Research Article

Cancer Science & Research

GSTM1 and GSTT1 Genetic Susceptibility and Interaction with Chemical Exposures in Childhood Acute Lymphoblastic Leukemia: A Systematic Review and Meta-analysis

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Received: 11 March 2018; **Accepted:** 01 April 2018

Citation: Samira BA Sesay, Kaka A Katiella, Mercy E Ngoya, et al. GSTM1 and GSTT1 Genetic Susceptibility and Interaction with Chemical Exposures in Childhood Acute Lymphoblastic Leukemia: A Systematic Review and Meta-analysis. Cancer Sci Res. 2018; 1(2); 1-7.

ABSTRACT

Background: *The glutathione s-transferase genes play an important role in the detoxification of carcinogenic substances, and null mutations of these genes are linked to increase in acute lymphoblastic leukemia (ALL) due to an increase in susceptibility to environmental exposures of toxins and carcinogens, and chemical exposures like tobacco smoke and pesticides are common carcinogenic substances that children could be vulnerable to as risk of developing childhood ALL.*

Objectives: *The aim of this study is to analyze the effect of glutathione s-transferase mu1 and theta1 genetic susceptibility and interaction of chemical pesticide and tobacco smoke exposures on childhood ALL.*

Data collection and Analysis: *A total of 22 published case-controls were included in the meta-analysis of over forty thousand participants with 14974 cases and 25841 controls.*

Main Results: *Overall, the meta-analysis of these studies showed increase risk of ALL among children (random-effect OR 1.36, 95% CI 1.18-1.57). Subgroup analysis showed that the GSTM1 and GSTT1 null genotype has more increase association to childhood ALL (random-effect OR 1.36, 95% CI 1.05-1.76), and chemical pesticide in comparison with tobacco smoke exposures did have an increase association with childhood ALL (random-effect OR 1.40, 95% CI 1.10-1.78), (random-effect OR 1.38, 95% CI 1.20-1.58) respectively.*

Authors' conclusions: *In this study, the GSTM1 null genotype is significantly associated with susceptibility to childhood acute lymphoblastic leukemia in Asians, and chemical pesticides also showing increase associations. The GSTM1 and GSTT1 null genotypes show increase interaction with chemical pesticides in childhood ALL as compared to Tobacco smoke exposures.*

Keywords

Acute lymphoblastic leukemia, Childhood, GSTM1, GSTT1, Environmental exposures, Meta-analysis.

Abbreviations

CH: Childhood, ALL: Acute Lymphoblastic Leukemia, OR: Odds Ratio, CI: Confidence Interval, GSTM1: Glutathione S-transferases Mu-1, GSTT1: Glutathione S-transferases Theta1.

Introduction

Acute Lymphocytic Leukemia is a cancer of the stem cells in the bone marrow that produce lymphocytes, the term 'acute' means the cancer cells multiply rapidly, crowding out the normal cells in the blood and bone marrow. It can start in either early B cells or T cells at different stages of maturity, B-cell leukemia are much common than T-cells [1,2]. Acute lymphoblastic leukemia is the most common cancer diagnosed in children, representing

about one third of all childhood cancer cases [3,4]. About 1,250 children younger than 15 years old are expected to die from cancer in 2016 and the 5-year survival rate for children with ALL has greatly increased over time and is now more than 85% overall [2]. Its annual incidence rate is approximately 9–10 cases per 100,000 children worldwide, with a peak incidence between 2 and 5 years old [5]. In China, the incidence of childhood ALL has increased annually since the middle of the last century, and 30 out of 1,000,000 children are diagnosed with ALL every year [6].

The etiology of ALL is complex and has not been fully clarified. It is generally considered that the development of ALL is the result of a combination of environmental and genetic risk factors as well as gene-environment interactions [7]. The exact cause of most childhood leukemia is not known, most children with leukemia do not have any known risk factors but certain changes like chromosome translocation in the DNA inside their normal bone marrow cells causes them to become leukemia cells [8]. However, there are few known risk factors of childhood leukemia which are, genetic risk factors that includes inherited syndromes or immune system problems and environmental risk factors which includes radiation exposures or exposures to chemotherapy or certain other chemicals during the treatment of cancers or the use of immune-suppressing drugs to avoid rejection of transplanted organs [9].

