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Review

Glutathione *s*-transferase polymorphisms (*GSTM1*, *GSTP1* and *GSTT1*) and the risk of acute leukaemia: A systematic review and meta-analysis

Zheng Ye [a,*], Honglin Song [b,*]

[a] *Department of Public Health and Primary Care, Institute of Public Health, University of Cambridge, Strangeways Research Laboratory, Worts Causeway, Cambridge CB1 8RN, UK*

[b] *Department of Oncology, University of Cambridge, Strangeways Research Laboratory, Worts Causeway, Cambridge CB1 8RN, UK*

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Abstract

Glutathione *s*-transferase (GST) polymorphisms (*GSTM1*, *GSTP1* and *GSTT1*) have been considered as risk factors for developing acute leukaemia in a number of studies; however the overall results of such studies are inconsistent. To investigate a putative association of GST polymorphisms with the risk of acute leukaemia, we performed a systematic review and meta-analysis of 30 published case–control studies. To take into account the possibility of heterogeneity across the studies, a statistical test was performed. The pooled odds ratios (ORs) were assessed using both a fixed-effects and a random-effects model. The pooled OR of acute leukaemia risks associated with *GSTM1* null genotype, *GSTP1* Val105 allele and *GSTT1* null genotype were 1.22 (95% confidence interval (CI) 1.07–1.38), 1.07 (95% CI 1.00–1.13) and 1.19 (95% CI 1.00–1.41), respectively. Significantly increased risk of acute lymphoblastic leukaemia associated with *GSTM1* and *GSTT1* null genotypes was observed. Their pooled ORs were 1.24 (95% CI 1.17–1.31) and 1.30 (95% CI 1.06–1.60), respectively. We also found substantial evidence of heterogeneity between the studies. Our results suggest that *GSTM1* and *GSTT1*, but not *GSTP1* polymorphisms, appear to be associated with a modest increase in the risk of acute lymphoblastic leukaemia. It is conceivable that *GSTM1* and *GSTT1* null genotypes may thus play a role in leukemogenesis. A review of the 30 case–control studies indicates that greater attention should be paid to the design of future studies.

Keywords: Glutathione *s*-transferase; *GSTM1*; *GSTP1*; *GSTT1*; Acute leukaemia; Meta-analysis; Case–control study; Odds ratio

1. Introduction

Acute leukaemia, including acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML), is a frequent malignancy affecting both children and adults. Despite much investigation, the causes are not yet fully understood. Like many other cancers, acute leukaemia is considered to be a complex disease, which is determined by a combination of genetic and environmental factors [1,2]. There is increasing evidence that predisposition to acute leukaemia is associated with exposure to chemicals such as benzene and chemotherapeutic agents [3,4]. The enzymes involved in the metabolism of these carcinogens have thus received a reasonable level of attention.

Glutathione *s*-transferase (GST) M1, P1 and T1 are phase II enzymes that are involved in conjugation and detoxification of a wide range of xenobiotics, including environmental carcinogens and chemotherapeutic agents. GST polymorphisms have thus been considered

* Corresponding authors. Tel.: +44 (0)1223 741530; fax: +44 (0)1223 741339 (Z. Ye); Tel.: +44 (0)1223 740161; fax: +44 (0)1223 740147 (H. Song).

E-mail addresses: zheng.ye@phpc.cam.ac.uk (Z. Ye), honglin@srl.cam.ac.uk (H. Song).

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as possible risk factors of acute leukaemia. Polymorphisms of *GSTM1*, *GSTP1*, and *GSTT1* exist in all populations. The GSTM1*0 (*GSTM1* null) and GSTT1*0 (*GSTT1* null) alleles represent deletions of *GSTM1* and *GSTT1* genes and result in a loss of enzymatic activity [5]. An increased frequency of *GSTM1* and *GSTT1* null genotypes has been associated with a number of human malignancies [6,7]. The 1578 A > G transition in *GSTP1* gives rise to the Ile105Val polymorphism, which confers reduced enzyme activity [8].

