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Original Article

Over-expression of TWIST, an epithelial-mesenchymal transition inducer, predicts poor survival in patients with oral carcinoma

Yan Zhou[1], Huiyu Zhang[1], Xianlu Zhuo[1,2], Yan Liu[3], Gang Zhang[1], Yinghui Tan[1]

[1]Department of Stomatology, Xinqiao Hospital, Third Military Medical University, Chongqing, China; [2]Affiliated Hospital of Guiyang Medical College, Guiyang, China; [3]Zunyi Health Team of Guizhou People's Armed Police Corps, Zunyi, China

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Abstract: TWIST, an epithelial-mesenchymal transition inducer, has been thought to play a critical role in the progression of a number of malignancies. Published studies reporting the association of TWIST expression with oral carcinoma risk has yielded conflicting results. Thus, we conducted a meta-analysis to address this controversy. After rigorous searching and screening, a total of seven studies were included. The results showed that the TWIST positive expression rate in oral cancer tissues was higher than that in the normal tissues. TWIST expression might have a correlation with clinical features such as low differentiation, advanced clinical stage, presence of lymph node metastasis and local recurrence, but not age, gender, T stage and smoking and drinking. The data suggested that TWIST might play critical roles in the cancer progression and act as a prognostic factor in oral cancer patients.

Keywords: TWIST, expression, metastasis, oral carcinoma, meta-analysis

Introduction

Oral carcinoma is a common malignancy of the upper respiratory tract that severely affects the life quality of patients, with compromise of ability to talk, drink and eat [1]. Complex interactions between many genetic and environmental factors might contribute to oral cancer risk. Previously, cigarette smoking, alcohol consumption [2], betel quid chewing, infection of human papilloma virus [3], diet low in nutritional value lacking vegetables and fruits and low socioeconomic status [4] are probably important etiological factors contributing to oral carcinoma. Besides, genetic variations also play important roles in the genesis of oral cancer [5]. Thus, the etiological factors for this cancer are complicated. To find new biomarkers for predicting the prognosis of oral cancer patients is required.

Previously, epithelial-mesenchymal transition (EMT), a key event of embryogenesis, has been shown to play a role in the development and progression of tumors [6]. EMT is an essential step for the formation of different organs during the process of embryonic development, while it may be inhibited for maintaining epithelial integrity and homeostasis in adult tissues [7]. Aberrant activation of EMT in epithelial tumors usually has been shown to have a correlation with tumor genesis. Several factors might be critical in the process of EMT. TWIST, a basic helix-loop-helix transcription factor, has been regarded as one of the important EMT inducers. In recent years, over-expression of TWIST has been detected in a number of cancers, such as gastric cancer, breast cancer and nasopharyngeal cancer, and might be associated with the development and unfavorable prognosis of these cancers [8-10]. On the basis of this understanding, TWIST has been regarded as a potential target for cancer therapy [11].

A number of studies have been devoted to the expression and significance of TWIST in oral carcinoma. However, the results were inconclusive. Thus, in the present study we conducted a quantitative meta-analysis containing published data up to Mar 2015 that increased statistical power to address this controversy.

