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Association between *GSTP1* Ile105Val polymorphism and urinary system cancer risk: evidence from 51 studies

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Abstract: The *GSTP1* gene plays an important role in detoxification of carcinogens. *GSTP1* gene polymorphisms may alter the susceptibility of urinary system cancer. Numerous studies have been performed to investigate the association between *GSTP1* Ile105Val (rs1695 A>G) polymorphism and urinary system cancer risk. Nevertheless, the results remain controversial and only prostate cancer and bladder cancer are covered. We identified eligible studies from PubMed, Elsevier, and three equivalent Chinese databases including the Chinese National Knowledge Infrastructure, Wanfang, and Weipu. Pooled odds ratios and 95% confidence intervals were used to assess the strength of the association between *GSTP1* Ile105Val polymorphism and urinary system cancer risk. In total, 11,762 cases and 15,150 controls from 51 studies were included in the final meta-analysis. The pooled results from all included studies showed a statistically significant association between *GSTP1* Ile105Val polymorphism and urinary system cancer. In the subgroup analyses, the *GSTP1* Ile105Val polymorphism was found to be significantly associated with prostate cancer risk and also a risk factor for urinary system cancer among Asians. In conclusion, our meta-analysis indicated that *GSTP1* Ile105Val polymorphism was associated with urinary system cancer susceptibility, which needs to be validated by more rigorous data from further large-scale population studies with different ethnicities.

Keywords: *GSTP1*, polymorphism, urinary system cancer, susceptibility, meta-analysis

Introduction

Urinary system cancer such as prostate cancer (PCa) and bladder cancer (BC) constitutes an enormous burden on the society in many countries.[1] PCa is the fifth leading cause of cancer death worldwide, with an estimated 1.1 million new cases reported in 2012.[1] Although BC incidence rates, on the other hand, have been declining or stable in some Western countries, the death rates still remain very high, eg, an estimated 429,800 new cases of BC and 165,100 deaths occurred in 2012 worldwide.[1] In addition to the environmental factors such as smoking, being overweight, and physical inactivity,[2,3] genetic factors also play an important role in the carcinogenesis of urinary system cancer.[4,5]

Glutathione S-transferases (GSTs) are members of a super family of genes the gene products of which are the most important Phase II metabolizing enzymes.[6,7] These enzymes catalyze a variety of potentially carcinogenic electrophonic compounds.[8,9] Therefore, *GST* genes and enzymes are considered to be involved in susceptibility to tumor formation. In humans, the GSTs super family has been categorized into eight distinct gene families: α, μ, κ, π, σ, ω, θ, and ζ.[10] The *GSTP1* gene, located on chromosome 11q13, belongs to the π gene family.[11] The *GSTP1* Ile105Val (rs1695 A>G) polymorphism may cause a substitution of

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isoleucine for valine at codon 105 in the protein, leading to substantial reduction in *GSTP1* enzyme activity and its capability of detoxification of carcinogens.[12]

Previous published studies investigating the association between *GSTP1* Ile105Val polymorphism and susceptibility to urinary system cancer reported controversial results. For instance, some studies suggest that the association between *GSTP1* Ile105Val polymorphism and PCa or BC susceptibility is significant,[13–15] whereas others suggest little or no association.[16,17] Moreover, no review on other types of urinary system cancer such as renal cell carcinoma (RCC) has been published. Hence, we performed a meta-analysis of 51 publications covering 11,762 cases and 15,150 controls to get a clearer overall picture of the effect of *GSTP1* Ile105Val polymorphism on the risk of urinary system cancer.

Materials and methods

Search strategies

We conducted a comprehensive literature search on PubMed, Elsevier, and three Chinese equivalents, including the Chinese National Knowledge Infrastructure, Wanfang, and Weipu databases (1999 to January 8, 2016), using the following keywords and free text words: "glutathione S-transferase P1 or GSTP1 or GSTP1|105V or Ile105Val or A313G", and "polymorphism or variant or variation" and "prostate or bladder or urocyst or urotheli* or renal or urinary". No language restriction was set. The reference lists of all eligible studies were searched manually to ascertain additional undetected published studies.

