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Original Article

CLPTM1L polymorphism and lung cancer risk

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Abstract: The association of Cleft Lip and Palate Transmembrane Protein 1 (CLPTM1L) rs31489 polymorphism with risk of lung cancer has been evaluated in many studies; however, the results from these studies are controversial. Thus, further analysis on association between CLPTM1L rs31489 polymorphism and risk of lung cancer is needed among a larger study population. A literature search in PubMed, Embase, Web of Science, Science Direct, SpringerLink, EBSCO, Wanfang, and Chinese National Knowledge Infrastructure (CNKI) databases was carried out to identify studies investigating the association between lung cancer risk and CLPTM1L rs31489 polymorphism. The strength of the association between CLPTM1L rs31489 polymorphism and lung cancer risk was estimated by calculating odds ratios (ORs) and corresponding 95% confidence intervals (CIs). In the overall analysis, there was significant association between CLPTM1L rs31489 polymorphism and lung cancer risk under an allele model (OR = 1.12; 95% CI, 1.06-1.18; P < 0.00001; I^2 = 57%). Subgroup analysis by ethnicity was performed. Stratified analysis by ethnicity showed that a statistically increased cancer risk was found in the Caucasian population (OR = 1.15; 95% CI, 1.10-1.21; P < 0.00001; I^2 = 22%), but there was no significant association between lung cancer risk and CLPTM1L rs31489 polymorphism in the Asian population (OR = 1.03; 95% CI, 0.97-1.08; P = 0.37; I^2 = 15%). In conclusion, this meta-analysis demonstrates that CLPTM1L rs31489 polymorphism significantly modified the risk of lung cancer.

Keywords: Lung cancer, CLPTM1L, genetics

Introduction

Lung cancer is currently one of the most common malignant tumours, and non-small cell lung cancer (NSCLC) accounts for about 75-80% of lung cancer [1]. Due to lack of early diagnostic methods 75% of patients are diagnosed too late and lose the opportunity for surgery [2-4]. Non-small cell lung cancer is prone to distant metastasis, and currently there is no effective treatment to control it. So far, in NSCLC, the 5-year survival rate after treatment is only 10% [5]. So how to further improve the efficacy of NSCLC is still a major issue of clinical research.

Cleft Lip and Palate Transmembrane Protein 1 (CLPTM1L) encodes a protein that has been found to be upregulated in cisplatin-resistant ovarian tumor cell lines and may be associated with apoptosis [6]. Furthermore, CLPTM1L has been observed to be overexpressed in human lung tumors and lung tumor cell lines [7, 8].

Some studies have shown the association of the CLPTM1L rs31489 polymorphism with lung cancer risk. However, the results remained inconsistent rather than conclusive. In the present study, we performed meta-analyses to evaluate and summary the contribution of this polymorphism to lung cancer susceptibility in different populations.

Methods

Publication search

A literature search in PubMed, Embase, Web of Science, Science Direct, SpringerLink, EBSCO, Wanfang, and Chinese National Knowledge Infrastructure (CNKI) databases was carried out to identify studies investigating the association between lung cancer risk and CLPTM1L rs31489 polymorphism, without language, time period, or sample size limitations, and covering all papers published up to Oct 2014. The sets of search terms were as follows: "Cleft Lip and

Table 1. Characteristics of the case-control studies

First author	Race	Case	Control	Cases			Controls			HWE
				AA	AC	CC	AA	AC	CC	
Wang a/2008	Caucasian	1951	1434	292	899	760	248	672	514	Yes
Wang b/2008	Caucasian	1153	1136	155	567	431	177	577	382	Yes
Wang c/2008	Caucasian	1916	2508	230	908	778	373	1197	938	Yes
Landi/2009	Caucasian	5739	5848	851	2717	2171	988	2831	2029	Yes
Pande/2011	Caucasian	1681	1635	220	777	684	290	797	548	Yes
Wauters/2011	Caucasian	203	241	34	89	80	46	126	69	Yes
Bae/2012	Asian	1094	1100	16	248	816	23	261	783	Yes
Shiraishi/2012	Asian	6029	13535	120	1461	4448	273	3298	9964	Yes
de Mello/2013	Caucasian	144	144	25	71	48	21	74	49	Yes
Zhao/2013	Asian	784	782	15	189	580	18	199	565	Yes

HWE, Hardy-Weinberg equilibrium.

