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ORIGINAL ARTICLE

Association of genetic polymorphisms of GSTM1 and smoking status with lung cancer risk*

Jiaheng Li, Lina Zhang, Yue Wang, Meng Gu, Ziyu Wang, Weiying Li (✉)

Cell Biology Laboratory, Capital Medical University, Beijing Chest Hospital, Beijing Tuberculosis and Thoracic Tumor Research Institute, Beijing 101149, China

Abstract

Objective Long-term cigarette smoke exposure damages the airway epithelium. However, the correlation among GSTM1 gene polymorphism, smoking status, and lung cancer susceptibility remains unclear. This study aimed to identify the genetic polymorphism of GSTM1 and examine the association of GSTM1 polymorphism and smoking history with lung cancer susceptibility.

Methods The genetic polymorphism of GSTM1 was genotyped by polymerase chain reaction (PCR) in 217 lung cancer patients and 198 controls. The demographic data and smoking history of the patients were collected. The age, sex, and residence of the two groups were also obtained.

Results Significant differences in GSTM1 polymorphism were observed between the case and control groups (P = 0.024). Smoking time and smoking index were significantly different between the case and control groups. With the increase in smoking time and smoking index, the differences became more obvious. There was a synergistic effect between GSTM1 and smoking (S = 3.35). The risk of developing lung cancer increased 4.82 fold in smokers carrying deficient-type GSTM1. Compared with patients carrying wild-type GSTM1, the risk of developing lung cancer was higher in those carrying deficient-type GSTM1 with the increase in smoking time and smoking index. In different pathological types, no significant differences were observed in GSTM1 polymorphism. In different pathological types, the proportions of patients increased with the increase in smoking time and smoking index, especially the proportion of patients with squamous cell carcinoma. Compared with wild-type GSTM1, the proportion of patients with deficient-type GSTM1 increased with the increase in smoking time and smoking index (P = 0.003 and 0.017). This trend was mainly observed in those with squamous cell carcinoma.

Conclusion GSTM1 mutation is associated with lung cancer susceptibility. Smokers carrying deficient-type GSTM1 are more likely to develop lung cancer. Compared with patients carrying wild-type GSTM1, smokers with deficient-type GSTM1 are more likely develop lung cancer when smoking time is more than 30 years and smoking index is more than 400. In patients carrying deficient-type GSTM1, the risk of developing squamous cell carcinoma increases with an increase in smoking time and smoking dose.

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Key words: GSTM1; genetic susceptibility; smoking; lung cancer

The occurrence of lung cancer is based on the interaction between genetic factors and the environment. Smoking is one of the major risk factors that causes lung cancer. Approximately 5 million people worldwide die each year because of smoking. However, only 10%–15% of smokers developed lung cancer. This finding suggests that except smoking, susceptibility to lung cancer may also be associated with genetic factors.

Previous studies showed that cigarette smoke contains 69 types of carcinogens, including polycyclic aromatic hydrocarbons (PAH), nitrosamines, benzo[a]pyrene, and aromatic amines [1]. Cigarette is a rich source of oxidants and reactive oxygen species (ROS) [2]. Smoking can not only result in directly take of exogenous ROS, but can also lead to the generation of endogenous ROS, which increases oxidativestress in tissues [3]. The increase of ROS during oxidative stress can break the balance between oxidation and antioxidation and lead to oxidative stress [4–6]. ROS can damage DNA, RNA, and protein, which causes chromosomal instability, gene mutation, or altered

✉ Correspondence to: Weiying Li. Email: li_weiying412@aliyun.com
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gene expression, and promotes tumor occurrence [7–8]. Long-term cigarette smoke exposure damages the airway epithelium, which induces the expression of related factors involved in oxidative stress. Therefore, polymorphisms of these genes associated with oxidative stress may be related to the susceptibility to lung cancer.

