Int J Clin Exp Pathol 2017;10(3):3209-3218
www.ijcep.com /ISSN:1936-2625/IJCEP0046230

Original Article

Glutathione S-transferase M_1 polymorphism and bladder cancer risk: a meta-analysis involving 50 studies

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Received September 27, 2016; Accepted January 20, 2017; Epub March 1, 2017; Published March 15, 2017

Abstract: Glutathione S-transferase M_1 ($GSTM_1$) is an important family of phase II isoenzymes involved in inactivation of procarcinogens, which are factors that contribute to cancer genesis and progression. Null status of $GSTM_1$ is associated with decreased enzyme activity, and it has been widely studied as risk factor in bladder cancer (BC) susceptibility. However, the $GSTM_1$ null variant and BC form unclear association. We carried out meta-analysis to clarify the influence of $GSTM_1$ deficiency on BC. We estimated the pooled odds ratio (OR) with its 95% confidence interval (CI) to assess the association of the two conditions. Fifty studies with a total of 12,527 cases and 16,275 controls were included into the meta-analysis, which was not confined to a specific population. Overall, our meta-analysis supports the hypothesis that the $GSTM_1$ null variant is a determinant of BC susceptibility (OR=1.41 [1.30, 1.52], P<0.00001). The same patterns were observed in Caucasians (OR=1.38 [1.23, 1.55], P<0.00001), Africans (OR=1.68 [1.04, 2.71], P=0.03) and Asians (OR=1.46 [1.33, 1.61], P<0.00001). Furthermore, positive associations were also observed in both hospital-based (OR=1.48 [1.35, 1.61], P<0.00001) and population-based (OR=1.26 [1.10, 1.43], P=0.0006) studies. When data were stratified based on smoking status, we noted that smoking modified the association between $GSTM_1$ deficiency and BC risk (OR=1.41 [1.20, 1.65], P<0.0001) in smokers. However, no association was observed in non-smoking populations. In conclusion, this meta-analysis suggests that $GSTM_1$ null variant is a risk factor of BC.

Keywords: Glutathione S-transferase M_1, polymorphism, bladder cancer, meta-analysis

Introduction

Bladder cancer (BC) is one of the most common cancers of the urinary tract and ranks fourth in the incidence of all common epidemic cancers. The disease also has increasing incidence and death rate. The United States estimates suggested that approximately 74,000 new BC cases were diagnosed, and 16,000 patients died in 2015 [1]. Although the etiology of BC remains largely unknown, a complex combination of genetic and environmental factors is currently accepted to contribute to BC development.

Glutathione S-transferases (GSTs) are members of a multigene family of isoenzymes; These enzymes currently include seven classes [2]. Among such compounds, polymorphisms of $GSTM_1$ ($GSTM_1$), which is expressed in many tissues, are among the most important and extensively studied in humans. $GSTM_1$ deletion was identified to cause formation of null alleles. Individuals with homozygous deletion of the $GSTM_1$ locus may have abolished enzyme activities and decreased ability to detoxify several xenobiotics. On the other hand, $GSTM_1$ null genotype exhibited weaker defence mechanisms against oxidative stress- and free radical-mediated cellular damage [3]. These types of cellular damage can produce chromosomal damage [4]. Therefore, individuals with $GSTM_1$ null genotypes may be at increased risks of developing cancer, especially lung, breast, gastric and BC [5-8]. However, various studies reported inconsistent results regarding the correlation between $GSTM_1$ genotype and individual susceptibility to BC [9, 10]. To clarify the effect of $GSTM_1$

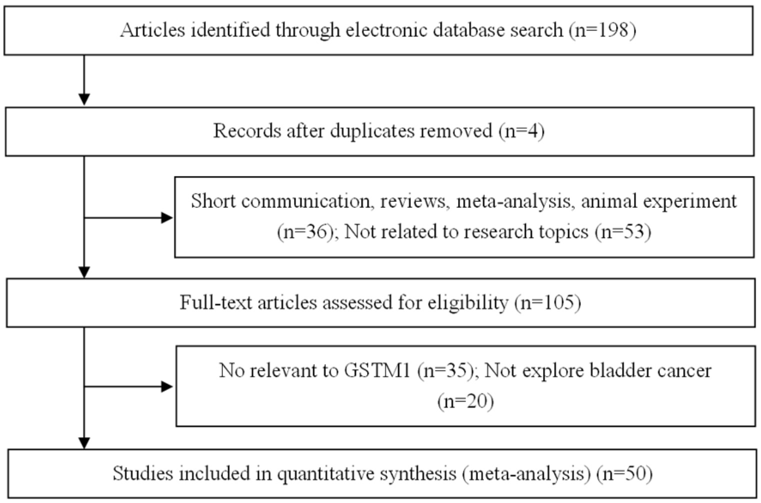

Figure 1. Flow chart of included studies in the current meta-analysis.

status on BC risk, we conducted an updated meta-analysis of published studies.

