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REVIEW – CANCER RESEARCH

Association of glutathione-*S*-transferase p1 gene promoter methylation and the incidence of prostate cancer: a systematic review and meta-analysis

Xueliang Zhou[1] · Dechao Jiao[1] · Mengmeng Dou[2] · Jianjian Chen[1] · Zhaonan Li[1] · Yahua Li[1] · Juanfang Liu[1] · Xinwei Han[1]

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Abstract

Objective Some studies have shown that the methylation status of the *GSTP1* gene promoter is related to the incidence of prostate cancer, but this finding is still controversial. The aim of this study was to evaluate the association between glutathione-*S*-transferase p1 (*GSTP1*) promoter methylation and the incidence of prostate cancer.

Methods The Medline, Embase, Web of Science, and Cochrane CENTRAL databases were searched from their inception to February 22, 2019. According to the inclusion criteria, studies of the association between the methylation status of the *GSTP1* gene promoter and prostate cancer were included. The difference in the incidence of *GSTP1* promoter methylation in tissues, blood, or urine between patients with prostate cancer and those without prostate cancer were compared, and the results were expressed as the odds ratio (OR) and 95% confidence interval (CI). The pooled OR of each study was estimated using a fixed-effects model or a random-effects model to generate forest plots.

Results Ultimately, 15 studies (1540 samples) were included. The estimated effect from our meta-analysis showed that the incidence of *GSTP1* promoter methylation was higher in patients with prostate cancer than in those without prostate cancer (OR 18.58, 95% CI 9.60–35.95, $P=0.000$). *GSTP1* promoter methylation was highly correlated with the incidence of prostate cancer.

Conclusions Methylation of the *GSTP1* promoter may increase the risk of prostate cancer. This study may provide a strategic direction for prostate cancer research. Pending validation of these findings, the methylation of the *GSTP1* promoter may be a potential biomarker to diagnose prostate cancer.

Keywords Prostate cancer · Glutathione-*S*-transferase p1 · Methylation · Meta-analysis

Abbreviations

GSTP1	Glutathione-*S*-transferase P1
OR	Odds ratio
CI	Confidence interval
PSA	Prostate-specific antigen
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
NOS	Newcastle–Ottawa Scale
MSP	Methylation-specific polymerase chain reaction
Q-MSP	Quantitative methylation-specific polymerase chain reaction
BPH	Benign prostatic hyperplasia

Xueliang Zhou and Dechao Jiao have contributed equally to this work.

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✉ Xinwei Han
13592583911@163.com

[1] Department of Interventional Radiology, The First Affiliated Hospital of Zhengzhou University, 1 Jianshe East Road, Zhengzhou, Henan, China

[2] Department of Neurology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China

Introduction

Prostate cancer is one of the most common malignancies among men in developed countries, and it is the third leading cause of death among all patients with cancer (Torre

et al. 2015). In 2018, prostate cancer accounted for nearly one-fifth of all newly diagnosed cancers in the United States (Siegel et al. 2018). In recent years, with the ageing of the population and changes in people's lifestyle habits, the incidence of prostate cancer in China has also shown a marked upward trend. Currently, the diagnosis of prostate cancer depends extensively on prostate-specific antigen (PSA) screening and/or digital rectal examination (Cook and Nelson 2011). However, it is controversial whether PSA screening can be used for the early diagnosis of prostate cancer (Fleshner et al. 2017). In recent years, increasing evidence has emerged, showing that epigenetic changes in tumour-associated genes are involved in the pathogenesis and development of prostate cancer, and can be used as indicators for cancer diagnosis and treatment (Damaschke et al. 2013; Mahapatra et al. 2012; Trock et al. 2012; Van Neste et al. 2012).

DNA methylation, as a manifestation of epigenetics, is an important mechanism of gene expression regulation. Hypermethylation of a gene promoter region often leads to transcriptional repression of the gene, which is the cause of gene silencing (Fukushige and Horii 2013; Massie et al. 2015; Nakamura et al. 2014). Glutathione-*S*-transferase (GST) is a key enzyme in the glutathione-binding reaction. GST can catalyse the binding of nucleophilic glutathione to various electrophilic exogenous chemicals, thus, playing an anticancer and detoxification role (Miyake et al. 2012). Among GST isoenzymes, GSTπ, encoded by *GSTP1*, is involved in a large number of detoxification and metabolic reactions and can prevent cell genome damage and cancer (Esteller et al. 1998; Saxena et al. 2012). In addition, the silencing of *GSTP1* expression induced by promoter methylation is associated with the pathogenesis of prostate cancer (Martignano et al. 2016b).

