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Impact of the deletion glutathione S-transferase (class Mu) on lung cancer risk among smokers

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Abstract

Background The results of several studies assessing the effect of the glutathione S-transferase class Mu 1 (GSTM1) null variant on the genetic susceptibility of tobacco-related cancers have been conflicting. In this work, we aim to identify the impact of the deletion of GSTM1 on lung cancer risk among smokers.

Methods This study was conducted on 20 patients diagnosed with primary lung cancer and 20 healthy individuals as a control group. They were subject to full medical history taking, complete clinical examination, and GSTM1 genotyping by PCR.

Results Both studied groups were matched for age, sex, and smoking status. No statistically significant difference was exhibited between the frequency of GSTM1 positive and GSTM1 null in the studied population. No risk of lung cancer associated with GSTM1 null genotype was demonstrated between the patients and control group ($n=14/20$ cases) ($p=0.110$, OR = 2.852, 95% CI 0.777–10.467). Additionally, there was no association between the risk of lung cancer and the presence of the gene either in smokers ($p=1$, OR = 1.8 and 95% CI 0.124–26.196) or non-smokers; ($p=0.063$, OR = 4.4 and 95% CI 0.889–21.78). No statistically significant risk was found between the frequencies of GSTM1 null and the various histopathological types of lung malignancy.

Conclusion The results of this work demonstrated no association between the occurrence of the GSTM1 null variant, even when stratified for smoking status, and the risk of lung cancer.

Background

Epidemiological studies have demonstrated that average tobacco smokers face approximately a 14-fold increased risk for the occurrence of lung malignancy. Additionally, individuals with a previous family history are present with about a 2.5-fold increase in risk of lung cancer development, even after accounting for tobacco smoke exposure [1, 2]. Noteworthy, tobacco consumption plays a negative role by causing the accumulation of genetic alterations eventually leading to lung cancer. Furthermore, lung malignancy follows a multistage process, occurring against a backdrop of increasing genomic instability [3, 4].

The role of GST (glutathione S-transferase) activity in metabolizing carcinogens has prompted numerous studies on the impact of GST polymorphisms on cancer susceptibility, particularly in tobacco-related cancers [5]. The GST gene family consists of four main classes: alpha (α), mu (μ), pi (π), and theta (θ) [6]. Most human tumor cell lines express significant levels of class pi GST, specifically,

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GSTP exon 5 polymorphisms have been linked to the development of lung malignancy [7], especially in adenocarcinoma, which was not significantly associated with smoking [8].

The GSTM1 gene, found on chromosome 1p13.3, is not manifested in approximately 50% of individuals due to a homozygous gene deletion, known as the GSTM1 null allele [6]. However, the results from several studies attempting to establish a relationship between the GSTM1 null genotype and the risk of incidence of lung cancer in various ethnic populations have been conflicting [9] which could suggest that the GSTM1 null variant has only a marginal impact on the genetic susceptibility to tobacco-related cancers [10].

This work aims to evaluate the role of the isoenzyme glutathione transferase gene deletion as a risk factor for the development of lung cancer among smokers.

Subjects and methods

This is a prospective case/control study that was performed on patients of the outpatient clinic of the chest department of Kasr El Ainy Hospital between September 2016 and March 2017.

Inclusion criteria

Patients consecutively included in the study, after their participation consent, were.

1 - Those with confirmed histopathological diagnosis, obtained by tissue biopsy, of primary lung cancer
2 - Not previously treated by radiotherapy and/or chemotherapy and categorized as the patient's group
3 - Not participating in another clinical trial.
4 - The control group consisted of unrelated healthy subjects taken as control with no previous history of malignancy.

Exclusion criteria

1 - Patients with prior malignancy or present with metastatic malignant manifestations were not included in the present study.
2 - Patients receiving radiotherapy and/ or chemotherapy
3 - Patients with severe morbidity or unfit general condition

All patients were subject to complete medical history, full clinical examination, and GSTM1 genotyping by PCR.

GSTM1 genotyping

Peripheral blood sampling was done, and Genomic DNA was extracted from peripheral blood mononuclear cells using a QIAamp DNA extraction DNA mini kit (Catalog No. 51104) (QIAGEN, Germany) according to the manufacturer's protocol. DNA was isolated from peripheral leukocytes using standard procedures with proteinase K digestion and extraction. GSTM1 gene deletion was determined by procedures described by [11] (Fig. 1).

