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The relationship between GSTA1, GSTM1, GSTP1, and GSTT1 genetic polymorphisms and bladder cancer susceptibility

A meta-analysis

Yajie Yu, MD[a], Xiao Li, MD[a,c], Chao Liang, MD[a], Jingyuan Tang, MD[a], Zhiqiang Qin, MD[a], Chengming Wang, MD[a], Weizhang Xu, MD[b], Yibo Hua, MD[a], Pengfei Shao, PhD[a,*], Ting Xu, MD[c,*]

Abstract

Background: Previous studies have investigated the relationship between GSTA1, GSTM1, GSTP1, and GSTT1 polymorphisms and bladder cancer (BCa) susceptibility, respectively, but the results remain inconsistent. So, we conducted this meta-analysis including 79 case–control studies to explore such relationships.

Methods: We searched PubMed, EMBASE, Cochrane library, Web of Science, and CNKI for relevant available studies. The pooled odds ratios (ORs) with 95% confidence intervals (CIs) were implemented to evaluate the intensity of associations. Publication bias was estimated using Begg funnel plots and Egger regression test. To assess the stability of the results, we used sensitivity analysis with the method of calculating the results again by omitting 1 single study each time. Between-study heterogeneity was tested using the I^2 statistic.

Results: No significant association between GSTA1 polymorphism and BCa susceptibility (OR=1.05, 95% CI 0.83–1.33) was noted. Besides, meaningful association between individuals who carried the GSTM1 null genotype and increased BCa risk was detected (OR=1.39, 95%CI 1.28–1.51). When stratified by ethnicity, significant difference was found in both Caucasian (OR=1.39, 95% CI 1.23–1.58) and Asian populations (OR=1.45, 95% CI 1.31–1.61). Moreover, in the subgroup analysis by source of controls (SOC), the results were significant in both hospital-based control groups (OR=1.49, 95% CI 1.35–1.64) and population-based control groups (OR=1.21, 95% CI=1.07–1.37). Additionally, the analysis revealed no significant association between GSTP1 polymorphism and BCa risk (OR=1.07, 95% CI 0.96–1.20). What is more, significant associations between GSTT1 polymorphism and BCa susceptibility were discovered (OR=1.11, 95% CI 1.00–1.22). In the subgroup analysis by ethnicity, significant associations between GSTT1 null genotype and BCa risk were observed only in Caucasians (OR=1.25, 95% CI 1.09–1.44). Furthermore, when stratified by SOC, no obvious relationship was found between the GSTT1 null genotype polymorphism with hospital-based population (OR=1.11, 95% CI 0.97–1.28) or population-based population (OR=1.10, 95% CI 0.96–1.27).

Conclusion: This study suggested that GSTM1 null genotype and GSTT1 null genotype might be related to higher BCa risk, respectively. However, no associations were observed between GSTA1 or GSTP1 polymorphisms and BCa susceptibility.

Abbreviations: BCa = bladder cancer, CI = confidence interval, GST = glutathione S-transferase, HB = hospital-based, OR = odds ratio, PB = population-based, SOC = source of controls.

Keywords: bladder cancer, glutathione S-transferases, meta-analysis, single gene polymorphism, susceptibility

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YY, XL, and CL contributed equally to this work.

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[a] Department of Urology, The First Affiliated Hospital of Nanjing Medical University, [b] Department of Thoracic Surgery, Nanjing Medical University Affiliated Cancer Hospital; Jiangsu Key Laboratory of Molecular and Translational Cancer Research, Cancer Institute of Jiangsu Province, [c] Department of Urologic Surgery, The Affiliated Cancer Hospital of Jiangsu Province of Nanjing Medical University, Nanjing, China.

[*] Correspondence: Pengfei Shao, Department of Urology, The First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, China (e-mail: spf_urology@sina.com); Ting Xu, Department of Urologic Surgery, The Affiliated Cancer Hospital of Jiangsu Province of Nanjing Medical University, Nanjing 210009, China (e-mail: xuting_urology@sina.com).

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1. Introduction

Bladder cancer (BCa), with an increasing incidence and mortality nowadays, has become the 9th most common cancer and the 14th leading cause of death due to cancer worldwide.[1] An estimated 429,800 new cases of BCa and 165,100 deaths took place in 2012 worldwide.[2] As a complicated and multifactorial procedure, the initiation and development of BCa are still not completely understood.[3] However, the risk factors could be mainly classified into 3 subgroups: long-term inflammation stimulation, specific chemical exposure, and genetic factors.[4] Interestingly, some people never get BCa even though exposed to specific chemicals. In contrast, many BCa patients do not have those known risk factors, suggesting that genetic factors might play a significant role in bladder carcinogenesis.[5,6]

Glutathione S-transferases (GSTs), existing in almost all living organisms, are members of a polygene family of isoenzymes.[7] GSTs are a family of multifunctional phase II enzymes that catalyze the combination of many exogenous and endogenous electrophilic compounds with glutathione, which are characterized with assisting the detoxification of various therapeutic drugs,

carcinogens, products of oxidative stress, toxins, and chemical mutants.[8,9] In humans, GSTs were encoded by 8 different gene families. Among them, 4 are mainly expressed in tissues: GSTA, GSTM, GSTP, and GSTT. Accordingly, the GSTA1, GSTM1, GSTP1, and GSTT1 genes are located at chromosome 6p12.1, 1p13.3, 11q13, and 22q11.23, respectively.

Over the last 2 decades, plentiful studies have been carried out to investigate the association between GSTs and the risk of BCa, but these studies have reported conflicting results. A single study might fail to demonstrate the complicated genetic relationship due to small sample size, but meta-analysis could increase the statistical power through detecting overall effects. Previously, meta-analysis has been performed to find out the relationship between GSTM1, GSTP1, GSTT1, and BCa, respectively.[10–14] Although the results remain inconclusive or even contradictory. In addition, the relationship between GSTA1 and BCa susceptibility has not been qualitatively studied before. Some related case–control studies have been released after the previous meta-analyses, which may generate influence on the conclusions. Therefore, we conducted such meta-analysis to assess these relationships by including all eligible articles.