GST polymorphisms (*GSTM1*, *GSTP1* and *GSTT1*) were first reported as risk factors for acute leukaemia in 1997 [9,10]. Since then, a number of studies have confirmed or refuted an association between GST polymorphisms and the risk of acute leukaemia [2,4,11–28]. These disparate findings may be due to insufficient power in some studies, differences between cancer types, type of study populations and study design. To investigate the effect of GST polymorphisms and the risk of acute leukaemia, we performed a systematic review and meta-analysis of all the available published case–control studies from January 1997 to July 2004.

2. Methods

2.1. Identification of studies

Studies published between January 1997 and July 2004 with information on *GSTM1*, *GSTP1* or *GSTT1* status and the risk of acute leukaemia were identified using two electronic databases: MEDLINE (National Library of Medicine, Washington, DC, USA) and EMBASE (Elsevier Science, New York, USA), using the search terms '*GSTM1*' or '*GSTP1*' or '*GSTT1*' and 'acute leukaemia'. Additional articles were also checked using the references cited in these publications. Articles selected for analysis were studies with case–control design and their primary references, which had no obvious overlap of cancer cases with other studies. Selected articles should provide enough data to calculate an effect size. One study [29] was excluded because of lack of genotype data. Studies that included groups from different populations were considered separately in our analysis [9,15,21]. When studies had data on the different types of acute leukaemia (e.g., ALL and AML), they were treated as independent studies [13,17]. Chronic leukaemia studies were excluded from our analysis [30] since we focused on acute leukaemia. The application of these criteria yielded 30 case–control studies eligible for meta-analysis [2,4,9–28].

2.2. Statistical analysis

The odds ratio (OR) of acute leukaemia associated with GST polymorphisms was re-calculated for each study, and their corresponding 95% confidence intervals (CI) were estimated by Woolf's method [31,32]. The results might not be exactly the same as those of some studies as different criteria were used in the statistical analysis. We focused on the null alleles of the *GSTM1* and *GSTT1* genes and the Val105 allele of the *GSTP1* gene in this analysis. A low-risk genotype (presence of *GSTM1* or *GSTT1*, homozygous Ile for *GSTP1*) was used as the baseline for calculating ORs. Hardy–Weinberg equilibrium (HWE) was estimated among the controls for *GSTP1* using the χ^2 test. To take into account the possibility of heterogeneity across the studies, a statistical test for heterogeneity was performed based on the Q statistic, in which a P value greater than 0.05 suggested a lack of heterogeneity [33]. If heterogeneity between studies was present, a sensitivity analysis was performed based on the magnitude of Q statistic [34]. Studies contributing the most to the heterogeneity were removed sequentially until homogeneity was achieved.

We carried out meta-analyses using both a fixed-effects [35] and a random-effects model [33]. The fixed-effects model assumes no significant heterogeneity between the results of the individual studies being pooled, whereas the random-effects model allows for such heterogeneity, and they add an empirical estimate of the between-study variance τ^2 to the within-study variance [33,36]. We reported results from a random-effects model if heterogeneity between studies was observed. The analyses were also conducted on the subgroups of studies based on the age, geographic region and ethnic origin. Childhood acute leukaemia was defined as age less than 18 years of age at the time of diagnosis, while adult acute leukaemia cases were those aged 18 and over at the time of diagnosis. Geographic subgroups were defined as three regions (America, Europe and Asia), while ethnic subgroups were considered as three ethnic groups (white, black and Asian).

We assessed potential publication bias via funnel plots, Begg's test [37] and Egger's test [38]. The results of the small studies more widely scattered in the funnel plot than those of the larger studies. In the absence of publication bias, the plot will resemble a symmetrical inverted funnel [39]. To identify gene–gene interaction, the joint effect of GST polymorphisms was also evaluated [33,35]. Since most of the studies assessed the joint effect of *GSTM1* and *GSTT1* null genotypes on the risk of acute leukaemia, we focused on the pooled analysis for these two genotypes. Presence of both *GSTM1* and *GSTT1* genotypes was used as the control reference for each study. All analyses were conducted using KDE 1.9 software (InforSense, London).

3. Results

We identified 30 eligible studies, including nearly 12,000 subjects in relation to GST polymorphisms,