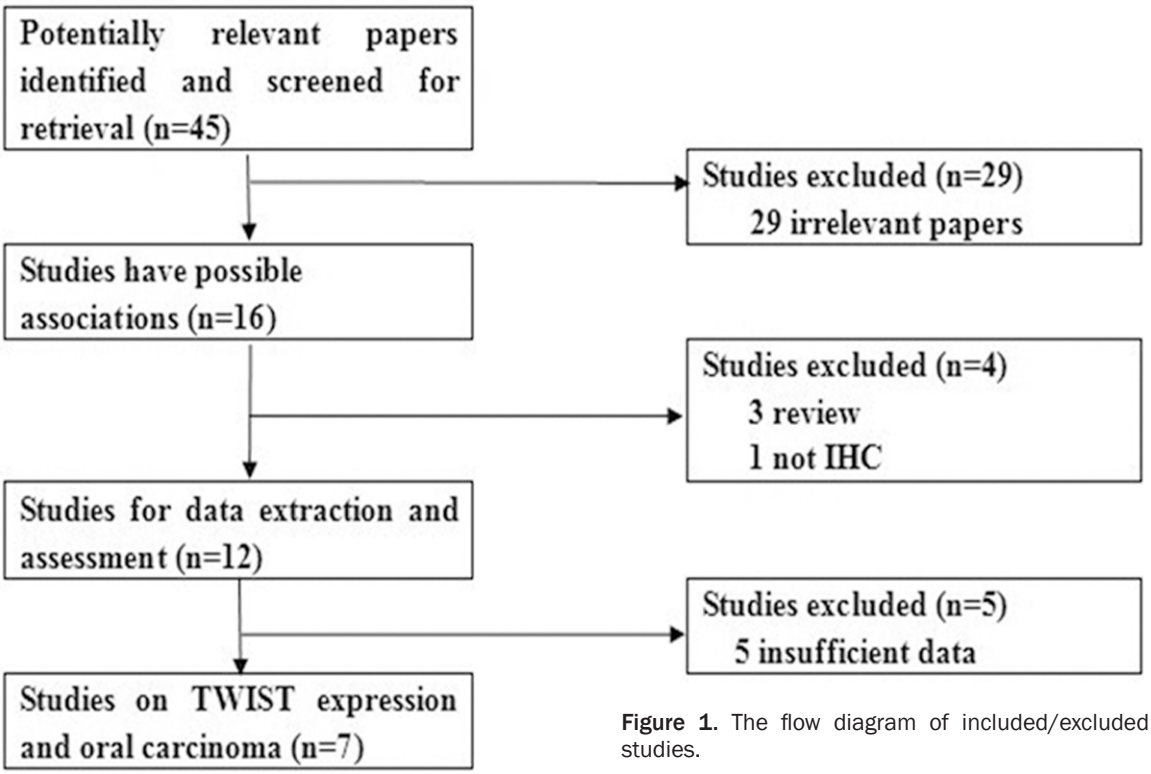

Figure 1. The flow diagram of included/excluded studies.

Materials and methods

Literature search strategy

A systematic search was carried out in the databases such as Medline, EMBASE, and CNKI without a language limitation, covering all papers published up to Mar 2015. A combination of the following keywords was used: *TWIST*, *EMT, neoplasm, tumor, cancer, head and neck, and oral*. All searched studies were retrieved and the bibliographies were checked for other relevant publications. Review articles and bibliographies of other relevant studies identified were hand searched to find additional eligible studies.

Inclusion criteria

The following criteria were used for the literature selection: first, studies focused on the correlation between TWIST expression in primary oral cancer tissues and pathological features; second, papers stated detailed clinical data of cancer cases who were not subjected to radiotherapy or chemotherapy prior to selection; third, papers regarding TWIST, TWIST1 or TWIST2 were involved as TWIST expression. Fourth, only studies using immunohistochemistry were selected.

Accordingly, the exclusion criteria were used as follows: first, papers showed an inconsistent judgment standard for positive TWIST expression or TWIST expression in non-primary tumor tissues including those detected from the blood circulation of patients; second, studies concerned animal experiments or cell line cultures; third, reviews and duplicate publications. After rigorous searching, we reviewed all papers in accordance with the criteria defined above for further analysis.

Data extraction

Data were carefully extracted from all eligible publications independently by two of the authors according to the inclusion criteria mentioned above. For conflicting evaluations, an agreement was reached following a discussion. If a consensus could not be reached, another author was consulted to resolve the dispute and then a final decision was made by the majority of the votes. Extracted information was entered into a database.

Statistical analysis

The association of TWIST expression with clinical features was evaluated by the pooled odd ratio (ORs) and their 95% confidence interval

Table 1. Characteristics of studies included in the present meta-analysis

First Author	Year	Number of Patients			Measurement method	Cut-off of IHC	Method of quantification	Hazard ratio (95% CI)	Outcome
		total	TWIST negative or low	TWIST positive or high					
Liang	2011	89	49	40	IHC	≥ 5%	Percentage of staining	3.06 (1.36-6.89)*	(1) (2) (3) (4) (5) (8) (9) (10) (11)
Gong	2012	62	14	48	IHC	≥ 5%	Percentage of staining	-	(1) (2) (4) (5) (6) (7)
Wang	2012	60	30	30	IHC	≥ 4	Sum of percentage and intensity	-	(1) (2) (3) (4) (5)
Wushou	2012	60	18	42	IHC	≥ 3	Sum of percentage and intensity	4.65 (1.06-20.45)	(1) (2) (3) (4) (5) (6) (7) (8) (9) (11)
Zheng	2012	69	20	49	IHC	≥ 1	Sum of percentage and intensity	-	(1) (2) (4) (5) (6) (7)
Fan	2013	114	40	74	IHC	≥ 2	Sum of percentage and intensity	0.89 (0.52-1.51)	(1) (2) (3) (4) (5) (6) (7) (8) (9) (11)
da Silva	2014	52	30	22	IHC	> 2	Extent of staining	4.28 (1.03-61.12)*	(3) (4) (5) (10) (11)

Clinical features: (1) Age; (2) Gender; (3) T stage; (4) Differentiation; (5) Lymph node metastasis; (6) Clinical stage; (7) The control benign tissue; (8) Smoking; (9) Drinking. (10) Local recurrence; (11) Survival analysis. *Estimated from the Kaplan-Meier curves in the text.

