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ORIGINAL ARTICLE

Polymorphisms of GSTA1 contribute to elevated cancer risk: evidence from 15 studies

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Summary

Purpose: *Glutathione S-transferases (GSTs) are involved in the detoxification of carcinogens, and may be linked to carcinogenesis. As a vital component of GSTs, GSTA1 plays an important role in carcinogenesis. However, the studies about the effect of GSTA1 polymorphisms on cancer risk are limited and the conclusions are contradictory. This meta-analysis aimed to evaluate the association between GSTA1 polymorphisms (-567T>G, -69C>T and -52G>A) and cancer risk.*

Methods: *A literature search of PubMed and Web of Science databases was conducted from their inception through December 2013. Crude odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the association of GSTA1 polymorphisms and cancer risk.*

Results: *A total of 15 studies were enrolled, and the results indicated that GSTA1 BB genotype was associated with elevated cancer risk, especially in colorectal cancer. Further stratifications showed that GSTA1 BB genotype was associated with increased cancer risk in Caucasian populations and in the study with population-based controls.*

Conclusions: *This meta-analysis suggested that GSTA1 BB genotype was a risk factor for colorectal cancer, especially in Caucasian populations.*

Key words: *cancer risk, GST, GSTA1, meta-analysis, polymorphism*

Introduction

In recent years, cancer has become one of the most serious problems in public health. It is known that a combination of environmental and genetic factors play important roles in the etiology of cancer. At present, genes which code for carcinogen-metabolizing enzymes are considered as low-penetrance genes in cancer risk. Among them, GSTs are a family of phase II enzymes that are involved in the detoxification of carcinogens, products of oxidative stress and environmental toxins by catalyzing the conjugation with glutathione [1,2]. The well characterized GST classes have been named α (GSTA), μ (GSTM), π (GSTP), and θ (GSTT). Almost all these members exhibit genetic variations, which result in a complete lack or lower enzyme activity. Previous studies regarding the role of *GSTM1*, *GSTP1*, *GSTT1* polymorphisms in cancer risk were extensive [3-5]. However, another member of GST family, *GSTA1*, has been investigated in a limited number of studies. It was said that inactivated or down-regulated *GSTA1* gene could increase genomic damage when individuals were exposed to carcinogens [6]. Three, apparently linked polymorphisms of *GSTA1*, result in differential expression with lower transcriptional activation of the variant *GSTA1* B (-567G, -69T, -52A) than the common *GSTA1* A allele (-567T, -69C,-52G) [7,8]. Earlier studies reported that *GSTA1* polymorphisms were related to colorectal cancer [9-12], prostate cancer [13,14],

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breast cancer [15,16] and bladder cancer [17,18]. However, there is no comprehensive conclusion about *GSTA1* polymorphisms and cancer risk. Therefore, this meta-analysis was conducted to evaluate the effect of *GSTA1* polymorphisms on cancer risk.

Methods

Identification and eligibility of relevant studies

Two online medical databases PubMed and Web of Science were searched (the last update was 10 December 2013) using the search term "GSTA1/glutathione S-transferase alpha 1","polymorphism/genetic variation" and "cancer/carcinoma/tumor". Additionally, studies were identified by manual search of the references listed in the retrieved studies.

Studies enrolled in this meta-analysis had to meet the following inclusion criteria: (1) be a case-control study; (2) be limited to English language; (3) evaluate *GSTA1* polymorphisms and cancer risk; (4) contain available genotype frequency; (5) present sufficient data to calculate ORs with 95% CI. Moreover, all case-only studies, case reports, editorials, reviews, meta-analyses and studies without raw data were eliminated.

Data extraction

Two authors (Qiwen Deng and Bangshun He) independently extracted the information of all eligible studies according to the inclusion and exclusion criteria. Discrepancies were resolved by discussion within our research team. Information of enrolled studies was extracted as follows: the first author's surname, year of publication, country of subjects, ethnicity, cancer type, source of controls, genotyping method, numbers of cases and controls and p value for Hardy-Weinberg equilibrium (HWE) (Table 1).