Ethical approval

This work was done according to the guidelines outlined in the Declaration of Helsinki. The Ethical Committee of the National Research Centre, Cairo, Egypt, reviewed and approved the study (number: 10088). each participant

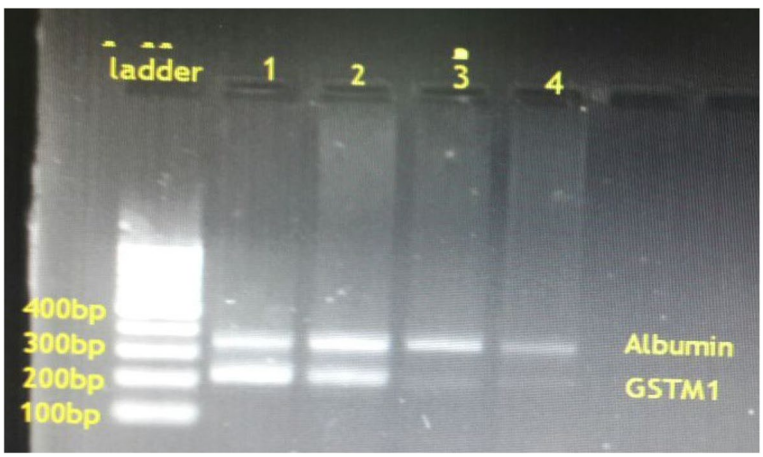

Fig. 1 PCR analysis: First Lane: 100 bp ladder, Lanes 1–2 GSTM1positive genotype, lanes 3–4 GSTM1null genotype. Housekeeping gene (albumin 350 bp) is the internal control and is present in all samples

provided a written informed consent before their inclusion in the study.

Statistical analysis

Data were coded and entered using the statistical package SPSS version 23. Data was summarized using mean and standard deviation, median, minimum, and maximum for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between quantitative variables were done using the non-parametric Mann–Whitney test. For comparing categorical data, a chi-square ($\chi 2$) test was performed. The exact test was used instead when the expected frequency was less than 5. Genotype frequency was compared between the disease and the control groups using chi-square tests. An odds ratio (OR) with 95% confidence intervals was calculated. *P* values less than 0.05 were considered statistically significant.

Results

Twenty patients (10 males and 10 females with a mean age of 57.3 years) were included in this study of whom 8 of them were smokers and 12 were non-smokers with histologically confirmed primary lung cancer diagnosis. The control group consisted of 20 healthy individuals unrelated genetically to the patient group and consisted of 12 males and 8 females, 4 smokers and 16 non-smokers, with a mean age of 52.05 years.

The control and lung cancer groups were matched as regards the mean values of age, sex, and smoking status; $p=0.066$, 0.525, and 0.168 respectively. The mean values of the smoking index (pack-years) were significantly higher in the patients (53.75 ± 15.98) compared to the control (16.50 ± 8.10); $p=0.006$. Patients with SCLC were in the extensive stage of the disease. As their number was relatively small, they were added to stage IV NSCLC to be studied statistically. Stage II lung cancer represented 45% of cases (9/20 patients), stage III represented 5% of cases (1/20 patients) and 10/20 patients (50%) were at stage IV (Table 1).

All studied subjects ($n=40$) showed no statistically significant difference between the GSTM1 positive and GSTM1 null as regards the frequency (17 and 23 respectively), the mean values of age, sex, smoking status, and smoking index; $p=0.110$, 0.298, 0.131, 0.443, and 0.341 respectively (Table 2, Fig. 1).

There was no risk of lung cancer demonstrated between the patients and control group though the frequency of GSTM1 null was lower in patients; 45% ($n=9/20$ cases) than in the control group 70% ($n=14/20$ cases) ($p=0.110$, OR = 2.852, 95% CI 0.777–10.467). The risk of lung cancer associated with the null genotype was examined by stratification for smoking status; although the frequency of deletion was higher in smokers patients (62.5%) than that of the positive genotype (37.5%); no risk of cancer was found to be associated with the gene among smokers ($p=1$, OR = 1.8 and 95% CI 0.124–26.196) or non-smokers; ($p=0.063$, OR = 4.4 and 95% CI 0.889–21.78) (Table 2).

Table 1 Clinical and demographic of the included subjects

Characteristics	Patients *N* (20)	Controls *N* (20)	*P*
Sex			
• Male	10	12	0.525
• Female	10	8	
Age (years) (mean ± SD)	57.3 (9.67)	52.05 (7.78)	0.066
Smoking status			
° No	12	16	0.168
° Yes	8	4	
Pack-years (mean ± SD)	53.75 (15.98)	16.50 (8.10)	0.006
Histopathology			
° SCLC	3		
° NSCLC	17		
• Adenocarcinoma	10		
• Squamous	4		
• Others[a]	3		
Staging *N* (%)			
° II	9 (45)		
° III	1 (5)		
° IV	10 (50)		

[a] Others: spindle cell sarcoma, sarcomatoid carcinoma, large cell neuroendocrine

The frequency of GSTM1 null was studied in the histopathological types of lung cancer; it was 33.3% of SCLC ($n=1/3$ cases), and 47.1% of NSCLC cases 8/17) compared to the control group 70% null genotype (14/20), but no risk of SCLC was found to be associated with the gene deletion ($p=0.523$, OR = 4.4 and 95% CI 0.319–60.614), or NSCLC ($p=0.208$, OR = 2.475 and 95% CI 0.597–10.269) or histological subtypes of NSCLC (Table 3). There was no statistically significant difference found between the frequency of GSTM1 null in stage IV of the disease 40% (4/10) compared to 55.6% ($n=5/9$) in stage II (Figs. 1 and 2).

