

Glutathione S-transferase M1 polymorphism and bladder cancer risk: a meta-analysis involving 33 studies

Zheng Jiang¹, Chunxiang Li² and Xishan Wang¹

¹Department of Abdominal Surgery, The Affiliated Tumor Hospital, Harbin Medical University, Harbin 150086; ²Laboratory of Medical Genetics, Harbin Medical University, Harbin 150081, China

Corresponding author: Xishan Wang. Email: wxshan1208@yahoo.com.cn

Abstract

Glutathione S-transferase M1 (*GSTM1*) might be involved in inactivation of procarcinogens that contribute to the genesis and progression of cancers. *GSTM1* null status has been extensively studied as a risk factor in bladder cancer susceptibility. The aim of this study is to evaluate the role of *GSTM1* null genotype in bladder cancer risk. All available studies were considered in this meta-analysis, including 7301 cases and 9405 controls from 33 studies. Significantly increased risk was detected between *GSTM1* deletion and bladder cancer susceptibility in all subjects (odds ratio [OR] = 1.409 [1.267–1.568], $P < 0.001$). The same patterns were observed in Caucasians (OR = 1.434 [1.212–1.697], $P < 0.001$) and Asians (OR = 1.485 [1.295–1.704], $P < 0.001$). When stratified with study design, a positive association was also found in hospital-based studies (OR = 1.552 [1.382–1.744], $P < 0.001$), but no association in population-based ones (OR = 1.088 [0.970–1.221], $P = 0.151$). In summary, our meta-analysis suggested that *GSTM1* null status is associated with a high increase in the risk of bladder cancer, and further studies based on population design are necessary to confirm our conclusion.

Keywords: glutathione S-transferase M1, bladder cancer, polymorphism, meta-analysis

Experimental Biology and Medicine 2011; **236**: 723–728. DOI: 10.1258/ebm.2011.010295

Introduction

Bladder cancer is one of the most common cancers of the urinary tract, and it is caused by a complex combination of genetic and environmental factors. Risk factors for bladder cancer include cigarette smoking, exposure to industrially related aromatic amines and intake of carcinogenic drugs such as phenacetine, chlornaphrazine and cyclophosphamide.^{1,2} Procarcinogens are mainly metabolized by various metabolizing enzymes, and a considerable number of studies have focused on the association of genes for metabolizing enzymes of carcinogens and cancers.

Mammalian glutathione transferases (GSTs) are dimeric enzymes with subunits of 199–244 amino acids in length that catalyze conjugation of electrophilic substrates with glutathione, usually resulting in detoxification of reactive intermediates.^{3,4} The glutathione S-transferase M1 (*GSTM1*) gene belongs to the GST gene family and catalyzes the detoxification of polycyclic aromatic hydrocarbons (PAHs) that consists of many well-recognized mutagenic or carcinogenic agents.

GSTM1 plays a protective role against the development of cancers. The deficiency of this enzyme activity is caused by the inherited homozygous absence of the *GSTM1* gene, the

'null' genotype (*GSTM1*, 0/0).⁵ Bell *et al.*⁶ first reported the association between *GSTM1* deficiency and increased bladder cancer risk, and subsequent studies have appeared with supporting findings.⁷ However, many researchers have not found such a relationship.^{5,8} Inconsistent results might be due to the relatively small sample sizes and differences in study populations. To strengthen the evidence, we performed a meta-analysis to examine the association between *GSTM1* polymorphism and bladder cancer risk.

Materials and methods

Identification and eligibility of relevant studies

To identify all articles that examined the association of *GSTM1* polymorphism with bladder cancer, we conducted a literature search of the PubMed database and the ISI Web of Knowledge database up to August 2010 using the following MeSH terms and keywords: 'Glutathione S-transferase M1 or *GSTM1*', 'bladder neoplasm or bladder cancer' and 'polymorphism'. Eligible studies included in the meta-analysis had to meet the following criteria: (a) a case-control bladder cancer study; (b) the

diagnosis of bladder cancer patients was confirmed pathologically; and (c) written in English.