Three main pathways related to acute leukemia genetic susceptibility includes the xenobiotic system, one of which is identified as a risk factor [10]. Carcinogenic substances which require metabolic activation by enzymes from the xenobiotic system are able to interact with genetic material and eventually cause somatic mutations [8]. The human glutathione S-tranferase mu-1 and theta1 genes are a phase II metabolic enzyme in the xenobiotic system with the ability to detoxify a wide variety of electrophilic compounds including the activated carcinogens [11]. Homozygote for null alleles or deletion of GSTM1 and GSTT1 have absent activity of the enzyme, therefore DNA-abduct formation and rates of somatic mutation have been reported to be increased in carriers of null alleles [12].

Children are more vulnerable and susceptible to environmental toxicants than adults because of physiological immaturity, and also indirect and unintended exposures [13]. Environmental agents such as tobacco and traffic smoke, pesticides, household chemicals, paintings, and diet are potential acute leukemia risk factors, as they may contain carcinogenic substances to humans, such as organic solvents or benzene derivatives, polycyclic aromatic hydrocarbons (PAHs), and organochloride compounds [14]. Certain genes normally control how our bodies break down and get rid of harmful chemicals and some people have different versions of these genes that make them less effective [9]. If children who inherit these genes are exposed, they may not be as able to break down harmful chemicals as adults and the combination of genes and harmful exposure might increase their risk for leukemia [7,15]. Case-control studies of molecular epidemiology suggest that children harboring null genotype of the GSTM1 and GSTT1 genes, might have an increased risk of the development of childhood acute leukemia [11]. This study focuses on both GSTM1 and GSTT1 genes and their interactions with exposures of chemical pesticides and tobacco smoke as a risk of developing acute lymphoblastic leukemia in children.

Methodology

Study selection

Identified studies were those addressing childhood acute leukemia associated with GSTM1 and GSTT1 polymorphisms and Chemical exposures in the environment. Extensive literature search was done for articles in these databases: PubMed, Google Scholar, Cochrane Library, Science Direct and PLOSone; up until the final search before analysis in September 2017. Titles and abstracts were initially screened by one researcher and then by a second researcher, repeating the screening process for verification decisions. Both quantitative and qualitative studies were included in this process.

Search strategy

Most prominent search terms used were: GSTM1 and GSTT1 genetic or gene polymorphism, environmental exposures, chemical exposures, pesticides, tobacco smoke, and childhood acute lymphoblastic or lymphocytic leukemia. These terms were used interchangeably, in various combinations to identify relevant studies and to obtain best search results. Restrictions were included on language and when the article was published. In addition, reference list of included studies was also searched.

Eligibility criteria

Studies were eligible for inclusion if they meet the following criteria: 1) patients diagnosed with ALL are children aged ≤ 15years, 2) case-control study design, 3) sufficient data provided on sample size, genotype distribution for cases and controls, 4) exposures of chemical pesticides and tobacco smoke, 5) full text available in English and published between the year 2006-2017, 6) A few Meta analyses were also included in this review. Studies were excluded if; 1) published in other languages other than English, 2) not a case control study, 3) provides limited data for estimating risk associations, 4) acute leukemia but not including ALL in children.

Data collection

Information from each eligible article was extracted by two reviewers independently, based on the above listed inclusion criteria. Discussions are generated between reviewers to settle disagreements. Variables extracted from each study are: first author's name, publication year, ethnicity, country of study, number cases and controls, GSTM1 and GSTT1 genotype distribution, chemical exposure type, and study outcome.

Statistical analysis

All statistical analysis was performed using the software program Review Manager (RevMan version 5.3) and using Statistical Package for the Social Sciences (SPSS Inc., Chicago IL, USA). The risk of childhood acute lymphoblastic leukemia and its strength of association with GSTM1 and GSTT1 null genotype

and chemical exposures were pooled by OR with corresponding 95% CI. To combine values from the studies and determine the statistical significance, a Z test (P<0.05 considered statistically significant) was done for the pooled OR and a fixed-effect model using the Mantel Haenszel method. Between-studies heterogeneity was estimated using the I2 statistical method, if there is an absence of heterogeneity among studies I2<50%, we used the fixed effect model to estimate the pooled OR. But on the contrary, when the studies are significantly heterogeneous I2>50%, the random-effect model was used to evaluate the pooled OR. Also, subgroup analysis was performed by risk factors. Possible publication risk bias was estimated by funnel plot.

