negative studies that would be required to nullify (ie, make $P>0.05$) the effect size was calculated, and a bigger number indicated a more stable pooled result. Stata (version 12.1) was used for all of the statistical tests.

Results

Study characteristics

In total, 893 articles were searched in electronic databases, which resulted in the inclusion of 28 studies. Among the articles, 18 and 18 were about the associations of the NQO1 C609T polymorphism with the risks of AML and ALL, respectively, two were about the association between the NQO1 C465T polymorphism and the AML risk, and three were about the association between the NQO1 C465T polymorphism and the ALL risk. Among these studies,

11 focused on Caucasians,^{1,3,12–20} 10 on Asians,^{2,9,10,21–27} four on mixed populations,^{5,28–30} two on Africans,^{31,32} and one on Javanese.³³ In terms of the genotype distribution of controls, 20 of the studies about the association between the NQO1 C609T polymorphism and the AL risk conformed with HWE,^{1,3,5,9,12,14–20,22–24,28,30–33} while seven did not,^{2,10,21,25–27,29} and the HWE test could not be applied to one study¹³ because of insufficient data. Two studies of the association between the NQO1 C465T polymorphism and the AL risk conformed with HWE,^{16,9} while two did not.^{23,24} Moreover, there were two studies of low quality.^{2,13} A flow diagram of the study selection procedure is shown in Figure 1, and the main characteristics of the included studies are presented in Table 1.

NQO1 C609T polymorphism and the ALL risk

Eighteen relevant studies were used to assess the association between the NQO1 C609T polymorphism and the ALL risk. The pooled result revealed a marginally increased risk of ALL for the NQO1 C609T polymorphism (OR =1.18, 95% CI =1.00–1.39, $P=0.05$; Figure 2A). The fail-safe number was 77.03. The heterogeneity was high ($I^2=73.0\%$), but meta-regression did not reveal the potential source of this heterogeneity. In addition, an increased ALL risk for adults was found in the subgroup analysis (OR =1.71, 95% CI =1.20–2.43, $P=0.003$). The results of the subgroup analysis are presented in Table 2.

When attempting to identify the presence of publication bias, it is difficult to assess whether a funnel plot is symmetric merely by visual examination. Egger's linear regression test provided evidence of asymmetry ($P=0.031$). The publication bias was adjusted by the trim-and-fill method; after that, the pooled result did not change (ie, the effect size from 1.322, 95% CI =1.091–1.554, to 3.752, 95% CI =2.977–4.730; Figure 2D), meaning that the analyses were stable, and moreover that future new research might not change the pooled results. In addition, the influence analysis of single study showed that the total pooled result was greatly affected by the 15 studies (Figure 2B).^{2,3,9,10,12,13,15,16,19,21,25,28–31} Excluding any of these studies resulted in the statistically significant loss of pooled OR values. Meanwhile, the sensitivity analysis revealed that deleting two studies of low quality,^{2,13} five studies that did not conform to HWE,^{2,10,21,25,29} or one study for which the HWE test was not applied did not change the pooled ORs,¹³ showing that these factors did not affect the stability of the pooled results. No stable tendency was found in the cumulative analysis by publication year (Figure 2C).

