RESEARCH ARTICLE

Glutathione-S-transferase (GSTM1, GSTT1) Null Phenotypes and Risk of Lung Cancer in a Korean Population

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Abstract

Purpose: The aim of this study was to evaluate any association of GSTM1 and GSTT1 null genotypes with the risk of lung cancer in a South Korean population. Methods: We conducted a large-scale, population-based case-control study including 3,933 lung cancer cases and 1,699 controls. Genotypes of GSTM1 and GSTT1 were determined using real-time polymerase chain reaction. Results: In logistic regression analysis adjusted for age and smoking, we did not find any association between GSTM1 or GSTT1 and LC risk in women. However, in men, the GSTM1 and GSTTI null genotypes were borderline associated with risk (OR=1.18, 95% CI=0.99-1.41 for GSTM1, OR=1.18, 95% CI=0.99-1.41 for GSTT1), and combined GSTM1 and GSTT1 null genotypes conferred an increased risk for LC in men (OR=1.39, 95% CI=1.08–1.78). The OR for the GSTT1 null genotype was greater in subjects aged 55 years old or younger (OR=1.45, 95% CI=1.09-1.92 for men; OR=1.36, 95% CI=0.97–1.90 for women), than in those over age 55 (OR=1.03, 95% CI=0.83-1.27 for men; OR=0.86, 95% CI=0.66–1.12 for women) in both genders (p for interaction <0.05). Conclusions: In the Korean population, the GSTM1 and GSTT1 null genotypes are risk factors for LC in men; the GSTT1 null genotype has a more prominent effect on LC risk in younger people (age 55 years and under) than in older individuals.

Keywords: GSTM1 - GSTT1 - null phenotypes - lung cancer - South Korean population

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Introduction

In Korea, incidence of lung cancer (LC) was ranked 3rd in male and 4th in female among cancers. The age-standardized incidence rate of LC was 47.5 and 13.3 per 100,000 for men and women, respectively, in 2007 (Jung et al., 2010). Tobacco smoking has been shown to play a major role in the development of this disease. However, only 15% of smokers develop LC in their lifetimes (Peto et al., 2000). Individual variation in genetic susceptibility is thought to lead to differences in risk for individuals with similar exposures (Shields, 1999).

The glutathione S-transferase (GST) enzymes are involved in detoxification of many potentially carcinogenic compounds. The enzymes are encoded by at least five distantly related gene families (the alpha, mu, pi, sigma, and theta GSTs). In humans, marked interindividual differences exist in the expression of mu (GSTM1), and theta (GSTT1) GSTs (Hayes and Pulford, 1995). Individuals with GSTM1 null genotype have been reported to have higher levels of polycyclic aromatic hydrocarbon —dGMP adducts in lung tissues, which can induce genetic mutations (Kato et al., 1995). GSTT1 is involved in the metabolism of smaller compounds found in tobacco smoke, such as monohalomethane and ethylene oxide (Landi, 2000).

The GSTM1 and GSTT1 null genotypes have been linked to increased risk of developing lung, bladder, colon, and skin cancers (Bell et al., 1993; Hayes and Pulford, 1995; Nakajima et al., 1995), and several studies have shown that GSTM1 or GSTT1 null genotypes were associated with increased risk of LC (Cote et al., 2005; Cote et al., 2009; Schneider et al., 2004; Spitz et al., 2000). However, some data have suggested that no relationship exists between the GSTM1 or GSTT1 null genotype and the risk of LC (Alexandrie et al., 2004; Larsen et al., 2006). Although many studies have assessed GSTM1 and GSTT1 polymorphisms in relation to LC, the results are conflicting. Besides different study designs, differences in the prevalence of genetic polymorphisms and linkage disequilibrium in different ethnic populations are possible explanations for the varying results obtained. Effect modifications by environmental or other genetic risk factors that differ between study populations are alternative causes. To avoid such influences, large studies on homogenous populations are warranted.

The present study aimed to evaluate the association of the GSTM1 and GSTT1 null genotypes with the risk of LC

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and to study its relationship to gender, age, smoking habits, and histologic subtypes. In addition, the study examined the association of combined genotypes of GSTM1 and GSTT1 and LC risk.

Materials and Methods

Ethics

This study was approved by the Institutional Review Board of the Chonnam National University Hwasun Hospital in Hwasun, Korea, and all patients provided informed written consent.

Subjects

The study was included 3933 newly diagnosed LC cases and 1699 controls. It was conducted in the Chonnam National University Hwasun Hospital in Jeollanam-do, South Korea, between January 2000 and August 2010. Cases were histologically confirmed, Cases with secondary or recurrent tumors were excluded.

