

## RESEARCH COMMUNICATION

# **hOGG1, p53 Genes, and Smoking Interactions are Associated with the Development of Lung Cancer**

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### **Abstract**

This study aimed to investigate the effects of Ser/Cys polymorphism in *hOGG1* gene, Arg/Pro polymorphism in *p53* gene, smoking and their interactions on the development of lung cancer. Ser/Cys polymorphism in *hOGG1* and Arg/Pro polymorphism in *p53* among 124 patients with lung cancer and 128 normal people were detected using PCR-RFLP. At the same time, smoking status was investigated between the two groups. Logistic regression was used to estimate the effects of Ser/Cys polymorphism and Arg/Pro polymorphisms, smoking and their interactions on the development of lung cancer. ORs (95% CI) of smoking, *hOGG1* Cys/Cys and *p53* Pro/Pro genotypes were 2.34 (1.41-3.88), 2.12 (1.03-4.39), and 2.12 (1.15-3.94), respectively. The interaction model of smoking and Cys/Cys was super-multiplicative or multiplicative, and the OR (95% CI) for their interaction item was 1.67 (0.36 -7.78). The interaction model of smoking and Pro/Pro was super-multiplicative with an OR (95% CI) of their interaction item of 5.03 (1.26-20.1). The interaction model of Pro/Pro and Cys/Cys was multiplicative and the OR (95% CI) of their interaction item was 0.99 (0.19-5.28). Smoking, *hOGG1* Cys/Cys, *p53* Pro/Pro and their interactions may be the important factors leading to the development of lung cancer.

**Keywords:** *hOGG1* gene - lung cancer - smoking - gene polymorphism - genetic susceptibility

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### **Introduction**

Lung cancer is one of the most common malignant tumors, and it is also one of the key foci of cancer research in the world. As we know, even in the same environment, some people may suffer from lung cancer whereas some may not. Thus, the initiation of lung cancer is somehow associated with different susceptibilities from individual to individual. To date, apart from the definite role played by smoking in leading to lung cancer, the role played by hereditary susceptibility has also attracted more and more attention. And in hereditary susceptibility, studies mainly focus on gene polymorphisms of carcinogen-metabolizing enzymes and DNA repair enzymes.

DNA damage and repair play an important role in the process of cellular canceration. DNA repair refers to a series of cellular reactions by which the DNA sequence structure is restored to normal and relatively stable genetic information is maintained. During the whole evolutionary process, a variety of prevention mechanisms have been formed in cells to deal with DNA damage on a large scale and bulky adducts. DNA repair-related enzymes and proteins were encoded by multiple genes, and mutations of those genes or their polymorphisms among population can lead to a low DNA repair ability or defect. Individuals with a lower DNA repair ability than the average level is more susceptible to tumors (Paz-Elizur et al., 2003). Therefore,

a low DNA repair ability caused by polymorphism of the DNA repair-related gene may be an important factor determining the hereditary susceptibility to lung cancer. Smoking is an important risk factor for the initiation of lung tumor. The active oxygen in cigarette smoke can induce DNA base radical injuries. As the production of 8-hydroxyguanine (8-OH-G) is mainly associated with active oxygen as well as the free radicals, it is regarded as the marker of DNA oxidative injuries. Cells can repair 8-OH-G via the base excision repair channel, and if the repair can't be done, cellular apoptosis avoid the mutations which may lead to the initiation of tumors. Therefore, polymorphisms of these repair-related genes may affect the repair ability, which, in turn, affect the susceptibility to lung tumor.

Human 8-hydroxyguanine glycosylase (*hOGG1*) is one type of DNA repair enzymes, and has the functions of specifically excising 8-OH-G and repairing the injured DNA. C/G polymorphism of *hOGG1* within base 1245 of exon 7 enables the 326 codon encoded as serine (Ser) or Cysteine (Cys). The activity of *hOGG1*-Cys326 protein in repairing 8-OH-G is notably lower than that of *hOGG1*-Ser326 (Kim et al., 2004), indicating that individuals with 326Cys alleles may suffer from a low repair ability or repair defect, and as consequence, they are probably more susceptible to tumors.