Glutathione-S-transferases (GSTs) belong to phase II metabolic enzymes, which are associated with the metabolism of carcinogens, drugs, and ROS. Therefore, GSTs protect DNAs against oxidative damage [9–10]. Among the GSTs, GSTM1 plays a key role in the detoxification of carcinogenic electrophiles of aflatoxin and PAHs in tobacco smoke [11–12]. Deletion of GSTM1 leads to loss of the enzyme's ability to detoxify carcinogens. Individuals with deficient-type GSTM1 are more likely to develop cancer, including lung cancer [13–15]. There is a synergistic effect between GSTM1 and smoking in lung cancer [15–17]. However, several studies have reported conflicting views [18–20].

In this study, we aimed to determine the potential link between GSTM1 polymorphism, smoking, and lung cancer. To further investigate the effect of smoking, smoking was graded according to smoking times and smoking doses. No previous studies have investigated the relationship between GSTM1 polymorphism and smoking time and dose.

Patients and methods

Patients

A total of 217 lung cancer patients from Beijing Chest Hospital, China and 198 healthy controls were enrolled between August 2005 and June 2006. These participants belonged to the Chinese Han ethnic group. The patients were pathologically diagnosed with lung cancer and did not undergo preoperative surgery, radiotherapy, chemotherapy, molecular targeted therapy, immunotherapy, etc. The patients had complete clinical information, basic data, and follow-up records. Patients with other malignancies were excluded. All healthy controls had no hereditary disorders or known medical illness. Patients' demographic data were accurately collected. Patients in the case group were aged 24–83 years [mean: (58.98 ± 11.33) years], while those in the control group were aged 26–88 years [mean: (53.39 ± 15.44) years]. The proportions of male and female were 68.2% and 31.8% in the case group and 64.7% and 35.3% in the control group. The distributions of age and sex were balanced in the two groups. This study was approved by the Ethical Committee of Beijing Chest Hospital, China.

Genotyping

Sodium citrate tube was used to collect peripheral blood from all participants. Serial phenol/chloroform extraction was used to extract genomic DNA.GSTM1 genotype was identified by polymerase chain reaction (PCR) using the following primer sequences:

P1: 5′–GAACTCCCTGAAAAGCTAAAGC–3′,
P2: 5′–GTTGGGCTCAAATATACGGTGG–3′,
β1: 5′–CAACTTCATCCACGTTCACC–3′, and
β2: 5′–GAAGAGCCAAGGACAGGTAC–3′.

The PCR amplification conditions used in this study were as follows: 94 °C for 7 minutes and 30 cycles (94 °C for 1 minute, 59 °C for 1 minute, and 72 °C for 1 minute) and 72 °C for 10 minutes. For better quality control, 80 samples were randomly selected for duplicate genotyping. The concordance rate was 100%.

Statistical analysis

Quantitative variables were compared using the one-way analysis of variance. Qualitative variables, genotype/allele frequency, and Hardy-Weinberg equilibrium of the polymorphism were tested using the χ^2 test. Odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were estimated using unconditional logistic regression (LR) models adjusted for potential confounders. Unconditional logistic regression analyses were used to calculate gene-environment interaction. Statistical significance was assessed using a P-value of < 0.05. All tests were two-sided, and statistical analyses were conducted using SPSS statistics 17.0 (SPSS Inc. Chicago, Illinois, USA).

Results

Patients' characteristics

Table 1 summarizes the characteristics of the patients in this study. A significant difference was observed between cases and controls in terms of smoking status ($P = 0.000$). Among male participants, the proportions of smokers and non-smokers were 75.7% and 24.3%, respectively. Among female participants, these proportions were 11.6% and 88.4%, respectively. Of the total participants, 29.5% had squamous carcinoma, 37.3% had adenocarcinoma, 17.1% had small cell carcinoma; and 16.1% had other types of cancer.