Materials and methods

Publication search

PubMed, Embase and Springer were separately searched (dated up to 4/20/2016) by two authors using combinations of the following keywords: "glutathione S-transferase M_1" or "$GSTM_1$", "bladder" or "urothelial", and "cancer" or "carcinoma", without any language restriction. A manual search was also conducted on reference lists of reviews and retrieved articles. Abstracts or unpublished studies were excluded. Additional articles were identified through a manual search of references cited in relevant articles.

Eligibility criteria

The studies included in this meta-analysis met the following criteria: (1) Case-control study of human BC; (2) Pathologically confirmed diagnosis of BC; (3) Sufficient data of sample size, odds ratio (OR) and 95% confidence interval (CI); (4) Most recent or contain complete data when identifying multiple studies with identical sample group or overlapping data.

Data extraction

Data were carefully and independently extracted from all eligible publications based on the inclusion criteria, and disagreement was resolved through discussion among the current authors. From each of the eligible study, the following data were extracted independently: First author, years of publication, sources of controls, ethnicity of studied population, number of genotyped cases and controls. Different ethnicities were categorised as Caucasian, Asian, African and mixed individuals. In terms of control sources, studies were also categorised as either population-based or hospital-based.

Statistical analysis

Statistical analysis was carried out using Review Manager 5.1. The OR corresponding to 95% CI was used to assess strength of association between $GSTM_1$ null polymorphism and BC risk. A Chi-square-based Q-statistic test and an I^2 test were performed to assess heterogeneity between studies (I^2<25%, no heterogeneity; I^2=25%-50%, moderate heterogeneity; I^2>50%, large or extreme heterogeneity). Significance levels for heterogeneity were defined as P<0.01 and I^2>50%. Publication bias of the meta-analysis was evaluated using funnel plot and Egger's weighted regression method.

Results

Study characteristics

We obtained 50 relevant articles examining $GSTM_1$ polymorphism and BC risk based on our eligibility criteria [11-60] (**Figure 1**). **Table 1** lists the identified studies and their major characteristics. The data for this analysis included 12,527 cases and 16,275 controls for $GSTM_1$ polymorphism. The studies were published between 1995 and 2014. These researches were conducted in various populations of different ethnicities: 30 involved Caucasians, 12 involved Asians and four involved Africans. We also stratified all studies based on the source of controls: 32 were hospital-based, and the other 18 were population-based. Although not universal, smoking histories were ascertained from cases and controls in 18 studies.