Data extraction

Two investigators independently extracted data and reached a consensus on all of the items. The following information was extracted from each study: first author, years of publication, ethnicity of study population, the source of controls and the number of cases and controls. The multiplex-polymerase chain reaction method was performed in all included studies. Different ethnicities were categorized as Caucasian, Asian, African and mixed individuals. Concerning the source of controls, studies were also categorized as either population-based or hospital-based (Table 1).

Statistical analysis

The effect of association was indicated as odds ratios (OR) with the corresponding 95% confidence interval (CI), and the OR was calculated according to the method of Woolf.⁴² A chi-square-based *Q*-statistic test⁴³ and an *I*² test⁴⁴ were performed to assess the heterogeneity between studies (*I*² < 25% no heterogeneity; *I*² = 25–50% moderate heterogeneity; *I*² > 50% large or extreme heterogeneity). The heterogeneity was considered statistically significant

with *P* < 0.10. For a *P* value greater than 0.10 for the *Q*-test, the pooled OR estimate of each study was calculated using the fixed effects (Mantel-Haenszel) model. Otherwise, the random effects (RE) (DerSimonian and Laird) model was used.⁴³ The significance of the pooled OR was determined by the *Z*-test; a *P* value of <0.05 was considered significant. Publication bias was investigated by funnel plot, and an asymmetric plot suggested possible publication bias. The funnel plot asymmetry was assessed by Egger's linear regression test.⁴⁵ The *t*-test was performed to determine the significance of the asymmetry, and a *P* value of <0.05 was considered a significant publication bias. Meta-analysis and meta-regression analysis were carried out using Stata version 8.0 (Stata Corporation, College Station, TX, USA).

Results

Eligibility

Through a literature search and selection based on the inclusion criteria, 33 studies were identified.^{9–41} Table 1 lists the identified studies and their main characteristics. The data for this analysis included 7301 cases and 9405 controls for *GSTM1* polymorphism. The studies were published between 1996 and 2010. All studies were

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

Author [Reference]	Year	Ethnicity	Design	Case		Control	
				Present	Null	Present	Null
Altayli ⁹	2009	Caucasian	HB	77	58	63	65
Grando ¹⁰	2009	Mixed	PB	60	40	67	33
Rouissi ¹¹	2009	African	PB	62	63	69	56
Song ¹²	2009	Asian	HB	77	131	104	108
Zupa ¹³	2009	Caucasian	PB	10	13	53	68
Covolo ¹⁴	2008	Caucasian	HB	9	17	16	14
Golka ¹⁵	2008	Caucasian	HB	109	184	88	88
Shao ¹⁶	2008	Asian	HB	117	85	191	81
Cengiz ¹⁷	2007	Caucasian	HB	33	18	42	11
Murta-Nascimento ¹⁸	2007	Caucasian	HB	251	428	368	367
Zhao ¹⁹	2007	Caucasian	HB	298	324	316	317
McGrath ²⁰	2006	Mixed	HB	156	35	776	148
Garcia-Closas ²¹	2005	Caucasian	HB	422	716	561	571
Karagas ²²	2005	Mixed	PB	115	163	140	211
Kellen ²³	2005	Caucasian	PB	267	312	466	597
Kim ²⁴	2005	Asian	HB	61	92	80	73
Sobti ²⁵	2005	Asian	PB	63	37	52	24
Srivastava ²⁶	2005	Asian	PB	63	43	230	140
Hung ²⁷	2004	Caucasian	HB	69	132	102	112
Moore ²⁸	2004	Mixed	PB	52	54	60	49
Srivastava ²⁹	2004	Asian	HB	64	42	128	54
Jeong ³⁰	2003	Asian	HB	51	75	105	99
Giannakopoulos ³¹	2002	Caucasian	HB	33	56	91	56
Lee ³²	2002	Asian	HB	83	149	79	86
Ma ³³	2002	Asian	PB	137	180	83	99
Aktas ³⁴	2001	Caucasian	HB	47	56	132	70
Toruner ³⁵	2001	Caucasian	PB	46	75	66	55
Kim ³⁶	2000	Asian	HB	34	78	97	123
Schnakenberg ³⁷	2000	Caucasian	PB	64	93	94	129
Steinhoff ³⁸	2000	Caucasian	HB	55	80	70	57
Salagovic ³⁹	1999	Caucasian	PB	36	40	125	123
Abdel-Rahman ⁴⁰	1998	African	PB	11	26	19	15
Brockmoller ⁴¹	1996	Caucasian	HB	156	218	171	202