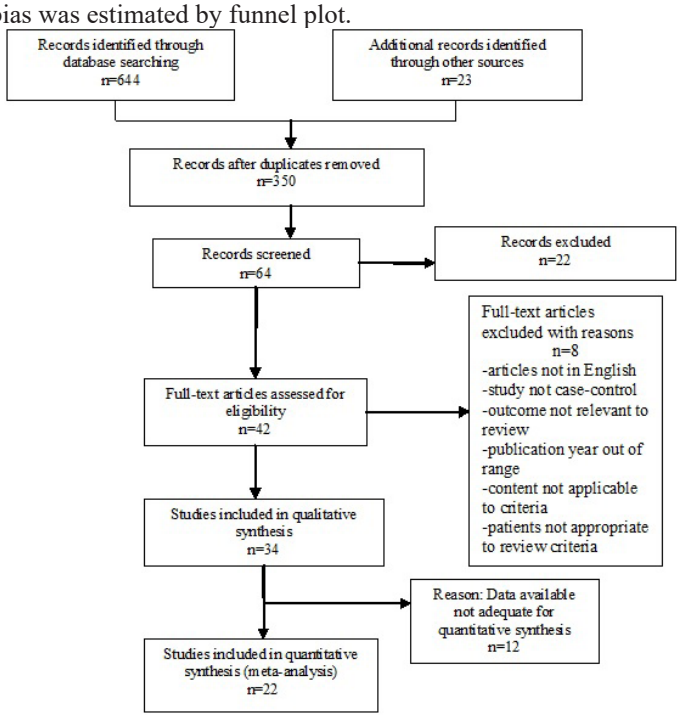

Figure 1: Flow diagram of study search, inclusion and exclusion.

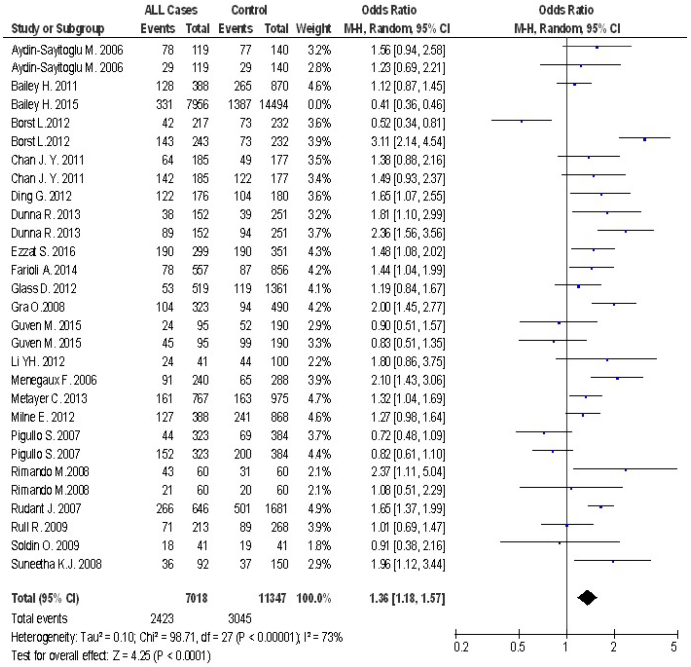

Figure 2: Forest plot for meta-analysis of GSTM1 & GSTT1, chemical pesticides and tobacco smoke exposures as risks of childhood acute lymphoblastic leukemia.

Results

Characteristics of analyzed studies

Based on the inclusion and exclusion criteria, 34 studies were relevant for the qualitative synthesis of which only 22 articles (all case-control studies) included for quantitative synthesis [11,16-36]. The flow diagram in figure 1 summarizes the study selection process. In total, 14974 cases of childhood ALL and 25841 controls were involved in this meta-analysis. The characteristics of the included studies are summarized in Tables 3 and 4.

GSTM1 and GSTT1 null genotype: a total of 10 studies were included in the meta-analysis with 1118 ch ALL cases and 1202 controls.

Chemical pesticides and tobacco smoke exposures: here, 12 studies in total were added for meta-analysis with 1636 exposed patients and 3230 controls.

