RESEARCH ARTICLE

Effects of the NQO1 609C>T Polymorphism on Leukemia Susceptibility: Evidence from a Meta-analysis

Fei-Fei Han[1&], Chang-Long Guo[2,3&], Li-Li Gong[1], Zhu Jin[1], Li-Hong Liu[1*]

Abstract

A functional polymorphism in the NQO1 gene, featuring a 609C>T substitution,leading to proline to serine amino-acid and enzyme activity changes, has been implicated in cancer risk. However, individually published investigations showed inconclusive results, especially for leukemia. In this study, we therefore performed a meta-analysis of 21 publications with a total of 3,634 cases and 4,827controls, mainly for leukemia. We summarized the data on the association between the NQO1 609C>T polymorphism and risk of leukemia and performed subgroup analyses by ethnicity and leukemia type. We found that the variant TT homozygous genotype o was associated with a modestly increased risk of leukemia (TT versus CT/CC: OR = 1.23, 95%CI = 1.00 - 1.51, heterogeneity = 0.76; I^2 = 0%). Following further stratified analyses, increased risk was only observed in subgroups of Caucasians. This meta-analysis suggests that the NQO1 609T allele is a high-penetrance risk factor for leukemia in Caucasians. The effect on leukemia may be modified by ethnicity and leukemia type, and the small sample sizes of the subgroup analyses suggest that further larger studies are needed.

Keywords: NQO1 609C>T polymorphism - leukemia - meta-analysis

Asian Pac J Cancer Prev, **14 (9)**, 5311-5316

Introduction

NQO1 (NAD(P)H dehydrogenase, quinone 1) is a member of the NAD(P)H dehydrogenase family and encodes a cytoplasmic 2-electron reductase. This FAD-binding protein forms homodimers and reduces quinones to hydroquinones (Snyder et al., 1996; North et al., 2011). In organism, NQO1 functions as a gatekeeper of the 20S proteasomes (Asher et al., 2005), it binds to a subset of short-lived proteins (such as p53, p73 and ornithine decarboxilase) and protects them from 20S proteasomal degradation. The NQO1 609C>T polymorphism is characterized by a single proline-to-serine amino acid substitution, that decreases the half time of NQO1 from 18 h (wild-type) to only 1.2 h via ubiquitination and proteasome pathways. Moreover, other research demonstrated that cell lines and tissues genotyped as homozygous for the NQO1 609C>T polymorphism are deficient in NQO1 activity (Siegel et al., 2001).

NQO1 protein prevents one electron reduction of quinones that results in the production of radical species. Mutations in this gene have been associated with tardive dyskinesia (TD) (Pae et al., 2004; Pae, 2008), an increased risk of hematotoxicity after exposure to benzene (Iskander et al., 2005; Ross, 2005), increased risk of childhood asthma (David et al., 2003; Li et al., 2009), susceptibility to various forms of cancer (Sameer et al., 2010; Pandith et al., 2011; Goode et al., 2013; Malik et al., 2013; Yang et al., 2013) and Alzheimer's disease (AD) (SantaCruz et al., 2004; Bian et al., 2008). Previous researches have revealed the association between NQO1 609C>T polymorphism and leukemia susceptibility. However, the results were conflicting, including an increased risk (Wiemels et al., 1999; Smith et al., 2001; Lanciotti et al., 2005; Yamaguti et al., 2009; Yamaguti et al., 2010; Yamaguti et al., 2010), a reduced risk (Malik et al., 2006; Silveira Vda et al., 2010; Yeoh et al., 2010), and no association (Seedhouse et al., 2002; Kracht et al., 2004; Wu et al., 2004; Zhang, 2005; Clavel et al., 2005; Eguchi-Ishimae et al., 2005; Guillem et al., 2007; Voso et al., 2007; Gra et al., 2007; Bolufer et al., 2007; Begleiter et al., 2009; Chan et al., 2011; Lozic et al., 2011).