HB: hospital-based study; PB: population-based study

conducted in various populations of different ethnicities: 17 were conducted in populations of Caucasian ethnicity,^{9,13–15,17–19,21,23,27,31,34,35,37–39,41} 10 involved Asians,^{12,16,24–26,29,30,32,33,36} four mixed^{10,20,22,28} and two Africans.^{11,40} We also stratified all studies considering the source of controls: 20 were hospital-based studies^{9,12,14–21,24,27,29–32,34,36,38,41} and 13 were population-based ones.^{10,11,13,22,23,25,26,28,33,35,37,39,40}

Meta-analysis results

Extreme heterogeneity was found among the 33 eligible studies ($I^2 = 72.6$; $P < 0.10$). The overall data showed that the individuals who carried the *GSTM1* null genotype had a significantly increased bladder cancer risk compared with those who carried the *GSTM1* present genotype in all subjects (OR = 1.409 [1.267–1.568], $P < 0.001$) (Figure 1a). In subgroup analyses, the same significant associations were found in Caucasians (OR = 1.434 [1.212–1.697], $P < 0.001$) and Asians (OR = 1.485 [1.295–1.704], $P < 0.001$) (Table 2).

In stratified analysis according to the source of controls, the *GSTM1* null genotype showed a significant association

with increasing bladder cancer susceptibility in hospital-based studies (OR = 1.552 [1.382–1.744], $P < 0.001$) (Figure 1b). However, no association was found in population-based studies (OR = 1.088 [0.970–1.221], $P = 0.151$) (Figure 1c).

Sensitivity analysis

Sensitivity analysis was performed both by sequential removal of individual study and cumulative statistics of all subjects and subgroups. The pooled ORs of *GSTM1* null genotype were not influenced by the result of any individual study in all subjects, subgroups and hospital-based studies. However, the pooled OR in population-based studies turned out to be subtly significant (OR = 1.181 [1.126–1.358], $P = 0.020$) when one study²³ was excluded. The same result was also produced using cumulative statistics.

Publication bias

Funnel plots and Egger's test were performed to assess publication bias. The data suggested that there was no evidence