Discussion

In the present work, we observed that the frequency of the GSTM1 null genotype in the studied population was 57.5%. Interestingly, this frequency was lower in lung cancer patients (45%) compared to the control group (70%). These findings align with a previous study conducted in Egypt by Ramzy et al. [12]. In their study, which included 48 patients diagnosed with lung cancer and 42 healthy individuals, they reported nearly similar GSTM1

Table 2 GSTM1 frequency in patients with lung carcinoma and healthy controls according to their age (years), sex, and smoking

		GSTM1	
		Positive	**Null**
Total *N* (%) *N* = 40		17 (42.5)	23 (57.5)
P value		0.110	
Age (years) (mean ± SD)		52.24 (11.76)	47.48 (12.43)
P value		0.298	
Sex	Male	7 (41.2%)	15 (65.2%)
	Female	10 (58.8%)	8 (34.8%)
P value		0.131	
Smoking	Smokers	4(23.5%)	8(34.8%)
	Non-smoker	12 (76.5%)	16 (65.2%)
P value		0.443	
Pack-years (mean ± SD)		50 (20)	37 (24.01)
P value		0.341	
Cases *N* (%) *N* = 20		11 (55)	9 (45)
Control *N* (%) *N* = 20		6 (30)	14 (70)
P value		0.110	
OR (95% CI)		2.852 (0.777–10.467)	
Smokers	Cases *N* (%) *N* = 8	3 (37.5)	5 (62.5)
	Control *N* (%) *N* = 4	1 (25)	3 (75)
	P value	1	
	OR (95% CI)	1.8 (0.124–26.196)	
Non-smoker	Cases *N* (%) *N* = 12	8 (66.7)	4 (33.3)
	Control *N* (%) *N* = 16	5 (31.2)	11 (68.8)
	P value	0.063	
	OR (95% CI)	4.4 (0.889–21.78)	

genotype distribution between the control group and lung cancer cases. Notably, the GSTM1 null allele was absent in 33.3% of controls and 31.25% of patients.

In various ethnic populations, the prevalence of polymorphic genes was extensively studied [12–16]. Notably, the GSTM1-null genotype has been a focus of investigation. In the Turkish population, the *GSTM1*-null variant was expressed in around half of the patients with lung cancer compared to a slightly higher prevalence of 52.6% in the control group [17]. Among the Brazilian population, the percentage was 45.5% for the *GSTM1* deletion in patients with lung cancer and 48.1% in their control group [18], in Caucasians, GSTM1 frequencies vary between 42 and 60% [19]. GSTM1 null allele has been observed in approximately 31% to 66% of Asian and Indian populations [20–22]. Alternatively, for African Americans, the GSTM1 deletion polymorphism was found to be 23 to 35% [23] and Among Chileans, the GSTM1 deletion frequency was 21% [24].

In the current study, we observed that the expression of the GSTM1 null genotype was not correlated to the susceptibility of lung tumors. Even when stratified by tobacco consumption, no increased cancer risk was found among tobacco consumers with the GSTM1 deletion. Interestingly, Ramzy et al. reached a similar conclusion in Egyptian patients, indicating that the GSTM1 null genotype alone does not impact lung cancer risk, however, when combined with GSTP1 polymorphism, there appears to be an increased risk for lung cancer [12].

Likewise, in Bangladeshi individuals, the GSTM1 null genotype does not appear to significantly increase the risk of developing lung cancer. Moreover, the risk of lung malignancy was not observed among both tobacco smokers and nonsmokers who carried either the null or present genotypes of GSTM1 [25]. These results are consistent with the conclusion reached by Masood et al. which suggests that the deletion of GSTM1 is not linked with the incidence of lung malignancy [26].

Additionally, an earlier meta-analysis reported that even though the number of patients carrying *GSTM1* null genotype was higher in those with lung cancer diagnosis, no causal relationship between carrying this genotype and an increased susceptibility to lung cancer could be demonstrated [27]. Kalikaki et al. also outlined the absence of a significant correlation between the presence of *GSTM1* gene polymorphism and the overall survival of patients with advanced NSCLC [28].