Correlation of GSTM1 and smoking with lung cancer risk

To evaluate the independent effect of GSTM1 and smoking on lung cancer susceptibility, we used unconditional LR models, as detailed in Tables 1 and 2. Deletion of GSTM1 was related to a 1.56-fold increase in lung cancer risk ($P = 0.024$). Smoking was related to a 2.59-fold increase in lung cancer risk ($P = 0.000$). OR values increased from 1.05 (95% CI = 0.49–2.21) to 3.62 (95% CI = 2.03–6.45) when smoking times were divided according to every 10 years. OR values increased from 2.64 (95% CI

Table 1 Controls and patients characteristics [*n* (%)]

Variables	Cases [*n* = 217 (%)]	Controls [*n* = 198 (%)]	*P* value
Age (years)			
Range	24–83	26–88	
Mean ± SD	58.98 ± 11.33	53.39 ± 15.44	0.305
Gender			
Male	148 (68.2)	128 (64.7)	0.443
Female	69 (31.8)	70 (35.3)	
Histology			
Squamous carcinoma	64 (29.5)		
Adenocarcinoma	81 (37.3)		
Small cell carcinoma	37 (17.1)		
Other	35 (16.1)		
Male			
Squamous carcinoma	58 (39.2)		
Adenocarcinoma	39 (26.4)		
Small cell carcinoma	27 (18.2)		
Other	24 (16.2)		
Female			
Squamous carcinoma	6 (8.7)		
Adenocarcinoma	42 (60.9)		
Small cell carcinoma	10 (14.5)		
Other	11 (15.9)		
Smoking history			
No smoking	97 (44.7)	134 (67.7)	0.000
Smoking	120 (55.3)	64 (32.3)	
Male			
No smoking	36 (24.3)	65 (50.8)	0.000
Smoking	112 (75.7)	63 (49.2)	
Female			
No smoking	61 (88.4)	69 (98.6)	0.017
Smoking	8 (11.6)	1 (1.4)	
Age starting smoking (years)			
Mean ± SD	27.69 ± 0.88	27.57 ± 1.42	0.862

= 1.17–5.96) to 3.43 (95% CI = 2.19–5.36) when smoking index increased from ≤ 200 to > 400. To analyze GSTM1-smoking interaction, LR model was used and showed a synergistic effect between smoking and GSTM1 (S = 3.35).

Relevance between GSTM1 polymorphism and smoking exposure

To further analyze GSTM1-smoking interaction, GSTM1 was layered to analyze. OR values were significantly different between wild-type and GSTM1 deletion when smoking time was analyzed (Table 3). OR values increased from 1.56 (95% CI = 0.37–6.59) to 2.84 (95% CI = 1.23–6.53) in smokers with wild-type GSTM1 and from 0.85 (95% CI = 0.23–3.14) to 4.51 (95% CI = 1.99–10.22) in smokers with GSTM1 deletion. Compared with non-smoker carrying wild-type GSTM1, smokers with GSTM1 deletion had a 5.55-fold increase in lung cancer risk when smoking time was equal or greater than 30 years. OR values were significantly different between wild-type and deletion GSTM1 when smoking index was analyzed (Table 4). OR values increased from 1.56 (95% CI = 0.37–6.59) to 2.56 (95% CI = 1.36–4.82) in smokers with wild-type GSTM1 and from 0.42 (95% CI = 0.04–4.17) to 4.75 (95% CI = 2.47–9.14) in smokers with GSTM1 deletion. Compared with non-smokers carrying wild-type GSTM1, smokers with GSTM1 deletion had a 5.85-fold increase in lung cancer risk when smoking index was more than 400.When smoking time and smoking index were the same, the risk of cancer in patients with mutated GSTM1 was doubled compared with that of patients with functional GSTM1.

