The genetic role of Glutathione S-Transferase Mu 3 (*GSTM3*) intron 6 polymorphism in the susceptibility to cancer

Yanyan Wang

The First Affiliated Hospital of Zhengzhou University

Han Feng

The First Affiliated Hospital of Zhengzhou University

Junlin Yu

The First Affiliated Hospital of Zhengzhou University

Yabing Du

The First Affiliated Hospital of Zhengzhou University

Shuiling Jin

The First Affiliated Hospital of Zhengzhou University

Wang Ma

The First Affiliated Hospital of Zhengzhou University

Kang Cui (✉ doctorcui@163.com)

The First Affiliated Hospital of Zhengzhou University <https://orcid.org/0000-0001-5534-3842>

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Abstract

Background

We retrieved different reports containing different genetic effects of A/B polymorphism within the Glutathione S-Transferase Mu 3 (GSTM3) intron 6 on the susceptibility to cancer in the overall population.

Methods

Herein, we first conducted a meta-analysis to comprehensively assess such a genetic relationship after collecting the available published evidence. STATA 12.0 software was used for the statistical analysis.

Results

By retrieving and screening database literature, a total of fifty-three eligible articles were finally selected. Even though no significant difference between overall cancer cases and negative controls was detected under the allelic, homozygotic, heterozygotic, dominant and recessive genetic model, we observed a reduced risk of head and neck cancer in cases, compared with controls, under the homozygotic model (BB vs. AA, $P = 0.047$, $OR = 0.75$) and recessive model (BB vs. AA+AB, $P = 0.045$, $OR = 0.76$), but not other models. Furthermore, a decreased risk of head and neck SCC cancer was detected under all the genetic models (allelic B vs. A, $P = 0.007$, $OR = 0.78$; BB vs. AA, $P = 0.006$, $OR = 0.54$; AB vs. AA, $P = 0.045$, $OR = 0.82$; AB+BB vs. AA, $P = 0.002$, $OR = 0.77$; BB vs. AA+AB, $P = 0.021$, $OR = 0.63$; carrier B vs. A, $P = 0.032$, $OR = 0.83$).

Conclusion

Our findings suggested that the GSTM3 intron 6 A/B polymorphism may confer the protective susceptibility to the squamous cell carcinoma of head and neck.

Background

Glutathione S-transferases (GSTs), a super family of phase II metabolizing enzymes, are implicated in the metabolic process of some xenobiotics/endogenous substrates or bioactive compounds, and the molecular mechanism regarding the development or potential therapeutic targets of different clinical cancer diseases [1–3]. There exist a group of genes, such as the Glutathione S-transferase alpha 1 (GSTA1), Glutathione S-transferase theta 1 (GSTT1), Glutathione S-Transferase pi (GSTP1), Glutathione S-transferase Mu1 (GSTM1) and Glutathione S-transferase Mu3 (GSTM3), in the GSTs supergene family [4, 5]. In addition, several variants, such as present/null of GSTM1 or GSTT1 gene, rs1695, rs1138272 of GSTP1 gene, rs1799735 of GSTM3, were observed [6, 7]. A deletion of three base pairs-induced GSTM3 rs1799735, also known as GSTM3 A/B or AGG/del, is situated in the intron 6 of the GSTM3 gene [8–10].

The variants with in the above GST family genes were reported to be associated with the genetic susceptibility to some clinical cancer diseases [6, 7, 11, 12]. For example, GSTP1 rs1138272 polymorphism may be linked to the risk of overall cancer in the Asian and African populations. It is possible that the GSTs polymorphism acts as the susceptibility factor of cancer, through affecting enzyme activity or the detoxification role of carcinogenic species. Our present study aims at exploring the role of GSTM3 intron 6 A/B polymorphism in the overall cancer disease.

As far as we know, there is still no report regarding the meta-analyses of GSTM3 intron 6 A/B polymorphism and cancer risk in the overall population. Therefore, it is important to conduct a meta-analysis to assess the role of the GSTM3 intron 6 A/B polymorphism in the risk of cancer. Thus, it is meaningful to shed the light on the genetic links between GSTM3 intron 6 A/B polymorphism and overall cancer susceptibility for the first time.