Statistics

Crude ORs with 95% CIs were used to evaluate the strength of association between *GSTA1* polymorphisms and cancer risk. The pooled ORs were estimated for homozygote comparison (BB vs AA), heterozygote comparison (AB vs AA), dominant model (BB+AB vs AA), recessive model (BB vs AA+AB) and allelic comparison in the polymorphisms. Moreover, stratified analyses were also performed by ethnicity, cancer type, source of controls ('others' group was defined as those ethnicities or cancer types that contained only one study). Chi-square test based Q-statistic test was performed to evaluate heterogeneity across studies. It was considered significant if $P_{\text{heterogeneity}}$ (P_h) <0.05.

Table 1. Characteristics of studies included in the meta-analysis

First author [Ref. no.]	*Year*	*Country*	*Ethnity*	*Cancer type*	*Source of control*	*Genotyping method*	*Cases/Controls*	*HWE*
Matic [17]	2013	Serbia	Caucasian	Bladder cancer	HB	PCR-RFLP	201/122	0.928
Savic-Radojevic [18]	2013	Serbia	Caucasian	Bladder cancer	HB	PCR-RFLP	80/60	-
Dura [31]	2013	Netherlands	Caucasian	Esophageal cancer	PB	PCR-RFLP	440/592	0.864
Chen [32]	2010	Taiwan	Asian	HCC	HB	PCR-RFLP	177/386	0.685
Olsen [15]	2008	Denmark	Caucasian	Breast cancer	PB	PCR-RFLP	396/396	0.089
Ladero [33]	2007	Spain	Caucasian	HCC	PB	PCR-RFLP	184/248	0.110
Martinez [12]	2006	Spain	Caucasian	CRC	PB	PCR-RFLP	142/329	0.110
Martinez [12]	2006	Spain	Caucasian	Gastric cancer	PB	PCR-RFLP	87/329	0.110
Ahn [16]	2006	USA	Mixed	Breast cancer	PB	PCR-RFLP	1036/1089	0.840
Komiya [34]	2005	Japan	Asian	Oral cancer	PB	PCR-RFLP	97/457	0.615
Komiya [35]	2005	Japan	Asian	Urothelial cancer	PB	PCR-RFLP	341/457	0.615
Komiya [13]	2005	Japan	Asian	Prostate cancer	PB	PCR-RFLP	190/294	0.091
van der Logt [9]	2004	Netherlands	Caucasian	CRC	PB	PCR-RFLP	371/415	0.455
Ning [14]	2004	USA	African–American	Prostate cancer	PB	PCR-RFLP	347/144	0.570
Ning [14]	2004	USA	Caucasian	Prostate cancer	PB	PCR-RFLP	347/144	0.336
Sweeney [10]	2002	USA	Caucasian	CRC	PB	PCR-RFLP	116/259	0.800
Coles [11]	2001	USA	Caucasian	CRC	PB	PCR-RFLP	100/226	0.259

PB: population based, HB: hospital based, PCR-RFLP: restriction fragment length polymorphism, HWE: Hardy-Weinberg equilibrium, HCC: hepatocellular carcinoma, CRC: colorectal cancer

