RESEARCH COMMUNICATION

Polymorphism in *GSTM1*, *GSTT1*, and *GSTP1* and Susceptibility to Lung Cancer in a Japanese Population

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Abstract

Polymorphisms in glutathione S-transferases (GSTs) may predispose to lung cancer through deficient detoxification of carcinogenic or toxic constituents in cigarette smoke, although previous results have been conflicting. Three *GST* polymorphisms (*GSTM1*, *GSTT1* and *GSTP1*) were determined among 86 male patients with lung carcinomas and 88 healthy male subjects. We found no significant increase in the risk of lung cancer for any genotypes for the nulled *GSTM1* [odds ratio (OR)=2.0; 95% confidence interval (95% CI)= 0.8-5.3], the nulled *GSTT1* (OR=2.0; 95% CI=0.8-5.1) or the mutated (the presence of a Val-105 allele) *GSTP1* (OR=0.96; 95% CI=0.4-5.5). The *GST* polymorphisms alone may thus not be associated with susceptibility to lung carcinogenesis in male Japanese. However, individuals with a concurrent lack of *GSTM1* and *GSTT1* had a significantly increased risk (OR=2.7; 95% CI=1.0-7.4) when compared with those having at least one of these genes. No other combinations were associated with lung cancer risk. These results suggest that there may be carcinogenic intermediates in cigarette smoke that are substrates for both GSTM1 and GSTT1 enzymes and that lung cancer risk is increased for individuals who are doubly deleted at *GSTM1* and *GSTT1* gene loci. Additional large studies are needed to confirm this observation.

Key words: lung cancer - genetic polymorphism - *GSTM1* -*GSTT1* - *GSTP1*

Asian Pacific J Cancer Prev, **1**, 293-298

Introduction

Polycyclic aromatic hydrocarbons (PAHs) are abundant in tobacco smoke and can be detoxified by glutathione S-transferase (GST) enzymes. GSTs are constitutively found in a wide variety of tissues, with different characteristic patterns of GST isozymes. *GST* genes form a superfamily of at least 13 genes consisting of five distinct families, named alpha (*GSTA*), sigma (*GSTS*), mu (*GSTM*), pi (*GSTP*) and theta (*GSTT*). The latter three are polymorphic in humans and the levels of individual enzymes expressed can be influenced by induction and by genetic polymorphism. Since these polymorphisms are considered in terms of risk from certain potentially carcinogenic chemicals, they are currently being investigated as possible cancer risk modifiers.

The GSTM1 enzyme catalyses the detoxification of genotoxins including aromatic hydrocarbon epoxides and products of oxidative stress such as DNA hydroperoxides (Smith et al. 1995; Heagerty et al., 1994). Similarly, the GSTP1 enzyme can utilize a variety of potential carcinogens, including cigarette smoke-derived chemicals such as benzo(a)pyrene diol epoxide and acrolein (Hayes and Pulford, 1995). The GSTT1 enzyme utilizes potential carcinogens including constituents of cigarette smoke such as alkyl halides (Pemble et al., 1994). As different GST isoemzyme are known to exhibit overlapping substrate specificities (Hayes and Pulford, 1995), deficiencies of GST isoenzyme may be compensated by other forms and utilization of alternative metabolic pathways.

The phenotypic absence of GSTM1 and GSTT1 activity

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is due to homozygosity for deletion of these genes, termed the null genotype (Seidegard et al., 1986; Pemble et al., 1994). The homozygous deletion of *GSTM1* gene has been shown to occur in approximately 50% of the populations of various ethnic origins (Kiyohara et al., 2000), while homozygous deletion of the *GSTT1* gene has distributed between 10 and 64 % in various ethnic groups (Kiyohara et al., 2000). The frequency of the *GSTT1* null genotype in Caucasian populations is 30% or less but that in Oriental populations may be similar to the frequency of the *GSTM1* null genotype.