The aim of this article is to review and evaluate the association between NQO1609C>T polymorphism and leukemia risk, mainly focusing on different ethnicity types.

Materials and Methods

Identification and eligibility of relevant studies

To identify all published articles that examined the association between NQO1 609C>T polymorphism and leukemia risk, we conducted a search in the PubMed database (before 2012-12-15). We identified 90 articles

*[1]Beijing Chao-Yang Hospital Affiliated with Beijing Capital Medical University, [2]Reproductive and Genetic Center of National Research Institute for Family Planning, [3]Graduate School; Peking Union Medical College, Beijing, China [&]Equal contributors *For correspondence: Hongllh@126.com*

Table 1. Characteristics of Studies on NQO1 609 C>T Polymorphism and Leukemia Risk

Year	Leukemia type	Age	First author	Ethnity	National	Cases				Controls				HW (*p*)
						C/C	C/T	T/T	Total	C/C	C/T	T/T	Total	
2010	ALL	Children	Allen Eng-Juh Yeoh	Asian	Singapore	100	76	33	209	109	146	45	300	0.732382
2009	CLL		Asher Begleiter	Caucasian	Canada	219	93	11	312	196	96	7	299	0.229799
2011	Leukemia	Children	Bernarda Lozi	Caucasian	Croatia	14	10	0	24	30	8	0	38	0.468314
2002	Therapy-related AML		Claire Seedhouse	Caucasian	England	95	30	9	134	110	53	12	175	0.119939
2006	AML		Elad Malik	Mixed	Israel	96	55	5	196	274	137	7	418	0.368066
				Mixed		56	44	6	106	146	104	20	170	0.803388
2010	ALL		Gabriela G. Yamaguti	Caucasian	Brazil	51	47	1	99	73	26	0	99	0.132568
2009	AML		Gabriela G. Yamaguti	Mixed	Brazil	78	54	1	133	95	38	0	187	0.054594
2005	ALL	Children	Jacqueline Clavel	Caucasian	France	122	59	10	191	68	33	3	104	0.67273
	ANLL	Children				20	8	0	28	68	33	3	104	0.67273
						142	67	10	219	68	33	3	104	0.67273
2011	ALL	Children	Jason Yong-Sheng Chan	Asian	Java	68	92	25	185	75	88	22	185	0.620394
1999	Leukemia	Pediatric	Joseph L	Caucasian	England	68	61	6	136	67	32	1	100	0.180416
2005	ALL	Children	M Lanciotti	Caucasian	Italy	23	C/T+T/T 27		50	91	C/T+T/T 56		147	
2007	AML		M. T. Voso	Caucasian	Italy	101	48	8	157	108	40	7	155	0.199683
2002	ALL	Children	Maja Krajinovic	Asian	Singapore	100	76	33	209	109	146	45	300	0.732382
2001	Acute leukemia	Adults	Martyn T. Smith	Caucasian	England	285C/T+T/T	205		490	562C/T+T/T	274		836	
2005	ALL		Minenori Eguchi-Ishimae	Asian	Japan	29	30	13	72	88	84	25	196	0.482312
	AML					10	19	2	31	88	84	25	197	0.482312
	Total					39	49	15	103					
2007	CML		OlgaA. Gra	Caucasian	Russia	52	28	3	83	119	52	6	177	0.913237
2007	AML		Pascual Bolufer	Caucasian	Spain	163	94	16	273	268	160	19	447	0.422155
	ALL					65	41	14	120	268	160	19	447	0.422155
	Total					227	135	30	393	268	160	19	447	0.422155
2004	ALL	Pediatric	Thorben Kracht	Caucasian	Germany	110	46	4	160	126	61	3	190	0.146514
2010	ALL	Children	Vanessa da Silva Silveira	Mixed	Brazil	123	65	16	204	182	156	24	362	0.218281
2007	Therapy-related AML/MS		VM Guillem	Caucasian	Spain	49	30	2	81	41	34	5	80	0.55599
2004	Leukemia	Children	Wu YX	Asian	China	12	32	17	61	22	30	11	63	0.888452
2005	Acute leukemia	Adult	Zhang Juan	Asian	China	33	C/T+T/T 66		99	44	C/T+T/T 55		99	

