SPANDIDOS PUBLICATIONS

Interactive effect of genetic polymorphism of glutathione S-transferase M1 and smoking on squamous cell lung cancer risk in Korea

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Received August 8, 2005; Accepted October 17, 2005

Abstract. To evaluate the role of the genetic polymorphisms of *CYP2E1*, *GSTM1* and *GSTT1*, and their interaction with smoking in lung cancer development in Korean males, a hospital-based case-control study was conducted. Histologically confirmed male lung cancer patients (n=171) and male patients with no present or previous history of systemic illness who visited the urology department (n=196) were recruited from Seoul National University Hospital, Korea (1998-1999). *CYP2E1* genotypes were determined by PCR-RFLP using *Rsa*I digestion and *GSTM1* and *T1* genotypes were determined by multiplex PCR. Risks were estimated as odds ratios (ORs) and 95% confidence intervals (CIs) using a logistic regression model adjusting for age and pack-year. Smoking was a significant risk factor for lung cancer (P<0.001). Although genetic polymorphisms of *CYP2E1*, *GSTM1* and *T1* were not associated with the overall risk of lung cancer, the *GSTM1* null genotype significantly increased the risk of squamous cell lung cancer (OR=1.9, 95% CI=1.04-3.60). An interactive effect between the *GSTM1* null genotype and smoking was observed (P=0.04). These results suggest that the *GSTM1* null genotype is associated with squamous cell lung cancer and modifies the effect of smoking on squamous cell lung cancer development in Korean males.

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Key words: lung cancer, *CYP2E1*, *GSTM1*, *GSTT1*, smoking, interaction

Introduction

Lung cancer is the most prevalent cancer worldwide. There was an estimated 1.24-million new cases of lung cancer in 2000 (1). Lung cancer mortality is also the highest in the world and in Korea (1,2).

Cigarette smoke, the major risk factor for lung cancer, contains a variety of carcinogens, such as polycyclic aromatic hydrocarbons (PAHs), N-nitrosoamins, and aromatic/heterocyclic amines (3). These carcinogens go through metabolic pathways by a number of enzyme systems, including P450 (CYP), glutathione S-transferase (GST) and N-acetyltransferase (NAT).

CYP2E1 catalyzes the oxidation of various N-nitrosamines, including potent tobacco-specific procarcinogens such as 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK) (4). The association between genetic polymorphisms of *CYP2E1* (*Dra*I, *Pst*I and *Rsa*I) and lung cancer risk showed inconsistent results; the protective effect of *CYP2E1 Rsa*I *c2* allele (5-7) or no association with *c2* allele (8,9).

GSTM1 catalyzes reactive electrophilic intermediates derived from cigarette smoking, such as BaP 7,8-diol-9,10-epoxides (BPDE), to less reactive and more easily excreted glutathione conjugates (10). Although earlier meta-analysis concluded that the *GSTM1* null genotype is associated with an increased risk of lung cancer (11,12), recent pooled analyses indicated that there is no evidence of an increased risk of lung cancer in the *GSTM1* null genotype (13). Moreover, studies conducted in the Asian population also showed inconsistent results (14-17). The results of previous studies on the association between the *GSTT1* null genotype and lung cancer risk are also inconsistent (18-20).

The lack of consistency might be due to the difference in ethnicity, genotype distribution, exposure to possible risk factors or risk modifiers, such as smoking, diet, and occupational chemicals, and distribution of histological cell types of lung cancer cases. The distribution of histological

cell types might be one of the reasons for the inconsistent results because of the heterogeneity of lung cancer risk by histological cell types (6). However, the potential role of genetic polymorphisms of *CYP2E1*, *GSTM1* and *T1* in a specific histological cell type of lung cancer with the interactive effect of smoking has not been thoroughly evaluated.

