Introduction

Prostate cancer (PCa) has become a major public health problem concern worldwide for its high morbidity and mortality levels. It is the second leading cause of cancer related to death in Europe, North America, Latin America, and some parts of Africa in men. It has been reported that PCa have a prominent variation in incidence among different ethnic groups and geographic regions. For instance, North Americans have the highest incidence, especially the African-Americans in USA, and the lowest is among Asian men [1–3]. However, the etiology and ethnic disparities of PCa are largely unknown. Clinical and epidemiologic data suggest that the development of PCa is a multiphase process. So far, a series environmental and lifestyle factors, including pollutants, smoking habit and diet, as well as geographical and racial factors have been pointed out as possible contributors to the risk of PCa [4]. In addition, the various risk, incidence, and mortality rates among worldwide of PCa suggest that genetic factors also play an important role in PCa initiation and progression, such as individual differences in the susceptibility to cancers, age and family history [5]. Therefore, the occurrence and development of PCa most likely involve a complex interplay between genetic and environmental factors. More specifically, variations in carcinogen metabolism genes may play a critical role in PCa development due to their activation or detoxification functions.

Glutathione S-transferases (GSTs) constitute a superfamily of ubiquitous, multifunctional phase II metabolic enzymes. These enzymes play a crucial function in the detoxification of both endogenous and exogenous carcinogens [6], but also participate in the activation and inactivation of oxidative metabolites of carcinogenic compounds so that to protect DNA from oxidative damage [7]. Hence, it has been speculated that GSTs were
### Table 1. Characteristics of eligible studies in the meta-analysis of \textit{GSTM1}, \textit{GSTT1} and \textit{GSTP1} polymorphisms with PCa.

| First author | Year | Source | \textit{GSTM1} | \textit{GSTT1} | \textit{GSTP1} | P value for HWE |
|--------------|------|--------|-----------------|-----------------|-----------------|----------------|
| **Caucasians** |      |        |                 |                 |                 |                |
| Harries LW   | 1997 | HB     | 10/26           | 79/76           | 0.440           |                |
| Rebbeck TR   | 1999 | PB     | 110/126         | 110/121         | 46/186          | 72/159         |
| Wadelius M   | 1999 | PB     | 75/68           | 71/49           | 0.321           |                |
| Autrup JL    | 1999 | PB     | 91/62           | 154/134         | 29/124          | 44/244         |
| Steinhoff C  | 2000 | HB     | 45/46           | 57/70           | 23/68           | 17/110         |
| Shepard TF   | 2000 | HB     | 290/300         | 365/438         | 0.893           |                |
| Gsur A       | 2001 | BPH    | 75/91           | 81/85           | 27/139          | 33/133         |
| Kote-Jarai Z | 2001 | PB     | 153/120         | 135/135         | 117/156         | 140/133        |
| Luscombe CJ  | 2002 | BPH    | 86/123          | 66/88           | 0.883           |                |
| Beer TM      | 2002 | PB     | 61/50           | 73/74           | 51/58           | 63/83          |
| Jeronimo C   | 2002 | mixed  | 45/60           | 61/80           | 0.374           |                |
| Kidd LC      | 2003 | /      | 84/116          | 100/88          | 24/178          | 92/78          |
| Nam RK       | 2003 | HB     | 235/248         | 266/282         | 90/393          | 127/421        |
| Acevedo C    | 2003 | BPH    | 37/65           | 29/99           |                |                |
| Debies JD    | 2004 | PB     | 369/545         | 184/298         | 0.310           |                |
| Medeiros R   | 2004 | PB     | 77/65           | 91/92           | 31/114          | 44/140         |
| Mao GE       | 2004 | HB     | 56/66           | 70/65           | 0.622           |                |
| Joseph MA    | 2004 | PB     | 97/81           | 142/123         | 55/122          | 61/204         |
| Mittal RD    | 2004 | BPH    | 55/48           | 35/82           | 35/68           | 13/104         |
| Antognelli C | 2005 | BPH    | 172/212         | 220/140         | 0.498           |                |
| Caceres DD   | 2005 | PB     | 37/65           | 30/102          | 6/94            | 14/115         |
| Srivastava DSL| 2005 | /      | 70/57           | 51/93           | 41/86           | 29/115         |
| **Asians**   |      |        |                 |                 |                 |                |
| Vijayalakshmi K | 2005 | HB     | 15/85           | 18/75           | 49/26           | 43/57          |
| Agalliu I    | 2006 | PB     | 311/248         | 248/274         | 92/466          | 88/434         |
| Quinones LA  | 2006 | HB     | 22/38           | 36/81           |                |                |
| Silig Y      | 2006 | HB     | 98/54           | 52/117          | 34/118          | 31/138         |
| Rybicki BA   | 2006 | HB     | 157/206         | 53/87           | 0.402           |                |
| Mittal RD    | 2006 | BPH    | 31/23           | 38/67           | 24/30           | 30/75          |
| Lima MM Jr   | 2008 | BPH    | 69/56           | 53/47           | 42/83           | 22/78          |
| Sivonová M   | 2009 | PB     | 69/60           | 130/98          | 24/105          | 45/183         |
| Steinbrecher A | 2010 | PB     | 126/122         | 270/221         | 44/204          | 77/415         |
| Kumar V      | 2011 | HB+BPH | 34/23           | 15/31           | 21/32           | 29/28          |
| Thakur H     | 2011 | HB+BPH | 87/63           | 62/110          | 82/68           | 39/111         |
| Rodrigues IS | 2011 | PB     | 71/83           | 86/68           | 42/112          | 40/114         |
| Qadri Q      | 2011 | PB+BPH | 26/24           | 59/21           | 22/23           | 0.083          |
| Hemelrijk MV | 2012 | PB     | 105/98          | 188/172         | 35/168          | 64/296         |

