Published in final edited form as:

Lung Cancer. 2013 May ; 80(2): 131–137. doi:10.1016/j.lungcan.2013.01.021.

Genetic Polymorphisms of *TERT* and *CLPTM1L* and Risk of Lung Cancer – a Case- Control Study in a Chinese Population

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Abstract

Background/objectives—Genetic variants of Telomerase reverse transcriptase (*TERT*) and cleft lip and palate trans-membrane 1 like (*CLPTM1L*) genes in chromosome 5p15.33 region were previously identified to influence the susceptibility to lung cancer. We examined the association of single nucleotide polymorphisms (SNPs) in *TERT* and *CLPTM1L* genes with lung cancer and explored their potential modifying effects on the relationship between environmental risk factors and lung cancer in a Chinese population.

Methods—We genotyped rs2736100 (*TERT*) and rs401681 (*CLPTM1L*) SNPs in a case-control study with 399 lung cancer cases and 466 controls from Taiyuan, China. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using unconditional logistic regression models. Potential confounders were controlled for in the adjusted models.

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Conflict of interest statement

None declared

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Results—We found that the GG genotype of *TERT* was positively associated with lung cancer (OR = 1.47, 95% CI: 1.00 – 2.16). The association was stronger in participants older than 60 years, exposed to low indoor air pollution and adenocarcinoma and squamous cell carcinoma (SCC) in recessive model analysis. The GA genotype of *CLPTMIL* was inversely associated with lung cancer (OR = 0.72, 95% CI: 0.54 – 0.97). The association was stronger in participants 60 years old or younger, males, heavy smokers, exposed to low indoor air pollution and SCC in dominant model analysis. Individuals carrying both *TERT* and *CLPTMIL* risk genotypes had higher risk of lung cancer (OR = 1.80, 95% CI: 1.15 – 2.82). Significant interaction was observed between *CLPTMIL* and indoor air pollution in association with lung cancer.

Conclusions—Our results reiterate that genetic variants of *TERT* and *CLPTMIL* contribute to lung cancer susceptibility in Chinese population. These associations need to be verified in larger and different populations.

Keywords

Lung cancer; *TERT*; *CLPTMIL*; SNPs; Susceptibility; Chinese population

1. Introduction

Lung cancer is the most common form of cancer and cause of death from cancer worldwide [1]. China bears a rising burden of lung cancer incidence and mortality [1, 2]. While smoking is the most important risk factor for lung cancer, a significant proportion of cases, 15% among men and 53% among women globally, occur in never smokers [4]. In U.S. women, an estimated 15% of cases occur in never smokers whereas 61% and 83% of cases in women occur in never smokers from East Asia and South Asia respectively [5]. The incidence of lung cancer in China is highly disproportionate to the prevalence of smoking in men (52.9%) and women (2.4%) estimated in 2010, [6] suggesting that factors other than smoking may contribute to these differences. In China, potential risk factors of lung cancer include environmental tobacco smoke (ETS), indoor air pollution from cooking fumes and burning coal, outdoor air pollution, infections and genetic factors [7].

Genetic predisposition is recognized as an important risk factor for lung cancer. Recent genome wide association studies (GWAS) found that polymorphisms in the telomerase reverse transcriptase (*TERT*) and cleft lip and palate trans-membrane 1 like (*CLPTMIL*) genes of chromosome 5p15.33 may play an important role in the development of lung cancer. Three GWAS in European populations showed consistent associations of these two genes with lung cancer [8–10].

In the current study we sought to replicate the association of lung cancer with *TERT* (rs2736100) and *CLPTMIL* (rs401681) genes in a case control study conducted in Taiyuan, China. We also tested the potential modifying effects of the genetic polymorphisms on the association of several known lung cancer risk factors with lung cancer.

