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Review Article

CLPTM1L rs401681 polymorphisms decrease the cancer risk: a meta-analysis involving twenty-five case-control studies

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Abstract: Background: CLPTM1L rs401681 polymorphism has a prominent association with cancer risk, as reported. However, these studies have yielded inconsistent results. Method: we systematically searched on PubMed, Medline, EMBASE and Chinese National Knowledge Infrastructure (CNKI), containing all articles published up to October 2016. The odds ratio (OR) and the 95% confidence interval (95% CI) were used to assess the strength of correlation between CLPTM1L rs401681 polymorphism and the risk of cancer. Result: 25 relevant studies containing 14,460 cases and 18,697 controls in an Asian population were included in the study. we observed that CLPTM1L rs401681 polymorphism was significantly related with the risk of cancer (T vs. C, OR = 0.88, 95% CI = 0.83-0.93, $P < 10^{-5}$; CT/TT vs. CC, OR = 0.85, 95% CI = 0.81-0.89, $P < 10^{-5}$; TT vs. CT/CC, OR = 0.82, 95% CI = 0.74-0.93, $P < 10^{-5}$; TT vs. CC, OR = 0.78, 95% CI = 0.69-0.88, $P < 10^{-5}$; CT vs. CC, OR = 0.87, 95% CI = 0.83-0.91, $P < 10^{-5}$). In the subgroup analysis by cancer type, a significant association was observed in the lung cancer subgroup. In addition, we found that rs401681 polymorphism was associated with bladder cancer risk under all genetic models except for CT vs. CC (OR = 0.90, 95% CI = 0.76-1.07). More importantly, the associations were also shown for the first time between CLPTM1L rs401681 polymorphism and esophageal cancer risk. Conclusions: our data suggests that the T allele of CLPTM1L rs401681 contributed to decreasing cancer risk, especially lung cancer, bladder cancer, and esophageal cancer.

Keywords: CLPTM1L, polymorphism, cancer, meta-analysis

Introduction

Cleft lip and palate transmembrane 1 like gene (CLPTM1L), located in chromosome 5p15.33, which was regularly reported to mediate the telomerase function. Telomeres gradually decreased in length during each cell division [1]. Telomere is synthesized by telomerase to make up for the telomere attrition in growing rapidly cells [2, 3]. However, the telomerase activity and telomere length may be reduced by the influence of CLPTM1L gene mutations. Certainly, cancer risk will increase when telomere length is too short to protect genomic stability [4-6]. Furthermore, with the in-depth study of the human gene, especially a genome-wide association study (GWAS), it has been found that variants at the 5p15.33 locus associated with several cancer risks such as esophageal cancer, lung cancer, and pancreatic cancer [5].

Currently, a few of studies have attached importance to the concern between CLPTM1L rs401681 (C > T) polymorphism and cancer susceptibility [7-30], but the results remain inconclusive. For example, some studies indicated that CLPTM1L rs401681 variant was significantly related to cancer risk such as lung cancer, bladder cancer, pancreatic cancer, esophageal cancer [15-17, 31]. Other studies demonstrated that CLPTM1L rs401681 polymorphism was not associated with the risk of cancer, including lung cancer, esophageal cancer [10, 12, 32]. Owing to the oppositely small sample size, these studies may not obtain completely accordant conclusions. So we carried out a meta-analysis on 25 published case-con-

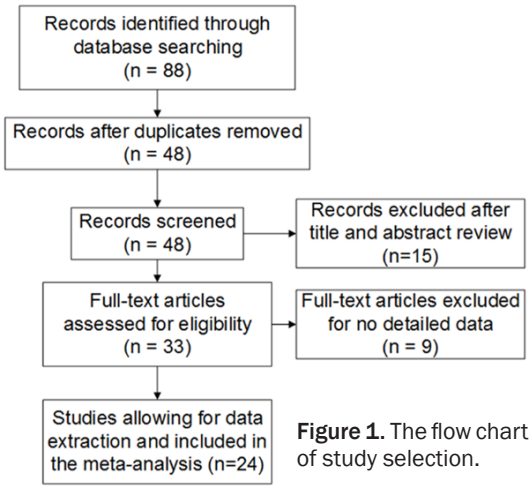


Figure 1. The flow chart of study selection.

trol studies to evaluate and summarize the contribution of this polymorphism to different cancer susceptibility.

Materials and methods

Primary search strategy

Using the following terms: "TERT-CLPTM1L" or "CLPTM1L" or "rs401681", "genetic variant" or "polymorphism", "cancer", and "carcinoma", we systematically searched on PubMed, Medline, EMBASE and Chinese National Knowledge Infrastructure (CNKI), containing all articles published up to October 2016. Furthermore, we hand-searched additional usable case-control studies from reference list of original studies or review articles. Meanwhile, we skimmed the titles and abstracts of potential papers to determine the relevance and eliminate any apparently unrelated studies. Finally, only relevant studies with full-text articles containing useful data were included. If studies were carried out with overlapped subjects, we only retained published ones that disseminate the most versatile information.

Inclusion and exclusion criteria

We read abstracts of all screening published articles. Studies must satisfy the inclusion criteria: (1) articles written in English or Chinese; (2) case-control studies of cancer with CLPTM1L rs401681 polymorphism; (3) obtainable genotype frequency data in cancer cases and controls; and (4) providing sufficient data to estimate an odds ratio (OR) with 95% confidence interval (CI); (5) all participants from Asian population. There are four main reasons why some studies are excluded: (1) case-only or family-based studies; (2) duplicated studies; (3) reviews and meta-analysis; and (4) insufficient data were reported.

