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Genetic polymorphisms of glutathione S-transferase M1 and bladder cancer risk: a meta-analysis of 26 studies

RongGui Zhang · GuangYong Xu · WenJun Chen · WeiLi Zhang

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Abstract Studies investigating the association between glutathione S-transferase M1 (GSTM1) polymorphism and bladder cancer risk report conflicting results. The objective of this study was to quantitatively summarize the evidence for such a relationship. We performed a systematic search of the National Library of Medline and Embase databases. This meta-analysis included 26 case-control studies, which included 5029 bladder cancer cases and 6680 controls. The combined results based on all studies showed that the GSTM1 null genotype was associated with an increased risk of bladder cancer (OR = 1.46, 95% confidence interval [CI] = 1.35, 1.57). When stratifying for race, results were similar among Asians (OR = 1.60, 95% CI = 1.27, 2.01) and Caucasians (OR = 1.44, 95% CI = 1.33, 1.57) except Africans (OR = 1.25, 95% CI = 0.76, 2.06). When stratifying by the smoking, stage, grade, and histological type of bladder cancer, we found no statistical association. Our meta-analysis suggests that the GSTM1 null genotype is associated with a modest increase in the risk of bladder cancer.

Keywords Bladder cancer · Glutathione S-transferase M1 · Gene polymorphism · Meta-analysis

Introduction

An estimated 357,000 cases of bladder cancer occurred worldwide in 2002, making this the ninth most common cause of cancer for both sexes combined. Bladder cancer is the second most common genitourinary malignant disease in the USA, with an expected 69,000 newly diagnosed cases in 2008, and 14,000 deaths [1]. It has been reported in literature that tobacco is one of the main risk factor for bladder cancer, approximately half of the cases of male urinary tract cancer and one-third of the cases of female urinary tract cancer could be attributable to cigarette smoking [2]. Risk factors for the development of bladder cancer can be classified into three subsets: genetic and molecular abnormalities, chemical or environmental exposures, and chronic irritation [3]. Several genetic susceptibility factors have been studied in relation to bladder cancer. A recent meta-analysis of glutathione S-transferase T1 (GSTT1) and bladder cancer, including 37 studies, 6,986 cases and 9,166 controls, found that that GSTT1 null status is associated with a modest increase in the risk of bladder cancer [4]. A previous meta-analysis of 16 studies, 4,273 cases and 5,081 controls, suggested that glutathione S-transferase P1 (GSTP1) *Ile 105Val* was associated with a modest increase in the risk of bladder cancer [5].

Glutathione S-transferases (GSTs) are a family of phase II enzymes that catalyze the conjugation of many endogenous and exogenous electrophilic compounds to glutathione [6, 7]. GSTs play an important role in the protection of cells from the products of oxidative stress, as well as from several environmental carcinogens [8–10]. In humans, eight distinct gene families encode soluble GSTs; among them, four are mainly expressed in human tissues: GSTA, GSTM, GSTT, and GSTP. GSTM1 null genotype is due to an inherited deletion of the paternal and maternal alleles of the respective genes and is associated with low ability to detoxify several xenobiotics and lower defense against oxidative stress and free radical-mediated cellular damage [11–13]. GSTM1 null genotype has been reported

R. Zhang · G. Xu · W. Chen · W. Zhang (✉)
Department of Urology, The Second Affiliated Hospital, Chongqing Medical University, Chongqing 400010, China
e-mail: wlzhang@hotmail.com

to be associated with cancers of the gastric [14], colorectum [15], lung [16], breast [17], head and neck [18].

Many case–control studies have investigated the association between GSTM1 null genotype and risk of bladder cancer over the last two decades, but these studies have reported conflicting results. Most of the studies conducted have been rather small with limited statistical power, and potential interaction with smoking has not been properly investigated. Although, in 2002, there has been one meta-analysis that suggested that GSTM1 null status was associated with a modest increase in the risk of bladder cancer, this meta-analysis did not include very recent studies [19]. So we conducted the meta-analysis to update and quantitatively summarize the evidence for such a relationship.

Methods

Literature search

We performed a systematic search of the National Library of Medline and Embase to identify studies on GSTM1 null genotype and bladder cancer published before 2010. The following key words were used: 'GSTM1' or 'Glutathione S-transferases', 'bladder', 'carcinoma' or 'cancer' or 'tumor'. The reference lists of reviews and retrieved articles were handsearched at the same time. We did not consider abstracts or unpublished reports. All studies on GSTM1 null genotype and bladder cancer published before 2010 were included. No language restrictions were applied; all non-English articles were translated if necessary.

