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The GSTT1 Genotype as A Marker for Susceptibility to Lung Cancer in Korean Female Never-Smokers

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=국문초록=

한국인 비흡연 여성에서 폐암의 유전적 감수성 표지자로서의 GSTT1 유전자형

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배 경 : Glutathione S-transferase(GST)는 발암 전구물질의 해독에 관여하는 효소로, GSTM1과 GSTT1 소실형을 갖는 개체는 폐암의 감수성이 높은 것으로 생각된다. 여성 폐암은 위험 인자, 조직형 등의 역학적 특성이 남성과 차이가 많기 때문에 유전적 감수성 인자 또한 차이가 있을 것으로 생각된다. 이에 저자들은 한국인에서 GSTM1과 GSTT1 유전자형과 폐암 발생 위험도의 상관 관계를 남성과 여성을 분리하여 조사하였다.

방 법 : 1997년 1월부터 1999년 12월까지 경북대학교 병원에서 폐암으로 확진된 253명의 환자를 대상으로 하였으며, 대조군은 경북대학교 병원 건강 검진센터를 방문한 검진자들을 대상으로 하였다. GSTM1과 GSTT1의 유전자형은 말초 혈액에서 DNA를 추출한 후 다중중합효소 연쇄 반응(multiplex PCR)을 통하여 조사하였다.

결 과 : 남성에서는 GSTM1과 GSTT1 유전자형에 따른 폐암 발생 위험도의 유의한 차이가 없었다. 여성에

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서는 GSTM1 유전자형과 폐암 발생 위험도는 유의한 차이가 없었으나, GSTT1 소실형의 빈도는 폐암군 70.3%, 대조군 55.3%로 폐암군에서 유의하게 높았다 [odds ratio(OR, 대응비)=2.18, 95% confidence interval (CI, 신뢰구간)=1.21-3.93). 흡연력과 연령에 따라 층화분석한 경우 GSTT1 소실형은 60세 이하(OR=4.82, 95% CI=1.61-14.4)와 비흡연자(OR=4.29, 95% CI=1.94-9.48]에서 여성 폐암 위험도와 유의한 관계가 있었다. **결 론** : GSTT1 유전자형은 한국인 비흡연 여성에서 폐암의 위험도를 결정하는 유전적 인자로 생각된다.(**Tuberculosis and Respiratory Diseases 2003, 54:485-494**)

Key words : Glutathione S-Transferase(GST), Genetic Susceptibility, Lung Cancer.

Introduction

Lung cancer is frequently cited as an example of a disease determined solely by exposure to environmental carcinogens. However, there is a growing realization that genetic constitution is of importance in determining an individual's susceptibility to lung cancer[1,2]. This genetic susceptibility may result from functional polymorphism of genes involved in carcinogen metabolism and DNA repair[3,4].

Glutathione S-transferase (GSTs) are a group of phase II enzymes that detoxify diverse electrophiles, including carcinogens, chiefly by conjugating them with glutathione. In human, there are four classes of cytosolic GST isoenzymes, namely alpha (GSTA), mu (GSTM), pi (GSTP), and theta (GSTT). They have different but overlapping specific activities and affinities for electrophilic substrates[5,6]. In human beings, the GSTM1 and GSTT1 genes are polymorphic, and the phenotypic absence of enzyme activity is due to a homozygous inherited depletion of the gene, the null genotype[7,8]. Individuals with GSTM1 and GSTT1 null genotype are less able to detoxify metabolites of environmental carcinogens and therefore may be presumably at an increased risk of lung cancer.

Several studies have been carried out to clarify the effect of GSTM1 and GSTT1 status on the risk of lung cancer[9-12]. However, it would be premature to form definite views of relevance of these genotypes to the lung cancer risk due to ethnic differences in allelic distribution, variation in the distribution of histologic types and the methods determining the GSTM1 and GSTT1 status among studies[11-14]. Furthermore, most previous studies have been focused mainly on male smokers.