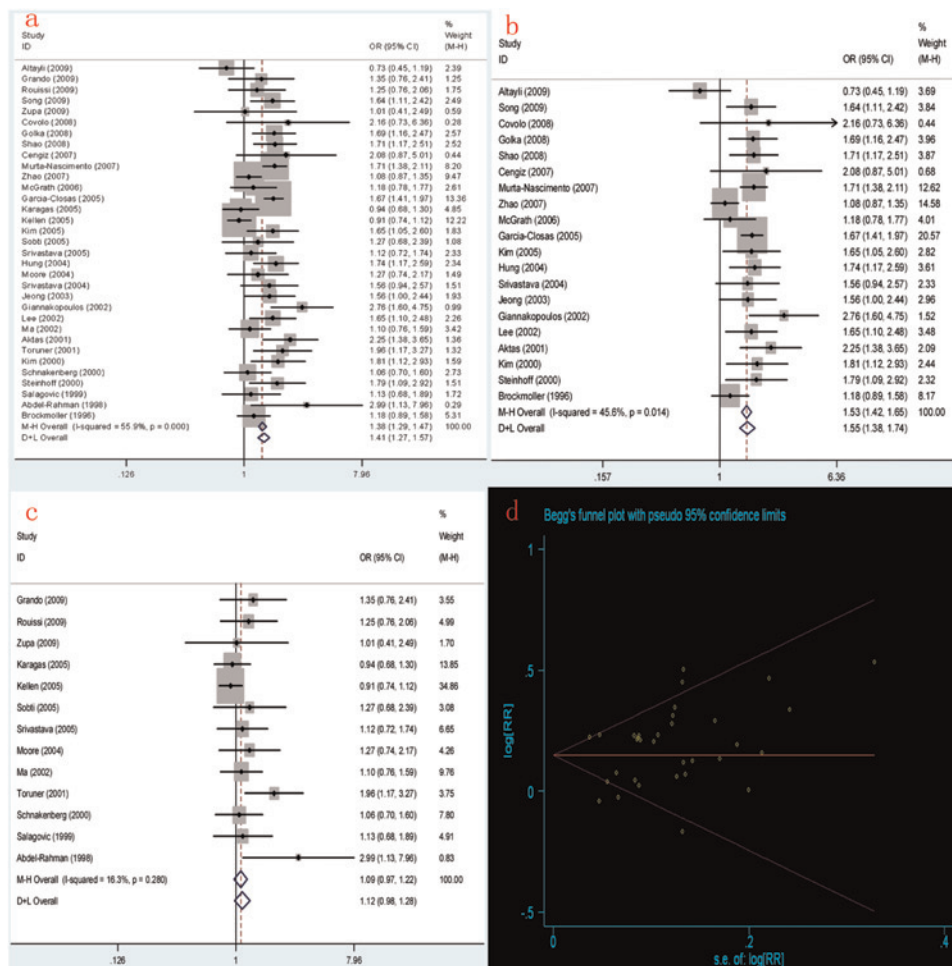


Figure 1 Meta-analysis of *GSTM1* polymorphism in bladder cancer. The study is shown by a point estimate of the OR and accompanying 95% CI: (a) overall analysis for contrasts under FE (M-H) and RE (D + L) models; (b) overall analysis for contrasts under FE and RE models in hospital-based studies; (c) overall analysis for contrasts under FE and RE models in population-based studies; (d) Begg's funnel plot of the Egger's test of the comparison for publication bias. FE, fixed effects; M-H, Mantel-Haenszel; RE, random effects; D + L, DerSimonian and Laird. (A color version of this figure is available in the online journal)

Table 2 Summary of ORs for GSTM1 polymorphism and bladder cancer risk

Subgroup	N*	OR (95% CI)	P	I ² (%)	Ph
Caucasian	17	1.434 (1.212–1.697)	<0.001	56.46	<0.001
Asian	10	1.485 (1.295–1.704)	<0.001	6.31	0.708
HB	20	1.552 (1.382–1.744)	<0.001	34.94	0.014
PB	13	1.088 (0.970–1.221)	0.151	14.34	0.280
Total	33	1.409 (1.267–1.568)	<0.001	72.60	<0.001

Ph: P value of Q test for heterogeneity test; OR, odds ratio; CI, confidence interval

*Number of comparisons

of publication bias in *GSTM1* polymorphism ($t = 1.41$, $P = 0.168$) (Figure 1d).

Discussion

GSTM1 detoxifies hydrophobic electrophiles derived from the metabolism of xenobiotics, including PAH-derived epoxides. Previous studies have indicated that the *GSTM1*-null genotype is associated with increased risk for tobacco-related cancer due to a decreased ability to detoxify PAH.^{46–48} In the present study, 33 studies on the *GSTM1* genotype (16,706 subjects) were critically reviewed. Meta-analysis showed significant associations between *GSTM1* null genotype and bladder cancer risk in all subjects, Caucasians and Asians. However, no association was found in population-based studies (OR = 1.088 [0.970–1.221], $P = 0.151$).

Our meta-analysis showed that the *GSTM1* null genotype has a strikingly increased risk in bladder cancer susceptibility, suggesting that carriers of homozygous deletions in *GSTM1* lack enzyme activity. Deficiency of the enzyme blocks effective metabolism of compounds involved in carcinogenesis, which may result in an increased risk of somatic mutations, contributing to tumor formation. A statistically significant increase was observed in hospital-based studies, while on the contrary no significance was observed in population-based ones. The data on hospital controls could provide relatively lower risk estimates if the diseases of the controls were associated with the gene variant being studied. Therefore, further studies based on population-design are necessary to confirm the association.