2. Materials and methods

2.1. Search strategy

We did a systematic search of PubMed, EMBASE, Cochrane library, Web of Science, and CNKI up to December 2015 by using the combination of the following key words: "glutathione S-transferase A1" or "GSTA1," "glutathione Stransferase M1" or "GSTM1," "glutathione S-transferase P1" or "GSTP1," "glutathione S-transferase T1" or "GSTT1," "bladder" or "urothelial," "cancer" or "carcinoma" or "neoplasm," and "polymorphism" or "polymorphisms" without any restriction on language. The reference lists of the selected papers were searched by hand for potentially eligible articles. We only included the study with the most recent and/or the largest sample size when several studies had partially overlapped or similar data.

2.2. Selection criteria

For this meta-analysis, the inclusion criteria were as follows: case–control studies with the original date for the evaluated associations between GSTA1, GSTM1, GSTP1 and/or GSTT1 polymorphisms, and BCa risk; the diagnosis of the patients with BCa was confirmed pathologically, and the controls were confirmed free of any cancer; and sufficient published data about the size of the sample, odds ratio (OR), and their 95% confidence interval (CI). The exclusion criteria were duplicates of previous publication; no control subjects; and patients without confirmation of BCa or mixed with other diseases.

If study populations were the same or duplicate data were published, only the study with the largest number of sample size was included. We did not need to obtain ethical approval or informed consent because our data were extracted from previous studies. Nevertheless, the included studies in our review did get patient consent, and each study was approved by an ethics committee.

2.3. Data extraction

Data were independently extracted from all eligible publications by 5 investigators (YJY, XL, CL, JYT, and ZQQ), and quality assessment was conducted by 3 authors (YJY, XL, and CL). When meeting conflicting opinions about inclusion, disagreements were resolved by discussion among team members. Relevant data were extracted from each eligible study and carefully recorded, including involved genes, 1st author name, year of publication, the ethnicity of the study population, subject source, total number of cases and controls, and different number of genotypes in cases and controls. If important unpublished information were needed, we also e-mailed the original authors. According to source of controls (SOC), studies were classified into hospital-based (HB) and population-based (PB) groups. Ethnic groups were principally defined as Caucasian, Asian, African, or Mixed.

2.4. Statistical analysis

ORs with 95% CIs were implemented. The heterogeneity was estimated using the χ^2-based Q statistic, and heterogeneity was considered statistically significant when P heterogeneity ≤ 0.1 or $I^2 > 50\%$.[15] If the presence of heterogeneity was found, the random-effects model would be utilized. Otherwise, fixed-effects model would be performed. Then, subgroup analysis was further carried out by ethnicity and SOC properly.

To assess the stability of the results, we used sensitivity analysis with the method of calculating the results again by omitting 1 single study each time.[16] To check the publication bias between the studies, Egger linear regression test and Begg funnel plots were executed.[17] Hardy–Weinberg equilibrium was assessed by the goodness-of-fit Chi-square test, and $P < 0.05$ was considered as an obviously selective bias.[18] All statistical analyses tests were performed with Stata software (version 12.0; Stata Corp LP, College Station, TX). All P values below 0.05 were considered statistically significant.

3. Results

3.1. Literature search and studies characteristics

Figure 1 shows the flowchart of literature search and selection process. Finally, a total of 79 case–control studies were included according to the inclusion criteria.[19–97] Characteristics of individual study qualified for the current meta-analysis (GSTA1, GSTM1, GSTP1, and GSTT1, respectively) are presented in Tables 1–4 individually. This meta-analysis results of association between GSTs polymorphism and BCa risk are shown in Table 5.

3.2. GSTA1

Four studies consisting of 585 cases and 702 controls were adopted in order to evaluate the relationship between GSTA1 polymorphism and BCa risk. As shown in Fig. 2, the results indicated no significant association between GSTA1 polymorphism and BCa susceptibility (OR = 1.05, 95% CI 0.83–1.33). Subgroup analysis was not performed owing to the limited studies.

3.3. GSTM1

As shown in Table 5, 48 studies including 11,473 cases and 13,795 controls were analyzed. Overall, significant associations between individuals who carried GSTM1 null genotype and increased BCa risk were observed (OR = 1.39, 95%CI 1.28–1.51) (Fig. 3). When stratified by ethnicity, significant difference was detected in Caucasian (OR = 1.39, 95% CI 1.23–1.58) and Asian populations (OR = 1.45, 95% CI 1.31–1.61) instead of African (OR = 1.23, 95% CI 0.95–1.59) or Mixed populations (OR =

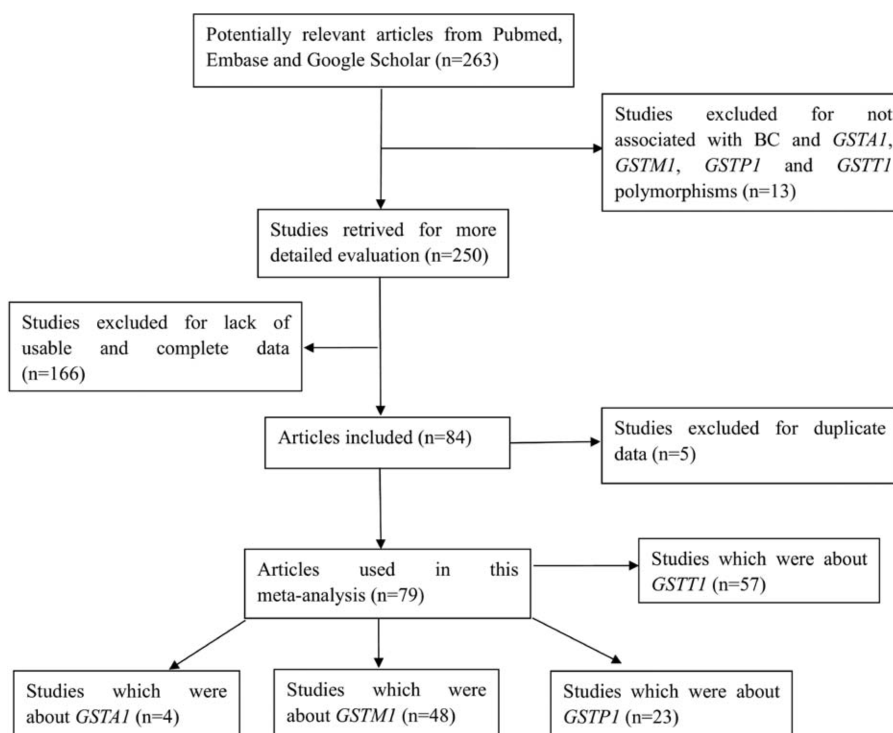

Figure 1. Flowchart of literature search and selection process.