The main histological types of LC are squamous cell carcinoma (SQC), adenocarcinoma (ADC), large cell carcinoma (LCC), mixed or unspecific carcinoma (ETC), and small cell carcinoma (SCC). For non-small-cell lung cancer (NSCLC), tumor stages were according to the WHO TNM classification, 7th version (Sobin et al., 2009). For SCC, the classification consisted of only two stages: limited disease (LD) and extended disease (ED).

The control group (n=1699) consisted of participants in the Thyroid Disease Prevalence Study (Kim et al., 2008). This study was performed in the Yeonggwang and Muan counties of Jeollanam-do Province and Namwon city of Jeollabuk-do province, Korea, between July 2004 and January 2006. The study selected 4,018 subjects randomly using 5-year age strata and gender, from the resident registration list of six areas in Namwon and Yeonggwang and Muan counties. Of the total, after excluding deaths and other residents at the registered address, 3,486 subjects were eligible. Of those eligible, 1699 (48.8% of the eligible subjects; 820 men and 879 women), underwent clinical examinations and genotyping. At the time of their peripheral blood collections, all control subjects provided their informed consent to participate in this study.

DNA isolation and genotyping

Blood samples were collected in EDTA-containing tubes, and DNA was extracted from the buffy coat for genotyping. Genomic DNA was extracted using a QIAamp DNA Blood Mini Kit (Qiagen, Valencia, CA) according to the manufacturer's protocol. GSTM1 and GSTT1 genotyping was determined by real-time PCR method as previously described (Piao et al., 2009).

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 19.0. All tests were conducted at the P=0.05 level of significance. The descriptive data for the major characteristics of study groups are expressed as mean (standard deviation) and percent. We used t-tests to determine statistical differences in continuous variables and chi-square tests for categorical variables. Adjusted odds ratios (OR) and their 95% confidence intervals (CI) were calculated using logistic regression models with adjustments for age and smoking status to estimate the association between individual and combined genotypes and LC. Interactions of genotype with age, smoking, and histologic type were estimated using the logistic regression model. Subjects with GSTM1 and GSTT1 wild genotype were considered to have baseline risk. Subjects for whom smoking status was unknown were excluded in interaction analysis.

Results

The LC group was significantly older than controls in both sexes. In men, smokers accounted for 90.8% of LC and 73.9% of controls; in women, smokers accounted for 13.8% of LC and 5.5% of controls ($p < 0.001$).

Table 1 shows genotype distributions for GSTM1 and GSTT1 and their adjusted OR and 95% CI in LC. In men, the GSTM1 and GSTT1 null genotypes were borderline associated with risk of LC (OR=1.18, 95% CI=0.99-1.41, OR=1.18, 95% CI=0.99-1.41, respectively), and combined GSTM1 and GSTT1 null genotype conferred an increased risk for LC (OR=1.39, 95% CI=1.08-1.78). These patterns were not evident in women. Because of this observed sex difference in the association of GSTM1 and GSTT1 genotypes with risk of LC, we performed further stratified analyses by age, smoking status, and histologic subtypes for men and women separately. Table 2 shows the results of the stratified analyses in men and women.

The OR for the GSTT1 null genotype was more prominent in subjects aged 55 years old or younger (OR=1.45, 95% CI=1.09-1.92 for men; OR=1.36, 95% CI=0.97-1.90 for women), than in those over age 55 (OR=1.03, 95% CI=0.83-1.27 for men; OR=0.86, 95% CI=0.66-1.12 for women) in both genders (p for interaction <0.05).

Table 1. GST(M1, T1) Genotype Frequencies of the Lung Cancer Cases and Controls

Genotypes		Men			Women		
		Cases	Controls	OR[a] (95% CI)	Cases	Controls	OR[a] (95% CI)
GSTM1	Wild	1331 (42.6)	369 (45.0)	1	365 (45.1)	407 (46.3)	1
	Null	1792 (57.4)	451 (55.0)	1.18 (0.99-1.41)	445 (54.9)	472 (53.7)	1.04 (0.84-1.29)
GSTT1	Wild	1469 (46.9)	412 (50.2)	1	394 (48.6)	429 (48.8)	1
	Null	1654 (52.9)	408 (49.7)	1.18 (0.99-1.41)	416 (51.4)	450 (51.2)	1.05 (0.85-1.31)
GSTM1*GSTT1	T1(W)*M1(W)	635 (20.3)	191 (23.3)	1	188 (23.2)	194 (22.1)	1
	T1(N)*M1(W)	696 (22.2)	178 (21.7)	1.19 (0.92-1.55)	177 (21.9)	213 (24.2)	0.86 (0.62-1.18)
	T1(W)*M1(N)	834 (26.7)	221 (26.9)	1.19 (0.93-1.53)	206 (25.4)	235 (26.7)	0.86 (0.63-1.17)
	T1(N)*M1(N)	958 (30.6)	230 (28.0)	1.39(1.08-1.78)	239 (29.5)	237 (27.0)	1.07 (0.79-1.45)