Two genetic polymorphisms at the *GSTP1* locus result from a single base pair substitution in exon 5 (Ile105Val) and exon 6 (Ala114Val) (Harries et al., 1997). In vitro cDNA expression study suggests that substitution of these amino acid reduces enzyme activity (Zimniak et al., 1994). An amino acid substitution from isoleucine to valine at residue 105 in the *GSTP1* gene (Ile105Val), which reduces catalytic activity of the enzyme. The *GSTP1* polymorphism in exon 6 is less common than that in exon 5 (Yamamura et al., 2000). Individuals homozygous for the 105 valine allele (the mutant allele) are most common among African-Americans (19 %) and least common among Japanese (0-3.1 %) with Caucasians (6.5-11.7 %) intermediate between these groups (Yamamura et al., 2000).

GSTM1 or *GSTT1* deficiency may be a moderate risk factor for lung cancer development. The association between those polymorphisms and lung cancer risk has been controversial in the published literature, however. On the other hand, less is known about the association between cancer risk and *GSTP1* polymorphisms. *GSTP1* seems a more likely candidate susceptibility gene because it is expressed at high levels in the lung (Sundberg et al., 1993; Terrier et al., 1990). However, no potentiation between the mutant genotype for lung cancer risk was suggested (Harris et al., 1998; Katoh et al., 1999; To-Figueras J. et al.1999). As GSTM1, GSTT1 and GSTP1 enzymes are involved in the detoxification of mechanism of PAHs , it would be plausible that the genetic polymorphisms of these enzymes interact to enhance the host susceptibility to lung cancer.

Since *GSTP* polymorphisms alone might not likely predispose to lung cancer, we investigated whether doubly or triply concurrent mutation for *GST* genes may be a risk factor for lung cancer development.

Materials and Methods

Subjects and Sample Collection

Eighty-eight Japanese healthy male volunteers and 86 primary lung cancer male patients (adenocarcinoma=40, squamous cell carcinoma=24, small cell carcinoma =12, large cell carcinoma=4), were newly diagnosed at Kyushu University Hospital (Research Institute for Diseases of Chest, Kyushu University) by histology and cytology during August 1995 - August 1996 and included in the present study after giving informed consent. Information about smoking habit, drinking habits, family history of cancer, possible occupational exposure and medication was gathered from both the patients and controls. Heparin (40 IU/ml) was used as an anticoagulant and the blood was generally processed within 2 to 3 hr after collection (time of blood collection: 9:00-10:00 a.m. or 12:00-13:00 p.m.). Characteristics with respect to age, Brinkman index (number of cigarettes smoked per day multiplied by number of years of smoking) and prevalence of smokers among lung cancer patients and healthy controls are summarized in Table 1.

Genotyping

DNA was isolated from peripheral blood samples (about 7 ml). For *GSTM1* and *GSTT1*, duplex PCR was performed for 30 cycles of 1 min at 94 °C for denaturation, 1 min at 50 °C for primer annealing and 1 min at 72 °C for primer extension. Other conditions were as described by Zhong et al. (1991) or Pemble et al. (1994). Both *GSTM1* and *GSTT1* genotypes are divided into two categories in relation to enzymatic activity. Lack of activity is caused by the homozygous deletion of an intact gene (the null genotype). The non-null genotype is wild-type or heterozygote. The genotype of *GSTP1* at exon 5 was basically identified as a restriction fragment length polymorphism by means of the PCR (Harries et al., 1997). PCR was performed for 30 cycles of 1 min at 94 °C for denaturation, 1 min at 53 °C for primer annealing and 1 min at 72 °C for primer extension. The genotype designated Ile/Ile is a predominant homozygote, in which the *BsmA* I (New England Biolabs, Beverly, MA) site is absent at base 1578. A homozygous rare allele was named genotype Val/Val, being derived from one base substitution of A with G to form the *BsmA* I site. Genotype Ile/Val is heterozygous for both alleles.