Data extraction

After reviewing the papers, unrelated and reduplicative studies are excluded. At the same time, two investigators (Tianming Zhao and Jing Zhu) carefully and independently decided whether single study was applicable to this meta-analysis. We extracted the relevant information from each effective study. Through great efforts of comparing the results, disagreement analysis and rigorous discussion, they finally reached a consensus. The following information were sought and recorded from each study: first author, years of publication, ethnicity of participants, tumor type, definition of cases, source of controls, and the number of cases and controls for each genotype, and results of the Hardy-Weinberg equilibrium (HWE) test.

Statistical analysis

Deviation from Hardy-Weinberg equilibrium (HWE) was examined by chi-square test with 1 degree of freedom. The odds ratio (OR) and the 95% confidence interval (95% CI) were used to assess the strength of correlation between CLPTM1L rs401681 polymorphism and the risk of cancer under five genetic model. Heterogeneity assumption was evaluated by Q-test. If P value of the Q-test was < 0.05 or I^2 > 50%, case-control study heterogeneity was regarded significantly [33]. When homogeneity existed, the fixed model (Mantel-Haenszel method) was used to calculate the summary ORs and 95% CIs; otherwise, the random-effects model (the Der Simonian and Laird method) was selected [34]. Both funnel plot and Egger's test were used to assess the publication bias. If P value > 0.05, the publication bias was non-existent [35]. Sensitivity analyses were carried out to estimate the stability of the results; namely. All statistical analyses were carried out with the Stata software version 13.0 (Stata Corporation, College Station, TX).

Results

Eligible studies

The flowchart of study selection process with specific reasons was presented in **Figure 1**. In

Table 1. Characteristics of published studies included in this meta-analysis

Authors	Year	Source of control	Tumor type	Definition of cases	Genotype method	No. of Cases/Controls	HWE P_{value}
Liu et al. [7]	2015	Healthy	Lung cancer	Pathologically	MassARRAY	292/319	0.696
Xun et al. [8]	2014	Healthy	Lung cancer	Pathologically	MassARRAY	228/299	0.819
Jin et al. [9]	2016	Healthy	Lung cancer	Pathologically	MassARRAY	554/695	0.441
Liang et al. [10]	2014	Healthy	Lung cancer	Pathologically	MassARRAY	309/308	0.631
Zhang et al. [11]	2014	Cancer-free	Lung cancer	Pathologically	TaqMan	366/364	0.097
Zhao et al. [12]	2014	Cancer-free	Lung cancer	Pathologically	TaqMan	951/954	0.502
Li et al. [13]	2013	Healthy	Lung cancer	Pathologically	TaqMan	464/536	0.865
Sun et al. [14]	2013	Healthy	Lung cancer	Pathologically	MassARRAY	200/200	0.942
Zhang et al. [15]	2014	Not described	Bladder cancer	Not described	Not described	367/420	0.683
Wang et al. [16]	2013	Healthy	Lung cancer	Not described	HRMA-PCR	492/486	0.076
Yin et al. [17]	2014	Cancer-free	EC	Pathologically	PCR-LDR	604/664	0.365
Bae et al. [18]	2012	Healthy	Lung cancer	Not described	Not described	1086/1079	0.162
Dominguez et al. [19]	2010	Not described	Bladder cancer	Pathologically	TaqMan	500/529	0.292
Myneni et al. [20]	2013	Healthy	Lung cancer	Not described	MassARRAY	350/441	0.668
Jiang et al. [21]	2013	Healthy	Lung cancer	Pathologically	TaqMan	726/860	0.805
Jiang et al. [21]	2013	Healthy	EC	Pathologically	TaqMan	753/860	0.805
Zhang et al. [22]	2011	Healthy	Other cancer (NPC)	Pathologically	PCR-RFLP	1782/1972	0.470
Liu et al. [23]	2015	Healthy	Lung cancer	Pathologically	MassARRAY	304/319	0.696
Lv et al. [24]	2013	Healthy	Lung cancer	Pathologically	TaqMan	602/1060	0.939
Liu et al. [25]	2014	Healthy	Other cancer (PC)	Pathologically	TaqMan	766/821	0.263
Wang et al. [26]	2015	Healthy	EC	Pathologically	MassARRAY	359/310	0.782
Su et al. [27]	2014	Cancer-free	Other cancer (HCC)	Not described	TaqMan	201/210	0.337
Yoon et al. [28]	2010	Healthy	Lung cancer	Pathologically	TaqMan	1425/3011	0.217
Ke et al. [29]	2013	Healthy	Lung cancer	Pathologically	TaqMan	602/1060	0.949
Ma et al. [30]	2012	Healthy	Bladder cancer	Pathologically	MassARRAY	177/920	0.442

EC: Esophageal cancer; NPC: Nasopharyngeal carcinoma; PC: Pancreatic cancer; HCC: Hepatocellular carcinoma.

total, twenty-four eligible articles on CLPTM1L rs401681 polymorphism in cancer was in accordance with the study inclusion [7-30]. One article reported two case-control studies [21]. Thus, 25 correlated studies involving 14,460 cases and 18,697 controls were ultimately selected for this meta-analysis. The major features of these studies showed in **Table 1**. All participants from the studies were from Asian region and most of cases were pathologically diagnosed. The distribution of genotypes frequencies in the controls consist with HWE test except for two studies [36, 37], which is ruled out.