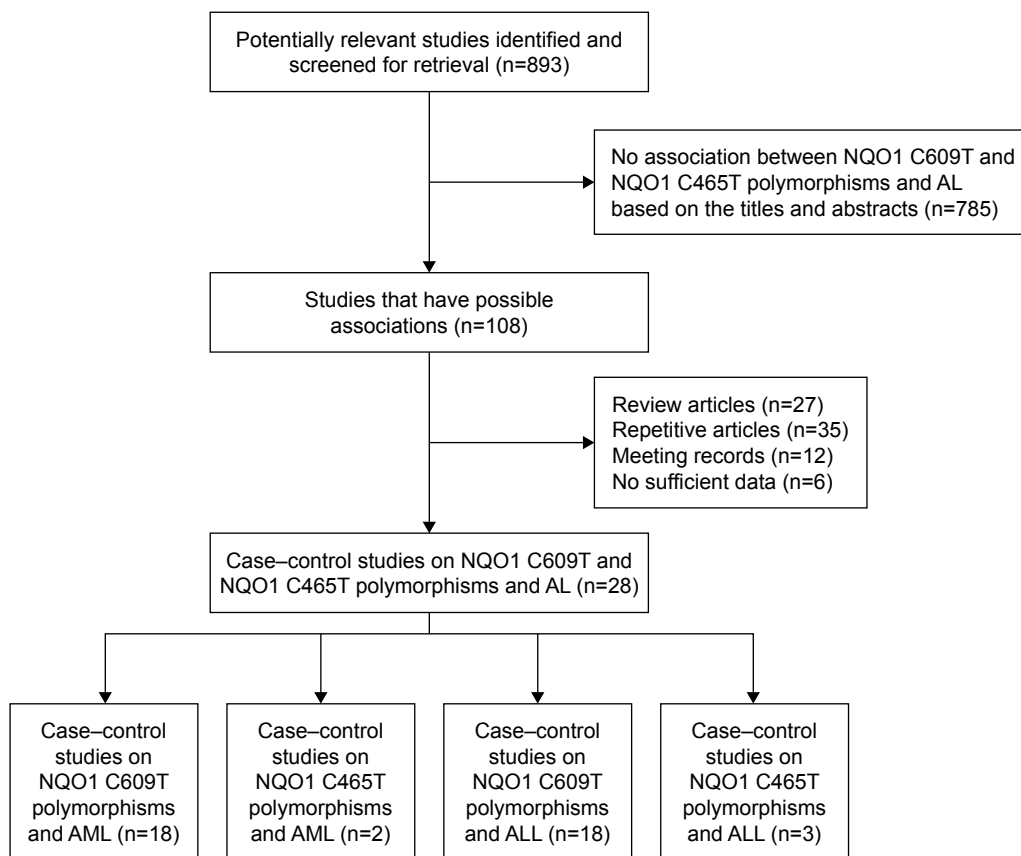


Figure 1 Flow diagram of the study selection process.

Abbreviations: NQO1, NAD(P)H:quinone oxidoreductase; AL, acute leukemia; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia.

NQO1 C609T polymorphism and the AML risk

Eighteen relevant studies were used to assess the association between the NQO1 C609T polymorphism and the AML risk. The pooled result was not statistically significant (OR=1.11, 95% CI=0.94–1.30, $P=0.23$; Figure 3A). The heterogeneity was high ($I^2=71.5\%$), and meta-regression revealed that race and the source of controls were potential sources of this heterogeneity. In addition, an increased AML risk for Asians, adults, and hospital-based control groups was found in the subgroup analysis. The results of the subgroup analysis are presented in Table 2. Egger's linear regression test provided evidence of symmetry ($P=0.338$, Figure 3B).

NQO1 C465T polymorphism and risks of AML and ALL

Three relevant studies assessed the association between the NQO1 C465T polymorphism and the ALL risk, of which two did not find a significant association^{9,16} and one found an increased risk of ALL for the NQO1 C465T polymorphism.²⁴ Two relevant studies researched the association between the

NQO1 C465T polymorphism and the AML risk, and both of them did not find a significant association.^{9,23}

Discussion

The method of meta-analysis was used in this study to integrate the published evidence on the associations of the NQO1 C609T and NQO1 C465T polymorphisms with the risk of AL. A heterogeneity evaluation, source searching, sensitivity analysis, publication bias analysis, and analysis of the stability of results were also conducted.

The NQO1 C609T polymorphism was found to be a risk factor for ALL. However, the P -value was only marginally significant, which may have been related to the sample size, and so a more precise result will need to be obtained in the future by using a larger sample. This polymorphism was associated with an increased ALL risk for adults. The different results for children and adults may have been due to the AL etiology differing between these two populations.³⁴ Children are generally more susceptible to environmental toxins because of their immature metabolism and their faster cell division and growth compared with adults.³⁵ This result