Table 1. Main characteristics of all studies included in the Meta-analysis

Author	Year	Country	Ethnicity	Design	Case		Control	
					Null	Present	Null	Present
Reszka [11]	2014	Poland	Caucasian	PB	149	95	165	200
Wang ML [12]	2014	China	Asian	HB	699	351	834	570
Ceylan GG [13]	2015	Ireland	Caucasian	HB	22	43	31	39
Matic [14]	2013	Serbia	Caucasian	HB	111	90	61	61
Berber [15]	2013	Turkey	Caucasian	PB	54	60	51	63
Kang [16]	2013	South Korea	Asian	HB	65	45	103	117
Savic-Radojevic [17]	2013	Serbia	Caucasian	HB	45	35	32	28
Ovsiannikov [18]	2012	Germany	Caucasian	HB	102	94	122	113
Lesseur [19]	2012	USA	Caucasian	PB	378	275	508	420
Safarinejad [20]	2013	Iran	Caucasian	HB	50	116	93	239
Öztürk [21]	2011	Turkey	Caucasian	PB	98	78	51	46
Goerlitz [22]	2011	Egypt	African	PB	344	274	564	578
Henríquez-Hernández [23]	2012	Spain	Caucasian	HB	23	67	17	64
Salinas-Sánchez [24]	2010	Spain	Caucasian	HB	109	92	78	115
Altayli [25]	2009	Turkey	Caucasian	HB	58	77	65	63
Grando [26]	2009	Brazil	mixed	PB	40	60	33	67
Rouissi [27]	2009	Tunisia	African	PB	63	62	56	69
Song [28]	2009	China	Asian	HB	131	77	108	104
Zupa [29]	2009	Italy	Caucasian	PB	13	10	68	53
Covolo [30]	2008	Italy	Caucasian	HB	128	69	111	100
Golka [31]	2008	Germany	Caucasian	HB	184	109	88	88
Shao [32]	2008	China	Asian	HB	85	117	81	191
Moore [33]	2007	Spain	Caucasian	HB	683	394	524	498
Cengiz [34]	2007	Turkey	Caucasian	HB	34	17	22	31
Murta-Nascimento [35]	2007	Spain	Caucasian	HB	428	251	367	368
Zhao [36]	2007	USA	Caucasian	HB	324	298	317	316
McGrath [37]	2006	USA	Mixed	HB	109	82	483	439
García-Closas [38]	2005	Spain	Caucasian	HB	716	422	571	561
Karagas [39]	2005	USA	mixed	PB	210	144	309	233
Kellen [40]	2005	UK	Caucasian	PB	312	267	597	466
Kim [41]	2005	Korea	Asian	HB	92	61	73	80
Sobti [42]	2005	India	Asian	PB	37	63	24	52
Srivastava [43]	2005	India	Asian	PB	43	63	140	230
Hung [44]	2004	Italy	Caucasian	HB	132	69	112	102
Moore [45]	2004	Argentina	mixed	PB	54	52	49	60
Srivastava [46]	2004	India	Asian	HB	42	64	54	128
Schroeder [47]	2003	USA	Caucasian	HB	137	93	101	112
Jeong [48]	2003	Korean	Asian	HB	75	51	99	105
Giannakopoulos [49]	2002	Greece	Caucasian	HB	56	33	56	91
Lee [50]	2002	Korean	Asian	HB	149	83	86	79
Ma [51]	2002	China	Asian	PB	20	12	99	83
Aktas [52]	2001	Turkey	Caucasian	HB	56	47	70	132
Törüner [53]	2001	Turkey	Caucasian	HB	75	46	55	66
Schnakenberg [54]	2000	Germany	Caucasian	HB	93	64	129	94
Steinhoff [55]	2000	Germany	Caucasian	HB	80	55	57	70
Salagovic [56]	1999	Slovak	Caucasian	PB	40	36	123	125
Abdel-Rahman [57]	1998	Egypt	African	PB	26	11	15	19
Anwar [58]	1996	Egypt	African	PB	19	3	10	11
Brockmöller [59]	1996	Germany	Caucasian	HB	218	156	192	181
Katoh [60]	1995	Japan	Asian	PB	51	32	43	58

Abbreviations: PB, population-based study; HB, hospital-based study.