Meta-analysis results

Table 2 listed the evaluation of association between CLPTM1L rs401681 polymorphism and cancer risk in Asian population. In all, CLPTM1L rs401681 polymorphism had a prominent correlation with risk of cancer (T vs. C, OR = 0.88, 95% CI = 0.83-0.93; CT/TT vs. CC, OR = 0.85, 95% CI = 0.81-0.89; TT vs. CT/CC, OR = 0.82, 95% CI = 0.74-0.93; TT vs. CC, OR = 0.78, 95% CI = 0.69-0.88; CT vs. CC, OR = 0.87, 95% CI = 0.83-0.91, **Figure 2**; **Table 2**). Furthermore, the results of stratified analysis by tumor type suggested that rs401681 polymorphism was relative with a significantly decreased risk of lung cancer (T vs. C, OR = 0.86, 95% CI = 0.82-0.89; CT/TT vs. CC, OR = 0.83, 95% CI = 0.78-0.88; TT vs. CT/CC, OR = 0.80, 95% CI = 0.71-0.91; TT vs. CC, OR = 0.74, 95% CI = 0.66-0.84; CT vs. CC, OR = 0.85, 95% CI = 0.80-0.90, **Table 2**). Additionally, we observed that under all genetic models, except for CT vs. CC (OR 0.90, 95% CI 0.76-1.07), other four models suggested that CLPTM1L rs401681 polymorphism was associated with bladder cancer risk. More importantly, the associations were also observed between CLPTM1L rs401681 polymorphism and esophageal cancer risk proved by T vs. C (OR = 0.86, 95% CI = 0.77-0.97), CT/TT vs. CC (OR = 0.80, 95% CI =

Table 2. Total and stratified analyses of the CLPTM1L rs401681 polymorphism on cancer risk

Variable	No[a]	Cases/controls	T vs. C			TT/CT vs. CC		
			OR: 95% CI	*P*[b]	*P*	OR: 95% CI	*P*[b]	*P*
Total	25	14460/18697	0.88 [0.83-0.93]	0.00[c]	0.00	0.85 [0.81-0.89]	0.01	0.00
Cancer type								
Lung cancer	16	8951/11991	0.86 [0.82-0.89]	0.57	0.00	0.83 [0.78-0.88]	0.75	0.00
Bladder cancer	3	1044/1869	0.85 [0.75-0.96]	0.89	0.01	0.85 [0.73-1.00]	0.85	0.05
Esophageal cancer	3	1716/1834	0.86 [0.77-0.97]	0.30	0.01	0.80 [0.70-0.92]	0.14	0.00
Other cancer	3	2749/3003	1.11 [0.78-1.59]	0.00	0.20	0.95 [0.86-1.06]	0.00	0.37
Sample size								
Small	11	3468/3676	0.86 [0.78-0.94]	0.08	0.00	0.84 [0.76-0.92]	0.02	0.00
Large	14	10992/15021	0.89 [0.83-0.95]	0.00	0.00	0.85 [0.81-0.89]	0.07	0.00
Variable	No[a]	TT vs. CT/CC			TT vs. CC			CT vs. CC		
		OR: 95% CI	*P*[b]	*P*	OR: 95% CI	*P*[b]	*P*	OR: 95% CI	*P*[b]	*P*
Total	25	0.82 [0.74-0.93]	0.00[c]	0.00	0.78 [0.69-0.88]	0.00[c]	0.00	0.87 [0.83-0.91]	0.07	0.00
Cancer type										
Lung cancer	16	0.80 [0.71-0.91]	0.09	0.00	0.74 [0.66-0.84]	0.15	0.00	0.85 [0.80-0.90]	0.75	0.00
Bladder cancer	3	0.73 [0.54-0.98]	0.28	0.04	0.69 [0.51-0.93]	0.30	0.02	0.90 [0.76-1.07]	0.96	0.23
Esophageal cancer	3	0.92 [0.74-1.14]	0.85	0.44	0.82 [0.66-1.03]	0.70	0.08	0.80 [0.69-0.92]	0.10	0.00
Other cancer	3	1.04 [0.53-2.05]	0.00	0.92	1.11 [0.51-2.42]	0.00	0.79	0.97 [0.87-1.08]	0.00	0.58
Sample size										
Small	11	0.76 [0.64-0.90]	0.32	0.00	0.70 [0.59-0.84]	0.33	0.00	0.87 [0.79-0.96]	0.01	0.00
Large	14	0.87 [0.75-1.00]	0.00	0.05	0.81 [0.69-0.95]	0.00	0.01	0.87 [0.82-0.91]	0.48	0.00

0.00 means value < 0.01; a. Number of studies; b. *P* value of Q test for heterogeneity test; c. Random effects model was used when I^2 > 50% for heterogeneity test; otherwise, fixed effects model was used.

0.70-0.92), and CT vs. CC (OR = 0.80, 95% CI = 0.69-0.92), (**Table 2**). Meanwhile, when stratified by sample size, significant effects for CLPTM1L rs401681 polymorphism on cancer risk were found in five different genetic models. As a whole, for CLPTM1L rs401681 polymorphism association, the carriers of T allele held lower cancer risk than carriers of C allele, especially in lung cancer, bladder cancer and esophageal cancer.

Test of heterogeneity

Prominent heterogeneity existed in these five genetic modules ($P_{heterogeneity} < 0.05$). Afterwards, we use cancer type to assess the source of heterogeneity for genetic models As a result, in subgroup analysis, every genetic model were not found to contribute to potential heterogeneity in lung cancer, bladder cancer, esophageal cancer.