2. Methods

2.1 Study population

We recruited participants for the case-control study from Taiyuan city, the capital of Shanxi province. Cases were recruited between 2005 and 2007 from the Shanxi Tumor Hospital, which includes approximately 70% of all cancer patients from the city. Eligible cases were newly diagnosed with lung cancer, aged 20 years or older, lived in Taiyuan city for 10 years or more, medically in stable condition and willing to participate in the study. A total of 399 out of 448 selected lung cancer patients completed a standardized questionnaire resulting in 89% response rate. Controls were randomly selected from 13 communities in Taiyuan city.

Eligible controls were 20 years or older, city residents for 10 years or more, were not diagnosed with cancer or any other serious chronic disease. Of the 548 people selected, a total of 466 controls participated and completed the questionnaire resulting in 85% response rate.

2.2 Data collection

Patients were interviewed at the hospital and controls were interviewed at community health service centers. All participants were interviewed face-to-face by study personnel. A structured questionnaire was used to collect information from participants regarding their demographic characteristics, residential history, living environment, indoor activities, dietary and cooking habits, active smoking history, alcohol and tea drinking habits, occupational history, physical activity level, family history and personal disease history.

2.3 Bio-specimen collection and analysis

Blood samples of 8 ml were collected from 97.9% of cases and 98.9% of controls. A standard process was performed immediately to separate the serum and blood clot. All samples were stored in a freezer maintained at a temperature of -80° Celsius. A modified phenol-chloroform protocol was used to isolate genomic DNA for further analysis.

Genotyping was performed in the Center for Genomics and Personalized Medicine Research at Wake Forest School of Medicine (Winston-Salem, North Carolina). SNP genotyping for *TERT* and *CLPTMIL* SNPs (rs2736100 and rs401681) was performed using Sequenom platform (Sequenom, Inc., San Diego, CA). Polymerase chain reaction (PCR) and extension primers were designed using MassARRAY Assay Design 3.1 software (Sequenom, Inc., San Diego, CA). Genotyping procedures were performed according to the manufacturer's iPLEX Application Guide (Sequenom, Inc., San Diego, CA). Technicians were masked with regard to case and control status of the samples.

2.4 Statistical analysis

We used two sided chi-square tests to test differences in distribution of age, sex, education, BMI, average income of the household 10 years ago, smoking (0 for non-smokers, > 0 – 20 and > 20 pack year categories), alcohol drinking (never/ever for lifetime drinking status), tea drinking (never/former/current) and level of exposure to indoor air pollution (low/high) in cases and controls. A *p-value* of less than 0.05 indicated statistically significant differences.

Unconditional logistic regression models were used to estimate crude and adjusted odds ratios (OR) and 95% confidence intervals (CI) with adjustment for age and sex. Associations between genotypes and lung cancer were evaluated in both dominant and recessive models but additive effects of the minor allele were also considered.

We conducted stratified analysis to assess the association of the SNPs with lung cancer among the covariate sub-groups. Further, we assessed additive and multiplicative statistical interaction with smoking, alcohol drinking, and tea drinking and indoor air pollution exposures. In the interaction analysis, we used the lowest risk genotypes (any T of *TERT* and any A of *CLPTMIL*) as reference to ease interpretation of results. Additive interaction was assessed by calculating the “relative excess risk due to interaction (RERI)”, which is defined as the departure from additivity of effect of risk factors on a relative risk scale [11, 12]. Analyses in SAS and Microsoft Excel were performed using methods described by Andersson et al (2005) to derive RERI and corresponding confidence interval values. RERI value of zero indicated no additive interaction. Multiplicative interaction was assessed using product terms in the logistic regression models. For the stratified and interaction analyses,

the adjusted models included age, sex, education, average income 10 years ago, smoking, alcohol drinking, tea drinking and indoor air pollution level variables. All analyses were performed using SAS 9.2 software.

3. Results

The distribution of demographic characteristics and risk factors among cases and controls are presented in Table I. We found slightly higher proportion of older individuals, tea non-drinkers and participants exposed to high indoor air pollution among cases. Education levels, BMI and average annual income per person in the household 10 years ago was higher among controls. Fifty five percent of the cases were smokers compared to 39% of controls.

