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ORIGINAL ARTICLE

Association between CLPTM1L–TERT rs401681 polymorphism and risk of pancreatic cancer: a meta-analysis

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Abstract Telomere biology plays a critical and complex role in the initiation and progression of cancer. Several recent studies have provided evidence that rs401681 polymorphisms in intronic region of cleft lip and palate trans-membrane 1-like (CLPTM1L) gene sequence are associated with pancreatic cancer (PC) development, but a comprehensive synopsis is not available. We performed a meta-analysis of 6 case–control studies that included 8,253 pancreatic cancer cases and 37,646 case-free controls. We assessed the strength of the association, using odds ratios (ORs) with 95 % confidence intervals (CIs). Overall, this meta-analysis showed that rs401681 allele T was associated with a significantly increased PC risk (OR = 1.17, 95 % CI = 1.12–1.22, $P_{\text{heterpgeneity}} = 0.596$ and $I^2 = 0$). Similarly, in the subgroup analysis by ethnicity, a significantly increased risk was found among Asians (OR = 1.15, 95 % CI = 1.07–1.24, $P_{\text{heterpgeneity}} = 0.297$ and $I^2 = 8.0$ %) and among Caucasian (OR = 1.13, 95 % CI = 1.02–1.26, $P_{\text{heterpgeneity}} = 0.385$ and $I^2 = 0$). No publication bias was found in the present study. This meta-analysis suggests that T allele of CLPTM1L–telomerase reverse transcriptase rs401681 polymorphism is associated with an increased PC risk, especially among Chinese. Further large and well-designed studies are needed to confirm this association.

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Introduction

Pancreatic cancer (PC), although infrequent, has a very poor prognosis, making it one of the four or five commonest causes of cancer mortality in developed countries [1]. Approximately 250,000 people are diagnosed with the disease worldwide each year, and about the same number die from it. These statistics have not significantly changed over the past several decades [2]. It is well known that the development of PC is a complex and multifactorial process [3, 4], and there are several risk factors of PC, such as smoking status, advanced age, alcohol consumption, body mass index, diabetes mellitus, and family history of PC [5–7]. However, not all people exposed to these risk factors develop PC, suggesting a genetic contribution to the development of PC.

The latest studies pay attention to telomerase reverse transcriptase (TERT), cleft lip and palate trans-membrane 1-like (CLPTM1L) gene variation whose locus is at chromosome 5p15.33. Several genome-wide association studies (GWASs) have shown that common TERT–CLPTM1L variants at 5p15.33 may influence the risk of developing PC as well as other types of cancer [8–11]. Both TERT and CLPTM1L are attractive candidate genes, as they have both been implicated in carcinogenesis. TERT encodes the catalytic subunit of telomerase, an enzyme that maintains telomere ends by adding the telomere repeat TTAGGG. Telomeres are the protein-bound DNA repeat structures at the ends of chromosomes and are important in maintaining genomic stability [12, 13]. Another potential candidate

causal gene in the 5p15.33 region is CLPTM1L, which has been reported to be involved in the cellular response to genotoxic stress and cisplatin resistance [14].

A number of studies have been conducted to investigate the potential association between TERT–CLPTM1L genomic region and cancer in humans. The rs401681 polymorphism, located in an intronic region of CLPTM1L, has been reported to be associated with PC risk based on several GWASs [9, 11, 15]. However, the results of previous studies have been unsatisfactory and even conflicting. To acquire more comprehensive evidences, we conducted a meta-analysis to assess the effect of the rs401681 polymorphisms on the risk of PC.

Materials and methods

Publication search

We searched the PubMed and Embase databases for all articles on the association between CLPTM1L–TERT rs401681 polymorphism and PC risk through April 2014. The following key words were used in this search: PC/pancreatic carcinoma, polymorphism/variant, and CLPTM1L–TERT/rs401681. The electronic searching was supplemented by checking reference lists from identified articles and reviews for additional original reports. The language of the reviewed articles was limited to English. All the studies must meet the following criteria: (1) case–control study; (2) the outcome had to be PC; and (3) at least two comparison groups (cancer group vs. control group). The major exclusion criteria were (1) duplicate data, (2) abstract, comment, review and editorial, and (3) no sufficient data were reported.

