Human Genome Epidemiology (HuGE) Review

GSTT1 Polymorphism and the Risk of Developing Prostate Cancer

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Initially submitted December 2, 2013; accepted for publication April 10, 2014.

A possible association between glutathione S-transferase theta 1 gene (GSTT1) polymorphism and the risk of developing prostate cancer is currently hotly debated, but evidence from various epidemiologic studies remains unclear. This investigation was performed to assess whether an association between GSTT1 polymorphism and prostate cancer risk exists by using meta-analysis to combine comparable studies, thereby increasing sample size and statistical significance, as well as to identify patterns in various studies. The association reports were identified from the PubMed database and the Cochrane Library on March 1, 2013, and data from eligible studies (from 1999–2012) were synthesized. Thirty-eight reports were included in this meta-analysis on the association of the null genotype of GSTT1 with prostate cancer risk. No solid association between the GSTT1 null genotype and prostate cancer risk could be established for the overall population (odds ratio = 1.11, 95% confidence interval: 0.97, 1.27; P = 0.13). However, the GSTT1 null genotype was distinctly associated with prostate cancer risk in Caucasians (odds ratio = 1.24, 95% confidence interval: 1.03, 1.48, P = 0.02). In conclusion, the GSTT1 null genotype is associated with prostate cancer risk in Caucasians, but not in the overall population.

gene polymorphism; glutathione S-transferase theta 1; meta-analysis; prostate cancer

Abbreviations: CI, confidence interval; GST, glutathione S-transferase; GSTT1, glutathione S-transferase theta 1 gene; OR, odds ratio.

Prostate cancer is a chronic, degenerative, and malignant disease of the prostate that predominantly affects men above the age of 50 years and generally requires a long period of development from an initial small lesion to clinical manifestation (1–3). The occurrence of prostate cancer varies widely across the world, with lower rates of incidence in Asia compared with Europe, Australia, and the United States (2, 4). Globally, prostate cancer is the sixth major cause of cancer-related death in men and the second in the United States (2, 4). Prostate cancer may remain organ confined indefinitely and in an indolent state. However, more aggressive forms occur, which either remain in situ or metastasize and then predominantly affect lymph nodes and bones. The molecular and biological behavior of this tumor type remains difficult to predict (5), and there is a distinct lack of well-documented diagnostic approaches for determining prostate cancer risk. Overall, the single most significant risk factor for prostate cancer is advanced age. However, prostate cancer cannot simply be considered a byproduct of aging. Nonetheless, aging-associated cellular changes are a result of the accumulation over time of changes (i.e., damage) induced by environmental, lifestyle, physiological, and molecular influences. In prostate cancer, aging-associated changes in gene expression have been described that include genes involved in oxidative stress, inflammation, and senescence (6–8), particularly in the prostate stroma.

The emergence of genomic medicine represents a shift from traditional medical genetics with its focus on rare genetic diseases toward more personalization in the practice of medicine and prevention of common diseases (9). Because current evidence indicates that polymorphisms involving various genes are associated with the susceptibility to developing particular diseases (10–13), scrutinizing the role of such polymorphisms in genes involved in oxidative stress and inflammation might be a sound strategy to determine prostate cancer risk. Glutathione S-transferases (GSTs) are a multigene family of isoenzymes, consisting of 16 genes encoding cytosolic proteins and at least 6 genes expressing...
membrane-associated proteins (14–16). GSTs are critical components of the phase II enzymatic detoxification of electrophilic xenobiotics, such as chemical carcinogens, environmental pollutants, and antitumor agents, as well as inactivate endogenous α, β-unsaturated aldehydes, quinones, epoxides, and hydroperoxides formed during oxidative stress (15–17). Furthermore, recent evidence has shown that GSTs modulate the signaling pathways of cell proliferation, cell differentiation, and apoptosis (18). An increasing number of GST genes are being recognized as polymorphic (14); particularly, those alleles that confer impaired catalytic activity may be associated with increased sensitivity to toxic compounds and, therefore, GST polymorphisms may be disease modifying (from an indolent to an aggressive state) and disease susceptibility enhancing. The glutathione S-transferase theta 1 gene (GSTT1), located on chromosome 22 (22q11), is one of the most important GST variants, and the GSTT1 enzyme is reported to catalyze the detoxification of ethylene oxide and methyl bromide, as well as other halogenated metabolites (19, 20). Dysfunction of this detoxification capacity has been implicated in the pathogenesis of various cancers, including prostate cancer. Several groups report that GSTT1 polymorphism (GSTT1 presence and GSTT1 null) is associated with an increased cancer risk, unresponsiveness to primary chemotherapy, and an increased risk of developing proximal disease (21–24). However, the epidemiologic evidence for an association between GSTT1 polymorphism and prostate cancer from investigations performed over the past few decades is turbid, predominantly because of heterogeneity in the data and study design or disagreements among the reported investigations. Evidence from an extensive meta-analysis might, therefore, shed more light on the association of GSTT1 polymorphism and prostate cancer and be more useful than data from individual investigations. Because of this murky picture, we performed the current meta-analysis to assess whether GSTT1 polymorphism is indeed associated with the risk of developing prostate cancer and how this risk is distributed with respect to ethnicity.