1.16, 95% CI 0.93–1.45). In addition, in the subgroup analysis by SOC, the results were significant both in HB populations (OR=1.49, 95% CI 1.35–1.64) and PB populations (OR=1.21, 95% CI 1.07–1.37).

3.4. GSTP1

Twenty-three studies involving 5080 cases and 6187 controls were included in this study. Because a few studies provided precise data of genotypes, only dominant model could be carried out with all studies. Generally, the analysis revealed no significant association between GSTP1 Ile105Val polymorphism and BCa risk (OR=1.07, 95% CI 0.96–1.20) (Fig. 4). No significant relationship was observed between GSTP1 polymorphism and BCa risk in patients when stratified by ethnicity. Meanwhile, there seems no relationship between GSTP1 polymorphism and the susceptibility of BCa when stratified by SOC (Table 5).

3.5. GSTT1

Fifty seven studies including 12,369 cases and 15,333 controls were analyzed. The results indicated significant association between GSTT1 polymorphism and BCa susceptibility (OR=1.11, 95% CI 1.00–1.22) (Fig. 5). In the subgroup analysis by ethnicity, significant associations between GSTT1 null genotype and BCa risk were noted only in Caucasians (OR=1.25, 95% CI 1.09–1.44). Additionally, when stratified by SOC, no obvious relationship was detected between the GSTT1 null genotype polymorphism with HB (OR=1.11, 95% CI 0.97–1.28) or PB (OR=1.10, 95% CI 0.96–1.27), respectively (Table 5).

3.6. Sensitivity analysis

Sensitivity analysis was utilized to identify the influence of each study on the pooled OR by consecutively omitting 1 study each time for all subjects and subgroups. The sensitivity analysis for GSTA1, GSTM1, GSTP1, and GSTT1 polymorphism showed that no individual study affected the pooled OR significantly, which indicated that our results were reliable.

3.7. Publication bias

The publication bias of studies GSTA1, GSTM1, GSTP1, and GSTT1 were assessed, respectively, using Begg and Egger funnel

Table 1

Characteristics of individual studies included in the meta-analysis.

GSTA1	rs3957357						Case (n)				Control (n)			
Year	Surname	Ethnicity	SOC	Genotyping	Case	Control	AA	AB	BB	AB+BB	AA	AB	BB	AB+BB
2014	Reszka	Caucasian	PB	RT-PCR	243	365	92	118	33	151	137	165	63	228
2013	Matic	Caucasian	HB	PCR-RFLP	201	122	67	112	22	134	49	57	16	73
2013	Savic-Radojevic	Caucasian	HB	PCR-RFLP	80	60	27	–	–	53	26	–	–	34
2005	Broberg	Caucasian	PB	TaqMan	61	155	24	28	9	37	45	75	35	110

HB=hospital-based (controls), PB=population-based (controls), PCR-RFLP=polymerase chain reaction-restriction fragment length polymorphism, RT-PCR=reverse transcription-polymerase chain reaction, SOC=source of controls.

Table 2

Characteristics of individual studies included in the meta-analysis.

GSTM1							Case (n)		Control (n)	
Year	Surname	Ethnicity	SOC	Genotyping	Case	Control	Present	Null	Present	Null
2015	Ceylan	Caucasian	HB	PCR-RFLP	65	70	43	22	39	31
2014	Reszka	Caucasian	PB	RT-PCR	244	365	95	149	200	165
2014	Wang	Asian	HB	Multiplex PCR	1050	1404	351	699	570	834
2013	Matic	Caucasian	HB	PCR	201	122	90	111	61	61
2013	Berber	Caucasian	HB	Multiplex PCR	114	114	60	54	63	51
2013	Kang	Asian	HB	Multiplex PCR	110	220	45	65	117	103
2013	Savic-Radojevic	Caucasian	HB	Multiplex PCR	80	60	35	45	28	32
2013	Safarinejad	Asian	HB	PCR	166	332	116	50	239	93
2012	Ovsiannikov	Caucasian	HB	Duplex-PCR	196	235	94	102	112	123
2011	ÖZTÜRK	Caucasian	PB	PCR	176	97	78	98	46	51
2011	Rouissi	African	PB	Multiplex PCR	125	125	62	63	69	56
2011	Goerlitz	African	PB	TaqMan	618	621	274	344	289	332
2009	Altayli	Caucasian	HB	Multiplex PCR	135	128	77	58	63	65
2009	Grando	Mixed	PB	Multiplex PCR	100	100	60	40	67	33
2009	Rouissi	African	PB	Multiplex PCR	125	125	62	63	69	56
2009	Song	Asian	HB	Multiplex PCR	208	212	77	131	104	108
2009	Zupa	Caucasian	PB	Multiplex PCR	23	121	10	13	53	68
2008	Abd	Caucasian	HB	PCR	20	20	9	11	11	9
2008	Covolo	Caucasian	HB	PCR-RFLP	197	211	69	128	100	111
2008	Golka	Caucasian	HB	PCR	293	176	109	184	88	88
2008	Shao	Asian	HB	Multiplex PCR	202	272	117	85	191	81
2007	Moore	Caucasian	HB	PCR	1077	1022	394	683	498	524
2007	Cengiz	Caucasian	HB	Multiplex PCR	51	53	17	34	31	22
2007	Murta-Nascimento	Caucasian	HB	TaqMan	679	735	251	428	368	367
2007	Zhao	Caucasian	HB	TaqMan	622	633	298	324	316	317
2005	Saad	Caucasian	PB	PCR	72	81	27	45	41	40
2005	García-Closas	Caucasian	HB	TaqMan	1138	1132	422	716	561	571
2005	Karagas	Mixed	PB	PCR	354	542	144	210	233	309
2005	Kellen	Caucasian	PB	PCR	579	1063	267	312	466	597
2005	Kim	Asian	HB	Multiplex PCR	153	153	61	92	80	73
2005	Sobti	Asian	PB	Multiplex PCR	100	76	63	37	52	24
2005	Srivastava	Asian	PB	Multiplex PCR	106	370	63	43	230	140
2004	Hung	Caucasian	HB	PCR	201	214	69	132	102	112
2004	Moore	Mixed	PB	PCR	106	109	52	54	60	49
2004	Srivastava	Asian	HB	Multiplex PCR	106	182	64	42	128	54
2003	Jeong	Asian	HB	PCR	126	204	51	75	105	99
2002	Giannakopoulos	Caucasian	HB	PCR	89	147	33	56	91	56
2002	Lee	Asian	HB	Multiplex PCR	232	165	83	149	79	86
2001	Aktas	Caucasian	HB	ELISA	103	202	47	56	132	70
2001	Törüner	Caucasian	PB	PCR	121	121	46	75	66	55
2000	Kim	Asian	HB	Multiplex PCR	112	220	34	78	97	123
2000	Schnakenberg	Caucasian	PB	Multiplex PCR	157	223	64	93	94	129
2000	Steinhoff	Caucasian	HB	Triplex PCR	135	127	55	80	70	57
1999	Salagovic	Caucasian	PB	PCR	76	248	36	40	125	123
1998	Abdel-Rahman	African	PB	Multiplex PCR	37	34	11	26	19	15
1996	Brockmöller	Caucasian	HB	PCR	374	363	156	218	171	192
1996	Anwar	Caucasian	HB	PCR-RFLP	22	21	3	19	11	10
1993	Zhong	Caucasian	PB	PCR	97	225	58	39	131	94