Methods

Database retrieval

We designed our meta-analysis in February 2019, following the guide of preferred reporting items for systematic reviews and meta-analyses (PRISMA) [13]. The PRISMA-based flow chart is shown in Fig. 1. Three investigators performed the literature search. Three online electronic databases, including PubMed, Embase and WANFANG, were used to retrieve data by combining the different terms of “GSTM3” and “cancer. The search strategy was shown in Table S1.

Study selection

After database retrieval, three investigators designed our inclusion and exclusion criteria to select the eligible case-control studies for synthetic analysis. Exclusion criteria: (1) case reports or meeting abstracts; (2) cell or animal assays; (3) meta-analyses or reviews; (4) other genes, SNPs or diseases; (5) lack case or control data; (6) lack genotype data. Inclusion criteria: (1) case and control study; (2) cancer; (3) A/B polymorphism within the GSTM3 gene; and (4) genotypic frequency data of cases and controls.

Data extraction

Subsequently, three investigators extracted basic information, including first author, publication time (year), country, ethnicity, genotypic frequency data in both controls and cases, source of control, genotyping assay, sample size, and Hardy-Weinberg equilibrium (HWE). The Newcastle-Ottawa quality assessment Scale (NOS) scores of study quality were also measured.

A thorough discussion was required to deal with the discrepancy that might happen during the study selection and data extraction.

Statistical analysis

We utilized STATA 12.0 software (Stata Corporation, College Station, TX, USA) to conduct the I^2 test and Q statistic test (for heterogeneity evaluation), DerSimonian-Laird and Mantel-Haenszel method (for association test), Begg's test and Egger's test (for publication bias evaluation) [14, 15], and sensitivity analysis (for the assessment of data stability). The high heterogeneity level was considered to perform the DerSimonian-Laird method under a random-effect model when I^2 was larger than 50% or the P value was less than 0.1. In contrast, the Mantel-Haenszel method under a fixed-effect model was used for the association test. In addition, the data of the odds ratio (OR), 95% confidence interval (CI) and P value were calculated under the allelic, homozygotic, heterozygotic, dominant and recessive genetic models in the overall meta-analysis as well as the relative subgroup analysis by the factors of ethnicity, control source, HWE and cancer type.

Results

Enrolled studies

As shown in Fig. 1, we initially identified a total of 908 articles, including PubMed (n = 488), Embase (n = 295), and WANFANG (n = 125), and we removed the 181 duplicates. Additionally, we ruled out another 650 studies by the exclusion criteria shown in Fig. 1. Moreover, after the eligibility assessment, we eliminated another 24 articles without the genotypic or allelic frequency data in cases or controls. As a result, a total of fifty-three eligible case-control studies [8, 10, 11, 16–65] with the summarized basic information (Table S2) and the high-quality (Table S3, all NOS scores greater than five).

The overall meta-analysis

During the overall meta-analysis (Table 1), fifty-eight case-control studies (17,125 cases/22,342 controls) were enrolled for the dominant model (AB + BB vs. AA), fifty case-control studies (15,160 cases/20,011 controls) were for the allelic model (B vs. A), heterozygotic model (AB vs. AA), and carrier model (carrier B vs. carrier A), and forty-nine case-control studies (15,072

cases/19,909 controls) were for the homozygotic model (BB vs. AA) and recessive model (BB vs. AA + AB). As shown in Table 1, a random-effect model (DerSimonian and Laird method) was used under the allelic, heterozygotic and dominant models (P-Heterogeneity < 0.05); while a fixed-effect model (Mantel-Haenszel method) was for other models (P-Heterogeneity > 0.05 and $I^2 < 50\%$).

Table 1
Overall meta-analysis data

Genetic model	Study	Case	Control	P-association	OR	95% CI	P-Heterogeneity	I^2	Fixed/Random
allelic model (allelic B vs. A)	50	15,160	20,011	0.610	0.98	0.92 ~ 1.05	0.001	44.2%	Random
homozygotic model (BB vs. AA)	49	15,072	19,909	0.542	0.96	0.84 ~ 1.09	0.294	9.1%	Fixed
heterozygotic model (AB vs. AA)	50	15,160	20,011	0.891	0.99	0.92 ~ 1.06	< 0.001	49.4%	Random
dominant model (AB + BB vs. AA)	58	17,125	22,342	0.833	0.71	0.49 ~ 1.01	< 0.001	46.6%	Random
recessive model (BB vs. AA + AB)	49	15,072	19,909	0.545	0.96	0.85 ~ 1.09	0.319	7.8%	Fixed
carrier model (carrier B vs. A)	50	15,160	20,011	0.626	0.99	0.94 ~ 1.04	0.234	12.2%	Fixed
OR, odds ratio; CI confidence interval.									

