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ORIGINAL PAPER

Genetic polymorphisms of *TERT* and *CLPTM1L*, cooking oil fume exposure, and risk of lung cancer: a case–control study in a Chinese non-smoking female population

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Abstract Genetic polymorphisms of telomerase reverse transcriptase (TERT) and cleft lip and palate transmembrane 1-like (CLPTM1L) genes in chromosome 5p15.33 region were previously identified to influence the risks of lung cancer. This study aimed to investigate the association between polymorphisms in TERT and CLPTM1L genes with the risk of lung cancer, as well as the interaction of the polymorphisms and the environmental risk factors in Chinese non-smoking females. A hospital-based case–control study of 524 cases and 524 controls was conducted. Two polymorphisms were determined by Taqman allelic discrimination method. The statistical analyses were performed mostly with SPSS. This study showed that the individuals with the TG or GG genotypes of TERT polymorphism (rs2736100) were at an increased risk for lung cancer compared with those carrying the TT genotype in Chinese non-smoking females [adjusted odds ratios (ORs) were 1.44 and 1.85, 95 % confidence intervals (CIs) were 1.09–1.90 and 1.29–2.65, respectively]. The stratified analysis suggested that increased risks were more pronounced in lung adenocarcinoma (corresponding ORs were 1.71 and 2.30, 95 % CIs were 1.25–2.35 and 1.54–3.43). Our results showed that exposure to cooking oil fume was associated with increased risk of lung cancer in Chinese non-smoking females (adjusted ORs 1.59, 95 % CI 1.13–2.23). However, we did not observe a significant interaction of cooking oil fume and TERT polymorphism on lung cancer among Chinese non-smoking females. TERT polymorphism (rs2736100) might be a genetic susceptibility factor for lung cancer in non-smoking females in China.

Keywords TERT gene · CLPTM1L gene · Single nucleotide polymorphism · Lung cancer · Non-smoker

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Introduction

Lung cancer is the most common form of cancer and cause of death from cancer worldwide [1]. Many Asian countries suffer a lot from cancer. The number of people diagnosed with cancer in Asia accounted for 48 % of the world, and lung cancer is the most common or second most common cancer in most Asian countries [2]. In China, lung cancer is the leading cause of cancer-related deaths in registration areas for both men and women [3]. Although tobacco consumption is thought to be the principal risk factor for

lung cancer, 10–25 % of lung cancer patients worldwide occur in never smokers [4]. The study showed that 15 % of lung cancer patients in men and 53 % in women globally were not caused by smoking [5]. Some studies indicated that among never smokers, lung cancer incidence in women was higher than that in men [6]. The epidemiologic characteristics and risk factors of lung cancer in non-smokers are not clear. As we know, both host susceptibility factors and environmental risk factors play important roles in this disease. So it is important and valuable to explore the genetic susceptibility gene and environmental risk factor, as well as their interaction, for lung cancer in non-smoking female population.

Recent genome-wide association studies (GWAS) have identified that the polymorphisms in the telomerase reverse transcriptase (TERT) and cleft lip and palate transmembrane 1-like (CLPTM1L) genes may play important roles in the development of lung cancer. The two genes are all located in chromosome 5p15.33. Three GWASs in European populations showed consistent associations of polymorphisms in these two genes with lung cancer [7–9].

In the present study, we describe a case–control study of lung cancer in a non-smoking female population in Shenyang City of China, to evaluate the role of the polymorphisms of TERT and CLPTM1L genes on risk of lung cancer and explore the interaction between genetic polymorphism and exposure to environmental risk factors in the development of lung cancer in non-smoking females.

Materials and methods

Study subjects and data collection

In this hospital-based case–control study, there were 524 cases and 524 controls. Cases were newly diagnosed non-smoking females with histologically confirmed lung cancer, and controls were with other diseases but free of cancer history and symptom between January 2004 and November 2010 in Shenyang city, the capital of Liaoning province. Controls were all non-smoking females and frequency matched to cases on age (±5 years). Controls suffered mainly from coronary disease, hypertension, diabetes mellitus, cholecystitis, gastritis, gastric ulcer and others. All subjects were unrelated ethnic Han Chinese. The human studies were approved by the Institutional Review Board of China Medical University, and informed consent was obtained from each participant or each participant's representatives if direct consent could not be obtained.

Individual with a total of 100 cigarettes in his lifetime was defined as a smoker; otherwise, he was considered as a non-smoker. Each participant donated 10 ml venous blood for SNP detection and was interviewed to collect demographic data and environmental exposure at the time they were admitted to the hospital. Information concerning demographic characteristics, passive smoking, cooking oil fume exposure, fuel smoke exposure, family history of cancer, occupational exposure, and dietary habit was obtained from each case and control by trained interviewers.

