GMR Genetics and Molecular Research
Online Journal
ISSN:1676-5680

Decreased risk of developing lung cancer in subjects carrying the *CLPTM1L* rs401681 (G>A) polymorphism: evidence from a meta-analysis

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Genet. Mol. Res. 13 (1): 1373-1382 (2014)
Received January 16, 2013
Accepted July 20, 2013
Published February 28, 2014
DOI http://dx.doi.org/10.4238/2014.February.28.10

ABSTRACT. A genome-wide association study revealed that a single nucleotide polymorphism, *CLPTM1L* - rs401681 (G>A), located at the 5p15.33 locus was significantly associated with increased risk of various cancers; however, its association with lung cancer is currently inconclusive. In order to explore the relationship between this polymorphism and lung cancer risk more precisely, we performed a meta-analysis of eight eligible studies involving 9935 cases and 11,261 controls. The pooled odds ratio (OR) and the 95% confidence interval (CI) were calculated using a fixed- or random-effect models. Results indicated that this polymorphism was significantly associated with lung cancer risk in all genetic models (*GA vs GG*: OR = 0.88, 95%CI = 0.83-0.94; *AA vs GG*: OR = 0.81, 95%CI = 0.70-0.93; *AA*/*GA vs GG*: OR = 0.86, 95%CI = 0.81-0.91; *AA vs GA*/*GG*:

OR = 0.86, 95%CI = 0.76-0.99). An analysis stratified by ethnicity and source of controls revealed a significantly decreased risk among European groups and population-based studies in all genetic models, and among Asian populations only in the dominant model comparison. Additionally, in a subgroup analysis by histology type, the *CLPTM1L* rs401681 polymorphism was found to significantly decrease the risks of both adenocarcinoma and squamous cell carcinoma of the lung in all genetic models. In conclusion, our study indicated that the *CLPTM1L* - rs401681 (G>A) polymorphism was significantly associated with decreased lung cancer risk, especially among European populations. Due to some minor limitations, our findings should be confirmed in further studies.

Key words: Genetic polymorphism; *TERT-CLPTM1L*; rs401681 (G>A); Lung cancer; Meta-analysis

INTRODUCTION

Lung cancer is the most frequently diagnosed cancer and the leading cause of cancer-related deaths throughout the world (Jemal et al., 2011). It has been estimated that there were nearly 221,130 newly diagnosed cases and 156,940 deaths caused by lung cancer in the United States in 2011 (Siegel et al., 2011). The high lethality of lung cancer is due to the late stage of its diagnosis, although early diagnosis and incorporation of targeted therapies have improved clinical outcomes only modestly (Zhang et al., 2011). Tobacco smoking and occupational environmental exposure are well established to be the major etiological risk factors for lung cancer (Steliga and Dresler, 2011). However, some nonsmokers can also develop lung cancer, suggesting that other risk factors, such as genetic susceptibility, might have tremendous importance to the development of individual lung cancer cases (Yokota et al., 2010; Brennan et al., 2011).

Recently, genetic studies, in particular genome-wide association studies (GWAS), have led to the discovery of several chromosomal regions that contain genes associated with lung cancer risk, including those encoding p53, *BRCA1*, and serine/threonine kinase (Reguart et al., 2008; Sreeja et al., 2008; Strazisar et al., 2009). In addition, 5p15.33 was recently identified as a susceptibility region for lung cancer, where the telomerase reverse transcriptase (*TERT*) and cleft lip and palate transmembrane 1-like (*CLPTM1L*) genes are located (Kang et al., 2008; McKay et al., 2008; Wang et al., 2008; Jin et al., 2009; Rafnar et al., 2009; Zienolddiny et al., 2009; Hsiung et al., 2010). *TERT* is a main functional subunit and key regulator of the telomerase enzyme. Although the function of the *CLPTM1L* is largely unknown, this predicted transmembrane protein was found to be up-regulated in a cisplatin-resistant ovary cancer cell line, and was suggested to be involved in the apoptotic response of cells under the genotoxic stress of cisplatin (Zienolddiny et al., 2009). Moreover, *CLPTM1L* variants are hypothesized to increase the metabolic activation of reactive metabolites and/or the formation and persistence of DNA adducts (Rafnar et al., 2009). Subsequent analysis indicated that the major allele (G) of rs401681 in intron 13 of *CLPTM1L*, which is located at the 5p15.33 locus, was associated with an increased risk of lung, prostate, bladder, and cervix cancers, but a decreased risk of melanoma and colorectal cancer (Wang et al., 2008; Choi et al., 2009; Rafnar et al., 2009; Mirabello et al., 2010; Hosking et al., 2011). Bae et al. (2012) found that

