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RESEARCH ARTICLE

# Glutathione *S*-transferase gene polymorphisms and susceptibility to chronic myeloid leukemia

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**Abstract** Glutathione *S*-transferase (GST), a phase II metabolizing enzyme, plays an important role in the cellar defense system, and its activity may modulate leukemia risk. A large body of evidence has shown the possible relevance of functional polymorphisms of the genes that encode GSTs μ, π, and θ (*GSTM1*, *GSTP1*, and *GST1*, respectively) to the genetic susceptibility of chronic myeloid leukemia (CML). Because of the lack of available conclusive data, we performed a meta-analysis of all relevant available studies to derive a more precise estimation of the relationship. A comprehensive literature search of PubMed and Web of Knowledge electronic databases was conducted to collect relevant studies until December 20, 2013, and the extracted data were statistically analyzed using Review Manager version 5.2. Finally, 16 eligible studies were identified in the literature. The *GSTT1* null genotype was associated with an increased risk of CML, as were the double null *GSTT1* and *GSTM1* genotypes. These findings suggest that heritable GST status influences the risk of developing CML and that more attention should be paid to carriers of these susceptibility genes.

**Keywords** Susceptibility · GSTM1 · GSTT1 · GSTP1 · Chronic myeloid leukemia

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## Introduction

Chronic myeloid leukemia (CML) is a malignancy of hematopoietic stem cells characterized by high levels of leukocytes, splenomegaly, myeloid hyperplasia in the bone marrow, and high levels of mature myeloid cells in the peripheral blood [1]. It was the first cancer for which a specific cytogenetic marker was found: the Philadelphia chromosome (the result of a reciprocal translocation between chromosomes 9 and 22: t(9;22)(q34,q11)) [2].

Although these clinical and biological aspects are well documented, little is known about the susceptibility of particular individuals to CML. DNA is at constant risk of being damaged by both endogenous and exogenous mechanisms. Detoxification and DNA repair enzymes protect DNA from damage. When the cellular processes of detoxification or repair are ineffective, the persisting DNA damage can cause severe failure of cellular functions, leading to either apoptosis or oncogenesis [3–5]. Thus, exposure to toxic substances could cause DNA damage, which when combined with inter-individual differences in the capacity to respond to and repair that DNA damage could affect the susceptibility to CML.

It had been claimed that cytotoxic and genotoxic environmental agents—especially ionizing radiation and similar factors—increase the risk of developing CML [6]. Meanwhile, the genetic polymorphisms that have been described for multiple genes associated with DNA repair might contribute to the reported interindividual variation in the ability to detoxify [7], which could explain the mechanism of individual differences in susceptibility to CML. The glutathione *S*-transferases (GSTs) are a family of phase II enzymes that are involved in the detoxification of xenobiotics and had been researched widely. They catalyze the conjugation reaction between glutathione and compounds containing an electrophilic center, such as chemotherapeutic drugs, carcinogens, environmental pollutants, and a broad spectrum of other xenobiotics [8].

Hence, GSTs play significant role in cellular defense. Human cytosolic GSTs can be characterized into four distinct families according to their isoelectric points: α, μ, π, and θ [9].

Functional polymorphisms have been reported for at least three of the genes that encode GSTs: *GSTM1* (μ), *GSTT1* (θ), and *GSTP1* (π). Both *GSTM1* and *GSTT1* exhibit a particularly high degree of polymorphism, one of them being the complete deletion of the gene could potentially cause a loss of enzymatic activity [10]. Approximately 20–50 % of individuals do not express the enzyme due to homozygous deletion, resulting in a diminished ability to detoxify various carcinogens; these individuals are more susceptible to DNA damage [11]. *GSTP1* is located on chromosome 11q13 and is overexpressed in various tumor types [12]. The A→G polymorphism at nucleotide 313 in exon 5 of *GSTP1* can lead to an amino acid substitution of isoleucine (Ile) by valine (Val) at amino acid position 105 (Ile105Val). This substitution potentially diminishes the ability to detoxify certain mutagens and carcinogens, which could result in increased DNA damage and mutation and hence a greater risk of developing cancer [13]. Biochemical studies have indicated that the conjugating activity is lower for Val homozygotes than for Ile homozygotes, with heterozygotes displaying intermediate activity [14]. Individuals with at least one Val allele might have an underlying predisposition toward cancer when they are exposed to environmentally derived or endogenously formed *GSTP1* substrates [15].