Selection criteria

Titles and abstracts of all citations and retrieved studies were reviewed by two independent researchers. To be eligible for inclusion, studies had to be case–control that reported genotypic frequencies for both case and control populations. Interim analyses, overlapping study populations, and comparisons of laboratory methods were excluded.

Statistical analysis

We imported data into STATA, version 9.2 (Stata Corporation, College Station, Texas). To determine whether to use the fixed- or random-effects model, we measured statistical heterogeneity between and within groups using the Q statistic, $P < 0.05$ was considered statistically significant. Heterogeneity was also assessed through visual examination of L'Abbe plots. We used fixed-effects methods if the result of the Q test was not significant. Otherwise, we calculated pooled estimates and confidence intervals assuming a random-effects model. While publication bias was not expected, we assessed this possibility using Begg funnel plots and Egger's bias test [20, 21]. We calculated separate pooled estimates for different ethnic groups and geographic regions. Subgroup analysis was conducted on the basis of the smoking, stage, grade, and histological type of bladder cancer.

Results

There were 156 papers relevant to the searching words. Through the step of screening the title, 52 of these articles were excluded (31 were not case–control studies, 21 were not conducted in humans). Abstracts from 104 articles were reviewed and an additional 67 trials were excluded (42 were not case–control studies, 25 were not conducted in humans), leaving 37 studies for full publication review. Of these, 12 were excluded (seven were not for GSTM1 [4, 5, 22–26], four did not report usable data [27–30], one was duplicate [31]); thus, 25 papers [32–56], which included 26 case–control studies, were found to conform to our inclusion criteria. This meta-analysis included 5,029 bladder cancer cases and 6,680 controls. Twenty-six studies, including six population-based case–control studies and twenty-one hospital-based case–control studies, were included in this meta-analysis. Of these studies, 21 reported on Caucasians, four reported on Asians, and one reported on Africans. Studies were carried out in UK, China, Egypt, Germany, Turkey, Italy, Argentina, India, Spain, Brazil, USA, Korea and Tunisia. Table 1 provides general characteristics of the studies.

The combined results based on all studies showed that the GSTM1 null genotype was associated with an increased risk of bladder cancer (OR = 1.46, 95% confidence interval [CI] = 1.35, 1.57). When stratifying for race, results were similar among Asians (OR = 1.60, 95% CI = 1.27, 2.01) and Caucasians (OR = 1.44, 95% CI = 1.33, 1.57) except Africans (OR = 1.25, 95% CI = 0.76, 2.06) (Fig. 1). When stratifying by the smoking, stage, grade, and histological type of bladder cancer, we found no statistical association (Table 2).

No statistically significant heterogeneity was observed between subgroups for overall test with the Q statistic ($P = 0.61$). In addition, L'Abbe plots did not show evidence of heterogeneity (Fig. 2). Review of funnel plots could not rule out the potential for publication bias for all analysis. Publication bias was not evident when the Begg rank correlation method ($P = 0.97$) and the Egger weighted regression method ($P = 0.91$) were used (Figs. 3, 4).