Inclusion and exclusion criteria

Studies were eligible for inclusion in this meta-analysis study when they met the following criteria: 1) studies evaluating the association between *GSTP1* Ile105Val polymorphism and urinary system cancer, ie, PCa, BC, and RCC; 2) case–control studies; 3) studies with a 95% confidence interval (CI) for risk ratio or odds ratio (OR) or with sufficient data to calculate these numbers.

We excluded review articles, conference abstracts, case reports, and editorials. When two or more articles shared the same study data or were published in both English and Chinese sources, we excluded the ones published earlier or in Chinese.

Data extraction

Two authors (Yixiang Zhang and Yeqing Yuan) extracted the following information independently from all eligible studies: first author, publication year, the country of origin, ethnicity of the study population, cancer type, source of controls, genotyping methods, and number of cases and controls with different *GSTP1* Ile105Val genotypes (AA, AG, and GG). Any disagreements were resolved by discussions between the two authors until consensus was reached.

Statistical analysis

Effect of heterogeneity was quantified with the I^2 statistic that measures the degree of between-study inconsistency. I^2 ranges between 0% and 100% with higher values indicating a greater degree of heterogeneity.[18] Random-effects model was chosen when the *P*-value of the heterogeneity test was <0.1 or $I^2>25\%$, otherwise, the fixed-effects model was selected to calculate the pooled-effect estimates. Subgroup analyses were performed on the basis of cancer type, source of controls, and ethnicity. Publication bias was assessed by visual inspection of funnel plots, the Begg's rank correlation method, and the Egger's weighted regression method. The overall analysis and stratified analysis were performed with STATA software (Version 11, StataCorp LP, College Station, TX, USA). $P<0.05$ was considered statistically significant.

Results

Study characteristics

As shown in Figure 1, a total of 51 eligible studies met the inclusion criteria after abstract and full-text assessment. In total, 11,762 cases and 15,150 controls were included in the pooled analyses. Of all the 51 included studies, there was one study about two types of cancer and thus there were totally 52 data points: 27 about PCa, 19 about BC, and six about RCC. The characteristics of the included studies are summarized in Table S1.

Meta-analyses results

The pooled results based on all the studies showed a statistically significant association between *GSTP1* Ile105Val (rs1695 A>G) polymorphism and urinary system cancer (Table 1). The association was most apparent for the genotype GG (GG vs AA: OR =1.34, 95% CI =1.13–1.59; Figure S1). The tests for heterogeneity between eligible studies on different genotypes were significant (Table 1); thus, the random-effects model was performed for the data analysis of studies on a certain genotype.

For each genotype, we performed subgroup analysis. When stratifying by cancer type, the ORs for *GSTP1* Ile105Val polymorphism were only significant in the analysis on PCa (GG vs AA: OR =1.39, 95% CI =1.10–1.76; GG vs AA + AG: OR =1.28, 95% CI =1.05–1.56; AG + GG vs

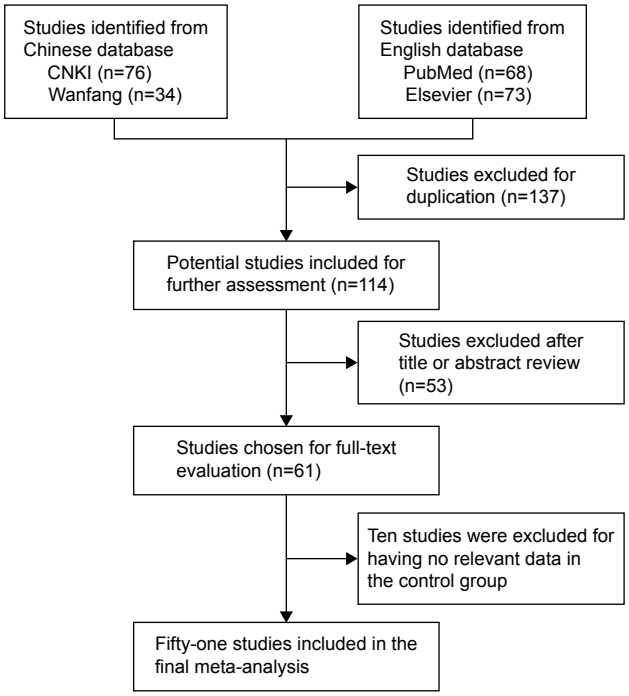

Figure 1 Flowchart of 51 studies included in the meta-analysis.