Numerous studies had investigated the association between these polymorphisms and the susceptibility to CML, with conflicting results [1, 6, 12, 16–28]. Clarification of this putative association was therefore necessary, and it was also the aim of the present study. To this end, data were collected from all published studies of the relationship between *GSTM1*, *GSTT1*, and *GSTP1* polymorphisms and the risk of CML. After adherence to strict inclusion criteria, a meta-analysis was applied to all of the eligible studies.

## Methods

### Literature and search strategy

All relevant studies published before December 20, 2013 were identified through an extended computer-based search of PubMed (www.ncbi.nlm.nih.gov/pubmed) and Web of Knowledge (http://isiknowledge.com/). The search strategy was based on a combination of the following keywords: "GSTM1," "GSTT1," "GSTP1," "acute myeloid leukemia" ("AML" or "acute myelocytic leukemia" or "acute myelogenous leukemia"), "chronic myeloid leukemia" ("CML" or "chronic myelocytic leukemia" or "chronic myelogenous leukemia"), "polymorphism," "susceptibility," and "risk." Only journal articles were included in the analysis. All references cited in the studies were also reviewed to identify additional relevant work. Only studies involving human subjects using standard genotyping methods were considered. Cases with CML were eligible regardless of whether or not they had a first-degree relative with any cancer.

### Inclusion criteria

The following inclusion criteria were applied:

1. The study must have a case–control design and investigate the relationship between *GSTM1*, *GSTT1*, and *GSTP1* polymorphisms and the risk of CML.
2. The study must provide sufficient data on the distribution of GST gene polymorphisms in cases and in control groups of healthy subjects or sufficient information for such data to be calculated.
3. The cases considered in the study must include a population of CML patients.

### Data extraction

The following information was extracted for the included studies: name of the first author, year of publication, numbers of patients and controls, ethnicities of the study population, median ages of the cases and controls, sex ratios of the cases and controls, genotype distributions for the cases and controls, and main single nucleotide polymorphism (SNP) susceptibility findings of the research.

### Statistical analysis

Review Manager (version 5.2) software was used for the meta-analysis. The raw data for genotype distribution were used to calculate the study-specific estimates of odds ratio (OR) and 95 % confidence interval (CI). The presence of heterogeneity was assessed using Cochran's $Q$ statistic and quantified using the $I^2$ statistic, which is proportional to the degree of heterogeneity; an $I^2$ value above 50 % indicates the presence of a very high degree of heterogeneity [29].

The overall pooled OR and corresponding 95 % CI were estimated using the Mantel–Haenszel method with a fixed effects model when no significant heterogeneity is present (below 50 %) [30]. When substantial heterogeneity was present, sensitivity analysis was performed by excluding individual studies. Outlying studies were identified and excluded, and the $I^2$ estimates for these different sets of studies were examined. When removing particular studies did not cause the heterogeneity index to fall below 50 %, the random effects model was used. This model can account for the heterogeneity in the data that undoubtedly exists due to within- and between-study variations, and thus, its estimated effect values are more

conservative [29]. The significance of the pooled OR was determined by a *z* test. The level of statistical significance was set at $P<0.05$.

Potential publication bias was estimated by constructing funnel plots. If most of the data appeared at the top of a funnel plot and was distributed roughly symmetrically, this would suggest the absence of obvious publication bias, and vice versa [31]. There was no need to construct funnel plots when there were too few analyzed studies (i.e., $n<5$).

### Meta-analyses

Based on the extensive data provided by the included studies, a meta-analysis was conducted to determine the influence of *GSTM1*, *GSTT1*, and *GSTP1* polymorphisms on the susceptibility CML. The role of the double null *GSTM1* and *GSTT1* genotypes on the risk of CML was also evaluated. In addition, the effects of the various GST gene polymorphisms were analyzed relative to gender among both the controls and CML patients.