In the association test shown in Table 1, we did not detect a significant difference between overall cancer cases and negative controls under all genetic models. Thus, the GSTM3 intron 6 A/B polymorphism may have no genetic effect on the risk of cancer.

The subgroup Meta-analysis

Next, we the subgroup analysis, based on the factor of ethnicity ("Asian", "Caucasian"), control source ("PB, population-based", "HB, Hospital-based"), HWE ("Y, P value of HWE > 0.05") and cancer type. As shown in Table 2, Table 3 and Table 4, we observed a statistically non-significant association in the subgroup analyses of "Asian", "Caucasian", "HB", "PB", "Y" and the most cancer type (P > 0.05). However, we observed the reduced risk of head and neck cancer in cases, compared with controls, under the homozygotic model (Table 3, BB vs. AA, P = 0.047, OR = 0.75) and recessive model (Table 4, BB vs. AA + AB, P = 0.045, OR = 0.76), but not other models.

Table 2
Subgroup meta-analysis data by ethnicity, control source and HWE.

Genetic model	Subgroup	Study	Case	Control	P	OR	95% CI
allelic model (allelic B vs. A)	Asian	8	12,53	1,829	0.529	0.92	0.71 ~ 1.20
	Caucasian	33	11,834	15,306	0.413	0.97	0.90 ~ 1.04
	HB	22	5,113	6,363	0.687	0.98	0.88 ~ 1.09
	PB	26	9,672	13,231	0.840	1.01	0.93 ~ 1.10
	Y	41	13,342	17,723	0.729	0.99	0.92 ~ 1.06
homozygotic model (BB vs. AA)	Asian	8	1,253	1,829	0.110	0.64	0.37 ~ 1.11
	Caucasian	32	11,746	15,204	0.680	0.97	0.83 ~ 1.13
	HB	22	5,113	6,363	0.262	0.88	0.71 ~ 1.10
	PB	25	9,672	13,231	0.478	1.06	0.90 ~ 1.25
	Y	40	13,254	17,621	0.830	1.02	0.88 ~ 1.17
heterozygotic model (AB vs. AA)	Asian	8	12,53	1,829	0.870	0.97	0.69 ~ 1.38
	Caucasian	33	11,834	15,306	0.476	0.97	0.88 ~ 1.06
	HB	22	5,113	6,363	0.813	1.02	0.89 ~ 1.16
	PB	26	9,672	13,231	0.771	0.98	0.87 ~ 1.11
	Y	41	13,342	17,723	0.608	0.98	0.89 ~ 1.07
dominant model (AB + BB vs. AA)	Asian	10	1,717	2,377	0.931	0.99	0.73 ~ 1.34
	Caucasian	36	12,561	16,304	0.297	0.96	0.89 ~ 1.04
	HB	26	5,776	7,209	0.866	1.01	0.89 ~ 1.15
	PB	30	10,974	14,716	0.915	1.00	0.91 ~ 1.09
	Y	43	13,806	18,271	0.762	0.99	0.90 ~ 1.08
recessive model (BB vs. AA + AB)	Asian	8	1,253	1,829	0.114	0.65	0.38 ~ 1.11
	Caucasian	32	11,746	15,204	0.764	0.98	0.84 ~ 1.14
	HB	22	5,113	6,363	0.194	0.87	0.71 ~ 1.07
	PB	25	9,672	13,231	0.388	1.08	0.91 ~ 1.27
	Y	40	13,254	17,621	0.734	1.02	0.89 ~ 1.18
carrier model (carrier B vs. A)	Asian	8	12,53	1,829	0.576	0.95	0.81 ~ 1.12
	Caucasian	33	11,834	15,306	0.436	0.98	0.93 ~ 1.03
	HB	22	5,113	6,363	0.660	0.98	0.91 ~ 1.06
	PB	26	9,672	13,231	0.971	1.00	0.94 ~ 1.06
	Y	41	13,342	17,723	0.626	0.99	0.94 ~ 1.04
OR, odds ratio; CI confidence interval; HB, hospital-based control; PB, population-based control; Y, P value of HWE > 0.05.							