[a]adjusted for age and smoking status; OR, odds ratios; CI, confidence interval

Table 2. Stratified Analysis of Genotypes and Lung Cancer Risk for Males and Females

		Male				Female			
		GSTM1 OR (95% CI)	P	GSTT1 OR (95% CI)	P	GSTM1 OR (95% CI)	P	GSTT1 OR (95% CI)	P
Age[a]	≤ 55	1.10 (0.83-1.46)	0.7	1.45 (1.09-1.92)	0.04	1.00 (0.72-1.40)	0.68	1.36 (0.97-1.90)	0.03
	> 55	1.18 (0.95-1.46)		1.03 (0.83-1.27)		1.08 (0.83-1.41)		0.86 (0.66-1.12)	
Smoking status[b]	Never	1.02 (0.66-1.58)	0.92	1.23 (0.79-1.89)	0.88	1.03 (0.82-1.29)	0.66	1.05 (0.84-1.31)	0.84
	Ever	1.22 (1.00-1.48)		1.17 (0.97-1.72)		1.19 (0.58-2.45)		1.08 (0.52-2.21)	
Histology type[c]	ADC	1.18 (0.96-1.46)	0.91	1.20 (0.97-1.47)	0.78	1.06 (0.84-1.34)	0.46	1.00 (0.80-1.26)	0.33
	SQC	1.18 (0.96-1.45)		1.11 (0.90-1.36)		1.04 (0.64-1.69)		1.45 (0.89-2.38)	
	SCC	1.31 (1.01-1.70)		1.04 (0.80-1.34)		1.37 (0.85-2.21)		0.82 (0.51-1.31)	
Others		1.19 (0.87-1.62)		1.17 (0.85-1.29)		0.70 (0.39-1.27)		1.40 (0.77-2.54)	

[a]Adjusted for smoking status; [b]Adjusted for age; [c]Adjusted for age and smoking status; OR, odds ratios; CI, confidence interval; P: for heterogeneity test; ADC, adenocarcinoma; SQC, squamous cell carcinoma; SCC, small cell lung cancer; Others, other type lung cancer

Although the effect of the GSTM1 null genotype was more prominent in smokers than in nonsmokers (men: OR=1.22, 95% CI=1.00-1.48 for smokers; OR=1.02, 95% CI=0.66-1.58 for nonsmokers; women: OR=1.19, 95% CI=0.58-2.46 for smokers; OR=1.03, 95 % CI=0.82-1.29 for nonsmokers), there was no differences in the heterogeneity test.

The effect of the GSTM1 null genotype was more prominent in SCC than in ADC and SQC in both genders, and the effect of the GSTT1 null genotype was higher in female SQC patients (OR=1.45, 95% CI=0.89-2.38). There was no heterogeneity among histologic subgroups (ADC, SQC, SCC, other types).

Discussion

We found that the GSTM1 and GSTT1 null genotypes have a role in LC susceptibility in men, but not in women. In particular, we observed a significant association between the GSTM1 null genotype and LC risk in subjects who smoked and in SCC patients, between the GSTT1 null genotype and LC risk in young patients, and between the combined GSTM1 and GSTT1 null genotype and LC risk in men.

Although many studies have assessed GSTM1 and GSTT1 polymorphisms in relation to LC risk, the results are conflicting. Four studies had relatively large sample sizes; one study reported that the GSTM1 and GSTT1 null genotypes were associated with increased risk of LC (Spitz et al., 2000), two reported that the GSTM1 null genotype was associated with increased risk of LC and the GSTT1 null genotype with decreased risk (Alexandrie et al., 2004; Schneider et al., 2004), and one reported that the GSTM1 null genotype was associated with decreased risk of LC and the GSTT1 null genotype with increased risk (Larsen et al., 2006). A recent meta-analysis found that the GSTM1 and GSTT1 null genotypes were associated with LC risk among East Asians (Langevin et al., 2010). Although in our study we did not find any significant association between GSTM1 or GSTT1 and LC risk in women, a borderline association was observed (OR=1.18, 95% CI=0.99-1.41 for GSTM1, OR=1.18, 95% CI=0.99-1.41 for GSTT1) in men, and the combined GSTM1 and GSTT1 null genotype conferred a significantly increased risk of LC (OR=1.39, 95% CI=1.08-1.78) in men. These findings suggest that the GSTM1 and GSTT1 null genotypes were risk factors for male LC patients.