DNA isolation and genotyping

Genomic DNA samples were isolated by phenol–chloroform method. Genotyping of the SNPs was done using Taqman® allelic discrimination (Applied Biosystems, Foster City, CA) with a commercially available primer probe set (assay ID C_1844009_10 for rs2736100 and C_29104314_10 for rs4975161). Genotyping was performed in a blinded mode, and appropriate controls were included in each run. A 10 % masked, random sample of patients was tested twice by different persons, and the results were found to be concordant for all of the masked duplicate sets.

Statistical analysis

All statistical analyses were performed with SPSS (version 12.0). All of the tests were two-sided, and statistical significance was defined as $P < 0.05$. Pearson's chi-square test was used to compare the distribution of the demographic variables and examine differences in risk factors and SNP genotypes and alleles between cases and controls. Hardy–Weinberg equilibrium (HWE) of the genotypes was tested by performing a goodness-of-fit χ^2 test. Unconditional logistic regression analysis was performed to calculate the odds ratios (ORs) with 95 % confidence intervals (CI) for estimating the association between certain genotypes and lung cancer. Crude ORs and adjusted ORs by age were all calculated. The stratified analyses and gene–environment interaction were evaluated by crossover analysis and logistic regression models. Rothman's synergy index (S) is an interaction measure between two discrete variables on a dichotomous outcome. The index equals 1 under additivity, $S > 1$ in the case of synergy and $S < 1$ in the presence of antagonism. The synergy index is originally constructed on (2×2) tables and is computed by $S = (A - 1)/(B - 1) + (C - 1)$ [10].

Results

Subject characteristics

In the present study, there were 524 cases and 524 controls who were all non-smoking females. Mean ages of cases and

controls (mean ± SD) were almost identical (56.1 ± 11.9 and 56.8 ± 11.1 years, respectively), and the difference was not statistically significant ($t = 0.922$, $P = 0.357$). There were no difference in income and education between cases and controls (P values were 0.071 and 0.779, respectively). Above results suggested that case and control groups were comparable in important characteristics. About pathological type, 365 patients were adenocarcinoma, 87 were squamous cells carcinoma, and 72 were other types.

SNPs frequencies and association with lung cancer

Table 1 shows the distribution of the SNPs in TERT (rs2736100) and CLPTM1L (rs4975616) in cases and controls, as well as their association with lung cancer risk. The frequencies of the rs2736100 T allele and rs4975616 G allele in the controls were 0.402 and 0.135, respectively. All allele distributions were consistent with Hardy–Weinberg equilibrium ($\chi^2 = 0.08$ and $P = 0.777$ for rs2736100; $\chi^2 = 0.03$ and $P = 0.856$ for rs4975616). For rs2736100 in TERT gene, heterozygous carriers of the TG genotype had a 1.44-fold risk of lung cancer compared with the homozygous wild genotype (95 % CI [1.09–1.90], $P = 0.010$). Individuals carrying GG homozygote genotype had a 1.85-fold increased risk of cancer compared with the wild genotype (95 % CI [1.29–2.65], $P = 0.001$). Dominant model and recessive model also showed significant results (adjusted ORs were 1.54 and 1.47; 95 % CIs were 1.18–2.00 and 1.07–2.02, respectively). Further analyses were carried on by allele comparison, and the G allele of rs2736100 was found to be associated with an increased risk of lung cancer with OR of 1.34 (95 % CI [1.13–1.60], $P = 0.001$). In contrast to TERT, there was no evidence that the SNP rs4975616 of CLPTM1L gene affected the risk of lung cancer no matter by genotype comparison or allele comparison.

According to the analyses of different pathological types, there was a significant association between rs2736100 polymorphism and lung adenocarcinoma risk, but not in squamous cell carcinoma. As shown in Table 2, individuals carrying TG or GG genotype of TERT gene were more likely to develop lung adenocarcinoma, and the corresponding ORs (95 % CIs) were 1.71 (1.25–2.35) and 2.30 (1.54–3.43), while no significant results were found for rs4975616 in CLPTM1L gene. Furthermore, G allele of rs2736100 was suggested to be risk allele for lung adenocarcinoma (OR 1.50, 95 % CI 1.24–1.81, $P < 0.001$).

Environmental risk factors and lung cancer risks

Among the subjects in the present study, there were 306 cases and 318 controls with data about environmental exposure, so we analyzed the association between environmental exposures and lung cancer risks (Table 3). There were no significant differences in the distribution of family history of cancer, passive smoking, and fuel smoke exposure between cases and controls. However, the cases were more likely than the controls to report cooking oil fume exposure (adjusted OR 1.59, 95 % CI [1.13–2.23], $P = 0.008$).

