

RESEARCH ARTICLE

GSTT1, an increased risk factor for prostate cancer in patients with metabolic syndrome

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Abstract

Background: Glutathione S-transferase (GSTs) gene polymorphism and metabolic syndrome (Mets) are generally considered to be risk factors for prostate cancer (PCa). However, this conclusion is still controversial. There is a close relationship between GSTs gene polymorphism and Mets. We suspect that the effect of GSTs gene polymorphism and Mets on PCa may be the result of their joint action. As a result, the purpose of this study was to investigate the potential effect of GSTs gene polymorphism on PCa in patients with Mets.

Methods: We collected blood samples from 128 patients with PCa and 200 controls. The GSTs gene polymorphism was detected by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Age, characteristics of Mets, frequencies of GSTs gene polymorphism, total prostate volume (TPV), Gleason score, and prostate-specific antigen (PSA) were recorded and analyzed.

Results: There were significant differences in BMI, TG, LDL-C, FBG, SBP, DBP, and HDL-C among the control group, N-PCa group, and Mets-PCa group ($p < 0.05$). *GSTT1* null genotype (OR = 2.844, 95% CI: 1.791–4.517), *GSTM1* null genotype (OR = 2.192, 95% CI: 1.395–3.446), and *GSTP1* (A/G + G/G) genotype (OR = 2.315, 95% CI: 1.465–3.657) were associated with PCa susceptibility and malignancy. Only the *GSTT1* null genotype in Mets patients was positively correlated with PCa.

Conclusions: Our study suggests that GSTs gene polymorphism may be a risk factor for PCa and can predict the susceptibility and malignancy of PCa. Secondly, in Mets patients, *GSTT1* null genotype significantly increased the risk of PCa. *GSTM1* null genotype and the effect of *GSTP1* (AG + GG) on PCa were not significantly related to Mets.

KEYWORDS

genetic polymorphism, glutathione transferase gene, metabolic syndrome, prostate cancer

Dongdong Liu, Bangwei Che, and Pan Chen contributed equally to this study.

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1 | INTRODUCTION

PCa is one of the most common malignant tumors in men after lung cancer. According to statistics, there are about 1.3 million new cases and 360,000 deaths in the world in 2018, which has become a global public health problem threatening men's health.¹ However, the pathogenesis of PCa remains unclear. Existing studies have summarized the risk factors of PCa into social factors, environmental factors, and genetic factors, which are closely related to oxidative stress, and the main culprit is reactive oxygen species (ROS).^{2,3} ROS, as an inevitable by-product of cell metabolism, may increase genetic instability, promote abnormal cell proliferation and produce somatic DNA mutation, resulting in the occurrence and progress of PCa.⁴ Correspondingly, GSTs, one of the main enzymes involved in carcinogenic inactivation, have extensive substrate characteristics. It can bind to electronic compounds such as ROS and catalyze glutathione reduction to maintain cell integrity, reduce oxidative stress and protect DNA from damage. Most studies have focused on considering gene deletions or mutations as risk factors for chemical carcinogenesis, among which *GSTT1*, *GSTM1*, and *GSTP1* are the most concerning.^{5,6} In particular, *GSTP1* is widely regarded as a tumor suppressor gene for PCa. The *GSTP1*-I105V polymorphism is due to the A→G substitution at the exon base binding site, resulting in the transformation of the 105th amino acid in the protein-peptide chain from ATC isoleucine (Ile) to GTC valine (Val).⁷ This change will reduce the activity and thermal stability of the enzyme. The deletion of alleles is the main cause of polymorphisms in the *GSTT1* and *GSTM1* genes,⁸ and the genetic deletion of this gene leads to the phenotypic loss of enzyme activity. The changes in the DNA of these individuals are called single nucleotide polymorphisms (SNPs). One of the reasons why SNPs are not uncommon in human individuals is the loss of gene methylation. Many studies have shown that CpG island methylation is the most common somatic genomic change in PCa, with a specificity of up to 95% in plasma or urine,^{9–12} which is the main reason why the expression of GSTs in PCa tissues is significantly lower than that in non-prostate cancer tissues.¹³ Therefore, GSTs gene polymorphism is highly likely to be used as a predictor of PCa. However, although the mechanism of GSTs gene polymorphism in PCa has been gradually discovered, the relationship between GSTs and PCa is often controversial in previous case-control studies.^{14,15} We speculate that this phenomenon is also affected by other unknown factors.