The pathogenesis of SCC is different from that of ADC. SCC is more often attributed to cigarette smoking (Kalemkerian et al., 2013), whereas ADC is more weakly associated with smoking than SCC (Sobue et al., 2002). Besides, genetic study indicated that SCC risk is closely linked to MTH1 gene (Kohno et al., 2006), while ADC risk is significantly associated with TERT, COMT, CYP1A1 and HLA-DQA1 genotypes (Kohno et al., 2010; Ji et al., 2012; Zhang et al., 2013). Several studies have investigated the association of the GSTM1 genotype with histologic subtypes of LC (To-Figueras et al., 1997; Stucker et al., 2002; Nazar-Stewart et al., 2003; Alexandrie et al., 2004; Schneider et al., 2004; Sobti et al., 2008). However, the results are conflicting. Three studies reported that the OR of the GSTM1null genotype was higher in ADC than in SCC (Alexandrie et al., 2004; Schneider et al., 2004; To-Figueras et al., 1997). In contrast, other studies reported that the OR of the GSTM1null genotype was higher in SCC than in ADC (Nazar-Stewart et al., 2003; Sobti et al., 2008; Stucker et al., 2002), which is in agreement with our results. A meta-analysis found that the increased risk of lung cancer with the GSTM1 null genotype is evident for all the major histological subtypes of LC and the effect of the GSTM1 genotype may vary according to histological subtype. The ORs were elevated for SCC (OR=1.33, 95% CI=1.10-1.60), and ADC (OR=1.13, 95% CI=1.02-1.25) (Carlsten et al., 2008). Similarly, in our data, the effect of GSTM1 null genotype was more prominent in SCC than in ADC, although there was no heterogeneity. These results suggest that the GSTM1 null genotype may be associated with greater susceptibility to SCC.

Early-onset LC theoretically may have a stronger genetic component (Sorensen et al., 2004). Cote et al. (Cote et al., 2005) and Taioli et al. (Taioli et al., 2003) found that the GSTT1 null genotype was associated with increased LC risk in Caucasian early-onset cases (<50 years, <45 years). Sorensen et al. (Sorensen et al., 2004) reported that the increased risk of LC associated with the GSTT1 null genotype was more pronounced in the 50-55 years age group than in those age 56 or older, which is consistent with our findings. Our data suggested that the GSTT1 null genotype is associated with greater susceptibility in younger (age ≤55 years) people in both genders. These findings suggest that the GSTT1 null genotype had a more prominent effect on LC risk in the younger group than in the older group.

Polycyclic aromatic hydrocarbons (PAHs) are the main carcinogens in tobacco smoke. Several carcinogens present in tobacco smoke are inactivated by GSTs (Bartsch

et al., 2000). Individuals with the null genotype of GSTM1 or GSTT1 would have less capacity for detoxification of PAHs, which would potentially increase their risk of chemical carcinogenesis (Piao et al., 2009). We examined the effects of GSTM1 or GSTT1 in subgroups according to smoking status and found that the OR for the GSTM1 null genotype was more prominent in smokers than in nonsmokers in both sexes, although there was no heterogeneity. This result is consistent with the findings of Wang and Lam (Wang et al., 2004; Lam et al., 2009).

The major strength of our study was its large sample size. Ours was the first investigation of the risk of LC based on GSTM1 and GSTT1 genotype in a large-scale Korean population. The limitations of our study must also be acknowledged. First, we could not rule out the possibility that differential misclassification bias may have occurred in our study because we retrospectively gathered information about smoking from electronic medical records in case groups, whereas cross-sectional surveys were used to gather information about smoking in controls (Piao et al., 2009). Second, although the overall LC sample size was relatively large, the numbers of subjects in subgroup analyses (e.g., LCC cases, women, those who had never smoked) were small.

In conclusion, in this Korean population study, the GSTM1 and GSTT1 null genotypes were risk factors for LC in men; the GSTT1 null genotype had a more prominent effect on LC risk in younger people (age 55 years and under) than on older ones.

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