METHODS

Search strategy for the association of GSTT1 polymorphism with the risk of prostate cancer

Relevant studies were extracted from the PubMed and Cochrane Library electronic databases on March 1, 2013. The retrieval string entered into these databases was “(glutathione S-transferase T1 OR GSTT1 OR GSTT) AND (prostate cancer OR prostate carcinoma).” Additional reports were identified by scrutinizing the references cited in the identified articles.

Inclusion and exclusion criteria

For inclusion, the study outcome had to be prostate cancer, there had to be at least 2 comparison groups (case group vs. control group), and the investigation had to provide data on the GSTT1 genotype distribution. We excluded review articles, editorials, case reports, studies with preliminary results not on GSTT1 polymorphism or outcome, and investigations of the role of GSTT1 expression related to disease. If multiple publications based on the same data from the same study group occurred, we included only the most recently published paper in our final analysis.

Data extraction and synthesis

The following information from each eligible study was extracted independently by 2 investigators (T.-B.Z. and Z.-P.J.): first author’s surname, year of publication, location of the study, subjects’ ethnicity, source of the control group, and the number of cases and controls for the GSTT1 genotype. The results were compared and disagreements were resolved by discussion (with Y.-H.Q.).

Statistical analysis

Cochrane Review Manager, version 5, software (Cochrane Library, London, United Kingdom) was used to calculate the available data from each study. The pooled statistics were counted using a fixed-effects model, but a random-effects model was used when the P value of the heterogeneity test was less than 0.1 (25). Results were expressed with odds ratios for dichotomous data, and 95% confidence intervals were calculated (26). A P value of less than 0.05 was required for the pooled odds ratio to be considered statistically significant (27). The I² statistic was used to test the heterogeneity

Figure 1. Flow chart for study recruitment into the meta-analysis of the glutathione S-transferase theta 1 gene (GSTT1) polymorphism and prostate cancer relationship, 1999–2012.
among the included studies. Additionally, sensitivity analysis was performed according to the source of the controls (population- or hospital-based controls) and the sample size of cases or controls (<100 or ≥100 subjects). Stata, version 11.0, software (StataCorp LP, College Station, Texas) was used to test for publication bias. The Begg adjusted rank correlation test (28) and the Egger regression asymmetry test (29) were used for exploring publication bias (P values less than 0.1 were considered significant) when the number of included studies was larger than 10.

RESULTS
Study characteristics
A total of 73 studies were retrieved from the databases independently by 2 investigators (T.-B.Z. and Z.-P.J.). The results were compared, and disagreements over 3 articles were resolved by discussion with Y.-H.Q. The information on the first author’s surname, year of publication, location of the study, subjects’ ethnicity, source of the control group, and the number of cases and controls for the GSTT1 genotype was in agreement. The data were entered into Cochrane Review Manager, version 5, and the results from both investigators were the same. An overview of the selection procedure is presented in Figure 1. Thirty-eight studies (30–67) reporting on the relationship between GSTT1 polymorphism and prostate cancer susceptibility were ultimately included in this meta-analysis (Figure 1); all reports were published in English (Table 1). The data of interest were extracted as summarized in Table 1. The included studies contained a total of 9,752 patients with prostate cancer and 10,530 controls.

The average distribution frequency of the GSTT1 null genotype in the prostate cancer group was 28.36%, and the average frequency in the control group was 25.97%. The average distribution frequency of the GSTT1 null genotype in the case group was similar to the control group (28.36% / 25.97% = 1.09). The average distribution of the GSTT1 null genotype frequency in Caucasians was 26.36% for cases and 22.31% for controls.

Association of the GSTT1 null genotype with prostate cancer susceptibility
The results from this meta-analysis showed clear trends with respect to the association between the GSTT1 null genotype and the risk of developing prostate cancer. No association between the GSTT1 null genotype and an increased prostate cancer risk could be established in the overall population (odds ratio (OR) = 1.11, 95% confidence interval (CI): 0.97, 1.27; P = 0.13; Figure 2 and Table 2).

Conversely, a clear association of the GSTT1 null genotype and prostate cancer risk could be established for Caucasians (OR = 1.24, 95% CI: 1.03, 1.48; P = 0.02; Figure 3 and Table 2). These results are in agreement with data from general epidemiologic and clinical observations that show a significantly higher prevalence of prostate cancer in Western and industrialized countries.