Data extraction

Two of the authors (L.C.L and W.C.) extracted all data independently, complied with the selection criteria, and reached a consensus on all items. In case of disagreement, a third author (C) assessed the articles. The following items were collected: first author's name, year of publication, country of origin, ethnicity, definition of study patients (cases), genotyping method, total number of cases and controls, and genotype information or additive OR and 95 % CI.

Statistical analysis

The strength of the association between rs401681 polymorphism and PC risk was measured by odds ratios (ORs) with 95 % confidence intervals (CIs). Heterogeneity across studies was checked using the Cochran's Q-test and considered significant at $P < 0.05$ [16]. 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 DerSimonian and Laird method) was utilized [16]. The quantity I^2 that presents the percentage of total variation across studies as a result of heterogeneity was also calculated [17]. Subgroup analyses were done by ethnicity. Relative influence of each study on the pooled estimate was assessed by omitting one study at a time for sensitivity analysis.

The Begg's rank correction method and the Egger's weighted regression method were used to statistically assess publication bias [18] ($P < 0.05$ was regarded as representative of statistical significance). All analyses were done using STATA software, version 11.0 (STATA Corp., College Station, TX, USA), and all tests were two sided.

Results

Characteristics of the studies

There were 78 papers relevant to the search words. The flowchart of selection of studies and reasons for exclusion

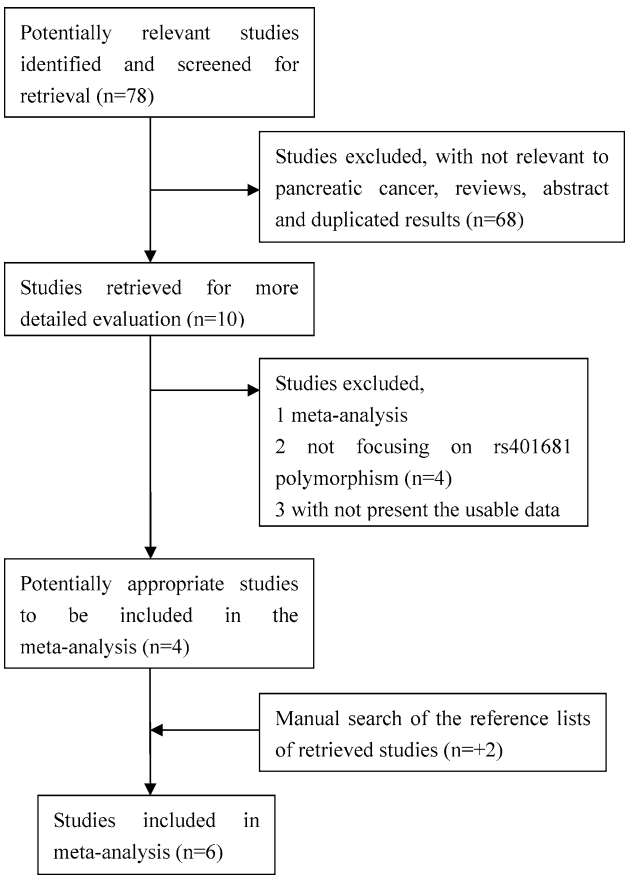

Fig. 1 Flow chart of selection of studies and specific reasons for exclusion from the meta-analysis

Table 1 Characteristics of studies included in this meta-analysis

Author	Year	Country	Ethnicity	Genotyping methods	Sample size (case/control)	OR (95 %CI)
Rafnar [9]	2009	Iceland	Caucasian	Illumina	301/28,890	1.01 (0.83–1.23)
Petersen [11]	2010	USA	Mixed	Illumina	3,532/3,642	1.19 (1.11–1.27)
Rizzato [32]	2011	Germany	Caucasian	PCR-based KASPar	661/1,267	1.18 (1.03–1.35)
Wu [15]	2012	China	Asian	Taqman	2,603/2,877	1.13 (1.04–1.23)
Willis [33]	2012	USA	Caucasian	Illumina	390/149	1.22 (0.91–1.62)
Liu [34]	2014	China	Asian	Taqman	766/821	1.24 (1.06–1.44)