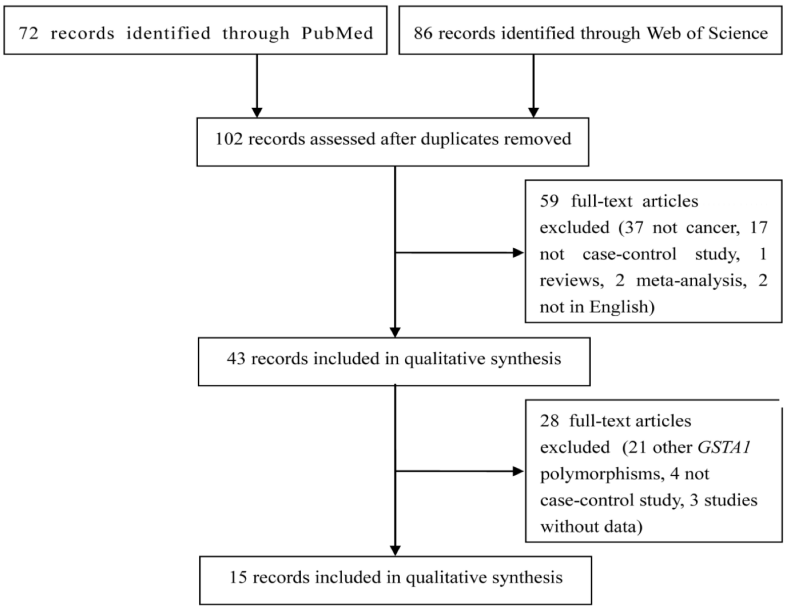

Figure 1. Flow chart of studies identified according to inclusion and exclusion criteria.

In the presence of heterogeneity (P<0.05 or I^2>50%), the data were combined using random-effects (DerSimonian and Laird method) [19]. Otherwise, fixed-effects (Mantel-Haenszel method) models [20] were used in the absence of heterogeneity (P>0.05 or I^2<50%). Furthermore, sensitivity analysis was performed to assess the stability of the results. Publication bias was statistically calculated using the Egger's linear regression test and graphically using funnel plots. HWE using a web-based program (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl) was used to assess the genotype frequencies of the polymorphisms. All statistical tests were performed with STATA 11.0 (College Station Corporation, TX, USA). All p values were two-sided.

Results

There were 15 studies enrolled in the pooled analysis (Table 1, Figure 1). The study by Martinez et al. [12] investigated two types of cancers (colorectal and gastric cancer) and the study by Ning et al. [14] investigated prostate cancer risk in two populations (Caucasian and African-American), so the study was divided into two substudies, respectively. These studies were related to colorectal cancer (4 studies), prostate cancer (3 studies), breast cancer (2 studies), bladder cancer (2 studies), hepatocellular cancer (2 studies) and other cancers (4 studies), which included Caucasians (11 studies), Asians (4 studies) and other populations (2 studies). Controls were all matched by sex and age, of which 14 were population-based and 3 were hospital-based. A classic PCR-restriction fragment length polymorphism (PCR-RFLP) assay was performed in all of the studies. The main characteristics are listed in Table 1.

Main results

Comparison revealed increased cancer risk of BB vs AA (OR=1.17, 95% CI: 1.02-1.34, P_h=0.796, I^2=0.0, Figure 2) and BB vs AA+AB (OR=1.18, 95% CI: 1.04-1.34, P_h=0.746, I2=0.0, Figure 3). Subgroup comparison by ethnicity revealed increased cancer risk in Caucasian populations for BB vs AA+AB (OR=1.21, 95% CI: 1.03-1.41, P_h=0.363, I^2=8.5). Moreover, stratified analysis by cancer type showed increased risk in colorectal cancer for BB vs AA (OR=1.35, 95% CI: 1.02-1.77, P_h=0.219, I^2=32.2) and BB vs AA+AB (OR=1.39, 95% CI: 1.08-1.79, P_h=0.177, I^2=39.2). Furthermore, in subgroup analysis by source of controls, increased cancer risk was observed in the studies among population-based controls for BB vs AA (OR=1.18, 95% CI: 1.03-1.36, P_h=0.722, I^2=0.0) and BB vs AA+AB (OR=1.20, 95% CI: 1.06-1.36, P_h=0.743, I^2=0.0) (Table 2).