Table 2. Main results of the meta-analysis

Clinical features	Overall OR (95% CI)	P	Heterogeneity test		Number of studies	Egger test		Model
			Q	P		t	P	
TWIST expression (Cancer vs Normal)	51.61 (13.72-194.15)	< 0.05	0.32	0.956	4	2.70	0.114	Fixed-effect
Age (≥ 60 vs < 60)	1.00 (0.68-1.49)	> 0.05	6.38	0.271	6	-0.30	0.778	Fixed-effect
Gender (Male vs Female)	1.15 (0.74-1.79)	> 0.05	2.44	0.786	6	-1.03	0.361	Fixed-effect
T stage (T3+T4 vs T1+T2)	0.95 (0.48-1.85)	> 0.05	9.63	0.247	5	0.03	0.979	Random-effect
Differentiation (Low vs Moderate+High)	2.44 (1.07-5.58)	< 0.05	19.83	0.003	7	0.88	0.420	Random-effect
Lymph node metastasis (Yes vs No)	2.91 (1.32-6.42)	< 0.05	17.66	0.007	7	1.33	0.240	Random-effect
Clinical stage (III+IV vs I+II)	3.11 (1.24-7.78)	< 0.05	6.66	0.083	4	2.35	0.143	Random-effect
Local recurrence (Yes vs No)	1.77 (1.00-3.15)	< 0.05	2.57	0.109	2	-	-	Fixed-effect
Smoking (Yes vs No)	1.03 (0.62-1.72)	> 0.05	3.12	0.210	3	-	-	Fixed-effect
Drinking (Yes vs No)	0.86 (0.51-1.47)	> 0.05	0.85	0.655	3	-	-	Fixed-effect
Survival analysis	Overall HR (95%CI)	P	Heterogeneity test		Number of studies	Egger test		Model
			Q	P		t	P	
TWIST (+) vs TWIST (-)	2.25 (0.88-5.76)*	> 0.05	9.91	0.019	4	1.92	0.195	Random-effect
	3.46 (1.77-6.77)	< 0.05	0.28	0.868	3	-	-	Fixed-effect

*The data were discarded after the sensitivity analysis.

(CIs). Hazard ratio (HRs) and their 95% CIs were used to evaluate the correlation between TWIST expression and the prognosis of patients with oral carcinoma. An HR > 1 was associated with poor outcome. HRs were estimated directly by the available data or estimated from the Kaplan-Meier curves according to the method raised by Tierney et al. [12] if they were not reported in the primary literature. A chi-square based Q statistic test was performed to assess heterogeneity. If a *P value* for a given Q-test was found to be more than 0.1, ORs were pooled according to a fixed-effect model (Mantel-Haenszel) [13]. Otherwise, a random-effect model (DerSimonian and laird) was used [14]. Publication bias was assessed by visual inspection of funnel plots [15], an asymmetrical plot indicated possible publication bias. Symmetry of the funnel plot was further evaluated by Egger's linear regression test [16]. Statistical analysis was carried out using the program STATA 11.0 software (Stata Corporation, Texas).

Results

Study characteristics

Publications relevant to the key words were retrieved and screened originally. A total of forty-five publications were searched, of which twenty-nine irrelevant papers were excluded. Sixteen publications were preliminary eligible. Then, three review articles [17-19] and one study in which IHC was not used [20] were discarded. Thus, twelve articles were selected for data extraction. Afterwards, five papers were further excluded because they provided insufficient information [21-25]. Lastly, seven studies were selected for data extraction and assessment [26-32] (**Figure 1**).

Of the seven studies, four were written in English [26, 28-30] while the remaining three were in Chinese [27, 31, 32]. All the studies were conducted on Chinese population except for one study on Brazilians [30]. No studies on other ethnicities were included because relevant reports could not be found in our searching process. The relevant information was listed in **Table 1**. According to the lists, the first author and the number and characteristics of cases for each study as well as other necessary information were presented. Notably, information about HR was reported in two studies [26, 29], while in another two studies [28, 30], HRs were estimated from the Kaplan-Meier curves according to the method reported by Tierney et al. [12].