the rs401681 polymorphism was associated with a significantly decreased risk of lung cancer under a dominant model in a Korean population. To date, several studies have reported an association between the rs401681 polymorphism of *CLPTM1L* and susceptibility to lung cancer; however, results are inconclusive. Hence, we conducted a meta-analysis on all eligible case-control studies, involving 9935 cases and 11,261 controls, in order to estimate the overall lung cancer risk of the rs401681 polymorphism as well as to quantify the potential between-study heterogeneity level.

MATERIAL AND METHODS

Identification and eligibility of relevant studies

We searched PubMed and Embase (updated to December 31, 2012) using the following search terms: "*TERT-CLPTM1L*" or "rs401681", "genetic variant" or "polymorphism", "lung cancer", and "carcinoma" or "cancer". The search was limited to English-language articles. We also used a manual search of references of original studies on this topic in order to identify additional studies. When several studies by the same author analyzed overlapping data, we selected data from only the most recent study with the largest number of subjects. Studies included in our meta-analysis met the following inclusion criteria: a) evaluated the *CLPTM1L* rs401681 polymorphism and cancer risk, b) used a case-control design, and c) contained available genotype frequency data.

Data extraction

Two investigators independently extracted data and reached a consensus on all items in cases of conflicting evaluations. For each eligible study, the following data were extracted: the first author's name, year of publication, ethnicity, country of origin, source of controls, Hardy-Weinberg equilibrium (HWE), genotyping method，and numbers of genotyped cases and controls. Ethnic descents were categorized as European and Asian. For studies including subjects of different histological types of lung cancer, adenocarcinoma (AC) and squamous cell carcinomas (SCC), data were extracted separately whenever possible.

Statistical analysis

The strength of the association between the *CLPTM1L* rs401681 polymorphism and lung cancer risk was assessed by the odds ratio (OR) and the 95% confidence interval (95%CI). Pooled ORs were obtained from the combination of individual studies by heterozygote comparison (*GA vs GG*), homozygote comparison (*AA vs GG*), a dominant model (*AA*/*GA vs GG*), and a recessive model (*AA vs GA*/*GG*). Considering the possibility of heterogeneity across studies, a statistical test for heterogeneity was performed based on the Q statistic (Handoll, 2006). If the P value of the Q-test was <0.05, indicating a lack of heterogeneity across studies, the summary OR estimate of each study was calculated by the fixed-effect model [the Mantel-Haenszel (1959) method]. Otherwise, the random-effect model [the DerSimonian and Laird (1986) method] was used. Stratified analyses were also performed by ethnicity, source of controls, and histological types of lung cancer. Sensitivity analyses were performed to evaluate the stability of the results

by deleting a single study in the meta-analysis each time to show the influence of the individual data set to the pooled OR. Funnel plots and the Egger linear regression test were used to assess the potential publication bias (Egger et al., 1997). All analyses were performed using the Stata software (version 8.2; StataCorp. LP, College Station, TX, USA), using two-sided P values.