## Results

### Overview of the study characteristics

A flow chart depicting the study selection process is shown in Fig. 1. In total, 736 articles were selected based on various combinations of the keywords listed in the "Methods." Checking for duplicates resulted in the removal of 352 articles. Of the remaining 384 articles, 309 were not on the topic of association between GST gene SNPs and the risk of myeloid leukemia, 26 were review articles, 31 focused on researching the association between GST gene SNPs and the risk of AML, and two did not provide sufficient data. After excluding these articles, only 16 studies of the relationship between GST gene SNPs and the risk of CML remained and qualified for inclusion in this meta-analysis. The basic data for every eligible study were extracted and are listed in Table 1.

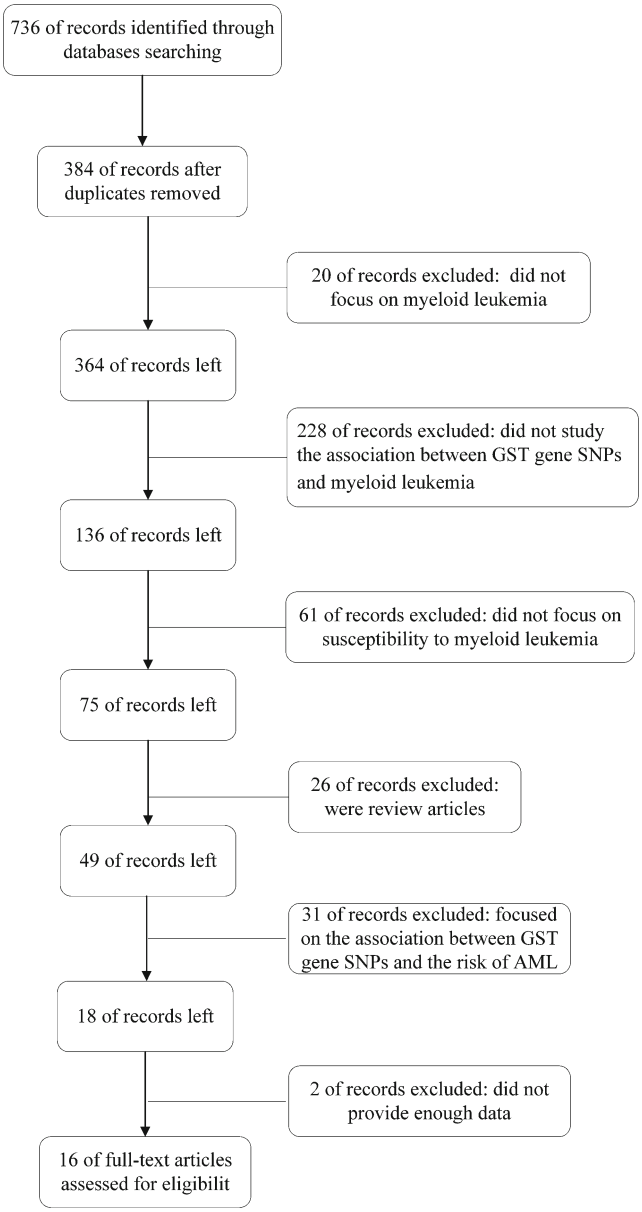


**Fig. 1** Flow chart of study selection

### Results of the meta-analysis

The literature search yielded 14 studies of the relationship between *GSTM1* polymorphism and the risk of CML and provided sufficient data to be eligible for inclusion of the present study [6, 16–28]. A meta-analysis of these 14 studies was conducted, which involved data from 1,175 CML patients and 3,060 controls. The *z* test verified no association between *GSTM1* polymorphism and the risk of CML. The $I^2$ value indicated the presence of a small degree of heterogeneity among the five studies, and thus, the fixed effects model was used. The funnel plot revealed good symmetry, suggesting that there was no obvious publication bias (Fig. 2a).

Thirteen studies surveyed the association between *GSTT1* polymorphism and the risk of CML [6, 16–26, 28]. A meta-analysis was performed on the data of 1,164 CML patients and 2,934 controls. The $I^2$ value indicated a high degree of heterogeneity among the 13 studies, and the $I^2$ value did not fall below 50 % regardless of which study was excluded. Therefore, the association was tested using a random effects model. Ultimately, it was found that the *GSTT1* null genotype significantly increased the susceptibility to CML ($P=0.004$, OR= 1.57, 95 % CI=1.15–2.14). The funnel plot suggested that no obvious publication bias was present (Fig. 2b).