Table 1. Characteristics of the Study Subjects

	Mean age (range)	Prevalence of smokers	Brinkman index Median (range)
Controls (88)	59.0 (20-77)	45.5	0 (0-1000)
All patients (86)	63.8 (35-86)	68.6	500 (0-2400)
Kreyberg I (40)	67.0 (49-76)	82.5	990 (0-2400)
Kreyberg II (46)	59.3 (35-79)	56.5	190 (0-2100)

Table 2. Frequencies of Mutant Genotypes of *GST* Genes

Mutant genotype (%)	*GSTM1* [a]	*GSTT1* [a]	*GSTP1* [b] + *GSTT1*	*GSTM* + *GSTP1*	*GSTM* + *GSTP1*	*GSTT1*
Controls (88)	49 (55.7)	39 (44.3)	26 (29.5)	24 (27.3)	16 (18.2)	12 (13.6)
All patients (86)	53 (61.6)	47 (54.6)	25 (29.1)	31 (36.1)	20 (23.3)	14 (16.3)
Kreyberg I (40)	24 (60.0)	21 (52.5)	13 (32.5)	11 (27.5)	11 (27.5)	7 (17.5)
Kreyberg II (46)	29 (63.0)	26 (56.5)	12 (26.1)	20 (43.5)*	9 (19.6)	7 (15.2)

a Null genotype
b Those having at lesat one mutant allele of GSTP1 gene
* As compared with control subjects, p=0.081

Table 3. Age and Smoking Status-Adjusted Odds Ratio and 95% Confidence Intervals

	Adjusted OR and 95% CI		
	GSTM1 [a]	*GSTT1* [a]	*GSTP1* [b]
Healthy controls (88)	1.0 (reference)	1.0 (reference)	1.0 (reference)
All patients (86)	2.00 (0.76-5.49)	1.99 (0.78-5.08)	0.96 (0.36-5.54)
Kreyberg I (40)	2.84 (0.59-13.61)	2.68 (0.61-11.85)	2.10 (0.46-9.58)
Kreyberg II (46)	1.87 (0.68-5.09)	1.96 (0.74-5.14)	0.84 (0.30-2.38)

a Null genotype
b Those having at least one mutant allele of the *GSTP1* gene

Statistical Analysis

Statistical analysis was performed with the Windows-SAS statistical package (SAS Institute Inc., Cary, NC). Smoking status was divided into two categories, non-smokers and current smokers; the former was combined with former smokers, who had quit more than 1 year ago, and never smokers. Statistical adjustment was made for smoking status and age. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated from logistic regression coefficients and standard errors for the corresponding indicator variables (SAS Institute Inc., 1996). All the P values are two-sided and P values < 0.05 were considered statistically significant.

Results

As shown in Table 2, the frequency of the *GSTM1* null individuals among lung cancer patients increased to 61.6 % compared to with the healthy controls (55.7 %); however, this difference did not reach statistical significance. The frequency of the *GSTT1* homozygous null genotype in healthy controls was 44.3%. This frequency was increased to 54.6 % in lung cancer patients but this increase was not significant. For *GSTP1* polymorphism, there was two individuals homozygous for the Val-105 allele among the patients while no individuals were detected among the controls. In the controls, 70.5% of individuals were homozygous and 29.5% were heterozygous for the Ile-105 allele. In the cases, the figures were 70.9 %, 26.7 % and 2.3 % respectively. The prevalence of the concurrent deficiency of both *GSTM1* and *GSTT1* genes did not significantly differ between the controls (27.3 %) and the patients (36.1 %). However, there was a borderline significant overrepresentation of concurrent lack of those genes among the patients with Kreyberg II lung cancer (43.5 %) when compared with the controls with those genotypes (p=0.08).

Both *GSTM1* (OR=2.00, 95% CI=0.76-5.49) and *GSTT1* (OR=1.99, 95% CI=0.78-5.08) polymorphism had a doubled, although not significant, risk for lung cancer (Table 3). Adjusted ORs for the mutated genotype in *GSTP1* polymorphism did not differ from unity. The effect of the genotype was somewhat different between the patients with Kreyberg I lung cancer and those with Kreyberg II lung cancer.