Table II shows association of the SNPs with lung cancer. The G allele (45.3% in cases and 41.2% in controls) of *TERT* (rs2736100) and A allele (29.0% in cases and 33.3% in controls) of *CLPTMIL* (rs401681) were the minor alleles in our study population. Lung cancer was significantly associated with *TERT* GG genotype in co-dominant [crude OR = 1.47, 95% CI: 1.00 – 2.16] and recessive models [crude OR = 1.60, 95% CI: 1.14 – 2.26]. For *CLPTMIL* gene, GA genotype in a co-dominant model [crude OR = 0.72, 95% CI: 0.54 – 0.97] and variant genotypes (GA+AA) in the dominant model [crude OR = 0.73, 95% CI: 0.55 – 0.97] showed a protective association with lung cancer. Crude and adjusted models gave similar results for both genes.

Table III shows associations between *TERT* and *CLPTMIL* genotype combinations and lung cancer. Using the subgroup with the lowest risk genotypes, any T (TT+GT) of *TERT* and any A (GA+AA) of *CLPTMIL* as reference, we found a significant increased risk of lung cancer in the subgroup with high risk genotypes, GG of *TERT* and GG of *CLPTMIL* [adjusted OR = 1.80; 95% CI: 1.15 – 2.82]. Test for linear trend showed statistical significance ($P_{\text{trend}} = 0.004$).

Figure 1 shows associations of *TERT* and *CLPTMIL* SNPs among the subgroups of selected covariates. *TERT* was significantly associated with lung cancer in older people (> 60 years age) [adjusted OR = 1.94, 95% CI: 1.01 – 3.70], alcohol non-drinkers [adjusted OR = 1.60, 95% CI: 1.03 – 2.51], tea ever-drinkers [adjusted OR = 1.87, 95% CI: 1.00 – 3.50] and those exposed to low indoor air pollution [adjusted OR = 2.50, 95% CI: 1.33 – 4.71]. No significant association was found with smoking. We found a significant association of *TERT* with squamous cell carcinoma and adenocarcinoma.

For the *CLPTMIL* gene, any A (GA+AA) genotype was significantly protective of lung cancer in younger people [adjusted OR = 0.60, 95% CI: 0.40 – 0.92], males [adjusted OR = 0.52, 95% CI: 0.32 – 0.84], heavy smokers (>20 pack years) [adjusted OR = 0.53, 95% CI: 0.30 – 0.94], alcohol non-drinkers [adjusted OR = 0.64, 95% CI: 0.44 – 0.92], in tea non-drinkers [adjusted OR = 0.64, 95% CI: 0.42 – 0.96] and in those exposed to low indoor air pollution [adjusted OR = 0.36; 95% CI: 0.20 – 0.63]. The association was significantly protective with squamous cell carcinoma.

Table IV presents possible interactions between gene polymorphisms and risk factor variables. An increased risk of lung cancer was associated with presence of GG in *TERT* and GG in *CLPTMIL* among smokers, alcohol non-drinkers and tea non-drinkers. The association of high risk genotypes (GG of *TERT* and GG of *CLPTMIL*) was greater with high indoor air pollution exposure compared to low levels of indoor air pollution exposure. RERI values indicated no statistically significant additive interactions. The only evidence of multiplicative interaction was found between *CLPTMIL* and indoor air pollution level [adjusted OR = 0.47, 95% CI: 0.24 – 0.92].

4. Discussion

In this study, we replicated the association between genetic variants of *TERT* and *CLPTMIL* genes with lung cancer in a Chinese population. We confirmed that *TERT* SNP is positively associated with lung cancer while *CLPTMIL* SNP is inversely associated with lung cancer. In the presence of risk genotypes of both the genes, (GG of *TERT* and GG of *CLPTMIL*), the risk of lung cancer was nearly doubled compared to presence of non-risk genotypes of both genes. In addition, *TERT* was more prominently associated with lung cancer in participants older than 60 years, those exposed to low levels of indoor air pollution and adenocarcinoma and squamous cell carcinoma. The association of *CLPTMIL* was stronger in participants 60 years old or younger, males, smokers (>20 pack years), those exposed to low indoor air pollution and squamous cell carcinoma.