Sensitivity analysis

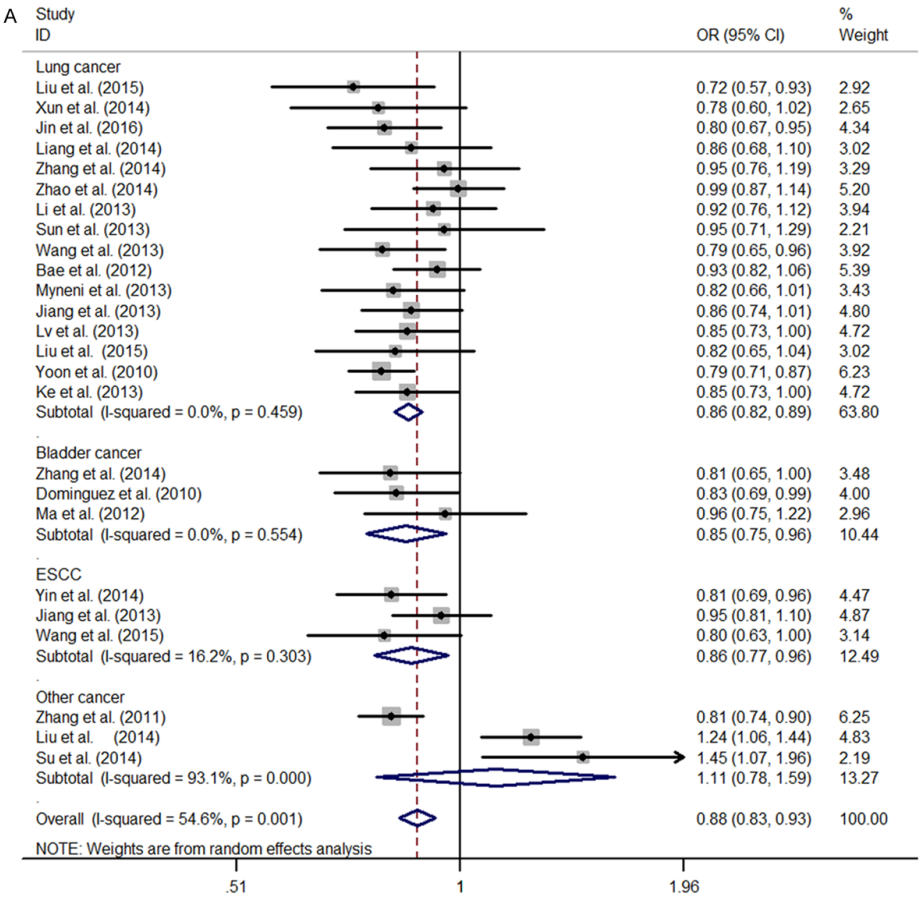
We performed sensitivity analysis by deletion of single study in whole subjects and subgroups. For CTLPM1L rs401681, influence of omission each individual study on pooled ORs used to assess. However, no single study influenced the pooled OR qualitatively, as indicated by sensitivity analyses, suggesting that results of this meta-analysis were statistically robust (**Figure 3**).

Publication bias

To determine the potential publication bias of the literature. The funnel plots were performed and did not reveal any evidence of obvious asymmetry (**Figure 4**). Further evaluation was to use Begg's funnel plot and Egger's test for these five genetic models. As a result, we didn't find any of publication bias.

Discussion

In this meta-analysis, a significant relationship between the SNP rs401681 and cancer risk was revealed under five different genetic models in an Asian population. The following meta-analysis including 25 previous studies with a total of 14,460 cases and 18,697 controls, found that rs401681 polymorphism not only can reduce the risk of lung cancer and bladder


A
Study ID
OR (95% CI)
% Weight
Lung cancer
Liu et al. (2015) 0.72 (0.57, 0.93) 2.92
Xun et al. (2014) 0.78 (0.60, 1.02) 2.65
Jin et al. (2016) 0.80 (0.67, 0.95) 4.34
Liang et al. (2014) 0.86 (0.68, 1.10) 3.02
Zhang et al. (2014) 0.95 (0.76, 1.19) 3.29
Zhao et al. (2014) 0.99 (0.87, 1.14) 5.20
Li et al. (2013) 0.92 (0.76, 1.12) 3.94
Sun et al. (2013) 0.95 (0.71, 1.29) 2.21
Wang et al. (2013) 0.79 (0.65, 0.96) 3.92
Bae et al. (2012) 0.93 (0.82, 1.06) 5.39
Myneni et al. (2013) 0.82 (0.66, 1.01) 3.43
Jiang et al. (2013) 0.86 (0.74, 1.01) 4.80
Lv et al. (2013) 0.85 (0.73, 1.00) 4.72
Liu et al. (2015) 0.82 (0.65, 1.04) 3.02
Yoon et al. (2010) 0.79 (0.71, 0.87) 6.23
Ke et al. (2013) 0.85 (0.73, 1.00) 4.72
Subtotal (I-squared = 0.0%, p = 0.459) 0.86 (0.82, 0.89) 63.80
Bladder cancer
Zhang et al. (2014) 0.81 (0.65, 1.00) 3.48
Dominguez et al. (2010) 0.83 (0.69, 0.99) 4.00
Ma et al. (2012) 0.96 (0.75, 1.22) 2.96
Subtotal (I-squared = 0.0%, p = 0.554) 0.85 (0.75, 0.96) 10.44
ESCC
Yin et al. (2014) 0.81 (0.69, 0.96) 4.47
Jiang et al. (2013) 0.95 (0.81, 1.10) 4.87
Wang et al. (2015) 0.80 (0.63, 1.00) 3.14
Subtotal (I-squared = 16.2%, p = 0.303) 0.86 (0.77, 0.96) 12.49
Other cancer
Zhang et al. (2011) 0.81 (0.74, 0.90) 6.25
Liu et al. (2014) 1.24 (1.06, 1.44) 4.83
Su et al. (2014) 1.45 (1.07, 1.96) 2.19
Subtotal (I-squared = 93.1%, p = 0.000) 1.11 (0.78, 1.59) 13.27
Overall (I-squared = 54.6%, p = 0.001) 0.88 (0.83, 0.93) 100.00
NOTE: Weights are from random effects analysis
.51
1
1.96
B
Study ID
OR (95% CI)
% Weight
Lung cancer
Liu et al. (2015) 0.66 (0.48, 0.90) 2.17
Xun et al. (2014) 0.82 (0.58, 1.16) 1.65
Jin et al. (2016) 0.80 (0.64, 1.00) 3.99
Liang et al. (2014) 0.91 (0.66, 1.24) 1.87
Zhang et al. (2014) 0.86 (0.64, 1.15) 2.29
Zhao et al. (2014) 1.00 (0.83, 1.20) 5.51
Li et al. (2013) 0.94 (0.73, 1.21) 2.97
Sun et al. (2013) 1.04 (0.70, 1.54) 1.14
Wang et al. (2013) 0.80 (0.62, 1.03) 3.16
Bae et al. (2012) 0.85 (0.72, 1.01) 6.80
Myneni et al. (2013) 0.73 (0.55, 0.97) 2.63
Jiang et al. (2013) 0.81 (0.67, 0.99) 5.07
Lv et al. (2013) 0.79 (0.65, 0.97) 5.01
Liu et al. (2015) 0.81 (0.59, 1.12) 1.99
Yoon et al. (2010) 0.78 (0.69, 0.89) 12.69
Ke et al. (2013) 0.79 (0.65, 0.97) 5.01
Subtotal (I-squared = 0.0%, p = 0.747) 0.83 (0.78, 0.88) 63.95
Bladder cancer
Zhang et al. (2014) 0.84 (0.63, 1.11) 2.46
Dominguez et al. (2010) 0.82 (0.65, 1.05) 3.28
Ma et al. (2012) 0.93 (0.67, 1.28) 1.79
Subtotal (I-squared = 0.0%, p = 0.849) 0.85 (0.73, 1.00) 7.53
ESCC
Yin et al. (2014) 0.73 (0.59, 0.92) 4.21
Jiang et al. (2013) 0.93 (0.76, 1.13) 4.84
Wang et al. (2015) 0.67 (0.50, 0.91) 2.34
Subtotal (I-squared = 50.1%, p = 0.135) 0.80 (0.70, 0.92) 11.39
Other cancer
Zhang et al. (2011) 0.81 (0.71, 0.92) 12.04
Liu et al. (2014) 1.19 (0.98, 1.45) 4.22
Su et al. (2014) 1.78 (1.21, 2.64) 0.88
Subtotal (I-squared = 90.5%, p = 0.000) 0.95 (0.86, 1.06) 17.14
Overall (I-squared = 43.7%, p = 0.011) 0.85 (0.81, 0.89) 100.00
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1
2.64