The purpose of this study was to determine the potential role of genetic polymorphisms of *CYP2E1 Rsa*I, *GSTM1*, and *T1* homozygous deletions in the overall risk of lung cancer and the specific cell types in Korean males. The interactive effect of these polymorphisms and smoking on lung cancer development was also evaluated.

Materials and methods

Subjects and data collection. Histologically confirmed male lung cancer patients who were 40 years or more in age were recruited as cases (n=180) from the Department of Internal Medicine, Seoul National University Hospital, Korea, from February 1998 to July 1999. Male patients who were also 40 years or more in age and visited the Department of Urology, Seoul National University Hospital were recruited as controls (n=223). Those with a history of malignant tumors or radiotherapy and chemotherapy were excluded from both cases and controls. Controls consisted of urolithiasis, benign prostatic hyperplasia, urethral stricture, hernia, and so on (21). Using these eligibility criteria, 171 lung cancer cases and 196 controls were selected. Information on age and smoking history as pack-years was collected by personal interview and medical record review.

Table I. Age distribution, smoking history and pathological type of 171 lung cancer cases and 196 hospital controls.

	No. of cases (%)	No. of controls (%)	P-value
Age			
40-59	73 (42.7)	82 (41.8)	0.87
≥60	98 (57.3)	114 (58.2)	
Mean ± SD	61.0±8.4	62.1±12.2	0.34
Smoking history[a]			
Never (<400 cigarettes/lifetime)	14 (8.3)	35 (18.6)	<0.001
Ever (≥400 cigarettes/lifetime)	154 (91.7)	153 (81.4)	
Pack-year in ever smokers			
0<PY<35	52 (33.8)	108 (70.6)	0.001
PY≥35	102 (66.2)	45 (29.4)	
Mean ± SD	40.6±16.1	26.0±19.4	<0.001
Pathological type			
Adenocarcinoma	48 (28.1)		
Squamous cell carcinoma	74 (43.3)		
Small cell carcinoma	31 (18.1)		
Other cell types	18 (10.5)		

[a]Missing data: 3 cases and 8 controls.

Genotyping. From the subjects, 5cc of peripheral blood was collected in an EDTA tube with informed consent. DNA was extracted from each blood sample using a Qiagen DNA extraction kit (Chatsworth, CA, USA) and stored at -20˚C until genotyping.

CYP2E1 genotypes were determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method with *Rsa*I digestion. In the *CYP2E1* genotyping analysis, primers (5'-CCA GTC GAG TCT ACA TTG TCA-3' and 5'-TTC ATT CTG TCT TCT AAC TGG-3') were used in the PCR employing the following amplification conditions: the 20 μl reaction mixtures contained 1.5 mM $MgCl_2$, 250 μM dNTPs, 1 μM primers, 1 μM template DNA and 1 U of Taq polymerase with the buffer (10 mM Tris-HCl, pH 9.0; 40 mM KCl) (Bioneer, Daejeon, Korea). After initial denaturation at 94˚C for 4 min, 34 cycles of 60 sec at 94˚C, 60 sec at 60˚C and 60 sec at 72˚C were performed, followed by a final extension step of 4 min at 72˚C. After PCR, an aliquot of the product was digested with *Rsa*I for 3 h at 37˚C.

