

RESEARCH ARTICLE

Glutathione-S-Transferase Polymorphisms (GSTM1, GSTT1 and GSTP1) and Acute Leukemia Risk in Asians: a Meta-analysis

Zhen-Hai Tang[&], Chi Zhang[&], Pan Cheng, Hong-Min Sun, Yu Jin, Yuan-Jing Chen, Fen Huang*

Abstract

The association between glutathione-S-transferase polymorphisms (GSTM1, GSTT1 and GSTP1) and risk of acute leukemia in Asians remains controversial. This study was therefore designed to evaluate the precise association in 23 studies identified by a search of PubMed and several other databases, up to December 2013. Using random or fixed effects models odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated. Heterogeneity across studies was assessed, and funnel plots were constructed to test for publication bias. The meta-analysis showed positive associations between GST polymorphisms (GSTM1 and GSTT1 but not GSTP1) and acute leukemia risk [(OR=1.47, 95% CI 1.18-1.83); (OR=1.32, 95% CI 1.07-1.62); (OR=1.01, 95% CI 0.84-1.23), respectively] and heterogeneity between the studies. The results suggested that the GSTM1 null genotype and GSTT1 null genotype, but not the GSTP1 polymorphism, might be a potential risk factors for acute leukemia. Further well-designed studies are needed to confirm our findings.

Keywords: Acute leukemia - glutathione-S-transferase - GST - polymorphism - meta-analysis

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Introduction

Acute leukemia, including acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), is a malignancy which is seen in both adults and children. The risk for acute leukemia has been associated with various factors, including genetic disorders, physical and chemical exposure and chemotherapy (Bonaventure et al., 2012; Wong et al., 2010; Deschler et al., 2006). Some enzymes are predominantly involved in the metabolism of carcinogens (Arruda et al., 2001) and lead to variability among individuals in their ability to metabolize environmental carcinogens.

Research on genetic factors that affect cancer susceptibility has the potential to improve our understanding of acute leukemia etiology. Glutathione-S-Transferase (GST) is a group of polymorphic enzymes of phase II which catalyze conjugation of glutathione onto the reactive electrophilic agents on the exogenous and endogenous compounds. Thus, GST polymorphisms have been considered as possible risk factors of acute leukemia. Functional polymorphisms have been reported in at least three of the genes that code for GSTs including GSTM1, GSTT1, and GSTP1. Polymorphism in GST genes lead to either decreased activity of the enzyme or complete loss of enzyme activity. Both GSTM1 and GSTT1 genes, exhibited a greater degree of polymorphism, one of them

being the complete deletion of the gene that causes the loss of enzymatic activity (Alves et al., 2002). GSTP1 (Ile105val) single nucleotide polymorphism affects substrate specific catalytic activity of the enzyme and its thermal stability (Ntais et al., 2005; Sundberg et al., 1998). Published studies have focused on GSTM1, GSTT1 and GSTP1 genetic variation with respect to various cancers, including acute leukemia. In Asians, although there are many studies assessing the association between GST polymorphisms and acute leukemia risk, the association between GST polymorphisms and acute leukemia is still inconclusive (Sasai et al., 1999; Balta et al., 2003; Yuan et al., 2003; Feng et al., 2004; Haranatha et al., 2006; Aydin-Sayitoglu et al., 2006; Dunna et al., 2013). In 2005, Ye et al. conducted a meta-analysis and concluded that the GSTM1 status, but not the GSTT1 status and GSTP1 Val status, was associated with acute leukemia risk in Asians (Ye et al., 2005). However, several new studies with more data have been published since 2005. What's more, some previous meta-analysis studies about the association between GST polymorphisms and acute leukemia risk just focused on Childhood acute leukemia (Tang et al., 2013) or one of the types of acute leukemia (Das et al., 2009; Xu et al., 2013). Therefore, to derive a more precise estimation of the association in Asians, with big sample size, we performed a meta-analysis of 23 studies including 3504 cases and 4876 controls.

Table 1. Characteristics of Studies on GSTM1 (Null Genotypes) Status and the Risk of Acute Leukaemia