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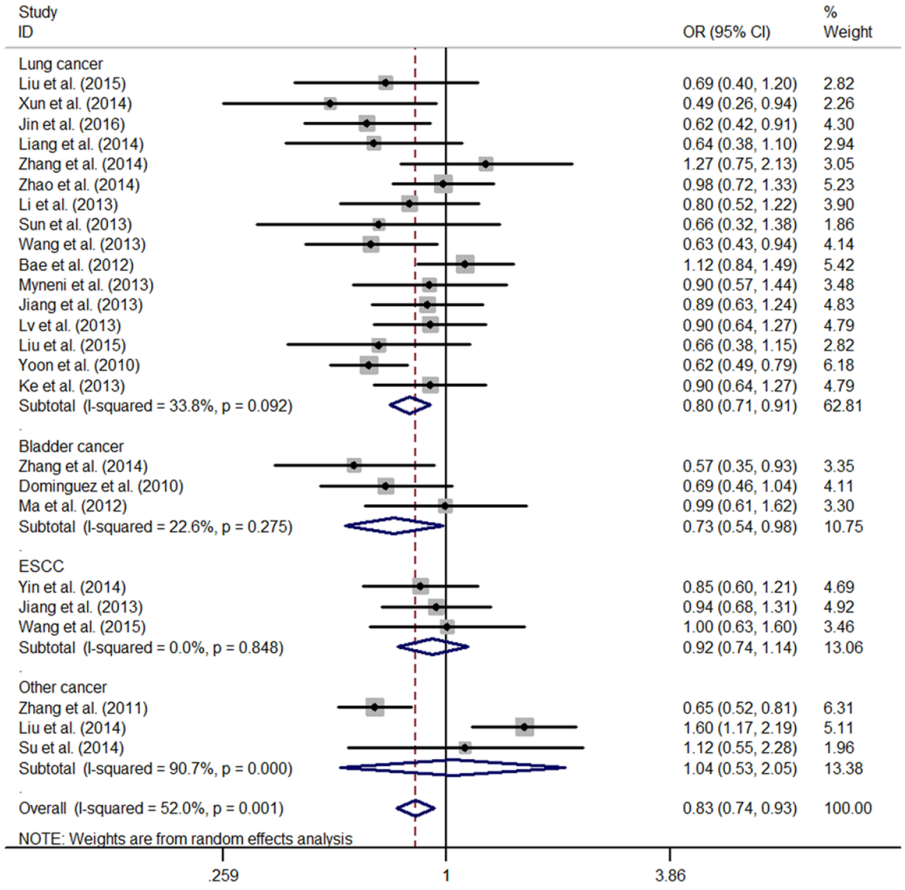
Study ID
OR (95% CI)
% Weight
Lung cancer
Liu et al. (2015) 0.69 (0.40, 1.20) 2.82
Xun et al. (2014) 0.49 (0.26, 0.94) 2.26
Jin et al. (2016) 0.62 (0.42, 0.91) 4.30
Liang et al. (2014) 0.64 (0.38, 1.10) 2.94
Zhang et al. (2014) 1.27 (0.75, 2.13) 3.05
Zhao et al. (2014) 0.98 (0.72, 1.33) 5.23
Li et al. (2013) 0.80 (0.52, 1.22) 3.90
Sun et al. (2013) 0.66 (0.32, 1.38) 1.86
Wang et al. (2013) 0.63 (0.43, 0.94) 4.14
Bae et al. (2012) 1.12 (0.84, 1.49) 5.42
Myneni et al. (2013) 0.90 (0.57, 1.44) 3.48
Jiang et al. (2013) 0.89 (0.63, 1.24) 4.83
Lv et al. (2013) 0.90 (0.64, 1.27) 4.79
Liu et al. (2015) 0.66 (0.38, 1.15) 2.82
Yoon et al. (2010) 0.62 (0.49, 0.79) 6.18
Ke et al. (2013) 0.90 (0.64, 1.27) 4.79
Subtotal (I-squared = 33.8%, p = 0.092) 0.80 (0.71, 0.91) 62.81
Bladder cancer
Zhang et al. (2014) 0.57 (0.35, 0.93) 3.35
Dominguez et al. (2010) 0.69 (0.46, 1.04) 4.11
Ma et al. (2012) 0.99 (0.61, 1.62) 3.30
Subtotal (I-squared = 22.6%, p = 0.275) 0.73 (0.54, 0.98) 10.75
ESCC
Yin et al. (2014) 0.85 (0.60, 1.21) 4.69
Jiang et al. (2013) 0.94 (0.68, 1.31) 4.92
Wang et al. (2015) 1.00 (0.63, 1.60) 3.46
Subtotal (I-squared = 0.0%, p = 0.848) 0.92 (0.74, 1.14) 13.06
Other cancer
Zhang et al. (2011) 0.65 (0.52, 0.81) 6.31
Liu et al. (2014) 1.60 (1.17, 2.19) 5.11
Su et al. (2014) 1.12 (0.55, 2.28) 1.96
Subtotal (I-squared = 90.7%, p = 0.000) 1.04 (0.53, 2.05) 13.38
Overall (I-squared = 52.0%, p = 0.001) 0.83 (0.74, 0.93) 100.00
NOTE: Weights are from random effects analysis
.259
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3.86