Table 1 Characteristics of included studies

Study	Year	Ethnicity	Sample size		Age	Genotyping method	Control sources	Polymorphism of NQO1	Cases	P-value for HWE	Quality score
			Cases	Controls							
Bolufer et al ³	2007	Caucasian	302	454	Adult	PCR-based methods	PB	C609T	AML	0.422	8
			141	454					ALL		8
Bonaventure et al ¹²	2012	Caucasian	433	441	Children	Imputation	PB	C609T	ALL	0.205	8
			51	441					AML		8
Chan et al ³³	2011	Javanese	185	177	Children	PCR-RFLP	PB	C609T	ALL	0.926	7
Clavel et al ³⁰	2005	Mixed	219	105	Children	PCR-RFLP	HB	C609T	ALL	0.673	7
de Aguiar	2012	Mixed	519	401	Children	PCR	PB	C609T	ALL	0.057	8
Goncalves et al ²⁸			107	401					AML		8
Eguchi-Ishimae et al ⁹	2005	Asian	103	185	Children	PCR-RFLP	PB	C609T	ALL	0.482	7
			103	185					C465T		7
Eyada et al ¹³	2007	Caucasian	19	11	NA	PCR-RFLP	NA	C609T	AML	NA	3
			13	11					ALL		3
Guillem et al ¹⁴	2007	Caucasian	81	64	Adult	PCR-RFLP	PB	C609T	AML	0.556	7
Jia et al ²	2012	Asian	102	150	Adult	LDR	HB	C609T	AML	0.005	5
			48	150					ALL		5
Kracht et al ¹⁵	2004	Caucasian	138	190	Children	PCR	PB	C609T	ALL	0.147	8
Krajcinovic et al ¹⁶	2002	Caucasian	174	323	Children	PCR	PB	C609T	ALL	0.312	7
									C465T		7
Malik et al ⁵	2006	Mixed	262	688	Adult	PCR-RFLP	PB	C609T	AML	0.295	7
Naoe et al ²⁶	2000	Asian	411	150	Adult	PCR	PB	C609T	AML	0.037	7
Ouerhani et al ³¹	2013	African	100	106	Adult	PCR-RFLP	PB	C609T	ALL	0.155	8
Rimando et al ²¹	2008	Asian	60	60	Children	PCR-CTPP	PB	C609T	ALL	<0.01	6
Seedhouse et al ¹	2002	Caucasian	168	178	Adult	PCR-RFLP	PB	C609T	AML	0.12	8
Silveira Vda et al ¹⁷	2010	Caucasian	206	364	Children	PCR-RFLP	HB	C609T	ALL	0.218	6
Sirma et al ²⁹	2004	Mixed	189	286	Children	PCR-RFLP	PB	C609T	ALL	0.016	6
			84	286					AML		6
Sorour et al ³²	2013	African	90	60	Adult	PCR-RFLP	PB	C609T	AML	0.299	7
Voso et al ¹⁸	2007	Caucasian	160	162	Adult	PCR-RFLP	PB	C609T	AML	0.12	8
Yamaguti et al ²⁰	2009	Caucasian	133	133	Adult	PCR-RFLP	PB	C609T	AML	0.054	6
Yamaguti et al ¹⁹	2010	Caucasian	99	99	Children	PCR	PB	C609T	ALL	0.133	6
Yang et al ²²	2005	Asian	228	241	Adult	PCR-RFLP	PB	C609T	AML	0.495	6
Zaker et al ²³	2011	Asian	140	160	Adult	PCR-RFLP	PB	C609T	AML	0.19	9
									C465T		<0.01
Zaker et al ²⁴	2012	Asian	100	135	Children	PCR-RFLP	PB	C609T	ALL	0.162	8
									C465T		<0.01
Zhang et al ²⁵	2009	Asian	170	458	Adult	PCR-RFLP	PB	C609T	ALL	0.017	7
Xu ¹⁰	2010	Asian	78	100	Adult	PCR-RFLP	HB	C609T	AML	0.001	6
			22	100					PCR-LDR		6
Yang ²⁷	2006	Asian	306	458	Adult	PCR-RFLP	PB	C609T	AML	0.017	7

Abbreviations: AL, acute leukemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HWE, Hardy-Weinberg equilibrium; NQO1, NAD(P)H:quinone oxidoreductase; NA, not available; HB, hospital-based; PB, population-based; PCR, polymerase chain reaction; PCR-CTPP, PCR confronting two-pair primer; LDR, ligase detection reaction; RFLP, restriction fragment length polymorphism.

also suggests the presence of age stratification for the AL risk, and so age-stratification studies are needed to clarify this. Moreover, this research result was very sensitive, which may be due to the number of raw studies being too small, and so more relevant studies are needed to verify the association between the NQO1 C609T polymorphism and the ALL risk in the future.