First author (year)	Country	Cases (n)	Frequency of null genotypes (n)	Controls (n)	Frequency of null genotypes (n)	Control Sources*	Leukemia types	Age
Sasai (1999)	Japan	18	11	43	23	PB	t-AML	Adults
Sasai (1999)	Japan	22	10	43	23	PB	AML	Adults
Naoe (2000)	Japan	411	227	150	77	PB	t-AML	Adults
Balta (2003)	Turkey	139	77	185	101	PB	ALL	Childhood
Balta (2003)	Turkey	31	19	185	101	PB	ANLL	Childhood
Zhang (2003)	China	32	23	146	77	PB	AML	Childhood
Feng (2004)	China	49	36	146	77	PB	AML	Childhood
Wang (2004)	China	67	51	146	77	PB	ALL	Childhood
Joseph (2004)	India	118	48	118	29	PB	ALL	Childhood
Zou (2004)	China	16	10	183	99	PB	ALL	All ages
Zou (2004)	China	25	17	183	99	PB	AML	All ages
Liu (2005)	China	112	68	204	113	HB	ALL	Childhood
Liu (2005)	China	120	68	204	113	HB	ANLL	Childhood
Haranatha (2006)	India	135	60	146	61	PB	ALL	Childhood
Aydin-Sayitoglu (2006)	Turkey	119	78	140	77	PB	ALL	Childhood
Aydin-Sayitoglu (2006)	Turkey	119	19	140	77	PB	ALL	Adults
Aydin-Sayitoglu (2006)	Turkey	44	28	140	77	PB	AML	Childhood
Aydin-Sayitoglu (2006)	Turkey	50	36	140	77	PB	AML	Adults
Majumdar (2007)	India	110	57	144	34	PB	AML	All ages
Jiang (2008)	China	88	53	120	65	HB	ALL	Childhood
Suneetha (2008)	India	92	36	150	37	HB	ALL	All ages
Jiang (2010)	China	89	68	90	49	HB	ALL	Childhood
Chan (2011)	Singapore	185	142	177	122	PB	ALL	Childhood
Chauhan (2011)	India	120	45	202	97	PB	AML	Adults
Kim (2012)	Korea	415	230	1700	923	PB	AML	Adults
Li (2012)	China	41	28	100	49	HB	ALL	Childhood
Dunna (2013)	India	142	90	251	94	PB	AML	All ages
Dunna (2013)	India	152	89	251	94	PB	ALL	All ages

*PB, Population-based; HB: Hospital-based; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; ANLL, acute non-lymphoblastic leukemia

Materials and Methods

Identification of relevant studies

The comprehensive search strategy was used to find eligible studies for this meta-analysis. Published studies were found through PubMed, Springer Link, Google Scholar, CBM (Chinese Biomedical Database), CNKI (Chinese National Knowledge Infrastructure), VIP (Chinese) Database and Wanfang (Chinese) Database, using the following keywords “GST”, “Glutathione S-transferase” and “leukemia”, “AML”, “ALL”. What’s more, we also searched the reference list of relevant publications to identify additional studies manually. All researches were limited to English or Chinese language articles published up to December 2013 and availability of paper and limited to humans species for review.

Inclusion and exclusion criteria

All identified studies were reviewed independently for eligibility by two authors. Studies were included in the meta-analysis if they met the following criteria: (1) Concerning the relationship between GST genetic polymorphisms (including GSTM1 or GSTT1 or GSTP1 or at least two of them) and acute leukemia; (2) A case-control study; (3) Providing complete data on genotype of the GST polymorphism (s) for calculating an odd ratio (OR) with 95% confidence interval (CI); (4) The distribution of the genotypes in control groups was in Hardy-Weinberg equilibrium; (5) studies about Asian

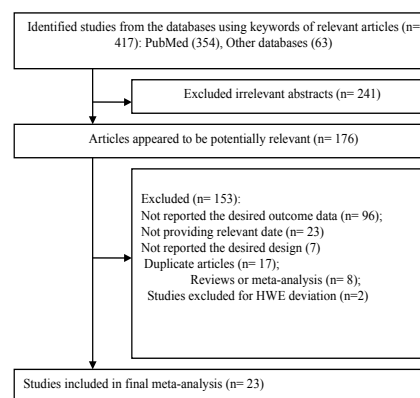


Figure 1. Flow Diagram of Screened, Excluded, and Analyzed Publications

population. The exclusion criteria include: (1) A review or case report; (2) A duplicated study. If studies contained overlapping cases and/or controls, the largest study was preferred.

Data extraction

All data were independently abstracted by two investigators (Tang ZH, Zhang C) using the standard protocol. The following variables were recorded: the first author’s name, publication year, country where the studies were performed, number of cases and controls for each genotype, source of controls, participant age.

Table 2. Characteristics of Studies on GSTT1 (Null Genotypes) Status and the Risk of Acute Leukemia