AA: OR =1.24, 95% CI =1.04–1.49). When stratifying by the source of controls, we found a significant difference between *GSTP1* Ile105Val and urinary system cancer risk in studies with hospital-based controls (Table 1). When stratifying by ethnicity, the significant association between *GSTP1* Ile105Val polymorphism and urinary system cancer risk was only identifiable in the analysis among Asians, in which *GSTP1* Ile105Val GG variant showed a marked increase in urinary system cancer risk compared to individuals carrying AA or AG genotype (Table 1).

Based on the results from Begg's rank correlation method and Egger's weighted regression method, we found that there was no evidence of publication bias in *GSTP1* Ile105Val polymorphism studies (Table 2).

Discussion

The current meta-analysis, including 11,762 cases and 15,150 controls from 51 published studies, evaluated the association between *GSTP1* Ile105Val polymorphism and urinary system cancer risk. To the best of our knowledge, this meta-analysis is the latest and largest one to explore *GSTP1* Ile105Val (rs1695 A>G) polymorphism in the development of urinary system cancer. We found that *GSTP1* Ile105Val polymorphism was significantly associated with the risk of urinary system cancer, and the association was even more evident for the genotype of *GSTP1* Ile105Val GG genotype in studies with PCa and Asians.

Table 1 Meta-analysis of the association between *GSTP1* Ile105Val (rs1695 A>G) polymorphism and the risk of urinary system cancer

Variables	GG vs AA			AG vs AA			GG vs AG			GG vs (AG + AA)			(AG + GG) vs AA		
	OR (95% CI)	I^2 (%)	P^{het}	OR (95% CI)	I^2 (%)	P^{het}	OR (95% CI)	I^2 (%)	P^{het}	OR (95% CI)	I^2 (%)	P^{het}	OR (95% CI)	I^2 (%)	P^{het}
All	**1.34 (1.13–1.59)**	66.1	<0.001	**1.15 (1.03–1.29)**	73.8	<0.001	**1.17 (1.02–1.34)**	44.4	<0.001	**1.26 (1.09–1.46)**	57.5	<0.001	**1.19 (1.07–1.33)**	76.9	<0.001
Cancer types															
Prostate	**1.39 (1.10–1.76)**	65.3	<0.001	1.19 (0.99–1.42)	81.1	<0.001	1.15 (0.97–1.37)	35.7	0.036	**1.28 (1.05–1.56)**	54.6	<0.001	**1.24 (1.04–1.49)**	83.0	<0.001
Bladder	1.36 (0.98–1.90)	71.0	<0.001	1.12 (0.95–1.31)	59.6	<0.001	1.25 (0.94–1.66)	59.4	0.001	1.30 (0.97–1.74)	66.2	<0.001	1.16 (0.98–1.37)	65.6	<0.001
RCC	1.10 (0.71–1.71)	59.9	0.041	1.06 (0.88–1.29)	40.2	0.137	1.11 (0.86–1.42)	5.8	0.374	1.08 (0.77–1.53)	41.9	0.142	1.07 (0.86–1.33)	56.2	0.044
Source of controls															
HB	**1.39 (1.11–1.73)**	65.4	<0.001	**1.21 (1.05–1.39)**	71.7	<0.001	1.15 (0.97–1.38)	46.5	0.003	**1.27 (1.05–1.54)**	57.9	<0.001	**1.26 (1.09–1.44)**	74.8	<0.001
PB	1.26 (0.94–1.69)	68.6	<0.001	1.07 (0.89–1.28)	76.3	<0.001	1.20 (0.97–1.49)	43.1	0.022	1.23 (0.97–1.57)	59.0	<0.001	1.10 (0.91–1.32)	79.6	<0.001
Ethnicity															
Asian	**1.96 (1.30–2.95)**	58.6	0.002	1.29 (0.91–1.82)	85.5	<0.001	**1.53 (1.20–1.95)**	0.0	0.655	**1.79 (1.32–2.43)**	32.4	0.109	1.38 (0.98–1.96)	0.870	<0.001
Caucasian	1.21 (0.97–1.51)	66.8	<0.001	**1.14 (1.01–1.27)**	59.8	<0.001	1.08 (0.89–1.32)	58.1	<0.001	1.15 (0.94–1.40)	62.7	<0.001	**1.15 (1.03–1.29)**	0.637	<0.001
African	1.51 (0.96–2.37)	–	–	1.05 (0.71–1.55)	–	–	1.44 (0.95–2.17)	–	–	1.47 (1.00–2.15)	–	–	1.18 (0.83–1.69)	–	–