Table 3

Subgroup meta-analysis data by cancer type under the allelic, homozygotic and heterozygotic model.

Genetic model	Subgroup	Study	Case	Control	P	OR	95% CI
allelic model (allelic B vs. A)	brain cancer	10	2,273	7,601	0.119	1.09	0.98 ~ 1.22
	head and neck cancer	14	2,515	2,691	0.168	0.89	0.76 ~ 1.05
	lung cancer	10	1,638	2,473	0.503	0.96	0.85 ~ 1.19
	skin cancer	7	678	1,252	0.877	0.99	0.82 ~ 1.19
	urinary system cancer	5	1,640	1,960	0.254	1.20	0.88 ~ 1.64
	breast cancer	3	3,860	6,081	0.932	1.00	0.92 ~ 1.08
	digestive system cancer	8	1,288	1,917	0.143	0.84	0.66 ~ 1.06
	oral cancer	5	757	1,176	0.902	0.99	0.84 ~ 1.17
	glioma	3	1,166	2,465	0.641	1.05	0.86 ~ 1.28
	colorectal cancer	3	692	876	0.668	0.91	0.59 ~ 1.40
	head and neck SCC	7	1,202	1,450	0.007	0.78	0.65 ~ 0.93
	skin SCC	3	195	478	0.752	0.95	0.68 ~ 1.32
	skin BCC	4	459	792	0.977	1.00	0.80 ~ 1.26
homozygotic model (BB vs. AA)	brain cancer	10	2,273	7,601	0.215	1.19	0.90 ~ 1.57
	head and neck cancer	13	2,427	2,589	0.047	0.75	0.56 ~ 1.00
	lung cancer	10	1,638	2,473	0.832	1.04	0.73 ~ 1.49
	skin cancer	7	678	1,252	0.971	1.01	0.59 ~ 1.72
	urinary system cancer	5	1,640	1,960	0.987	1.00	0.63 ~ 1.58
	breast cancer	3	3,860	6,081	0.565	1.08	0.82 ~ 1.43
	digestive system cancer	8	1,288	1,917	0.150	0.70	0.44 ~ 1.14
	oral cancer	5	757	1,176	0.343	0.82	0.55 ~ 1.23
	glioma	3	1,166	2,465	0.463	1.16	0.26 ~ 1.07
	colorectal cancer	3	692	876	0.077	0.53	0.26 ~ 1.07
	head and neck SCC	6	1,114	1,348	0.006	0.54	0.36 ~ 0.84
	skin SCC	3	195	478	0.701	1.22	0.45 ~ 3.33
	skin BCC	4	459	792	0.850	0.94	0.50 ~ 1.77
heterozygotic model (AB vs. AA)	brain cancer	10	2,273	7,601	0.141	1.09	0.97 ~ 1.21
	head and neck cancer	14	2,515	2,691	0.445	0.93	0.77 ~ 1.12

OR, odds ratio; CI confidence interval; SCC, squamous cell carcinoma; BCC, basal cell carcinoma.

Genetic model	Subgroup	Study	Case	Control	P	OR	95% CI
	lung cancer	10	1,638	2,473	0.391	0.93	0.78 ~ 1.10
	skin cancer	7	678	1,252	0.825	0.97	0.78 ~ 1.22
	urinary system cancer	5	1,640	1,960	0.327	1.21	0.83 ~ 1.77
	breast cancer	8	3,860	6,081	0.636	0.98	0.89 ~ 1.07
	digestive system cancer	5	1,288	1,917	0.320	0.85	0.89 ~ 1.07
	oral cancer	3	757	1,176	0.355	1.11	0.89 ~ 1.39
	glioma	3	1,166	2,465	0.864	1.02	0.81 ~ 1.28
	colorectal cancer	7	692	876	0.918	1.03	0.58 ~ 1.83
	head and neck SCC	7	1,202	1,450	0.045	0.82	0.68 ~ 1.00
	skin SCC	4	195	478	0.516	0.88	0.59 ~ 1.30
	skin BCC	3	459	792	0.855	1.03	0.78 ~ 1.35
OR, odds ratio; CI confidence interval; SCC, squamous cell carcinoma; BCC, basal cell carcinoma.							