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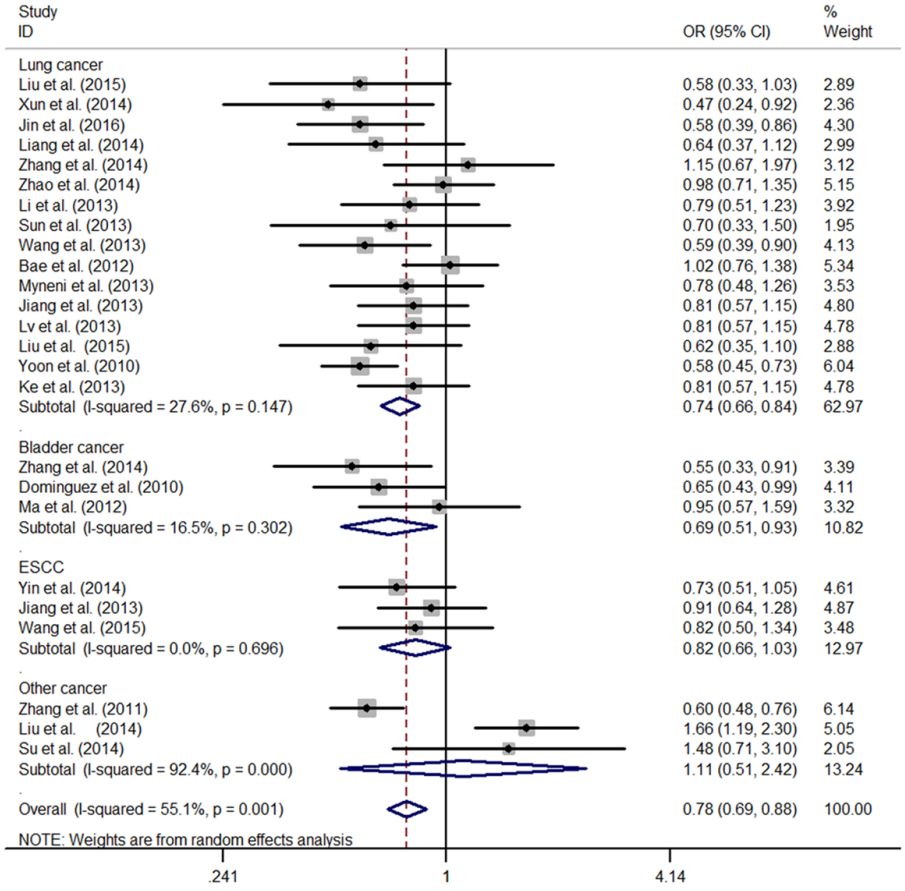
Study ID
OR (95% CI)
% Weight
Lung cancer
Liu et al. (2015) 0.58 (0.33, 1.03) 2.89
Xun et al. (2014) 0.47 (0.24, 0.92) 2.36
Jin et al. (2016) 0.58 (0.39, 0.86) 4.30
Liang et al. (2014) 0.64 (0.37, 1.12) 2.99
Zhang et al. (2014) 1.15 (0.67, 1.97) 3.12
Zhao et al. (2014) 0.98 (0.71, 1.35) 5.15
Li et al. (2013) 0.79 (0.51, 1.23) 3.92
Sun et al. (2013) 0.70 (0.33, 1.50) 1.95
Wang et al. (2013) 0.59 (0.39, 0.90) 4.13
Bae et al. (2012) 1.02 (0.76, 1.38) 5.34
Myneni et al. (2013) 0.78 (0.48, 1.26) 3.53
Jiang et al. (2013) 0.81 (0.57, 1.15) 4.80
Lv et al. (2013) 0.81 (0.57, 1.15) 4.78
Liu et al. (2015) 0.62 (0.35, 1.10) 2.88
Yoon et al. (2010) 0.58 (0.45, 0.73) 6.04
Ke et al. (2013) 0.81 (0.57, 1.15) 4.78
Subtotal (I-squared = 27.6%, p = 0.147) 0.74 (0.66, 0.84) 62.97
Bladder cancer
Zhang et al. (2014) 0.55 (0.33, 0.91) 3.39
Dominguez et al. (2010) 0.65 (0.43, 0.99) 4.11
Ma et al. (2012) 0.95 (0.57, 1.59) 3.32
Subtotal (I-squared = 16.5%, p = 0.302) 0.69 (0.51, 0.93) 10.82
ESCC
Yin et al. (2014) 0.73 (0.51, 1.05) 4.61
Jiang et al. (2013) 0.91 (0.64, 1.28) 4.87
Wang et al. (2015) 0.82 (0.50, 1.34) 3.48
Subtotal (I-squared = 0.0%, p = 0.696) 0.82 (0.66, 1.03) 12.97
Other cancer
Zhang et al. (2011) 0.60 (0.48, 0.76) 6.14
Liu et al. (2014) 1.66 (1.19, 2.30) 5.05
Su et al. (2014) 1.48 (0.71, 3.10) 2.05
Subtotal (I-squared = 92.4%, p = 0.000) 1.11 (0.51, 2.42) 13.24
Overall (I-squared = 55.1%, p = 0.001) 0.78 (0.69, 0.88) 100.00
NOTE: Weights are from random effects analysis
.241
1
4.14