Study or Subgroup	case Events	case Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Abdel-Rahman 1998	26	37	15	34	0.6%	2.99 [1.13, 7.96]
Aktas 2001	56	103	70	202	1.7%	2.25 [1.38, 3.65]
Altayli 2009	58	135	65	128	1.7%	0.73 [0.45, 1.19]
Anwar 1996	19	22	10	21	0.3%	6.97 [1.57, 30.87]
Berber 2013	54	114	51	114	1.5%	1.11 [0.66, 1.87]
Brockmöller 1996	218	374	192	373	2.9%	1.32 [0.99, 1.76]
Cengiz 2007	34	51	22	53	0.8%	2.82 [1.27, 6.26]
Ceylan GG 2015	22	65	31	70	1.0%	0.64 [0.32, 1.29]
Covolo 2008	128	197	111	211	2.1%	1.67 [1.12, 2.49]
García-Closas 2005	716	1138	571	1132	3.9%	1.67 [1.41, 1.97]
Giannakopoulos 2002	56	89	56	147	1.4%	2.76 [1.60, 4.75]
Goerlitz 2011	344	618	564	1142	3.7%	1.29 [1.06, 1.57]
Golka 2008	184	293	88	176	2.2%	1.69 [1.16, 2.47]
Grando 2009	40	100	33	100	1.3%	1.35 [0.76, 2.41]
Henríquez-Hernández 2012	23	90	17	81	0.9%	1.29 [0.63, 2.64]
Hung 2004	132	201	112	214	2.1%	1.74 [1.17, 2.59]
Jeong 2003	75	126	99	204	1.8%	1.56 [1.00, 2.44]
Kang 2013	65	110	103	220	1.8%	1.64 [1.03, 2.61]
Karagas 2005	210	354	309	542	3.0%	1.10 [0.84, 1.44]
Katoh 1995	51	83	43	101	1.3%	2.15 [1.19, 3.89]
Kellen 2005	312	579	597	1063	3.6%	0.91 [0.74, 1.12]
Kim 2005	92	153	73	153	1.8%	1.65 [1.05, 2.60]
Lee 2002	149	232	86	165	2.1%	1.65 [1.10, 2.48]
Lesseur 2012	378	653	508	928	3.6%	1.14 [0.93, 1.39]
Ma 2002	20	32	99	182	0.8%	1.40 [0.65, 3.03]
Matic 2013	111	201	61	122	1.8%	1.23 [0.79, 1.94]
McGrath 2006	109	191	483	922	2.7%	1.21 [0.88, 1.65]
Moore 2004	54	106	49	109	1.4%	1.27 [0.74, 2.17]
Moore 2007	683	1077	524	1022	3.8%	1.65 [1.38, 1.96]
Murta-Nascimento 2007	428	679	367	735	3.5%	1.71 [1.38, 2.11]
Ovsiannikov 2012	102	196	122	235	2.2%	1.01 [0.69, 1.47]
Reszka 2014	149	244	165	365	2.6%	1.90 [1.37, 2.64]
Rouissi 2009	63	125	56	125	1.6%	1.25 [0.76, 2.06]
Safarinejad 2013	50	166	93	332	2.0%	1.11 [0.74, 1.67]
Salagovic 1999	40	76	123	248	1.5%	1.13 [0.68, 1.89]
Salinas-Sánchez 2010	109	201	78	193	2.1%	1.75 [1.17, 2.60]
Savic-Radojevic 2013	45	80	32	60	1.0%	1.13 [0.57, 2.20]
Schnakenberg 2000	93	157	129	223	2.0%	1.06 [0.70, 1.60]
Schroeder 2003	137	230	101	213	2.2%	1.63 [1.12, 2.38]
Shao 2008	85	202	81	272	2.2%	1.71 [1.17, 2.51]
Sobti 2005	37	100	24	76	1.1%	1.27 [0.68, 2.39]
Song 2009	131	208	108	212	2.2%	1.64 [1.11, 2.42]
Srivastava 2004	42	106	54	182	1.6%	1.56 [0.94, 2.57]
Srivastava 2005	43	106	140	370	1.9%	1.12 [0.72, 1.74]
Steinhoff 2000	80	135	57	127	1.6%	1.79 [1.09, 2.92]
Törüner 2001	75	121	55	121	1.5%	1.96 [1.17, 3.27]
Wang ML 2014	699	1050	834	1404	3.9%	1.36 [1.15, 1.61]
Zhao 2007	324	622	317	633	3.4%	1.08 [0.87, 1.35]
Zupa 2009	13	23	68	121	0.6%	1.01 [0.41, 2.49]
Öztürk 2011	98	176	51	97	1.6%	1.13 [0.69, 1.86]
Total (95% CI)		**12527**		**16275**	**100.0%**	**1.41 [1.30, 1.52]**
Total events	7262		8097			

Heterogeneity: Tau² = 0.03; Chi² = 99.92, df = 49 (P < 0.0001); I² = 51%
Test for overall effect: Z = 8.63 (P < 0.00001)

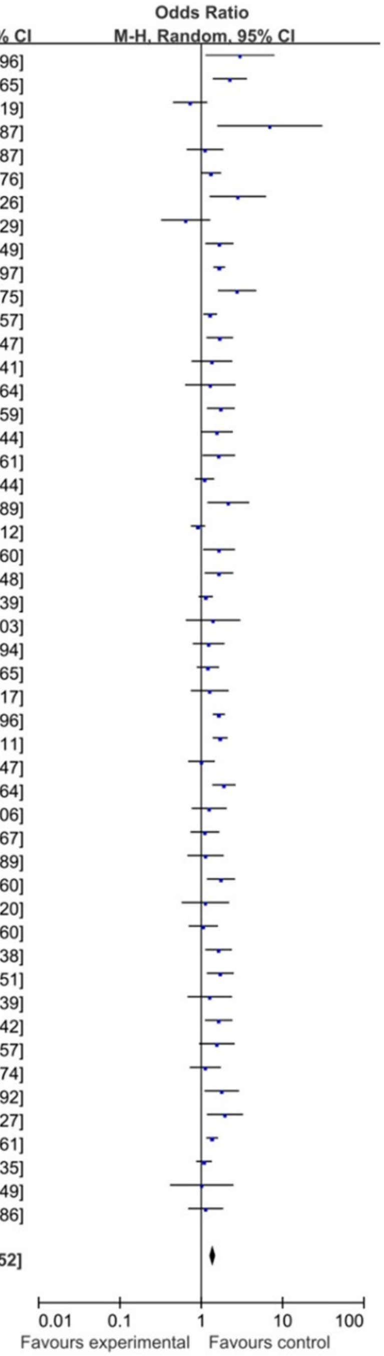

Figure 2. Forest plot for association between $GSTM_1$ polymorphism and BC risk. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