The *GSTM1* and *GSTT1* genotypes were determined by multiplex polymerase chain reaction (PCR). The ß-globin specific primer pair (B1, 5'-CAA CTT CCA CGT TCA CC-3'; and B2, 5'-GAA GAC CCA AGG ACA GGT AC-3') was used together with the *GSTM1* specific primer pair (G1, 5'-GAA CTC CCT GAA AAG CTA AAG C-3'; and G2, 5'-GTT GGG CTC AAA TAT ACG GTG G-3') and the *GSTT1* specific primer pair (T1, 5'-TTC CTT ACT GGT CCT CAC ATC TC-3'; and T2, 5'-TCA CCG GAT CAT GGC CAG CA-3') in PCR reactions. PCR was carried out in a total volume of 50 μl, containing 5 μl of DNA template (50-100 ng), 50 pmole of each of the above primers, and 1.25 units of Taq polymerase (Promega, Madison, WI, USA). The reaction was incubated at 94˚C for 4 min, prior to 30 cycles of denaturation for 20 sec at 94˚C, annealing for 20 sec at 57˚C, and extension for 45 sec at 72˚C, followed by a final extension of 5 min at 72˚C. Subsequent to PCR, an 10 μl aliquot was run on a 3% Metaphor agarose gel (FMC BioProducts, Rockland, ME, USA) in ethidium bromide-stained TAE buffer (50 Volt, 1 h), after which the bands were visualized and photographed under UV transillumination. The internal standard fragment amplified from ß-globin was 268 bp in length, whereas the presence of *GSTM1* and *GSTT1* genes was identified by 210-bp and 480-bp fragments, respectively.

The reliability of the PCR analyses conducted in the Korean laboratory was controlled by re-assaying 40 randomly selected samples in the Finnish laboratory; the results were found to be identical in both laboratories.

Statistical analyses. The risk of lung cancer was estimated as odds ratio (OR) and 95% confidence interval (CI) by unconditional logistic regression adjusting for age and pack-year. Age and pack-year were used as continuous variables in the model. Considering statistical power, *CYP2E1* genotypes were divided into two categories (c1/c2+c2/c2 vs. c1/c1) as *GSTM1* and *T1* genotypes (present vs. null). Stratified analyses for cases with specific histological cell types (adenocarcinoma,

CYP2E1, *GSTM1*, *GSTT1* genotypes and lung cancer risk by histological type in Korean males.

	No. of controls (%)	No. of all cases (%)	OR (95% CI)	No. of adeno-carcinoma (%)	OR (95% CI)	No. of squamous cell carcinoma (%)	OR (95% CI)	No. of small cell carcinoma (%)	OR (95% CI)
CYP2E1									
c1/c1	90 (47.1)	64 (37.9)	1.0 (reference)	17 (36.2)	1.0 (reference)	30 (41.1)	1.0 (reference)	11 (35.5)	1.0 (reference)
c1/c2	89 (46.6)	97 (57.4)	1.3 (0.81-2.11)	28 (59.6)	1.6 (0.77-3.15)	37 (50.7)	1.1 (0.57-1.97)	20 (64.5)	1.9 (0.80-4.58)
c2/c2	12 (6.3)	8 (4.7)	0.8 (0.29-2.22)	2 (4.3)	0.8 (0.16-3.97)	6 (8.2)	1.4 (0.45-4.16)	-	-
c1/c2+c2/c2	101 (52.9)	105 (62.1)	1.2 (0.78-1.98)	30 (63.9)	1.5 (0.73-2.90)	43 (58.9)	1.1 (0.60-1.99)	20 (64.5)	1.7 (0.70-3.96)
GSTM1									
Present	91 (46.4)	71 (42.0)	1.0 (reference)	22 (45.8)	1.0 (reference)	24 (32.9)	1.0 (reference)	19 (63.3)	1.0 (reference)
Null	105 (52.6)	98 (58.0)	1.4 (0.85-2.14)	26 (54.2)	1.1 (0.57-2.13)	49 (67.1)	1.9 (1.04-3.60)	11 (36.7)	0.6 (0.24-1.33)
GSTT1									
Present	89 (45.4)	89 (52.7)	1.0 (reference)	26 (54.2)	1.0 (reference)	39 (53.4)	1.0 (reference)	12 (40.0)	1.0 (reference)
Null	107 (54.6)	80 (47.3)	0.7 (0.45-1.12)	22 (45.8)	0.6 (0.33-1.24)	34 (46.6)	0.7 (0.39-1.27)	18 (60.0)	1.1 (0.46-2.46)

ORs were adjusted for age and pack-year.

squamous cell carcinoma, and small cell carcinoma) were also performed.