Overall effects for alleles

Allele comparisons were also conducted in this meta-analysis. Increased cancer risk was observed in *GSTA1* polymorphism and cancer risk in the pooled analysis (B allele vs A allele: OR=1.07, 95% CI: 1.01-1.14, P_h=0.444, I^2=0.7, Figure 4). In the subgroup analysis, a significant association

Table 2. Stratified analyses of the GSTA1 polymorphisms and cancer risk

Variables	*n*[a]	*BB vs AA*			*AB vs AA*			*BB+AB vs AA*			*BB vs AA+AB*			*B allele vs A allele*		
		OR(95%CI)	*P*[b]	I^2	*OR(95%CI)*	*P*[b]	I^2	*OR(95%CI)*	*P*[b]	I^2	*OR(95%CI)*	*P*[b]	I^2	*OR(95%CI)*	*P*[b]	I^2
Total	17	**1.17 (1.02,1.34)**	0.796	0.0	1.02 (0.92,1.11)	0.374	7.0	1.06 (0.97,1.15)	0.447	0.6	1.18 (1.04,1.34)	0.746	0.0	1.07 (1.01,1.14)	0.444	0.7
Ethnicity																
Caucasian	11	1.17 (0.99,1.38)	0.435	0.3	0.95 (0.83,1.07)	0.453	0.0	1.01 (0.90,1.14)	0.448	0.0	1.21 (1.03,1.41)	0.363	8.5	1.06 (0.97,1.15)	0.360	8.9
Asian	4	1.07 (0.53,2.16)	0.847	0.0	1.17 (0.94,1.44)	0.263	24.8	1.16 (0.94,1.42)	0.232	30.1	1.02 (0.51,2.06)	0.880	0.0	1.13 (0.94,1.36)	0.244	28.0
Others	2	1.20 (0.94,1.53)	0.497	0.0	1.07 (0.89,1.28)	0.685	0.0	1.10 (0.92,1.31)	0.559	0.0	1.16 (0.93,1.44)	0.567	0.0	1.09 (0.97,1.23)	0.475	0.0
Cancer type																
CRC	4	**1.35 (1.02,1.77)**	0.219	32.2	0.95 (0.77,1.17)	0.260	25.3	1.04 (0.86,1.27)	0.265	24.4	1.39 (1.08,1.79)	0.177	39.2	1.12 (0.98,1.29)	0.187	37.6
Prostate cancer	3	0.99 (0.56,1.74)	0.792	0.0	1.18 (0.86,1.61)	0.303	16.2	1.17 (0.87,1.58)	0.272	23.3	1.00 (0.59,1.67)	0.874	0.0	1.10 (0.87,1.38)	0.239	30.0
Breast cancer	2	1.22 (0.99,1.52)	0.989	0.0	1.04 (0.89,1.23)	0.555	0.0	1.09 (0.93,1.27)	0.637	0.0	1.19 (0.99,1.44)	0.750	0.0	1.10 (0.99,1.22)	0.865	0.0
Bladder cancer	2	1.01 (0.48,2.11)	–	–	1.44 (0.88,2.34)	–	–	1.38 (0.94,2.03)	0.845	0.0	0.81 (0.41,1.62)	–	–	1.10 (0.80,1.54)	–	–
HCC	2	1.30 (0.78,2.19)	0.393	0.0	0.94 (0.69,1.28)	0.364	0.0	0.98 (0.73,1.32)	0.206	37.6	1.28 (0.79,2.06)	0.429	0.0	1.05 (0.83,1.32)	0.123	58.0
Others	4	0.93 (0.68,1.28)	0.831	0.0	0.96 (0.79,1.15)	0.209	33.9	0.97 (0.81,1.15)	0.263	24.7	1.02 (0.76,1.38)	0.825	0.0	0.98 (0.86,1.13)	0.423	0.0
Source of controls																
PB	14	**1.18 (1.03,1.36)**	0.722	0.0	1.01 (0.92,1.12)	0.089	65.5	1.06 (0.96,1.16)	0.476	0.0	1.20 (1.06,1.36)	0.743	0.0	1.08 (1.01,1.15)	0.440	0.8
HB	3	0.93 (0.46,1.86)	0.578	0.0	1.05 (0.76,1.47)	0.435	1.3	1.09 (0.81,1.45)	0.183	41.2	0.78 (0.41,1.50)	0.729	0.0	0.97 (0.75,1.26)	0.228	31.3