Meta-analysis results

Table 2 lists the main results of the meta-analysis. Positive expression of TWIST in oral cancer tissues were significantly higher than that in the normal tissues (OR = 51.61, 95% CI = 13.72-194.15). No correlation was found between TWIST expression and several clinicopathological features, such as age, gender, smoking, drinking and T stage. Nevertheless,

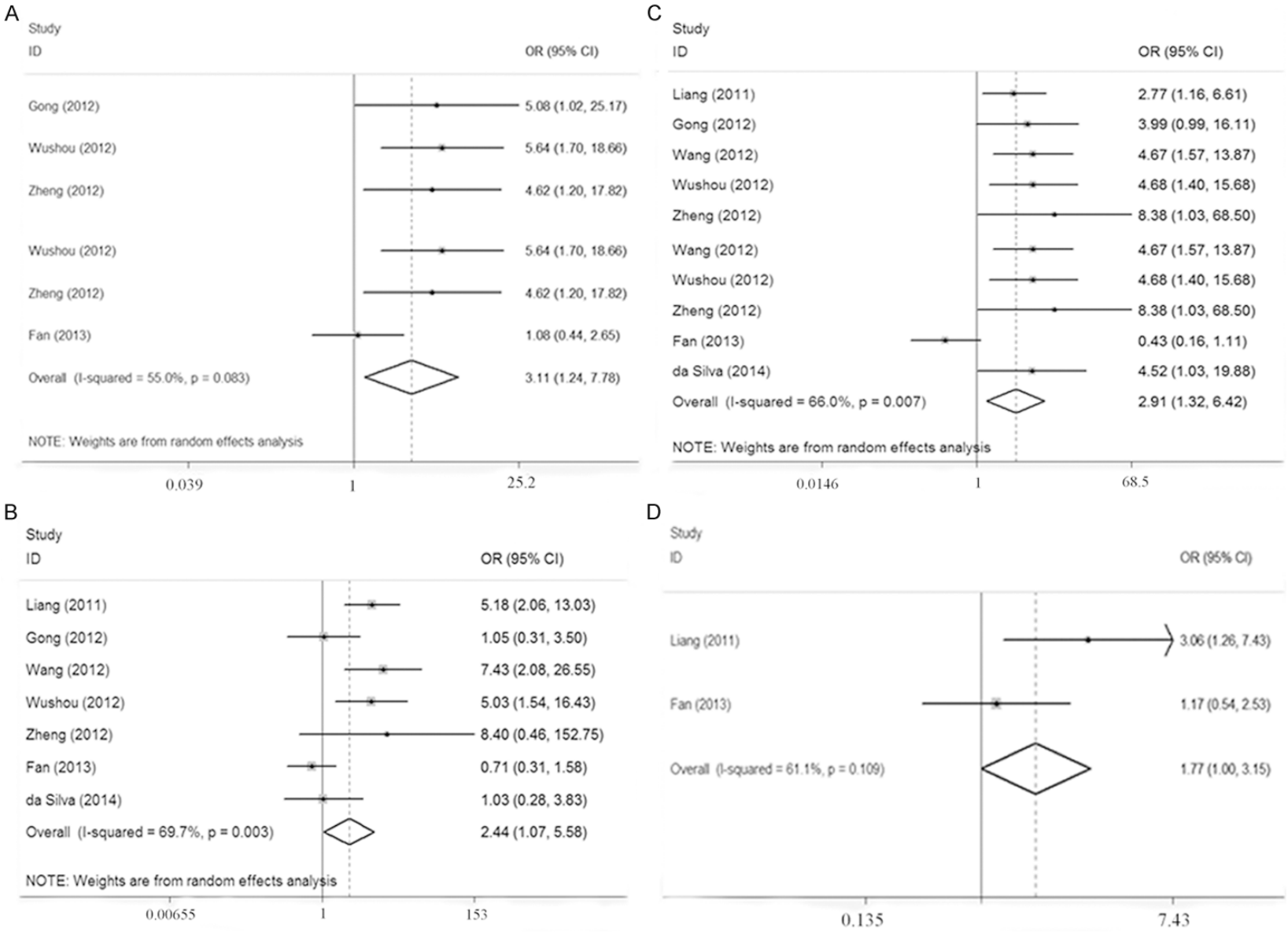

Figure 2. Forest plots showed that TWIST over-expression was associated with clinical stage (A), differentiation (B), lymph node metastasis (C) and local recurrence (D).