First author (year)	Country	Cases (n)	Frequency of null genotypes (n)	Controls (n)	Frequency of null genotypes (n)	Control Sources*	Leukemia types	Age
Sasai (1999)	Japan	18	12	43	13	PB	t-AML	Adults
Sasai (1999)	Japan	22	7	43	13	PB	AML	Adults
Naoe (2000)	Japan	411	197	150	81	PB	t-AML	Adults
Balta (2003)	Turkey	139	29	185	42	PB	ALL	Childhood
Balta (2003)	Turkey	31	2	185	42	PB	ANLL	Childhood
Zhang (2003)	China	32	19	146	72	PB	AML	Childhood
Feng (2004)	China	49	30	146	72	PB	AML	Childhood
Wang (2004)	China	67	41	146	72	PB	ALL	Childhood
Joseph (2004)	India	118	17	118	10	PB	ALL	Childhood
Zou (2004)	China	16	14	183	89	PB	ALL	All ages
Zou (2004)	China	25	14	183	89	PB	AML	All ages
Liu (2005)	China	112	57	204	100	HB	ALL	Childhood
Liu (2005)	China	120	66	204	100	HB	ANLL	Childhood
Haranatha (2006)	India	135	48	146	23	PB	ALL	Childhood
Aydin-Sayitoglu (2006)	Turkey	119	29	140	29	PB	ALL	Childhood
Aydin-Sayitoglu (2006)	Turkey	119	2	140	29	PB	ALL	Adults
Aydin-Sayitoglu (2006)	Turkey	44	6	140	29	PB	AML	Childhood
Aydin-Sayitoglu (2006)	Turkey	50	15	140	29	PB	AML	Adults
Majumdar (2007)	India	110	16	144	11	PB	AML	All ages
Jiang (2008)	China	88	44	120	59	HB	ALL	Childhood
Jiang (2010)	China	89	54	90	44	HB	ALL	Childhood
Suneetha (2011)	India	92	11	150	20	HB	ALL	All ages
Chan (2011)	Singapore	185	64	177	49	PB	ALL	Childhood
Chauhan (2011)	India	120	26	202	58	PB	AML	Adults
Kim (2012)	Korea	415	214	1700	859	PB	AML	Adults
Li (2012)	China	41	24	100	44	HB	ALL	Childhood
Dunna (2013)	India	142	57	251	39	PB	AML	All ages
Dunna (2013)	India	152	38	251	39	PB	ALL	All ages

*PB, Population-based; HB: Hospital-based; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; ANLL, acute non-lymphoblastic leukemia

Statistical analysis

The strength of correlation between GST gene polymorphisms (GSTM1, GSTT1, GSTP1) and acute leukemia was assessed by ORs with 95% CIs. We focused on the null alleles of the GSTM1 and GSTT1 genes and the Val105 allele of the GSTP1 gene in this meta-analysis. A chi-square test was used to detect whether the frequencies observed of the genotypes among the controls conformed to Hardy Weinberg-Equilibrium (HWE) expectations. Considering possible heterogeneity across the studies, I^2 statistics were used to assess heterogeneity, $I^2 > 50\%$ indicated an obvious between-study heterogeneity (Higgins et al., 2003). OR (95% CI) was calculated by the random effects model (DerSimonian et al., 1986); otherwise, the fixed effects model was used (Mantel et al., 1959). If between-study heterogeneity was present, a sensitivity analysis was performed based on the magnitude of Q statistic (Lohmueller et al., 2003). Studies contributing the most to the heterogeneity were removed sequentially until homogeneity was achieved. Subgroup analyses were mainly conducted using control sources, which were defined as two parts (Population-based and Hospital-based). An estimation of potential publication bias was conducted using the funnel plot, and it was assessed using the tests of Egger and Begg (Egger et al., 1997; Begg et al., 1994). All analyses were conducted using Stata 12.0 (StataCorp, College station, TX). Statistical significance was considered if P value less than 0.05.

Results

Characteristics of Eligible Studies

A total of 417 studies, based on the search criteria, were preliminarily eligible. Detailed process for selecting eligible studies was showed in Figure 1. Among these, two studies (Dunna et al., 2012; Zhou et al., 2013) were excluded for HWE deviation. Finally, 23 studies, which control individuals did not departure from HWE (P-value of HWE > 0.05 , respectively), were included in the meta-analysis. A total of 3504 cases and 4876 controls were included in this study, and the characteristics of eligible studies were listed in Table 1-3.

Meta-analysis

Characteristics of studies

Overall, the frequency of GSTM1 null genotype was 56.32% and 50.49% in cases and controls, respectively; the frequency of GSTT1 null genotype was 37.67% and 37.00%, respectively; while the Ile/Val GSTP1 polymorphism, the prevalence of Val in cases and controls was 21.76% and 21.56%, respectively.