HB = hospital-based (controls), PB = population-based (controls), PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, RT-PCR = reverse transcription-polymerase chain reaction, SOC = source of controls.

plot. The overall outcomes revealed that our results were statistically dependable.

4. Discussion

BCa is one of the most common cancers of the urinary tract. However, the exact mechanisms of bladder carcinogenesis remain unclear. There is a growing realization that the development of BCa is caused by a complex interaction of both genetic and environmental factors.[98] Although genetic factors are considered to be a crucial part of the pathogenic process of BCa, especially the polymorphisms in metabolic pathways.[99] As one of the most important parts of phase II super family of metabolism enzymes, GSTs are composed of 7 classes (α, μ, ω, π, σ, θ, ξ).[100] Among them, GSTA1, GSTM1, GSTP1, and GSTT1 are considered to be the most important. Almost all members of the GST family show genetic polymorphism, which leads to a complete absence or lowering of enzyme activity.

GSTA1 has 3 single nucleotide polymorphisms (SNPs): −567TOG, −69COT, and −52GOA.[101] Differential expression with lower transcriptional activation of variant GSTA1*B (−567G, −69T, and −52A) than common GSTA1*A allele

Table 3

Characteristics of individual studies included in the meta-analysis.

GSTP1	rs1695						Case (n)				Control (n)			
Year	Surname	Ethnicity	SOC	Genotyping	Case	Control	AA	AG	GG	AG+GG	AA	AG	GG	AG+GG
2014	Reszka	Caucasian	PB	RT-PCR	244	365	116	109	19	128	160	166	39	205
2013	Matic	Caucasian	HB	PCR-RFLP	201	122	84	95	22	117	49	52	21	73
2013	Safarinejad	Asian	HB	PCR-RFLP	166	332	54	88	24	112	172	152	8	160
2013	Pandith	Asian	HB	PCR-RFLP	180	210	129	45	6	51	159	48	3	51
2012	Lesseur	Caucasian	PB	SNP Panel	658	928	294	289	75	364	411	414	103	517
2011	Zhang	Asian	HB	PCR-RFLP	200	200	83	72	45	117	92	81	27	108
2009*	Grando	Caucasian	PB	PCR-RFLP	100	100	73	–	–	27	67	–	–	33
2009	Fontana	Caucasian	HB	TaqMan	51	45	20	27	4	31	28	13	4	17
2009	Altayli	Caucasian	HB	PCR-RFLP	135	128	75	46	14	60	62	58	8	66
2008	Yuan	Caucasian	PB	PCR-RFLP	657	684	301	274	82	356	284	327	73	400
2008	Kopps	Caucasian	HB	PCR-RFLP	143	196	66	56	21	77	82	82	32	114
2006	Xing	Asian	HB	PCR-RFLP	108	112	59	42	7	49	69	39	4	43
2005	Srivastava	Caucasian	PB	PCR-RFLP	106	370	33	58	15	73	191	166	13	179
2005	Saad	Caucasian	PB	PCR-RFLP	72	82	40	19	13	32	44	32	6	38
2005	García-Closas	Caucasian	HB	TaqMan	1141	1138	486	525	130	655	488	531	119	650
2005	Cao	Caucasian	HB	PCR-RFLP	145	170	77	66	2	68	93	66	11	77
2005	Broberg	Caucasian	PB	TaqMan	61	155	24	27	10	37	71	69	15	84
2004	Hung	Caucasian	HB	PCR-RFLP	201	214	103	77	21	98	112	78	24	102
2002	Ma	Asian	PB	PCR-RFLP	61	179	33	27	1	28	110	59	10	69
2001	Törüner	Caucasian	HB	PCR-RFLP	121	121	67	42	12	54	83	33	5	38
2000	Steinhoff	Caucasian	HB	PCR-RFLP	135	127	67	59	9	68	70	46	11	57
2000†	Peluso	Caucasian	HB	PCR-RFLP	123	54	50	–	–	73	32	–	–	22
1997	Harries	Caucasian	PB	PCR-RFLP	71	155	25	32	14	46	79	66	10	76

HB = hospital-based (controls), PB = population-based (controls), PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, RT-PCR = reverse transcription-polymerase chain reaction, SOC = source of controls.