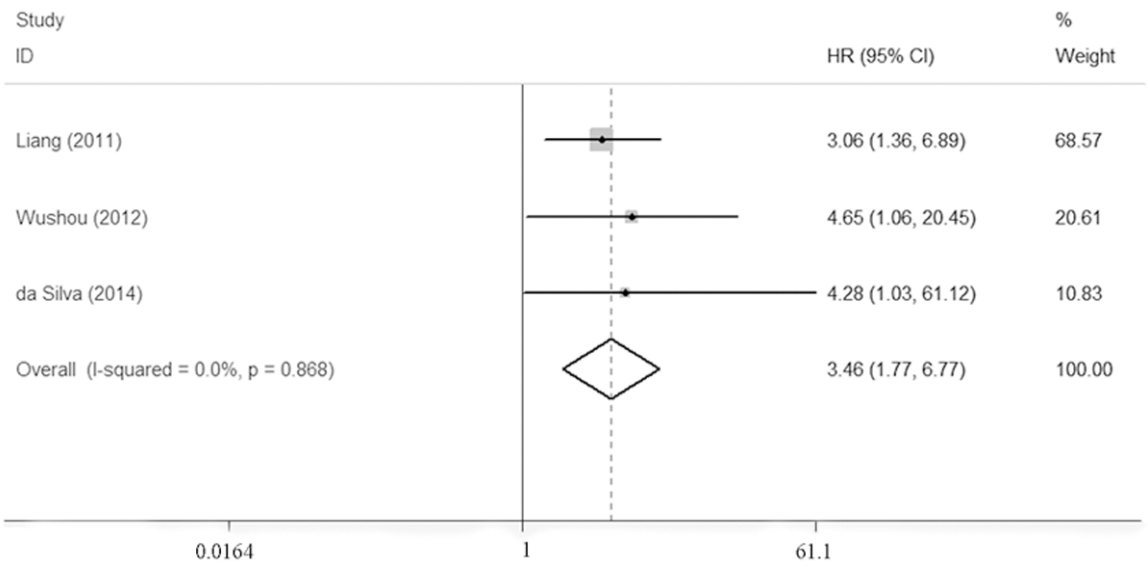

Figure 3. Forest plots showed that TWIST over-expression indicate a poor prognosis of patients with oral carcinoma.

as shown in **Figure 2**, TWIST over-expression was correlated with clinical stage (III + IV vs I + II, OR = 3.11, 95% CI = 1.24-7.78) and differentiation (Low vs Moderate + High, OR = 2.44, 95% CI = 1.07-5.58), indicating that TWIST might have an association with the elevated levels of malignancy. In addition, TWIST over-expression has a correlation with lymph node metastasis (Yes vs No, OR = 2.91, 95% CI = 1.32-6.42), and local recurrence (Yes vs No, OR = 1.77, 95% CI = 1.00-3.15), suggesting that TWIST might contribute to cancer progression.

With respect to the prognostic value of TWIST for oral carcinoma, HRs for the overall survival were pooled. As shown in **Table 2**, the overall HR was 2.25 (95% CI = 0.88-5.76), with the data insignificant and the presence of evident heterogeneity (P = 0.019). However, when the sensitivity analysis was conducted, we found that HR from Fan et al [26] contributed to the unsteady of the overall results, and thus, the data was further omitted. Then, the pooled HR for overall survival was recalculated and the value was 3.46 (95% CI 1.77-6.77) with no heterogeneity (P = 0.868), implying that over-expression was a prognostic factor for oral carcinoma (**Figure 3**).

One-way sensitivity analysis [33] was carried out to determine the stability of the above comparisons. The statistical significance of the results was not altered when any single study was deleted (data not shown), confirming the stability and credibility of the results.

Bias diagnostics

Funnel plots were created to detect possible publication bias. Then, Egger's linear regression tests were used to assess the symmetries of the plots. For comparisons with limited number of included studies (< 4), the publication bias was not evaluated. As shown in **Table 2**, the Egger's tests indicated that the potential publication bias was not significant for all comparisons, indicating that the publication bias might not have an evident effect on the results.

Discussion

In the present study, the results showed that TWIST over-expression might have an association with low differentiation, advanced clinical stage, presence of lymph node metastasis and local recurrence, indicating that TWIST expression might contribute to the development and progression of oral carcinoma. Moreover, TWIST might act as a prognostic factor for oral cancer.