Palate Transmembrane Protein 1 or CLPTM1L" and "lung cancer, or lung carcinoma, or lung tumor, or lung neoplasma" and "polymorphism, or variant, or SNP".

Inclusion and exclusion criteria

The selection criteria of the retrieved articles in our meta-analysis were as follows: a) case-control studies or cohort studies; b) studies evaluating the association between CLPTM1L rs31489 polymorphism and lung cancer risk; c) identification of lung cancer patients was confirmed histologically or pathologically; and d) sufficient data available to calculate an odds ratio (OR) with 95% confidence interval (CI). The exclusion criteria of the meta-analysis were: a) case-only studies; b) studies with incomplete data; and c) meta-analyses, letters, reviews, and editorial articles. If more than one study was published by the same author using the same patient population or overlapping case series, the study with the largest size of samples was included.

Data extraction

Three investigators reviewed and extracted information independently from selected publications in accordance with the above mentioned inclusion and exclusion criteria. Any conflicts over study/data inclusion were settled by a discussion between the investigators. The following data were extracted from included studies: first author, study period, race, the number of cases and controls, genotype number of CLPTM1L rs31489 polymorphism in cases and controls, and Hardy-Weinberg equilibrium (HWE).

Statistical analysis

Deviations from HWE were tested using Fisher's exact test to evaluate the genetic equilibrium of each study. The strength of the association between CLPTM1L rs31489 polymorphism and lung cancer risk was estimated by calculating ORs with 95% CIs, based on the genotype frequencies in cases and controls in allele model. Tests for heterogeneity were made among studies using the Cochran's Q and I^2 test statistic. For the Cochran's Q test statistic, a P value < 0.10 was accepted as statistically significant heterogeneity. Random-effects models were used to estimate summary ORs and 95% CIs. To examine potential sources of heterogeneity, we also conducted subgroup analyses by ethnicity (Asian and Caucasian population). Galbraith plot was also performed to identify sources of heterogeneity. Sensitivity analyses were conducted to assess the strength of our findings by excluding one study at a time. Begg's funnel plot and Egger's regression test were used to evaluate publication bias. In Egger's test, when P value < 0.10, it was considered statistically significant publication bias. All analyses were conducted using Stata v.12 (StataCorp LP, TX) statistical software.

Results

Study characteristics

Eight studies (10 case-control studies), with 20680 cases and 28330 controls, were included in this meta-analysis [9-16]. **Table 1** lists the studies identified and their main characteristics. There were three studies conducted in Asian populations and seven studies in Cau-

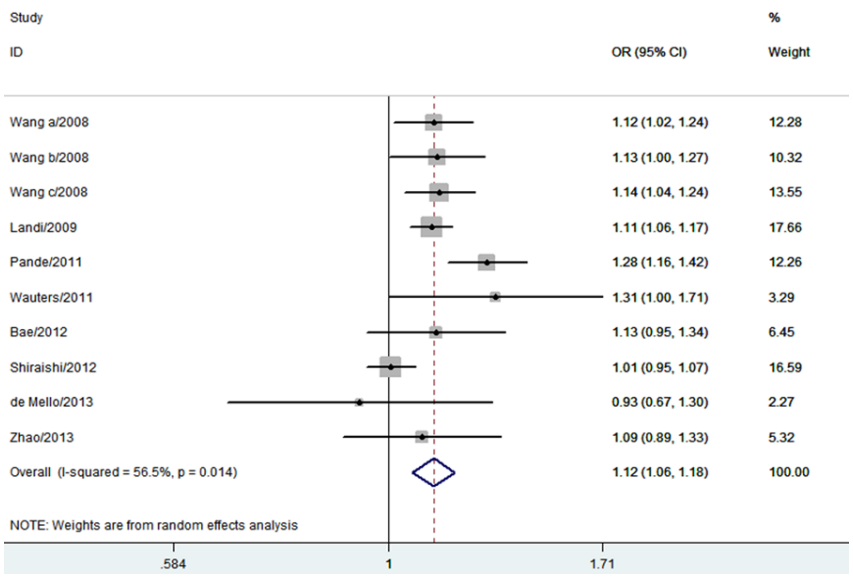

Figure 1. Forest plot for association between CLPTM1L rs31489 polymorphism and lung cancer risk.