Correlation between GSTM1 and smoking and pathological type

To evaluate the effect of GSTM1 and smoking on pathological type, we used unconditional LR models, as detailed in Table 5. There was no significant difference in GSTM1 polymorphism between different pathological types ($P = 0.932$). A significant difference was observed in smoking status between different pathological types ($P = 0.000$). Approximately 40.83% of smokers had squamous carcinoma, while 20% (17.5%–23.3%) had other types of cancer. In the squamous carcinoma group, the proportion of smokers was increased from 0% to 35.9% when smoking times changed from < 10 years to ≥ 30 years and from 0% to 67.2% when smoking index changed from ≤ 200 to > 400. In the adenocarcinoma group, the proportion of smokers increased from 8.6% to 12.3% when smoking times changed from < 10 years to ≥ 30 years and from 4.9% to 25.9% when smoking index changed from ≤ 200 to > 400.

Relevance of GSTM1 polymorphism and smoking exposure with pathological type

The results were shown in Table 6 when smoking exposure was analyzed in detail. The proportions of squamous carcinoma increased from 0% to 23.1% in smokers with wild-type GSTM1 and from 0% to 44.7% in smokers with GSTM1 deletion. There were considerable proportions of patients with other types of cancer who had wild-type GSTM1 and GSTM1 deletion. Table 7 shows the results of the analyses of smoking index. In wild-type GSTM1 smokers, the proportion of patients with squamous carcinoma increased from 0% to 61.5% and that of patients with adenocarcinoma increased from 8.6% to 25.7%. In deletion-type GSTM1 smokers, the proportion of patients with squamous carcinoma increased from 0% to 71.1% and that of patients with adenocarcinoma increased from 2.2% to 26.1%.

Table 2 Association between lung cancer risk, GSTM1 and smoking

Factors		Control [*n* (%)]	Case [*n* (%)]	Risk estimate OR* (95% CI)	*P* value**	S***
GSTM1	Wide-type	104 (52.5)	90 (41.5)	1.00 (Reference)		
	Deletion	94 (47.5)	127 (58.5)	1.56 (1.06–2.30)	0.024	
Smoking history	No smoking	134 (67.7)	97 (44.7)	1.00 (Reference)		
	Smoking	64 (32.3)	120 (55.3)	2.59 (1.74–3.87)	0.000	
Smoking time (years)	No smoking	134 (68.2)	97 (44.7)	1.00 (Reference)		
	< 10	10 (5.1)	8 (3.7)	1.05 (0.49–2.21)	0.919	
	10–	15 (7.6)	15 (6.9)	2.60 (1.08–6.28)	0.034	
	20–	18 (9.1)	45 (20.7)	3.25 (1.12–9.41)	0.030	
	30–	20 (10.1)	52 (24.0)	3.62 (2.03–6.45)	0.000	
Smoking index	No smoking	134 (67.2)	97 (55.2)	1.00 (Reference)		
	SI ≤ 200	18 (9.1)	6 (2.8)	2.64 (1.17–5.96)	0.019	
	SI (200–400)	7 (3.5)	16 (7.4)	3.44 (1.04–11.49)	0.044	
	SI > 400	40 (20.2)	99 (45.6)	3.43 (2.19–5.36)	0.000	
GSTM1						
Wide-type	No smoking	64 (32.3)	41 (18.9)			
Wide-type	Smoking	40 (20.2)	49 (22.6)	1.91 (1.08–3.39)	0.026	
Deletion	No smoking	71 (35.9)	56 (25.8)	1.23 (0.73–2.08)	0.438	
Deletion	Smoking	23 (11.6)	71 (32.7)	4.82 (2.61–8.89)	0.000	3.35

SI, smoking index, which is the number of cigarettes smoked per day × years of smoking; * Associations were determined using multivariate logistic regression models to estimate the risk of developing lung cancer using GSTM1 wild-type, and no smoking as the reference; ** Differences in the frequency of high-risk and low-risk groups between cases and controls were determined using the χ^2 test of association with a significance level of 0.05; *** S, synergy index = $(RR_{++} - 1.0) / (RRi - 1.0)$, RR: relative risk