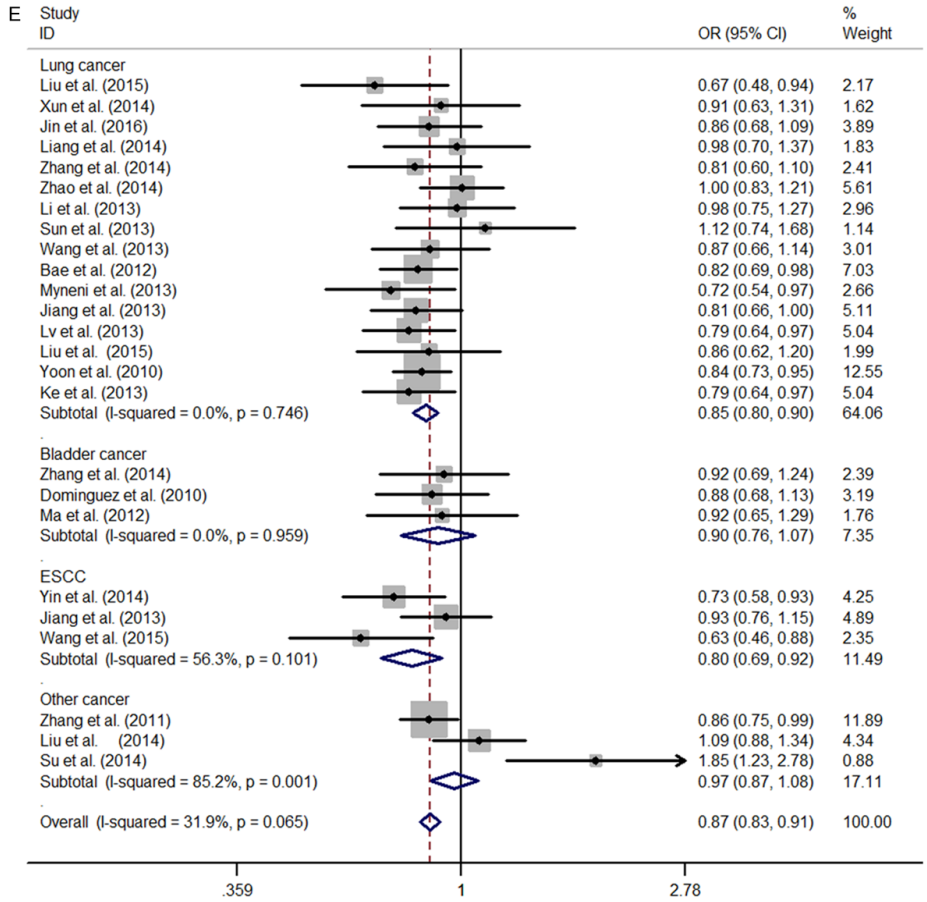

Figure 2. Forest plot for the association between the CLPTM1L rs401681 polymorphism and cancer risk (A: T vs. C, B: TT/CT vs. CC, C: TT vs. CT/CC, D: TT vs. CC, E: CT vs. CC).

cancer but decrease the risk of esophageal cancer. The relationship between CLPTM1L rs401681 and esophageal cancer was reported for the first time. After the stratified analysis of the tumor type, the original studies were homogeneous and the publication bias was not found.

The CLPTM1L genetic variations have been associated with of multiple cancer types, including cancers of lung, liver, urinary bladder, and pancreas [38, 39]. Single nucleotide polymorphism (SNP), one of the important and common causes of population multiformity, is relative with cancer susceptibility [40]. Recently, much research have been carried out to explore the relationship between CLPTM1L rs401681 gene polymorphism and progression various tumor. Clarifying the association between CLPTM1L gene SNPs and cancer risk will be helpful to further elucidate the potential mechanism of carcinogenesis which will offer a novel method to screen high-risk populations for cancer and promote the development of molecular-targeted therapy.

CLPTM1L was highly expressed in lung cancer, and it can prevent cell apoptosis by regulating Bcl-xL [41]. Wang and his colleagues, for the first time, found that SNP rs401681 polymorphism was associated with lung cancer in European populations [42]. However, a case-control study included 980 patients with lung cancer and a control group of 1000 patients without tumor, indicated that CLPTM1L rs401681 polymorphism was not associated with the occurrence of lung cancer [12]. In addition, Rafnar and his colleagues found that CLPTM1L rs401681 polymorphism increased the risk of lung cancer, prostate cancer and bladder cancer [43]. There are many studies on the relationship between rs401681 and susceptibility