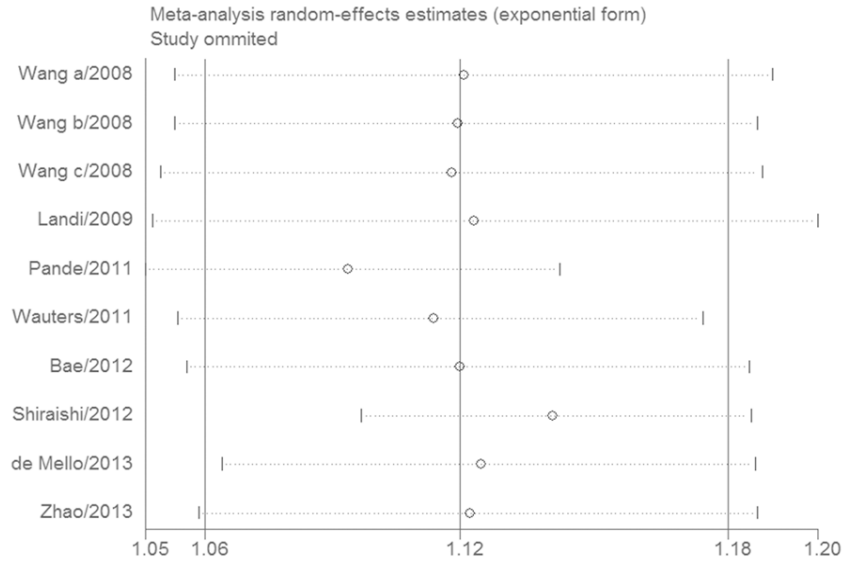

Figure 2. Sensitivity analysis for the association between CLPTM1L rs31489 polymorphism and lung cancer risk.

casian populations. The genotype distribution of CLPTM1L rs31489 polymorphism in the controls was in compliance with HWE.

Results of meta-analysis

In the overall analysis, there was significant association between CLPTM1L rs31489 polymorphism and lung cancer risk under an allele model (OR = 1.12; 95% CI, 1.06-1.18; P < 0.00001; I^2 = 57%; **Figure 1**). Subgroup analysis by ethnicity was performed. Stratified analysis by ethnicity showed that a statistically increased cancer risk was found in the Caucasian population (OR = 1.15; 95% CI, 1.10-1.21; P < 0.00001; I^2 = 22%), but there was no significant association between lung cancerrisk and CLPTM1L rs31489 polymorphism in the Asian population (OR = 1.03; 95% CI, 0.97-1.08; P = 0.37; I^2 = 15%). Sensitivity analysis was performed to evaluate the stability of the meta-analysis. Statistically similar data were obtained after sequentially excluding each study, indicating that our results were statistically reliable (**Figure 2**).

The Galbraith plot was used to find the source of the heterogeneity. As shown in **Figure 3**, two studies were the outliers. After excluding these studies, the between-study heterogeneity decreased and there was no obvious heterogeneity among the twenty-four remaining studies (I^2 = 0%, P = 0.91). Besides, the result was still statistically significant (OR = 1.12, 95% CI 1.08-1.16, P < 0.00001).

A Begg's funnel plot was generated, showing nearly symmetrical pattern (**Figure 4**), indicating low possibility of publication bias. Egger's test was also used to quantitatively evaluate publication bias, which confirmed no evidence of bias (P = 0.507).

Discussion

CLPTM1L has been identified as an overexpressed protein in human ovarian tumor cell lines that are resistant to cisplatin [6]. The

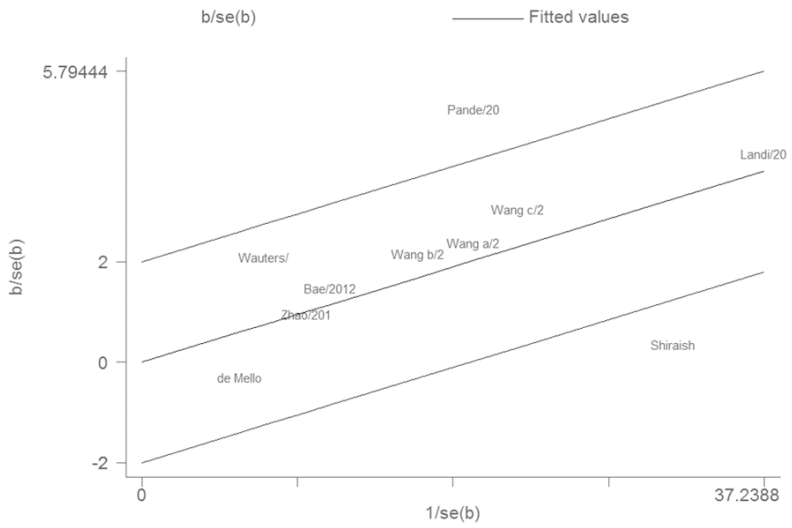

Figure 3. Galbraith plot for the association between CLPTM1L rs31489 polymorphism and lung cancer risk.