RESULTS

Study characteristics

A total of eight eligible studies involving 9935 cases and 11,261 controls were included in the pooled analyses (Amos et al., 2008; Hung et al., 2008; Wang et al., 2008, used twice; Zienolddiny et al., 2009; Yoon et al., 2010; Bae et al., 2012; Chen et al., 2012). The main characteristics of these studies are summarized in Table 1. All studies are case-control studies, in which five involved European descendants (American, British, French, and Norwegian), and three involved Asian descendants (Korean and Chinese). Controls were mainly matched for gender and age, including four population-based controls and four hospital-based controls. The TaqMan assay was performed in four of the eight studies. With the exception of two studies (Amos et al., 2008; Chen et al., 2012), the distribution of genotypes in the controls did not deviate from HWE. In addition, five studies provided genotype frequency data for different histological types of patients (Amos et al., 2008; Wang et al., 2008; Yoon et al., 2010; Chen et al., 2012).

Table 1. Characteristics of the literature included in meta-analysis.

Author	Year	Country	Ethnicity	Genotyping method	Source of controls	Case			Control			HWE
						GG	GA	AA	GG	GA	AA	
Wang[1]	2008	England	European	Illumina & PCR	Population	689	927	334	451	701	286	0.648
Wang[2]	2008	England	European	Illumina & PCR	Population	868	1134	394	994	1506	551	0.640
Amos	2008	America	European	TaqMan	Population	396	570	187	336	596	205	0.035
Hung	2008	France	European	Illumina & PCR	Hospital	710	949	261	857	1239	421	0.453
Zienolddiny	2009	Norway	European	TaqMan	Population	117	224	90	107	177	57	0.261
Yoon	2010	Korean	Asian	TaqMan	Hospital	424	324	56	685	626	159	0.373
Bae	2012	Korean	Asian	PCR	Hospital	545	434	107	499	484	96	0.162
Chen	2012	China	Asian	TaqMan	Hospital	95	90	10	126	77	25	0.016

HWE = Hardy-Weinberg equilibrium; [1]UK GWA Study; [2]UK-Replication GWA Study.

Quantitative synthesis

The evaluation of the association between the *CLPTM1L* rs401681 polymorphism and the susceptibility to lung cancer is presented in Table 2. Overall, the variant A allele of rs401681 G>A could significantly decrease the risk of lung cancer in all genetic models (heterozygote comparison, *GA vs GG*: OR = 0.88, 95%CI = 0.83-0.94, $P_{heterogeneity}$ = 0.084; homozygote comparison, *AA vs GG*: OR = 0.81, 95%CI = 0.70-0.93, $P_{heterogeneity}$ = 0.024; dominant model, *AA*/*GA vs GG*: OR = 0.86, 95%CI = 0.81-0.91, $P_{heterogeneity}$ = 0.117; recessive model, *AA vs GA*/*GG*: OR = 0.86, 95%CI = 0.76-0.99, $P_{heterogeneity}$ = 0.016).

In the analysis stratified by ethnicity, every genetic comparison produced a significantly decreased risk in the European group (*GA vs GG*: OR = 0.88, 95%CI = 0.83-0.95, $P_{heterogeneity}$ = 0.392; *AA vs GG*: OR = 0.80, 95%CI = 0.73-0.88, $P_{heterogeneity}$ = 0.080; *AA*/*GA vs GG*: OR = 0.86, 95%CI = 0.81-0.92, $P_{heterogeneity}$ = 0.207; *AA vs GA*/*GG*: OR = 0.87, 95%CI =