Sensitivity analysis
We performed sensitivity analysis for the relationship between the GSTT1 null genotype and prostate cancer risk according to the source of the controls (i.e., population- or hospital-based). We found that the results were similar to those obtained from the main analysis (Table 2). Similarly, sensitivity analysis for the relationship between the GSTT1 null genotype and prostate cancer risk according to sample size of cases or controls (i.e., <100 or ≥100 subjects) produced results that were similar to those of the main analysis (Table 2). Overall, no significant deviations were found between the main analysis and sensitivity analyses.

Evaluation of publication bias
Publication bias was established for the overall population (Begg P = 0.131, Egger P = 0.406) (Figure 4), for Caucasians (Begg P = 0.673, Egger P = 0.117), for the sample size of cases or controls (≥100 subjects) (Begg P = 0.020, Egger P = 0.013), for population-based controls (Begg P = 0.128, Egger P = 0.025), and for hospital-based controls (Begg P = 0.063, Egger P = 0.144).

DISCUSSION
Although the genetic component of prostate cancer has been the focus of intense research over the past decades, the exact genetic etiology underpinning prostate cancer is not yet fully understood. Some investigations have found that genetic aberrations might be used as an early diagnostic indicator to predict the onset of particular cancers (68–71) and, for some forms of cancer, such diagnostics tools have been implemented clinically. However, the situation for prostate cancer is less clear, and the need for determining suitable genetic markers is evident.

Genetic changes, especially gene polymorphisms associated with oxidative stress, inflammation, and senescence, have been implicated in the development of prostate cancer (7–8, 10, 14, 72). Because GSTs play such a central role in phase II enzymatic detoxification and protect against cellular oxidative stress and xenotoxic chemicals (17), and because they are involved in and modulate various signaling pathways (18), including the biosynthesis of leukotrienes, prostaglandins, testosterone, and progesterone, derangements in normal GST function might play particularly pivotal roles in slowly developing cancers, such as prostate cancer.

Various investigations indicate that derangements in GSTT1, which takes part in the inactivation of procarcino- gens, are associated with the etiology of prostate cancer. However, studies on the association of the GSTT1 null genotype with the susceptibility to prostate cancer have been controversial since the first investigation was reported. Our meta-analysis showed that the average distribution frequency of the GSTT1 null genotype in cases was 1.06-fold larger compared with the control group. Furthermore, we found that the GSTT1 null genotype was not associated with a higher risk of developing prostate cancer in the overall population. However, a clear association was established for Caucasians, and no publication bias in the meta-analysis.
Table 1. Characteristics of Studies Evaluating the Effects of GSTT1 Polymorphism on Prostate Cancer Risk, 1999–2012

<table>
<thead>
<tr>
<th>First Author, Year (Reference No.)</th>
<th>Study Country</th>
<th>Subject Ethnicity</th>
<th>Study Design</th>
<th>Source of Controls</th>
<th>No. of Cases</th>
<th>No. of Controls</th>
<th>GSTT1 Null</th>
<th>GSTT1 Presence</th>
<th>GSTT1 Total</th>
<th>GSTT1 Null</th>
<th>GSTT1 Presence</th>
<th>GSTT1 Total</th>
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</table>
for Caucasians was observed. Consequently, an association between the GSTT1 null gene polymorphism and prostate cancer risk in Caucasians may safely be established, and the GSTT1 null genotype might be a useful clinical indicator to predict the risk of prostate cancer in this ethnic group. Our meta-analysis included 5 studies of Asians and 2 studies for Africans or African Americans. Consequently, with the small number of studies and limited data sets, meta-analyses and subanalyses in Asians, Africans, and African Americans were not performed. In the sensitivity analyses according to the source of controls, the sample size of cases, and the study type, we found that the results were similar to those from the main analysis. Although there was significant publication bias in the analysis of sample size of cases, population-based controls, and hospital-based controls, the results were robust when the fixed-effects and random-effects models were applied, and the final outcomes were similar. Therefore, we conclude that the results from our meta-analysis bear significance, but we still believe that further investigations might increase the statistical accuracy.