Table 3 Frequencies of GSTM1 in different histopathological types of lung cancer

		Control *N* (%) *N* = 20	**SCLC *N* (%) *N* = 3**	**NSCLC *N* (%) *N* = 17**	**Subtypes of NSCLC N (%)**		
					Adenocarcinoma *N* = 10	**Squamous cell carcinoma *N* = 4**	**Others *N* = 3**
GSTM1	Positive	6 (30)	2 (66.7)	9 (52.9)	6(60)	1 (25)	2(66.7)
	Null	14(70)	1 (33.3)	8 (47.1)	4 (40)	3 (75)	1 (33.3)
P value			0.523	0.208	0.228	1	0.523
OR (95% CI)			4.4 (0.319–60.614)	2.48 (0.597–10.269)	3.3 (0.635–17.16)	0.733 (0.06–8.915)	4.4 (0.319–60.614)

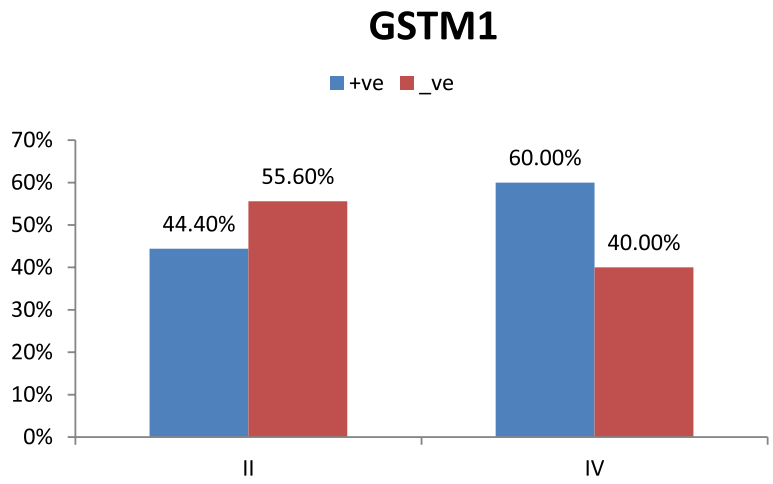

Fig. 2 Frequencies of GSTM1 according to the stage of lung cancer

On the other hand, contrasting findings related to the GSTM1 null polymorphism and its association with lung cancer risk were observed in the Turkish population. Pinarbasi and colleagues [29] reported a significant correlation between GSTM1 and lung cancer ($p=0.0001$) while other trials showed the opposite ($p>0.05$) [20]. GSTM1 has been implicated in cancer etiology in multiple studies with some even noting a significantly increased risk associated with GSTM1 deletion [30–33] consistent with large Asian studies that observed an obvious relationship of the GSTM1 null genotype with lung cancer [10, 34] in accordance with an earlier meta-analysis, revealing that the GSTM null allele was a risk factor for lung cancer development [32]. These diverse findings underscore the complexity of genetic factors in lung cancer susceptibility and emphasize the necessity for further research to unravel their underlying mechanisms.

Moreover, it was reported in both Caucasians and Indians, that a notable link exists between lung adenocarcinoma and the GSTM1 null genotype [33, 35, 36]. Additionally, Liu and colleagues showed that Asians carrying the GSTM1 null variant are considered more predisposed to lung cancer and when stratified by smoking status, this genotype increases the risk of both adenocarcinoma and squamous cell carcinoma in both smokers and non-smokers [31]. However, in addition to the previous findings of the current work, no association was exhibited between the *GSTM1* gene deletion and the histological types of lung cancer.

Despite the results of the present work, the authors recognize that the study is limited by being single-centered and that further large more diverse multicentric studies are needed to extrapolate these data on the general population along with extensive research to fully elucidate the complex relationships between genetic interactions and disease susceptibility.

Conclusion

According to our findings, we conclude that *GSTM1* null, even when stratified for smoking status, is not related to an increased risk of incidence of lung cancer.

Abbreviations

DNA	Deoxyribonucleic acid
GST	Glutathione S-transferase
GSTM1	Glutathione S-transferase class Mu 1
GSTP1	Glutathione S-transferase class Pi 1
GSTT1	Glutathione S-transferase class Theta1
NSCLC	Non-small cell lung cancer
PAH	Polycyclic aromatic hydrocarbons
PCR	Polymerase chain reaction
SCLC	Small cell lung cancer

Authors' contributions

G.H.: Data collection, editing and revision. A.G.: Manuscript writing, review, editing and final revision. N.A.E.: Genetic analysis and PCR. E.A.: Genetic analysis and PCR. M.F.H: revision R.I.EK.: revision N.E.G.: Data collection, editing and revision. All authors have read and approved this manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the ethical committee of the National Research Centre. Reference number: 10088. All subjects gave written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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