| First author | Year | Source | \textit{GSTM1} | \textit{GSTT1} | \textit{GSTP1} | P value for HWE |
|--------------|------|--------|-----------------|-----------------|-----------------|----------------|
| Murata M     | 2001 | BPH    | 57/58           | 115/85          | 47/68           | 104/96         |
| Nakazato H   | 2003 | HB     | 38/43           | 53/52           | 40/41           | 44/61          |
| Aktaş D      | 2004 | BPH    | 19/81           | 14/93           |                |                |
| Guan TY      | 2005 | PB     | 48/35           | 48/67           |                |                |
| Komiyama Y   | 2005 | PB     | 93/93           | 157/131         | 74/112          | 139/149        |
| Wang YL      | 2005 | PB     | 44/37           | 40/50           | 43/38           | 48/42          |
probably involved in the development of cancers [3]. As the enzymes are widely distributed in nature and found in essentially all eukaryotic species, individual genetic differences may influence the activity level of GSTs and susceptibility to cancer. To date, the GSTs have been assigned to eight distinct classes: \( \text{GSTM} \), \( \text{GSTM}1 \), \( \text{GSTM}2 \), \( \text{GSTM}3 \), \( \text{GSTM}4 \), \( \text{GSTM}5 \), \( \text{GSTM}6 \), and \( \text{GSTM}7 \). The \( \text{GSTM} \) genes are widely distributed in nature and found in essentially all eukaryotic species, and individual genetic differences may influence the activity level of GSTs and susceptibility to cancer. To date, the GSTs have been assigned to eight distinct classes: \( \text{GSTM} \), \( \text{GSTM}1 \), \( \text{GSTM}2 \), \( \text{GSTM}3 \), \( \text{GSTM}4 \), \( \text{GSTM}5 \), \( \text{GSTM}6 \), and \( \text{GSTM}7 \).

In recent years, \( \text{GSTM1} \), \( \text{GSTM1} \), and \( \text{GSTT1} \) have been studied most. The \( \text{GSTM1} \) and \( \text{GSTT1} \) genes were located on chromosome \( \text{p}13.3 \), \( \text{q}12.1 \), and \( \text{q}12.3 \) respectively \( [11,12] \). Both \( \text{GSTM1} \) and \( \text{GSTT1} \) exhibit an inherited homozygous deletion polymorphism (null genotype), which has been associated with the loss of enzyme activity and increased vulnerability to cytogenetic damage \( [13] \). As a result of decreased efficiency in protection against carcinogens, the individuals with homozygous deletion polymorphism are considered to be at an increased risk for malignancies \( [10,14] \). Whereas for \( \text{GSTP1} \) polymorphism, a single nucleotide polymorphism in exon 5 (Ile105Val, rs1695) received most attention. The A-to-G transition results in an amino acid change from isoleucine to valine so that leading to significantly lower conjugating activity among individuals who carry one or more copies of the G allele (Ile/Val or Val/Val) compared with those who have the A/A (Ile/Ile) genotype \( [15–17] \).

Recently, many studies focused on the association between PCa risk and \( \text{GSTM1} \), \( \text{GSTM1} \), or \( \text{GSTT1} \) polymorphisms, but inconsistent results have been reported. In 2009, Zengnan Mo et al. conducted a meta-analysis \( [10] \) suggested that \( \text{GSTM1} \) null genotype conferred an increasing risk of PCa on a wide population basis, but no relationship was found between \( \text{GSTT1} \) and \( \text{GSTP1} \) polymorphisms and the PCa risk. During recent three years, many new researches were performed to study the association between PCa risk and \( \text{GSTM1} \), \( \text{GSTM1} \), or \( \text{GSTP1} \) polymorphisms, so an updated meta-analysis is needed.