Analysis of rs2736100 and cooking oil fume exposure interaction

Furthermore, we evaluated the interaction of rs2736100 polymorphism and cooking oil fume exposure by crossover analysis and logistic model. Crossover analysis suggested that the individuals with both the variant allele and exposure to cooking fumes were at a higher risk of lung cancer than those with only one of them (ORs were 2.19 vs. 1.79 and 1.44) (Table 4). However, the synergy index [$S = (A - 1)/[(B - 1) + (C - 1)]$) was 0.967, which

Table 1 Genetic polymorphisms and lung cancer risk

SNP	Cases *n* (%)	Controls *n* (%)	OR [95 % CI][a]	*P* value
rs2736100				
TT	139 (26.5)	186 (35.5)	1.00	–
TG	273 (52.1)	255 (48.7)	1.44 [1.09–1.90]	0.010
GG	112 (21.4)	83 (15.8)	1.85 [1.29–2.65]	0.001
Dominant model			1.54 [1.18–2.00]	0.001
Recessive model			1.47 [1.07–2.02]	0.017
Allele model			1.34 [1.13–1.60]	0.001
rs4975616				
AA	391 (74.6)	392 (74.8)	1.00	–
AG	126 (24.0)	123 (23.5)	1.03 [0.77–1.36]	0.862
GG	7 (1.3)	9 (1.7)	0.78 [0.29–2.13]	0.633
Dominant model			1.01 [0.76–1.33]	0.949
Recessive model			0.78 [0.29–2.11]	0.623
Allele model			0.99 [0.77–1.28]	0.949

SNP single nucleotide polymorphism, *OR* odds ratio, *CI* confidence interval

[a] ORs were calculated by unconditional logistic regression and adjusted for age

Table 2 Genetic polymorphisms and lung adenocarcinoma risk

SNP	Cases *n* (%)	Controls *n* (%)	OR [95 % CI][a]	*P* value
rs2736100				
TT	84 (23.0)	186 (35.5)	1.00	–
TG	196 (53.7)	255 (48.7)	1.71 [1.25–2.35]	0.001
GG	85 (23.3)	83 (15.8)	2.30 [1.54–3.43]	<0.001
Dominant model			1.85 [1.37–2.51]	<0.001
Recessive model			1.63 [1.16–2.28]	0.005
Allele model			1.50 [1.24–1.81]	<0.001
rs4975616				
AA	271 (74.2)	392 (74.8)	1.00	–
AG	90 (24.7)	123 (23.5)	1.06 [0.77–1.45]	0.727
GG	4 (1.1)	9 (1.7)	0.65 [0.20–2.12]	0.470
Dominant model			1.03 [0.76–1.40]	0.853
Recessive model			0.64 [0.19–2.08]	0.455
Allele model			1.00 [0.76–1.32]	0.986

SNP single nucleotide polymorphism, *OR* odds ratio, *CI* confidence interval

[a] ORs were calculated by unconditional logistic regression and adjusted for age

Table 3 Environmental exposure and lung cancer risks

Variable	Cases *n* (%)	Controls *n* (%)	OR [95 % CI][a]	*P* value
Family history of cancer	41 (13.4)	33 (10.5)	1.37 [0.84–2.23]	0.213
Passive smoking	180 (58.8)	170 (53.5)	1.28 [0.93–1.76]	0.135
Fuel smoke exposure	86 (28.1)	80 (25.2)	1.18 [0.82–1.68]	0.375
Cooking oil fume exposure	112 (36.6)	85 (26.7)	1.59 [1.13–2.23]	0.008

OR odds ratio, *CI* confidence interval

[a] ORs were calculated by unconditional logistic regression and adjusted for age

Table 4 Joint analysis of rs2736100 polymorphism and cooking oil fume exposure in non-smoking female lung cancer

rs2736100 polymorphism	Cooking oil fume exposure	Case	Control	OR	95 % CI	*P* value
TT	−	51	79	1.00		
TT	+	37	32	1.79 (*C*)	0.99–3.23	0.052
TG/GG	−	143	154	1.44 (*B*)	0.95–2.19	0.089
TG/GG	+	75	53	2.19 (*A*)	1.33–3.61	0.002

meant there was not almost additive interaction between rs2736100 and cooking oil fume exposure. And the hypothesis testing suggested that the interaction was not statistically significant. Logistic analysis also showed there was no significant multiplicative interaction between rs2736100 and cooking oil fume exposure ($P = 0.286$).

Discussion

Lung cancer is a complicated disease of multiple etiologies, and the study results were inconsistent. As we know, besides tobacco smoking, other impact factors of lung cancer are not definitive. Cigarette smoking cannot completely make clear the etiology of lung cancer in Chinese women, who smoke rarely but develop lung cancer comparatively often. Apparently, non-smoking females are the ideal population to explore the unknown and important environmental and genetic factors of lung cancer. So we chose the non-smoking female population as the study subjects to study the association between risk of lung cancer and genetic polymorphisms in genes suggested by GWASs, as well as environmental risk factors and gene–environment interaction.