Association of GSTM1 null genotype with acute leukemia

For the GSTM1 null genotype, the overall OR of the acute leukemia risk association with the polymorphism was 1.47 (95% CI 1.18-1.83), with a statistically significant between-study heterogeneity. However, when four outlying studies were excluded (Aydin-Sayitoglu et

Table 3. Characteristics of Studies on GSTP1Val Status and the Risk of Acute Leukemia

First author (year)	Country	Cases (n)	Frequency of null genotypes (n)	Controls (n)	Frequency of null genotypes (n)	Control Sources*	Leukemia types	Age
Balta (2003)	Turkey	136	23.9	185	24.59	PB	ALL	Childhood
Balta (2003)	Turkey	33	25.76	185	24.59	PB	ANLL	Childhood
Yuan (2003)	China	80	8.75	85	17.06	HB	AML	Childhood
Yuan (2003)	China	80	30	85	17.06	HB	ALL	Childhood
Gatedee (2007)	Thailand	100	23	100	20.5	HB	ALL	Childhood
Suneetha (2008)	India	92	31.52	150	27	HB	ALL	All ages
Chan (2011)	Singapore	185	20.54	177	22.88	PB	ALL	Childhood
Chauhan (2011)	India	120	29.17	202	28.22	PB	AML	Adults
Kim (2012)	Korea	415	17.59	1700	20	PB	AML	Adults

*PB, Population-based; HB: Hospital-based; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; ANLL, acute non-lymphoblastic leukemia

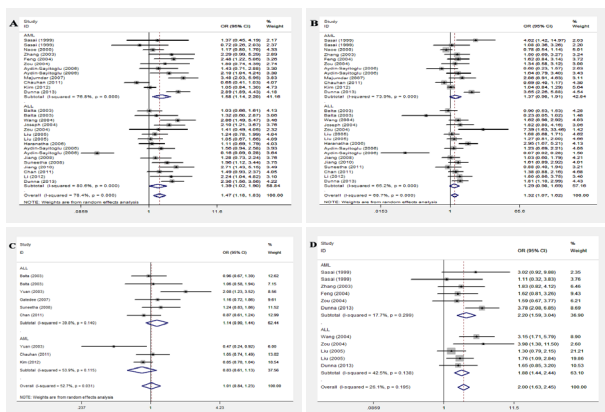


Figure 2. Forest Plots for the Association between GST Polymorphisms and Acute Leukemia in Overall Studies. A for GSTM1 null genotype; B for GSTT1 null genotype; C for GSTP1 polymorphism; D for GSTM1 and GSTT1 null genotypes

al., 2006; Majumdar et al., 2008; Chauhan et al., 2011; Dunna et al., 2013), the heterogeneity was no longer statistically significant, with the amended overall OR was 1.41 (95% CI 1.27-1.57). The pooled ORs were 1.58 (95% CI 1.14-2.20) and 1.39 (95% CI 1.02-1.90), respectively, in AML and ALL (Table 4). Heterogeneity between studies was shown for both ALL and AML. For AML, after three outlying studies were excluded (Majumdar et al., 2008; Chauhan et al., 2011; Dunna et al., 2013), the heterogeneity was no longer statistically significant, with the amended OR was 1.24 (95% CI 1.06-1.45). And for ALL, after one outlying study were excluded (Aydin-Sayitoglu et al., 2006), the heterogeneity was no longer statistically significant, with the amended OR was 1.56 (95% CI 1.36-1.79). By considering study control sources subgroup, the overall ORs were 1.43 (95% CI 1.09-1.87) and 1.55 (95% CI 1.15-2.09), respectively, in Population-based and Hospital-based, with evidences of heterogeneity exist in both of them.

Association of GSTT1 null genotype with acute leukemia

For the GSTT1 null genotype, the overall OR of the acute leukemia risk association with the polymorphism was 1.32 (95% CI 1.07-1.62). After tests for heterogeneity fund that the heterogeneity was significant. However, when four outlying studies were excluded (Sasai et al., 1999; Zou et al., 2004; Aydin-Sayitoglu et al., 2006;

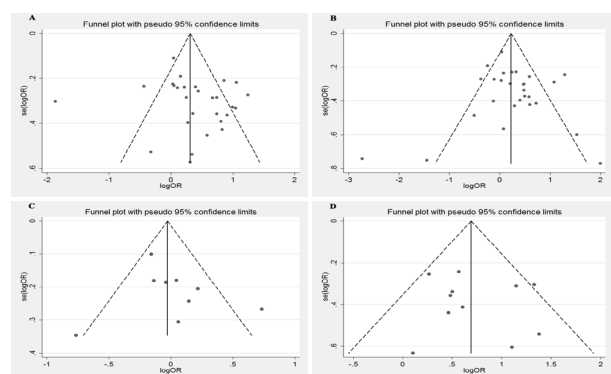


Figure 3. Funnel Plot Analysis to Detect Publication Bias. Each point represents a separate study for the indicated association. A Funnel plot for GSTM1 null genotype in overall analysis; B Funnel plot for GSTT1 null genotype in overall analysis; C Funnel plot for GSTP1 polymorphism in overall analysis; D Funnel plot for GSTM1 and GSTT1 null genotypes in overall analysis