* AG + GG genotypes: 27 cases and 33 controls.

† AG + GG genotypes: 73 cases and 22 controls.

(−567T, −69C, and −52G) are resulted from these replacements.[102] GSTM1 plays an important role in preventing the development of cancers. The inherited homozygous absence of the GSTM1 gene results in the deficiency of the enzyme activity.[103] GSTP1 is an important part of GST families, and the most commonly studied GSTP1 variant is exon 5 Ile105Val, encoding an Ile/Val exchange at codon 105 (Ile105Val; A105G) (rs947894), which has been shown to be linked to lower expression of metabolic activity.[104] People with the GSTT1 null genotype was reported to have decreased enzyme activity and decreased ability to detoxify the environmental and dietary agents, especially 1,3-butadiene and ethylene oxide, which could induce chromosomal damage and make people more susceptible to cancer.[105] By catalyzing the detoxification of electrophilic compounds through conjugation with glutathione, these enzymes can prevent cells from damage.[106] Besides, GSTs are able to regulate the induction of other proteins and enzymes which is important for cellular functions. The polymorphisms affect the enzyme activity, leading to increased genotoxic damage and affect the transportation of steroid hormones, causing the development of cancer eventually.[107,108] GSTs are essential for maintaining genomic integrity because electrophilic compounds could damage the DNA.[109] Therefore, GSTA1, GSTM1, GSTP1, and GSTT1 may play an important role in the development of BCa.

Recently, there were increasing case–control studies concerned with the associations between GSTs polymorphisms and BCa susceptibility.[19–97] Nevertheless, the inconsistent results of them might owe to limited sample size, various methodologies, and race and dissimilar source of controls. Although several meta-analyses have explored the relationship between GSTM1, GSTP1, and GSTT1 polymorphisms and BCa susceptibility, respectively,[10–14] the results remain unclear. Besides, because of relatively small number of studies, no meta-analysis on GSTA1 has been performed before. What is more, additional studies have been published since the last meta-analysis. So, all these might have generated great influence to the previous conclusions. Thus, we did this meta-analysis.

For the first time, we performed meta-analysis on the relationship between GSTA1 polymorphism and BCa susceptibility. We included 4 case–control studies in this meta-analysis, and the results suggested that there was no association. According to the published papers, the conclusion on the relationship between GSTA1 polymorphism and BCa susceptibility is inconsistent. The exact mechanism of the influence of GSTA1 polymorphism on BCa is still unclear. However, in association with smoking, low activity GSTA1 seems to increase individual susceptibility to BCa.[20] The limited amount of involved studies may become a major factor which could influence the evaluation of the real association between GSTA1 polymorphism and BCa risk.

The analysis of the present studies indicated that the null genotype of GSTM1 polymorphism significantly increases BCa susceptibility. Jiang et al[10] performed a meta-analysis indicating the similar results with ours in 2011, which included 33 studies. Nevertheless, 48 studies were involved in our meta-analysis, which could provide more comprehensive and reliable results.

Meanwhile, similar to the outcome of the meta-analysis conducted by Gong et al in 2012,[14] significant associations between GSTT1 polymorphism and BCa susceptibility were discovered. However, we included 7 more studies, which could be more credible.

Table 4

Characteristics of individual studies included in the meta-analysis.

