Original Article

The effects of proliferating cell nuclear antigen and *p53* in patients with oral squamous cell carcinoma: a systematic review and meta-analysis

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Background: To evaluate the effect of proliferating cell nuclear antigen (*PCNA*) and *p53* in patients with oral squamous cell carcinoma (OSCC).

Methods: Multiple databases, including PubMed, Embase, Cochrane library, and China National Knowledge Database, were searched for relevant studies and full-text articles that evaluated the effect of *PCNA* and *p53* in patients with OSCC. Review Manager 5.2 was adopted to estimate the impact of the results among the selected articles. Forest plots, NOS table, sensitivity analysis, and bias analysis were also conducted.

Results: In total, nine eligible studies satisfied the included criteria. High *PCNA* expression (>50%) was significantly more prevalent in OSCC than low *PCNA* expression (<50%) (OR =3.88; 95% CI: 2.04–7.37; P<0.0001; I^2=0%). However, there was no significant difference between *p53* and OSCC (OR =1.60; 95% CI: 0.18–14.63; P=0.68; I^2=86%). Low *PCNA* expression had a higher 5-year overall survival in OSCC patients than high *PCNA* expression (OR =0.47; 95% CI: 0.27–0.80; P=0.005; I^2=41%). Meanwhile, *p53* negative had a higher 5-year overall survival than *p53* positive (OR =0.20; 95% CI: 0.10–0.42; P<0.0001; I^2=0%). There was no difference between high and low *PCNA* in terms of metastasis (OR =0.80 with 95% CI: 0.18–3.45, I^2=63%, P of over effect =0.76). The overall results showed no difference between *p53* and metastasis (OR =0.38 with 95% CI: 0.13–1.10, I^2=0%, P of over effect =0.07).

Discussion: *PCNA* and *p53* might be suitable for prognostic and survival evaluation in OSCC patients.

Keywords: Oral squamous cell carcinoma (OSCC); proliferating cell nuclear antigen (*PCNA*); *p53*; meta-analysis

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Introduction

Globally, head and neck cancers are estimated to comprise 500,000 patients with squamous cell carcinoma (SCC) every year. SCC is the most common malignant tumor of the head and neck, accounting for 90% (1). Due to the location of oral SCC (OSCC) in the body, the social and medical impact of these lesions is more significant than other more common tumors. OSCCs are close to vital structures in the head and neck, making treatment difficult, and the results are often severely deformed (2). Part of the reason for the poor prognosis (5-year survival of approximately 50%) and high recurrence rate (about 645,000 per year) of OSCC is the lack of an accurate and clinically applicable staging system. Also, the current clinical diagnosis system

for predicting the local control and survival rate of OSCC is limited (3).

As a marker of cell proliferation, *PCNA* is considered a convenient tool for quickly assessing the proportion of proliferating cells in tumors. *PCNA* is a nuclear non-histone antigen that appears in the nucleus in the late G1 phase. It increases in the S phase and declines in the G2 and M phases. *PCNA* is a 36kda molecule that plays an essential role in nucleic acid metabolism due to the replication and repair mechanism (4). It serves as an accessory protein for DNA polymerase; it is needed to synthesize S-phase chromosomal DNA and interact with cellular proteins involved in regulating the cell cycle and checkpoint control (5). Some studies have suggested that *PCNA* expression is a marker of abnormal cell proliferation and could be used as a reference index for early cancer diagnosis (4,5).

The tumor suppressor gene, *p53*, is a genetic biomarker that regulates cell growth and proliferation. The wild-type p53 protein controls the cell cycle's progression by acting as transcription factors for multiple genes, which induces transcriptional regulation of the cyclin-dependent kinase inhibitor p21 (6). The stability and overexpression of the *p53* gene might be related to *p53* gene mutation or genotoxic stress, and *p53* gene changes are the most common genetic abnormality in many cancers. In OSCC, multiple studies have shown that overexpression of *p53* plays a vital role in the development of OSCC (7). *p53* is an important anticancer gene; its wild type can induce apoptosis of cancer cells and prevent canceration, and could also help cells repair gene defects (3). In addition, it was reported that there was significant correlation between the expression level of p53 protein and postoperative survival time of oral squamous cell carcinoma and the expression of PCNA protein was closely related to the risk of OSCC, and could be used as an important index to judge the prognosis of OSCC patients (5-7).

In recent years, the value of *PCNA* and *p53* in OSCC has been noted (7), but the detailed role of *PCNA* and *p53* in OSCC has not been fully elucidated. Herein, we conducted a meta-analysis to evaluate the effects of *PCNA* and *p53* in patients with OSCC. This research is a comprehensive analysis from four aspects and can be a supplement for this topic. In this research, we analyzed the association between oral squamous cell carcinoma and *p53* or *PCNA*, respectively. We present the following article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/atm-21-6133).

Methods

Literature search strategy

We searched articles published between January 2000 and March 2020 for *PCNA* and *p53* in OSCC patients in the PubMed, Embase, Cochrane database, and China National Knowledge databases using the following strategy: (oral OR mouth OR tongue) AND (cancer* OR squamous cell carcinoma* OR neoplasm* OR tumor*) AND (*PCNA* OR *p53*). There were no restrictions on the publication language in the literature search. To maximize the specificity and sensitivity of our search, we checked the research reference list to seek other relevant research that were not found through the search strategy.

Study selection

Inclusion criteria and exclusion criteria

We used the following inclusion criteria for our research: (I) studies with case-control design; (II) studies evaluating the effect of *PCNA* and *p53* in prognosis, survival, and metastasis; (III) articles containing eligible data; and (IV) articles with available full text. Research meeting any one of the following conditions was excluded: (I) studies with overlapping data or overlapping review articles; (II) studies involving patients with other head and neck tumors, and (III) articles involving other biomarkers for OSCC patients.