Some studies have investigated the methylation status of *GSTP1* in patients with prostate cancer; however, there were some differences among the results of these studies. Whether methylation of the *GSTP1* promoter is related to the occurrence of prostate cancer remains controversial. Therefore, we conducted a meta-analysis of published clinical studies to assess the relationship between *GSTP1* promoter methylation and the incidence of prostate cancer. The purpose of this study is to provide a new research direction for the diagnosis of prostate cancer and to identify potential biomarkers.

Materials and methods

The study protocol was registered through PROSPERO (http://www.crd.york.ac.uk/PROSPERO), and the registration number is CRD42019127008, which can be found online at https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=127008.

Search strategy

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria (Moher et al. 2009). We searched the Medline (www.ncbi.nlm.nih.gov/pubmed), EMBASE (www.embase.com), Web of Science (http://apps.webofknowledge.com), and Cochrane Library (www.cochranelibrary.com) databases for English language articles published from the inception of the database through February 22, 2019. A combination of MeSH and Emtree, title and abstract, and keywords was used. The search terms included "prostate cancer", "prostate carcinoma", "prostatic neoplasms", "*GSTP1*", "glutathione-*S*-transferase p1", and "methylation". The detailed search strategy is shown in Additional file: Table S1.

Inclusion and exclusion criteria

The following inclusion criteria were developed to guide the selection of studies: (1) clinical randomised-controlled study, cohort study, or case–control study; (2) the study design included the incidence of *GSTP1* promoter methylation in patients with prostate cancer and in those without prostate cancer; (3) original full-text articles designed to evaluate the association between *GSTP1* promoter methylation and prostate cancer; and (4) studies with sufficient data that utilised appropriate statistical methods for the analyses.

The following studies were excluded from the meta-analysis: (1) duplicate studies, reviews, letters, case reports, conference papers, and studies based on animal models or cell models; (2) studies conducted in the same centre; (3) studies lacking relevant data; and (4) studies lacking sufficient data for extraction.

Study selection and data extraction

According to the pre-designed inclusion and exclusion criteria, two researchers independently screened the literature and then evaluated the titles and abstracts of the retrieved publications. If the title and abstract were difficult to judge, they read the full text for verification, and any differences were resolved by discussion with a third investigator. Data extraction was also performed independently by two researchers, and any differences were resolved through group discussion. The following information was extracted from each study: (1) the first author, year of publication, country, and region; (2) specimen type, methylation detection method, control type, and the number of participants; and (3) the incidence of *GSTP1* promoter methylation in the case and control groups.

Quality assessment

The quality was assessed for each outcome in all included studies using the Newcastle–Ottawa Scale (NOS) for case–control studies (Wallis et al. 2016). The assessment of quality using the NOS is based on three parameters: Selection, comparability, and outcomes. Studies can receive a maximum possible score of nine stars. NOS scores of 7–9 indicate high-quality reports, and scores of 4–6 represent medium-quality reports.

Statistical analysis

The outcome was the incidence of prostate cancer. The estimated effect size of the outcome was determined using the odds ratios (ORs) and 95% confidence intervals (CIs). The pooled OR of each study was estimated using a fixed-effects model or a random-effects model to generate forest plots. In addition, the Higgins I^2 statistic and Cochran's Q test were used to measure heterogeneity, and if $p > 0.1$ or $I^2 < 50\%$, the heterogeneity was not considered significant. If the heterogeneity was significant, the random-effects model was used; otherwise, the fixed-effects model was used. Potential sources of heterogeneity were further investigated using stratified analysis. Potential publication bias was assessed using Begg's funnel plot (Begg and Mazumdar 1994) and Egger's linear regression (Stuck et al. 1998). Funnel plots were assessed visually for asymmetry. All statistical analyses were performed using STATA 14.0 (College Station, TX, 77845, USA, Serial number: 401406267051).