*p53* is an important gene responsible for cell cycle

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control and apoptosis, and one of its key role is repairing the cells with injured DNA or inducing their apoptosis. CGC/CCC polymorphism of *p53* within codon 72 of exon 4 can lead to the change in amino acids from arginine (Arg) to proline (Pro) (Cañas et al., 2009), which is probably related to the hereditary susceptibility to tumors.

Apart from the polymorphisms of different genes, the effects of gene-environmental interactions on diseases have also become the hotspots of studies nowadays. Interaction effects can be analyzed by using different statistical methods. Though stratified analysis is one of the most commonly used methods today, it does have some drawbacks. And compared with stratified analysis, crossover table analysis can provide more relevant information by the analyses of the effects of separate different risk factors as well as their interactions.

Recent years has also seen disagreements in conclusions drawn from studies on the relationship between the polymorphism of *p53* and lung cancer. In this study, the analyses of genotypes in lung cancer patients and the normals from Henan (China) were carried out using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method, and smoking status among these people was investigated in order to explore the relationships between the polymorphisms of *hOGG1* and *p53* genes, smoking and lung cancer. Meanwhile, crossover table analyses were implemented for the interaction models among different risk factors.

## Materials and Methods

### Subjects

A total of 124 tissue samples were collected from patients from January to January, 2010, Which were diagnosed lung cancer from Henan Han people, including 101 males and 23 females, Whose ages rang from 32 to 80 with the mean age of  $59.03 \pm 10.33$ . According to the pathological classification of WHO, 76 cases were diagnosed as squamous carcinoma, and 48 as adenocarcinoma. According to 2009 P-TNM staging standards of IUCC, 38 cases were in Stage I, 50 in Stage II and 36 in Stage III, among which 78 cases were with lymph node metastasis and 90 cases smoked > 400 cigarettes per year. All of these patients hadn't undergone any radiation or chemical therapy before operation, without other malignant tumor history. Meanwhile 126 peripheral blood samples of healthy people from Henan Han people were collected as controls.

All the patients gave a complete history. All samples and data used in this study were maintained in accordance with institutional patient care, quality assurance polices. The use of the data for this study was reviewed and approved by the the Ethics Committee of Zhengzhou University, Written informed consent was obtained from all participants. All procedure were in accordance with the recommendation found in the Helsinki Declaration of 1975

### Genotype detection

DNA was extracted from the peripheral blood lymphocytes or the samples of excised lung cancer tissues.

Genotypes were detected by PCR-RFLP. PCR primers for Ser 326Cys of *hOGG1* and Arg/Pro of *p53* were designed by Primer premier 5.0 software based on DNA sequences provided by the Genebank. The sequences of upstream and downstream primers of *hOGG1* was 5'-TGG ATT CTC ATT GCC TTC GG-3' and 5'-CCT CCT CAC CTG CTT CCC TA-3'. In the PCR conditions, an initial pre-denaturation was done at 95 °C for 3 min, followed by 35 cycles at 95 °C for 30 s, 58 °C for 30 s and 72 °C for 30 s, and then a final exposure to 72 °C for 10 min. 6 µl PCR products were digested with 5U *SatI* in 20 µl reaction system at 37 °C overnight. The upstream and downstream primers of *p53* were 5'-GTC CCA AGC AAT GGA TGA T-3' and 5'-CAA AAG CCA AGG AAT ACA CG-3'. In the PCR conditions, an initial pre-denaturation was done at 95 °C for 3 min, followed by 35 cycles at 95 °C for 30 s, 55 °C for 30 s and 72 °C for 30 s, and then a final exposure to 72 °C for 10 min. 4µl PCR products were digested with 5 U *Bsh1236I* in 20 µl reaction system at 37 °C overnight. Fragments of digestion products were isolated by 2% agarose gel electrophoresis, and then analyzed by Bio Imaging System for image analyses and aim band detections.

### Statistical analysis

Data were analyzed by SPSS10.0 software. Genetic equilibrium of the control group was determined by Hardy-Weinberg equilibrium test, different smoking distributions among the patients and healthy people were detected by  $\chi^2$  test, and the odds ratios (ORs) and confidence intervals (CIS) by Logistic regression were utilized for the risk evaluations and interaction model analyses. All statistical tests were double side ratio tests with  $\alpha=0.05$ .