Table 4

Subgroup meta-analysis data by cancer type under the allelic, homozygotic and heterozygotic model.

Genetic model	Subgroup	Study	Case	Control	P	OR	95% CI
dominant model (AB + BB vs. AA)	brain cancer	11	2,589	8,044	0.209	1.07	0.96 ~ 1.20
	head and neck cancer	15	2,825	3,039	0.179	0.89	0.74 ~ 1.06
	lung cancer	11	1,873	2,567	0.453	0.95	0.83 ~ 1.09
	skin cancer	7	678	1,252	0.824	0.98	0.79 ~ 1.21
	urinary system cancer	5	1,640	1,960	0.281	1.22	0.85 ~ 1.75
	breast cancer	3	3,860	6,081	0.763	0.99	0.90 ~ 1.07
	digestive system cancer	11	1,731	2,734	0.844	0.97	0.73 ~ 1.29
	oral cancer	6	1,067	1,524	0.741	0.97	0.79 ~ 1.18
	glioma	4	1,482	2,908	0.963	1.00	0.84 ~ 1.21
	colorectal cancer	3	692	876	0.890	0.96	0.56 ~ 1.65
	head and neck SCC	8	1,512	1,798	0.002	0.77	0.65 ~ 0.91
	skin SCC	3	195	478	0.598	0.90	0.62 ~ 1.32
	skin BCC	4	459	792	0.925	1.01	0.94 ~ 1.07
recessive model (BB vs. AA + AB)	brain cancer	10	2,273	7,601	0.233	1.18	0.90 ~ 1.55
	head and neck cancer	13	2,427	2,589	0.045	0.76	0.58 ~ 0.99
	lung cancer	10	1,638	2,473	0.684	1.08	0.76 ~ 1.53
	skin cancer	7	678	1,252	0.952	1.02	0.60 ~ 1.73
	urinary system cancer	5	1,640	1,960	0.998	1.00	0.63 ~ 1.58
	breast cancer	3	3,860	6,081	0.532	1.09	0.83 ~ 1.44
	digestive system cancer	8	1,288	1,917	0.167	0.71	0.44 ~ 1.15

OR, odds ratio; CI confidence interval.

Genetic model	Subgroup	Study	Case	Control	P	OR	95% CI
	oral cancer	5	757	1,176	0.230	0.80	0.56 ~ 1.15
	glioma	3	1,166	2,465	0.415	1.17	0.80 ~ 1.73
	colorectal cancer	3	692	876	0.071	0.52	0.26 ~ 1.06
	head and neck SCC	6	1,114	1,348	0.021	0.63	0.43 ~ 0.98
	skin SCC	3	195	478	0.618	1.29	0.47 ~ 3.51
	skin BCC	4	459	792	0.820	0.93	0.50 ~ 1.74
carrier model (carrier B vs. A)	brain cancer	10	2,273	7,601	0.190	1.07	0.97 ~ 1.18
	head and neck cancer	14	2,515	2,691	0.156	0.92	0.82 ~ 1.03
	lung cancer	10	1,638	2,473	0.512	0.96	0.84 ~ 1.09
	skin cancer	7	678	1,252	0.874	0.98	0.80 ~ 1.21
	urinary system cancer	5	1,640	1,960	0.593	1.04	0.90 ~ 1.20
	breast cancer	8	3,860	6,081	0.867	0.99	0.91 ~ 1.08
	digestive system cancer	5	1,288	1,917	0.100	0.87	0.74 ~ 1.03
	oral cancer	3	757	1,176	0.900	1.01	0.84 ~ 1.22
	glioma	3	1,166	2,465	0.574	1.04	0.90 ~ 1.21
	colorectal cancer	7	692	876	0.518	0.93	0.75 ~ 1.16
	head and neck SCC	7	1,202	1,450	0.032	0.83	0.70 ~ 0.98
	skin SCC	4	195	478	0.725	0.94	0.85 ~ 1.36
	skin BCC	3	459	792	0.959	1.01	0.78 ~ 1.30
OR, odds ratio; CI confidence interval.							