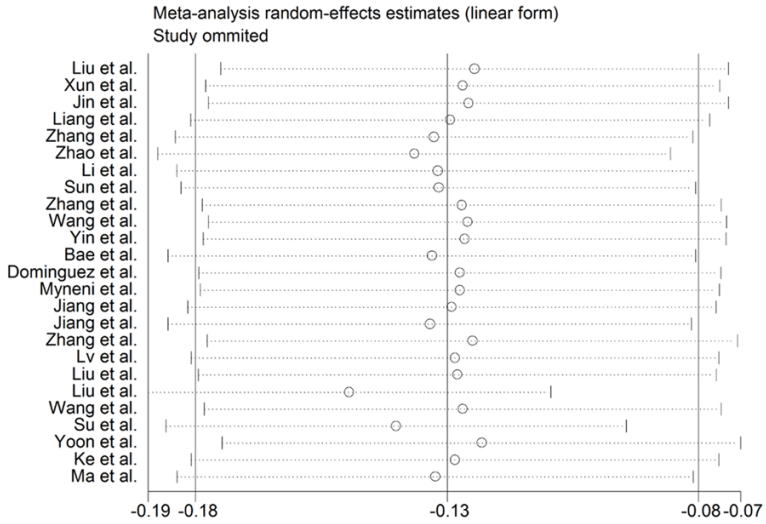

Figure 3. Sensitivity analysis for the association between CLPTM1L rs401681 polymorphism and lung cancer risk (T vs. C).

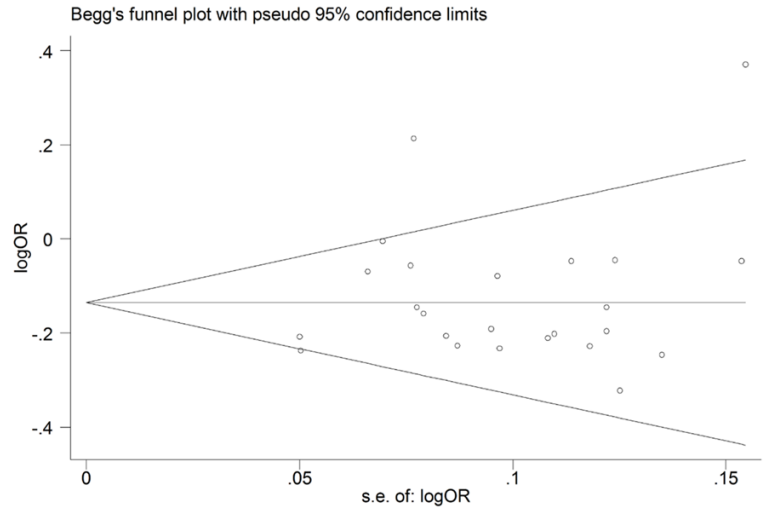

Figure 4. Begg's Funnel plot analysis to detect publication bias (T vs. C).

to lung cancer, but the results are inconsistent. The reasons for this result may be related to race, the pathological type of lung cancer, environmental factors, smoking, etc. In order to obtain a more accurate conclusion, we included 16 case-control studies with 8,951 cases and 11,991 controls, finding that rs401681 polymorphism contributed to the risk decrease of lung cancer under five genetic models in Asian populations. Results were consistent with conclusions of previous original studies [9, 12, 18, 36, 44] and meta-analysis [45]. While this meta-analysis [45], whose sample size is small, make it impossible to evaluate association rs401681 polymorphism with lung cancer in Asian population. Furthermore, Zhao's [46] and Wu's [47] meta-analysis reported that rs401681 polymorphism associated with increased lung cancer risk. The opposite result of these studies is that they may consider the C allele. In other words, C allele of rs401681 may increase lung cancer susceptibility. Here, we use five genetic models to assess the association strength, making the results more valuable.

A case-control study has been reported that T allele of rs401681 may decrease risk of esophageal cancer [26]. However, in an original study involving 753 esophageal cancer cases and 860 controls, it was reported that SNP rs401681 was not associated with risk of esophageal cancer [48]. Here after quantitative data synthesis, our meta-analysis revealed for the first time that rs401681 polymorphism reduces the incidence of esophageal cancer proving by allele model (T vs. C), dominant model (TT/CT vs. CC), and heterozygote (CT vs. CC) comparison. In addition, we found that CLPTM1L rs401681 was associated with bladder cancer risk under all genetic models except for CT vs. CC, but the number of studies included was small. Given the important roles of CLPTM1L rs401681 in cancer risk, it was biologically possible that CLPTM1L rs401681 polymorphism is associated with the risk of cancer by affecting telomerase activity and telomere length [5]. The study of CLPTM1L rs401681 polymorphism will help us to better understand the biology and behavior of cancer, and help us to predict the risk of cancer. However, there was no association between CLPTM1L rs401681 polymorphism and other

caner (nasopharyngeal carcinoma; pancreatic cancer; hepatocellular carcinoma). Possibly, there is no sufficient statistical power to assess the true effects on small size sample. Therefore, more case-control studies based on large sample should be conducted to further estimate this association.

Inevitably, the information we could follow is also limited in this meta-analysis. Firstly, all of subjects included were only from Asian populations. Regional differences have different effects on the occurrence of tumors. So, in other regions, we cannot determine that the same correlation between CLPTM1L rs401681 polymorphism and cancer risk. Secondly, the weakness of stratified analysis is the inadequate sample size of different tumor types, which renders us unable to detect the real relation with insufficient statistical power on bladder cancer, esophageal cancer; pancreatic cancer and hepatocellular carcinoma. Thirdly, this meta-analysis need more information on different languages and more applicable data to avoid possible publication bias and overestimation of the true impact. Finally, the pathological types of tumors are various, but we could not evaluate the relationship between CLPTM1L rs401681 and tumor pathological types.

In conclusion, our meta-analysis suggested that the CLPTM1L rs401681 (C > T) polymorphism was associated with overall cancer risk in an Asian populations. In the stratified analysis by type of cancer, our review provided a more precise estimation: CLPTM1L rs401681 polymorphism may contribute to decreased risk of lung based on larger sample size under all genetic models, and was also related to bladder cancer and esophageal cancer under some genetic models. Nevertheless, the associations between CLPTM1L rs401681 polymorphisms and other cancer risk were unclear, so larger samples and well-designed studies should be carried out to confirm our findings.

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Disclosure of conflict interest

None.

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