GSTT1							Case (n)		Control (n)	
Year	Surname	Ethnicity	SOC	Genotyping	Case	Control	Present	Null	Present	Null
2015	Ceylan	Caucasian	HB	PCR-RFLP	65	70	46	19	61	9
2014	Reszka	Caucasian	PB	RT-PCR	244	365	212	30	288	77
2013	Matic	Caucasian	HB	PCR	201	122	145	56	88	34
2013	Berber	Caucasian	HB	Multiplex PCR	114	114	83	31	98	16
2013	Kang	Asian	HB	Multiplex PCR	110	220	46	64	92	128
2013	Safarinejad	Asian	HB	PCR	166	332	131	35	263	69
2012	Lesseur	Caucasian	HB	–	662	923	556	106	780	143
2012	Ovsiannikov	Caucasian	HB	Duplex PCR	196	235	163	33	188	47
2011	Goerlitz	Caucasian	PB	TaqMan	617	620	470	147	464	156
2011	Henríquez-Hernández	Caucasian	HB	Multiplex PCR	90	81	30	60	41	40
2011	Moore	Caucasian	PB	Melt curve/copy number assays	1004	1179	794	210	942	237
2011	Salinas-Sánchez	Caucasian	HB	Multiplex PCR	190	163	148	42	138	25
2011	Rouissi	African	PB	Multiplex PCR	125	125	95	30	87	38
2010	Cantor	Caucasian	HB	TaqMan	678	710	542	136	550	160
2009	Altayli	Caucasian	HB	Multiplex PCR	135	128	104	31	119	9
2009	Song	Asian	HB	Multiplex PCR	208	212	98	110	107	105
2008	Yuan	Caucasian	PB	Multiplex PCR	658	680	518	140	556	124
2008	Covolo	Caucasian	PB	PCR-RFLP	197	211	155	42	178	33
2008	Song	Asian	HB	Multiplex PCR	108	112	37	71	54	58
2008	Grando	Mixed	PB	Multiplex PCR	100	100	49	51	63	37
2007	Cengiz	Caucasian	HB	Multiplex PCR	51	53	33	18	42	11
2007	Zhao	Mixed	PB	TaqMan	623	634	520	103	519	115
2006	Kogevinas	Caucasian	HB	—	99	91	75	24	74	17
2006	Shao	Asian	PB	Multiplex PCR	405	389	201	204	194	195
2006	Ouerhani	African	PB	Multiplex PCR	62	79	36	26	44	35
2006	McGrath	Mixed	PB	PCR	191	924	156	35	776	148
2005	Sobti	Caucasian	PB	Multiplex PCR	100	76	70	30	65	11
2005	Srivastava	Caucasian	PB	Multiplex PCR	106	370	78	28	291	79
2005	Saad	Caucasian	PB	PCR	72	81	46	26	67	14
2005	Broberg	Caucasian	PB	PCR	61	154	54	7	132	22
2005	García-Closas	Caucasian	HB	TaqMan	1146	1137	916	230	889	248
2005	Golka	Caucasian	HB	PCR	136	163	106	30	125	38
2005	Kim	Asian	HB	Multiplex PCR	153	153	82	71	64	89
2005	Karagas	Mixed	PB	PCR	354	541	301	53	458	83
2004	Moore	Caucasian	PB	PCR	106	109	89	17	97	12
2004	Sanyal	Caucasian	PB	Duplex PCR	270	122	204	66	110	12
2004	Srivastava	Caucasian	HB	Multiplex PCR	106	182	78	28	153	29
2004	Hung	Caucasian	HB	PCR	201	214	158	43	181	33
2004	Chen	Asian	PB	Multiplex PCR	62	81	30	32	30	51
2003	Jong Jeong	Asian	HB	PCR	126	204	58	68	91	113
2003	Gago-Dominguez	Mixed	PB	Multiplex PCR	196	176	146	50	142	34
2002	Lee	Caucasian	HB	Multiplex PCR	232	165	97	135	80	85
2002	Giannakopoulos	Caucasian	HB	PCR	89	147	84	5	131	16
2002	Ma	Asian	PB	PCR	61	182	32	29	94	88
2002	Kim	Asian	PB	Multiplex PCR	216	449	125	91	221	228
2001	Törüner	Caucasian	HB	PCR	121	121	97	24	100	21
2000	Schnakenberg	Caucasian	PB	Multiplex PCR	157	223	129	28	175	48
2000	Steinhoff	Caucasian	HB	Triplex PCR	135	127	115	20	110	17
2000	Peluso	Caucasian	HB	PCR-RFLP	122	54	108	14	48	6
2000	Kim	Asian	HB	Multiplex PCR	112	220	65	47	119	101
1999	Salagovic	Caucasian	PB	PCR	76	248	55	21	206	42
1999	Lee	Asian	HB	Multiplex PCR	158	131	65	93	65	66
1998	Abdel-Rahman	Caucasian	PB	Multiplex PCR	37	34	20	17	29	5
1998	Salagovic	Caucasian	PB	PCR	67	248	47	20	206	42
1998	Katoh	Asian	PB	Multiplex PCR	112	112	66	46	59	53
1998	Kim	Asian	HB	–	67	67	49	18	38	29
1996	Kempkes	Caucasian	PB	PCR	113	170	93	20	139	31

HB = hospital-based (controls), PB = population-based (controls), PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, RT-PCR = reverse transcription-polymerase chain reaction, SOC = source of controls.

Table 5

Meta-analysis results of association between GSTs polymorphism and bladder cancer risk.

	GSTA1				GSTM1				GSTP1				GSTT1			
	N*	Sample size	OR (95%CI)†	P‡	N*	Sample size	OR (95%CI)†	P‡	N*	Sample size	OR (95%CI)†	P‡	N*	Sample size	OR (95%CI)†	P‡
Total	4	1278	1.05 (0.83–1.33)	0.184	48	25268	**1.39 (1.28–1.51)**	0	23	11267	1.07 (0.96–1.20)	0.062	57	27702	**1.11 (1.00–1.22)**	0
Ethnicity																
Caucasian	–	–	–	–	29	15666	**1.39 (1.23–1.58)**	0	18	9519	1.05 (0.92–1.19)	0.038	36	18544	**1.25 (1.09–1.44)**	0
Asian	–	–	–	–	12	6481	1.45 (1.31–1.61)	0.818	5	1748	1.26 (0.99–1.60)	0.983	14	4928	0.89 (0.78–1.03)	0.226
African	–	–	–	–	4	1810	1.23 (0.95–1.59)	0.257	–	–	–	–	2	391	0.79 (0.52–1.22)	0.610
Mixed	–	–	–	–	3	1311	1.16 (0.93–1.45)	1.765	–	–	–	–	5	3839	1.13 (0.90–1.42)	0.179
SOC																
PB	–	–	–	–	18	7862	1.21 (1.07–1.37)	0.092	9	5048	0.99 (0.84–1.17)	0.171	28	15074	1.10 (0.96–1.27)	0.000
HB	–	–	–	–	30	17406	**1.49 (1.35–1.64)**	0.002	14	6219	1.14 (0.98–1.31)	0.129	29	12628	1.11 (0.97–1.28)	0.001
Mixed	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
n	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

CI = confidence interval, GST = glutathione S-transferase, HB = hospital-based (controls), OR = odds ratio, PB = population-based (controls), PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, RT-PCR = reverse transcription-polymerase chain reaction, SOC = source of controls.
* Number of studies.
† Random-effects model was used when P value for heterogeneity test <0.1; otherwise, fixed-effects model was used.
‡ P value of Q test for heterogeneity.

In the aspect of GSTP1, contrary to the previous meta-analysis (Wang et al[13] and Kellen et al[111]), this analysis revealed no significant relationship between GSTP1 polymorphism and BCa risk. Wang et al internalized 25 studies, but there were 2 duplicates of previous publication, so we excluded them. Although the result changes, we think it is more believable. And Kellen et al included 16 studies (4273 cases and 5081 controls), whereas we selected 23 studies involving 5080 cases and 6187 controls. Additional studies have been published since the last meta-analysis, which would might change the previous results. So, we think the result of our study is more reliable. More studies are required to validate our results.