Dunna et al., 2013), the heterogeneity was no longer statistically significant, with the amended OR was 1.18 (95% CI 1.06-1.31). The pooled ORs were 1.37 (95% CI 0.98-1.91) and 1.29 (95% CI 0.98-1.69), respectively, in AML and ALL (Table 4). And there was a significant heterogeneity among studies for both AML and ALL. For AML, after two outlying studies were excluded (Sasai et al., 1999; Dunna et al., 2013), the amended OR was 1.03 (95% CI 0.89-1.20), with the heterogeneity was no longer statistically significant. For ALL, after two outlying studies were excluded (Zou et al., 2004; Aydin-Sayitoglu et al., 2006), the heterogeneity was no longer statistically significant, with the amended OR was 1.34 (95% CI 1.15-1.56). Restricting analyses to control sources, the overall ORs were 1.34 (95% CI 1.03-1.74) and 1.22 (95% CI 0.97-1.54), respectively, in Population-based and Hospital-based. The heterogeneity was significant in Hospital-based, but not in Population-based.

Association of GSTP1 Ile105val polymorphism with acute leukemia

For GSTP1 Ile105val polymorphism, the overall OR of the association between acute leukemia risk and the polymorphisms was 1.01 (95% CI 0.84-1.23). There was an evidence of heterogeneity across overall studies. However, after one outlying study was excluded (Yuan et al., 2003), the heterogeneity was no longer statistically

Table 4. Main Meta-analysis of GST Polymorphisms and the Risk of Acute Leukemia

	GSTM1				GSTT1				GSTP1			
	Number	Pooled odds risk	Heterogeneity		Number	Pooled odds risk	Heterogeneity		Number	Pooled odds risk	Heterogeneity	
	of studies	(95% CI)	I ² (%)	P	of studies	(95% CI)	I ² (%)	P	of studies	(95% CI)	I ² (%)	P
All studies	20	1.47 (1.18-1.83)	78.4	0	20	1.32 (1.07-1.62)	68.7	0	7	1.01 (0.84-1.23)	52.7	0.03
Region												
China-Japan*	10	1.57 (1.25-1.96)	33.6	0.11	10	1.36 (1.08-1.72)	40.6	0.06	1	1.00 (0.23-4.35)	91.5	0
Others	10	1.37 (0.98-1.92)	86.7	0	10	1.19 (0.86-1.66)	78.9	0	6	0.95 (0.84-1.06)	0	0.65
Types												
AML	10	1.58 (1.14-2.20)	76.8	0	10	1.37 (0.98-1.91)	73.9	0	3	0.83 (0.61-1.13)	53.9	0.11
ALL	13	1.39 (1.02-1.90)	80.6	0	13	1.29 (0.98-1.69)	65.2	0	5	1.14 (0.90-1.44)	39.8	0.14
Age												
Childhood	12	1.54 (1.29-1.84)	30.2	0.13	12	1.33 (1.09-1.62)	31.9	0.12	4	1.02 (0.74-1.40)	62.7	0.02
Adults	5	0.81 (0.48-1.37)	86.9	0	5	0.93 (0.59-1.47)	78.6	0	2	0.90 (0.75-1.07)	0	0.32
All ages	4	2.49 (1.99-3.11)	0	0.5	4	2.04 (1.25-3.35)	63.8	0.02	1	1.24 (0.83-1.86)		
Control sources [⊕]												
PB	15	1.43 (1.09-1.87)	81.9	0	15	1.34 (1.03-1.74)	74.7	0	4	0.91 (0.79-1.05)	0	0.84
HB	5	1.55 (1.15-2.09)	40.8	0.13	5	1.22 (0.97-1.54)	0	0.67	3	1.13 (0.68-1.87)	74.5	0.01

* Region of China and Japan; [⊕]PB, Population-based; HB, Hospital-based; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; ANLL, acute non-lymphoblastic leukemia

significant, with the amended overall OR was 1.00 (95% CI 0.88-1.13). The pooled ORs in AML and ALL was 0.83 (95% CI 0.61-1.13) and 1.14 (95% CI 0.90-1.44), respectively (Table 4). Heterogeneity between studies was shown for AML. For AML, the amended OR was 0.90 (95% CI 0.75-1.06). Restricting analyses to control sources, the overall ORs were 0.91 (95% CI 0.79-1.05) and 1.13 (95% CI 0.68-1.87), respectively, in Population-based and Hospital-based, the heterogeneity was significant in Hospital-based, but not in Population-based.

Association of GSTM1 and GSTT1 null genotypes with acute leukemia and subgroup analysis

The association between acute leukemia and joint of GSTM1 and GSTT1 null genotypes was also estimated in this study. There are seven studies, and the overall OR of the acute leukemia risk association with the polymorphism was 2.02 (95% CI 1.58-2.59). Tests for heterogeneity showed no evidence across studies. The pooled ORs were 2.14 (95% CI 1.47-3.11) and 1.96 (95% CI 1.36-2.82), respectively, in AML and ALL. Considering the region, ages may be confounding factors, so the analyses were also conducted based on them. The analyses data were listed in table 4.