Note: Results in bold are significant findings.
Abbreviations: CI, confidence interval; GSTP1, glutathione S-transferase P1; HB, hospital-based; OR, odds ratio; PB, population based; RCC, renal cell carcinoma; het, heterogeneity.

Table 2 Statistical analysis of publication bias

Genotype	Begg	*P*-value	Egger	*P*-value
AG vs AA	1.33	0.18	−1.37	0.18
GG vs AA	1.46	0.14	−1.34	0.19
GG vs AG	0.29	0.77	−0.28	0.78
GG vs AA + AG	0.54	0.59	−0.88	0.38
AG + GG vs AA	1.81	0.07	−1.63	0.11

Previous meta-analyses on the association between *GSTP1* Ile105Val polymorphism and PCa risk were contradicting. Two studies found that *GSTP1* Ile105Val polymorphism was significantly associated with PCa risk, with further subgroup analyses identifying significant association among Caucasians rather than Asians and African Americans.[13,14] However, another meta-analysis with a total of 5,301 cases and 5,621 controls by Mo et al[16] concluded no association between *GSTP1* Ile105Val polymorphism and the risk of PCa. The results of the current study show that there is indeed significant association between *GSTP1* Ile105Val polymorphism and PCa risk, but only among Asians, as suggested in the subgroup analyses of our study.

The results of the current study show that *GSTP1* Ile105Val polymorphism is not significantly associated with BC risk, which is consistent with the finding of a meta-analysis by Kellen et al[17] that *GSTP1* Ile105Val polymorphism was not strongly associated with BC risk. However, Wu et al[15] found that a specific genotype of *GSTP1* 313GG genotype was a strong predisposing risk factor for BC, while as for in our study, the specific genotype of *GSTP1* 313GG polymorphism is only associated with PCa.

As there are very few studies on the association between *GSTP1* Ile105Val polymorphism and RCC, we only identified five studies in the current meta-analysis. Results of our meta-analysis show that *GSTP1* Ile105Val polymorphism is not significantly associated with RCC risk, but the estimation may not be precise because of the paucity of data. More studies with large samples in different ethnicities are needed to provide more accurate estimation of the effect of *GSTP1* Ile105Val polymorphism on RCC.

Before concluding this report, we should admit some limitations in this study. First, our results were based on unadjusted estimates due to the missing of individual data on lifestyles and environmental exposure such as smoking status and alcohol consumption. These lifestyle and environmental factors had been reported to play an important role in the development of urinary system cancer. Second, the sample size is not always large enough to provide precise estimation. For instance, the subgroup analyses regarding RCC might have insufficient statistical power to reveal the real association.

Conclusion

Despite the limitations, our meta-analysis indicated that *GSTP1* Ile105Val polymorphism may be associated with urinary system cancer susceptibility. Further large-scale population studies with different ethnicities should be conducted to provide more rigorous data to validate our findings.

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Disclosure

The authors report no conflicts of interest in this work.

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