Table 1 Characteristics of studies included in the meta-analysis

Study (author, year)	Design	Study period	Population (country)	Genotyping method	No. of cases	No. of controls	Null of cases	Null of controls
Zhong, 1993	PCC	DNR	Caucasians (UK)	PCR	97	225	39	94
Anwar, 1996	HCC	DNR	Caucasians (Egypt)	PCR-RFLP	22	21	19	10
Brockmoller, 1996	HCC	1991–1994	Caucasians (Germany)	PCR-RFLP	374	373	218	192
Kim, 2000	HCC	1997–1998	Asians (Korea)	PCR	112	220	78	123
Aktas, 2001	HCC	1997–1999	Caucasians (Turkey)	PCR	103	202	56	70
Toruner, 2001	HCC	DNR	Caucasians (Turkey)	PCR	121	121	75	55
Ma, 2002	HCC	DNR	Asians (China)	PCR	61	182	37	99
Jong, 2003	HCC	2002	Asians (Korea)	PCR	126	204	75	99
Hung, 2004	HCC	1997-2000	Caucasians (Italy)	PCR-RFLP	201	214	132	112
Moore, 2004	PCC	1996-2000	Caucasians (Argentina)	PCR	106	109	54	49
Saad, 2005	PCC	DNR	Caucasians (Egypt)	PCR	72	81	45	40
Sobti, 2005	PCC	DNR	Caucasians (India)	PCR	100	76	37	24
Srivastava, 2005	HCC	2001–2003	Caucasians (India)	PCR-RFLP	106	370	43	140
McGrath, 2006a	PCC	1989–1990	Caucasians (USA)	PCR	64	648	31	340
McGrath, 2006b	PCC	1989–1990	Caucasians (USA)	PCR	127	274	78	143
Cengiz, 2007	HCC	2003–2005	Caucasians(Turkey)	PCR	51	53	34	22
Moore, 2007	HCC	1998–2001	Caucasians (Spain)	PCR	1077	1022	683	524
Murta, 2007	HCC	1998–2001	Caucasians (Spain)	PCR	679	735	428	367
Zhao, 2007	HCC	1999-DNR	Caucasians (USA)	PCR	622	633	324	317
Abd, 2008	HCC	DNR	Caucasians (Egypt)	PCR	20	20	11	9
Covolo, 2008	HCC	1997–2000	Caucasians (Italy)	PCR-RFLP	197	211	128	111
Altayli, 2009	HCC	2005–2007	Caucasians (Turkey)	PCR-RFLP	135	128	58	65
Grando, 2009	HCC	2004–2007	Caucasians (Brazil)	PCR-RFLP	100	100	51	37
Rouissi, 2009	HCC	DNR	Africans (Tunisia)	PCR	125	125	63	56
Song, 2009	HCC	2004–2005	Asians (China)	PCR-RFLP	208	212	131	108
Zupa, 2009	HCC	DNR	Caucasians(Italy)	PCR-RFLP	23	121	13	68

HCC hospital-based case–control, *PCC* population-based case–control, *DNR* data not reported, *PCR* polymerase chain reaction, *RFLP* restriction fragment length polymorphism

Discussion

Although, in 2002, there has been one meta-analysis that suggested that GSTM1 null status was associated with a modest increase in the risk of bladder cancer [19], many new case–control studies have investigated the association between GSTM1 null genotype and risk of bladder cancer over the last 10 years. Small studies of genetic associations often have insufficient power, increasing the risk that chance could be responsible for their conclusions. Combining data from many studies has the advantage of reducing random error [57]. Meta-analysis enabled us to apply the same kind of criteria to all the study datasets and to obtain precise estimates for subgroups. Our meta-analysis of 5,029 bladder cancer cases and 6,680 controls from 26 case–control studies provides evidence that the GSTM1 null genotype is associated with a modest increase in the risk of bladder cancer.

GSTM1 null genotype also has been extensively studied for many other cancers. To explore the real association between GSTM1 polymorphisms and lung cancer risk, Carlsten et al. conducted a literature-based systematic HuGE review and meta-analysis of 98 published genetic association studies including 19,638 lung cancer cases [58]. All studies considered, the GSTM1 null variant was associated with an increased risk of lung cancer, but no increase in risk was seen when only the five largest studies (>500 cases each) were considered. Furthermore, while GSTM1 null status conferred a significantly increased risk of lung cancer to East Asians, such a genotype did not confer increased risk to Caucasians. The meta-analysis by Tripathy et al. suggested that GSTM1 null genotype as a risk factor associated with head and neck cancer [18]. The meta-analysis by La Torre et al. revealed that GSTM1 null genotype might modulate tobacco-related carcinogenesis of gastric cancer [59]. Results of these meta-analyses are consistent with our meta-analysis.

Systematic review and meta-analysis by Zeegers concluded that current cigarette smokers have an approximately