OR odds ratio, *CI* confidence interval

are presented in Fig. 1. Overall, 6 publications with 6 case–control studies including 8,253 cases and 37,646 controls were available for this analysis. Study characteristics are summarized in Table 1. Among those 6 studies, there were 3 Caucasian, 2 Asian, and 1 mixed studies.

Quantitative synthesis

As shown in Fig. 2a, the overall meta-analysis showed that rs401681 allele T was associated with a significantly increased PC risk (OR = 1.17, 95 % CI = 1.12–1.22, $P_{\text{heterpgeneity}} = 0.596$ and $I^2 = 0$). Similarly, in the subgroup analysis by ethnicity, a significantly increased risk was found among Asians (OR = 1.15, 95 % CI = 1.07–1.24, $P_{\text{heterpgeneity}} = 0.297$ and $I^2 = 8.0$ %) and among Caucasian (OR = 1.13, 95 % CI = 1.02–1.26, $P_{\text{heterpgeneity}} = 0.385$ and $I^2 = 0$; Fig. 2b). Furthermore, according to the analysis, we found that there was no evidence of heterogeneity in the association between rs401681 polymorphism and PC risk among the overall and stratified studies.

Sensitivity analysis

Sensitivity analysis was carried out by investigating the influence of each study on the overall OR, and the result showed that no individual study affected the overall OR dominantly, since the omission of any single study made no substantial difference (Fig. 3). This procedure confirmed the stability of our overall results.

Publication bias

The Begg's rank correction method and the Egger's weighted regression method were used to statistically assess publication bias. Furthermore, the Egger's test and Begg's test did not detect any publication bias for rs401681 in additive model (Egger's test $P = 0.759$, Begg's test $P = 0.851$) (Fig. 4). Therefore, there was no significant publication bias in the studies included in current analyses.

Discussion

Pancreatic cancer remains the fifth leading cause of cancer-related deaths with an overall 5-year survival rate <4 % [1]. Both developed and developing countries are in the grip of this deadly disease. Despite the considerable progress in the fight against other cancers in recent years, the prognosis for patients diagnosed with PC has remained extremely poor. In the past, considerable efforts have been carried out to identify potential biomarkers that include aberrantly expressed genes, proteins, miRNA detectable through noninvasive techniques in cancerous tissue and body fluids [19, 20]. In addition, mutations in few genes have also been identified to be associated with the progression of PC [21, 22].

Telomeres, the ends of chromosomes, are critical for maintaining genomic stability and grow shorter with age. Telomere biology plays a critical and complex role in the initiation and progression of cancer. Shortened telomeres in pancreatic tissue play a key role in the pathogenesis of PC, and shorter telomeres in peripheral blood leukocytes (PBLs) have been associated with higher risk for several cancers including bladder [23], lung [24], esophageal [25], gastric [26], as well as cancer overall [27, 28]. In addition, telomere shortening in tissue has been reported for pancreatic ductal adenocarcinoma [29] and premalignant pancreatic intraepithelial neoplasia (PanIN) compared with normal tissue and has been implicated in the pathogenesis of a variety of other malignancies [30, 31]. Rs401681 is located at 5p15.33, encompassing two known genes TERT and CLPTM1L. Although little was known about the function of rs401681 which was situated within the intronic region of CLPTM1L, bioinformatics analysis indicated that it might be transcription regulatory and further affect the expression of the gene. The rs401681 polymorphism was reported to be associated with telomere length [9], which is in favor of its involvement in telomere biology and even cancer development.