PB: population based, HB: hospital based, HCC: hepatocellular carcinoma, CRC: colorectal cancer.
The study by Savic-Radojevic [18] has no data in some comparison models. So there is no data of *P* and I^2 for bladder cancer.

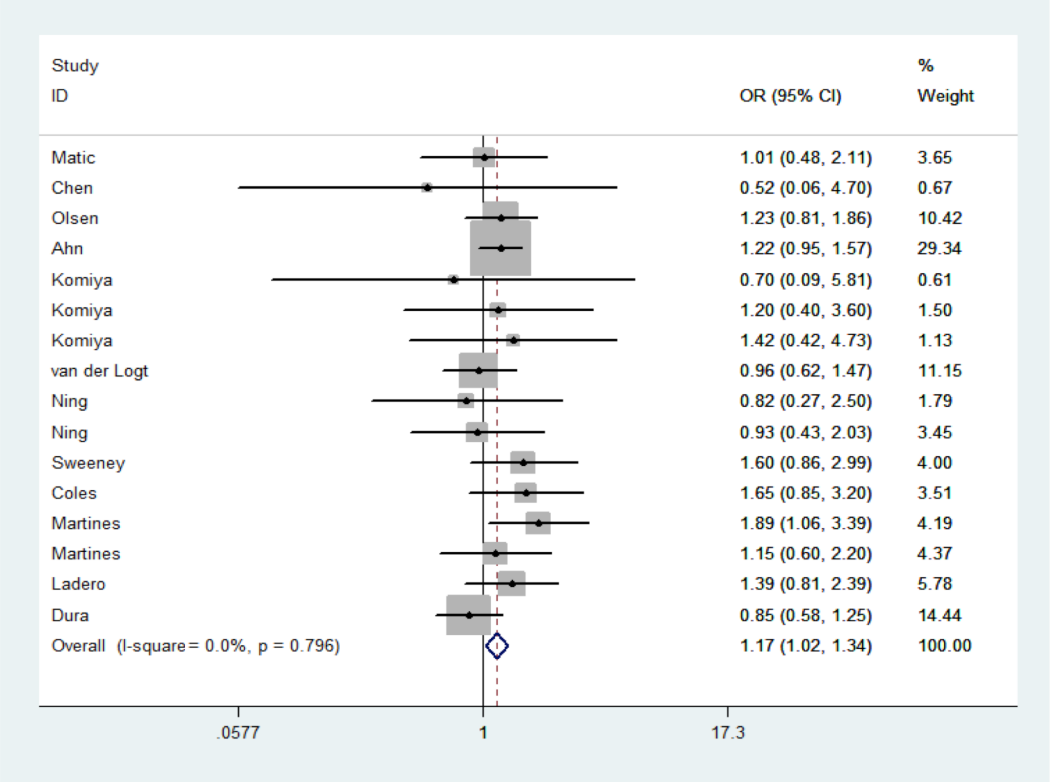

Figure 2. Forest plots of effect estimates for GSTA1 polymorphism (BB vs AA). For each of the studies, the estimation of OR and its 95% CI is plotted with a box and a horizontal line. Filled diamond pooled OR and its 95% CI.

