

RESEARCH COMMUNICATION

The GSTT1 Null Genotype Contributes to Increased Risk of Prostate Cancer in Asians: a Meta-analysis

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Abstract

Background: Many studies have investigated the association between glutathione S-transferase T 1 (GSTT1) null genotype and risk of prostate cancer, but the impact of GSTT1 null genotype in Asians is still unclear owing to inconsistencies across results. This present meta-analysis aimed to quantify the strength of the association between GSTT1 null genotype and risk of prostate cancer. **Methods:** We searched the PubMed, Embase and Wangfang databases for studies of associations between the GSTT1 null genotype and risk of prostate cancer in Asians and estimated summary odds ratio (OR) with their 95% confidence interval (95% CI). **Results:** A total of 11 case-control studies with 3,118 subjects were included in this meta-analysis, which showed the GSTT1 null genotype to be significantly associated with increased risk of prostate cancer in Asians (random-effects OR = 1.49, 95% CI 1.15-1.92, P = 0.002), also after adjustment for heterogeneity (fixed-effects OR = 1.45, 95% CI 1.23-1.70, P < 0.001). No evidence of publication bias was observed. **Conclusions:** This meta-analysis of available data suggested the GSTT1 null genotype does contribute to increased risk of prostate cancer in Asians.

Keywords: Prostate cancer - GSTT1 - meta-analysis - polymorphism

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Introduction

Prostate cancer is one of the most frequently diagnosed malignancies a common cause of cancer mortality in men (Jemal et al., 2011). In developed countries, prostate cancer is the second most frequently diagnosed cancer, and the third most common cause of death from cancer in men (Damber and Aus, 2008). Identifying risk factors for prostate cancer is critically important to develop potential interventions and to expand our understanding of the biology of this disease (Foulkes, 2008; Hoffman, 2011). Despite the fact that the complex etiology of prostate cancer remains obscure, various risk factors play an important role in prostate cancer development such as advanced age, environmental variations, and genetic variations (Foulkes, 2008; Hoffman, 2011). The Glutathione S-Transferases (GSTs) are the most important family of phase II isoenzymes known to detoxify a variety of electrophilic compounds, including carcinogens, chemotherapeutic drugs, environmental toxins, and DNA products generated by reactive oxygen species, chiefly by conjugating them with glutathione (Hayes et al., 2005). In addition to this role in phase II detoxification, GSTs are able to modulate the induction of other enzymes and proteins important for cellular functions, such as DNA repair (Hayes et al., 2005). The Theta class of GSTs is encoded by the GSTT1 gene, which is mapped to chromosome 22q11.23 and contains six exons (Hayes et al., 2005). Among the numerous GST genes,

GSTT1 polymorphism has been extensively examined in association with risk of various diseases (Hayes and Strange, 2000). The most common variant of GSTT1 gene is homozygous deletion (null genotype), which has been suggested to be associated with the loss of enzyme activity, increased vulnerability to cytogenetic damage and oxidative DNA damage and resulted in the susceptibility to prostate cancer (Hayes and Strange, 2000). Many studies have investigated the association between GSTT1 null genotype and risk of prostate cancer, but the impact of GSTT1 null genotype on prostate cancer in Asians was still unclear owing to the obvious inconsistency among those studies (Murata et al., 2001; Nakazato et al., 2003; Mittal et al., 2004; Komiya et al., 2005; Srivastava et al., 2005; Kwon et al., 2011). This study aimed to quantify the strength of association between GSTT1 null genotype and risk of prostate cancer.

Materials and Methods

Search strategy

We conducted a comprehensive search of the PubMed, Embase and Wangfang databases from its inception through January 2012. We combined search terms for GSTT1 polymorphism and CHD. Search terms included GSTT, GSTT1, glutathione S-transferase T1; and prostate cancer. There was no language limitation. The retrieved studies were manually screened in their entirety to assess their appropriateness for eligibility criteria. All references

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cited in the studies were also reviewed to identify additional published articles not indexed in the common database.

Study eligibility

Eligibility criteria included the following: (i) Case-control design with the genotyping of men with and without prostate cancer; (ii) provided information on genotype frequency. In studies with overlapping cases or controls, the most recent and/or the largest study with extractable data was included in the meta-analysis. Studies investigating progression, severity, phenotype modification, response to treatment, or survival were excluded from this review. Genome scans investigate linkages and were also excluded. In addition, family-based association studies were excluded because they use different study designs.