TERT is a component of the telomerase ribonucleoprotein complex, which maintains the length of telomeres in chromosomes [16]. Telomerase is expressed in stem cell lines and inactive in somatic cells [17]. Telomeres can become dysfunctional due to various reasons - gradual shortening because of incomplete replication of chromosomes, oxidative DNA damage or mutations in structural proteins like *TERT* [18]. There may be a higher probability of telomere dysfunction in cells/tissues of individuals carrying mutated genotype (GG) of *TERT* compared to those with TT or GT genotypes. Cells with dysfunctional telomeres are subjected to p53/Rb dependent tumor suppressor mechanisms – senescence or apoptosis [18, 19]. In the absence of effective tumor suppressor activity, some cells with dysfunctional telomeres continue to divide resulting in genomic instability and the potential for development of malignant phenotypes [18, 19]. Pre-neoplastic and neoplastic cells reactivate or gain telomerase activity in order to maintain continued cell replication [20]. *TERT* mRNA and *TERT* protein were reported to be over expressed in lung cancer tissues compared to normal lung tissues [20–22] and human telomerase reverse transcriptase gene was found to be amplified more frequently in malignant pleural effusions compared to benign effusions [23]. The augmented telomerase activity might help in regaining lost telomeres and maintain adequate telomere length for continued cell division rendering the cell immortal. Continued elevated rate of proliferation, genomic instability and ineffective p53/Rb tumor suppressor activity may lead to further progression of cancer in lung tissues. This evidence supports the role of *TERT* in lung cancer initiation and promotion.

In our study population the frequency of *TERT* minor allele (G) was 43% in cases and 41% in controls. Our results showing significant higher association of GG genotype of *TERT* with lung cancer compared to TT and GT genotypes were similar to studies in Chinese [13] and Korean population [14] with similar minor allele frequencies. Our findings were similar in direction but lower in magnitude than the results from a pooled analysis in White population with higher minor allele frequencies [24].

In the subgroup analyses, we observed a stronger association of *TERT* with lung cancer in older people, which is not unexpected given that the length of telomeres may provide an estimation of “genetic age” (also referred to as “mitotic clock”) [25] and telomeres shorten with age [16, 26]. Since shorter and dysfunctional telomeres could lead to DNA damage and genomic instability [18] and malignant cells acquire or increase telomerase activity through over-expression of *TERT* [20], the stronger association in older individuals may be due to higher expression or re-expression of *TERT* in the pre-neoplastic or neoplastic lung tissues. The association of *TERT* with lung cancer was more pronounced in alcohol non-drinkers and tea ever-drinkers although the underlying mechanisms of associations in these risk factor subgroups are not known.

TERT was significantly associated with lung cancer in participants who were exposed to low levels of indoor air pollution. Indoor air pollution is a major risk factor for lung cancer in China [27]. Solid fuel used for cooking and heating purposes along with lack of proper ventilation and exposure to second hand smoke contribute to lung cancer risk [27]. One explanation for our findings is that in participants exposed to high indoor air pollution levels, the effect of indoor air pollution could have masked the association of *TERT* with lung cancer.

Among the histo-pathological subtypes of lung cancer, *TERT* was significantly associated with adenocarcinoma and squamous cell carcinoma but not with small cell carcinoma. Previous studies have reported a stronger association of *TERT* with adenocarcinoma than squamous cell carcinoma in Chinese population [13] and White and Asian population in a pooled analysis [24].

The role of *CLPTMIL* was initially described in ovarian cancer cells where over expression of the gene induced apoptosis in cisplatin-sensitive cells [28]. A recent study reported that *CLPTMIL* is also involved in mitochondrial apoptosis in normal cells [29]. While limited knowledge is available into the function of this gene, the available information supports a role of *CLPTMIL* in apoptosis.