Publication Bias

Plots of the ORs (95% CI) of acute leukemia associated with GST polymorphisms were showed in Figure 2. The funnel plots were symmetrical, with neither the funnel plots nor the Begg's and Egger's tests (data not shown) found any obvious evidence for the publication bias. Figure 3 showed Funnel plot.

Discussion

Up to now, numerous of studies have indicated that GST polymorphisms may contribute to the risk of acute leukemia, including AML and ALL. However, the results of these studies assessing the association of acute leukemia risk with GST genotypes have been contradictory. The

results may be due to the small sample size and limited power of individual study. Hence, with hope, this meta-analysis was performed that increasing the sample size will reveal a stronger conclusion.

For the overall data, the results showed that the association between GST polymorphisms (GSTM1, GSTT1 and GSTP1) and acute leukemia risk were 1.47 (95% CI 1.18-1.83), 1.32 (95% CI 1.07-1.62), 1.01 (95% CI 0.84-1.23), respectively. There were some evidences of heterogeneity across studies. Seven studies were the major sources of heterogeneity (Sasai et al., 1999; Yuan et al., 2003; Zou et al., 2004; Aydin-Sayitoglu et al., 2006; Majumdar et al., 2008; Chauhan et al., 2011; Dunna et al., 2013). It might attribute to uncontrolled confounding and inherent bias of study design. For instance, three studies used samples from blood donors (Naoe et al., 2000; Wang et al., 2004; Aydin-Sayitoglu et al., 2006). Several studies used subjects from hospital (Yuan et al., 2003; Liu et al., 2005; Gatedee et al., 2007; Jiang et al., 2008; Suneetha et al., 2008; Jiang et al., 2010; Suneetha et al., 2011; Li et al., 2012). Numerous of studies used samples matched age and sex (Zhang et al., 2003; Joseph et al., 2004; Haranatha et al., 2006; Jiang et al., 2008; Jiang et al., 2010; Chauhan et al., 2011; Dunna et al., 2013), however, others had not. Some studies used samples may have heterogeneous ethnic origin. What's more, the samples size and selection bias may produce heterogeneity. Although some evidences of heterogeneity were present across studies, yet studies that contribute to heterogeneity do not significantly influence the estimate of the overall OR.

Considering that the GST genotypes frequencies might be different between the Population-based and Hospital-based controls. The subgroup analysis base on control sources was conducted. All of the overall ORs were not changed, except GSTT1 base on control sources from Hospital-based. Since Hospital-based controls might not be always truly representative of the general population, which may show that using Population-based controls is more appropriate in the association studies.

The subgroup of region (China-Japan, Others) was also

conducted. The results showed that the OR of the acute leukemia risks association with GSTM1 null genotype and GSTT1 null genotype were statistically significant in subgroup of China-Japan, with the heterogeneity was not significant across studies. While, there was a reverse results in the group of Others. Since the association between cancer and a particular polymorphic site in one population might be of limited value as a biomarker for cancer in another population (Ye et al., 2005), the reason of above-mentioned phenomenon might be due to that population were different.

The results illustrated that the OR of the acute leukemia risks association with GSTs polymorphisms were significant in group of Childhood, however, not in group of Adults. It might be due to that the genetic susceptibility of different age categories may be different, when people exposure to chemicals such as benzene and chemotherapeutic agents. Therefore, more well-designed studies, with a larger sample size, are needed to further confirm our assumption.

Deserve to be mentioned, some limitations of the current meta-analysis should be acknowledged. Firstly, the studies on the subtype of acute leukemia were not included. The more original studies based on the subtype of acute leukemia are needed to ascertain the relationship between the GST polymorphisms and risk of acute leukemia. Secondly, attributing to the unavailable original data of these eligible articles, the effects of environment exposure or lifestyle about association between GST polymorphisms and acute leukemia could not be determined by this meta-analysis. Despite these limitations, our results were also robust. Firstly, the quality of studies included in this study was met our inclusion criteria and satisfactory. Secondly, no publication bias was detected, which indicated that the pooled results should be unbiased.

In conclusion, the results of the present meta-analysis suggest that GSTM1 null genotype and GSTT1 null genotype, but not GSTP1 polymorphism, might have an association with acute leukemia risk in Asians. Thus GSTM1 null genotype and GSTT1 null genotype may play a part in leukemogenesis. More well-designed studies, with a larger sample size, are needed to further confirm our findings.