Alternatively, subgroup analysis was performed according to ethnicity in GSTM1, GSTP1, or GSTT1 genetic variants. For GSTM1, when stratified by ethnicity, significant difference was detected in both Caucasian and Asian populations instead of African populations and Mixed populations. No significant relationship was observed between GSTP1 polymorphism and BCa risk in patients when stratified by ethnicity. For GSTT1, significant associations were observed only in Caucasians. As a complicated multigenetic disease, cancer has diversity among different ethnic populations, and the existence of the discrepancy might owing to different genetic background.[110] As a result of ethnic differences, the incidence of gene polymorphisms may vary notably among different phyletic populations. Although the possible reasons of the conflicting results were unknown, there might be several explanations for it. First, among different ethnic groups, various environmental factors and genetic backgrounds might not be exposed sheerly, which might also be affected by unidentified genes. Second, the selection bias and limitation of sample size should also be taken into consideration.

In the present meta-analysis, the cases and controls were from dissimilar sources. The results suggest that there is association between GSTM1 null genotype and BCa susceptibility both in the subgroup analysis of studies with HB and PB controls. Our meta-analysis also revealed there is no relationship between other GSTs polymorphisms and BCa risk in their respective SOC groups. Subgroup analysis was not performed owing to the limited studies for GSTA1. However, more prospective studies should be performed to evaluate if there has indeed an association between the other GSTs polymorphisms and BCa risk exists in the subgroup analysis of SOC.

Despite the certain conclusions generated in this study, there still exist several limitations. First, the sample sizes of GSTM1, GSTP1, and GSTT1 were large enough, nevertheless which caused possible false positive conclusions. Second, the number of some subgroups was relatively small, and it is hard to search for the reliable association with limited statistical power. Third, when it comes to GSTA1 polymorphism, the sample size was too small. Additional studies with higher quality and larger sample size should be included in the future to verify our result. Fourth, BCa results from complex interactions between a variety of genetic and environmental factors, thereby suggesting that BCa susceptibility would not be influenced by any single gene. BCa is a multifactorial disease, so the complex interactions like gene-environment factors could not be ignored. Last, the total outcomes were based on unadjusted effect estimates without enough data for the adjustment by other covariates, such as smoking status, age, gender, and so on. The influence of confounding factors should be payed more attention. Hence, a more precise meta-analysis could be conducted if detailed data of some individual studies can be accessed.

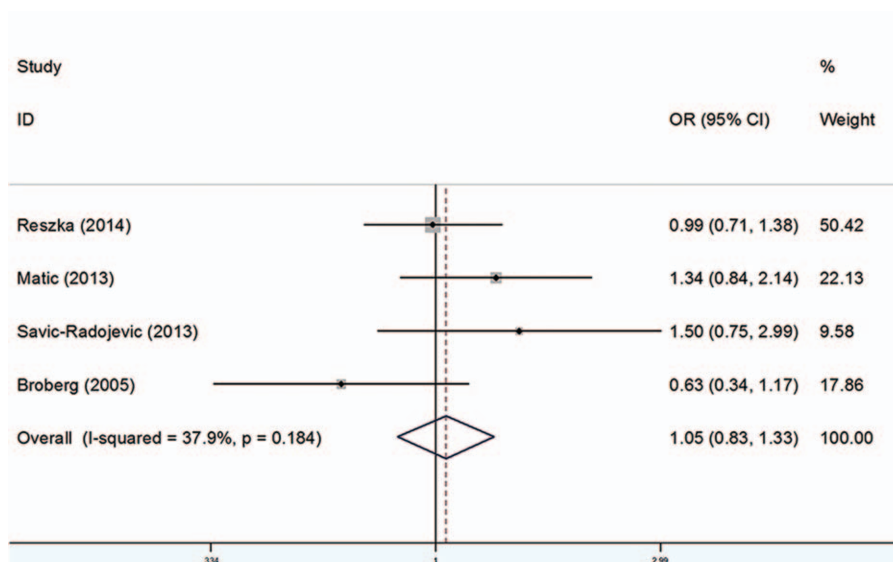

Figure 2. Forest plots of the association between GSTA1 polymorphism and bladder cancer susceptibility. CI=confidence interval, OR=odds ratio.

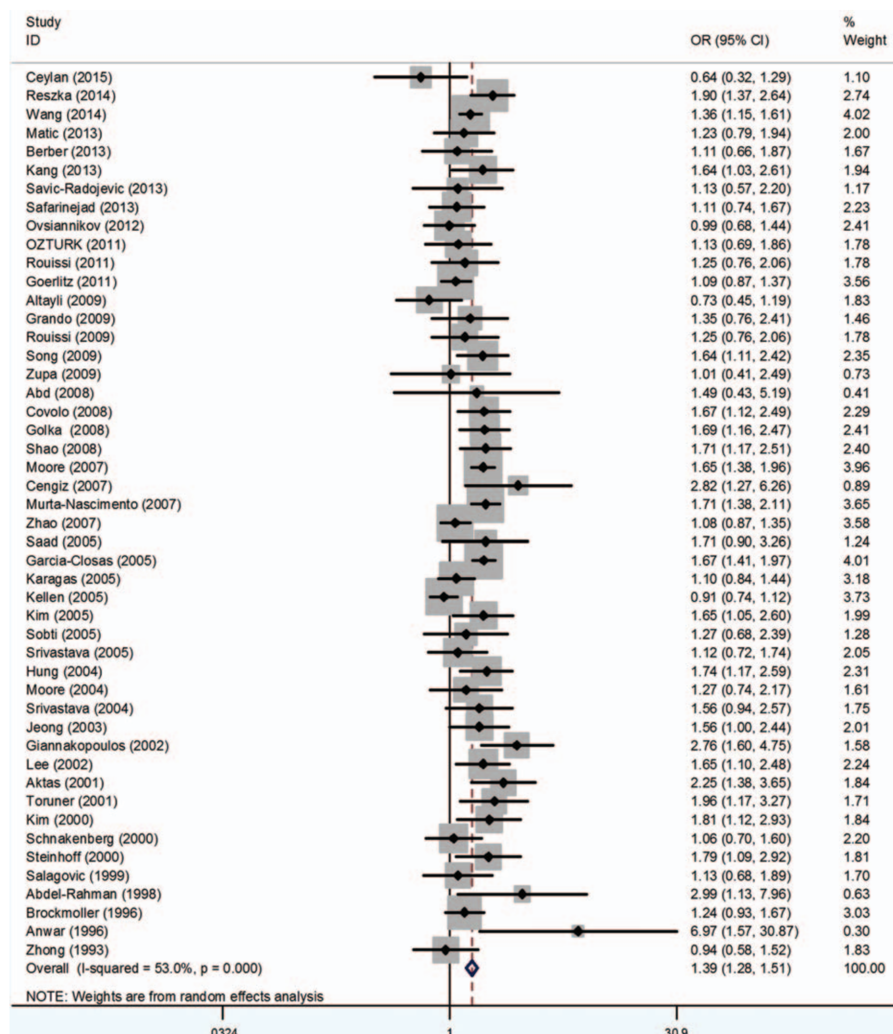

Figure 3. Forest plots of the association between GSTM1 polymorphism and bladder cancer susceptibility. CI=confidence interval, OR=odds ratio.