Since epidemiological characteristics, histologic types and risk factors are different in female and male lung cancers, we investigated the association between these genotypes and lung cancer risk in males and females separately to evaluate the gender-specific effect of these genotypes on the risk of lung cancer.

Materials and Methods

1. Study Population

Cases were 253 patients (153 males and 100 females) who agreed to this study among 789 patients diagnosed as lung cancer between

January 1997 and December 1999. The histologic types of cancer were as follows; 111 squamous cell carcinoma, 95 adenocarcinoma, 40 small cell carcinoma, and 7 large cell carcinoma. The controls consisted of healthy persons recruited through the general health check-up center during the same period. Information concerning gender, age, tobacco consumption, and past history was obtained from clinical records for the patients and from interview for the controls.

2. GSTM1 and GSTT1 Genotyping

Genomic DNA was extracted from peripheral blood lymphocytes by proteinase K digestion and phenol/chloroform extraction. GSTM1 and GSTT1 genotypes were determined by a multiplex PCR using three sets of primers to amplify a 215-bp sequence of the GSTM1 gene, a 268-bp sequence of the β-globin gene, and a 480-bp sequence of the GSTT1 gene[15]. The absence of the GSTM1 or GSTT1-specific fragment indicated the corresponding null genotype, whereas the β-globin specific fragment indicated the presence of amplifiable DNA in the reaction mixture.

3. Statistical Analysis

The comparison of ages was performed by Student's t-test and the comparison of smoking status (current/former/never) by χ^2-test or Fisher's exact test. The statistical significance of the differences in the frequencies of GSTM1 and GSTT1 null genotypes between groups was calculated by χ^2-test. The odds ratios (ORs) were calculated and were expressed together with the 95% confidence interval (CI). They were repeated after cases and controls were stratified by age ($\leq$60 years, >60 years), cigarette consumption ($\leq$30 pack-years, >30 pack-years) in males or smoking status (smoker: current and former smoker, never-smoker) in females, and histologic type of cancer. Additionally, adjusted OR and 95% CI for lung cancer in females were calculated from multiple logistic regression analysis using age, smoking status, GSTM1 genotype and GSTT1 genotype as dependent variables. All analyses were performed using Statistical Analysis Software (SAS) for Window, version 6.12 (SAS institute, Cary NC).

Results

The details of cases and controls enrolled in this study are shown in **Table 1**. The mean age of cases (61$\pm$8.6 years) was similar to controls (60 $\pm$8.9 years) in males, but the mean age was higher for cases than controls in females (62$\pm$ 10.5 years versus 58$\pm$10.5 years; $p<0.05$). Cases showed a higher prevalence of current smokers compared with controls in both males and females ($p<0.05$).

In the male populations, the frequencies of GSTM1 and GSTT1 null genotypes were not significantly different between cases (56.2% and 56.9%, respectively) and controls (55.7% and 55.0%, respectively). The frequencies of GSTM1 and GSTT1 null genotypes among controls were similar to the results of previous studies for Koreans[16-17], and did not differ significantly

Table 1. Characteristics of the study population

	Male		Female	
	Case	Control	Case	Control
Population	153	140	100	103
Age (years)	61±8.6	60±8.9	62±10.5	58±10.5[a]
Smoking Status(%)				
Current	146(95.4)[b]	95(67.9)[a]	37(37.0)	9(8.7)[a]
Former	5(3.3)	36(25.7)	3(3.0)	3(2.9)
Never	2(1.3)	9(6.4)	60(60.0)	91(88.4)

[a]p <0.05; [b]numbers in parenthesis, percentage

Table 2. Association between GSTM1 and GSTT1 genootypes, and lung cancer risk in males