0.80-0.94, $P_{heterogeneity}$ = 0.150), whereas a significant association was only detected in the dominant model comparison in the Asian group (*AA*/*GA vs GG*: OR = 0.85, 95%CI = 0.76-0.96, $P_{heterogeneity}$ = 0.060). Considering the control source, studies with population-based controls showed reduced risks in four genetic comparisons (*GA vs GG*: OR = 0.87, 95%CI = 0.80-0.94, $P_{heterogeneity}$ = 0.324; *AA vs GG*: OR = 0.82, 95%CI = 0.74-0.92, $P_{heterogeneity}$ = 0.056; *AA*/*GA vs GG*: OR = 0.86, 95%CI = 0.79-0.92, $P_{heterogeneity}$ = 0.124; *AA vs GA*/*GG*: OR = 0.90, 95%CI = 0.82-0.99, $P_{heterogeneity}$ = 0.179). By contrast, studies with hospital-based controls only presented significant associations in homozygote and dominant model comparisons (*AA vs GG*: OR = 0.75, 95%CI = 0.65-0.86, $P_{heterogeneity}$ = 0.057; *AA*/*GA vs GG*: OR = 0.87, 95%CI = 0.80-0.94, $P_{heterogeneity}$ = 0.124). Additionally, in the analysis grouped by histological types of lung cancer, the *CLPTM1L* - rs401681 (G>A) polymorphism significantly decreased the risk of both AC and SCC of the lung in all genetic models (Table 2).

Table 2. Stratified analyses of effects of the *CLPTM1L* rs401681 G>A polymorphism on lung cancer risk.

Variables	N[1]	Case/control	GA *vs* GG		AA *vs* GG		AA/GA *vs* GG		AA *vs* GA/GG	
			OR	P	OR	P	OR	P	OR	P
Total	8	9935/11261	0.88 (0.83-0.94)	0.084	0.81 (0.70-0.93)[1]	0.024	0.86 (0.81-0.91)	0.117	0.86 (0.76-0.99)[1]	0.016
Ethnicity										
Asian	3	2085/2777	0.96 (0.73-1.26)[1]	0.015	0.71 (0.45-1.13)[1]	0.024	0.85 (0.76-0.96)	0.060	0.72 (0.43-1.21)[1]	0.006
European	5	7850/8484	0.88 (0.83-0.95)	0.392	0.80 (0.73-0.88)	0.080	0.86 (0.81-0.92)	0.207	0.87 (0.80-0.94)	0.150
Source										
Population	4	5930/5967	0.87 (0.80-0.94)	0.324	0.82 (0.74-0.92)	0.056	0.86 (0.79-0.92)	0.124	0.90 (0.82-0.99)	0.179
Hospital	4	4005/5294	0.93 (0.78-1.09)[1]	0.032	0.75 (0.65-0.86)	0.057	0.87 (0.80-0.94)	0.124	0.77 (0.57-1.02)[1]	0.017
Histology										
AC	5	2324/7324	0.82 (0.74-0.91)	0.152	0.72 (0.62-0.84)	0.160	0.80 (0.72-0.88)	0.434	0.82 (0.71-0.94)	0.068
SCC	5	2097/7324	0.88 (0.79-0.98)	0.530	0.74 (0.64-0.86)	0.708	0.85 (0.77-0.94)	0.715	0.81 (0.70-0.93)	0.497

AC = adenocarcinoma, SCC = squamous cell carcinomas. N = number of comparisons. P value of the Q-test for heterogeneity test. [1]Random-effect model was used when P < 0.05 for the heterogeneity test; otherwise, fixed-effect model was used.

Test of heterogeneity

There was significant heterogeneity for the homozygote comparison (*AA vs GG*: $P_{heterogeneity}$ = 0.024) and recessive model comparison (*AA vs GA*/*GG*: $P_{heterogeneity}$ = 0.016), but not for the heterozygote comparison (*GA vs GG*: $P_{heterogeneity}$ = 0.084) and dominant model comparison (*AA*/*GA vs GG*: $P_{heterogeneity}$ = 0.117). Thus, we assessed the source of heterogeneity for the homozygote comparison by examining ethnicity, source of controls, and the genotyping method. Meta-regression analyses showed that none of these concomitant variables could account for the substantial heterogeneity observed (ethnicity: P = 0.478, genotyping method: P = 0.808, source of controls: P = 0.352).