Oral carcinoma can affect the life quality of patients because this cancer may directly influence the patients' speaking and eating due to its specific site. The underlying mechanisms of oral cancer development are not clear. Recently, EMT has attracted much attention because this term describes a process in which epithelial cells lose their cell polarity and in the meantime gain mesenchymal characteristics, and thus, cancer cells become more malignant.

This process can be induced in hypoxic microenvironment that is common to cancer cells [34], usually accompanied by a loss of cell-cell cohesiveness and enhanced cell migratory capacity [35]. Evidence suggests EMT as a key event in the development of head and neck cancer including oral carcinoma [19]. Therefore, the EMT pathway is regarded as a novel target for anti-cancer therapeutics [36].

In the present study, over-expression of TWIST was shown in cancerous tissues compared with normal tissues, indicating that TWIST might have a relation with the oral cancerigenesis. The results also showed that TWIST might contribute to the development of oral cancer because significant differences could be observed in the groups regarding low differentiation, advanced clinical stage, presence of lymph node metastasis and local recurrence, respectively. However, the mechanisms of TWIST in cancer progression have not been fully defined. Evidence indicated that TWIST can regulate gene expression and promote loss of cell-cell adhesion, thus leading to a shift in cytoskeletal dynamics and a change from epithelial morphology and physiology to the mesenchymal phenotype [37], and hence, the cancer cells acquired elevated malignant abilities. Moreover, Twist can also promote angiogenesis through recruitment of stromal macrophages [38] and up-regulation of MMP-9 expression [39]. The understandings might help clarify the possible relations of TWIST expression with advanced oral cancer stages. However, since the progression of oral cancer is a multi-step complicated process, future studies are needed to clarify the exact mechanisms.

Previous reports indicated that benzo(a)pyrene in tobacco might modulate TWIST expression and promote the migration and invasion of cancer cells [40]. In a bladder cancer study, tobacco use has been shown to correlate with up-regulated TWIST expression [41]. Thus, three of the included studies assessed the association of smoking with TWIST expression [26, 28, 29]. Nevertheless, no associations were found in this comparison, probably due to the limited sample sizes. The relationship between alcohol exposure and TWIST expression has rarely been reported in the literature. The results of the present meta-analysis failed to reveal a significant association between them. Another important epidemiological factor, betel quid chewing, has been shown to increase oral cancer risk, particularly in some regions of Asia. However, of the included studies, only one concerned this issue [26], and thus, this topic has not been assessed in the present analysis.

A total of four studies reported the survival data, and nevertheless, the HR values could be extracted directly from two papers [26, 29] and indirectly estimated from the Kaplan-Meier curves in another two papers [28, 30]. The pooled HRs for the overall survival failed to show a significant difference between TWIST positive cases and negative cases. However, after the sensitivity analysis, when the study by da Silva et al. [30] contributing to the evident heterogeneity was excluded, the results showed that patients with positive or high TWIST expression had a worse prognosis relative to the ones with negative or low TWIST expression (HR = 3.46, 95% CI = 1.77-6.77). However, since some data were estimated from the Kaplan-Meier curves, systematic errors were inevitable. Thus, any bias might exist and the results should be interpreted with caution.

Several limitations might be included in this study. First, only published data in Chinese and English were involved. Papers written in other languages were missed. Therefore, selection bias might exist. Second, the cut-off definition of TWIST appeared to be different in each study. This might also lead to any bias. Third, the selected studies focused on TWIST expression in tissues, instead of serum. Circulating prognostic markers seemed to be more valuable and convenient for detection throughout the life of patients. Therefore, further well-designed investigations testing circulating biomarkers might be of value and interest for oral cancer research. Furthermore, most included studies in this meta-analysis concerned Chinese population and only one concerned other ethnicities. Thus, the results might only be representative of a proportion of people in the world. Therefore, future primary research on various ethnicities is also required.

Despite the limitations, the data of the present meta-analysis showed a marked association of TWIST over-expression with low differentiation, advanced clinical stages, lymph node and local recurrence, suggesting that TWIST might play critical roles in the development of oral carcinoma. In addition, TWIST over-expression might

predict poor survival in patients with oral carcinoma.

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Disclosure of conflict of interest

None.

Address correspondence to: Drs. Xianlu Zhuo and Yinghui Tan, Department of Stomatology, Xinqiao Hospital, Third Military Medical University, Chongqing, China. E-mail: zhuoxianlu@gmc.edu.cn (XLZ); sydtyh@aliyun.com (YHT)

References

[1] Furness S, Glenny AM, Worthington HV, Pavitt S, Oliver R, Clarkson JE, Macluskey M, Chan KK and Conway DI. Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy. Cochrane Database Syst Rev 2011; CD006386.