Interaction models were analyzed by crossover table method (Table 1). Specifically, risk factors A and B, and their interaction item as independent variables were brought into Logical regression model to test whether there was an interaction effect or not. And whether the interaction model of A and B fitted the multiplicative model was evaluated based on OR interaction item and its significance. The evaluation standards were as follows: OR = 1 means that the interaction model is subjected to the multiplicative model without interaction effect; OR > 1 means the interaction model belongs to a super-multiplicative model with an interaction effect; and OR < 1 means the interaction model is a secondary-multiplicative model with an interaction effect.

## Results

### General data

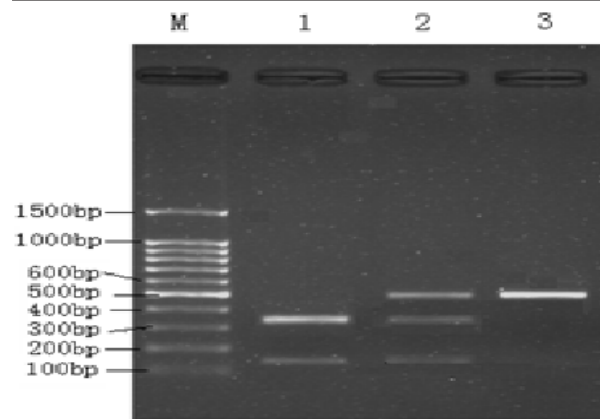
In this study, the lung cancer group with 124 patients including 101 males and 23 females, and their age ranged from 32 to 80 years old with the mean age of  $59.03 \pm 10.33$ . The control group with 128 healthy people including 100 males and 28 females, and their age ranged from 35 to 83 with the mean age of  $58.23 \pm 9.19$ . There were no significant differences in age and sex between two groups ( $P > 0.05$ ).

**Table 1. The Interaction Risks Analyzed by Crossover Table Method**

Exposure factor A	Exposure factor B	The controls	Patients	OR	Reaction information
-	-	a	b	1	Common controls
+	-	c	d	ORA	Effect of A alone
-	+	e	f	ORB	Effect of B alone
+	+	g	h	ORAB	Interaction effect of A and B

**Table 2. The Relationships Between Exposure Factors and the Risk of Lung Cancer**

Exposure	The cases		The controls		OR (95% CI)	$\chi^2$	P
	Exposure	non-exposure	Exposure	non-exposure			
Smoking	80	44	56	72	2.34(1.41~3.88)	10.77	0
hOGG1Cys/Cys	24	100	13	115	2.12(1.03~4.39)	4.25	0.04
p53Pro/Pro	35	89	20	108	2.12(1.15~3.94)	5.86	0.02

**Figure 1. The Electrophoresis Results of hOGG1 Amplified Fragments after Digestion.** M: DNA molecular weight standard; Lane 1, 2 and 3: Cys/Cys, Ser/Cys and Ser/Ser genotypes, respectively

#### PCR amplification results

After genomic DNA was extracted from tissues and whole blood by kit, the electrophoresis result showed bright and clear bands, indicating genomic DNA was effectively extracted and no fragmentation of DNA happened during the process

*hOGG1* was amplified by PCR method. The products were detected by 2% agarose gel electrophoresis, and the results showed that specific bands of 505bp were obtained, which were consistent with those expected.

*p53* was amplified by PCR method. The products were detected by 2% agarose gel electrophoresis, and the results showed that specific bands of 551bp were obtained, which were consistent with those expected.

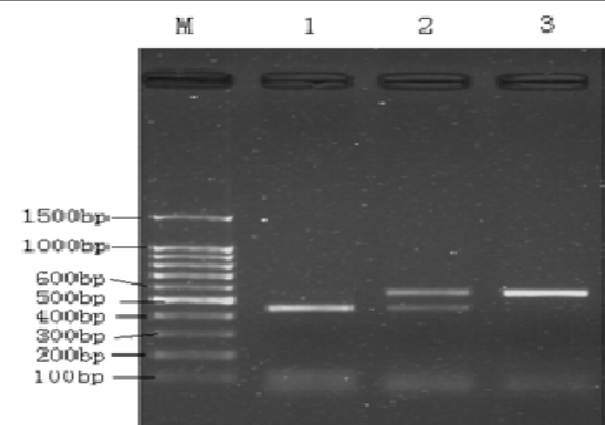
#### Genotype detection

*hOGG1* was amplified by PCR method. The products were detected by 2% agarose gel electrophoresis, and the results showed that specific bands of 505bp were obtained. After digestion, three different kinds of electrophoresis bands were obtained. Ser/Ser genotype generated one fragment of 505bp, Cys/Cys genotype generated two fragments of 153bp and 352bp because of the addition of an extra enzyme site caused by its mutation, and Ser/Cys genotype generated three fragments of 153bp, 352bp and 505bp (Figure 1).