### Materials and Methods

#### Search Strategy and Selection Criteria

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Checklist S1), we identified all publications (updated to June 2, 2012) by conducting computer-based searches of PubMed, Embase, Google Scholar and China National Knowledge Infrastructure (CNKI). The combination of key words were as follows: ‘glutathione S-transferase M1’ or ‘\( \text{GSTM1} \)’, ‘glutathione S-transferase T1’ or ‘\( \text{GSTT1} \)’, ‘glutathione S-transferase P1’ or ‘\( \text{GSTP1} \)’, prostate or ‘urothelial’, cancer or ‘carcinoma’ or ‘neoplasm’, ‘polymorphism’ or ‘polymorphisms’. To minimize potential publication bias, no

### Table 1. Cont.

| First author | Year | Source | Cases | Controls | BPH | Cases | Controls | BPH | Cases | Controls | BPH | Cases | Controls | BPH | Cases | Controls | BPH | P value for HWE |
|--------------|------|--------|-------|----------|-----|-------|----------|-----|-------|----------|-----|-------|----------|-----|-------|----------|-----|-------------|
| Lai MT       | 2005 | HB     | 57/39 | 55/66    |     |       |          |     |       |          |     |       |          |     |       |          |     | 0.373       |
| Yang J       | 2006 | HB     | 99/64 | 112/90   | 89/74| 95/107|          |     |       |          |     |       |          |     |       |          |     | 0.786       |
| Wang YL      | 2008 | PB     | 41/40 | 58/32    |     |       |          |     |       |          |     |       |          |     |       |          |     | 0.300       |
| Li M         | 2008 | HB     | 121/87| 96/134   |     |       |          |     |       |          |     |       |          |     |       |          |     | 0.373       |
| Ansari BS    | 2009 | PB     | 34/26 | 25/35    | 13/47| 9/51  |          |     |       |          |     |       |          |     |       |          |     | 0.924       |
| Xu XX        | 2010 | PB     | 68/35 | 70/33    |     |       |          |     |       |          |     |       |          |     |       |          |     | 0.001       |
| Kwon DD      | 2011 | PB     | 90/76 | 125/202  | 85/81| 163/164| 117/49  | 209/118|       |          |     |       |          |     |       |          |     | 0.921       |
| Ashiani ZO   | 2011 | PB+BPH | 50/60 | 10/90    | 47/52| 38/72 | 47/53   | 37/62|       |          |     |       |          |     |       |          |     | 0.540       |
| Safarinejad  | 2011 | PB     | 72/96 | 94/242   | 58/110| 70/266| 54/114  | 174/162|       |          |     |       |          |     |       |          |     | <0.001      |

### Africans

| First author | Year | Source | Cases | Controls | BPH | Cases | Controls | BPH | P value for HWE |
|--------------|------|--------|-------|----------|-----|-------|----------|-----|-------------|
| Mallick S    | 2007 | HB     | 26/108| 36/98    | 30/104| 49/85 |          |     | 0.540       |
| Lavander NA  | 2009 | PB     | 47/141| 137/441  | 36/153| 102/482| 55/135  | 186/386| 0.001       |
| Souiden Y    | 2010 | PB     | 58/52 | 68/54    | 30/80 | 18/104|          |     |             |

### African-Americans

| First author | Year | Source | Cases | Controls | BPH | Cases | Controls | BPH | P value for HWE |
|--------------|------|--------|-------|----------|-----|-------|----------|-----|-------------|
| Agalliu I    | 2006 | PB     | 9/22  | 7/8      | 7/24 | 4/11  | 11/20   | 1/14 | 0.019       |
| Rybicki BA   | 2006 | PB     | 82/192| 29/104   |     |       |          |     |             |

### Mixed

| First author | Year | Source | Cases | Controls | BPH | Cases | Controls | BPH | P value for HWE |
|--------------|------|--------|-------|----------|-----|-------|----------|-----|-------------|
| Catsburg C   | 2012 | PB     | 606/774| 321/417 | 242/1158| 153/583| 569/843 | 300/449| 0.373       |

*Null/present.

**Used both healthy people and BPH patients as controls.

GSTM1, glutathione S-transferase M1; GSTT1, glutathione S-transferase T1; GSTP1, glutathione S-transferase P1.

PB, population-based controls; HB, hospital-based controls; BPH, benign prostate hyperplasia.

Table 1. Cont.
restrictions were placed on language, time period, sample size, type of study and population. All eligible articles were retrieved and their references were checked for other relevant studies. The inclusion criteria were: (1) studies which evaluated associations between *GSTM1*, *GSTT1*, and *GSTP1* polymorphisms and PCa risk; (2) control population did not contain malignant tumor patients. The exclusion reasons of studies were: (1) insufficient original data for the calculation of odds ratios (ORs) with corresponding 95% confidence intervals (95%CIs); (2) when multiple reports were available for the same study population, we included only the most recent or the largest report. Two investigators independently reviewed the titles, abstracts to determine if an individual study was eligible for the inclusion and exclusion criteria and all disagreements were resolved during a consensus meeting among all reviewers.