The frequency of *CLPTMIL* minor allele (A) in our study population was 33% in cases and 31% in controls which are comparable to those in Chinese (16) and Korean population (17) studies but are lower than those in a Norwegian population study [30]. Our results showed that GA genotype of *CLPTMIL* was significantly associated with decreased risk of lung cancer. The dominant model also indicated a significant association of lung cancer with any A (GA+AA) genotypes of *CLPTMIL*, which was similar in direction and magnitude found in GWAS in Korean [14], U.K. and US [31] populations. The Norwegian study reported a decreased risk of lung cancer in association with *CLPTMIL* with ORs similar in direction and magnitude, however not statistically significant [30].

We found a significant protective association of *CLPTMIL* with lung cancer in younger people, males and heavy smokers and with squamous cell carcinoma. The involvement of *CLPTMIL* in apoptosis was reported to increase in cells under genotoxic stress caused by cisplatin chemotherapy [28]. Tobacco smoking is one of the major factors causing genotoxic stress and DNA damage, which can result in malignant transformation of cells. The results from our stratified analyses might indicate that the association between *CLPTMIL* and lung cancer could be affiliated with smoking related carcinogen exposure. A Korean population study reported that *CLPTMIL* (rs401681 SNP) was significantly associated with adenocarcinoma. However, our findings, which showed a significant association with squamous cell carcinoma, uphold the affiliation of *CLPTMIL* with smoking exposure. *CLPTMIL* was reported to be overexpressed in lung cancer cells [29]. The significant results from our study might indicate that people who carry the variant A allele could have a higher activity of *CLPTMIL* due to its over-expression in pre-neoplastic and neoplastic cells which may explain the protective association with lung cancer based of its involvement in apoptosis.

In the subgroup analysis, we also found significant associations of *CLPTMIL* with lung cancer in alcohol non-drinkers and tea non-drinkers. However, the odds ratios in the other groups (alcohol drinkers and tea drinkers) were similar but did not reach significance. Similar to *TERT*, *CLPTMIL* was also significantly associated with lung cancer in those exposed to low levels of indoor air pollution. Again, we purport that the individual risk of lung cancer among those exposed to high indoor air pollution may be strong enough to mask the association between *CLPTMIL* and lung cancer. This may be further suggested by the

significant multiplicative interaction and the highest risk of lung cancer associated with high indoor air pollution and the risk genotype (GG) of *CLPTMIL*.

We also found that carrying risk genotypes of *TERT* and *CLPTMIL* increases the odds of lung cancer significantly. The findings provide evidence for the replication of the associations of lung cancer with 5p15.33 chromosome region reported in European, U.S. [8, 9, 15], Chinese [13] and Korean populations [14].

The most important limitation of study was the sample size. We may have found more prominent associations especially in stratified analysis where some of the subgroups were too small in sample size. Furthermore, we may have needed more participants to detect interactions between the risk factors and genetic polymorphisms in association with lung cancer. Consequently, some of the results we present could be attributed to chance.

5. Conclusion

In this study, we found that GG genotype of *TERT* increases the risk and any A genotypes of *CLPTMIL* decrease the risk of lung cancer in a Chinese population. The association of *TERT* with lung cancer was stronger in older people and in those exposed to low levels of indoor air pollution. The association of *CLPTMIL* with lung cancer was stronger in younger people, males, and heavy smokers and in those exposed to low levels of indoor air pollution. *TERT* was significantly associated with both adenocarcinoma and squamous cell carcinoma. *CLPTMIL* was significantly associated with squamous cell carcinoma. Further studies on the association of these two genes with lung cancer in affiliation with risk factors are warranted in larger studies and in different populations. Additionally, the functional mechanisms of the two genes need to be studied further to better understand their role in risk of lung cancer.

Acknowledgments

This work was supported in part by the National Nature Science Foundation of China grant award to Dr. Lina Mu (NSFC-30500417). The work is also partially supported by NIH grants (ES018846, ES06718, CA09142, DA11386) and the Alper Research Center for Environmental Genomics of the UCLA Jonsson Comprehensive Cancer Center.