Seven studies analyzed the influence of combined *GSTM1* and *GSTT1* null genotypes on the susceptibility to CML [6,

**Table 1** List of 43 studies that analyzed association between the *GSTM1*, *GSTT1*, and *GSTP1* SNPs and the susceptibility to CML

| Study | Year | Ethnicity | No. of cases | Median age of cases | No. of male cases | No. of controls | Median age of controls | No. of male controls | GST SNPs studied | | Main results | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bajpai, P. [16] | 2007 | Indian | 80 | 36.2±10.9 | 55 | 105 | 36.8±11.3 | 59 | M1 | T1 | T1(+) | M1(−) |
| Bhat, G. [17] | 2012 | Kashmiri | 75 | 42.3±13.4 | 43 | 124 | 41.5±12.9 | 76 | M1 | T1 | T1(+) | M1(−) |
| Chen, H. C. [18] | 2008 | Chinese | 108 | NA | NA | 204 | 40.9 | 137 | M1 | T1 | T1(−) | M1(−) |
| Hishida, A. [19] | 2005 | Japanese | 51 | 47.4 | 32 | 476 | 49.7 | 291 | M1 | T1 | T1(−) | M1(−) |
| Karkucak, M. [1] | 2012 | Turkish | 71 | 49±12.84 | 31 | 67 | 49.86±10 | 29 | P1 | | P1(−) | |
| Loffler, H. [20] | 2001 | German | 141 | NA | 78 | 150 | NA | 97 | M1 | T1 | T1(−) | M1(−) |
| Lordelo, G. S. [21] | 2012 | Brazilian | 105 | NA | 54 | 273 | NA | 128 | M1 | T1 | T1(−) | M1(+) |
| Lourenco, G. J. [22] | 2005 | Mixed | 125 | 39.0±16.4 | 73 | 341 | 53.0±4.3 | 198 | M1 | T1 | T1(−) | M1(−) |
| Mondal, B. C. [23] | 2005 | Indian | 81 | 40 | 57 | 123 | 35 | 68 | M1 | T1 | T1(+) | M1(−) |
| Ovsepian, V. A. [24] | 2010 | Russian | 83 | 56.9 | NA | 205 | NA | NA | M1 | T1 | T1(+) | M1(−) |
| Ozten, N. [25] | 2012 | Turkish | 106 | 35.1±10.4 | 60 | 190 | 38.3±12.9 | 107 | M1 | T1 | T1(+) | M1(−) |
| Sailaja, K. [12] | 2010 | Indian | 260 | NA | 178 | 248 | NA | NA | P1 | | P1(+) | |
| Souza, C. L. [26] | 2008 | Brazilian | 53 | 41±21 | 30 | 304 | 29±9.5 | 131 | M1 | T1 | T1(−) | M1(−) |
| Taspinar, M. [6] | 2008 | Turkish | 107 | 40.6±13.3 | 64 | 135 | 34.3±9.7 | 90 | M1 | T1 | T1(+) | M1(−) |
| Lemos, M. C. [27] | 1999 | Portuguese | 11 | NA | NA | 128 | 30.8±14.2 | 56 | M1 | | M1(−) | |
| Ouerhani, S. [28] | 2011 | Tunisian | 49 | NA | NA | 309 | NA | NA | M1 | T1 | T1(−) | M1(−) |

*NA* not available, *M1 GSTM1*, *T1 GSTT1*, *P1 GSTP1* Ile105Val

16, 17, 22, 25, 26, 28]. A meta-analysis was conducted with a fixed effects model using the data from 595 patients and 1,506 controls. The $I^2$ value indicated a high degree of heterogeneity among the seven studies. Sensitivity analysis identified the study by Ozten et al. [25] as an outlier; the removal of this study reduced the heterogeneity to 47 %. A further meta-analysis was conducted using a fixed effects model based on the data from the remaining six studies. The combined null genotype was found to increase the risk of CML ($P$=0.002, OR=1.79, 95 % CI=1.24–2.58). No obvious publication bias was indicated by the funnel plot (Fig. 2c).