Sensitivity analysis

Sensitivity analyses indicated that no single study significantly influenced the summary OR or the 95%CI. Although genotype distributions in two studies failed to meet HWE, corresponding pooled ORs were not quantitatively altered by their inclusion in the study. Similarly, no single study influenced the pooled OR qualitatively, as indicated by sensitivity analyses, suggesting that results of this meta-analysis were statistically robust.

Publication bias

Begg's funnel plot and the Egger test were performed to assess the publication bias of the literature. The shape of the funnel plots did not reveal any evidence of obvious asymmetry (Figure 1 shows the funnel plot of the overall *GA vs GG* and *AA*/*GA vs GG* comparisons). Then, the Egger test was used to provide statistical evidence of funnel plot symmetry. Results still did not show any obvious evidence of publication bias (*GA vs GG*: $P_{heterogeneity} = 0.065$; *AA*/*GA vs GG*: $P_{heterogeneity} = 0.054$), indicating that our results were statistically robust.

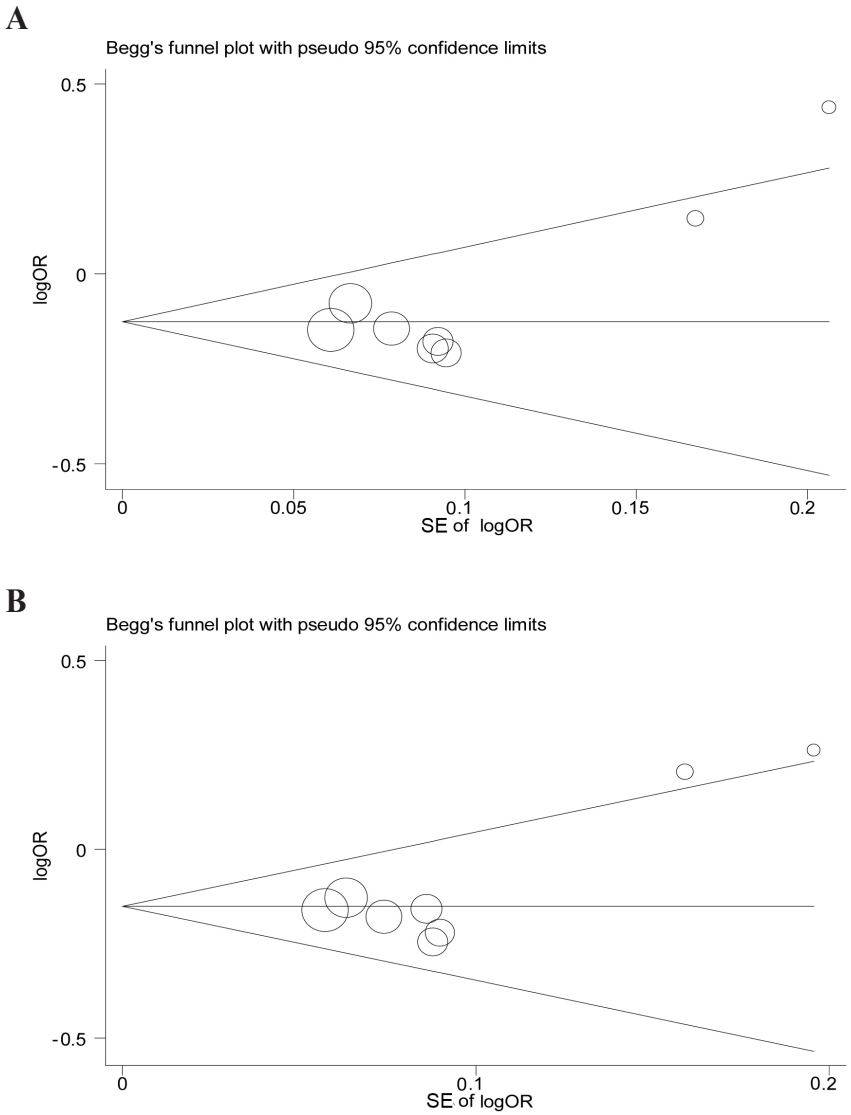

Figure 1. Begg's funnel plot of publication bias test. **A.** *GA vs GG*; **B.** *AA*/*GA vs GG*. Each point represents a separate study for the indicated association. Log (OR) = natural logarithm of odds ratio. Horizontal line = mean effect size.