*p53* was amplified by PCR. The products were

**Table 3. The Interaction of Cys/Cys Genotype and Smoking and the Risk of Lung Cancer**

Cys/Cys	Smoking	Cont-rols	cases	OR (95% CI)	$\chi^2$	P
-	-	63	35	1		
+	-	9	9	1.80(0.65~4.95)	1.3	0.26
-	+	52	65	2.25(1.30~3.90)	8.32	0
+	+	4	15	6.75(2.08~21.92)	10.1	0

**Figure 2. The Electrophoresis Results of p53 Amplified Fragments after Digestion.** Lane M: DNA molecular weight standard; Lane 1, 2 and 3: Arg/Arg, Arg/Pro and Pro/Pro genotypes, respectively

detected by 2% agarose gel electrophoresis, and the results showed that specific bands of 551bp were obtained. After digestion, three different kinds of electrophoresis bands were obtained. Pro/Pro genotype generated one fragment of 551bp because of the loss of an enzyme site, Arg/Arg genotype generated two fragments of 108bp and 443bp, and Arg/Pro genotype generated three fragments of 108bp, 443bp and 551bp (Figure 2).

Hardy-Weinberg genetic equilibrium test among the controls showed that the genotypic frequencies at Ser/Cys and Arg/Pro sites both met the genetic equilibrium standard ( $P > 0.05$ ). Therefore, the controls in this study can be considered representative among population.

#### Genotype and the risks of lung cancer

The comparison of smoking status between the sample group and the control group was made using  $\chi^2$  test. The result showed that there was statistically significant difference between two groups ( $P < 0.01$ ), and OR (95% CI) of smokers was 2.34 (1.41-3.88). The comparison of *hOGG1* Cys/Cys distribution between two groups showed the difference was statistical significant ( $P < 0.01$ ), and OR (95% CI) was 2.12 (1.03 - 4.39). The comparison of *p53* Pro/Pro distribution showed that there was a significant difference between two groups ( $P < 0.01$ ), and OR (95% CI) was 2.12 (1.15 - 3.94). The analyses of the relationships of smoking, Cys/Cys and Pro/Pro with the

**Table 4. The Interaction of Pro/Pro Genotype and Smoking and the Risk of Lung Cancer**

Pro/Pro	Smoking	Controls	Cases	OR(95%CI)	$\chi^2$	P
-	-	57	35	1		
+	-	15	9	0.98 (0.39~2.47)	0	0.96
-	+	51	54	1.72 (0.98~3.05)	3.78	0.05
+	+	5	26	8.47(2.98~24.09)	15.37	0

**Table 5. The Interaction of Pro/Pro and Cys/Cys Genotypes and the Risk of Lung Cancer**

Pro/Pro	Cys/Cys	controls	Cases	OR(95%CI)	$\chi^2$	P
-	-	98	74	1		
+	-	17	26	2.03(1.02~4.01)	4.12	0.04
-	+	10	15	1.99(0.85~4.67)	2.47	0.16
+	+	3	9	3.97(1.04~15.19)	4.07	0.04

risk of lung cancer were seen in Table 2.

#### Analyses of the interaction models

Nonsmokers with non-Cys/Cys genotypes were taken as the controls. The relative risks of Cys/Cys alone, smoking alone and their interaction were respectively calculated, and the interaction effect of Cys/Cys and smoking on lung cancer was analyzed. Cys/Cys, smoking and their interaction item as independent variables were taken into Logistic regression model to detect whether there was an interaction or not. The results indicated that the ORJ (95% CI) of the interaction item was 1.67 (0.36 – 7.78) and the interaction model was multiplicative ( $P > 0.05$ ). The interaction of smoking and Cys/Cys was seen in Table 3.