Table 3 Association between lung cancer risk, GSTM1 and smoking time

GSTM1	Smoking time (years)	Control [*n* (%)]	Case [*n* (%)]	OR (95% CI)	*P* value**
Wide-type	No smoking	64 (61.5)	41 (45.6)		
	< 10	4 (3.8)	4 (4.4)	1.56 (0.37–6.59)	0.542
	10–	12 (11.5)	7 (7.8)	0.91 (0.33–2.50)	0.856
	20–	13 (12.5)	18 (20.0)	2.16 (0.96–4.88)	0.060
	30–	11 (10.6)	20 (22.2)	2.84 (1.23–6.53)	0.012
Deletion	No smoking	71 (75.5)	56 (44.1)		
	< 10	6 (6.4)	4 (3.1)	0.85 (0.23–3.14)	0.802
	10–	3 (3.2)	8 (6.3)	3.38 (0.86–13.34)	0.068
	20–	5 (5.3)	27 (21.3)	6.85 (2.48–18.92)	0.000
	30–	9 (9.6)	32 (25.2)	4.51 (1.99–10.22)	0.000
				5.55 (2.40–12.82)*	0.000

* OR values of smokers (smoking time was more than 30 years) with deletion type GSTM1 and no smokers with wide-type GSTM1; ** Differences in the frequency of high-risk and low-risk groups between cases and controls were determined using the χ^2 test of association with a significance level of 0.05

Discussion

Previous studies showed that 85%–90% of lung cancer patients are smoking [21–23]. In this study, 55.3% of patients in the case group were smokers, which is higher than that in the control group ($P = 0.000$). When smoking was analyzed according to smoking time and smoking dose, we found an increasing trend in the risk of developing cancer with the extension of smoking time and smoking dose. When smoking time is greater than or equal to 30 years, the risk of developing cancer increases by 3.62 times. When smoking index is more than 400, the hazard to lung cancer increases by 3.43 times. A multicenter study found that the risk of lung cancer was 11.95 times in heavy smokers [24]. This value is higher than that reported in our study. This may be related to the differences in patients' behavior. Among European patients, 44% of women were heavy smokers, whereas none of our study patients were heavy smokers. The kitchen fume is also a risk factor for lung cancer among Chinese women.

The pathological types of lung cancer have changed since the 1950s. The most common type of lung cancer is lung adenocarcinoma [25–28]. This may be related to the recent advancements in the production of cigarettes and

Table 4 Association between lung cancer risk, GSTM1 and smoking index

GSTM1	Smoking index	Control [*n* (%)]	Case [*n* (%)]	OR (95% CI)	*P* value**
Wide-type	No smoking	64 (61.5)	41 (45.6)		
	SI ≤ 200	4 (3.8)	4 (4.4)	1.56 (0.37–6.59)	0.542
	SI (200–400)	11 (10.6)	4 (4.4)	0.57 (0.17–1.90)	0.352
	SI > 400	25 (24.0)	41 (45.6)	2.56 (1.36–4.82)	0.003
Deletion	No smoking	71 (75.5)	56 (44.1)		
	SI ≤ 200	3 (3.2)	1 (0.8)	0.42 (0.04– 4.17)	0.448
	SI (200–400)	4 (4.3)	10 (7.9)	3.17 (0.94–10.64)	0.052
	SI > 400	16 (17.0)	60 (47.2)	4.75 (2.47– 9.14)	0.000
				5.85 (2.98–11.52)*	0.000

* OR values of smokers (smoking index was more than 400) with deletion GSTM1 and no smokers with wide-type GSTM1; ** Differences in the frequency of high-risk and low-risk groups between cases and controls were determined using the χ^2 test of association with a significance level of 0.05