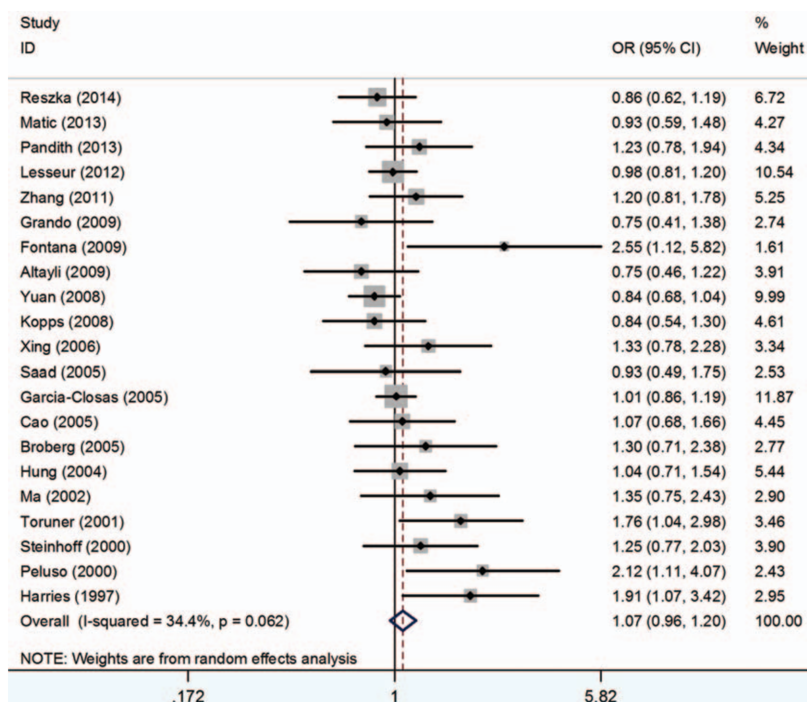

Figure 4. Forest plots of the association between GSTP1 polymorphism and bladder cancer susceptibility. CI=confidence interval, OR=odds ratio.

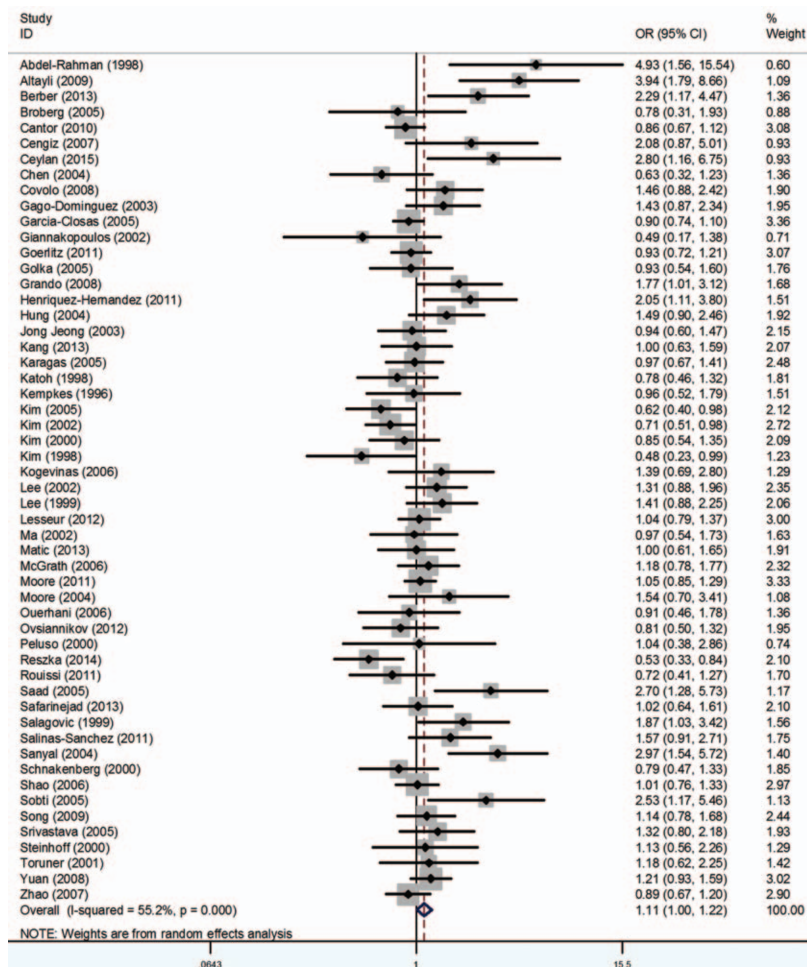

Figure 5. Forest plots of the association between GSTT1 polymorphism and bladder cancer susceptibility. CI=confidence interval, OR=odds ratio.

The results indicated that the GSTM1 null genotype might elevate BCa susceptibility, and the GSTT1 polymorphism might enhance BCa risk. No significant associations were observed between GSTA1 or GSTP1 polymorphism and BCa risk. For the 1st time, we performed this meta-analysis to evaluate the association between GSTA1 polymorphism and BCa risk. However, taking the restriction of sample size into consideration, analysis with larger and more well-designed studies is required to validate our results. In the future, the analysis of different combinations of polymorphisms of the 4 isoforms could be performed if the data is available.

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