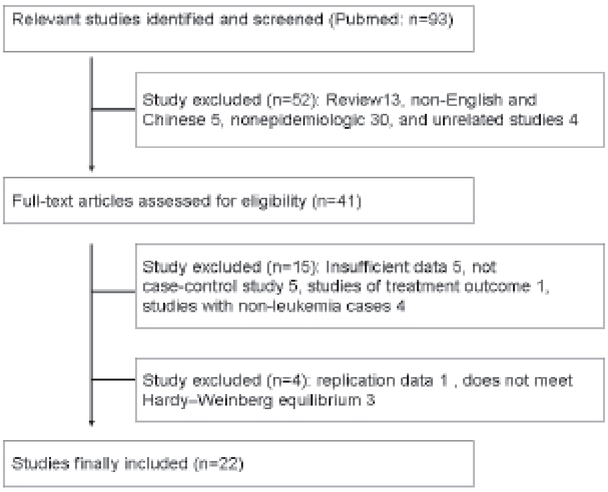

Figure 1. Flow Diagram of the Study Selection Process

with the search terms (''NAD(P)H Dehydrogenase (Quinone)'' [MeSH] or ''NQO1'') and ''leukemia'' and limiting the search to studies in human populations. Articles with the following characteristics were excluded from the review: 1) non-English articles; 2) review articles; 3) non-epidemiological studies (e.g., studies on animals or cell culture); 4) treatment outcome studies (Figure 1); 5) studies with control that did not meet Hardy-Weinberg equilibrium (HWE). As of December 15, 2012, we had identified 22 published studies describing the association between NQO1 polymorphisms and leukemia included case-control analyses.

Data extraction and assessment of study quality

Two authors (Fei-fei Han and Chang-long Guo) extracted data and reached a consensus on all of the eligibility items, including author, journal and year of publication, location of study, selection and characteristics of cancer cases and controls, control source, age grades of patients, ethnicity, and leukemia types.

Meta-analysis

The risks (odds ratios, OR) of cancer associated with NQO1 609C>T polymorphism were estimated for each study independently. Also we estimated the risk for the NQO1 609C>T polymorphism and breast cancer, colorectal cancer separately.

Statistical analysis

The meta-analysis was performed in a fixed/random effect model. The OR and its 95% CI were estimated for each study. The chi-squared test-based Q-statistic was used to assess the between-study heterogeneity. Heterogeneity was significant for $P < 0.10$, and then the result of random effect model was selected. Otherwise, the result of fixed effect model was selected. Meanwhile, we measured the effect of heterogeneity by another measure, $I^2 = 100\% \times (Q\text{-}df)/Q$. The I^2-statistic measures the degree of inconsistency in the studies by calculating what percentage of the total variation across studies is as a result of heterogeneity rather than by chance.

The effect of association was indicated as OR with the corresponding 95% confidence interval (CI). The combined OR was estimated using fixed effects (FE) models (Mantel-Haenszel) and random-effects (RE) models (DerSimonian and Laird) (Sarlauskas et al., 2004). We did the Q test to assess the heterogeneity between these studies, and it was considered statistically significant