**Data Extraction**

Table 1 summarized the following information which was extracted from all eligible studies: the name of the first author, year of publication, ethnicity, source of controls, number of cases and controls and P-value for Hardy Weinberg Equilibrium (HWE). To ensure the accuracy of extracted information, two independent researchers (Gong and Dong) extracted raw data according to the inclusion criteria. The conflicting evaluations were settled by a discussion among all investigators. Ethnic groups were mainly defined as Caucasian, Asian, African and African-American. Study designs were stratified into three groups: population-based studies, hospital-based studies and benign prostatic hyperplasia (BPH) based studies.

**Statistical Analysis**

We used crude ORs with corresponding 95% CIs as a measure of the association between *GSTM1*, *GSTT1* and *GSTP1* polymorphisms and risk of PCa. The significance of the pooled OR was determined by the Z test and P value (two-tailed) < 0.05 was considered significant. In our study, the $\bar{F}$ test was used to assess the heterogeneity between studies ($\bar{F}$ < 25% no heterogeneity; $\bar{F}$ = 25–50% moderate heterogeneity; $\bar{F}$ > 50% large or extreme heterogeneity) [19]. The heterogeneity was considered statistically significant with $\bar{F}$ > 50% or P < 0.10. When there was no heterogeneity ($\bar{F}$ ≤ 50% or P ≥ 0.10), the fixed-effects model (the Mantel-Haenszel method) was used, otherwise, the random-effects model (the DerSimonian and Laird method) was used when the heterogeneity existed ($\bar{F}$ > 50% or P < 0.10) [20,21]. Subgroup analyses were performed by ethnicity, source of controls and gene-gene combinations. In addition, sensitivity analysis was performed by omitting each study in turn to assess the stability of results. To determine the evidence of publication bias, the funnel plot and Egger’s test were both used. An asymmetric plot suggested possible publication bias. For the interpretation of Egger’s test, statistical significance was defined as P < 0.05 [22]. All the statistical analyses were performed with MIX statistical software (Version 1.7 for windows).
Figure 2. Meta-analysis of GSTM1 null genotype and PCa risk.
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Results

After searching with our eligibility criteria, initially a total of 94 potentially relevant publications were identified. When screening the title or abstract, 32 studies were excluded because they are not associated with PCa risk and the polymorphisms of GSTM1, GSTT1, and GSTP1. Therefore, we obtained 62 relevant articles that examined the association between the polymorphisms of GSTM1, GSTT1 or GSTP1 and PCa risk. Out of them, three studies were excluded because of the insufficient data for OR calculation. Four researches [23–26] were eliminated because they were conducted on overlapping populations with other eligible studies [27–30]. Hence, 55 studies [27–81] met our inclusion criteria and were selected in this meta-analysis. However, one of the eligible studies [61] provided data of both tissue and blood samples from the overlapping population, and we only considered...
the data of blood samples. In addition, two articles contained separate data on two different ethnic groups [30,58], and we treated them as two separate studies. Finally, a total of 57 studies were involved in our meta-analysis (Fig.1). The following information was collected from each study: the name of the first author, date of publication, ethnicity, control source, number of cases and controls (Table 1). Most of the researches contained in this meta-analysis were case-control studies, except two nested case-control studies [67,79] and one cohort study [81]. Among the studies, 44 discussed the association between the \textit{GSTM1} polymorphism and PCa risk, 37 were about \textit{GSTT1}, and 35 were about \textit{GSTP1}. In all eligible studies, there were 26 studies on \textit{GSTM1} genotype of Caucasians, 13 studies of Asians, 3 studies of Africans, 1 study of African-Americans and 1 of mixed populations. Accordingly, 23 studies on \textit{GSTT1} genotype were of Caucasians, 9 studies of Asians, 3 studies of Africans, 1 study of African-Americans and 1 of mixed populations. About \textit{GSTP1} genotype, there were 25 studies of Caucasians, 6 studies of Asians, 2 studies of African-Americans and 1 of mixed populations. According to the control source, 26 were population-based...
researches, 15 were hospital-based researches, 9 studies were used BPH patients as controls, two were used both healthy people and BPH patients as controls, while the other two studies used hospital-based and BPH patients as controls. In addition, there was one study mixed the healthy people and BPH patients as controls, and the other two were not clarified.