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Fig. 1.

Forest plots depicting the association of *TERT* and *CLPTMIL* with lung cancer among different subgroups. AC: adenocarcinoma, SCC: squamous cell carcinoma, SmCC: small cell carcinoma. Dotted line represents the overall odds ratio. Size of square represents the inverse of log odds ratio. Adjusted ORs in bold indicate significant values. ORs adjusted for age, sex, education, average income/person 10 years ago, smoking (pack years), alcohol drinking, tea drinking and indoor air pollution level.

Table I

Distribution of general characteristics among lung cancer cases and cancer-free controls

Variables	Cases	Controls	p value ^a
	N (%)	N (%)	
Age			
45 years	59 (14.8)	83 (17.8)	0.07
45 – 55 yrs	96 (24.1)	139 (29.8)	
55 – 65 yrs	111 (27.8)	116 (25.0)	
> 65 yrs	133 (33.3)	128 (27.4)	
Sex			
Male	202 (50.6)	234 (50.2)	0.90
Female	197 (49.4)	232 (49.8)	
Education			
Less than primary school	43 (10.8)	23 (4.9)	*** < 0.0001
Primary School	106 (26.6)	81 (17.4)	
Junior Middle School	124 (31.1)	175 (37.5)	
Senior Middle School	68 (17.0)	120 (25.8)	
College or Higher	58 (14.5)	67 (14.4)	
BMI (kg/m ^b)			
< 18.5	22 (5.5)	9 (1.9)	*** < 0.0001
18.5 – 24.9	250 (62.7)	259 (55.6)	
25 – 29.9	90 (22.6)	162 (34.8)	
30	15 (3.7)	30 (6.4)	
Average annual income/person 10 years ago (RMB) ²			
< 1000	104 (26.1)	106 (22.7)	*** < 0.0001
1000 – 2500	236 (59.1)	197 (42.3)	
> 2500	59 (14.8)	163 (35.0)	
Pack years of smoking			
Non smokers ^c	179 (44.9)	285 (61.2)	*** < 0.0001
< 20 pyrs	39 (9.8)	62 (13.3)	
20 < 40 pyrs	64 (16.0)	72 (15.4)	
40 pyrs	117 (29.3)	47 (10.1)	
Alcohol drinking ^d			
Never	298 (74.7)	345 (74.0)	0.83
Ever	101 (25.3)	121 (26.0)	
Tea drinking			
Never	242 (60.6)	263 (56.5)	*** < 0.0001
Former	47 (11.8)	15 (3.2)	
Current	110 (27.6)	188 (40.3)	
Indoor air pollution ^e			
Low	115 (28.8)	238 (51.1)	*** < 0.0001

Variables	Cases	Controls	p value ^a
	N (%)	N (%)	
High	237 (59.4)	220 (47.2)	
Total	399	466	

^a from two sided χ^2 test

^b RMB = Renminbi, the Chinese currency

^c less than 100 cigarettes per year or less than 2 cigarettes/week for a year

^d lifetime alcohol drinking status

^e Indoor air pollution index was calculated by summarizing participant's exposure to solid fuel for cooking and heating, ventilation in kitchen, opening of windows in winter and second hand smoking. An index of 0/1 represented low and an index of 2/3/4/5 represented high indoor air pollution exposure