Looking for possible intervention factors may become the next research direction. Fortunately, Mets has been emphasized in various results, and it is also the focus of the etiology of prostate diseases, although the results are equally contradictory.^{16,17} Similarly, the etiology of Mets remains unclear, but it is considered to be the result of multiple gene-environment interactions and is associated with the occurrence and development of most cancers, including PCa. When the body has Mets and its components, it is often accompanied by inflammation and oxidative stress injury.¹⁸ Interestingly, we note that in the United States, Mets is associated with an increased risk of PCa in African American men but not in whites. Coincidentally, we

also found that African American men with Mets tend to have higher DNA methylation, including *GSTT1*.^{19,20} It is not difficult to imagine that the possible effects of Mets or GSTs gene polymorphisms on PCa do not act alone. Regrettably, there have been no such studies in the past. Therefore, this study aims to fill this gap and explore whether GSTs gene polymorphism and Mets work together to affect the occurrence of PCa.

2 | MATERIALS AND METHODS

2.1 | Patients and samples

This study was conducted at the affiliated hospital of Guizhou Medical University. The subjects included 128 newly diagnosed localized PCa patients and 200 matched healthy elderly men of similar ages. Patients were diagnosed according to the American Urological Association (AUA) PCa treatment guidelines (2013)²¹ and the International Diabetes Federation (IDF) Mets Clinical Standard (2006).²² A total of 128 PCa patients were divided into two groups: simple PCa (N-PCa) and Mets (Mets-PCa group), including 70 cases in the simple PCa group (N-PCa), 58 cases in the Mets-PCa group (Mets-PCa), and normal elderly men, including Mets patients in the non-PCa group.

Exclusion criteria: age ≤50 years old; history of prostate surgery and tumor; recent history of taking 5 α reductase inhibitor (at least three months) or history of transurethral operation or rectal examination (at least one month). and patients with organ failure and other malignant lesions.

2.2 | Data collection

Through case review and a questionnaire survey, the patient's history and prostate characteristics were obtained. In the hospital laboratory department, PSA, Gleason score, total prostate volume (TPV), and characteristics of metabolic syndrome (triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and fasting blood glucose (FBG)) were detected.

The clinical history data and blood samples obtained from the study obtained the written informed consent of the patients or their relatives. This study was approved by the Ethics Committee of the affiliated hospital of Guizhou Medical University.

2.3 | Detection of gene polymorphism

Peripheral venous blood (4 ml) was collected by peripheral venipuncture. Disodium ethylenediaminetetraacetate was used as an anticoagulant. Anticoagulant blood was mixed and placed in a refrigerator at -80 °C. The total DNA of peripheral blood cells was extracted according to the method provided by the Tiangen Biotech company. *GSTT1*, *GSTM1*, and *GSTP1* genotypes were detected by multiplex

polymerase chain reaction (PCR) or polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) using primer sequences published by GENEWIZ (Suzhou) Biotechnology, as mentioned earlier.²³ 2% agarose gel electrophoresis was used to detect PCR-RFLP products, and the GenSens1850 gel file and analysis system (Clinx Science Instruments) was used for visualization and coding.

2.4 | Statistical analysis

All analyses were carried out on SPSS version 20.0 (SPSS, Inc.). The data, by a normal distribution, were expressed by mean \pm SD. An independent sample *t*-test was used for pairwise comparison. Analysis of the relationship between the PCa index and GSTs gene (T1/M1/P1) polymorphism by a logistic regression model. The Chi-square test and the Cochran–Mantel–Haenszel test were used to evaluate the risk of Mets and GSTs gene (M1/T1/P1) polymorphism for PCa.

3 | RESULTS

There was no significant difference in age among the three groups (control group 65.84 ± 4.45 , N-PCa group 66.14 ± 5.38 , Mets-PCa

group 65.57 ± 4.72 , $p > 0.05$). There were significant differences in Mets characteristics (BMI, TG, HDL-C, LDL-C, DBP, SBP, FBG) among the three groups ($p < 0.05$). Except for HDL-C, BMI, TG, LDL-C, FBG, SBP, and DBP in the N-PCa group were significantly higher than those in the control group ($p < 0.05$). The data also showed that BMI, TG, LDL-C, FBG, SBP, and DBP of the Mets-PCa group were higher than those of the N-PCa group or control group ($p < 0.05$), while HDL-C of the Mets-PCa group was lower than that of the N-PCa group or control group ($p < 0.05$). In addition, the prostate characteristic values (TPV and PSA) of the N-PCa group were higher than those of the control group, and the prostate characteristic values (TPV and PSA) in the Mets-PCa group were higher than those in the control group and the N-PCa group ($p < 0.05$). In addition, there was no significant difference in Gleason score between the N-PCa and Mets-PCa groups ($p > 0.05$). (Table 1).