Only two studies researched the effect of the *GSTP1* Ile105Val polymorphism on the risk of CML [1, 12]. While we found that controls in both of the two studies were not in accordance with the Hardy–Weinberg equilibrium, this would mean that the two studies could not be used for the meta-analysis. More researches were thus needed to clarify the association.

The distribution of *GSTM1* and *GSTT1* genotypes between the genders was investigated via meta-analysis using data from the three studies that provided sufficient relevant data [21–23]. The frequency of the *GSTM1* null genotype was higher among the male patients than among the female cases (Fig. 3a; $P$=0.009, OR=1.91, 95 % CI=1.18–3.09), while there was no gender difference in the frequency of the *GSTT1* null genotype among CML patients (Fig. 3b). However, since only three studies were included in this gender-based analysis, more relevant research is needed to confirm this finding.

## Discussion

Both individual genotypic differences and the level of expression of these carcinogen-metabolizing enzymes are crucial for determining the susceptibility of developing cancer [32]. Mutations of *GSTM1*, *GSTT1*, and *GSTP1* have been linked with an increase in the number of cancers, probably due to an increased susceptibility to environmental toxins and carcinogens [33]. Many experiments have been performed with the aim of determining how these three gene polymorphisms influence the susceptibility to CML in different areas and in different ethnic groups. The findings of these studies were often contradictory, with the main sources of these differences being certain objective factors, such as race, geographic region, and age. Meta-analysis, which is recognized as one of the best methods of secondary research, can be implemented to integrate these contradictions. In the present study, meta-analysis was used to systematically summarize and analyze the relevant identified literature. The following main conclusions were drawn from the analyses:

1. The *GSTT1* null genotype is a risk factor for CML. Furthermore, the double null *GSTM1* and *GSTT1* genotypes can also further increase the risk of CML.
2. The impact of the *GSTM1* null genotype on the risk of CML did not reach statistical difference. This is consistent with the conclusions of most of the included studies.