Gene-smoking interactions, i.e. the modification of an increasing pattern of lung cancer risk as the pack-year increases by different genotype, were evaluated by the significance of the coefficient of product term genotype*pack-year in the model without main effect term of genotype as follows; Logit (lung cancer) = $ß_0 + ß_1$age + $ß_2$pack-year + $ß_3$genotype*pack-year (22). This model assumes that, if there is no exposure to cigarette smoking, there is no difference in the risk of lung cancer between genotypes (23). The test was equal to evaluate the difference of the slopes of two fitted lines stratified by categorized genotypes with common intercept assumption. The assumption was tested by evaluating the significance level of main effect term of genotype in full model. All statistical analyses were performed using Statistical Analysis System software (version 8.01, SAS Institute, Cary, NC, USA).

Results

The distribution of age, smoking history, and histological cell type of 171 lung cancer cases and 196 hospital controls are summarized in Table I. The mean age was 61.0±8.4 in cases, and 62.1±12.2 in controls (P=0.25). The proportion of ever-smokers (≥400 cigarettes/lifetime) was higher in cases (91.7%) than in controls (81.4%) (P<0.001). When ever-smokers were divided into light and heavy smokers by 35 pack-years, the proportion of heavy smokers in cases (66.2%) was higher than that in controls (29.4%) (P=0.001). Also, the mean pack-year in ever-smokers was higher in cases (40.6±16.1) than in controls (26.0±19.4). The most common cell type was squamous cell carcinoma (43.3%).

The distribution of *CYP2E1 Rsa*I in the control group did not divert from Hardy-Weinberg equilibrium (P=0.26). The frequency of *CYP2E1 c2* allele in Korean (30%) in this study was higher than that of Caucasian (4.8%) (24) and Japanese (19.1%) (8), and lower than that of Chinese (66.4%) (7). *CYP2E1* genotype was not associated with the lung cancer risk (Table II).

The frequency of the *GSTM1* null genotype in Korean was similar to that of Caucasian (52.6% vs. 53.1%), whereas the frequency of both *GSTT1* genotypes was higher than that of Caucasian (54.6% vs. 19.7%) (24). *GSTM1* and *T1* null genotypes were not associated with overall lung cancer (OR=1.4, 95% CI=0.85-2.14 and OR=0.7, 95% CI=0.45-1.12, respectively). However, when the lung cancer cases were stratified by the histological cell types, the risk of squamous cell lung cancer was significantly associated with the *GSTM1* null genotype (OR=1.9, 95% CI=1.04-3.60) (Table II). Also, the interactive effect between the *GSTM1* null genotype and smoking was observed in squamous cell lung cancer development (P for interaction=0.04) (Fig. 1).