 $p < 0.0001$

Table II

Association of *TERT* and *CLPTMIL* gene polymorphisms with lung cancer

Gene3	Genotype	Cases		Controls		Crude OR (95% CI)	Adjusted OR ^a (95% CI)
		N (%)	N (%)	N (%)	N (%)		
<i>TERT</i> (rs2736100)	TT	352	447				
		122 (34.6)	157 (35.1)			1.00	1.00
	GT			141 (40.1)	212 (47.4)	0.86 (0.62 – 1.18)	0.87 (0.63 – 1.19)
	GG			89 (25.3)	78 (17.5)	1.47 (1.00 – 2.16)	1.46 (0.99 – 2.15)
	GT+GG			230 (65.3)	290 (64.9)	1.02 (0.76 – 1.37)	1.03 (0.76 – 1.38)
Dominant model							
Recessive model (ref: TT+GT)	GG			89 (25.3)	78 (17.5)	1.60 (1.14 – 2.26)	1.58 (1.12 – 2.23)
Allele OR	G					1.17 (0.96 – 1.41)	1.17 (0.96 – 1.41)
<i>CLPTMIL</i> (rs401681)		350	441				
	GG	181 (51.7)	194 (44.0)			1.00	1.00
	GA	135 (38.6)	200 (45.3)			0.72 (0.54 – 0.97)	0.72 (0.54 – 0.97)
	AA	34 (9.7)	47 (10.7)			0.78 (0.48 – 1.26)	0.77 (0.47 – 1.25)
	GA+AA	169 (48.3)	247 (56.0)			0.73 (0.55 – 0.97)	0.73 (0.55 – 0.97)
Dominant model							
Recessive model (ref: GG+GA)	AA			34 (9.7)	47 (10.7)	0.90 (0.56 – 1.44)	0.89 (0.56 – 1.42)
Allele OR	A					0.82 (0.66 – 1.02)	0.82 (0.66 – 1.01)

- OR values in **bold** represent significant values.^a adjusted for age and sex.

Table III

Association of combined genotypes of *TERT* and *CLPTMIL* with lung cancer

<i>TERT</i>	<i>CLPTMIL</i>	# of risk genotypes	Cases		Controls		Crude OR (95% CI)	Adjusted OR ^a (95% CI)
			N (%)		N (%)			
			332		435			
TT + GT	GA + AA	0	132 (39.8)		216 (49.7)		1.00	1.00
TT + GT	GG	1	118 (35.5)		143 (32.9)		1.35 (0.98 – 1.87)	1.36 (0.98 – 1.88)
GG	GA + AA	1	29 (8.7)		28 (6.4)		1.70 (0.97 – 2.98)	1.66 (0.95 – 2.92)
GG	GG	2	53 (16.0)		48 (11.0)		1.81 (1.16 – 2.82)	1.80 (1.15 – 2.82)
<i>P_{trend}</i>							^{**} 0.003	^{**} 0.004

- OR values in **bold** represent significant values.^a adjusted for age and sex.***
p < 0.01

Table IV

Potential interactions between risk factors and genetic polymorphisms in association with lung cancer

	Cases		Controls		Crude OR (95%CI)	Adjusted OR ^a (95%CI)
	N	N	N	N		
Smoking						
Smoking	<i>TERT</i>					
	TT + GT	125	227		1.00	1.00
	GG	44	48		1.67 (1.04 – 2.65)	1.52 (0.92 – 2.52)
	TT + GT	138	142		1.77 (1.28 – 2.43)	1.75 (0.94 – 3.26)
Ever	GG	45	30		2.72 (1.63 – 4.54)	3.11 (1.44 – 6.73)
OR for interaction ^b						
					0.93 (0.46 – 1.86)	1.17 (0.53 – 2.58)
RERI ^c					0.29 (–1.20 – 1.79)	0.84 (–1.15 – 2.84)
Alcohol drinking						
Alcohol drinking	TT + GT	205	276		1.00	1.00
	GG	65	56		1.56 (1.05 – 2.33)	1.60 (1.02 – 2.49)
	TT + GT	58	93		0.84 (0.58 – 1.22)	0.78 (0.47 – 1.30)
	GG	24	22		1.47 (0.80 – 2.69)	1.36 (0.64 – 2.92)
OR for interaction ^b						
					1.12 (0.52 – 2.43)	1.09 (0.44 – 2.70)
RERI ^c					0.07 (–1.00 – 1.13)	–0.02 (–1.22 – 1.19)
Tea drinking						
Tea drinking	TT + GT	103	161		1.00	1.00
	GG	37	33		1.75 (1.03 – 2.98)	1.85 (0.98 – 3.47)
	TT + GT	160	208		1.20 (0.87 – 1.66)	1.31 (0.86 – 2.00)
	GG	52	45		1.81 (1.13 – 2.89)	1.98 (1.22 – 3.49)
OR for interaction ^b						
					0.86 (0.43 – 1.72)	0.81 (0.37 – 1.80)
RERI ^c					–0.15 (–1.31 – 1.01)	–0.19 (–1.61 – 1.24)
Indoor air pollution						
Indoor air pollution	TT + GT	75	194		1.00	1.00
	GG	28	34		2.13 (1.21 – 3.76)	2.31 (1.26 – 4.25)
	TT + GT	157	170		2.39 (1.69 – 3.37)	2.12 (1.44 – 3.11)
	GG	51	41		3.22 (1.97 – 5.25)	2.75 (1.60 – 4.73)