[2] Zygogianni AG, Kyrgias G, Karakitsos P, Psyrri A, Kouvaris J, Kelekis N and Kouloulias V. Oral squamous cell cancer: early detection and the role of alcohol and smoking. Head Neck Oncol 2011; 3: 2.

[3] Lambert R, Sauvaget C, de Camargo Cancela M and Sankaranarayanan R. Epidemiology of cancer from the oral cavity and oropharynx. Eur J Gastroenterol Hepatol 2011; 23: 633-641.

[4] Krishna Rao SV, Mejia G, Roberts-Thomson K and Logan R. Epidemiology of oral cancer in Asia in the past decade--an update (2000-2012). Asian Pac J Cancer Prev 2013; 14: 5567-5577.

[5] Tan M, Myers JN and Agrawal N. Oral cavity and oropharyngeal squamous cell carcinoma genomics. Otolaryngol Clin North Am 2013; 46: 545-566.

[6] Wendt MK, Balanis N, Carlin CR and Schiemann WP. STAT3 and epithelial-mesenchymal transitions in carcinomas. JAKSTAT 2014; 3: e28975.

[7] Macara IG, Guyer R, Richardson G, Huo Y and Ahmed SM. Epithelial Homeostasis. Curr Biol 2014; 24: R815-R825.

[8] Gao XH, Yang XQ, Wang BC, Liu SP and Wang FB. Overexpression of twist and matrix metalloproteinase-9 with metastasis and prognosis in gastric cancer. Asian Pac J Cancer Prev 2013; 14: 5055-5060.

[9] Huang J, Ang L, Liu MQ, Hu HG, Wang J, Zou Q, Zhao Y, Zheng L, Zhao M and Wu ZS. Serum and tissue expression of gelatinase and Twist in breast cancer. Eur Rev Med Pharmacol Sci 2014; 18: 2662-2669.

[10] Zhuo X, Chang A, Huang C, Yang L, Xiang Z and Zhou Y. Expression of TWIST, an inducer of epithelial-mesenchymal transition, in nasopharyngeal carcinoma and its clinical significance. Int J Clin Exp Pathol 2014; 7: 8862-8868.

[11] Khan MA, Chen HC, Zhang D and Fu J. Twist: a molecular target in cancer therapeutics. Tumour Biol 2013; 34: 2497-2506.

[12] Tierney JF, Stewart LA, Ghersi D, Burdett S and Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007; 8: 16.

[13] Mantel N and Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959; 22: 719-748.

[14] DerSimonian R and Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-188.

[15] Munafo MR, Clark TG and Flint J. Assessing publication bias in genetic association studies: evidence from a recent meta-analysis. Psychiatry Res 2004; 129: 39-44.

[16] Egger M, Davey Smith G, Schneider M and Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634.

[17] Scanlon CS, Van Tubergen EA, Inglehart RC and D'Silva NJ. Biomarkers of epithelial-mesenchymal transition in squamous cell carcinoma. J Dent Res 2013; 92: 114-121.

[18] Wu KJ and Yang MH. Epithelial-mesenchymal transition and cancer stemness: the Twist1-Bmi1 connection. Biosci Rep 2011; 31: 449-455.

[19] Smith A, Teknos TN and Pan Q. Epithelial to mesenchymal transition in head and neck squamous cell carcinoma. Oral Oncol 2013; 49: 287-292.

[20] Zhou C, Liu J, Tang Y, Zhu G, Zheng M, Jiang J, Yang J and Liang X. Coexpression of hypoxia-inducible factor-2alpha, TWIST2, and SIP1 may correlate with invasion and metastasis of salivary adenoid cystic carcinoma. J Oral Pathol Med 2012; 41: 424-431.

[21] Sakamoto K, Imanishi Y, Tomita T, Shimoda M, Kameyama K, Shibata K, Sakai N, Ozawa H, Shigetomi S, Fujii R, Fujii M and Ogawa K. Overexpression of SIP1 and downregulation of E-cadherin predict delayed neck metastasis in stage I/II oral tongue squamous cell carcinoma after partial glossectomy. Ann Surg Oncol 2012; 19: 612-619.