	GSTM1				GSTT1			
	Case null/total	Control null/total	OR[a]	95% CI[b]	Case null/total	Control null/total	OR	95% CI
All	86/153(56.2)[c]	78/140(55.7)	1.02	0.64-1.62	87/153(56.9)	77/140(55.0)	1.08	0.68-1.71
Age(years)								
≤60	33/65(50.8)	36/63(57.1)	0.77	0.39-1.55	35/66(53.9)	32/63(50.8)	1.13	0.57-2.26
>60	53/88(60.2)	42/77(54.6)	1.26	0.68-2.34	52/88(59.1)	45/77(58.4)	1.03	0.55-1.91
Pack-Years in Smokers[d]								
≤30	29/51(56.9)	36/66(54.6)	1.10	0.53-2.29	23/51(45.1)	35/66(53.0)	0.73	035-1.52
>30	56/100(56.0)	36/65(55.4)	1.03	0.55-1.92	63/100(63.0)	36/65(55.4)	1.37	0.73-2.59

[a]odds ratio; [b]confidence interval; [c]numbers in parenthesis, percentage; [d]current and former smokers

according to age (≤60 years, >60 years) and cigarette consumption (≤30 pack-years, >30 pack-years). When the male populations were stratified by age and cigarette consumption, neither GSTM1 or GSTT1 null genotype frequency showed significant difference between cases and controls in each subgroup (**Table 2**).

The frequencies of GSTM1 and GSTT1 null genotypes in the female populations are shown in **Table 3**. Among controls, the frequencies of GSTM1 and GSTT1 null genotypes did not differ significantly according to age (≤60 years, >60 years) and smoking status (current and former smoker, never-smoker). The frequencies of GSTM1 null genotype showed no significant difference between cases and controls (54.0% and 55.3%, respectively). When stratifying the female subjects by age and smoking status, the frequency of GSTM1 null genotype was also not significantly different between cases and controls in each subgroup. In contrast to GSTM1 genotype, the frequency of GSTT1 null genotype

Table 3. Association between GSTM1 and GSTT1 genotypes, and lung cancer risk in females

	GSTM1				GSTT1			
	Case null/total	Control null/total	OR[a]	95% CI[b]	Case null/total	Control null/total	OR	95% CI
All	54/100(54.0)[c]	57/103(55.3)	0.95	0.55-1.65	73/100(73.0)	57/103(55.3)	2.18	1.21-3.93[f]
Age(years)								
≤60	14/32(43.8)	30/53(56.6)	0.60	0.22-1.58	27/32(84.4)	28/53(52.8)	4.82	1.46-16.9[g]
>60	40/68(58.8)	27/50(54.0)	1.22	0.58-2.54	46/68(67.7)	29/50(58.0)	1.51	0.71-3.23
Smoking status								
NS[d]	35/60(58.3)	51/91(56.0)	1.10	0.57-2.12	50/60(82.0)	49/91(53.9)	4.29	1.94-9.4[h]
S[e]	19/40(47.5)	6/12(50.0)	0.91	0.25-3.29	23/40(57.5)	8/12(66.7)	0.68	0.18-2.62

[a]odds ratio; [b]confidence interval; [c]numbers in parenthesis, percentage
[d]never-smokers; [e]current and former smokers; [f]p=0.009; [g]p=0.003; [h]p=0.001

Table 4. Multiple logistic regression analysis for females

	OR	95% CI	*P*
GSTM1(+/-)	0.892	0.651-1.223	0.479
GSTT1(+/-)	1.710	1.219-2.400	0.002
Age (≤60/>60 years)	2.086	1.123-3.876	0.020
Smoking status (NS/S)[a]	5.328	2.477-11.46	<0.001

[a]NS : never-smokers, S : current and former smokers χ^2=37.534, P=0.001

was significantly higher in cases (70.3%) than controls (55.3%, OR=2.18; 95% CI=1.21-3.93). When the female populations were stratified by age and smoking status, the ORs for GSTT1 null genotype were significantly higher in subgroups of ≤60 years (OR=4.82; 95% CI=1.61-14.4) and never-smokers (OR=4.29; 95% CI=1.94-9.48), but not in subgroups of >60 years or smokers.