Table 5 Association between pathological type, GSTM1 and smoking

Factors		Pathological type [*n* (%)]				χ^2 value	*P* value*
		Squamous carcinoma	Adenocarcinoma	Small cell carcinoma	Other		
GSTM1	Wide-type	26 (40.6)	35 (43.2)	16 (43.2)	13 (37.1)	0.44	0.932
	Deletion	38 (59.4)	46 (56.8)	21 (56.8)	22 (62.9)		
Smoking	No smoking	15 (23.4)	53 (65.4)	15 (40.5)	14 (40.0)	26.43	0.000
	Smoking	49 (76.6)	28 (34.6)	22 (59.5)	21 (60.0)		
Smoking time (years)	No smoking	15 (23.4)	53 (65.4)	15 (40.5)	14 (40.0)	44.13	0.000
	< 10	0 (0.0)	7 (8.6)	1 (2.7)	0 (0.0)		
	10–	6 (9.4)	2 (2.5)	3 (8.1)	4 (11.4)		
	20–	20 (31.2)	9 (11.1)	7 (18.9)	9 (25.7)		
	30–	23 (35.9)	10 (12.3)	11 (29.7)	8 (22.9)		
Smoking index	No smoking	15 (23.4)	53 (65.4)	15 (40.5)	14 (40.0)	35.05	0.000
	SI ≤ 200	0 (0.0)	4 (4.9)	1 (2.7)	0 (0.0)		
	SI (200–400)	6 (9.4)	3 (3.7)	3 (8.1)	2 (5.7)		
	SI > 400	43 (67.2)	21 (25.9)	18 (48.6)	19 (54.3)		

* χ^2 test

Table 6 Association between pathological type, GSTM1 and smoking time

GSTM1	Smoking time (years)	Pathological type [*n* (%)]				χ^2 value	*P* value*
		Squamous carcinoma	Adenocarcinoma	Small cell carcinoma	Other		
Wide-type	No smoking	7 (26.9)	23 (65.7)	6 (37.5)	5 (38.5)	21.16	0.048
	< 10	0 (0.0)	3 (8.6)	1 (6.2)	0 (0.0)		
	10–	3 (11.5)	1 (2.9)	1 (6.2)	2 (15.4)		
	20–	10 (38.5)	3 (8.6)	2 (12.5)	3 (23.1)		
	30–	6 (23.1)	5 (14.3)	6 (37.5)	3 (23.1)		
Deletion	No smoking	8 (21.1)	30 (65.2)	9 (42.9)	9 (40.9)	30.28	0.003
	< 10	0 (0.0)	4 (8.7)	0 (0.0)	0 (0.0)		
	10–	3 (7.9)	1 (2.2)	2 (9.5)	2 (9.1)		
	20–	10 (26.3)	6 (13.0)	5 (23.8)	6 (27.3)		
	30–	17 (44.7)	5 (10.9)	5 (23.8)	5 (22.7)		

* χ^2 test

the application of cigarette filter [29–30]. In this study, the number of adenocarcinoma cases was slightly higher than that of squamous carcinoma cases. However, the results were significantly different when patients were stratified by sex. The number of squamous carcinoma cases was obviously higher than that of adenocarcinoma cases in male patients, and lower in female patients. The difference may be related to the different proportions of

Table 7 Association between pathological type, GSTM1 and smoking index

GSTM1	Smoking index	Pathological type [*n* (%)]				χ^2 value	*P* value*
		Squamous carcinoma	Adenocarcinoma	Small cell carcinoma	Other		
Wide-type	No smoking	7 (26.9)	23 (65.7)	6 (37.5)	5 (38.5)	19.14	0.024
	SI ≤ 200	0 (0.0)	3 (8.6)	1 (6.2)	0 (0.0)		
	SI (200–400)	3 (11.5)	0 (0.0)	1 (6.2)	0 (0.0)		
	SI > 400	16 (61.5)	9 (25.7)	8 (50.0)	8 (61.5)		
Deletion	No smoking	8 (21.1)	30 (65.2)	9 (42.9)	9 (40.9)	20.22	0.017
	SI ≤ 200	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)		
	SI (200–400)	3 (7.9)	3 (6.5)	2 (9.5)	2 (9.1)		
	SI > 400	27 (71.1)	12 (26.1)	10 (47.6)	11 (50.0)		

* χ^2 test

male and female smokers. Approximately 75.7% of men were smokers, while only 11.6% of women were smokers. Approximately 66.3% of men were heavy smokers, in contrast to 0.0% of women who were heavy smokers. Smokers who smoked for more than 30 years accounted for approximately 45.7% of men and 3.6% of women subjects.