Nonsmokers with Non-Pro/Pro genotypes were taken as the controls. The relative risks of Pro/Pro alone, smoking alone and their interaction were respectively calculated, and the interaction effect of Pro/Pro and smoking on lung cancer was analyzed. Pro/Pro, smoking and its interaction item as independent variables were taken into Logistic regression model to detect whether there was any interaction or not. The results indicated that the ORJ (95% CI) of the interaction item was 5.03 (1.26 – 20.11) and the interaction model of Pro/Pro and smoking was super-multiplicative ( $P > 0.05$ ). The interaction of smoking and Pro/Pro was seen in Table 4.

Non-Cys/Cys plus non-Pro/Pro genotypes were taken as the controls to respectively calculate the relative risks of Pro/Pro alone, Cys/Cys alone and their interaction. The interaction effect of Pro/Pro and smoking on lung cancer was analyzed. Pro/Pro, Cys/Cys and their interaction item as independent variables were taken into Logistic regression model to detect whether there was any interaction. The results indicated that the ORJ (95% CI) of the interaction item was 0.99 (0.19 – 5.28), which showed there was no interaction between them, and the interaction model of Pro/Pro and Cys/Cys was multiplicative ( $P > 0.05$ ) (Table 5).

## Discussion

Lung cancer is one of the most common malignant tumors in the world, and it is counted as the most

threatening malignant tumor to human health and life nowadays. Smoking is a key risk factor for the initiation of lung cancer, because the active oxygens in cigarette smoke can induce DNA base injuries. Cells can repair these injuries, and if the repair can't be done, they can induce cellular apoptosis to avoid mutations which may lead to tumors. Therefore, the polymorphisms of repair-related genes in cells may affect the repair ability, which, in turn, affect the susceptibility to lung tumor. *hOGG1* is a key DNA injury-repairing gene and *p53* is an important gene responsible for cell cycle control and cellular apoptosis. Both of them are closely related to DNA repair. Ser/Cys and Arg/Pro are the polymorphism sites of *hOGG1* and *p53*, respectively. Thus, the possible functional differences among proteins encoded by different polymorphism genes are very likely to influence the susceptibility to diseases.

Many studies support that Cys/Cys genotype is the risk genotype of lung cancer. The risks of exposure to adenocarcinoma of lung and small cell lung cancer were obviously higher among individuals with Cys/Cys genotype than those with Ser/Cys or Ser/Ser (Okasaka et al., 2009). Individuals with Cys/Cys genotype had a higher risk of lung cancer than those with Ser/Cys or Ser/Ser (Le Marchand et al., 2002). Cys/Cys genotype notably increased the risk of lung cancer among the white smokers with an OR value up to 4.9 (Park et al., 2004). However, some studies hold a different view. Polymorphism had no relation with the risk of adenocarcinoma of lung among Japanese (Ito et al., 2002; Sunaga et al., 2002). It bore no correlation with lung cancer among Danes (Vogel et al., 2004). However, Guan et al found that the *hOGG1* Ser326Cys polymorphism might contribute to the risk of non-small cell lung cancer in the Asian population (Guan et al., 2011).

Our results proved that Cys/Cys genotype is the risk genotype of lung cancer. The risk of lung cancer among Henanese with Cys/Cys is 2.12 (1.03 - 4.39) times high of that among Henanese with Ser/Ser or Ser/Cys genotype. These results are similar with the previous studies (Chang et al., 2009; Liu et al., 2010).

The relationship between the polymorphism of *p53* and lung cancer has also attracted lot of attention. The risk factors of lung cancer among Japanese smokers were correlated with the polymorphism of *p53* (Kiyohara et al., 2010), hold that Pro alleles of *p53* gene can increase the risk of lung cancer, especially that induced by smoking. Compared with Arg/Arg genotype, Pro/Pro genotype was a susceptible factor of small cell lung cancer among Chinese northerners (sex, age and smoking status adjusted OR = 2.30), and it was the risk factor independent on smoking (Kiyohara et al., 2010).

On the other hand, some hold that Pro alleles are the outcomes of the protective genes. A study conducted in Greek showed Arg homozygote of *p53* within codon 72 was correlated with lung cancer, Arg/Arg genotype of *p53* could increase the risk of lung cancer ( $P < 0.002$ ), and Arg alleles tended to be better preserved when the loss of heterozygosity occurred (Zhang et al., 2003).