Meta-analysis

This analysis shows an obvious between-study heterogeneity among all the 22 studies, total 40815 participants with I^2 = 73%, and also shows a statistical significant in overall childhood acute lymphoblastic leukemia among the cases and controls (random-effect OR 1.36, 95% CI 1.18-1.57; I^2 = 73%) Figure 2. Subgroup analyses among four different risk factors are as follows;

- Meta-analysis of GSTM1 and GSTT1 null genotype and childhood ALL: overall analysis of the null genotypes of GST M1 and T1 are associated with increased risk of childhood acute lymphoblastic leukemia with higher heterogeneity (random-effect OR 1.36, 95% CI 1.05-1.76; Test for overall effect: Z = 2.33 (P <0.00001); I2 = 80%). Individually, analysis shows that the association of GSTT1 null genotype is not statistically significant to childhood ALL as compared to the GSTM1 null genotype (OR 1.15, 95%CI 0.82-1.62), (OR1.62, 95%CI 1.09-2.41) respectively, as shown in figure 3.
- Meta-analysis of Chemical pesticide exposures and childhood ALL: there is increase heterogeneity in this analysis and shows statistically significant difference between groups, indicating an obvious association between pesticides and ALL in children (random effect OR 1.40, 95% CI 1.10-1.78; Test for overall effect: Z = 2.77 (P=0.01); I2 = 65%) Shown in figure 4.
- Meta-analysis of Tobacco smoke exposures and childhood ALL: there was no obvious heterogeneity detected and result shows a certain degree of unbalance in the exposures of tobacco smoke in association with ALL in children (random effect OR 1.38, 95% CI 1.20-1.58; Test for overall effect: Z = 4.44 (P=0.94); I2 = 0%) Shown in Figure 4.
- Meta-analysis of Ethnicity and childhood ALL: Asians are more significantly associated with childhood ALL as compared to the Whites (OR 1.60, 95% CI 1.30-1.96; Test for overall effect: Z =4.44 (P<0.00001); I2=0%), (OR 1.23,

95% CI 0.99-1.53; Test for overall effect: Z =1.87 (P=0.06); I2=80%) respectively (Figure 5).

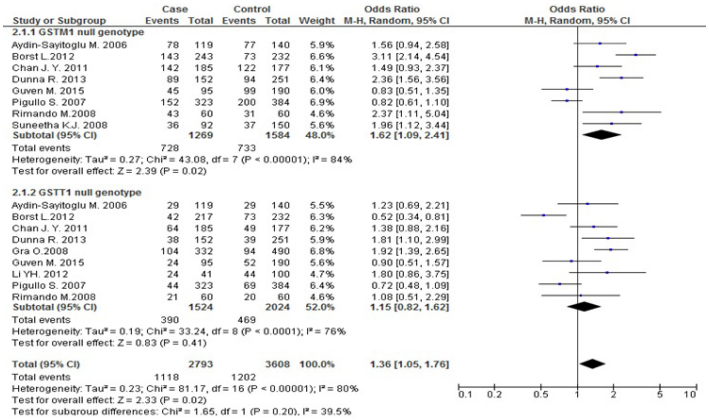

Figure 3: Forest plot for meta-analysis of GSTM1 and GSTT1 null genotype associated with childhood ALL.

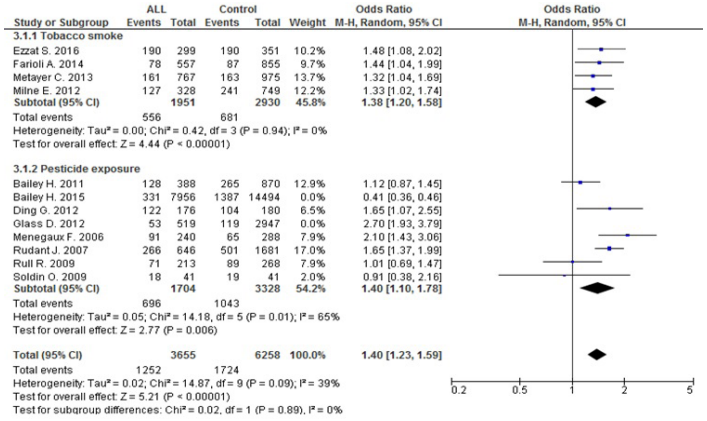

Figure 4: Forest plot of chemical pesticides and tobacco smoke exposures associated with childhood ALL.