Table 2. Meta-Analysis of the Risk of Leukemia for NQO1 609 C>T Polymorphism

Genotype	Populations		OR	I^2(%)	$P_{heterogeneity}$	P	Model
Ser/Ser + Pro/Ser versus Pro/Pro	All populations		1.21 (1.02, 1.44)	69	<0.00001	0.03	random
		Asian	1.19 (0. 87, 1.62)	72	0.006	0.41	random
		Caucasian	1.22 (1.00, 1.49)	59	0.003	0.05	random
	AML populations		0.96 (0.64, 1.44)	83	<0.00001	0.85	random
		Caucasian	0.94 (0.76, 1.16)	30	0.23	0.57	fixed
	ALL populations		1.08 (0.81, 1.45)	69	0.0007	0.58	random
		Asian	0.93 (0.59, 1.46)	69	0.04	0.75	random
		Caucasian	1.36 (0.9, 2.06)	63	0.03	0.15	random
	Children		1.13 (0.83, 1.55)	71	0.0006	0.44	random
		Asian	1.01 (0.57, 1.79)	75	0.02	0.98	random
		Caucasian	1.41 (0.95, 2.09)	55	0.07	0.09	random
Ser/Ser versus Pro/Ser + Pro/Pro	All populations		1.25 (1.02, 1.53)	0	0.94	0.03	fixed
		Asian	1.19 (0.87, 1.62)	0	0.76	0.27	fixed
		Caucasian	1.44 (1.02, 2.01)	0	0.77	0.04	fixed
	AML populations		0.93 (0.64, 1.33)	4	0.4	0.68	fixed
		Caucasian	1.09 (0.69, 1.72)	0	0.55	0.72	fixed
	ALL populations		1.29 (0.99, 1.67)	0	0.47	0.06	fixed
		Asian	1.17 (0.84, 1.65)	0	0.73	0.36	fixed
		Caucasian	2.35 (1.27, 4.37)	0	0.64	0.007	fixed
	Children		1.28 (0.96, 1.7)	0	0.82	0.1	fixed
		Asian	1.20 (0.85, 1.69)	0	0.56	0.31	fixed
		Caucasian	2.03 (0.84, 4.93)	0	0.68	0.12	fixed

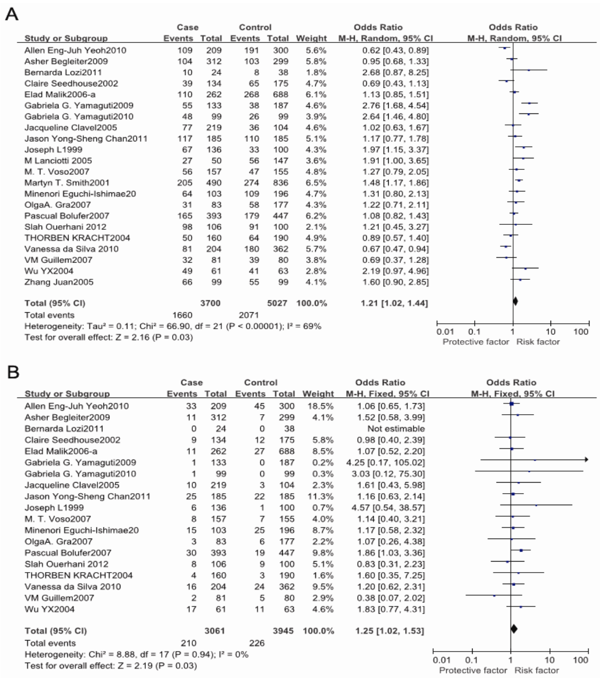

Figure 2. Forest Plot of Leukemia Risk Associated with NQO1 609 C>T Polymorphism Analysis

with $P < 0.10$ (Yuan et al., 2010). The heterogeneity was quantified by I^2 metric ($I^2 = 100\% \times$ (Q-df)/Q), which is independent of the number of studies in the meta-analysis ($I^2 < 25\%$ no heterogeneity; $I^2 = 25$–50% moderate heterogeneity; $I^2 > 50\%$ extreme heterogeneity) and P value ($P > 0.1$ no heterogeneity). Publication bias was investigated by funnel plot and Egger's linear regression test (Egger et al., 1997). The significant of asymmetry was determined by t test and $P < 0.05$ was considered as a significant publication bias. Hardy-Weinberg equilibrium (HWE) was tested by the Chi-square test. Meta-analysis was performed using Review Manager 5.0 software. Sensitivity analysis was performed by sequential remove (statistics of study remove) of individual studies (Review Manager 5.0 software).