The association between the NQO1 C609T polymorphism and the ALL risk was analyzed by Li and Zhou³⁶ in four models. They found that this polymorphism increased

the ALL risk in a recessive model and a model of T/T versus C/C, while no statistical significance was seen in a dominant model or a model of C/T versus C/C. Their subgroup analysis found that the NQO1 C609T polymorphism increased the ALL risk for adults in a dominant model and a model of T/T versus C/C. The allele-comparison model was used in this study, and it was found that the NQO1 C609T polymorphism increased the ALL risk, with the effect size of an increased ALL risk for adults still being significant in the subgroup analysis. Only the allele-contrast model was selected for this

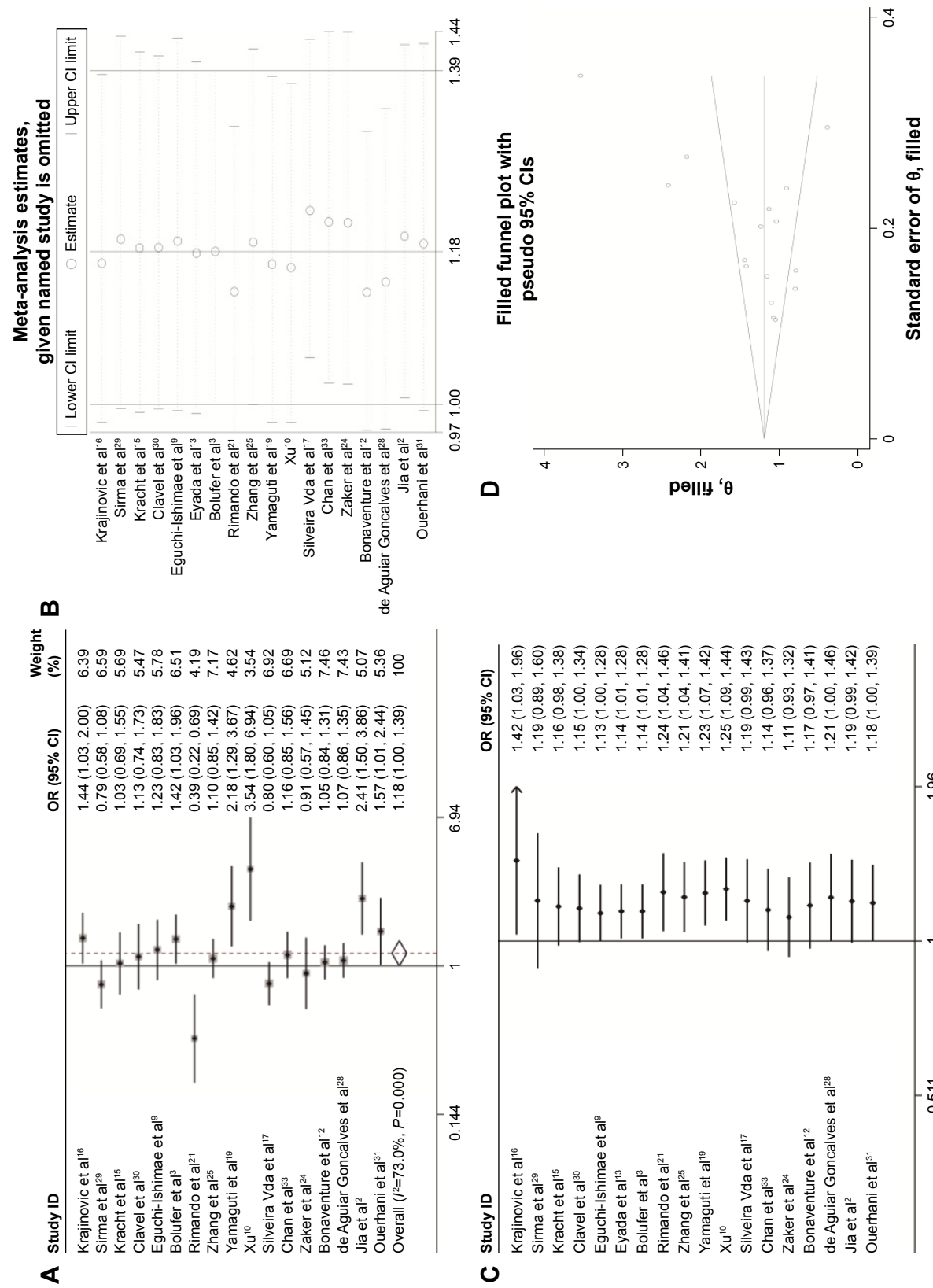


Figure 2 The associations between NQO1 C609T and the ALL risk. (A) Calculated ORs and 95% CIs for the association. (B) Sensitivity analysis via deletion of each individual study. (C) Cumulative meta-analysis according to publication year. (D) Trim-and-fill plot to correct publication bias. Note: Weights are from random-effects analysis. Abbreviations: NQO1, NAD(P)H:quinone oxidoreductase; ALL, acute lymphoblastic leukemia; OR, odds ratio; CI, confidence interval.