In the present study, we included genetic polymorphisms of TERT (rs2736100) and CLPTM1L (rs4975616), and some environmental risk factors. The frequencies of minor allele of rs2736100 and rs4975616 were 0.402 and 0.135 in controls, which are identical to the Hapmap data (0.437 and 0.168 for Chinese population, respectively). Our

study showed that TG and GG genotypes, as well as G allele of rs2736100 in TERT gene all showed significant associations with increased risks of lung cancer in non-smoking female population. For environmental factors, exposure to cooking oil fume is a risk factor for lung cancer in non-smoking females.

Telomere, the end nucleoprotein structure of the linear chromosome, plays an important role in keeping the stability of chromosome. The main biological function of TERT, which is composed of telomerase ribonucleoprotein complex, is to maintain the length of the telomere [11]. Telomeres can become dysfunctional due to various reasons including mutations in structural proteins like TERT [12]. Telomere dysfunction may be more likely to occur in cells/tissues of individuals carrying variant genotypes (GT/GG) of TERT compared to those with TT genotype. When telomerase activity is repressed, telomeres gradually shorten during cell divisions, and these replication and stability changes are closely related to senescence and apoptosis. Without effective tumor suppressor activity, some cells with dysfunctional telomeres continue to divide, resulting in genomic instability and the probability for developing malignant phenotypes [12]. Pre-neoplastic and neoplastic cells reactivate or gain telomerase activity in order to maintain continued cell replication [13]. Increased expression of telomerase can be detected in germ line and stem cells, while increased telomerase activity in somatic cells may lead to abnormal proliferation [14]. Some studies have found increasing expression level of TERT mRNA and protein in lung tumor tissues compared to normal lung tissues [13, 15, 16]. Human TERT gene was found to be amplified more frequently in malignant lung cancer than in effusions from patients with benign lung disease [17]. Above evidence supports the role of TERT gene in lung cancer initiation and development. Since rs2736100 SNP in TERT gene was firstly reported to be associated with lung cancer in 2009 [18], the same results were suggested in recent years in whole population [19–21]. We may infer from our study results that the variation from T allele to G allele of rs2736100 is a risk factor for non-smoking female lung cancer in Northeastern China.

In the subgroup analyses by different pathological types, we observed a stronger association of TERT with lung adenocarcinoma, but not significant association with squamous cell lung cancer. Previous studies have reported a stronger association of TERT with adenocarcinoma in Chinese population [22] and White or Asian population in a pooled analysis [23]. The possible reason is that the sample size of squamous cell lung cancer patients in present study is too small to obtain the statistically significant results. So larger population of squamous cell lung cancer is needed to verify the conclusion in future.

In the present study, individuals with exposure to cooking oil fume had a 1.59-fold increased risk of developing lung cancer. Our previous studies reported significant associations between cooking oil fume exposure and lung cancer or lung adenocarcinoma risk in Chinese non-smoking females [24, 25]. There are studies showing that cooking oil fume condensates can induce DNA damages and influence DNA integrality [26, 27]. Tung et al. [28] found that exposure to cooking oil fume could inhibit cell growth and induce oxidative stress in lung epithelial cells. Above evidences support the important roles of cooking oil fume exposure in lung cancer development. The interaction analysis results suggested that no statistically significant interaction was found between TERT gene polymorphism and cooking oil fume exposure in the development of lung cancer in non-smoking female population. Because it is just a statistical estimation, larger sample size studies and further studies concerning their biological validity are required.

This study is one of the largest studies among non-smoking female population to evaluate the correlation between polymorphisms in TERT and CLPTM1L genes with risks of lung cancer, and also the gene–environment interaction in the development of lung cancer. The strength of this study is its low rate of misclassification of outcome, as all of the cases were pathologically confirmed. The most important limitation of the study was the sample size in stratified analyses and interaction analyses, where some of the subgroups were too small in sample size. Consequently, some of the results in the present study could be attributed to chance.

In summary, our study sheds light on the relationship between polymorphisms in the TERT and CLPTM1L genes with environmental risk factors and susceptibility to lung cancer in non-smoking females in northeast China. Our results show that the rs2736100 in TERT gene may be associated with risk of lung cancer in Chinese non-smoking female population. While the functional biological validity remains elusive, additional larger studies are needed to validate our findings.

Conclusion

The present study indicates that TERT polymorphism (rs2736100) might be a genetic susceptibility factor for lung cancer in non-smoking females in China.

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Conflict of interest The authors declare that they have no conflict of interest.

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