[22] Silva BS, Yamamoto FP, Pontes FS, Cury SE, Fonseca FP, Pontes HA and Pinto-Junior DD. TWIST and p-Akt immunoexpression in normal

oral epithelium, oral dysplasia and in oral squamous cell carcinoma. Med Oral Patol Oral Cir Bucal 2012; 17: e29-34.
[23] de Freitas Silva BS, Yamamoto-Silva FP, Pontes HA and Pinto Junior Ddos S. E-cadherin down-regulation and Twist overexpression since early stages of oral carcinogenesis. J Oral Pathol Med 2014; 43: 125-131.
[24] Jia J, Zhang W, Liu JY, Chen G, Liu H, Zhong HY, Liu B, Cai Y, Zhang JL and Zhao YF. Epithelial mesenchymal transition is required for acquisition of anoikis resistance and metastatic potential in adenoid cystic carcinoma. PLoS One 2012; 7: e51549.
[25] Wu T, Jia J, Xiong X, He H, Bu L, Zhao Z, Huang C and Zhang W. Increased expression of Lin28B associates with poor prognosis in patients with oral squamous cell carcinoma. PLoS One 2013; 8: e83869.
[26] Fan CC, Wang TY, Cheng YA, Jiang SS, Cheng CW, Lee AY and Kao TY. Expression of E-cadherin, Twist, and p53 and their prognostic value in patients with oral squamous cell carcinoma. J Cancer Res Clin Oncol 2013; 139: 1735-1744.
[27] Wang B, Zhang C, Zhang S, Yue K and Wang X. Epithelial-Mesenchymal Transformation-Mediated Lymph Node Metastasis of Oral Squamous Cell Carcinoma and Its Mechanism. Chin J Clin Oncol 2012; 39: 1877-1885.
[28] Liang X, Zheng M, Jiang J, Zhu G, Yang J and Tang Y. Hypoxia-inducible factor-1 alpha, in association with TWIST2 and SNIP1, is a critical prognostic factor in patients with tongue squamous cell carcinoma. Oral Oncol 2011; 47: 92-97.
[29] Wushou A, Pan HY, Liu W, Tian Z, Wang LZ, Shali S and Zhang ZY. Correlation of increased twist with lymph node metastasis in patients with oral squamous cell carcinoma. J Oral Maxillofac Surg 2012; 70: 1473-1479.
[30] da Silva SD, Alaoui-Jamali MA, Soares FA, Carraro DM, Brentani HP, Hier M, Rogatto SR and Kowalski LP. TWIST1 is a molecular marker for a poor prognosis in oral cancer and represents a potential therapeutic target. Cancer 2014; 120: 352-362.
[31] Zheng J and Nan X. Expression and significance of TWIST in oral squamous cell carcinoma. Guide of China Med 2012; 10: 212-213.
[32] Gong Z and Yan Y. Expression of Twist and E-cadherin in tongue squamous cell carcinoma and its clinical significance. Anhui Med Pharm J 2012; 16: 941-943.
[33] Tobias A. Assessing the influence of a single study in the meta-analysis estimate. Stata Techn Bull 1999; 8: 15-17.
[34] Jiang J, Tang YL and Liang XH. EMT: a new vision of hypoxia promoting cancer progression. Cancer Biol Ther 2011; 11: 714-723.
[35] Steinestel K, Eder S, Schrader AJ and Steinestel J. Clinical significance of epithelial-mesenchymal transition. Clin Transl Med 2014; 3: 17.
[36] Moyret-Lalle C, Ruiz E and Puisieux A. Epithelial-mesenchymal transition transcription factors and miRNAs: “Plastic surgeons” of breast cancer. World J Clin Oncol 2014; 5: 311-322.
[37] Gonzalez DM and Medici D. Signaling mechanisms of the epithelial-mesenchymal transition. Sci Signal 2014; 7: re8.
[38] Low-Marchelli JM, Ardi VC, Vizcarra EA, van Rooijen N, Quigley JP and Yang J. Twist1 induces CCL2 and recruits macrophages to promote angiogenesis. Cancer Res 2013; 73: 662-671.
[39] Che N, Zhao XL, Sun T, Zhao XM, Gu Q, Dong XY, Zhao N, Liu YR, Yao Z and Sun BC. The role of Twist1 in hepatocellular carcinoma angiogenesis: a clinical study. Hum Pathol 2011; 42: 840-847.
[40] Wang Y, Zhai W, Wang H, Xia X and Zhang C. Benzo(a)pyrene promotes A549 cell migration and invasion through up-regulating Twist. Arch Toxicol 2015; 89: 451-458.
[41] Fondrevelle ME, Kantelip B, Reiter RE, Chopin DK, Thiery JP, Monnien F, Bittard H and Wallerand H. The expression of Twist has an impact on survival in human bladder cancer and is influenced by the smoking status. Urol Oncol 2009; 27: 268-276.