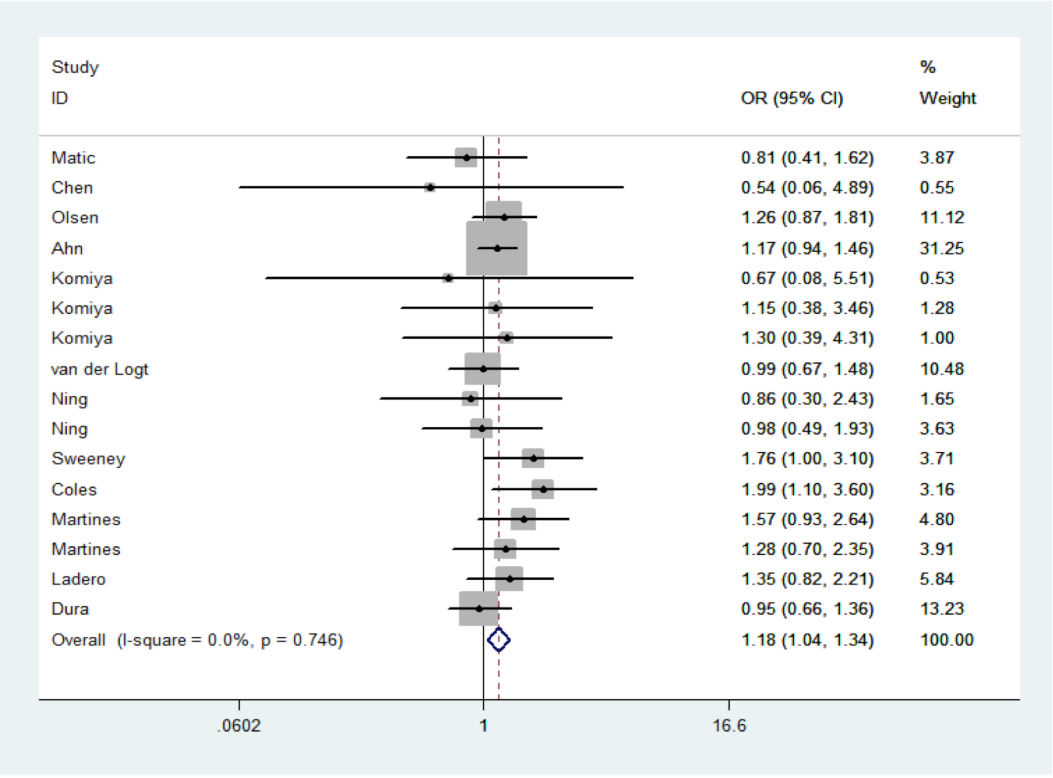

Figure 3. Forest plots of effect estimates for GSTA1 polymorphism (BB vs AA+AB). For each of the studies, the estimation of OR and its 95% CI are plotted with a box and a horizontal line. Filled diamond pooled OR and its 95% CI.