Multivariate logistic regression analysis showed that TPV and Gleason scores were positively correlated with *GSTT1* null genotype, *GSTM1* null genotype, and *GSTP1* (AG + GG) ($p < 0.05$). PSA was positively correlated with *GSTT1* null genotype and *GSTP1* (AG + GG) ($p < 0.05$), but not significantly correlated with *GSTM1* null genotype ($p > 0.05$). (Table 2).

The results showed that *GSTT1* null genotype, *GSTM1* null genotype, and *GSTP1* (AG + GG) were positively correlated with PCa. The *GSTT1* null genotype increased the susceptibility to PCa by 2.844

TABLE 1 Comparison of general clinical data of control group, N-PCa group, and Mets-PCa group ($\bar{x} \pm s$)

Clinical index	Control group	N-PCa	Mets-PCa
AGE	65.84 ± 4.45	66.14 ± 5.38	65.57 ± 4.72
BMI(kg/m ²)	19.13 ± 0.5	22.07 ± 0.85^a	$28.46 \pm 1.54^{a,b}$
TG(mmol/L)	1.15 ± 0.20	1.46 ± 0.12^a	$2.02 \pm 0.18^{a,b}$
HDL-C(mmol/L)	1.77 ± 0.24	1.30 ± 0.18^a	$0.54 \pm 0.17^{a,b}$
LDL-C(mmol/L)	1.62 ± 0.35	2.49 ± 0.29^a	$3.61 \pm 0.20^{a,b}$
DBP(mmHg)	68.98 ± 5.41	76.70 ± 3.63^a	$99.82 \pm 6.63^{a,b}$
SBP(mmHg)	116.42 ± 4.39	119.31 ± 3.80^a	$150.51 \pm 6.16^{a,b}$
FBG(mmol/L)	4.54 ± 0.38	5.20 ± 0.36^a	$7.58 \pm 0.53^{a,b}$
TPV(m ³)	18.15 ± 1.19	31.37 ± 4.05^a	$45.60 \pm 4.76^{a,b}$
PSA(ng/L)	2.00 ± 0.31	7.88 ± 0.45^a	$10.05 \pm 0.23^{a,b}$
Gleason score	–	7.78 ± 1.20	7.54 ± 1.19

Abbreviations: DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, Triglycerides; TPV, total prostate volume.

^aComparison between Mets-PCa group and control group, $p < 0.05$;

^bComparison between Mets-PCa group and N-PCA group, $p < 0.05$.

TABLE 2 Multiple Logistic regression analysis of GSTs gene (T1/M1/P1) polymorphism and related parameters of PCa in the case group

	<i>GSTT1</i> (–)			<i>GSTM1</i> (–)			<i>GSTP1</i> (AG + GG)		
	β	<i>p</i>	95%CI	β	<i>p</i>	95%CI	β	<i>p</i>	95%CI
TPV	0.229	0.024	1.028–1.109	0.149	0.012	1.033–1.305	0.092	0.001	1.055–1.139
PSA	0.257	0.023	0.247–1.488	0.190	0.863	0.139–1.537	1.243	0.001	1.757–6.343
Gleason	0.545	0.003	1.208–2.463	0.406	0.014	1.087–2.072	0.400	0.013	1.090–2.044

95% CI, 95% confidence interval; β represents Regression coefficient.

times, and its distribution frequency was 66.4% in the patient group and 41% in the control group, while the *GSTT1* genotype was 33.6% in the patient group and 59% in the control group (OR = 2.844, 95% CI = 1.791–4.517). The distribution frequency of the *GSTM1* null genotype was 59.4% in the patient group and 40% in the control group, while the *GSTM1* genotype was 40.6% in the patient group and 60% in the control group. The *GSTM1* null genotype increased the susceptibility to PCa by 2.192 times (OR = 2.192, 95%CI = 1.395–3.446). Similar to the results of the *GSTM1* null genotype and *GSTT1* null genotype, *GSTP1* (AG + GG) increased the susceptibility to PCa by 2.315 times (OR = 2.315, 95%CI = 1.465–3.657). The distribution frequencies of *GSTP1* (AA) and *GSTP1* (AG + GG) in the patient group were 48.4% and 51.6%, respectively, while those in the control group were 68.5% and 31.5%. (Table 3).