Several meta-analyses on the association of GSTT1 polymorphism and the risk of prostate cancer have been reported. Katoh et al. (73) conducted a meta-analysis that included 12 studies and showed that polymorphisms in GSTT1 were unlikely to be major determinants of susceptibility to prostate cancer. Mo et al. (74) reported that no association between the GSTT1 null gene polymorphism and prostate cancer risk could be established for the overall population and other ethnic groups on the basis of 21 studies. Pan et al. (75) conducted a meta-analysis that focused exclusively on the relationship between the GSTT1 null genotype and prostate cancer risk in Asians, which suggested that the GSTT1 null genotype contributed to a higher risk of developing prostate cancer in this ethnic group. Gong et al. (76) recently performed a meta-analysis that included 37 studies and found that no enhanced risk could be established for the null genotype of the GSTT1 polymorphism and prostate cancer in Caucasians. It is worth noting that, in their meta-analysis, 23 studies were included for Caucasians, and these authors found no association between the GSTT1 null genotype and prostate cancer risk, but the pooled odds ratio was favorable with respect to the prostate cancer group (OR = 1.10, 95% CI: 0.96, 1.26; \( P = 0.11 \)). Conversely, in our meta-analysis, we included 24 studies for Caucasians and found that there was a distinct association between the GSTT1 null genotype and prostate cancer risk. In the meta-analysis by Gong et al. (76), the populations of 3 included studies in which the ethnic composition was not specified were regarded as Caucasians by the authors, and these 3 studies (33, 54, 56) were all conducted in the United States. Conversely, because the US population is ethnically mixed, we regarded these 3 populations as mixed race in our meta-analysis. We also included 4 additional studies (31, 36, 47, 58) by widely searching the databases. Because the number of included studies in our analyses was larger, the inclusion criteria were rigorous, and publication bias was excluded for the Caucasian group, we consider the results to carry considerable statistical significance and believe that they may therefore be seen as more robust. In addition, we performed sensitivity analysis according to the source of the controls (population- or hospital-based).
Figure 2. Results from prospective studies of the glutathione S-transferase theta 1 gene null genotype and prostate cancer risk in the overall population, 1999–2012. The summary estimate (diamond) was calculated using a random-effects model. Odds ratios (ORs) less than 1 favor cases; ORs greater than 1 favor controls. Assessment of heterogeneity: $\tau^2 = 0.11$, $\chi^2 = 125.36$, df $= 37$ ($P < 0.00001$), $I^2 = 70\%$. Test for overall effect: $Z = 1.51$ ($P = 0.13$). Bars, 95% confidence intervals (CIs).

Table 2. Meta-Analysisa of the Association of GSTT1 Polymorphism With Prostate Cancer Risk, 1999–2012

<table>
<thead>
<tr>
<th>Study Characteristic</th>
<th>No. of Studies</th>
<th>$P$ Value From $Q$ Test</th>
<th>OR</th>
<th>95% CI</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian subjects</td>
<td>24</td>
<td>$&lt;0.00001$</td>
<td>1.24</td>
<td>1.03, 1.48</td>
<td>0.02</td>
</tr>
<tr>
<td>Population-based controls</td>
<td>22</td>
<td>$&lt;0.00001$</td>
<td>1.10</td>
<td>0.94, 1.30</td>
<td>0.23</td>
</tr>
<tr>
<td>Hospital-based controls</td>
<td>14</td>
<td>$&lt;0.00001$</td>
<td>1.11</td>
<td>0.86, 1.42</td>
<td>0.43</td>
</tr>
<tr>
<td>$\geq 100$ Subjects</td>
<td>32</td>
<td>$&lt;0.00001$</td>
<td>1.07</td>
<td>0.93, 1.22</td>
<td>0.33</td>
</tr>
<tr>
<td>$&lt;100$ Subjects</td>
<td>6</td>
<td>0.02</td>
<td>1.43</td>
<td>0.89, 2.30</td>
<td>0.14</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td>$&lt;0.00001$</td>
<td>1.11</td>
<td>0.97, 1.27</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; GSTT1, glutathione S-transferase theta 1 gene; OR, odds ratio.

a The pooled statistics were derived by using the random-effects model.
and the sample size of cases or controls (<100 or ≥100 subjects), which increased objectivity.

Although meta-analyses aim to combine comparable studies, in an effort to increase sample sizes and statistical significance and to identify patterns in various studies, the quality of such analyses can be limited by publication bias, the sampling method, variations in the genetic background of the subjects, and differences in the study protocols. We aimed to minimize these limitations by using appropriate inclusion and exclusion criteria to reduce selection bias and by using a funnel plot and Egger’s linear regression test to assess publication bias. Nonetheless, some constraints remain in the current meta-analysis.

Furthermore, there was notable heterogeneity among the included studies in this meta-analysis. We conducted sensitivity analysis according to the source of the controls (population- or hospital-based) and the sample size of cases (<100 or ≥100 subjects), but we were unable to eliminate the heterogeneity or identify its cause. Overall, the results from our study support the notion that the null genotype of GSTT1 is associated with the risk of developing prostate cancer in Caucasians, but not in the overall population. Further well-designed studies might maximize the statistical robustness and meta-analysis quality and further minimize the heterogeneity factor between studies.
ACKNOWLEDGMENTS

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This study was supported by The Hundred Talents Program Foundation subitem of the Project 985 Foundation of Sun Yat-Sen University (grant 880000-3311300).

Conflict of interest: none declared.

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