Although several meta-analyses have investigated *GSTM1* polymorphism and bladder cancer risk,⁴⁹ our study was more stringent and comprehensive. First, more up-to-date studies (33 studies) were recruited to provide statistically significant results. Second, stratified analyses have been performed in detail to investigate the association between the *GSTM1* null genotype and bladder cancer risk with different control designs. We suggested that the role of the *GSTM1* null genotype on bladder cancer susceptibility was mainly influenced by study design based on different control individuals in this meta-analysis. More importantly, we have explored the biological significance that is valuable for further epidemiological studies.

There are some limitations in this meta-analysis. First, heterogeneity for *GSTM1* polymorphism among the studies was extreme. Meta-regression analyses have been

conducted using Stata 8.0 to examine the association of methodological and substantive factors with potential sources of heterogeneity, and found that 1.8%, 4.9% and 51.7% variability can be accounted for by publication year, ethnicity and study design, respectively. Therefore, one main reason for heterogeneity is the study design based on different controls in this meta-analysis. We had subgrouped the studies based on study design, but the moderate heterogeneity still existed in hospital-based studies. The one possible reason for heterogeneity may be relatively wide variation in various hospital controls. Second, although the data showed that there was no evidence of publication bias in population-based studies, we found that the impact of a specific study²³ on the result was enormous. Finally, the overall outcomes were based on individual unadjusted OR, while a more precise evaluation should be adjusted by other potentially suspected factors.

In conclusion, our meta-analysis suggested that *GSTM1* null status is associated with a high increase in the risk of bladder cancer. Further studies based on population design are necessary to confirm the conclusion on the role of *GSTM1* in bladder cancer risk.

Author contributions: ZJ conducted the experiment; ZJ and CL extracted the data; and ZJ and XW wrote and revised the manuscript. All authors participated in the design, interpretation of the results and analysis of the data and review of the manuscript.

ACKNOWLEDGEMENTS

This study was supported by the National Natural Science Foundation of China (No. 30872375).

REFERENCES

- Cohen SM, Shirai T, Steineck G. Epidemiology and etiology of premalignant and malignant urothelial changes. *Scand J Urol Nephrol Suppl* 2000;**205**:105–15
- Hayes JD, Flanagan JU, Jowsey IR. Glutathione transferases. *Annu Rev Pharmacol Toxicol* 2005;**45**:51–88
- Sanyal S, Festa F, Sakano S, Zhang Z, Steineck G, Norming U, Wijkström H, Larsson P, Kumar R, Hemminki K. Polymorphisms in DNA repair and metabolic genes in bladder cancer. *Carcinogenesis* 2004;**25**:729–34
- Sheehan D, Meade G, Foley VM, Dowd CA. Structure, function and evolution of glutathione transferases: implications for classification of non-mammalian members of an ancient enzyme superfamily. *Biochem J* 2001;**360**:1–16
- Zhong S, Wyllie AH, Barnes D, Wolf CR, Spurr NK. Relationship between the *GSTM1* genetic polymorphism and susceptibility to bladder, breast and colon cancer. *Carcinogenesis* 1993;**14**:1821–4
- Bell DA, Taylor JA, Paulson DF, Robertson CN, Mohler JL, Lucier GW. Genetic risk and carcinogen exposure: a common inherited defect of the carcinogen-metabolism gene glutathione S-transferase M1 (*GSTM1*) that increases susceptibility to bladder cancer. *J Natl Cancer Inst* 1993;**85**:1159–64
- Brockmüller J, Kerb R, Drakoulis N, Staffeldt B, Roots I. Glutathione S-transferase M1 and its variants A and B as host factors of bladder cancer susceptibility: a case-control study. *Cancer Res* 1994;**54**:4103–11
- Lin HJ, Han CY, Bernstein DA, Hsiao W, Lin BK, Hardy S. Ethnic distribution of the glutathione transferase Mu 1-1 (*GSTM1*) null genotype in 1473 individuals and application to bladder cancer susceptibility. *Carcinogenesis* 1994;**15**:1077–81