**GSTM1**

Data from 44 case-control studies comprising 7,893 PCa cases and 9,668 controls were pooled together for analysis of the *GSTM1* polymorphism. The overall data showed that the individuals who carried the *GSTM1* null genotype had a significantly increased PCa risk compared with those who carried the *GSTM1* present genotype in all subjects (OR = 1.2854, 95% CI = 1.1405–1.4487, \( I^2 = 0.0001, F = 69.69\% \), Fig. 2). Because the heterogeneity among studies was significant, the random-effects model was conducted. When stratified by ethnicity, the same dramatic risks were found in Caucasians (OR = 1.3028, 95% CI = 1.1093–1.5301, \( P = 0.0013, F = 72.76\% \)) and Asians (OR = 1.4513, 95% CI = 1.1682–1.803, \( P = 0.0008, F = 61.46\% \)). But it seems that there was no association between PCa risk and the *GSTM1* null genotype in Africans (OR = 0.9108, 95% CI = 0.6943–1.1949, \( P = 0.371, F = 0.0\)). When considered the source of the control groups, two studies [43,55] were excluded for unclear source of controls. Also, high risks were found between PCa and *GSTM1* null genotype in population-based (OR = 1.2192, 95% CI = 1.0489–1.4172, \( P = 0.0009, F = 68.48\% \)), hospital-based (OR = 1.5431, 95% CI = 1.1417–2.0856, \( P = 0.0048, F = 78.24\% \)) or in BPH-based controls (OR = 1.3522, 95% CI = 1.0067–1.8163, \( P = 0.043, F = 64.6\% \)).

**GSTT1**

Totally, 37 studies met the inclusion criteria and were selected in the meta-analysis with 7,187 cases and 8,761 controls for analysis of the PCa risk and *GSTT1* null genotype. Overall, no enhanced risk was found between the null genotype of *GSTT1* polymorphism and PCa (OR = 1.102, 95% CI = 0.9396–1.2655, \( P = 0.1119, F = 65.96\% \), Fig. 3). As the dramatic heterogeneity, the random-effects model was used. In the subgroup analysis by ethnicity, no associations were observed in Caucasians (OR = 1.3345, 95% CI = 0.8308–2.1436, \( P = 0.1172, F = 65.48\% \)) or Africans (OR = 1.0465, 95% CI = 0.8789–1.2427, \( P = 0.8376, F = 51.39\% \)), in hospital-based (OR = 1.1988, 95% CI = 0.8387–1.7135, \( P = 0.3199, F = 73.55\% \)) or in BPH-based controls (OR = 1.3345, 95% CI = 0.8308–2.1436, \( P = 0.2327, F = 79.51\% \)).

**GSTP1**

We obtained 35 articles after searching and data extraction based on our eligibility criteria. In total, 8,360 cases and 9,094 controls were pooled for the association between PCa risk and *GSTP1* A131G polymorphism. However, the result showed no significant risk between PCa and the *GSTP1* A131G polymorphism (OR = 1.0643, 95% CI = 0.96–1.2251, \( P = 0.1926, F = 69.27\% \), Fig. 4). As the heterogeneity was observed, the random-effects model was used. Among the 35 studies, there were 15 case-control studies, 9,668 controls were pooled together for analysis of the *GSTP1* polymorphism. The overall data showed that the individuals who carried the *GSTP1* A131G polymorphism had a significantly increased PCa risk compared with those who carried the *GSTP1* A131G present genotype in all subjects (OR = 1.1626, 95% CI = 1.0712–1.2597, \( P = 0.0066, F = 65.48\% \)). Because the heterogeneity among studies was significant, the random-effects model was conducted. When stratified by ethnicity, the same dramatic risks were found in Caucasians (OR = 1.0152, 95% CI = 0.8789–1.1727, \( P = 0.8358, F = 51.39\% \)), in hospital-based (OR = 1.1988, 95% CI = 0.8387–1.7135, \( P = 0.3199, F = 73.55\% \)) or in BPH-based controls (OR = 1.3345, 95% CI = 0.8308–2.1436, \( P = 0.2327, F = 79.51\% \)).

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Table 2. Characteristics of eligible studies in the meta-analysis for the combination of *GSTM1*, *GSTT1* and *GSTP1* polymorphisms with PCa.

| First author       | Year | Source | Both nulla | Totala | Both null &AG+GGa | Totala | Both null &AG+GGa | Totala | Both null &AG+GGa | Totala |
|--------------------|------|--------|------------|--------|-----------------|--------|-----------------|--------|-----------------|--------|
| Rebeck TR          | 1999 | PB     | 22/31      | 468/462| 46/92           | 135/288| 22/24           | 153/288| 1/1             | 91/127 |
| Autrup JL          | 1999 | PB     | 19/24      | 153/288| 20/25           | 91/127 | 10/5            | 91/127 | 1/1             | 91/127 |
| Steinhoff C        | 2000 | HB     | 8/4        | 91/127 | 9/11            | 75/100 |                 |        |                 |        |
| Kote-Jarai Z       | 2001 | PB     | 3/5        | 99/129 | 21/16           | 269/263|                 |        |                 |        |
| Caceres DD         | 2005 | PB     | 58/14      | 81/105 | 5/14            | 81/105 |                 |        |                 |        |
| Srivastava DSL     | 2005 | /      | 23/12      | 127/144| 41/25           | 127/144| 25/14           | 127/144| 14/7            | 127/144|
| Vijayalakshmi K    | 2005 | HB     | 48/42      | 558/521| 166/145         | 558/521| 48/49           | 557/522|                 |        |
| Agalliu I          | 2006 | PB     | 16/8       | 57/46  | 16/12           | 57/53  |                 |        |                 |        |
| Lima MM Jr         | 2008 | BPH    | 21/9       | 125/97 |                 |        |                 |        |                 |        |
| Kumar V            | 2011 | HB+BPH | 16/8       | 57/46  | 16/12           | 57/53  |                 |        |                 |        |
| Thakur H           | 2011 | HB+BPH | 23/12      | 150/172| 23/10           | 150/155|                 |        |                 |        |
| Nakazato H         | 2003 | HB     | 38/42      | 168/336| 49/49           | 168/336| 36/36           | 168/336| 26/11           | 168/336|
| Safarinejad MR     | 2011 | PB     | 9/11       | 75/100 |                 |        |                 |        |                 |        |
| Sroutil Y          | 2010 | PB     | 11/17      | 122/110|                 |        |                 |        |                 |        |