Data extraction

Two investigators independently extracted data, and disagreements were resolved through consensus. The extracted data included the year of publication, ethnicity of the study population, inclusion criteria for prostate cancer patients and normal controls, demographics, matching, clinical status of controls, genotyping method, and the genotype distribution of cases and controls for the GSTT1 polymorphism. The frequencies of GSTT1 null genotype were extracted or calculated for cases and controls. All data were extracted from published articles, and we did not contact individual authors for further information.

Statistical analysis

We calculated the overall odds ratio (OR) with the corresponding 95% confidence interval (CI) to assess the strength of the association between GSTT1 null genotype and risk of prostate cancer. The significance of the pooled OR was determined by the Z test and a p value of less than 0.05 was considered significant. In our study, two models of meta-analysis for dichotomous outcomes were conducted: the random-effects model and the fixed-effects model (Mantel and Haenszel, 1959; DerSimonian and Laird, 1986). The random-effects model was conducted using the DerSimonian and Laird's method, which assumed that studies were taken from populations with varying effect sizes and calculated the study weights both from in-study and between-study variances (DerSimonian and Laird, 1986). The fixed-effects model was conducted using the Mantel-Haenszel's method, which assumed that studies were sampled from populations with the same effect size and made an adjustment to the study weights according to the in-study variance (Mantel and Haenszel, 1959). To assess the between-study heterogeneity more precisely, both the chi-square based Q statistic test (Cochran's Q statistic) to test for heterogeneity and the I² statistic to quantify the proportion of the total variation due to heterogeneity were calculated (Cochran, 1954; Higgins et al., 2003). The I² index expressing the percentage of the total variation across studies due to heterogeneity was calculated to assess the between-study heterogeneity. I² values of 25%, 50%, and 75% were used as evidence of low, moderate, and high heterogeneity, respectively

(Higgins et al., 2003). If moderate or high heterogeneity existed, the random-effects model was used to pool the results; otherwise, the fixed-effects model was used to pool the results when I² value was less than 50%. Besides, Galbraith plot was also used to spot the outlier as the possibly major source of between-study heterogeneity (Galbraith, 1988). To validate the credibility of outcomes in this meta-analysis, sensitivity analysis was performed by sequential omission of individual studies or by omitting studies without high quality (Tobias, 1999). Publication bias was investigated by Begg's funnel plot, in which the standard error of logor of each study was plotted against its logor, and an asymmetric plot suggested possible publication bias (Stuck et al., 1998). In addition, funnel-plot's asymmetry was assessed by the method of Egger's linear regression test (Egger et al., 1997). All analyses were performed using STATA version 12.0 (StataCorp LP, College Station, Texas). A P value < 0.05 was considered statistically significant, except where otherwise specified.

Results

Study selection

With our search criterion, 67 individual records were found, and 11 studies with a total of 3,118 subjects were finally included into this meta-analysis (Murata et al., 2001; Nakazato et al., 2003; Mittal et al., 2004; Komiya et al., 2005; Srivastava et al., 2005; Mittal et al., 2006; Yang et al., 2006; Ashtiani et al., 2011; Kumar et al., 2011; Kwon et al., 2011; Thakur et al., 2011). All included studies were English language literature. Among these 11 case-control studies, 6 (75.0%) were from India (Mittal et al., 2004; Srivastava et al., 2005; Mittal et al., 2006; Ashtiani et al., 2011; Kumar et al., 2011; Thakur et al., 2011), and 3 (12.5%) were from Japan (Murata et al., 2001; Nakazato et al., 2003; Komiya et al., 2005), 1 from Korea (Kwon

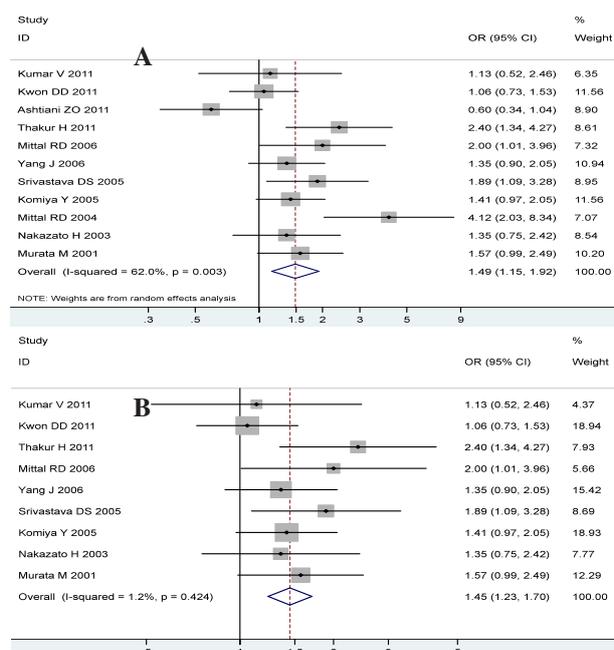


Figure 1. Forest Plots Showed Obvious Association Between GSTT1 Null Genotype and Prostate Cancer. (A) Analysis of total 11 studies. (B) Analysis of 9 studies after adjustment for heterogeneity