Heavy smoking has been strongly associated with the development of squamous carcinoma [31–33]. This explains our study results. In women, second-hand smoke and cooking oil fumes are the most important risk factors, mainly for lung adenocarcinomas [21, 30, 34–35].

Smoking is the known major cause of lung cancer, but only a small proportion of smokers develop lung cancer. This finding suggests the possible involvement of genetic factors. GSTM1 catalyzes the covalent binding of GSH to polycyclic aromatic hydrocarbons. A meta-analysis suggested that the presence of mutated GSTM1 increases the risk of lung cancer [12, 36–38]. However, other studies reported contrasting results [39–41]. This study found that the presence of mutated GSTM1 is associated with the risk of lung cancer. Long-term cigarette smoke exposure damages the airway epithelium, which induces the expression of related factors involved in oxidative stress. GSTM1 is involved in the metabolism of carcinogens, drugs, and ROS. This study reported a synergistic effect between GSTM1 and smoking. Smokers with mutated GSTM1 have a 4.82-fold increased risk of lung cancer compared with nonsmokers carrying functional GSTM1. To further investigate GSTM1 and smoking interaction, a stratified analysis of GSTM1 was conducted. Results showed that the risks of lung cancer increased in patients with both functional GSTM1 and mutated GSTM1 with the increase of smoking time and smoking index. If the smoking time and smoking index are the same, the risk of cancer in patients with mutated GSTM1 is doubled compared with that in patients with functional GSTM1. These results suggest that smokers with deficient-type GSTM1 are more likely to develop lung cancer. In particular, when smoking time is more than 30 years and smoking index is more than 400, the risk of lung cancer in patients with mutated GSTM1 is five times higher than their counterparts.

Several studies have shown that patients with GSTM1 are susceptible to SCLC and AC [23, 42–43]. However, some studies reported contradicting results [44–45]. In our study, GSTM1 is not related to the pathological type of lung cancer. This discrepancy may be relevant to different research populations. Cigarette is a rich source of oxidants and ROS. Deletion of GSTM1 leads to loss of the enzyme's ability to detoxify carcinogens. Hence, smoking, GSTM1, and pathological types were analyzed. After GSTM1 was layered, lung adenocarcinoma accounted for majority of non-smokers. In the smoking population, the proportions of patients with squamous carcinoma have an obvious increase in the number of mutated GSTM1 with the increase of smoking time and smoking index compared with those with functional GSTM1. When smoking time and smoking index are the same, the proportions of patients with squamous carcinoma carrying a mutated GSTM1 are higher than those with functional GSTM1. However, the proportion of patients with other pathological types had no obvious difference after GSTM1 was layered. In other words, the number of cases with mutated GSTM1 is equivalent to that of cases with functional GSTM1 when smoking time and smoking index are the same. This finding suggests that people with mutated GSTM1 are susceptible to squamous cell carcinoma when smoking time is greater than or equal to 30 years and smoking index is greater than 400.

In summary, mutated GSTM1 is associated with lung cancer susceptibility. In particular, smokers carrying deficient-type GSTM1 more easily develop lung cancer, because of the loss of the enzyme's ability to detoxify carcinogens. In addition, with the increase of smoking time and smoking index, respiratory epithelial cells are repeatedly stimulated by carcinogens and ROS produced by cigarettes and are damaged due to the inability to detoxify these carcinogens; hence, smokers with deficient-

type GSTM1 are more likely to develop lung cancer. This result indicates that the occurrence of lung cancer is related to respiratory inflammation.

Conflicts of interest

The authors indicate no potential conflicts of interest.

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