*Cases/controls.
Used BPH patients as controls.
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Table 3. Summary of meta-analysis of GSTM1, GSTT1 and GSTP1 polymorphisms and PCa risk.

| Groups              | No. of studies | No. of subjects | OR (95% CI)                  | Statistical method | P%   | P-value for Z test |
|---------------------|----------------|-----------------|------------------------------|--------------------|------|-------------------|
| GSTM1               | 44             | 17561           | 1.2854(1.1405–1.4487)        | Random             | 69.69| <0.0001           |
| Caucasians          | 26             | 10134           | 1.3028(1.1093–1.5301)        | Random             | 72.76| <0.0001           |
| Asians              | 13             | 3997            | 1.4513(1.1682–1.803)         | Random             | 61.46| 0.0008            |
| Africans            | 3              | 1266            | 0.9108(0.6943–1.1949)        | Fixed              | 0.371|                   |
| hospital-based studies | 12         | 3821            | 1.5431(1.1417–2.0856)        | Random             | 78.24| 0.0048            |
| population-based studies | 23       | 11091           | 1.2192(1.0488–1.4172)        | Random             | 68.48| 0.0099            |
| BPH-based studies   | 10             | 2307            | 1.3522(1.0067–1.8163)        | Random             | 64.6 | 0.045             |
| GSTT1               | 37             | 15948           | 1.1020(0.9596–1.2655)        | Random             | 65.96| 0.1119            |
| Caucasians          | 23             | 9556            | 1.1626(0.9712–1.3917)        | Random             | 65.48| 0.1006            |
| Asians              | 9              | 2937            | 1.0533(0.8015–1.3842)        | Random             | 65.68| 0.7096            |
| Africans            | 3              | 1273            | 1.0465(0.4937–2.2181)        | Random             | 83.85| 0.9057            |
| hospital-based studies | 8           | 2814            | 1.1988(0.8387–1.7135)        | Random             | 73.55| 0.3199            |
| population-based studies | 22         | 10919           | 1.0152(0.8789–1.1727)        | Random             | 51.39| 0.8376            |
| BPH-based studies   | 8              | 1870            | 1.3345(0.8308–2.1436)        | Random             | 79.51| 0.2327            |
| GSTP1               | 35             | 17644           | 1.0845(0.96–1.2251)          | Random             | 69.27| 0.1926            |
| GSTP1*              | 32             | 16726           | 1.0572(0.9391–1.1902)        | Random             | 65.87| 0.3574            |
| Caucasians          | 25             | 12230           | 1.0944(0.9483–1.2629)        | Random             | 70.19| 0.2173            |
| Asians              | 6              | 2038            | 1.1924(0.7953–1.7879)        | Random             | 75.57| 0.3945            |
| hospital-based studies | 9           | 4361            | 0.9667(0.7548–1.238)         | Random             | 66.95| 0.7883            |
| population-based studies | 18         | 10604           | 1.0675(0.9221–1.2359)        | Random             | 62.58| 0.3817            |
| BPH-based studies   | 6              | 1874            | 1.2012(0.7568–1.9065)        | Random             | 81.31| 0.4367            |
| GSTM1+GSTT1*        | 11             | 4550            | 1.4353(1.0345–1.9913)        | Random             | 55.91| 0.0306            |
| GSTT1+GSTP1a         | 5              | 2493            | 1.7335(1.1067–2.7152)        | Random             | 62.42| 0.0163            |
| GSTM1+GSTT1+GSTP1b  | 6              | 2689            | 1.3867(0.9763–1.9697)        | Random             | 67.33| 0.0679            |
| Three polymorphisms | 5              | 1711            | 1.6903(0.6823–4.1874)        | Random             | 76.3 | 0.2568            |

OR, odds ratio; CI, confidence interval.

*aGSTP1 the total result of after excluding three researches deviated from Hardy-Weinberg equilibrium (HWE).

*bGSTM1 (−/−) and GSTT1 (−/−) vs. GSTM1 (+/−) and GSTT1 (−/−) with GSTM1 (−/−) and GSTT1 (+/−).