Results

Study selection

According to the established search strategy, 1002 studies were initially identified, and 507 studies remained after duplicate articles were removed. After the preliminary screening of titles and abstracts, 52 studies related to the outcome of our study were identified for full-text review. However, only 15 studies (Bastian et al. 2004; Chu et al. 2002; Chuang et al. 2007; Dimitriadis et al. 2013; Hanson

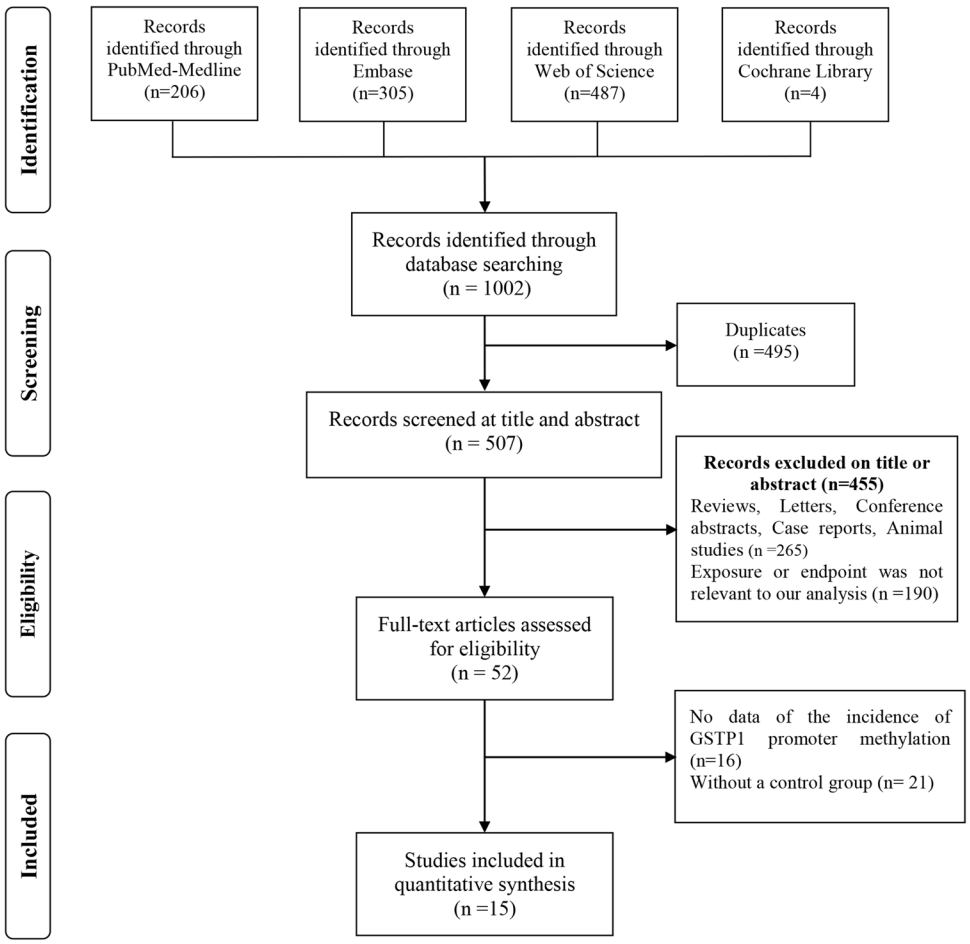

Fig. 1 Flow diagram to assess the evidence following the PRISMA guidelines. PRISMA: preferred reporting items for systematic review and meta-analysis

et al. 2006; Hashad et al. 2011; Jeronimo et al. 2002; Kang et al. 2004; Lan et al. 2015; Martignano et al. 2016a; Maruyama et al. 2002; Richiardi et al. 2013; Sanchez et al. 2018; Vo et al. 2016; Zhang et al. 2015), including 1540 samples, were ultimately included in this meta-analysis. The flow diagram is shown in Fig. 1.

Study characteristics

All 15 studies were case–control studies; four were published in North America, five in Europe, and six in Asia. The sample type of 13 of the 15 studies was tissue, and the sample types of the other two studies were urine and blood. All studies used methylation-specific polymerase chain reaction (MSP) or quantitative methylation-specific polymerase chain reaction (Q-MSP) to detect the sample's methylation status. The characteristics and methylation frequency of *GSTP1* in the experimental and control groups of the included studies are summarised in Table 1.

Quality assessment

The 15 eligible studies were case–control studies, all of which were assigned seven or more points according to the NOS classification. The specific details of each study are presented in Table 2.