DISCUSSION

In the current meta-analysis, we ascertained that the *CLPTM1L* - rs401681 (G>A) polymorphism was significantly associated with decreased lung cancer risk, especially within the European population. To our knowledge, this is the first study to investigate the association between the *CLPTM1L* - rs401681 (G>A) polymorphism and the risk of lung cancer across different ancestries and diverse histological types.

CLPTM1L was previously found to be enriched in the mitochondria compared with plasma membrane protein extracts, and its mRNA expression level was an average of 2.24-fold higher in tumor tissues compared to tumor-adjacent tissues, although the exact mechanism of this regulation remains unknown (James et al., 2012; Ni et al., 2012). A previous study showed that *CLPTM1L* was an up-regulated transcript in cisplatin-resistant ovarian tumor cell lines (Yamamoto et al., 2001). Interestingly, it was found that the *CLPTM1* homolog was expressed at higher levels in doxorubicin-resistant breast cancer (Folgueira et al., 2005). Recently, a genetic variant within the *CLPTM1L* gene (rs402710) was shown to be associated with the accumulation of DNA adducts in lung tissue adjacent to tumors (Zienolddiny et al., 2009). Recent studies have demonstrated that *CLPTM1L* is over-expressed in lung tumor cells, which are protected from genotoxic stress-induced apoptosis through the regulation of *Bcl-xL* (James et al., 2012). Three GWAS (UK-GWA, IARC-GWA, and Texas-GWA) were the first to show the association between the *CLPTM1L* - rs401681 (G>A) polymorphism and the risk of lung cancer in the European population (Amos et al., 2008; Hung et al., 2008; Wang et al., 2008). In a study involving 20,726 cases and 134,650 controls, it was reported that *CLPTM1L* - rs401681 [G] genotypes significantly increased the risk of lung cancer, bladder cancer, prostate cancer, and basal cell carcinoma (Rafnar et al., 2009). Several studies have revealed a significant association between the *CLPTM1L* - rs401681 (G>A) polymorphism and lung cancer risk, but results are inconclusive because of various reasons, such as different ethnicities, resident areas, sample sizes, environmental factors, and smoking state. To provide a more comprehensive analysis of this association, we carried out a meta-analysis involving 9935 cases and 11,261 controls. Results of this meta-analysis suggested that the *CLPTM1L* - rs401681 (G>A) polymorphism was significantly associated with decreased risk of lung cancer under all genetic models. Results were consistent with conclusions of previous studies (Amos et al., 2008; Hung et al., 2008; Wang et al., 2008; Zienolddiny et al., 2009; Yoon et al., 2010; Bae et al., 2012; Chen et al., 2012).

In the analysis stratified by ethnicity, statistically significant decreased risks were found for every genetic comparison among Europeans, but only for the dominant model comparison among Asians. Many genetic variants that were significantly associated with one disease in one population did not necessarily show the same association in another population. Although the exact mechanism for these ethnic differences is still unknown, one possible reason is due to differences in genetic backgrounds and in the environmental and lifestyle context (such as dietary habits, alcohol consumption, and tobacco smoking) (Bunney et al., 2009). In addition, the influence of the *CLPTM1L* - rs401681 (G>A) polymorphism might be masked by the presence of other important single nucleotide polymorphisms that scan in the *TERT-CLPTM1L* region, especially those in high linkage disequilibrium with rs401681 (such as rs31490 and rs414965) or those in similar biological pathways involved in lung cancer risk. Other factors, such as different matching criteria, selection bias, and limited number of studies with available data, may have insufficient statistical power to detect a slight difference and

may also generate a fluctuated risk estimate. The different results demonstrated the importance of evaluating genetic effects on the development and progression of the disease in various populations.