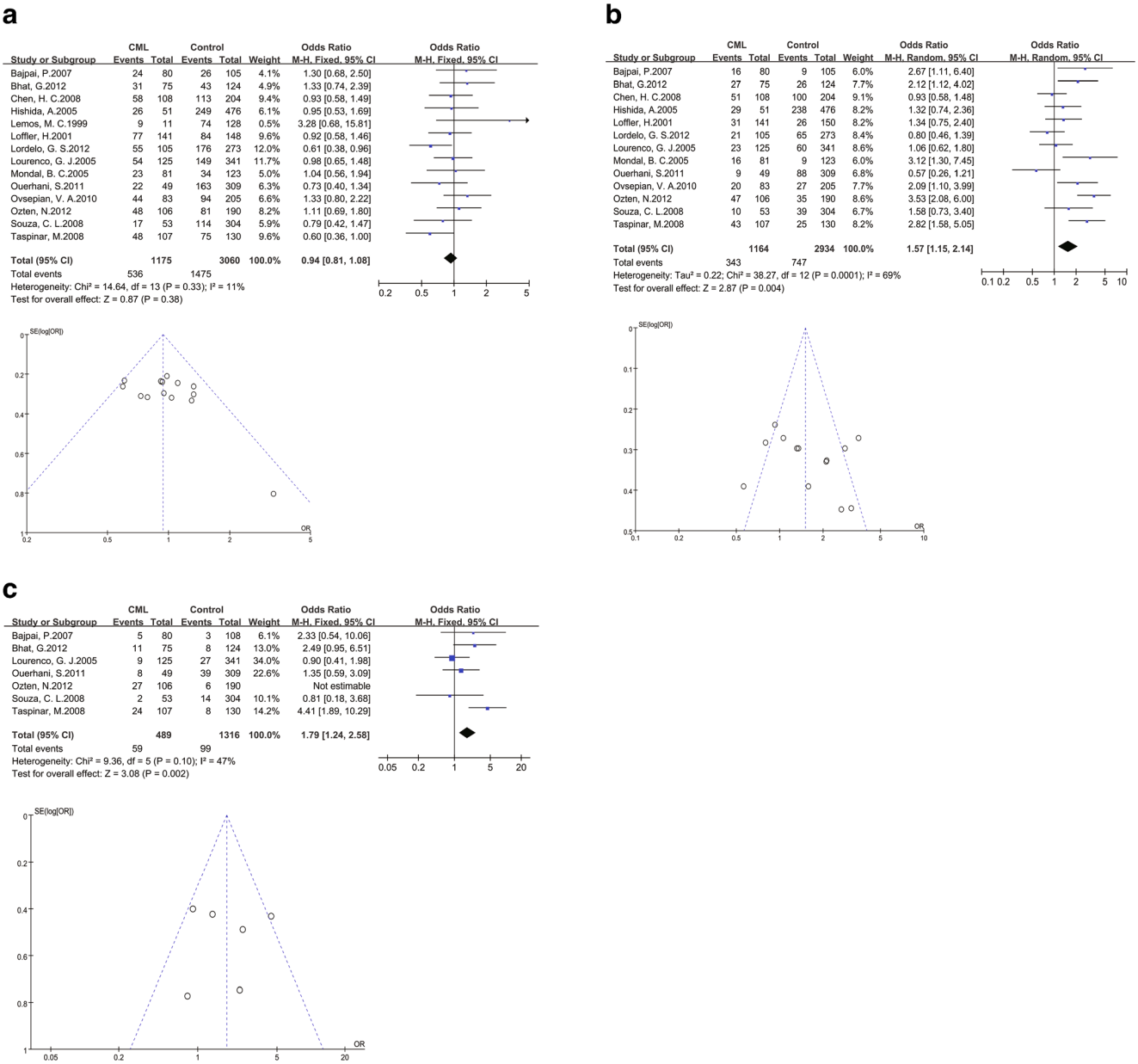


**Fig. 2** Odds ratio (OR) estimates with the corresponding 95 % confidence interval (CI) for **a** *GSTM1* null vs. *GSTM1* presence genotype contrast, **b** *GSTT1* null vs. *GSTT1* presence genotype contrast, and **c** double null vs. not double null genotype contrast, and the risk of chronic myeloid leukemia (CML)

A meta-analysis similar to that presented herein was performed by Zintzaras et al. in 2009, who investigated the influence of *GSTM1* and *GSTT1* polymorphisms on the susceptibility to CML, with similar conclusions [34]. The contrast models for *GSTM1* and *GSTT1* polymorphisms were the same between the two studies of Zintzaras et al. and ours. The main differences between the two studies came from three sides. Firstly, the work of Zintzaras et al. assessed the association between the combined *GSTM1* null/*GSTT1* null genotype and the risk of developing CML relative to the *GSTM1* normal/*GSTT1* normal genotype and they got nonsignificant results, while our analysis used different contrast models of combined *GSTM1* null/*GSTT1* null genotype versus other genotype, and significant result was achieved that the double null genotype increased the risk of CML compared with other genotypes. Secondly, our study also considered the role of *GSTP1* Ile105Val SNP on the risk of CML, which was absent in the other study, although the meta-analysis was not available for the limitation of included studies. Thirdly, the literature search in the meta-analysis of Zintzaras et al. was conducted before 1 January 2009. Several more studies were published regarding the GST gene polymorphisms and