After Mets was considered, *GSTT1* null genotype was only significantly associated with PCa in Mets, and the risk of PCa occurrence increased by 7.867 times (95%CI: 3.073–20.141, $p < 0.05$), indicating that *GSTT1* null genotype may be a significant predictor of PCa occurrence in Mets patients. The OR of the *GSTM1* null genotype

TABLE 3 Distribution of glutathione transferase genotypes in patients and controls

Group	Controls, No. (%)	Patients, No. (%)	OR	95%CI
GSTT1				
(+)	118(59.0)	43(33.6)	2.844	1.791–4.517
(-)	82(41.0)	85(66.4)		
GSTM1				
(+)	120(60)	52(40.6)	2.192	1.395–3.446
(-)	80(40)	76(59.4)		
GSTP1				
(AA)	137(68.5)	62(48.4)	2.315	1.465–3.657
(AG + GG)	63(31.5)	66(51.6)		

Abbreviations: -, null genotype; +, present genotype; 95% CI, 95% confidence interval; OR, odds ratio.

was 2.124 (95%CI: 0.908–4.965, $p > 0.05$) in Mets and 1.904 (95%CI: 1.081–3.352, $p < 0.05$) in non-Mets. *GSTP1* (AG + GG) OR was 2.226 (95% CI: 0.952–5.207, $p > 0.05$) in Mets and 1.976 (95% CI: 1.110–3.519, $p < 0.05$) in non-Mets. The OR values of the *GSTM1* null genotype and *GSTP1* (AG + GG) were very similar in Mets and non-Mets, but there was no statistical difference in Mets. The results suggested that the interaction between *GSTT1* null genotype and Mets increased the risk of PCa, while the effects of *GSTM1* null genotype and *GSTP1* (AG + GG) on PCa might not be related to Mets. (Table 4).

4 | DISCUSSION

In several studies, it has been observed that the lack or decreased expression of key enzyme genes that help reduce cellular oxidative stress leads to an increased risk of PCa.^{24,25} This has been observed in the correlation study between *GSTs* gene polymorphism and PCa. *GSTP1*, for example, can increase the risk of PCa through methylation modification,²⁶ whereas increased *GSTM1* gene expression protects against the occurrence and progression of PCa.²⁷ This is consistent with our results that *GSTT1* null genotype, *GSTM1* null genotype, and *GSTP1* (AG + GG) genotype are positively correlated with the susceptibility and malignancy of PCa. In addition, previous studies almost only studied *GSTs* gene as independent predictors to draw corresponding conclusions. For *GSTT1* null genotype, it is often considered to be related to the occurrence of PCa only when interacting with environmental factors.^{28,29} Our study seems to confirm that *GSTT1* null genotypes may play an important role in the development of PCa in patients with Mets. This may also be the problem with the contradictory conclusion that there is a contradiction between the *GSTT1* gene and the occurrence and development of PCa, that is, the effect of Mets is not taken into account.

The mechanism by which this interaction between *GSTT1* and Mets increases the risk of PCa is unclear. Nevertheless, linking some studies seems to explain the relationships we have observed.

TABLE 4 Association of metabolic syndrome and glutathione S-transferase gene (M1/T1/P1) polymorphism with PCa

Group	Metabolic syndrome					Metabolic syndrome null				
	Controls, No. (%)	Patients, No. (%)	OR	95%CI	p	Controls, No. (%)	Patients, No. (%)	OR	95%CI	p
GSTT1										
-	-	-	7.867	3.073–20.141	$p < 0.05$	-	-	1.746	0.992–3.074	$p > 0.05$
(+)	25(69.4)	13(22.4)	-	-	-	93(56.7)	30(42.9)	-	-	-
(-)	11(30.6)	45(77.6)	-	-	-	71(43.3)	40(57.1)	-	-	-
GSTM1										
-	-	-	2.124	0.908–4.965	$p > 0.05$	-	-	1.904	1.081–3.352	$p < 0.05$
(+)	19(52.8)	20(34.5)	-	-	-	101(61.8)	32(45.7)	-	-	-
(-)	17(47.2)	38(65.5)	-	-	-	63(38.2)	38(54.3)	-	-	-
GSTP1										
-	-	-	2.226	0.952–5.207	$p > 0.05$	-	-	1.976	1.110–3.519	$p < 0.05$
(AA)	22(61.1)	24(41.4)	-	-	-	115(70.1)	38(54.3)	-	-	-
(AG + GG)	14(38.9)	34(58.6)	-	-	-	49(29.9)	32(45.7)	-	-	-