Meta-analysis results

Extreme heterogeneity was observed among the 50 eligible studies (I^2=51%, P<0.0001). Overall data showed that individuals who carried the $GSTM_1$ null genotype had significantly increased BC risks compared with those who carried the $GSTM_1$ genotype (OR=1.41 [1.30, 1.52], P<0.00001) (**Figure 2**). In the subgroup analyses, the same significant associations were observed among Caucasians (OR=1.38 [1.23, 1.55], P<0.00001), Africans (OR=1.68 [1.04, 2.71], P=0.03) and Asians (OR=1.46 [1.33, 1.61], P<0.00001) (**Table 2**).

Table 2. Summary of ORs for $GSTM_1$ polymorphism and bladder cancer risk

Subgroup	N	OR (95% CI)	P	I^2 (%)	Ph^a
Total	50	1.41 [1.30, 1.52]	<0.00001	51	<0.0001
Ethnicity					
Caucasian	24	1.38 [1.23, 1.55]	<0.00001	65	<0.00001
Asian	18	1.46 [1.33, 1.61]	<0.00001	25	=0.16
African	4	1.68 [1.04, 2.71]	=0.03	60	=0.06
Source of control					
PB	18	1.26 [1.10, 1.43]	=0.0006	41	=0.04
HB	32	1.48 [1.35, 1.61]	<0.00001	44	=0.004
Smoking status					
Smoking	18	1.41 [1.20, 1.65]	<0.0001	42	=0.03
No-smoking	18	1.17 [0.94, 1.46]	=0.15	37	=0.06
Sex					
Male	6	1.37 [1.11, 1.69]	=0.003	0	=0.72
Female	5	1.89 [1.19, 3.00]	=0.007	4	=0.39

Notes: [a]*P*-value for heterogeneity. Abbreviations: OR, odds ratio; PB, population-based study; HB, hospital-based study.

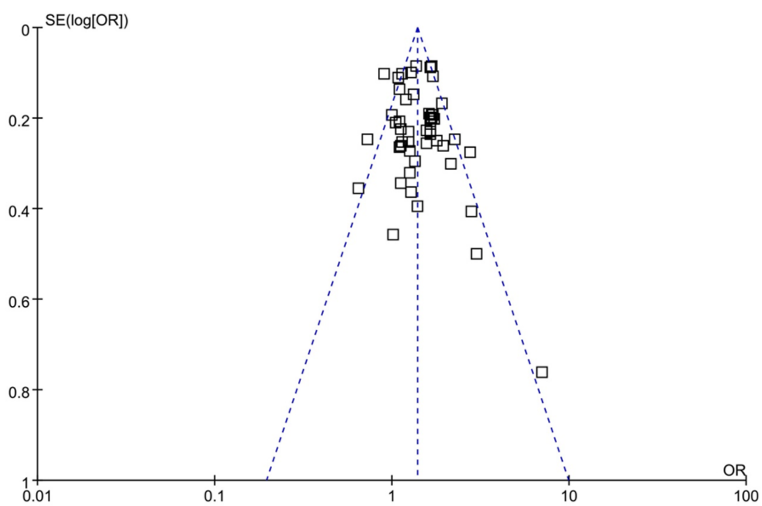

Figure 3. Funnel plot analysis for detecting publication bias. OR values for the main effects of $GSTM_1$ are shown.

In the stratified analyses based on source of controls, the $GSTM_1$ null genotype showed a significant association with increased BC susceptibility in hospital-based (OR=1.48 [1.35, 1.61], P<0.00001) and population-based studies (OR=1.26 [1.10, 1.43], P=0.0006).

We noted that smoking modified the association between $GSTM_1$ polymorphism and BC risk (OR=1.41 [1.20, 1.65], P<0.0001) in smokers. When we stratified the population based on gender, we observed a significant association between $GSTM_1$ polymorphism and BC risk in males (OR=1.37 [1.11, 1.69], P=0.0003) and females (OR=1.89 [1.19, 3.00], P=0.007).