Tobacco smoke is known to contain multiple substrate for *GSTM1*, *GSTT1* and *GSTP1*. Individuals with having a defective genotype for more than one of theses genes can thus be expected to be at greater risk for lung cancer than those having a defective genotype of only one gene. Individuals with concurrent lack of *GSTM1* and *GSTT1* genes had a 2.7-fold risk (95%CI=1.00-7.39) when compared with carriers of at least one wild-type gene (Table 4). This effect was also found in the patients with Kreyberg II lung cancer

Table 4. Lung Cancer Risk and the Combined Genotypes

	Adjusted OR and 95% CI		
	GSTM1[a] + *GSTT1*[a]	*GSTM1* + *GSTP1*[b]	*GSTT1*[a] + *GSTP1*[b]
Healthy controls (88)	1.0 (reference)	1.0 (reference)	1.0 (reference)
All patients (86)	2.71 (1.00-7.39)	1.37 (0.47-4.00)	0.94 (0.28-3.15)
Kreyberg I (40)	2.27 (0.46-11.09)	3.15 (0.59-16.79)	1.41 (0.25-8.13)
Kreyberg II (46)	2.86 (1.03-7.96)	1.22 (0.39-3.88)	0.83 (0.22-3.05)

a Null genotype
b Those having at lesat one mutant allele of the *GSTP1* gene

(OR=2.86, 95% CI=2.03-7.96). Adjusted ORs did not statistically differ in any other combinations of GST polymorphisms. It is not possible to combine the three mutated genotypes to estimate the cancer risk due to the limited number of study subjects. As for concurrent lack of *GSTM1* and *GSTT1* genes, the cancer risk was higher among the patients with Kreyberg II lung cancer than those with Kreyberg I lung cancer.

Discussion

The molecular epidemiology of cancer involves the use of biomarkers of exposure and response in studies of exogenous or endogenous agents and/or host factors that play a role in its etiology. This approach has the potential for identifying susceptible individuals. Individual differences in genetic susceptibility to lung cancer may be partly accounted for by the activity of the drug-metabolizing enzyme GSTs.

The frequencies of the *GSTM1* and *GSTT1* null genotype, around 50% each, among healthy controls were comparable to those among other Japanese populations (Kihara et al., 1993; Katoh et al., 1996). We did not find any individuals with Val-105 in healthy controls. The population frequency of the Val-105 variant had been reported in several recent reports (Watson et al., 1998; Kihara et al., 1999; Katoh et al., 1999; Yamamura et al., 2000). Asian populations have been reported to have a low Val-105/Val-105 genotype frequency; Japanese populations have 0-4.1 % for the mutant homozygote (Kihara et al., 1999; Katoh 1999; Yamamura et al.,2000); Caucasian populations had 6.5-11.7 % for the genotype (Yamamura et al., 2000).

We found a somewhat large, nonsignificant association (OR of about 2.0) of the *GSTM1* polymorphism and lung cancer risk. This figure is consistent with the studies in Japanese populations (Kihara et al, 1993; Kihara et al., 1994). The first study (Seidegard et al., 1990) reported increased frequency (63.4 %) of the *GSTM1* null phenotype in smokers with lung cancer (particularly adenocarcinoma) compared with controls (41.7 %). These data were not supported by a study showing similar frequencies of the *GSTM1* null genotype in controls and cases; a negative correlation with adenocarcinoma; and a positive association between the *GSTM1* null genotype and squamous cell cancer (Zhong et al., 1991). While the influence of the *GSTM1* polymorphism on susceptibility to lung cancer has been evaluated in a number of published studies, some data are conflicting and the significance of the polymorphism remains unclear. Recent meta analyses indicate that the null genotype confers a small but significant increased risk of 1.40 (McWilliams et al., 1995) or 1.13 (Houlston, 1999).

Individuals with the *GSTT1* null genotype had a doubled, although not significant, risk for lung cancer. This finding is in agreement with other studies (Deakin et al., 1996; Jourenkova et al., 1997; To-Figueras et al., 1997; Saarikoski et al., 1998). There is less information on the role of the *GSTP1* gene as a cancer risk modifier. Given that *GSTP1* is the most abundant isoform in the lungs (Anttila et al., 1993), it is anticipated to be of particular importance in the detoxification of inhaled carcinogens. The data here reported do not show significant differences between the lung cancer patients and the controls. It was suggested that the *GSTP1* polymorphism in exon 5 did not increase the risk of lung cancer (Katoh et al., 1999; To-Figueras et al., 1999).