When compared by source of control, we observed a significantly decreased lung cancer risk for every genetic comparison among studies using population-based controls, whereas using hospital-based controls, only the homozygote and dominant model comparisons showed a decreased risk. Because biases may exist in hospital-based studies, such controls may represent a sample of an ill-defined reference population instead of the general population, particularly when genotypes investigated were associated with the disease that the hospital-based controls may have. Thus, these findings emphasized the advantages of population-based studies, including greater efficiency in sample recruitment and external validity, compared to other study designs (Szklo, 1998; Hancock and Scott, 2007).

AC and SCC are the major histological types of non-small cell lung cancer (NSCLC). Although it was previously acceptable to classify lung carcinomas as either small cell or NSCLC without further division, growing biological and epidemiological data suggest that SCC and AC, differing by their histopathological and clinical characteristics and their relationship with smoking, are distinct etiological entities that should be analyzed separately (Sato et al., 1994). Ni et al. (2012) indicated that the percentage of strong staining of *CLPTM1L* expression in AC was higher than that in SCC. A previous study found that the effect of rs401681 on the risk of lung cancer was significant only for AC and not for SCC (Bae et al., 2012). Therefore, in the present study, stratified analyses were performed by histological type. We observed that the *CLPTM1L* - rs401681 (G>A) polymorphism was significantly associated with decreased risk of lung cancer in all genetic models in both the SCC and AC groups. Moreover, the decreased risk in the AC group was 5% more than that of the SCC group when compared in the dominant model (OR: 0.80 *vs* 0.85). Future studies incorporating more data of the histological characteristics of lung cancer should be conducted to confirm our results.

As with all meta-analysis, some limitations of our meta-analysis may have affected the objectivity of the conclusions and must be considered when interpreting the results. First, unadjusted estimates were applied in our meta-analysis owing to a lack of adjusted estimates, and a more precise evaluation should be conducted if more detailed individual data become available, such as information about age and gender. Lack of information may cause serious confounding bias. Second, the quantity of published studies was not sufficiently large for a comprehensive analysis, and lacking original data in some studies limited our further evaluation of potential interactions, such as detailed genotypes, histological types, and tumor staging of lung cancer. Finally, gene-gene and gene-environment interactions were not fully addressed in our meta-analysis owing to lack of sufficient data. Previous studies have demonstrated that interactions among smoking and some genetic polymorphisms were associated with lung cancer risk (Herbst et al., 2008; Li et al., 2009). Further studies are expected to explore potential gene-gene and gene-environment interactions.

In spite of these limitations, our present meta-analysis also had some advantages. First, to our knowledge, this was the first meta-analysis to report the association between the *CLPTM1L* - rs401681 (G>A) polymorphism and lung cancer risk, and to further show the association by ethnicity and histological type. Second, we pooled a substantial number of cases and controls from different studies, which greatly increased the statistical power of the analysis. Third, no publication biases were detected, which indicated that the results were likely unbiased.

In conclusion, our meta-analysis suggests that the *CLPTM1L* - rs401681 (G>A) polymorphism is associated with lung cancer risk, especially within the European population. The *CLPTM1L* - rs401681 (G>A) polymorphism is an independent protective factor for the development of lung cancer. Nevertheless, larger and well-designed multicentric studies based on various ethnic groups and histological types should be carried out to validate our findings and to investigate further associations between *CLPTM1L* polymorphisms and lung cancer risk in relation to other potential lung cancer risks.

ACKNOWLEDGMENTS

Research partially supported by the Jiangsu Provincial 12th Five-Year Program on Developing Health by Technology and Education Project.

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