Moreover, a decreased risk of head and neck SCC cancer was detected under all the genetic models (Table 3, allelic B vs. A, $P = 0.007$, $OR = 0.78$; BB vs. AA, $P = 0.006$, $OR = 0.54$; AB vs. AA, $P = 0.045$, $OR = 0.82$; Table 4, AB + BB vs. AA, $P = 0.002$, $OR = 0.77$; BB vs. AA + AB, $P = 0.021$, $OR = 0.63$; carrier B vs. A, $P = 0.032$, $OR = 0.83$). Forest plot data of subgroup analysis by ethnicity under the allelic model (Fig. 2) and subgroup meta-analysis of head and neck SCC under the allelic model (Fig. 3)

were provided. The other forest plots were shown in Figure S1-S8. Our findings suggested that the GSTM3 intron 6 A/B polymorphism may be associated with a decreased risk of head and neck SCC.

Publication bias and sensitivity analysis

In addition, we did not observe a large publication bias in any of the above analyses (Table 5, all $P > 0.05$). Under the allelic model, Begg’s funnel plot with pseudo 95% confidence limits (Fig. 4A) and Egger’s publication bias plot (Fig. 4B) are displayed. Our sensitivity analysis data in Fig. 5 also suggested the statistical stability of pooling outcomes under the allelic model. Similar data were observed in other models (data not shown).

Table 5
Publication bias data.

Genetic model	Begg's Test		Egger's test	
	z	P	t	P
allelic model (allelic B vs. A)	1.09	0.277	0.10	0.924
homozygotic model (BB vs. AA)	0.22	0.829	-0.59	0.561
heterozygotic model (AB vs. AA)	0.30	0.763	0.18	0.855
dominant model (AB + BB vs. AA)	1.15	0.249	0.39	0.695
recessive model (BB vs. AA + AB)	0.01	0.993	-0.50	0.620
carrier model (carrier B vs. A)	0.97	0.332	0.15	0.881

Discussion

The different results regarding the genetic effect of GSTM3 intron 6 A/B polymorphism on the risk of cancer were reported by individual researchers. For example, GSTM3 A/B polymorphism seems not to be linked to the risk of oral cancer in the African-American population [59], but not in the Indian population [53]. In the present study, we searched the available case-control studies for the comprehensive assessment of the role of GSTM3 A/B polymorphism in the overall cancer.

Even though no meta-analysis of overall cancer and GSTM3 intron 6 A/B polymorphism were reported, there are several meta-analyses regarding the association between GSTM3 A/B polymorphism and specific cancer type, including head and neck cancer [66], lung cancer [4, 67], and osteosarcoma [68]. In 2006, Ye, Z. enrolled a total of five case-control studies for a meta-analysis of head and neck cancer, reported the no significant overall association between GSTM3 A/B polymorphism and lung cancer risk [4]. In 2012, Feng, X. performed an updated meta-analysis with eight case-control studies, and the similar negative result was detected [67]. For the meta-analysis of osteosarcoma [68], only two case-control studies were included. In 2014, Xu, Y. conducted the meta-analysis of head and neck cancer with 14 case-control studies, and reported that GSTM3 A/B polymorphism seems to be linked the decreased risk of head and neck cancer. In the present study, a total of fifty-eight case-control studies (17,125 cases / 22,342 controls) from the fifty-three articles were enrolled. And the six genetic models, including the allelic B vs. A, BB vs. AA, AB vs. AA, AB + BB vs. AA, BB vs. AA + AB, carrier B vs. A, were applied. However, no positive genetic association between GSTM3 intron 6 A/B polymorphism and the risk of overall cancer was detected. We then performed the subgroup meta-analysis, based on the factors of ethnicity, control source, HWE and cancer type. The subgroup analysis of “brain cancer”, “head and neck cancer”, “lung cancer”, “skin cancer”, “urinary system cancer”, “breast cancer”, “digestive system cancer”, “oral cancer”, “glioma” and “colorectal cancer” were conducted. Our data suggested the potential association between BB genotype of GSTM3 and the decreased risk of head and neck cancer. Furthermore, we focused on the specific SCC or BCC type of cancer and performed the meta-analysis of “head and neck

SCC”, “skin SCC”, or “skin BCC”. Our data supported the protective role of GSTM3 intron 6 A/B polymorphism on the risk of head and neck SCC cancer.