Table 2 Subgroup analysis for the association of NQO1 C609T with AL risk

Association	Factors	Subgroups	N	OR	95% CI	P-value ^a	I ² (%)
C609T and ALL	Ethnicity	Caucasians	6	1.20	0.94–1.53	0.005	70
		Asians	6	1.25	0.78–2.00	<0.00001	86
		Mix	3	0.98	0.79–1.22	0.12	32
		Javanese	1	1.16	0.85–1.56	NA	NA
		African	1	1.57	1.01–2.44	NA	NA
	Age	Children	12	1.03	0.87–1.22	0.001	64
		Adult	5	1.71	1.20–2.43	0.003	75
	Control source	PB	13	1.12	0.96–1.30	0.001	63
		HB	4	1.59	0.83–3.05	<0.00001	89
C609T and AML	Ethnicity	Caucasians	7	1.02	0.83–1.26	0.14	40
		Asians	7	1.34	1.03–1.74	0.0002	77
		Mix	3	0.83	0.58–1.19	0.05	66
		African	1	1.06	0.58–1.94	NA	NA
	Age	Children	4	0.80	0.63–1.01	0.4	0
		Adult	13	1.19	1.00–1.42	<0.0001	72
	Control source	PB	15	1.03	0.88–1.21	<0.0001	67
		HB	2	1.92	1.45–2.55	0.81	0

Note: ^aP-value for heterogeneity test.

Abbreviations: AL, acute leukemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CI, confidence interval; N, numbers of comparisons; NA, not available; NQO1, NAD(P)H:quinone oxidoreductase; OR, odds ratio; HB, hospital-based; PB, population-based; NA, not available.

meta-analysis, which could avoid the reuse of data and thus reduce false positive results.

No statistically significant results were found for AML in this study. Meta-regression revealed race to be a potential source of heterogeneity. The subgroup analysis showed that the NQO1 C609T polymorphism is a risk factor for AML in Asians. The meta-analysis showed that the NQO1 C609T polymorphism is a risk factor for bladder and bowel cancer in Caucasians, but a protective factor in Asians;¹² these differences indicate that genetic mechanisms may differ between Asians and Caucasians. In addition, the NQO1 C609T polymorphism was a risk factor for AML when the controls were from hospitals, but there were only two raw studies involving hospital-based controls, which suggests that caution is required when interpreting this result owing to the small number of samples and the corresponding low statistical power.

The association between the NQO1 C609T polymorphism and the AML risk was analyzed by Li et al⁴ in four models. They found that the NQO1 C609T polymorphism increased the AML risk using the recessive fixed-effects model and the model of TT versus CC. However, no statistical significance was seen in the dominant random-effects model or the model of CT versus CC. In addition, the NQO1 C609T polymorphism increased the risks of AML in adults and Asians in the subgroup analysis in the recessive random-effects model in their study. In this study, no statistically significant association was found between this SNP and the AML risk under the allele-comparison model, but significant associations

were found for Asians, adults, and hospital-based control groups, which was consistent with the study by Li et al.⁴ The main differences between this study and the two articles by Li et al^{4,36} were mainly reflected in the following two aspects: 1) this sample was larger because several raw studies were newly added and 2) the stability of pooled results was also analyzed to provide a more objective evaluation.

Only a small amount of the literature focuses on the relationships of the NQO1 C465T polymorphism with the risks of ALL and AML, which was definitely not enough the meta-analysis in this study. So the results of original articles were described.

This study was subject to three main limitations. First, leukemia is associated with several risk factors including age, previous blood disease, genetic variants, occupational hazards, chemotherapy, and exposure to viruses, X-rays, and chemicals. However, only gene polymorphisms were considered in this study. The effects of gene–environment interactions on the initiation and development of leukemia need to be analyzed further in individual patients. Second, only relevant studies published in English or Chinese were included in this study, and so there is a possibility of language bias. Third, the number of raw studies was small in some of the subgroup analyses, which could have led to overestimations of real relationships.