Because carcinogenic intermediates in cigarette smoke are substrates for GSTM1, GSTT1 and GSTP1 enzymes, lung cancer risk is increased for individuals with combined susceptible genotypes. In this study, the adjusted OR for individuals who were doubly deleted at *GSTM1* and *GSTT1* gene loci was 2.71 (Table 4). A significant association was also observed for concurrent lack of the *GSTM1* and *GSTT1* genes and susceptibility to squamous cell carcinoma (Saarikoski et al., 1998). For that cell type, the risk was 2.3-fold (95% CI=1.0-5.3) when compared with that of individuals having other genotype combinations. In contrast, that genotype combination did not affect the risk for other histological types of lung cancer (Saarikoski et al 1998). Kelsey et al. (1997) also showed that the OR for the association of lung cancer and the presence of both null polymorphisms compared with one (either *GSTT1* or *GSTM1*) or no null genotype to be 2.9 (95% CI=1.1-7.7). However, these findings are in contrast to some previous

studies, in which no association between the concurrent lack of these genes and susceptibility to lung cancer was observed (Deakin et al., 1996; To-Figueras et al., 1997). Unexpectedly, the cancer risk for concurrent lack of the *GSTM1* and *GSTT1* genes was higher among the patients with Kreyberg II lung cancer than those with Kreyberg I lung cancer (Table 4). This result may have arisen by chance due to our limited small sample size and somewhat biased sample.

Because the effect of metabolic genotypes on lung cancer susceptibility has been suggested to depend on the extent of exposure to tobacco smoke (London et al., 1995; Rebbeck et al., 1997), we examined the prevalence of the mutated *GST* genotypes in 2 groups (Brinkman index ≥300 vs. < 300). Unfortunately, a limitation of our study, i.e., a low degree of overlap of the distribution of Brinkman index between the cases and the controls, restricted us from properly evaluating the potential differences in lung cancer risk between different smoker categories (data not shown). In addition, when study subjects were divided into two subgroups based on smoking status, (smokers vs. non-smokers), the impact of concurrent lack of the *GSTM1* and *GSTT1* genes was similar between tow subgroups (data not shown). This suggests that individuals with concurrent lack of the *GSTM1* and *GSTT1* genes are at a high risk factor for lung cancer, but smoking may not play a role in this relationship.

Despite many studies published to date, the role of GST genes in lung cancer susceptibility remains unclear. The resolution of this ambiguity will require carefully designed studies with sufficient sample sizes to detect small effects. The potentially high attributable risk associated with *GSTM1* (irrespective of ethnic origin) or *GSTT1* (in Asian populations) suggest that these genes are important candidates for studies that attempt to understand the complex and multifactorial etiology of lung cancer in the general population. However, studies that specifically evaluate the utility of these genotypes in lung cancer risk prediction have yet to be conducted. Such studies are crucial to establish the value of *GST* genes in lung cancer prevention or control strategies.

Acknowledgments

We wish to thank Professor S. Kono (Department of Preventive Medicine, Graduate School of Medical Sciences, Kyushu University) for his helpful advice. This work was supported in part by a Grant-in-Aid from the Ministry of Education, Science and Culture (09670361).

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Born in Fukuoka, Kyushu, Japan in 1958, she graduated from the Department of Applied Genetics and Pest Management, Faculty of Agriculture, Kyushu University in 1980. After obtaining her M.Sc. degree in 1982 at the Graduate School of Bioresources and Bioenvironmental Sciences, Kyushu University, she went on to be awarded her Ph.D. degree in 1990 at the Graduate School of Medical Sciences, Kyushu University .

Dr Kiyohara studied cancer epidemiology under the supervision of Professor Tomio Hirohata (who she looks up as a great scientist, instructor and private individual) and is now very interested in the molecular epidemiology of lung cancer.

Actually she has another first name, 'SOMEKA', SOME originating from the name of her flower arrangement mistress, combined with KA from her real name, Chikako. Among the many schools of flower arrangement, Sogetsu is one of the most modern. Dr Kiyohara took lessons from a Sogetsu school in flower arrangement for a long time. SOMEKA was awarded when her skill improved. Reminiscent of the arts of a geisha, the name has character and she would be pleased to be called SOMEKA when you happen to see her at a meeting.

For the forthcoming new century, she is concerned about what kind of materials to choose and how to produce excellent work in both flower arrangement† and research.