Meta-analysis

The relationship between methylation of the *GSTP1* promoter and the incidence of prostate cancer

Fifteen studies reported the association between *GSTP1* promoter methylation and the incidence of prostate cancer. There was significant heterogeneity among the studies ($Q = 43.17$, $P = 0.000$, $I^2 = 67.6\%$, $\text{Tau}^2 = 0.9634$); therefore, the random-effects model was used for the analysis. The estimated effect from our meta-analysis showed that the incidence of *GSTP1* promoter methylation was higher in patients with prostate cancer than in those without prostate cancer (OR 18.58, 95% CI 9.60–35.95, $P = 0.000$) (Fig. 2). *GSTP1* promoter methylation was highly correlated with the incidence of prostate cancer.

Subgroup analysis

To explore the source of the heterogeneity, we used the methylation detection method or sample type as subgroups for analysis; however, no source of heterogeneity was found (Fig. 3a, b). However, in the regional subgroup analysis (Fig. 3c), the heterogeneity among the indicated studies was low ($Q = 0.56$, $I^2 = 0.0\%$, $P = 0.906$, $\text{Tau}^2 = 0.000$) in the studies from North America. The results of this subgroup

Table 1 Characteristics of studies included in the meta-analysis

Study (year)	Study design	Region	Specimen type	Methylation detection method	Control type	Experimental (*n*) Positive/total	Control (*n*) Positive/total
Sanchez et al. (2018)	Case–control	North America	Tissue	Q-MSP	BPH	14/83	2/103
Vo et al. (2016)	Case–control	Asia	Tissue	MSP	BPH	39/59	4/37
Martignano et al. (2016a, b)	Case–control	Europe	Tissue	Q-MSP	Non-prostate cancer	51/56	3/56
Zhang et al. (2015)	Case–control	Asia	Tissue	MSP	BPH	41/56	1/10
Lan et al. (2015)	Case–control	Asia	Tissue	MSP	BPH	23/50	2/17
Richiardi et al. (2013)	Case–control	Europe	Tissue	MSP	Non-prostate cancer	132/157	66/157
Dimitriadis et al. (2013)	Case–control	Europe	Urine	MSP	Non-prostate cancer	6/14	12/52
Hashad et al. (2011)	Case–control	North America	Tissue	Q-MSP	BPH	38/44	12/50
Chuang et al. (2007)	Case–control	Asia	Blood	Q-MSP	BPH	11/36	2/27
Hanson et al. (2006)	Case–control	North America	Tissue	Q-MSP	Normal tissue	5/5	2/4
Kang et al. (2004)	Case–control	Asia	Tissue	MSP	Normal tissue	32/37	0/20
Bastian et al. (2004)	Case–control	Europe	Tissue	Q-MSP	BPH	28/31	0/5
Chu et al. (2002)	Case–control	Asia	Tissue	Q-MSP	BPH	19/21	1/72
Jeronimo et al. (2002)	Case–control	Europe	Tissue	MSP	BPH	89/105	9/43
Maruyama et al. (2002)	Case–control	North America	Tissue	MSP	Non-prostate cancer	36/101	1/32

MSP methylation-specific polymerase chain reaction, *Q-MSP* quantitative methylation-specific polymerase chain reaction, *BPH* benign prostatic hyperplasia

Table 2 The Newcastle–Ottawa Scale (NOS) to assess the quality of the case–control studies

Studies	Selection			Comparability			Exposure			Total score
Authors (year)	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Studies controlling the most important factors	Studies controlling the other main factors	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	
Sanchez et al. (2018)	*	*	*	*	*		*	*		7
Vo et al. (2016)	*	*	*	*	*	*	*	*		8
Martignano et al. (2016a, b)	*	*	*	*	*	*	*	*		8
Zhang et al. (2015)	*	*	*	*	*		*	*		7
Lan et al. (2015)	*	*	*	*	*		*	*		7
Richiardi et al. (2013)	*	*	*	*	*	*	*	*		8
Dimitriadis et al. (2013)	*	*	*	*	*		*	*		7
Hashad et al. (2011)	*	*	*	*	*	*	*	*		8
Chuang et al. (2007)	*	*	*	*	*	*	*	*		8
Hanson et al. (2006)	*	*	*	*	*	*	*	*		8
Kang et al. (2004)	*	*	*	*	*	*	*	*		8
Bastian et al. (2004)	*	*	*	*	*		*	*		7
Chu et al. (2002)	*	*	*	*	*	*	*	*		8
Jeronimo et al. (2002)	*	*	*	*	*		*	*		7
Maruyama et al. (2002)	*	*	*	*	*		*	*		7

*Each star represents one point. NOS scores of 7–9 indicate high-quality reports and scores of 4–6 represent medium-quality reports

analysis suggest that the heterogeneity of this meta-analysis may be due to the regional differences in the included studies. The results of the heterogeneity test are shown in Additional file: Table S2.