	Cases		Controls		Crude OR (95%CI)	Adjusted OR ^a (95%CI)
	N	N	N	N		
OR for interaction ^b					0.63 (0.30 – 1.32)	0.56 (0.26 – 1.23)
RERI ^c					–0.30 (–2.11 – 1.51)	–0.68 (–2.55 – 1.19)
<hr/>						
Smoking	CLPTMIL					
Never	GA + AA	81	153	1.00		1.00
Never	GG	82	121	1.28 (0.87 – 1.89)		1.43 (0.93 – 2.20)
Ever	GA + AA	88	94	1.77 (1.19 – 2.63)		2.12 (1.07 – 4.20)
Ever	GG	99	73	2.56 (1.71 – 3.84)		3.71 (1.85 – 7.46)
OR for interaction ^b					1.13 (0.64 – 2.01)	1.22 (0.64 – 2.34)
RERI ^c					0.51 (–0.48 – 1.51)	1.16 (–0.61 – 2.93)
<hr/>						
Alcohol drinking						
Never	GA + AA	127	182	1.00		1.00
Never	GG	137	147	1.34 (0.97 – 1.85)		1.53 (1.06 – 2.20)
Ever	GA + AA	42	65	0.93 (0.59 – 1.45)		0.88 (0.48 – 1.61)
Ever	GG	44	47	1.34 (0.84 – 2.15)		1.39 (0.75 – 2.57)
OR for interaction ^b					1.09 (0.57 – 2.08)	1.04 (0.48 – 2.24)
RERI ^c					0.08 (–0.68 – 0.84)	–0.02 (–0.95 – 0.91)
<hr/>						
Tea drinking						
Ever	GA + AA	62	109	1.00		1.00
Ever	GG	71	82	1.52 (0.98 – 2.38)		1.39 (0.85 – 2.26)
Never	GA + AA	107	138	1.36 (0.91 – 2.04)		1.35 (0.85 – 2.15)
Never	GG	110	112	1.73 (1.15 – 2.60)		1.96 (1.22 – 3.16)
OR for interaction ^b					0.83 (0.47 – 1.48)	1.05 (0.56 – 1.96)
RERI ^c					–0.16 (–0.99 – 0.0.67)	0.22 (–0.66 – 1.11)
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Indoor air pollution						
Low	GA + AA	36	127	1.00		1.00
Low	GG	62	97	2.26 (1.38 – 3.68)		2.44 (1.44 – 4.12)
High	GA + AA	109	114	3.37 (2.14 – 5.31)		3.04 (1.84 – 5.05)
High	GG	100	95	3.71 (2.33 – 5.91)		3.51 (2.10 – 5.87)

	Cases		Controls		Adjusted OR ^a (95%CI)
	N		N		
OR for interaction ^b					0.47 (0.24 – 0.92)
RERI ^c					–0.98 (–2.74 – 0.79)

- OR values in **bold** represent significant values;

^a adjusted for age, sex, education, average annual income/person 10 years ago, smoking (pack years), alcohol drinking, tea drinking and indoor air pollution level;

^b Results of interaction on a multiplicative scale;

^c Results of Relative Excess Risk due to Interaction on an additive scale. A RERI equal to 0 indicates no biological interaction.