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References

- Alves S, Amorim A, Ferreira F, Norton L, Prata MJ (2002). The GSTM1 and GSTT1 genetic polymorphisms and susceptibility to acute lymphoblastic leukemia in children from north Portugal. *Leukemia*, **16**, 1565-7.
- Arruda VR, Lima CS, Grignoli CR, et al (2001). Increased risk for acute myeloid leukaemia in individuals with glutathione S-transferase mu 1 (GSTM1) and theta 1 (GSTT1) gene defects. *Eur J Haematol*, **66**, 383-388.
- Aydin-Sayitoglu M, Hatirnaz O, Erensoy N, Ozbek U (2006). Role of CYP2D6, CYP1A1, CYP2E1, GSTT1, and GSTM1 genes in the susceptibility to acute leukemias. *Am J Hematol*, **81**, 162-70.
- Balta G, Yuksek N, Ozyurek E, et al (2003). Characterization of MTHFR, GSTM1, GSTT1, GSTP1, and CYP1A1 genotypes in childhood acute leukemia. *Am J Hematol*, **73**, 154-60.
- Begg CB, Mazumdar M (1994). Operating characteristics of a rank correlation test for publication bias. *Biometrics*, **50**, 1088-1101.
- Bonaventure A, Goujon-Bellec S, Rudant J, et al (2012). Maternal smoking during pregnancy, genetic polymorphisms of metabolic enzymes, and childhood acute leukemia: the ESCALE study (SFCE). *Cancer Causes Control*, **23**, 329-45.
- Chan JY, Ugrasena DG, Lum DW, Lu Y, Yeoh AE (2011). Xenobiotic and folate pathway gene polymorphisms and risk of childhood acute lymphoblastic leukaemia in Javanese children. *Hematol Oncol*, **29**, 116-23.
- Chauhan PS, Ihsan R, Yadav DS, et al (2011). Association of glutathione S-transferase, EPHX, and p53 codon 72 gene polymorphisms with adult acute myeloid leukemia. *DNA Cell Biol*, **30**, 39-46.
- Das P, Shaik AP, Bammidi VK (2009). Meta-analysis study of glutathione-S-transferases (GSTM1, GSTP1, and GSTT1) gene polymorphisms and risk of acute myeloid leukemia. *Leuk Lymphoma*, **50**, 1345-51.
- DerSimonian, R., Laird, N (1986). Meta-analysis in clinical trials. *Control Clin Trials*, **7**, 177-88.
- Deschler B, Lubbert M (2006). Acute myeloid leukemia: epidemiology and etiology. *Cancer*, **107**, 2099-2107.
- Dunna NR, Vure S, Sailaja K, et al (2013). Deletion of GSTM1 and T1 genes as a risk factor for development of acute leukemia. *Asian Pac J Cancer Prev*, **14**, 2221-4.
- Dunna NR, Vuree S, Kagita S, et al (2012). Association of GSTP1 gene (I105V) polymorphism with acute leukaemia. *J Genet*, **91**, e60-3.
- Egger M, Davey Smith G, Schneider M, Minder C (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ*, **315**, 629-63.
- Feng JF, Wang J, Zhang L, Yi B, Wang H (2004). [Analysis on GSTM1, T1 genetic polymorphisms in children with AML]. *Laboratory Medicine*, **3**, 260-262.
- Gatedee J, Pakakassama S, Muangman S, Pongstaporn W (2007). Glutathione S-transferase P1 genotypes, genetic susceptibility and outcome of therapy in thai childhood acute lymphoblastic leukemia. *Asian Pac J Cancer Prev*, **8**, 294-6.
- Haranatha RP, Jamil K (2006). Polymorphisms in the GST (M1 and T1) gene and their possible association with susceptibility to childhood acute lymphocytic leukemia in Indian population. *African Journal of Biotechnology*, **5**, 1454-1456.
- Higgins J.P., Thompson, S.G., Deeks, J.J., Altman, D.G. (2003). Measuring inconsistency in meta-analyses. *BMJ*, **327**, 557-560.
- Jiang LJ, Chen M, Tan GF (2008). The association between polymorphism of cytochrome P4501A1 and glutathione S-transferase M1, T1 genes and acute lymphoblastic leukemia. *J Youjiang Medical College for Nationalities*, **5**, 721-3 (in Chinese).
- Jiang LJ, Tan GF (2010). [The association between polymorphism of cytochrome P4501A1 and glutathione S-transferase M1, T1 genes and acute lymphoblastic leukemia]. *Chinese Journal of New Clinical Medicine*, **3**, 810-13.
- Joseph T, Kusumakumary P, Chacko P, Abraham A, Radhakrishna Pillai M (2004). Genetic polymorphism of CYP1A1, CYP2D6, GSTM1 and GSTT1 and susceptibility to acute lymphoblastic leukaemia in Indian children. *Pediatr Blood Cancer*, **43**, 560-7.