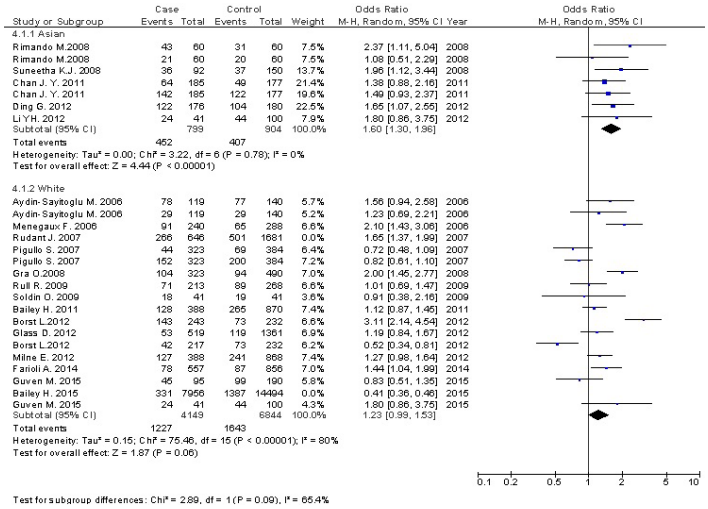

Figure 5: Forest plot of ethnicity associated with childhood ALL.

Publication Bias

Funnel plot was performed to assess the risk of publication bias of literatures. The shape of the funnel plot seemed symmetrical, but indicating that there is an obvious risk of publication bias in this meta-analysis, on the left hand side of the funnel (Figure 6).

Sensitivity analysis

Sensitive analyses were conducted to determine whether modification of the inclusion criteria of the meta-analysis affected the final results. For the exclusion of individual study, the corresponding pooled ORs did altered this significant result, indicating that the results were influenced by a single study (not shown).

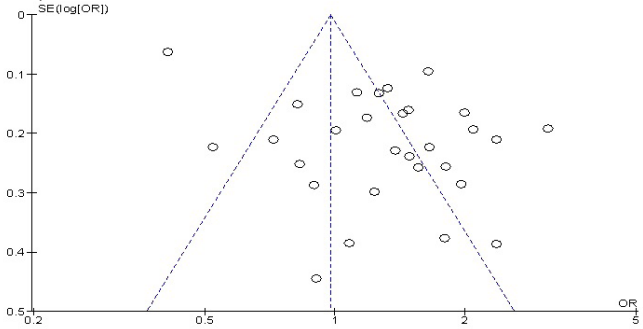

Figure 6: Funnel plot analysis detecting publication bias in the meta-analysis.

Stratification Analysis

This analysis was done to stratify by ethnicity of the GSTM1 and GSTT1 null genotypes, and from the four different ethnic groups involved in this study; two were most predominant groups, Asians and Whites as shown in table 1 below.

	GSTM1			GSTT1			
	Studies	OR (95% CI)	P for hetero-geneity	I2 (%)	Studies	OR (95% CI)	I2 (%)	P for hetero-geneity
Total	7	1.53 [0.99-2.38]a	0.05	84.0	8	1.09 [0.76-1.57]a	77.0	0.65
Ethnic groups								
Asian	3	1.78 [1.29-2.46]	0.005	0.0	3	1.39 [0.99-1.95]	0.0	0.06
White	4	1.35[0.68-2.65]	0.39	91.0	5	0.96 [0.57-1.62]	85.0	0.88

Table 1: The relationship between polymorphisms of GSTM1 & GSTT1 and the childhood ALL by stratification according to ethnicity.

[a]Random-effect was used when the p-value for heterogeneity test was ≤ 0.05 or I2 ≥ 50%, otherwise the fixed-effect model was used.

Gene-Environment Interaction

This analysis was done to combine the frequency of GSTT1 and GSTM1 null genotypes and their influence with exposure to chemicals in the environment, shown in table 2

	GSTM1 na	GSTT1 na	OR	95% CI
Chemical Pesticides	21.3	50.2	0.779	0.39-1.68
Tobacco smoke Exposure	45.5	57.3	0.502	0.39-1.68

Table 2: The interaction of the polymorphism of GSTM1 and GSTT1 with Chemical exposures.

[a]Weighted Mean adjusted and expressed in percentage.

Discussion

Many studies have analyzed the Glutathione S-Tranferase

polymorphisms and their association with risk of childhood ALL but has yielded conflicting results. Human cytosolic GSTs which may include GSTM1, GSTT1, and GSTP1 polymorphisms are commonly investigated, and the GSTM1 and GST1 null genotype is the most studied loci and are both similar. Although when studied alone, GSTT1 is significantly associated with childhood ALL, but GSTM1 is most significantly associated with childhood acute lymphoblastic leukemia as compared to the other GSTs [37-39]. GSTM1 null genotype is associated with many cancer risks [11,40] and also in certain population like the Chinese, many studies have reported the association between GSTM1 and childhood acute leukemias [41]. Published meta-analyses also shows cumulative trend of more obvious association between GSTM1 null polymorphisms and childhood acute lymphoblastic leukemia risk [11,22,40,42,43].