When stratifying the female never-smokers by age, the ORs for GSTT1 null genotype were significantly higher in both age groups of ≤60 years (OR=7.64; 95% CI=2.00-29.2) and >60 years (OR=2.89; 95% CI=1.05-7.94). However, in female smokers, there was no significant association between GSTT1 null genotype and lung cancer risk in both age groups (data not shown). B[b]

In multiple logistic regression analysis for females, the GSTT1 null genotype was a significant lung cancer risk factor (OR=1.71; 95% CI=1.22-2.40), together with smoking status (never-smoker/ current and former smoker, OR=5.33; 95% CI=2.48-11.46), and age (≤60 years/>60 years, OR=2.09; 95% CI=1.12-3.88) in female populations (**Table 4**).

The frequencies of GSTM1 and GSTT1 null genotypes according to histologic types of cancer are shown in **Table 5**. GSTM1 null genotype was no apparent relationship with any of the

Table 5. Association between GSTM1 and GSTT1 genotypes, and lung cancer risk: stratified by histologic types

	Histologic type	GSTM1			GSTT1		
		Case null/total	OR[a]	95% CI[b]	Case null/total	OR	95% CI
Male	SQ[c]	45/81(55.6)[f]	0.99	0.55-1.79	48/81(59.3)	1.16	0.64-2.09
	SC[d]	16/24(66.7)	1.59	0.59-4.37	12/24(50.0)	0.82	0.32-2.11
	AD[e]	21/43(48.8)	0.76	0.36-1.59	23/43(53.5)	0.94	0.45-1.97
Female	SQ	14/30(46.7)	0.71	0.31-1.60	21/30(70.0)	1.88	0.79-4.50
	SC	7/16(43.8)	0.63	0.22-1.81	13/16(81.3)	3.50	0.94-13.01
	AD	31/52(59.6)	1.19	0.61-2.34	37/52(71.2)	1.99	0.97-4.07[g]

[a]odds ratio referred to control group; [b]confidence interval
[c]squamous cell carcinoma; [d]small cell carcinoma; [e]adenocarcinoma
[f]numbers in parenthesis, percentage; [g]p=0.057

histologic types in males and females. Although failing to reach statistic significance, however, GSTT1 null genotype was associated with increased risk of adenocarcinoma in females (OR=1.99; 95% CI=0.92-4.34, p=0.057). We also investigated the effect of concurrent GSTM1 and GSTT1 null genotypes on lung cancer risk, but the lung cancer risk related to the GSTT1 null genotype in the female populations was not increased in carriers of the GSTM1 null genotype (data not shown).

Discussion

This is the first study showing that GSTT1 null genotype is associated with an increased risk of lung cancer in female never-smokers. GSTT1 is involved in detoxification of potential carcinogens such as ethylene oxide and butadiene found in cigarette smoke[8,18,19]. Therefore, individuals with GSTT1 null genotype may be presumably at increased risk of tobacco smoker-related cancers such as lung cancer. GSTT1 null genotype was also associated with increased risk of various tumors[20-22] although the causative substrates of GSTT1 was not identified. However, the previous studies conducted in male smokers have not demonstrated a significant increase of lung cancer risk in individuals carrying GSTT1 null genotype[11,12,20,23]. Our study also did not show a significant association between GSTT1 null genotype and lung cancer risk among smokers in both genders. In the present study, however, we found a significant association between GSTT1 null genotype and lung cancer risk among female never smokers.

GSTT1 may not be involved in the biotransformation of the major smoke carcinogens. This is supported by the study of Rojas et al.[24] in which there was no differences in benzo[a]pyrene diol epoxide-DNA adduct levels between GSTT1 null and active genotypes among workers exposed to polycyclic aromatic hydrocarbon, one of major carcinogens in tobacco-smoke. In Korea, the proportion of never-smokers in female lung cancer cases is about 70-80%[25,26],

which is remarkably higher than 9-13% of female cases in the United States[27]. Unidentified risk factors other than smoking, such as diet, indoor exposure to fumes from cooking oil and coal combustion[28-30], may play an important role on the development of lung cancer in Korean females. The prevalence of GSTT1 null genotype shows remarkable inter-racial differences[31]. The prevalence of GSTT1 null genotype is higher in Korean (50-60%)[16,17] than in Caucasians (20% or less)[31].