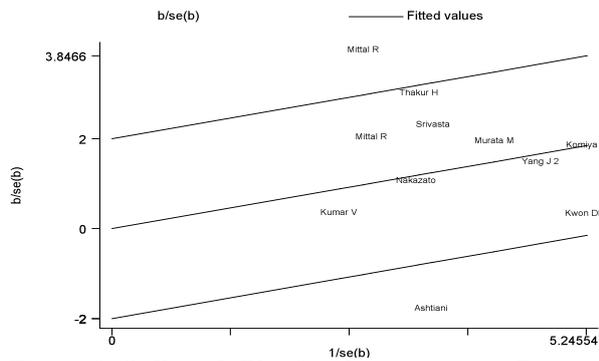


Figure 2. Galbraith Plot for the Association Between GSTT1 Null Genotype and Prostate Cancer Risk

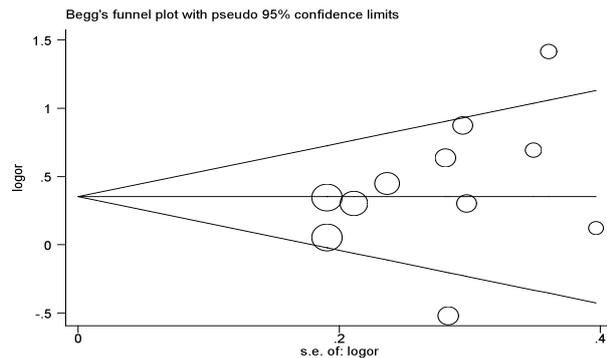


Figure 3. Begg's Funnel Plots for Assessing the Publication Bias Risk (P Egger = 0.268)

et al., 2011) and 1 from China (Yang et al., 2006). The number of cases varied from 54 to 186, with a mean of 119, and the numbers of controls varied from 46 to 327, with a mean of 164.

Main results

There was obvious between study heterogeneity among those total 11 studies ($I^2 = 62.0\%$), thus the random-effects model was used to pool data. Meta-analysis showed that GSTT1 null genotype was obviously associated with increased risk of prostate cancer in Asians (random-effects OR = 1.49, 95% CI 1.15-1.92, $P = 0.002$) (Figure 1-A). Sensitivity analyses by omitting those studies also did not materially alter the overall combined ORs.

For meta-analysis of total studies, two studies (Mittal et al., 2004; Ashtiani et al., 2011) were spotted by Galbraith plot as possible major sources of heterogeneity (Figure 2). There was no obvious between study heterogeneity among those remained 9 studies ($I^2 = 1.2\%$), thus the fixed-effects model was used to pool the ORs. Meta-analysis showed GSTT1 null genotype was associated increased risk of prostate cancer in Asians (fixed-effects OR = 1.45, 95% CI 1.23-1.70, $P < 0.001$) (Figure 1-B). Sensitivity analyses by omitting those studies also did not materially alter the overall combined ORs.

Publication bias

Begg's funnel and Egger's test were performed to access the publication bias in this meta-analysis. Funnel plots' shape did not reveal obvious evidence of asymmetry, and the P value of Egger's test was 0.268 (>0.05), providing statistical evidence of funnel plots' symmetry (Figure 3). Thus, the results above suggested that publication bias was not evident in this meta-analysis.