Results

Eligible studies for meta-analysis

This study is focusing on NQO1 609C>T polymorphism and leukemia risk. After a careful evaluation of the published literature, only 22 studies met our inclusion criteria for this meta-analysis (Table 1). The retrieved papers were then read in entirety to assess their appropriateness for the inclusion in this study. The basic information, including leukemia type, ethnicity, the number of cases and controls of each study, are listed in Table I. In all studies, the controls were free of leukemia. In the total 22 studies, 8 articles provided the data of AML (acute myeloid leukemia) patients and 10 articles provided the data of ALL (acute lymphoblastic leukemia) patients. All of the researches were then conducted in different ethnicity, mainly Asian and Caucasian: 13 studies provided Caucasian and 5 studies provided Asian data.

Leukemia susceptibility analysis

22 studies (3700 cases and 5027controls) examining the association between NQO1 609C>T polymorphism and leukemia were included. Significant heterogeneity was observed in dominant genetic model (Ser/Ser + Pro/Ser versus Pro/Pro) and the original data were combined by means of the random effect model. In this model there showed no association of NQO1 609C>T polymorphism with leukemia (OR=1.21, 95%CI = 1.02-1.44, Heterogeneity<0.00001; I^2 =69%),), and there is an association of NQO1 609C>T polymorphism with leukemia in recessive genetic model (Ser/Ser versus Pro/Ser + Pro/Pro: OR = 1.25, 95%CI = 1.02-1.53, Heterogeneity =0.94; I^2 = 0%). The forest plot (Figure 3A.) showed that the distribution of the ORs from individual

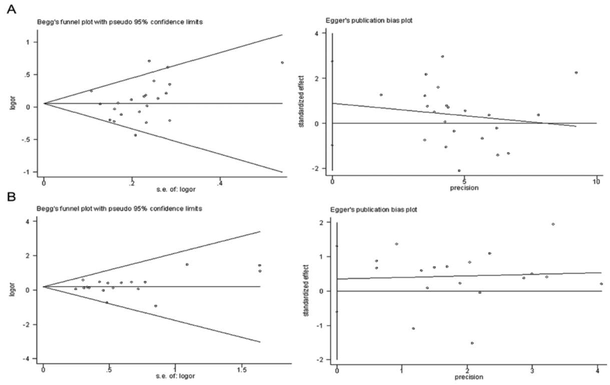

Figure 3. Begg's and Egger's Funnel Plot for Publication bias Test in the Recessive Genetic Model Analysis

studies in relation to their respective standard deviation was symmetric in funnel plot. Similarly, the Egger's test provided no evidence of publication bias in reviewed studies for dominant genetic model (t = 1.22, *P* = 0.235) and for recessive genetic model (t = 1.01, *P* = 0.328) (Figure 3B).

Ethnicity analysis

In different ethnicity populations we found the results are different. Both results of dominant genetic model and recessive genetic model showed the associations of NQO1 609C>T polymorphism with leukemia (Ser/Ser + Pro/Ser versus Pro/Pro OR = 1.22, 95% CI = 1.22-1.45, *P* = 0.05; Ser/Ser versus Pro/Ser + Pro/Pro OR = 1.25, 95% CI = 1.02-1.53, *P* = 0.04) in Caucasian population. The Egger's test provided no evidence of publication bias in reviewed studies (t = 0.36, *P* = 0.772 for recessive genetic model and t = 0.22, *P* = 0.832 for dominant genetic model). In Asian population there are no significant results (Ser/Ser + Pro/Ser versus Pro/Pro OR = 1.19, 95% CI = 0.78-1.82, *P* = 0.41; Ser/Ser versus Pro/Ser + Pro/Pro OR = 1.19, 95% CI = 0.87-1.62, *P* = 0.27).