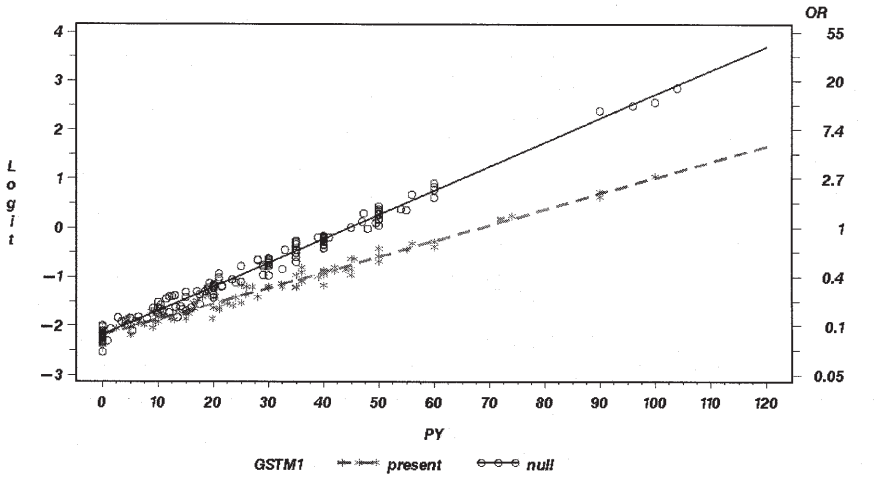

Figure 1. The interactive effect between the *GSTM1* null genotype and smoking in squamous cell lung cancer was observed. It was evaluated by the difference of slopes of two fitted lines by genotypes using the following model with the assumption of common intercept; Logit (lung cancer) = $ß_0$ + $ß_1$age + $ß_2$pack-year + $ß_3$GSTM1*pack-year) (H_0: $ß_3$=0; P=0.04). This assumption, i.e. genetic effect does not exist if there is no exposure to smoking, was evaluated by the significance level of the main effect term of genotype in the full model (P=0.44).

Discussion

Our results suggest that the *GSTM1* null genotype is associated with squamous cell lung cancer and there is an interactive effect between the *GSTM1* genotype and smoking in squamous cell lung cancer development in Korean males.

Although stratified analyses by histological cell type in some previous studies did not show the association between *GSTM1* null genotype and the risk of squamous cell lung cancer (SCC) (25,26), the increased risk of SCC in relation with the *GSTM1* null genotype in this study is consistent with the results of previous studies, including one meta-analysis (6,12,27-29). Le Marchand *et al* (6) hypothesized that genetic susceptibility to PAHs (*CYP1A1* and *GSTM1*) predominantly causes SCC. In the study conducted by Le Marchand *et al* (6), *CYP1A1 Msp*I variant allele was associated with a 3.1-fold risk of SCC when combined with a *GSTM1* deletion. The decreasing trend of SCC associated with filter-tipped cigarettes in developed countries indirectly supports this hypothesis (30). The same trend was observed in Korea (31).

BPDE is known to induce G:C to T:A transversion mutations in the hotspot codons of the p53 tumor suppressor gene (32), which is found more frequently in SCC than in AD (33). The BPDE-DNA adduct level is elevated in lung parenchyma of smokers with the *GSTM1* null genotype (34). Thus, it is speculated that our finding of the association between the *GSTM1* null genotype and the risk of SCC is related with PAH exposure derived from smoking because PAHs are primarily metabolized by *GSTM1*.

We evaluated the interactive effect of genotypes with pack-year on lung cancer development under the assumption that, if there is no environmental exposure, there is no difference in the risk of lung cancer between genotypes (22,23). We found that the association between cigarette smoking and squamous cell lung cancer was stronger among those with *GSTM1* null genotypes. Although a number of previous studies examined the effect of interactions between the GST polymorphisms and smoking on the risk of lung cancer (13,27,29,35-37), only a few studies found the interactive effects (27,35).

Fig. 1 shows that, as the level of exposure to cigarette smoking increases, the effect of the *GSTM1* genotype on the association between smoking and lung cancer risk also increases. This kind of effect was named as the high exposure-gene (HEG) effect (23) and is consistent with previous studies (27,35). Therefore, it is speculated that cigarette smoke exposure did not cause enzyme saturation of GSTM1 in this study population.

There were several limitations, including not collecting various potential confounding factors, and small sample size. Although potential confounding factors, such as occupational exposure and dietary factors, were not collected in this study, they seem to be relatively weakly associated with lung cancer compared with cigarette smoking, and the association with genotypes determined in this study seems unlikely. However, more subjects need to be recruited to evaluate the association of genotypes with the risk of lung cancer by specific cell type.

In summary, the results of our study suggest that genetic polymorphism of *GSTM1* and its interaction with smoking play a role in squamous cell lung cancer development in Korean males. To investigate further the complex mode of interaction between genetic factors and environmental exposure, study including the comprehensive coverage of genes and collection of information on potential confounding factors is needed in the future.

Acknowledgements

This study was supported by the General Research Fund, Seoul National University (1998).

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