Discussion

Previous studies investigating the association between GSTT1 polymorphism and prostate cancer risk provided inconsistent results, and most of those studies involved no more than a few hundred prostate cancer cases, which were too few to assess any genetic effects reliably. Meta-analysis has been recognized as an important tool to more precisely define the effect of selected genetic polymorphisms on risk of disease and to identify potentially important sources of between-study heterogeneity (Petitti, 2000; Attia et al., 2003). Hence, to provide the most comprehensive assessment of the association between GSTT1 null genotype and prostate cancer risk in Asians, we performed this meta-analysis of all available studies. At last, we performed this meta-analysis by critically reviewing 11 individual case-control studies with a total of 3,118 subjects. Meta-analysis of total 11 studies showed GSTT1 null genotype was obviously associated with increased risk of prostate cancer in Asians (random-effects OR = 1.49, 95% CI 1.15-1.92, $P = 0.002$). After adjustment for heterogeneity, meta-analysis showed GSTT1 null genotype was associated increased risk of prostate cancer in Asians (fixed-effects OR = 1.45, 95% CI 1.23-1.70, $P < 0.001$). No evidence of publication bias was observed. Thus, meta-analyses of available data suggest the GSTT1 null genotype contributes to increased risk of prostate cancer in Asians.

Heterogeneity is a potential problem when interpreting the results of all meta-analyses, and finding of the sources of heterogeneity is one of the most important goals of meta-analysis (Ioannidis et al., 2007). In this present meta-analysis, we found obvious heterogeneity in the meta-analysis of total 11 studies ($I^2 = 62.0\%$). Studies with low quality design usually don't exclude those possible factors that may bias the estimate of the real effects, and may result in incorrect conclusions (Attia et al., 2003; Ioannidis et al., 2007; Guyatt et al., 2011). Since the findings from studies with low quality design often deviate obviously from that from studies with high quality design, Galbraith plot was used to spot the outliers as the possible studies with low quality design and sensitivity analysis was further performed by omitting studies spotted by Galbraith plot's method as the outliers. or meta-analysis of total studies, two studies (Mittal et al., 2004; Ashtiani et al., 2011) were spotted by Galbraith plot as possible major sources of heterogeneity (Figure 2). There was no obvious between study heterogeneity among those remained 9 studies ($I^2 = 1.2\%$), and meta-analysis showed GSTT1 null genotype was associated increased risk of prostate cancer in Asians (fixed-effects OR = 1.45, 95% CI 1.23-1.70, $P < 0.001$). Thus, the outcomes above provide further evidence for the association between GSTT1 null genotype and increased risk of prostate cancer in Asians.

GSTs are the most important family of phase II isoenzymes known to detoxify a variety of electrophilic compounds, including carcinogens, chemotherapeutic drugs, environmental toxins, and DNA products generated by reactive oxygen species, chiefly by conjugating them with glutathione (Hayes et al., 2005). In addition to this

role in phase II detoxification, GSTs are able to modulate the induction of other enzymes and proteins important for cellular functions, such as DNA repair (Hayes et al., 2005). GSTT1 null genotype has been suggested to be associated with the loss of enzyme activity, increased vulnerability to cytogenetic damage and oxidative DNA damage and resulted in the susceptibility to prostate cancer (Hayes and Strange, 2000). Thus, there is obvious biological evidence for the association between GSTT1 null genotype and the susceptibility to prostate cancer.

Some possible limitations in this meta-analysis should be acknowledged. Firstly, the eligibility criteria for inclusion of controls were different from each other. The controls in some studies were selected from asymptomatic healthy individuals, while the controls in other several studies were selected from non-cancer individuals. Additionally, misclassification bias was possible. For example, most studies could not exclude latent prostate cancer cases in the controls. Finally, gene-environmental and gene-gene interactions were not fully addressed in this meta-analysis for the lack of sufficient data. Further studies can assess the possible gene-environmental and gene-gene interactions in the association between gene polymorphisms and prostate cancer risk.

Despite of those limitations, this meta-analysis suggests GSTT1 null genotype contributes to increased risk of prostate cancer in Asians. Further studies are needed to further assess the possible gene-environmental or gene-gene interactions in the association between gene polymorphisms and prostate cancer risk.

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The author(s) declare that they have no competing interests.

References

Ashtiani ZO, Hasheminasab SM, Ayati M, et al (2011). Are GSTM1, GSTT1 and CAG repeat length of androgen receptor gene polymorphisms associated with risk of prostate cancer in Iranian patients? *Pathol Oncol Res*, **17**, 269-75.

Attia J, Thakkestian A, D'Este C (2003). Meta-analyses of molecular association studies: methodologic lessons for genetic epidemiology. *J Clin Epidemiol*, **56**, 297-303.

Cochran WG (1954). The combination of estimates from different experiments. *Biometrics*, **10**, 101-29.

Damber JE, Aus G (2008). Prostate cancer. *Lancet*, **371**, 1710-21.

DerSimonian R, Laird N (1986). Meta-analysis in clinical trials. *Control Clin Trials*, **7**, 177-88.