Publication bias

Funnel plot and Egger's test were conducted to estimate publication bias of the meta-analysis. **Figure 3** shows the absence of publication bias in the funnel plots. Results of Egger's test provide statistical evidence for the funnel plot symmetry (t=1.46, P=0.151).

Discussion

At present, the underlying mechanisms of BC remain unknown. Researchers recognize that BC development is caused by complex interactions of both genetic and environmental factors. Environmental factors, such as procarcinogens, are mainly metabolised by various metabolising enzymes in the human body. Different degrees of BC risk are possibly associated with interindividual variations in genetic and cellular mechanisms of detoxification of carcinogenic chemicals, such as sequence variations in genes coding for the GST family.

GSTs are a family of phase II enzymes, which are primarily involved in detoxification of primary metabolites through conjugation with glutathione to produce readily excreted hydrophilic products. Until recently, a number of studies focused on GSTs, especially $GSTM_1$, and BC risk.

In 1993, Bell et al. firstly reported the association between $GSTM_1$ deficiency and increased BC risk. Following the first report, similar studies were conducted in different countries by other researchers [61]. However, most of these studies were based on relatively small samples, and some studies reported conflicting results. A small sample often has insufficient influence, which may lead to inaccurate conclusions. Therefore, combining data from various studies reduces the random error [62]. The meta-analysis enabled us to apply the same criteria to all study datasets and to obtain more accurate estimates of results.

In 2011, Jiang conducted a meta-analysis of data from previous studies and suggested that $GSTM_1$ null status is associated with increased BC risk [63]. Afterward, many new case-control studies investigated the association between $GSTM_1$ null genotype and BC risk in the past five years. Thus, an updated meta-analysis is needed.

Our meta-analysis of 12,527 BC cases and 16,275 controls from 50 case-control studies provides evidence that the $GSTM_1$ null genotype is associated with increased BC risk. Compared with previous research, the meta-analysis by Jiang 2011 yielded significant association between the $GSTM_1$ polymorphism and BC risk in worldwide populations (OR=1.409 [1.267-1.568], P<0.001); The observation was similar to our study results (OR=1.41 [1.30, 1.52], P<0.00001). Our research revealed the possible association of $GSTM_1$ with increased BC risk in Africans through analysis of four studies. However, the previous meta-analysis did not show this result. In the stratified analysis based on source of controls, the previous meta-analysis showed that patients with BC had no association with $GSTM_1$ in population-based studies (OR=1.088 [0.970-1.221], P=0.151); This result was different from that of our study. Furthermore, our meta-analysis also indicates that $GSTM_1$ is possibly associated with increased BC risk in smoking people but not in non-smoking individuals. When considering the gender, we observed a significant association between $GSTM_1$ polymorphism and BC risk in both males and females. All these outcomes were not included in the previous meta-analysis.

Our study was more stringent and comprehensive compared with previous meta-analyses. Firstly, more up-to-date studies (50 studies) were selected to provide statistically significant results. Secondly, we observed lower heterogeneity (I^2=51% vs. 72.6%), although our meta-analysis embodied more studies. Thirdly, stratified analyses were performed in detail to investigate the association between $GSTM_1$ null genotype and BC risk with various control designs. We suggest that the determination of the role of the $GSTM_1$ null genotype on BC susceptibility is mainly influenced by study designs based on different control individuals in this meta-analysis.

Despite the clear strengths of our study, it does have some limitations. Firstly, only published studies were included. Therefore, publication bias possibly occurred. Secondly, extreme heterogeneity was noted in the studies analysed in the meta-analysis. Such degree of heterogeneity might be caused by study designs, source of controls and differences in genetic backgrounds. Thirdly, overall outcomes were based on individual unadjusted ORs. Thus, a more precise evaluation requires adjustment for other potentially suspected factors.

Conclusion

Our meta-analysis suggests that the $GSTM_1$ null genotype is associated with enhanced BC risk. Specifically, increased BC risk was observed among Caucasians, Asians and Africans with the $GSTM_1$ null genotype. A significant gene-environment interaction was observed to influence the association between the $GSTM_1$ null genotype and BC risk. In addition, our results showed the strong association between BC risk and $GSTM_1$ null genotype in both males and females and in the smoking group. We suggest that well-designed, high-quality epidemiological studies with larger populations can be conducted to further support our findings.

Acknowledgements

We thank all participating investigators in this study.

Disclosure of conflict of interest

None.

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