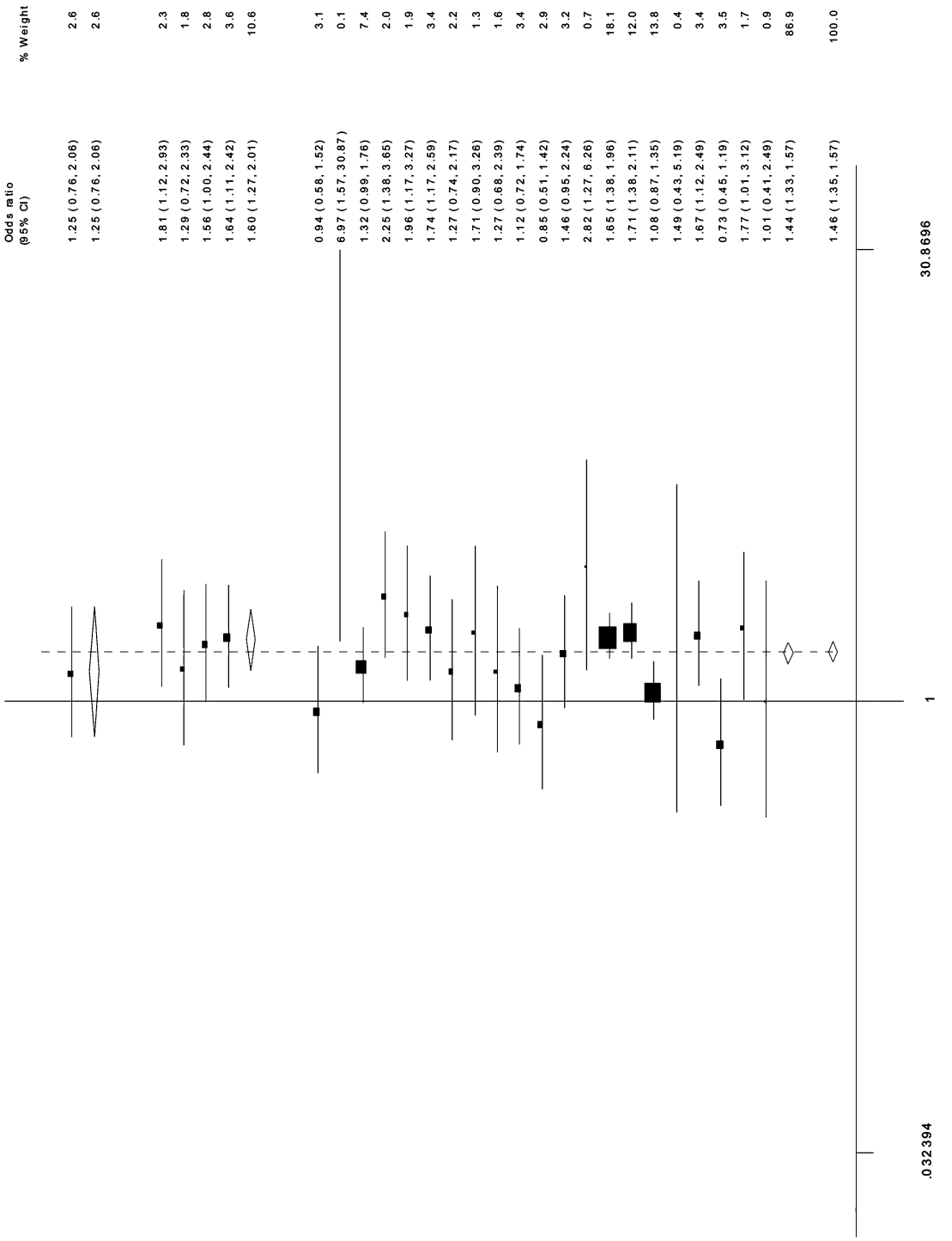

Fig. 1 Meta-analysis of glutathione S-transferase M1 null genotype and bladder cancer risk

Table 2 Subgroup analysis of glutathione S-transferase M1 null genotype and bladder cancer

Stratification of bladder cancer	No. of studies	OR (95% CI)	*P* of OR	*P* of heterogeneity
Smoking: smokers versus nonsmokers	11	1.18 (0.95,1.46)	0.13	0.56
Africans	1	1.50 (0.56,4.03)	0.42	NA
Asians	2	1.59 (0.99,2.57)	0.06	0.22
Caucasians	8	1.08 (0.84,1.37)	0.56	0.68
Stage: invasive versus superficial	3	1.03 (0.75,1.41)	0.85	0.22
Asians	1	0.88 (0.49,1.57)	0.66	NA
Caucasians	2	1.10 (0.75,1.41)	0.61	0.10
Grade: high versus low	4	1.20 (0.89,1.62)	0.22	0.17
Asians	2	1.49 (0.93,2.40)	0.10	0.12
Caucasians	2	1.05 (0.72,1.53)	0.80	0.25
Histological type: papillary versus nonpapillary	1	0.90 (0.55,1.48)	0.68	NA
Caucasians	1	0.90 (0.55,1.48)	0.68	NA