Sensitivity analyses

Sensitivity analysis was performed to verify the effect of any one study on the overall estimate by omitting one individual study each time. Our findings showed good consistency and indicated that removing any one of the studies did not significantly affect the combined estimate. The sensitivity analysis indicated that our analyses were robust and reliable (Fig. 4).

Publication bias

Publication bias was assessed using Begg's funnel plots and Egger's linear regression test. Figure 5a shows that the funnel plots were slightly asymmetric. However, the results of Begg's test and Egger's linear regression tests showed that there was no significant publication bias in the analysis (Begg's test, $P=0.428$; Egger's test, $P=0.062$). Duval and Tweedie's trim-and-fill were further used to verify whether the results of this meta-analysis study were robust. The funnel plot of the trimmed and imputed study is displayed in Fig. 5b. Funnel plots in Fig. 5 were constructed using STATA 14.0. Under the fixed-effect model, the OR estimate (95% CI) of the combined studies before and after using the trim-and-fill method were 2.549 (2.227–2.872) and 2.251 (1.945–2.558), respectively. In the random-effects model, the point estimate (95% CI) for the combined studies before and after using the trim-and-fill method were 1.13569 (2.921–3.579) and 2.269 (1.549–2.990), respectively. There was no significant change in the estimated value after adjustment by the trim-and-fill method, which indicated that the results of this meta-analysis were reliable and robust.

Discussion

After a systematic review of the literature, 15 studies of the association between *GSTP1* promoter methylation and the risk of prostate cancer were analysed in this meta-analysis. Our findings showed that the incidence of *GSTP1* promoter methylation in patients with prostate cancer was much higher than that in patients without prostate cancer.

The pathogenesis of prostate cancer is not clear, and the risk factors can be divided into genetic and environmental factors. Up to 58% of the risk is caused by genetic factors (Mancuso et al. 2018). *GSTP1* is a member of the metabolic