*cGSTT1 (−/−) and GSTP1 (AG+GG) vs. GSTT1 (+/−) and GSTP1 (AA) with GSTT1 (−/−) and GSTP1 (AG+GG).

*dGSTM1 (−/−), GSTT1 (−/−) and GSTP1 (AG+GG) vs. the other combinations of the GSTM1, GSTT1 and GSTP1 polymorphisms.

OR = 1.0572, 95% CI = 0.9391–1.1902, P = 0.3574, F = 65.87% was similar with the previous one. We also performed subgroup analysis stratified by ethnicity and control source. By ethnicity, we did not acquire remarkable enhanced risks of PCa with GSTP1 A131G polymorphism either in Caucasians (OR = 1.0944, 95% CI = 0.9463–1.2629, P = 0.2173, F = 70.19%) or in Asians (OR = 1.1924, 95% CI = 0.7953–1.7879, P = 0.3945, F = 75.57%). By control source, two studies [43,55] were eliminated as not mentioned the source of controls. The available data revealed a result that there were no enhanced PCa risks for population-based (OR = 1.0675, 95% CI = 0.9221–1.2359, P = 0.3817, F = 62.58%), hospital-based (OR = 0.9667, 95% CI = 0.7548–1.238, P = 0.7883, F = 66.95%) or BPH-based (OR = 1.2012, 95% CI = 0.7568–1.9065, P = 0.4367, F = 81.31%) controls with the GSTP1 A131G polymorphism.

Combination of Genotypes

Several studies reported the combination of GSTM1, GSTT1 and GSTP1 genotypes (Table 2). For the PCa patients contrast with controls, we detected the remarkable increased PCa risks for people with dual null genotype of GSTM1 and GSTT1 (OR = 1.4353, 95% CI = 1.0345–1.9913, P = 0.0306, F = 55.91%) and people with GSTT1 null genotype and GSTP1 A131G polymorphism (OR = 1.7335, 95% CI = 1.1067–2.7152, P = 0.0163, F = 62.42%). However, when combined the GSTM1 null genotype and GSTP1 A131G polymorphism (OR = 1.3067, 95% CI = 0.9763–1.9697, P = 0.0679, F = 67.33%), or the three genotypes (OR = 1.6903, 95% CI = 0.6823–4.1874, P = 0.2568, F = 76.3%), no dramatic PCa risks were obtained.

Sensitivity Analyses

Sensitivity analyses were performed by sequential omission of individual studies for all subjects and subgroups. The corresponding pooled ORs were not materially altered in all subjects and subgroups of GSTM1, GSTT1 or GSTP1 genotypes (data not shown). The results of sensitivity analyses indicated the stability of the results of this meta-analysis.

Publication Bias

Funnel plot and Egger’s test were both performed to access the publication bias in this meta-analysis. The funnel plot shapes of GSTM1 and GSTP1 polymorphisms were symmetrical (data not
shown) and the $P$ values of Egger’s test were 0.0625 and 0.4738 respectively, so the results showed no evidence of publication biases. However, the shape of $GSTT1$ genotype revealed a little unsymmetrical (data not shown), therefore the Egger’s test was further applied to provide statistical evidence and the result suggested the publication bias might be existed, and the $P$ value was 0.0415. Hence, we conducted the trim-and-fill in order to get further information. The result revealed that the number of imputed studies was zero, and also the corrected OR was 1.102 (95% CI = 0.9596–1.2655) which was the same as the uncorrected one.

**Discussion**

PCa is the most commonly diagnosed non-skin malignancy among men and its incidence is expected to increase as the population age elevated [82]. The molecular genetics of PCa is poorly understood. Its heterogeneous nature suggests that predisposition to PCa may involve multiple genes and variable phenotypic expression. The glutathiones S-transferases (GSTs) are the most important parts of phase II superfamily of metabolism enzymes. In humans, there are several GST classes that are encoded by distinct gene families [83]. Among them, $GSTM1$, $GSTT1$ and $GSTP1$ should be pointed out because the polymorphisms of these genes may influence the enzyme activity, and eventually increase vulnerability to genotoxic damage [14]. Therefore, the association between the polymorphisms of $GSTM1$, $GSTT1$ or $GSTP1$ and PCa has been intensively investigated.

In this study, association between $GSTM1$, $GSTT1$ or $GSTP1$ genetic variants and PCa risk were examined and all the results of the present meta-analysis were summarized in Table 3. Our result suggested that a significant increased risk existed between PCa and $GSTM1$ null genotype, whereas no elevated PCa risks were observed with the $GSTT1$ null genotype and $GSTP1$ polymorphism. It is consistent with the result of former meta-analysis, which was conducted by Zengnan Mo et al. in 2009. However, we included 11313 cases and 12934 controls from 57 studies in the present meta-analysis, which is much more than the previous one including 7,984 cases and 9,143 controls from 39 case-control studies. Hence, a more stringent and comprehensive result has been obtained.