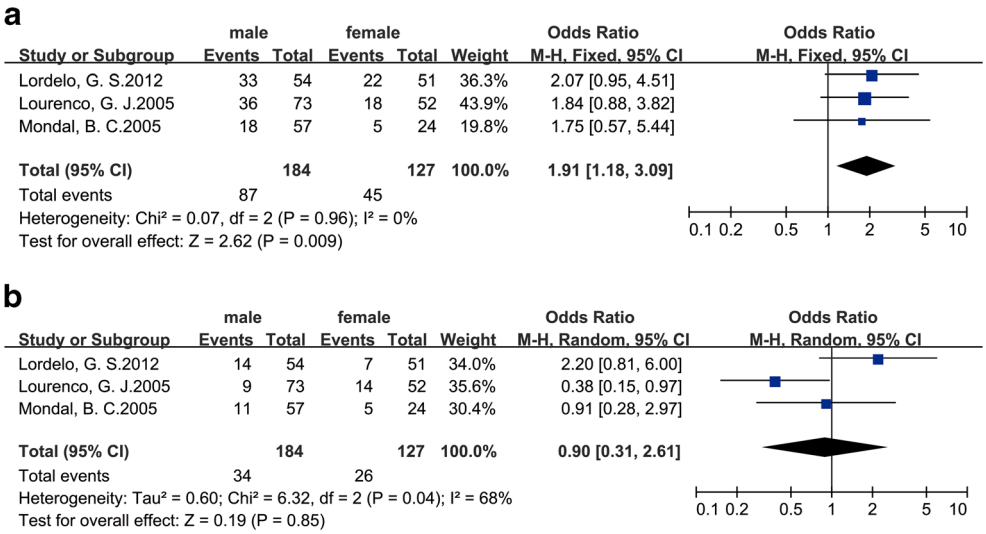


**Fig. 3** Distributions of *GSTM1* genotype (**a**) and *GSTT1* genotype (**b**) between male CML and female CML

susceptibility to CML. Therefore, the sample was larger (i.e., number of studies included), and thus, the statistical power was greater in our meta-analysis.

The results of this study have important practical significance. Individual genotypic differences and also the level of expression of carcinogen-metabolizing enzymes are crucial in determining the susceptibility of developing the cancer [32]. Although there is a considerable amount of research on this topic, the results have not received sufficient attention in clinical settings. The present meta-analysis revealed that the *GSTT1* and double null genotypes can significantly increase the risk of CML, while the *GSTM1* polymorphism had no effect on the susceptibility to CML. Thus, genotype testing is very important, since it can identify people who are carrying the risk genotypes that would make them more susceptible to CML induced by environmental carcinogens. If identified, these people will be able to take the necessary protective measures, which is particularly important for those with long-term exposure to environmental pollutants.

In this study, we just analyzed the role of phase II enzymes, based on the theory that individuals may be more or less susceptible to developing CML as a result of DNA variants in the genes encoding xenobiotic-metabolizing enzymes; we supposed phase I enzymes, mainly the cytochrome P450 (CYP) superfamily, might exert some effect on the risk of suffering CML. Several studies had been performed from that point, focusing on two genes: *CYP1A1* and *CYP2D6*. The study of Taspinar et al. revealed that persons carrying *CYP1A1* Val allele had an increased risk of CML [6], while no significant difference was observed between the healthy individuals and CML patients in the frequency of polymorphic variants of *CYP1A1* genes in the work of Ovsepian [24]. Another study researched both *CYP1A1* and *CYP2D6*, and the combined genotypes study of *CYP1A1* and *CYP2D6* was also performed. No significant results were found [18]. These controversial results did not support a clear association between the phase I enzyme gene polymorphisms and susceptibility to CML, and we hence suggested that further studies should be done in this respect.

Some problems arose during the process of data integration. First, the number of studies included in some meta-analyses was low, as was the number of cases. It is recognized that sample size plays an important role in predicting the association between genotypes and risk of cancer in case–control studies. Therefore, the inclusion of studies with very small samples may lead to an overestimation of the true association [35]. The results of meta-analyses that are based on relatively small numbers of studies should be interpreted with caution. In addition, there was some heterogeneity between several of the studies as a result of uncontrolled confounding factors and internal selection bias. Heterogeneity cannot be avoided. We solve this problem by adopting sensitivity analysis and the random effects model. The former reduced the heterogeneity among studies, and the latter fully allowed for the diversity between studies. Meanwhile, two limitations of this meta-analysis should be considered when interpreting its findings. First, the results were based on unadjusted estimates; a more precise analysis should be conducted using data from individuals, which would allow researchers to adjust for covariates including age, ethnicity, family history, environmental factors, and lifestyle. Second, only published studies were included in this meta-analysis. There is always a certain degree of publication bias, and nonsignificant or negative findings may be unpublished.

In summary, although studies investigating the association between GST gene polymorphisms and the risk of CML arrive at different conclusions, this meta-analysis suggests that the *GSTT1* null genotype is a risk factor for CML. Other studies

will need to be conducted to investigate the relationship between the SNPs within the phase I enzyme gene and *GSTP1* and CML susceptibility.

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**Conflicts of interest** None

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