Based on the eligibility criteria above, articles searched on environmental exposures associated with childhood ALL obtained tobacco smoke and chemical pesticides as the most commonly reported exposures, and most studies evaluated the exposures as before conception, during pregnancy and after birth. Paternal smoking before conception and passive maternal smoking during pregnancy were significantly associated with childhood ALL [25,39]. Studies have reported consistent results on exposures to pesticides and risk of chALL, therefore they strongly recommend that parents and those contemplating pregnancy should limit pesticide exposure in the home during the year before birth and the child's early years [16].

Our meta-analysis was conducted with a large sample size, and has high between-studies heterogeneity. This stratified meta-analysis of risk factors demonstrated that GSTM1 null polymorphisms has increase significant influence on childhood acute lymphoblastic leukemia as compared to GSTT1 null polymorphism, and exposures to chemical pesticides has more significant influence on childhood acute lymphoblastic leukemia as compared to tobacco smoke exposures. The influence of GSTM1 and GSTT1 null polymorphism seems to agree with reports on many similar studies. Also another possible explanation for the negative associations found in this meta-analysis is that different studies were combined to increase statistical power and a more reliable result but rather highly inconsistent findings across the studies. When polymorphisms of both GST genes were stratified according to ethnicity, it was shown (Table 1) that Childhood ALL in Asian groups is more associated with GSTM1 null genotype than the GSTT1 null gene.

In table 2, the odds ratio for the association between combinations of both gene-environment interactions is large for chemical pesticides and null genotypes of GSTM1 and GSTT1 as compared to the tobacco smoke exposure, reflecting the large difference in percentages of outcome given exposure and thus a strong relation between the variables in this analysis. The association of the null polymorphism of GSTM1 but not the GSTT1 with childhood ALL may be an indication of substrate specificity of GSTM1 in metabolism of agents that are involved in the etiology of childhood ALL. However, outcome of individual studies in this review showed that in distribution of GSTM1 genotype, three had increase risk of association with null genotype [19,27,44] and two had no significant difference in prevalence of null genotype [22,24] whiles one study with a gender stratified analysis showed that the null genotype was over-represented in boys [21]. In environmental exposures of chemical pesticides and tobacco smoke 83.3% shows increase risk of childhood ALL [20,23,27-33] and 16.7% shows no association with childhood acute lymphoblastic leukemia [34,35].

We acknowledge serious limitations in our meta-analysis results. Firstly, the total number of studies with their cases and controls across the subgroup analysis of childhood ALL was relatively small, with less statistical power to evaluate the real association. Secondly, there are possibilities of misclassification bias and our results were based on unadjusted estimates. Thirdly, there was limited quality of case-control studies so we could not make adequate adjustment of other cofounders. Finally, the gene-environment interactions could not be well addressed and compared with previous studies for lack of relevant data.

Acute lymphoblastic leukemia is a complex, multifactoral and heterogeneous disease but its etiology can be better explained with the role of combining genetics and environmental factors. Therefore, recommendations for further research should be considered, to better study their interactions for clearer and more accurate results.

Conclusion

In this study, the GSTM1 null genotype is significantly associated with susceptibility to childhood acute lymphoblastic leukemia in Asians, and chemical pesticides also showed increase associations. The GSTM1 and GSTT1 null genotypes show increase interaction with chemical pesticides in childhood acute leukemia as compared to Tobacco smoke exposures. Our result showed childhood acute lymphoblastic leukemia has an increase risk of environmental exposures in all subjects of risk incorporated into this study. The present meta-analysis show statistical significance of childhood acute lymphoblastic leukemia associated with GSTM1 and GSTT1 null genotypes. An elevation of significant association between GSTM1 null genotype and childhood ALL was found. In this regard, to clarify this genetic susceptibility, it is necessary to conduct larger sample studies. A more stratified analysis by different ethnic groups indicates a significantly elevated risk in Asian children with null genotypes of GSTM1. Other risk factors of childhood ALL can be investigated in the future. These children with null genotype of GSTM1 gene lacks it activity and ability to efficiently eliminate chemical exposures to pesticides and tobacco smoke which increases their risk of childhood ALL.

Acknowledgment

The author thanks all the team of reviewers in their contribution to this work.

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