Conclusion

The NQO1 C609T polymorphism may be associated with an increased risk of AL. T allele carriers might be more

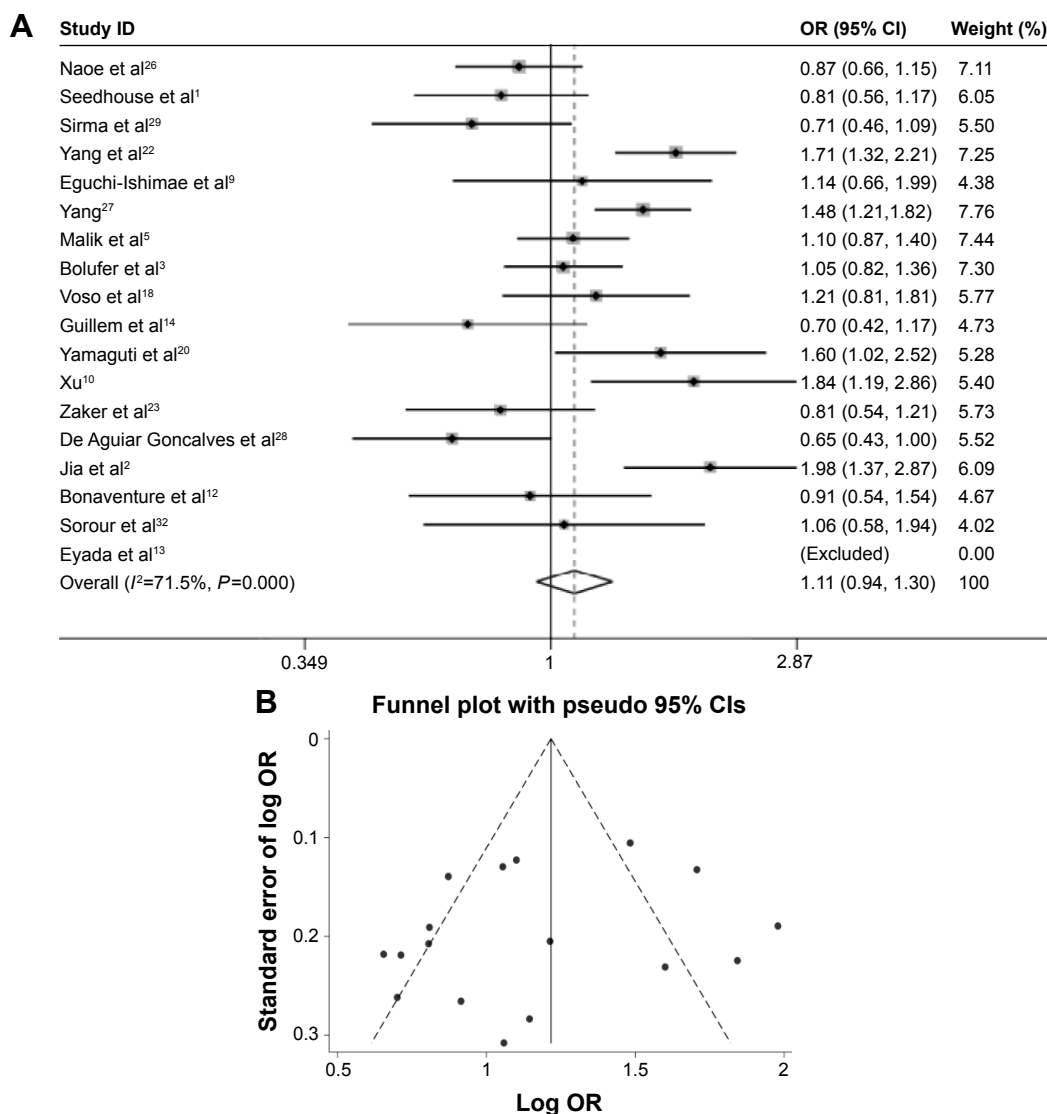


Figure 3 The associations between NQO1 C609T and AML risk. **(A)** Calculated ORs and 95% CIs for the association. **(B)** Funnel plot for detecting publication bias. **Note:** Weights are from random-effects analysis.

Abbreviations: NQO1, NAD(P)H:quinone oxidoreductase; AML, acute myeloid leukemia; OR, odds ratio; CI, confidence interval.

susceptible to AL and thus should pay more attention to away from environmental and lifestyle risk factors. In order to provide better guidance for clinical practice, future studies need to verify the relationships of the NQO1 C609T polymorphism with the risks of ALL and AML.

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Disclosure

The authors report no conflicts of interest in this work.

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