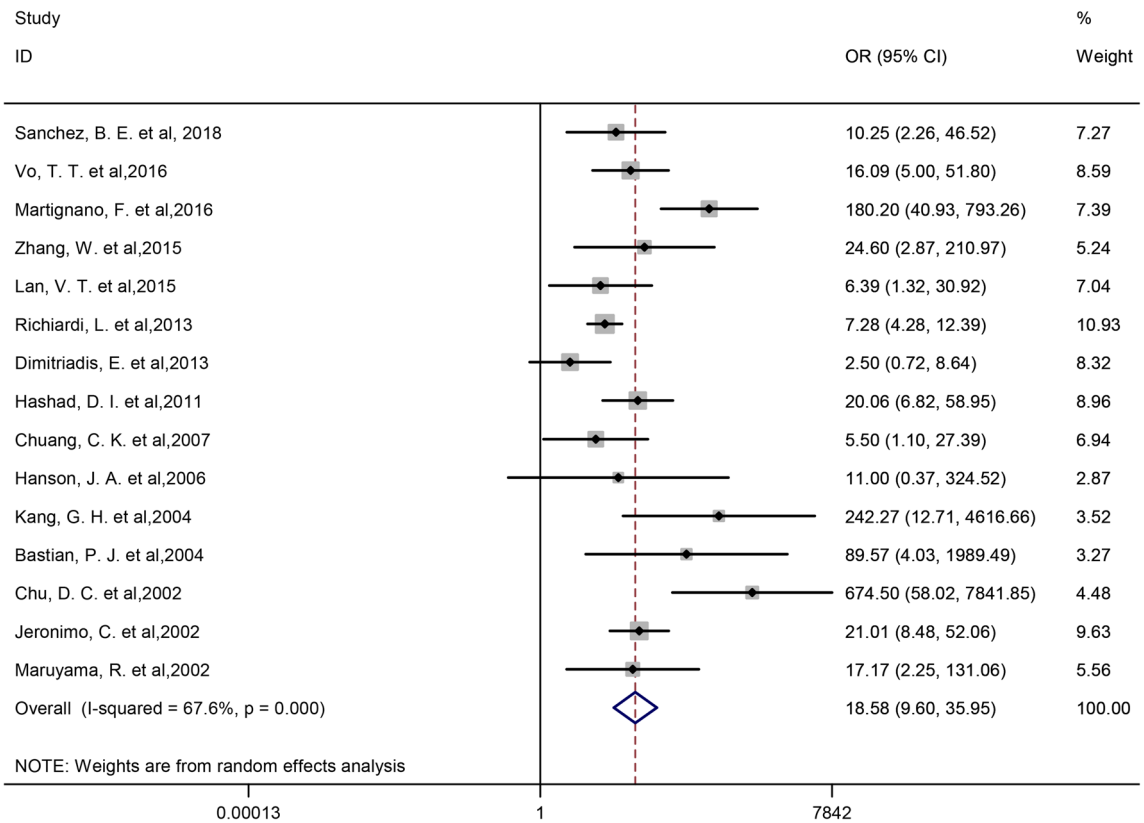

Fig. 2 Forest plots of the association between *GSTP1* methylation and prostate cancer risk. *OR* odds ratio, *CI* confidence interval

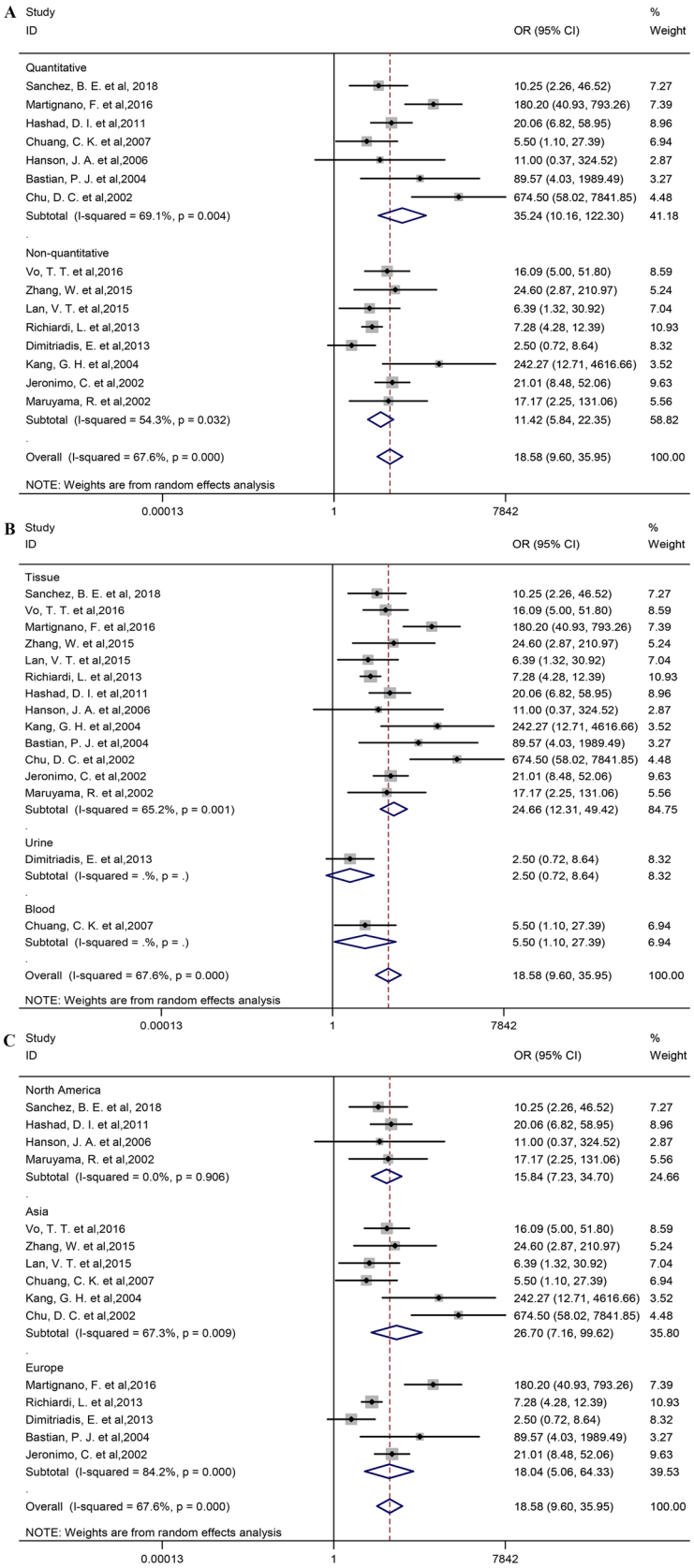

Fig. 3 **a** Forest plots of the subgroup analysis according to methylation detection methods. **b** Forest plots of the subgroup analysis according to sample type. **c** Forest plots of the subgroup analysis according to region. *OR* odds ratio, *CI* confidence interval