In the current study, we performed a meta-analysis to examine the association between rs401681 polymorphism

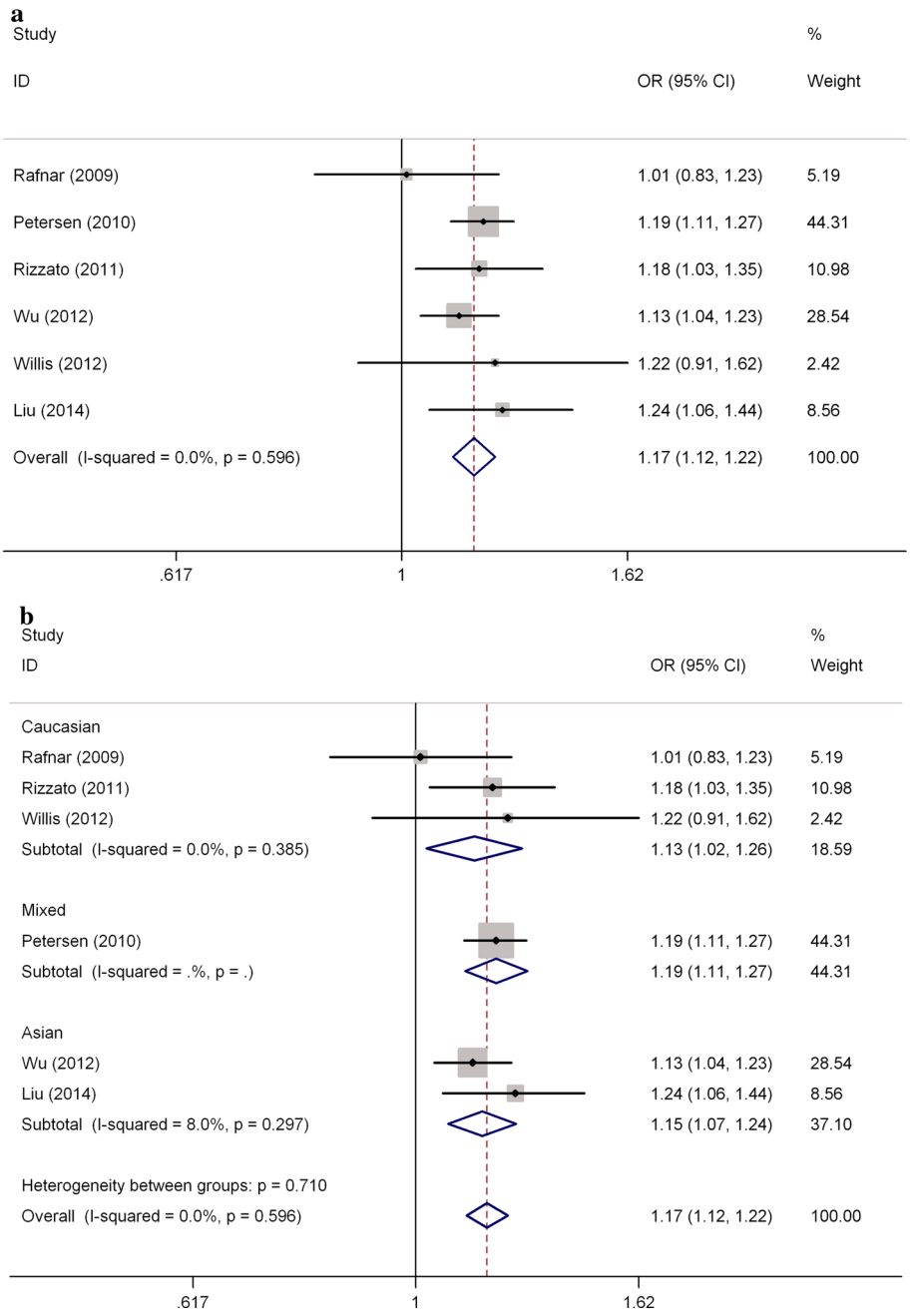

Fig. 2 Meta-analysis with a fixed-effects model for the association between pancreatic cancer risk and CLPTM1L–TERT rs401681 Polymorphism in additive model. **a** In overall analysis; **b** In subgroup analysis. *OR* odds ratio, *CI* confidence interval, I^2 measure to quantify the degree of heterogeneity in meta-analyses