Leukemia type analysis

Most of studies involved in this research provided the data of AML and ALL. 7 studies (1111 cases and 1829 controls) examining the association between NQO1 609C>T polymorphism and AML were included. We found no association of NQO1 609C>T polymorphism with AML (Ser/Ser + Pro/Ser versus Pro/Pro OR = 0.96, 95% CI = 0.64-1.44, *P* = 0.85; Ser/Ser versus Pro/Ser + Pro/Pro OR = 0.93, 95% CI = 0.64-1.33, *P* = 0.68). 10 studies (1248 cases and 1489 controls) examining the association between NQO1 609C>T polymorphism and ALL population were included. And we found an association of NQO1 609C>T polymorphism with ALL in recessive genetic model but not in dominant genetic model (Ser/Ser + Pro/Ser versus Pro/Pro OR = 1.18, 95% CI = 0.77-1.81, *P* = 0.45; Ser/Ser versus Pro/Ser + Pro/Pro OR = 1.33, 95% CI = 1.02-1.75, *P* = 0.04). The forest plot showed that the distribution of the ORs from individual studies in relation to their respective standard deviation was symmetric in funnel plot. Similarly, we performed an analysis for ethnicity in AML and ALL populations. The results were shown in Table 2.

Age phase analysis

Because of some studies applied the data of children or pediatric, we performed an analysis of NQO1 609C>T polymorphism and children leukemia. Nine studies (1248 cases and 1489 controls) examining the association between NQO1 609C>T polymorphism and children leukemia were included. We found there is no association between NQO1 609C>T polymorphism and children leukemia (Ser/Ser + Pro/Ser versus Pro/Pro OR = 1.13, 95% CI = 0.83-1.55, *P* = 0.44; T/T versus C/T+C/C OR = 1.28, 95% CI = 0.96-1.7, *P* = 0.1). The forest plot (Figure 3C) showed that the distribution of the ORs from individual studies in relation to their respective standard deviation was symmetric in funnel plot.

Discussion

The NQO1, which is generally involved in Xenobiotic-Metabolizing, has been studied extensively on its relationship with different types of cancer, such as breast cancer, colorectal cancer, leukemia and so on. Previous conclusions of numerous studies on association between NQO1 609C>T polymorphism and leukemia remain conflicting and contradictory, this was largely attributed to the small samples or the relatively low statistical power of published studies. Meta-analysis is a powerful method for resolving inconsistent findings with a relatively large number of subjects. So, this meta-analysis was applied to provide a quantitative approach for combining the different results. To the author's knowledge, this is the most comprehensive meta-analysis investigating the genetic susceptibility of NQO1 gene C609T polymorphism to leukemia.

In the present meta-analysis with 3700 cases and 5027controls, the variant TT homozygous genotype and the combined CT/TT genotype of the NQO1 609 C>T polymorphism was found to be associated with a increased risk of leukemia, especially in Caucasian populations. These findings suggestted that the NQO1 609C>T polymorphism may modify the risk of leukemia mainly in Caucasian populations but not in Asian populations. Publication bias was not observed in this study. In the subgroup analysis of age phase we found that NQO1 609C>T polymorphism was not associated with children leukemia.

Several limitations of this meta-analysis should be pointed out. First, although the Begg's test and Egger's test did not show any publication bias, selection bias could have occurred, because only studies published in English and Chinese were included in our meta-analysis. Second, this analysis was based on unadjusted published estimates, and hence, it was unable to adjust them by possible confounders such as sex, smoking status and living environment risk factors. Furthermore, due to a limited number of published studies available to be included, it was unable to perform further subgroup analyses for AML in Asian populations.

In summary, this meta-analysis provided robust evidence of the association between NQO1 609 C>T polymorphism and leukemia risk on Caucasian population, supporting the results of published paper that NQO1

609 C>T polymorphism is a strong susceptibility marker of leukemia, especially in Caucasian population. Moreover, sophisticated gene-gene interaction should be considered in future analysis, which would lead a better, comprehensive understanding of the association between NQO1 609 C>T polymorphism and leukemia risk.

Acknowledgements

This research is supported by the Foundation of Health industry research special item 200902008. The author(s) declare that they have no competing interests.

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