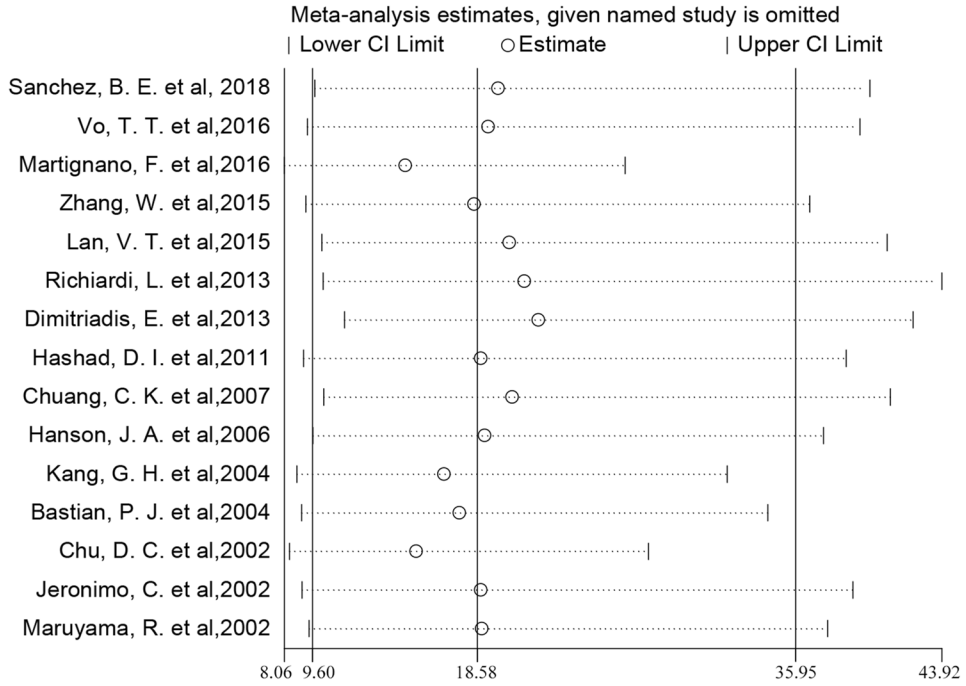

Fig. 4 Sensitivity analysis of the association between *GSTP1* methylation and incidence of prostate cancer

enzyme family and plays an important role in preventing the initial occurrence of cancer when the body is exposed to carcinogenic substances (Arai et al. 2006). Moreover, as a tumour suppressor gene, abnormal methylation of the *GSTP1* promoter usually occurs in different cancer types, including lung cancer (Haroun et al. 2014), breast cancer (Krassenstein et al. 2004; Pongtheerat et al. 2011), and prostate cancer (Pandey et al. 2010). Hypermethylation of the *GSTP1* promoter in patients with prostate cancer may lead to the inactivation of *GSTP1* expression, leading to tumour progression. Therefore, epigenetic silencing of *GSTP1* may be a marker of the transformation of the normal prostate epithelium to prostate cancer (Mian et al. 2016). Maldonado et al. (2014) used Q-MSP to evaluate the correlation between the methylation of the *GSTP1*, *RARB* (retinoic acid receptor beta), and *SSBP2* (single-stranded DNA-binding protein 2) promoters and the risk of recurrence in 452 cases of prostate cancer. The results showed that the degree of methylation of the *GSTP1* promoter was higher in patients with early recurrence of prostate cancer, suggesting that methylation of the *GSTP1* promoter may be a potential biomarker for the recurrence of prostate cancer. Rosenbaum et al. (2005) analysed tumour tissues from 74 patients with prostate cancer and found that hypermethylation of the *GSTP1* promoter was an independent risk factor for recurrence of prostate cancer (HR 0.23; 95% CI 0.09–0.64, $P=0.004$). However, Hanson et al. (Hanson et al. 2006) compared the methylation status of the *GSTP1* promoter in prostate cancer and non-prostate cancer tissues, and found that there was no significant difference in *GSTP1* promoter methylation between patients with prostate cancer and those without (OR 11.0, 95% CI 0.37–324.52, $P=0.165$). Therefore, whether methylation of the *GSTP1* promoter can increase the risk of prostate cancer is a controversial subject.