Our meta-analysis exhibits several advantages. First, more than fifty case-control studies were enrolled for our comprehensive assessment. Second, our results of Begg’s and Egger’s tests ruled out the presence of large publication bias. Third, our sensitivity analyses support the stability of pooling results.

Despite this, some disadvantages still may limit our statistical evaluation. First, as in other meta-analyses, a small sample size was enrolled in some subgroup analyses. For example, only three case-control studies were included in the subgroup meta-analysis of “breast cancer”, “glioma”, “colorectal cancer”, and “skin SCC”. Even though the positive result was observed in the subgroup analysis of “head and neck SCC”, no more than ten case-control studies were included. Moreover, due to the lack of enough genotypic data, we did not perform the subgroup of specific head and neck SCC in the Asian or Caucasian population. Second, a high heterogeneity level among studies was observed in the allelic, heterozygotic or dominant meta-analyses. Third, the genotypic distribution of control groups in some studies was not in line with the Hardy-Weinberg equilibrium. Fourth, of the eligible case-control studies, only the combined “AB + BB” genotypic frequency data were extracted in some studies [18, 20, 25, 31, 35, 44, 50, 58]. Fifth, in this study, we only study the GSTM3 intron 6 A/B polymorphism. And the role of other polymorphisms within GSTM3 gene in the risk of cancer, such as rs1055259, rs3814309, or 5776997, or the combined genetic effect of GSTM3 gene and other GST genes, such as GSTM1, GSTP1, GSTT1, should be investigated, when the enough genotypic data was available. Moreover, the additional adjusted clinical or environmental factors should be conducted when we can obtain access to more association investigation data for years to come.

Conclusions

In summary, we performed the first meta-analysis regarding the genetic link between GSTM3 intron 6 A/B polymorphism and cancer risk in the overall population. The GSTM3 intron 6 A/B polymorphism may act as the protective factor of head and neck SCC, which would be greatly strengthened by a larger sample size.

Abbreviations

GSTM3: Glutathione S-Transferase Mu 3; GSTs: Glutathione S-transferases; GSTA1: Glutathione S-transferase alpha 1; GSTT1: Glutathione S-transferase theta 1; GSTP1: Glutathione S-Transferase pi; GSTM1: Glutathione S-transferase Mu1; PRISMA: preferred reporting items for systematic reviews and meta-analyses; HWE: Hardy-Weinberg equilibrium; NOS: Newcastle-Ottawa quality assessment Scale; OR: odds ratio; CI: confidence interval.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during the present study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

WM and KC designed the study. YW, HF and JY performed the database retrieval and study selection. YW, YD and SJ extracted and analysed the data. WM and KC interpreted the data and drafted the manuscript. All authors read and approved the final manuscript.

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Supporting Information

Figure S1 Forest plot of subgroup meta-analysis by control source (allelic model).

Figure S2 Forest plot of subgroup meta-analysis by HWE (allelic model).

Figure S3 Forest plot of subgroup meta-analysis by cancer type (allelic model).

Figure S4 Forest plot of subgroup meta-analysis of head and neck SCC (homozygotic model).

Figure S5 Forest plot of subgroup meta-analysis of head and neck SCC (heterozygotic model).

Figure S6 Forest plot of subgroup meta-analysis of head and neck SCC (dominant model).

Figure S7 Forest plot of subgroup meta-analysis of head and neck SCC (recessive model).

Figure S8 Forest plot of subgroup meta-analysis of head and neck SCC (carrier model).

Figures

Figure 1

Figure 1

Flow chart of case-control study inclusion.

Figure 2

Figure 2

Forest plot of subgroup meta-analysis by ethnicity (allelic model).

Figure 3

Figure 3

Forest plot of subgroup meta-analysis of head and neck SCC (allelic model).

Figure 4

Figure 4

Publication bias plots (allelic model). (A) Begg's test; (B) Egger's test.

Figure 5

Figure 5

Sensitivity analysis (allelic model).

Supplementary Files

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