Our results are contrary to the previous studies that GSTT1 null genotype was not associated with an increased risk for lung cancer in female never-smokers[32,33]. This discrepancy may be explainable by the reasons mentioned above such as different risk factors and higher prevalence of GSTT1 null genotype in Korean. Environmental tobacco smoking (ETS), a major cause of lung cancer in never-smokers[34], could modify the risk of lung cancer associated with GSTT1 null genotype. Although we did not analyze the association between ETS and GSTT1 null genotype, our finding that the risk of lung cancer associated with GSTT1 null genotype was significantly higher in the age group of ≤60 years, probably having shorter duration of ETS exposure than in the age group of >60 years, suggests that ETS does not strongly modify the association of GSTT1 null genotype and lung cancer risk in female never-smokers.

Regarding the association of GSTM1 genotype and lung cancer risk, we could not find a significant association between GSTM1 null genotype and lung cancer risk in both males and females. A number of studies have been conducted to evaluate the potential role of GSTM1 null genotype as a risk factor for lung cancer. An earlier review[9] of 12 case-control studies concluded GSTM1 deficiency is a moderate risk factor for all histologic subtypes of lung cancer with odds ratio of 1.41 (95% CI=1.2-1.6). However, when these studies were stratified to race, an elevated OR was detected in Japanese population (OR=1.60; 95% CI=1.3-2.1), but not in Caucasian (OR=1.17; 95% CI=0.98-1.40). Moreover, the overall OR of lung cancer risk associated with GSTM1 deficiency in the studies determining GSTM1 status by genotyping was lower (OR=1.13; 95% CI=1.04-1.25) than that of studies based on phenotyping methods (OR=2.12; 95% CI=1.43-3.13)[10]. These results may suggest that the estimates of lung cancer risk associated with GSTM1 deficiency in the early studies determined GSTM1 status by phenotyping methods were exaggerated. Thus it seems reasonable that the role of GSTM1 deficiency as a lung cancer risk factor should be assessed in each ethnic population differently.

In conclusion, we found that GSTT1 null genotype was associated with an increased risk of lung cancer in Korean female never-smokers. This result suggests that GSTT1 null genotype could be used as a biomarker for genetic susceptibility to lung cancer in Korean female never-smokers.

Summary

Background : Most previous studies regarding the role of GSTM1 and GSTT1 on lung cancer risk have been focused mainly on male smokers.

However, epidemiological characteristics, histologic types and risk factors are different in female and male lung cancers, we investigated the association between these genotypes and lung cancer risk in males and females separately.

Materials and Methods : The study population consisted of 253 lung cancer (153 males and 100 females) and 243 controls (140 males and 103 females). GSTM1 and GSTT1 genotypes were determined by a multiplex PCR.

Results : In the male population, neither GSTM1 nor GSTT1 null genotype showed significant difference between cases and controls. In the female population, the frequencies of GSTM1 null genotype showed no significant difference between cases and controls. However, the frequencies of GSTT1 null genotype was significantly higher in cases (70.3%) than controls (55.3%, odds ratio (OR)=2.18; 95% confidence interval (CI=1.21-3.93). When the female population was stratified by age and smoking status, the ORs for GSTT1 null genotype were significantly higher in subgroups of ≤60 years (OR=4.82; 95% CI=1.61-14.4) and never-smokers (OR=4.29; 95% CI=1.94-9.48) but not in subgroups of >60 years or smokers. When stratifying the female never-smokers by age, the ORs for GSTT1 null genotype were significantly higher in both age groups of ≤60 years (OR=7.64; 95% CI=2.00-29.2) and >60 years (OR=2.89; 95% CI=1.05-7.94).

Conclusion : We found that GSTT1 null genotype was associated with an increased risk of lung cancer in Korean female never-smokers. This result suggests that GSTT1 null genotype could be used as a biomarker for genetic susceptibility to lung cancer in Korean female never-smokers.

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