It is known that the allele frequencies of metabolic genes are not equally distributed throughout the human population but follow diverse ethnic patterns, therefore, the subgroups according to ethnicity were performed. Our results indicated that significant PCa risks of people with $GSTM1$ null genotype are in all subjects, especially in Caucasians and Asians, but not in Africans. The possible reason of the conflicting results among diverse ethnicities could be that different genetic backgrounds and environment they exposed to may have different effects on the PCa risk. Additionally, as limited sample size may have not enough statistical power to detect a real effect or generate a fluctuated estimation, the small sample size of Africans in this meta-analysis should also be taken into consideration.

Furthermore, we also showed that $GSTM1$ null genotype has strikingly increased the risk of PCa susceptibility when stratified by control source. However, we obtained the highest risk of PCa when only considered the hospital-based controls. The possible reason may be that $GSTM1$ null genotype could influence the susceptibility to non-cancer diseases, such as COPD [84], alcoholic liver disease [85], and coronary heart disease [86], so its genotype frequency possibly differed between the hospital-based and population-based controls. Besides, we got a higher PCa risk of BPH-based controls than population controls. For this result, the probably reason could be the selection bias. To be specific, the differences of selection criteria or selection chance between population and BPH-based controls may be the main reasons of the selection bias. On the other hand, we did not exclude that the BPH could be affected by the $GSTM1$ null genotype [97] was one of the reasons for the result. However, the exactly reason need to be further confirmed.

In addition, we first observed the association between the combination of $GSTM1$, $GSTT1$ or $GSTP1$ genotypes and PCa risk and revealed important results. Eleven articles examined the people with dual null genotype of $GSTM1$ and $GSTT1$, and our result proved a remarkable increased PCa risk for these people. Moreover, the result also revealed a very strong risk of PCa for people who with $GSTT1$ null genotype and $GSTP1$ A131G polymorphism from five articles. The present meta-analysis is the earliest one to evaluate the potential interaction of the gene-to-gene and PCa risk. However, we should treat the results with caution for the limited sample size.

For the $GSTT1$ null genotype and $GSTP1$ A131G polymorphism, we failed to find the association between PCa risk and the polymorphisms, even though we stratified for ethnicity and control source, which is consistent with the previous meta-analysis [18].

However, there are some limitations in this meta-analysis. First of all, even though we performed subgroup analyses stratified by ethnicity and control source, the heterogeneity for $GSTM1$ polymorphism among the studies was extreme. It suggested that there were other potential confounding factors in the included studies, such as the genotyping error, selection bias, or population-specific gene-gene or gene-environment interaction, allelic heterogeneity, or chance [88,89]. Although evidence of heterogeneity exists, it was found through sensitivity analysis that studies contribute to the heterogeneity do not significantly alter the estimate of overall odds ratio. Secondly, only published studies were included, therefore the publication bias may have been occurred. The Egger’s test provided statistical evidence of that. We observed the publication bias when only considered studies about the association between $GSTT1$ polymorphism and PCa risk, but did not find it in the studies about the PCa risks with $GSTM1$ and $GSTP1$ polymorphisms. It is known that positive results usually have a greater probability of being published, and such bias may occur when studies with null or unexpected results. In addition, we also performed the trim-and-fill and the corrected OR was the same as the uncorrected one. Therefore, our result of $GSTT1$ null genotype was reliable and stable to some extent. Thirdly, the overall outcomes were based on unadjusted effect estimates. Although the cases and controls were matched on age, sex and residence in all studies, these confounding factors might slightly modify the effective estimates and a more precise evaluation needed to be adjusted by the potentially suspected factors. Finally, as the meta-analysis remains a retrospective research which is subject to the methodological deficiencies of the included studies, we tried to develop a detailed protocol before initiating the study, and then performed an explicit method for study researching, selection, data extraction and data analysis to minimize the likelihood of bias.

**Conclusions**

In conclusion, our meta-analysis suggested that $GSTM1$ null genotype is associated with a high increased risk of PCa and no significant PCa risks were obtained for $GSTT1$ and $GSTP1$ polymorphisms. To our knowledge, the present study is the first
meta-analysis to date to report the interaction between the combination of GSTM1, GSTT1 or GSTP1 genotypes and PCa risk. In the meta-analysis, we proved remarkable elevated PCa risks for people who with dual null genotype of GSTM1 and GSTT1, and also for people who with GSTT1 null genotype and GSTP1 A131G polymorphism. Larger and more rigorous analytical studies will be required to confirm our findings and evaluate gene-environment interactions with PCa risk.

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Supporting Information

Checklist S1. (DOC)

Author Contributions

Conceived and designed the experiments: RA. Performed the experiments: MG WD ZS. Analyzed the data: MG WD ZS. Contributed reagents/materials/analysis tools: YX WN. Wrote the paper: MG WD.
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