Our meta-analysis showed that the methylation level of *GSTP1* was significantly higher in patients with prostate cancer than in those without prostate cancer, suggesting that GSTP1 plays a potential role in the pathogenesis of prostate cancer. We also performed a subgroup analysis to further explore whether the effects of *GSTP1* promoter methylation on the risk of prostate cancer are related to regional differences. The results showed that *GSTP1* promoter methylation was closely related to the risk of prostate cancer in North America (OR 15.84, 95% CI 7.23–34.70, $P=0.000$), Asia (OR 26.70, 95% CI 7.16–99.62, $P=0.000$), and Europe (OR 18.04, 95% CI 5.06–64.33, $P=0.000$); however, the correlation was stronger in Asia than in North America and Europe.

This meta-analysis had the following strengths. First, the meta-analysis confirmed that *GSTP1* promoter methylation is associated with the risk of prostate cancer, which may provide new directions for the diagnosis of prostate cancer. Second, the 15 articles included in the literature had high NOS scores, diverse sample sources, and good representativeness; additionally, the strict implementation of the inclusion and screening criteria was a strength. Finally, the sensitivity analysis showed that the results did not change significantly when any of the 15 articles were excluded. Therefore, the results of this meta-analysis are stable and reliable.

However, this study had several limitations. There are some important confounding factors beyond our control that

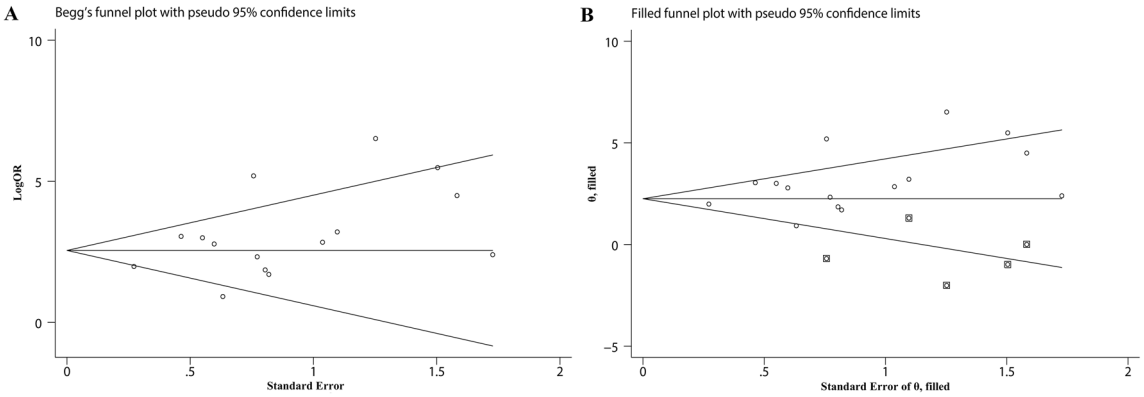

Fig. 5 **a** Begg's funnel plot to evaluate the publication bias of *GSTP1* promoter methylation and the incidence of prostate cancer. **b** Funnel plot of pooled analysis adjusted with Duval and Tweedie's trim-and-fill method

may have affected the results of the comprehensive analysis. Moreover, some original studies did not provide complete data on tissue type, stage, and age; therefore, comprehensive subgroup analyses could not be performed. Finally, when we searched the literature, we found that all the studies that met the inclusion criteria were case–control trials, and more randomised-controlled trials may be needed to provide more reliable evidence.

The results of this study indicated that promoter methylation of *GSTP1* might increase the risk of prostate cancer. This study might provide a strategic direction for prostate cancer research. Pending validation of these finding, the methylation of the *GSTP1* promoter may be a potential biomarker to diagnose prostate cancer. However, a large number of randomised-controlled clinical studies are still needed to confirm this.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest regarding the present study.

Ethics approval and consent to participate The article does not contain any studies with human participants performed by any of the authors.

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