Abbreviations: -, null genotype; +, present genotype; 95% CI, 95% confidence interval; OR, odds ratio.

GSTT1 is a subtype of *GSTs* that is mainly involved in the metabolism of halogenated alkanes and ethylene oxides. Brominated diphenyl ethers (PBDEs) are halogenated hydrocarbons and have been added to many consumer goods as flame retardants. Due to its persistence, toxicity, and potential bioaccumulation, it has attracted wide attention. Although PBDEs have attracted much attention due to environmental pollution, they can be easily detected in human serum and breast milk samples.³⁰ When the body is in the state of Mets, the expression and activity of *GSTT1* are decreased.³¹ In the absence of *GSTT1*, PBDE can damage insulin signaling and inhibit glucose transport, resulting in insulin resistance.³² High insulin levels increase the risk of PCa by inhibiting IGF1R and increasing IGF-1.³³

Alternatively, Mets has been shown to promote inflammation, especially in the abdominal area. Dysfunctional adipose tissue releases disordered adipose factors, including a large number of pro-inflammatory factors and growth factors, such as TNF- α , IL-1, IL-6, IL-10, VEGF, and so on.³⁴ As a result of the immune response, inflammatory cells tend to local anoxic tissue of the prostate and then release large amounts of ROS to maintain high levels of oxidative stress.³⁵ *GSTT1* is involved in detoxifying chemicals, including ROS. However, a controlled study showed that in individuals with Mets, especially abdominal obesity, the *GSTT1* gene showed hypermethylation, and the activity of its expression product was inhibited.¹⁹ When local prostate tissue continues to be in a microenvironment of high oxidative stress and immune disorder, genetic instability and uncontrolled cell division in the mixture of Proliferative Inflammatory Atrophy (PIA), prostatic intraepithelial neoplasia (PIN), and inflammatory cells lead to cancer.³⁶⁻³⁸ In this study, patients with Mets were diagnosed with PCa at a younger age, with higher levels of PSA and larger TPV. Moreover, our study also shows that patients with both *GSTT1* null genotype and Mets are at high risk for PCa.

To our knowledge, this is the first time we have reported that there is a significant interaction between *GSTT1* null genotype and Mets, which significantly increases the risk of PCa in patients with Mets. Other *GSTs* polymorphisms (*GSTM1*, *GSTP1*) were not associated with Mets, suggesting that they are more likely to be independent risk factors for PCa.

This study has several advantages. First of all, Mets and its composition are associated with the *GSTs* gene for the first time to study its role in the occurrence and development of PCa. Secondly, we reduced the possibility of misdiagnosis of undiagnosed PCa and avoided deviations in experimental results by limiting the control group to men who received PSA after blood collection. In addition, more research is needed to confirm our findings. In the future, the mechanism of *GSTs* gene polymorphism combined with Mets and its effect on the prognosis of PCa may become the focus of our research.

In conclusion, our results suggest that *GSTs* gene polymorphism may be a predictor of susceptibility and malignancy of PCa. In addition, compared with healthy people, *GSTT1* null genotype is more likely to be a risk factor for PCa in patients with Mets, which should be paid more attention to.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

K.T conceived and designed the experiments. D.L, P.C, B.C, J.H, Y.M, K.C, W.Z, and S.X performed the experiments. D.L, and P.C analyzed the data. B.C drafted the manuscript.

RESEARCH INVOLVING HUMAN PARTICIPANTS AND/OR ANIMALS

This research involving Human Participants, and all the participants provided written informed consent. This research was approved by the Ethics Committee of the Affiliated Hospital of Guizhou Medical University (Trial registration number: ChiCTR-IPR-14005580) And all the works have been carried out in compliance with the Helsinki Declaration.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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