Egger M, Davey Smith G, Schneider M, et al (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ*, **315**, 629-34.

Foulkes WD (2008). Inherited susceptibility to common cancers. *N Engl J Med*, **359**, 2143-53.

Galbraith RF (1988). A note on graphical presentation of estimated odds ratios from several clinical trials. *Stat Med*, **7**, 889-94.

Guyatt G, Oxman AD, Akl EA, et al (2011). GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*, **64**, 383-94.

Hayes JD, Flanagan JU, Jowsey IR (2005). Glutathione transferases. *Annu Rev Pharmacol Toxicol*, **45**, 51-88.

Hayes JD, Strange RC (2000). Glutathione S-transferase polymorphisms and their biological consequences. *Pharmacology*, **61**, 154-66.

Higgins JP, Thompson SG, Deeks JJ, et al (2003). Measuring inconsistency in meta-analyses. *BMJ*, **327**, 557-60.

Hoffman RM (2011). Clinical practice. Screening for prostate cancer. *N Engl J Med*, **365**, 2013-9.

Ioannidis JP, Patsopoulos NA, Evangelou E (2007). Uncertainty in heterogeneity estimates in meta-analyses. *BMJ*, **335**, 914-6.

Jemal A, Bray F, Center MM, et al (2011). Global cancer statistics. *CA Cancer J Clin*, **61**, 69-90.

Komiya Y, Tsukino H, Nakao H, et al (2005). Human glutathione S-transferase A1, T1, M1, and P1 polymorphisms and susceptibility to prostate cancer in the Japanese population. *J Cancer Res Clin Oncol*, **131**, 238-42.

Kumar V, Yadav CS, Datta SK, et al (2011). Association of GSTM1 and GSTT1 polymorphism with lipid peroxidation in benign prostate hyperplasia and prostate cancer: a pilot study. *Dis Markers*, **30**, 163-9.

Kwon DD, Lee JW, Han DY, et al (2011). Relationship between the Glutathione-S-Transferase P1, M1, and T1 Genotypes and Prostate Cancer Risk in Korean Subjects. *Korean J Urol*, **52**, 247-52.

Mantel N, Haenszel W (1959). Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst*, **22**, 719-48.

Mittal RD, Mishra DK, Mandhani A (2006). Evaluating polymorphic status of glutathione-S-transferase genes in blood and tissue samples of prostate cancer patients. *Asian Pac J Cancer Prev*, **7**, 444-6.

Mittal RD, Srivastava DS, Mandhani A, et al (2004). Polymorphism of GSTM1 and GSTT1 genes in prostate cancer: a study from North India. *Indian J Cancer*, **41**, 115-9.

Murata M, Watanabe M, Yamanaka M, et al (2001). Genetic polymorphisms in cytochrome P450 (CYP) 1A1, CYP1A2, CYP2E1, glutathione S-transferase (GST) M1 and GSTT1 and susceptibility to prostate cancer in the Japanese population. *Cancer Lett*, **165**, 171-7.

Nakazato H, Suzuki K, Matsui H, et al (2003). Association of genetic polymorphisms of glutathione-S-transferase genes (GSTM1, GSTT1 and GSTP1) with familial prostate cancer risk in a Japanese population. *Anticancer Res*, **23**, 2897-902.

Petitti DB. (2000) Meta-analysis, decision analysis, and cost effectiveness analysis: methods for quantitative synthesis in medicine(2nded). New York, NY: *Oxford University Press*.

Srivastava DS, Mandhani A, Mittal B, et al (2005). Genetic polymorphism of glutathione S-transferase genes (GSTM1, GSTT1 and GSTP1) and susceptibility to prostate cancer in Northern India. *BJU Int*, **95**, 170-3.

Stuck AE, Rubenstein LZ, Wieland D (1998). Bias in meta-analysis detected by a simple, graphical test. Asymmetry detected in funnel plot was probably due to true heterogeneity. *BMJ*, **316**, 469.

Thakur H, Gupta L, Sobti RC, et al (2011). Association of GSTM1/T1 genes with COPD and prostate cancer in north Indian population. *Mol Biol Rep*, **38**, 1733-9.

Tobias A (1999). Assessing the influence of a single study in the meta-analysis estimate. *Stata Tech Bull*, **8**, 15-7.

Yang J, Wu HF, Zhang W, et al (2006). Polymorphisms of metabolic enzyme genes, living habits and prostate cancer susceptibility. *Front Biosci*, **11**, 2052-60.