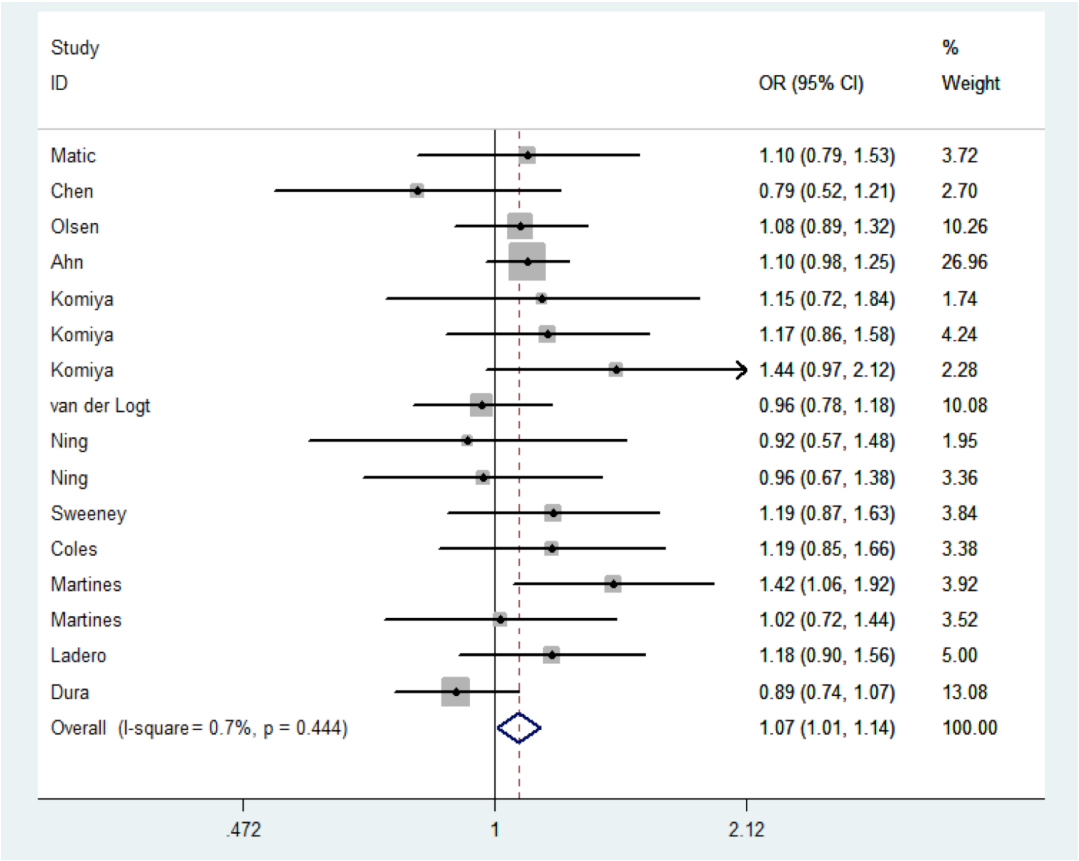

Figure 4. Forest plots of effect estimates for GSTA1 polymorphism (B vs A). For each of the studies, the estimation of OR and its 95% CI are plotted with a box and a horizontal line. Filled diamond pooled OR and its 95% CI.

was observed only in the studies among population-based controls (OR=1.08, 95% CI: 1.01-1.15, P_h=0.440, I^2=0.8).

Test of heterogeneity and sensitivity analysis

There was no apparent between-study heterogeneity in the pooled analysis. Moreover, sensitivity analysis was performed to assess the stability of the results by sequential removal of each individual eligible study. As a result, no single study influenced the pooled ORs. Therefore, it was believed that the results of this study were robust and credible.

Publication bias

Funnel plot and Egger's test were performed to assess the publication bias. The shape of the funnel plot did not indicate any evidence of obvious asymmetry (Figure 5). Meanwhile, the Egger's test revealed absence of publication bias (BB vs AA: t=-0.27, *P*=0.789; AB vs AA: t=0.04, *P*=0.967; BB+AB vs AA: t=0.57, *P*=0.580; BB vs AA+AB: t=-0.24, *P*=0.816; B vs A: t=0.48, *P*=0.639).

Discussion

To the best of our knowledge, this was the first study to assess the effect of *GSTA1* polymorphisms on cancer risk, in which a total of 15 studies were included. The results showed that increased cancer risk was observed in BB genotype carriers, especially colorectal cancer in Caucasians.

As previously reported, chemical carcinogens such as polycyclic aromatic hydrocarbons (PAHs) and heterocyclic aromatic amines (HAAs) are implicated in colorectal carcinogenesis [21]. These carcinogens are present in tobacco smoke and also in meat cooked on an open flame or at a high temperature [22-24]. As GSTs play important roles in the detoxification of PAH and HAA, they are involved in the etiology of colorectal cancer. *GSTA1* is the most abundant among GSTs which is found in the human liver and its corresponding gene is located at 6p12. A previous study has reported that a significant decrease in luciferase activity in *GSTA1* B allele (-567G, -67T, -52A) and the base change at position -52 might explain the difference [25]. Therefore, these results were consistent with our result that the BB genotype was a risk factor for colorectal cancer. A previous study detected greater colorectal risk linked to *GSTA1* B