OR odds ratio, *CI* confidence interval, *NA* not applicable

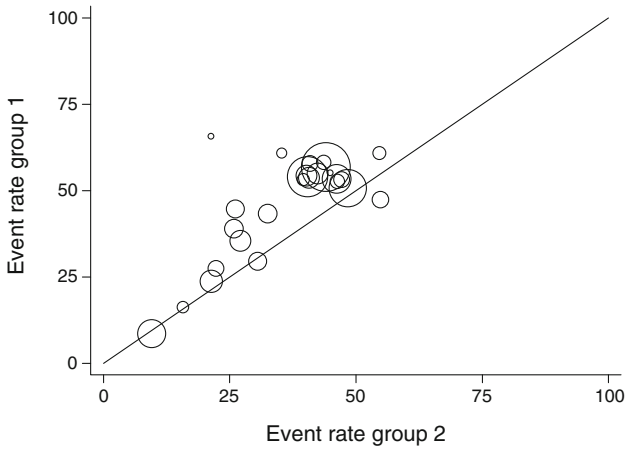

Fig. 2 L'Abbe plots for heterogeneity

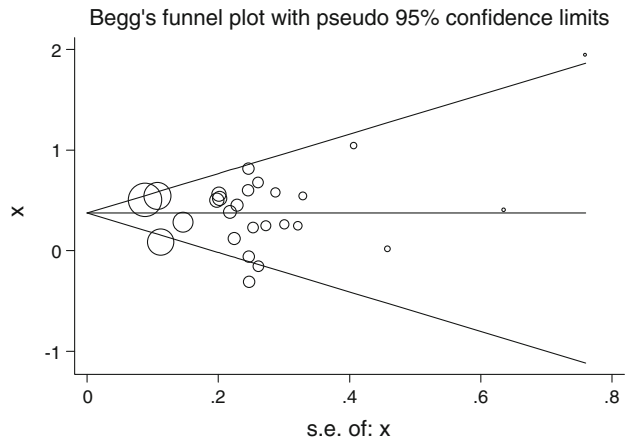

Fig. 3 Begg rank correlation method for publication bias

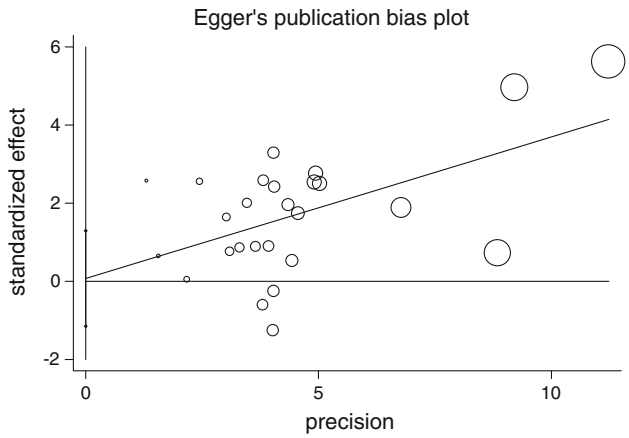

Fig. 4 Egger weighted regression method for publication bias

threefold higher risk of urinary tract cancer than nonsmokers [2]. In Europe, approximately half of urinary tract cancer cases among males and one-third of cases among females might be attributable to cigarette smoking [2]. But no statistical association was found between GSTM1 null genotype and smoking status in our meta-analysis of 11 studies. The apparent discrepancy between these findings could be explained as follows: (i) No gene–gene interactions were detected by different GSTs (GSTT1, GSTM1 and GSTP1) inducing resulting in joint action; (ii) Not all of the studies analyzed the same environmental factors such as diet [50], occupational exposure [41], drinking water chlorination or arsenic exposure and hair dyes [60, 61]; (iii) This result also may be influenced by the different weight of each study, which was dictated by the different size; (iv) Confounding is likely to have occurred, because different ethnic groups smoke different types of cigarettes. Differences in the methods of obtaining detailed smoking histories may

account for the variation observed. The crude exposure classification represented by the smokers or nonsmokers measure may have masked an interaction between level of smoking and GSTM1 on bladder cancer risk. Larger and more rigorous analytical studies will be required to clarify this issue in the future.

Our study has a number of possible limitations. First, the database for the meta-analysis included limited numbers of studies on ethnic minority groups; only four studies reported on Asians and only one study reported on Africans, reflecting the current lack of epidemiologic studies in these populations. Second, only published studies were included in the meta-analysis; therefore, publication bias may have occurred. Further studies should search thoroughly to obtain as many papers as possible, especially the unpublished ones in remote countries. Third, this meta-analysis is based on unadjusted estimates, while a more precise analysis could be performed if individual data were available. Another potential limitation was the small sample size in the analyses. Therefore, the power in the analyses was not sufficient to detect small increased risks. Finally, meta-analysis remains retrospective research that is subject to the methodological deficiencies of the included studies.

In conclusion, this meta-analysis supports conclusions that the GSTM1 null genotype is associated with a modest increase in the risk of bladder cancer. Larger and more rigorous analytical studies will be required to evaluate gene-environment interactions and clarify the interaction between GSTM1 null genotype and smoking status in the future.

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Conflict of interest None.

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