- 9 Altayli E, Gunes S, Yilmaz AF, Goktas S, Bek Y. CYP1A2, CYP2D6, GSTM1, GSTP1, and GSTT1 gene polymorphisms in patients with bladder cancer in a Turkish population. *Int Urol Nephrol* 2009;**41**: 259–66
- 10 Grando JP, Kuasne H, Losi-Guembarovski R, Sant'ana Rodrigues I, Matsuda HM, Fuganti PE, Gregório EP, Júnior FL, de Menezes RP, de Freitas Rodrigues MA, de Syllos C, ólus IM. Association between polymorphisms in the biometabolism genes CYP1A1, GSTM1, GSTT1 and GSTP1 in bladder cancer. *Clin Exp Med* 2009;**9**:21–8
- 11 Rouissi K, Ouerhani S, Marrakchi R, Ben Slama MR, Sfaxi M, Ayed M, Chebil M, El Gaaied AB. Combined effect of smoking and inherited polymorphisms in arylamine N-acetyltransferase 2, glutathione S-transferases M1 and T1 on bladder cancer in a Tunisian population. *Cancer Genet Cytogenet* 2009;**190**:101–7
- 12 Song DK, Xing DL, Zhang LR, Li ZX, Liu J, Qiao BP. Association of NAT2, GSTM1, GSTT1, CYP2A6, and CYP2A13 gene polymorphisms with susceptibility and clinicopathologic characteristics of bladder cancer in Central China. *Cancer Detect Prev* 2009;**32**:416–23
- 13 Zupa A, Sgambato A, Bianchino G, Improta G, Grieco V, LA Torre G, Campisi B, Traficante A, Aieta M, Cittadini A. GSTM1 and NAT2 polymorphisms and colon, lung and bladder cancer risk: a case-control study. *Anticancer Res* 2009;**29**:1709–14
- 14 Covolo L, Placidi D, Gelatti U, Carta A, Scotto Di Carlo A, Lodetti P, Picciché A, Orizio G, Campagna M, Arici C, Porru S. Bladder cancer, GSTs, NAT1, NAT2, SULT1A1, XRCC1, XRCC3, XPD genetic polymorphisms and coffee consumption: a case-control study. *Eur J Epidemiol* 2008;**23**:355–62
- 15 Golka K, Schmidt T, Seidel T, Dietrich H, Roemer HC, Lohlein D, Reckwitz T, Sokeland J, Weistenhofer W, Blaszkewicz M, Selinski S. The influence of polymorphisms of glutathione S-transferases M1 and M3 on the development of human urothelial cancer. *J Toxicol Environ Health A* 2008;**71**:881–6
- 16 Shao J, Gu M, Zhang Z, Xu Z, Hu Q, Qian L. Genetic variants of the cytochrome P450 and glutathione S-transferase associated with risk of bladder cancer in a south-eastern Chinese population. *Int J Urol* 2008;**15**:216–21
- 17 Cengiz M, Ozaydin A, Ozkilic AC, Dedekarginoglu G. The investigation of GSTT1, GSTM1 and SOD polymorphism in bladder cancer patients. *Int Urol Nephrol* 2007;**39**:1043–8
- 18 Murta-Nascimento C, Silverman DT, Kogevinas M, García-Closas M, Rothman N, Tardón A, García-Closas R, Serra C, Carrato A, Villanueva C, Dosemeci M, Real FX, Malats N. Risk of bladder cancer associated with family history of cancer: do low-penetrance polymorphisms account for the increase in risk? *Cancer Epidemiol Biomarkers Prev* 2007;**16**:1595–600
- 19 Zhao H, Lin J, Grossman HB, Hernandez LM, Dinney CP, Wu X. Dietary isothiocyanates, GSTM1, GSTT1, NAT2 polymorphisms and bladder cancer risk. *Int J Cancer* 2007;**120**:2208–13
- 20 McGrath M, Michaud D, De Vivo I. Polymorphisms in GSTT1, GSTM1, NAT1 and NAT2 genes and bladder cancer risk in men and women. *BMC Cancer* 2006;**6**:239