and PC risk. To the best of our knowledge, this is the first systematic review of the literature by a meta-analysis so far exploring the association between rs401681 polymorphism and PC risk. This meta-analysis conducted here included in total 6 case–control studies with 8,253 cases and 37,646 controls. Overall, the meta-analysis showed that rs401681 allele T was associated with a significantly increased PC risk. Similarly, in the subgroup analysis by ethnicity, a significantly increased risk was found among Asians and among Caucasian. Furthermore, we found that there was no evidence of heterogeneity in the association between rs401681 polymorphism and PC risk among the overall and stratified studies.

In interpreting the current results, some limitations should be considered. Firstly, the number of studies and the number of samples included in the meta-analysis were relatively small. Secondly, PC is a complex trait related to environmental and genetic risk factors. However, insufficient environmental information limited us to further investigate the gene–environment interaction. Thirdly, only published studies were included in this meta-analysis, and unpublished data and ongoing studies were not sought,

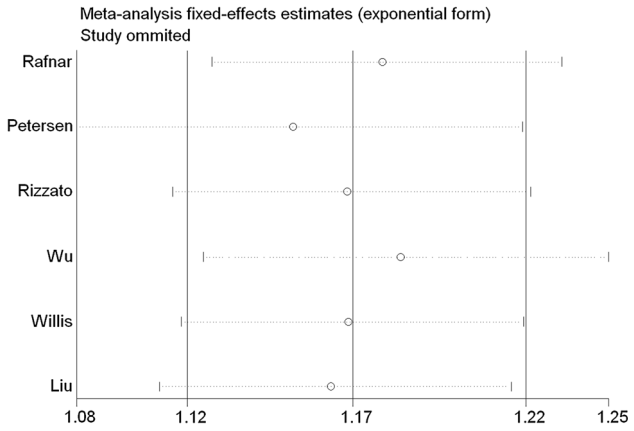

Fig. 3 The influence of individual studies on the summary OR. The *middle vertical axis* indicates the overall OR, and the *two vertical axes* indicate its 95 % CI. Every *hollow round* indicates the pooled OR when the left study was omitted in this meta-analysis. The two ends of every *broken line* represent the 95 % CI

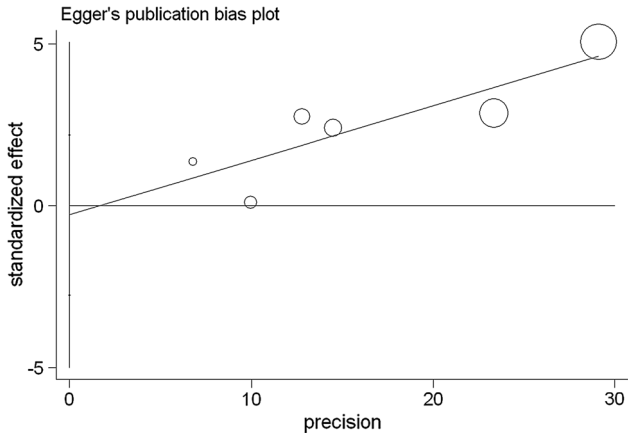

Fig. 4 Egger's publication bias of CLPTM1L–TERT rs401681 polymorphism and risk of pancreatic cancer. Each *point* represents a separate study for the indicated association

which may have biased our results. In spite of these, our meta-analysis has some advantages. First, according our selection criteria, the quality of studies included in our meta-analysis was satisfactory. Second, no publication bias was detected, indicating that the whole pooled results may be unbiased.

In conclusion, this meta-analysis suggests that T allele of CLPTM1L–TERT rs401681 polymorphism is associated with an increased PC risk, especially among Chinese. Caution must be made about the interpretation of the results because of the limited sample size. Additional large case–control studies are necessary to validate our findings.

Conflict of interest None.

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