- Kim HN, Kim NY, Yu L, et al (2012). Association of GSTT1 polymorphism with acute myeloid leukemia risk is dependent on smoking status. *Leuk Lymphoma*, **53**, 681-7.
- Li YH, Wen FQ, Xiao ZH, et al. (2012). Genetic polymorphism of GST gene in children with infectious mononucleosis and acute lymphoblastic leukemia. *Chin J Contemp Pediatr*, **4**, 260-63.
- Liu QX, Chen HC, Liu XF, et al. (2005). Study on the relationship between polymorphisms of CYP1A1, GSTM1, GSTT1 genes and the susceptibility to acute leukemia in the general population of Hunan province. *Chin J Epidemiol*, **12**, 975-79 (in Chinese).
- Lohmueller KE, Pearce CL, Pike M, Lander ES, Hirschhorn JN (2003). Meta-analysis of genetic association studies supports a contribution of common variants to susceptibility to common disease. *Nat Genet*, **33**, 177-82.
- Majumdar S, Mondal BC, Ghosh M, et al (2008). Association of cytochrome P450, glutathione S-transferase and N-acetyl transferase 2 gene polymorphisms with incidence of acute myeloid leukemia. *Eur J Cancer Prev*, **17**, 125-32.
- Mantel, N., Haenszel, W (1959). Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst*, **22**, 719-48.
- Naoe T, Takeyama K, Yokozawa T, et al (2000). Analysis of genetic polymorphism in NQO1, GST-M1, GST-T1, and CYP3A4 in 469 Japanese patients with therapy-related leukemia/ myelodysplastic syndrome and de novo acute myeloid leukemia. *Clin Cancer Res*, **6**, 4091-5.
- Ntais C, Polycarpou A, Ioannidis JP (2005). Association of GSTM1, GSTT1 and GSTP1 gene polymorphisms with the risk of prostate cancer: A meta-analysis. *Cancer Epidemiol Biomarkers Prev*, **14**, 176-81.
- Sasai Y, Horiike S, Misawa S, et al (1999). Genotype of glutathione S-transferase and other genetic configurations in myelodysplasia. *Leuk Res*, **23**, 975-81.
- Sundberg K, Johansson AS, Stenberg G, et al (1998). Differences in the catalytic efficiencies of allelic variants of glutathione transferase P1-1 towards carcinogenic diol epoxides of polycyclic aromatic hydrocarbons. *Carcinogenesis*, **19**, 433-6.
- Suneetha KJ, Nancy KN, Rajalekshmy KR, et al. (2011). Role of glutathione-s-transferase and CYP1A1*2A polymorphisms in the therapy outcome of south Indian acute lymphoblastic leukemia patients. *Indian J Med Paediatr Oncol*, **32**, 25-9.
- Suneetha KJ, Nancy KN, Rajalekshmy KR, Sagar TG, Rajkumar T (2008). Role of GSTM1 (Present/Null) and GSTP1 (Ile105Val) polymorphisms in susceptibility to acute lymphoblastic leukemia among the South Indian population. *Asian Pac J Cancer Prev*, **9**, 733-6.
- Tang Q, Li J, Zhang S, et al (2013). GSTM1 and GSTT1 null polymorphisms and childhood acute leukemia risk: evidence from 26 case-control studies. *PLoS One*, **8**, e78810.
- Wang J, Zhang L, Feng JF, et al (2004). Genetic polymorphisms analysis of Glutathione s-transferase m1 and t1 in children with acute lymphoblastic leukemia. *JHuazhong University of Science and Technology [Med Sci]*, **24**, 243-4 (in Chinese).
- Wong O, Harris F, Armstrong TW, Hua F (2010). A hospital-based case-control study of acute myeloid leukemia in Shanghai: analysis of environmental and occupational risk factors by subtypes of the WHO classification. *Chem Biol Interact*, **184**, 112-28.
- Xu LY, Cao LF (2013). GSTT1 genetic polymorphism and susceptibility to childhood acute lymphoblastic leukemia: a meta-analysis. *Tumour Biol*, [Epub ahead of print].
- Ye Z, Song H (2005). Glutathione s-transferase polymorphisms (GSTM1, GSTP1 and GSTT1) and the risk of acute leukaemia: a systematic review and meta-analysis. *Eur J Cancer*, **41**, 980-9.
- Yuan XJ, Gu LJ, Xue HL, et al (2003). Analysis on GSTP genetic polymorphism in children with acute leukemia. *Natl Med J China*, **21**, 1863-66 (in Chinese).
- Zhang L, Zhang XX, Wang J (2003). Glutathione S-transferase M1, T1 genetic polymorphisms in childhood leukemia Zhengzhou University ??.
- Zhou L, Zhu YY, Zhang XD, Li Y, Liu ZG (2013). Risk effects of GST gene polymorphisms in patients with acute myeloid leukemia: a prospective study. *Asian Pac J Cancer Prev*, **14**, 3861-4.
- Zou LL, Lin GF, Ma QW, Zhang DS, Shen JH (2004). Glutathione S-transferase T1, M1 genetic polymorphisms in leukemia patients in Shanghai area. *Chin J Oncol*, **11**, 649-51 (in Chinese).