Our results showed Pro genotype is a risk factor for lung cancer, and Pro is a hereditary susceptible factor (OR 2.12; 95% CI 1.15).



In addition, the interaction of related genes and environmental factors has also become a hotspot of research at present. In this study, the relative risks of Cys/Cys alone, smoking alone and their interaction were respectively detected, taking non-smokers with non-Cys/Cys genotypes as the controls. The results showed that the interaction model was multiplicative, and the interaction had no statistical significance ( $P > 0.05$ ). However, taking these factors into consideration such as OR (1.67) and 95% CI (0.36 - 7.78), a small number of samples on each stratum after stratification, more samples needed for statistical tests when there is an interaction, etc, there is still the possibility of an interaction, whose model belongs to a super-multiplicative model. Whether or not, an increased number of samples for further tests seem viable.

The relative risks of Pro/Pro genotype alone, smoking alone and their interaction were respectively detected, taking non-smokers with non-Pro/Pro genotypes as the controls. The results showed that the OR (95% CI) of the interaction item was up to 5.03 (1.26 - 20.11), which confirmed that there is an interaction and the interaction model is super-multiplicative. From the perspective of different risk degrees, the Pro/Pro alone has no effect on the initiation of lung cancer (OR 0.98). However, when there co-exists the environmental factor of smoking, Pro/Pro genotype will play an effect modification role for smoking, and their interaction has a far more severe effect on the initiation and development of lung cancer than smoking alone.

Because of many influencing factors associated with lung cancer, more and more related genes have fallen into the scope of studies on lung cancer. In addition, as the effect of the polymorphism of a single gene is always minute, it is often necessary to combine multiple genes and environmental factors to give a more comprehensive and effective evaluation to the susceptibility to lung cancer. The OR (95% CI) among Caucasians with GSTP1 GG + p53 Arg/Pro or Pro/Pro is adjusted to 1.99 (1.12 - 3.53) compared to those with wild type genes, and even more, among those under 55, the OR (95% CI) reaches as high as 5.10 (1.42 - 18.30) (Miller et al., 2002). The risk of adenocarcinoma among people with p53 Pro genotype and GSTM1 null genotype is 1.80 (1.1- 2.8) times high of that of squamous cancer, indicating that the interaction of p53 and GSTM1 can increase the subtype morbid risk of specific pathological types of non-small cell lung cancer. The polymorphism of p53 can increase lightly the risk of lung cancer among smokers with GSTM1 null genotype, and the OR (95% CI) of the interaction of GSTM1 absense and Pro/Pro or Arg/Pro is 1.97 (1.03 - 3.73) compared to the interaction of GSTM1 and Arg/Arg genotypes (Klinchid et al., 2009).

To the best of our knowledge, though there have been a lot of reports concerning interactions of genes and environmental factors released till now, studies on the interaction of Ser326Cys polymorphism of *hOGG1* and Arg/Pro polymorphism of p53 still remain unreported. Thus, in this study, the interaction of Ser326Cys polymorphism and Arg/Pro polymorphism were detected, and the effect of their interaction on the hereditary susceptibility to lung cancer was analyzed. The results

of Logistic regression analyses displayed that the ORs (95% CI) of Pro/Pro genotype alone, Cys/Cys alone and their co-existence showed that the interaction model of Pro/Pro and Cys/Cys was multiplicative and there was no interaction ( $P < 0.05$ ) between these two genotypes ( $P > 0.05$ ).

The decrease of OGG1 was not only a high risk factor of lung cancer, but it was also the high risk factor of other smoking-related cancer (El-Zein et al., 2010). The polymorphism of *hOGG1* was correlated with adenocarcinoma of lung (Okasaka et al., 2009).

Among different causes of lung cancer, both environmental factors and genetic factors take some certain roles. And the interactions between environmental factors and genes are probably important factors of lung cancer. At present, the influence of smoking has been widely accepted. The results in this study showed that there is an interaction between smoking and p53 gene, and the interaction model is super-multiplicative. The interaction model of smoking and *hOGG1* is also super-multiplicative, probably. Based on these findings, the intervention of smoking behavior among high-risk population should be placed at an important position in lung cancer prevention.

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