- 21 García-Closas M, Malats N, Silverman D, Dosemeci M, Kogevinas M, Hein DW, Tardón A, Serra C, Carrato A, García-Closas R, Lloreta J, Castaño-Vinyals G, Yeager M, Welch R, Chanock S, Chatterjee N, Wacholder S, Samanic C, Torà M, Fernández F, Real FX, Rothman N. NAT2 slow acetylation, GSTM1 null genotype, and risk of bladder cancer: results from the Spanish Bladder Cancer Study and meta-analyses. *Lancet* 2005;**366**:649–59
- 22 Karagas MR, Park S, Warren A, Hamilton J, Nelson HH, Mott LA, Kelsey KT. Gender, smoking, glutathione-S-transferase variants and bladder cancer incidence: a population-based study. *Cancer Lett* 2005;**219**:63–9
- 23 Kellen E, Zeegers M, Paulussen A, Vlietinck R, Vlem EV, Veulemans H, Buntinx F. Does occupational exposure to PAHs, diesel and aromatic amines interact with smoking and metabolic genetic polymorphisms to increase the risk on bladder cancer? The Belgian case control study on bladder cancer risk. *Cancer Lett* 2007;**245**:51–60
- 24 Kim EJ, Jeong P, Quan C, Kim J, Bae SC, Yoon SJ, Kang JW, Lee SC, Jun Wee J, Kim WJ. Genotypes of TNF-alpha, VEGF, hOGG1, GSTM1, and GSTT1: useful determinants for clinical outcome of bladder cancer. *Urology* 2005;**65**:70–5
- 25 Sobti RC, Al-Badran AI, Sharma S, Sharma SK, Krishan A, Mohan H. Genetic polymorphisms of CYP2D6, GSTM1, and GSTT1 genes and bladder cancer risk in North India. *Cancer Genet Cytogenet* 2005;**156**:68–73
- 26 Srivastava DS, Mishra DK, Mandhani A, Mittal B, Kumar A, Mittal RD. Association of genetic polymorphism of glutathione S-transferase M1, T1, P1 and susceptibility to bladder cancer. *Eur Urol* 2005;**48**: 339–44
- 27 Hung RJ, Boffetta P, Brennan P, Malaveille C, Hautefeuille A, Donato F, Gelatti U, Spaliviero M, Placidi D, Carta A, Scotto di Carlo A, Porru S. GST, NAT, SULT1A1, CYP1B1 genetic polymorphisms, interactions with environmental exposures and bladder cancer risk in a high-risk population. *Int J Cancer* 2004;**110**:598–604
- 28 Moore LE, Wiencke JK, Bates MN, Zheng S, Rey OA, Smith AH. Investigation of genetic polymorphisms and smoking in a bladder cancer case-control study in Argentina. *Cancer Lett* 2004;**211**:199–207
- 29 Srivastava DS, Kumar A, Mittal B, Mittal RD. Polymorphism of GSTM1 and GSTT1 genes in bladder cancer: a study from North India. *Arch Toxicol* 2004;**78**:430–4
- 30 Jong Jeong H, Jin Kim H, Young Seo I, Ju Kim H, Oh GJ, Cheon Chae S, Sik Lim J, Taeg Chung H, Joong Kim J. Association between glutathione S-transferase M1 and T1 polymorphisms and increased risk for bladder cancer in Korean smokers. *Cancer Lett* 2003;**202**:193–9
- 31 Giannakopoulos X, Charalabopoulos K, Baltogiannis D, Chatzikiriakidou A, Alamanos Y, Georgiou I, Evangelou A, Agnantis N, Sofikitis N. The role of N-acetyltransferase-2 and glutathione S-transferase on the risk and aggressiveness of bladder cancer. *Anticancer Res* 2002;**22**:3801–4
- 32 Lee SJ, Cho SH, Park SK, Kim SW, Park MS, Choi HY, Choi JY, Lee SY, Im HJ, Kim JY, Yoon KJ, Choi H, Shin SG, Park TW, Rothman N, Hirvonen A, Kang D. Combined effect of glutathione S-transferase M1 and T1 genotypes on bladder cancer risk. *Cancer Lett* 2002;**177**:173–9