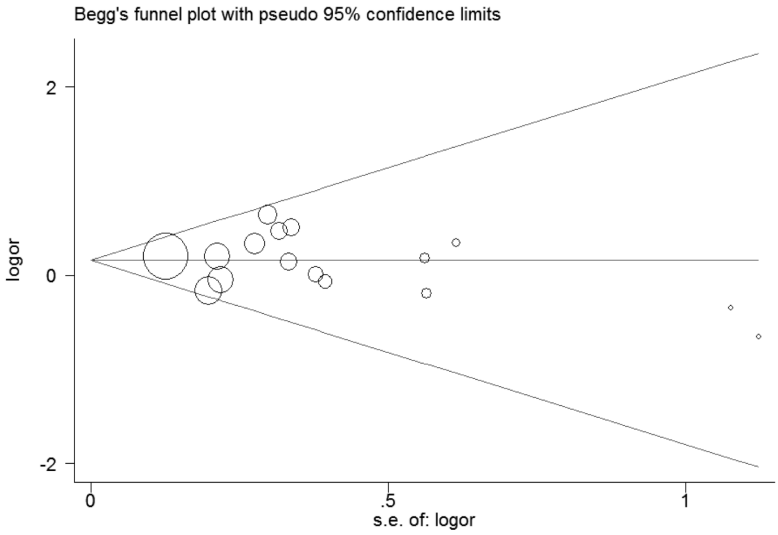

Figure 5. Publication bias test for all included studies (BB vs AA).Each circle represents an independent study for the indicated association. Log [OR]: natural logarithm of OR. Horizontal line shows mean effect size. s.e: standard error

allele [11]. However, three other studies [9,10,12] didn't observe association between *GSTA1* polymorphisms and colorectal cancer risk. Their failure to detect the effect of *GSTA1* polymorphisms on colorectal cancer risk might be attributed to the influence of other *GST* members, such as *GSTM1*, *GSTT1* and *GSTP1*, which were widely investigated in the etiology of colorectal cancer due to their high expression in the intestinal tract and their vital roles in the detoxification of carcinogens [26]. Deficiency in *GSTA1* enzyme due to polymorphisms may be compensated by the presence of other GST enzymes. Moreover, some of these studies didn't consider the effect of smoking and diet, while both were major contributors of carcinogenic PAHs and HAAs.

Increased cancer risk was noticed in Caucasian populations with BB genotype carrier. Earlier studies have indicated that Western diet contains high HAA and PAHs [27-30], while dietary PAH/HAA is relatively low in other ethnicities, a fact that may contribute to the different effects on cancer risk.

The current study suggested an increased cancer risk with B allele in the population-based controls, while the results were not affected in the hospital-based controls. This discrepancy might be that hospital-based controls only represented the sick people being under bland diet and restricted smoking.

This study still has some limitations. First, the number of eligible studies in this meta-analysis was limited. Second, this meta-analysis enrolled only studies in English, which could lead to missing some studies in other languages that were consistent with the inclusion criteria. Third, some suspected factor like smoking, drinking, eating habits, age, sex, other polymorphisms were not considered in this study. Despite all these, this study still has some strength. First, all enrolled studies were consistent well with the inclusion criteria. Second, there was no publication bias observed which suggested that the whole results might be unbiased.

In conclusion, this study indicated that *GSTA1* B allele was associated with increased cancer risk, especially colorectal cancer in Caucasian populations. To achieve a more accurate conclusion, well-designed, unbiased, large case-control studies should be conducted.

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Conceived and designed the experiments: SKW, QWD and BSH

Performed the experiments: QWD, HLS, YQP and XL

Analyzed the data: BSH, HQY and QWD

Contributed reagents/materials/analysis tools: HLS and JC

Wrote the manuscript: SKW and QWD

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