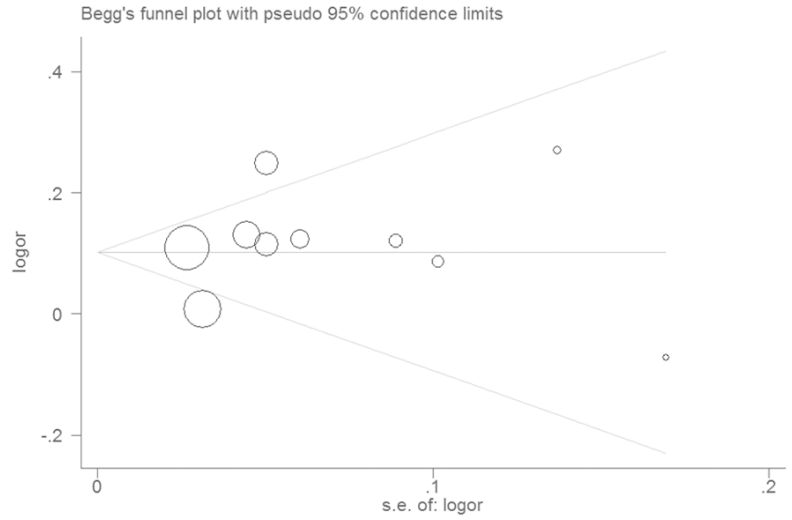

Figure 4. Funnel plots for publication bias of CLPTM1L rs31489 polymorphism and lung cancer risk.

expression of CLPTM1L was also increased in several types of tumor cell lines, including lung, cervical, and renal carcinoma lines [17, 18]. Moreover, the expression of CLPTM1L is increased in a number of different tumor tissues, such as lung cancer and laryngeal squamous cell carcinoma [19]. In vitro experiments demonstrated that CLPTM1L has a protective role against DNA damage-induced apoptosis in lung tumorigenesis through increased accumulation of Bcl-xL, an antiapoptotic Bcl2 family member [8].

Lung cancer is considered to be a complex and multistep disease that results from interactions between environmental and genetic factors, and SNPs are associated with intersubject variation and diversity, and have been recently considered as important genetic factors involved in the development of lung cancer. Several polymorphisms have been described in CLPTM1L gene. The most common polymorphism is rs31489 polymorphism. To date, many studies have investigated the role of the CLPTM1L rs31489 polymorphism in lung cancer. However, the results of these studies remain inconclusive. We, therefore, performed a meta-analysis by pooling 8 eligible studies to clarify this inconsistency and to achieve a more precise estimation of the relationship. Our results demonstrated that CLPTM1L rs31489 polymorphism was significantly associated with increased lung cancer risk.

The stratified analysis by ethnicity revealed a significant association between CLPTM1L rs31489 polymorphism and lung cancer in Caucasians, while the association was not significant in the Asian subgroup. The result in the Asian subgroup was based on 3 studies, suggesting that the studies do not estimate the same effect due to different degree of bias.

The findings in this meta-analysis should be interpreted with caution because of several limitations. First, in the subgroup analysis by ethnicity, the included studies were mainly in Asians and Caucasians, and future study should evaluate the association between CLPTM1L rs31489 polymorphism and lung cancer in different ethnicities, especially in Africans. Second, the meta-analysis was limited by a relatively small number of available studies. It is difficult to perform subgroup analysis for every type of lung cancer. Third, only

published studies in the selected databases were included in this meta-analysis. It is possible that some studies that were not included in these databases or some unpublished studies with null results were not identified, and this may have biased our results. Fourth, gene-gene and gene-environment interactions may play important roles in the function of CLPTM1L rs31489 polymorphism, but the effect was not addressed in our meta-analysis, due to unavailable data.

In conclusion, this meta-analysis demonstrates that CLPTM1L rs31489 polymorphism significantly modified the risk of lung cancer.

Disclosure of conflict of interest

None.

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