- 33 Ma QW, Lin GF, Chen JG, Shen JH. Polymorphism of glutathione S-transferase T1, M1 and P1 genes in a Shanghai population: patients with occupational or non-occupational bladder cancer. *Biomed Environ Sci* 2002;**15**:253–60
- 34 Aktas D, Ozen H, Atsu N, Tekin A, Sozen S, Tuncbilek E. Glutathione S-transferase M1 gene polymorphism in bladder cancer patients. a marker for invasive bladder cancer? *Cancer Genet Cytogenet* 2001;**125**:1–4
- 35 Törüner GA, Akyerli C, Uçar A, Aki T, Atsu N, Ozen H, Tez M, Cetinkaya M, Özçelik T. Polymorphisms of glutathione S-transferase genes (GSTM1, GSTP1 and GSTT1) and bladder cancer susceptibility in the Turkish population. *Arch Toxicol* 2001;**75**:459–64
- 36 Kim WJ, Lee HL, Lee SC, Kim YT, Kim H. Polymorphisms of N-acetyltransferase 2, glutathione S-transferase mu and theta genes as risk factors of bladder cancer in relation to asthma and tuberculosis. *J Urol* 2000;**164**:209–13
- 37 Schnakenberg E, Lustig M, Breuer R, Werdin R, Hübötter R, Dreikorn K, Schloot W. Gender-specific effects of NAT2 and GSTM1 in bladder cancer. *Clin Genet* 2000;**57**:270–7
- 38 Steinhoff C, Franke KH, Golka K, Thier R, Römer HC, Rötzel C, Ackermann R, Schulz WA. Glutathione transferase isozyme genotypes in patients with prostate and bladder carcinoma. *Arch Toxicol* 2000;**74**:521–6
- 39 Salagovic J, Kalina I, Habalová V, Hrivnák M, Valanský L, Biros E. The role of human glutathione S-transferases M1 and T1 in individual susceptibility to bladder cancer. *Physiol Res* 1999;**48**:465–71
- 40 Abdel-Rahman SZ, Anwar WA, Abdel-Aal WE, Mostafa HM, Au WW. GSTM1 and GSTT1 genes are potential risk modifiers for bladder cancer. *Cancer Detect Prev* 1998;**22**:129–38
- 41 Brockmöller J, Cascorbi I, Kerb R, Roots I. Combined analysis of inherited polymorphisms in arylamine N-acetyltransferase 2, glutathione S-transferases M1 and T1, microsomal epoxide hydrolase, and cytochrome P450 enzymes as modulators of bladder cancer risk. *Cancer Res* 1996;**56**:3915–25
- 42 Woolf B. On estimating the relation between blood group and disease. *Ann Hum Genet* 1955;**19**:251–3
- 43 Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. *Ann Intern Med* 1997;**127**:820–6
- 44 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557–60
- 45 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629–34

- 46 Mooney LA, Bell DA, Santella RM, Van Bennekum AM, Ottman R, Paik M, Blaner WS, Lucier GW, Covey L, Young TL, Cooper TB, Glassman AH, Perera FP. Contribution of genetic and nutritional factors to DNA damage in heavy smokers. *Carcinogenesis* 1997;**18**:503–9
- 47 Lazarus P, Sheikh SN, Ren Q, Schantz SP, Stern JC, Richie Jr, JP Park JY. p53, but not p16 mutations in oral squamous cell carcinomas are associated with specific CYP1A1 and GSTM1 polymorphic genotypes and patient tobacco use. *Carcinogenesis* 1998;**19**:509–14
- 48 Sram RJ. Effect of glutathione S-transferase M1 polymorphisms on biomarkers of exposure and effects. *Environ Health Perspect* 1998;**106**Suppl 1:231–9
- 49 Johns LE, Houlston RS. Glutathione S-transferase mu1 (GSTM1) status and bladder cancer risk: a meta-analysis. *Mutagenesis* 2000;**15**:399–404

(Received October 1, 2010, Accepted February 24, 2011)