Data extraction and quality assessment

Two commentators independently scanned the full texts of the manuscripts. They extracted the following data from each eligible study: first author's name, patient's age and gender, country of origin, year of publication, sample size, and the study period of each article. The Cochrane risk of the bias assessment tool, which is a comprehensive tool to consider multiple biases, was used to evaluate the methodological quality of the studies.

Statistical analysis

We used Review Manager (version 5.2, Cochrane Collaboration, 2011) to assess the impact of the results in selected reports. For continuous outcomes, the mean difference was calculated by the average difference. Heterogeneity was evaluated by the I^2 statistic, which is the

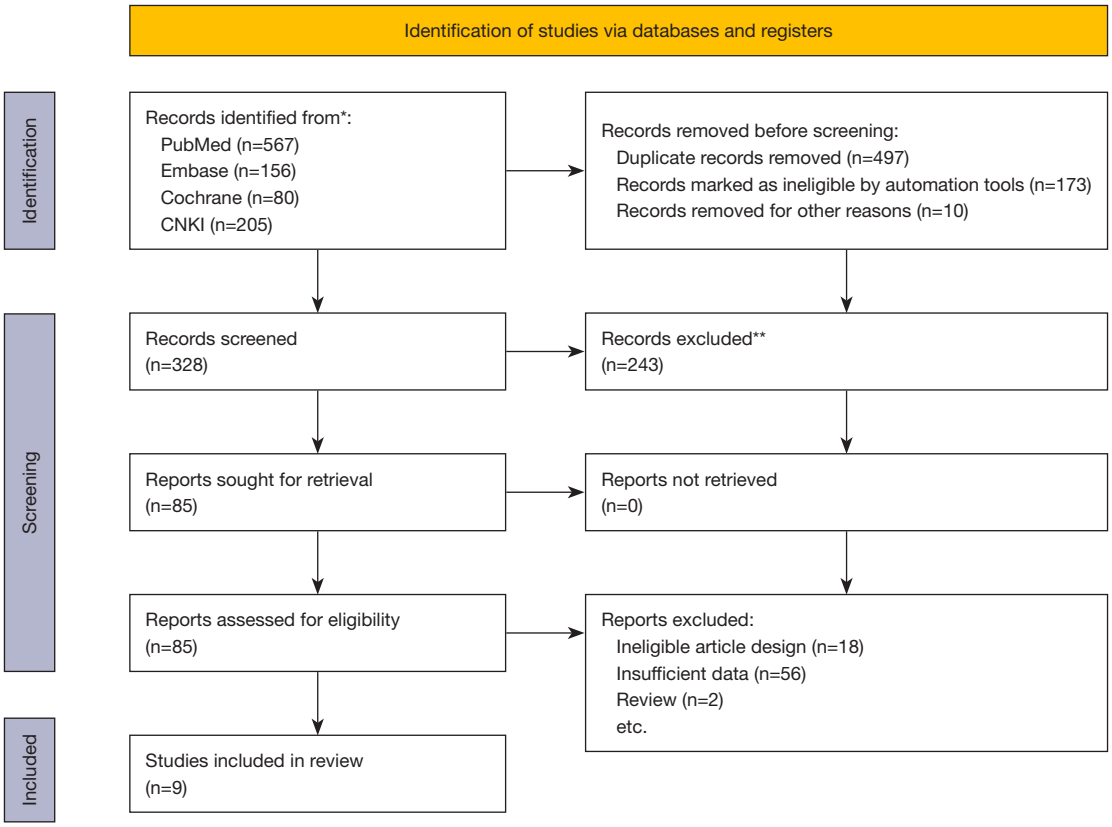

Figure 1 Flow diagram of the study selection. This flow diagram shows the process of study inclusion and exclusion in this meta-analysis. *, consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers); **, if automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

percentage of heterogeneity among studies in the absolute difference and a quantitative measure of inconsistency in research. We confirmed that studies with an I^2 of 25–50% were considered to have low heterogeneity, studies with an I^2 of 50–75% were deemed to be medium heterogeneity, and studies with I^2>75% were considered to have high heterogeneity. If I^2>50%, the potential sources of heterogeneity were examined by sensitivity analysis, which omits one study in each round and investigates the impact of a single portfolio survey estimation. Also, when heterogeneity was observed, the random effects model was used; otherwise, the fixed effects model was used. We used funnel charts, Begger's test, and Egger's test to check for potential publication bias.

Results

Search process

The electronic search retrieved 328 articles. After careful reading, 85 papers have met the preliminary standard. Upon further screening, 76 articles were excluded because of duplication, irrelevant studies, incomplete data, and incomplete comparison. Finally, nine papers were selected for analysis. *Figure 1* displays a flowchart of the search process, highlighting the identification, inclusion, and

Table 1 Characteristics of studies included in this meta-analysis

Study	Year	Language	Country	Age (years)	Groups	n	Years of onset
Fernanda (8)	2005	English	Brazil	58.2±6.8	High *PCNA*	17	1970 to 2000
					Low *PCNA*	17	
Kato (9)	2011	English	Japan	66.8±10.1	High *PCNA*	11	2002 to 2006
					Low *PCNA*	48	
Keum (10)	2006	English	Korea	54±12.3	High *PCNA*	5	1986 to 1997
					Low *PCNA*	15	
Lee (11)	2005	English	China	47±18.5	High *PCNA*	38	1995 TO 2001
					Low *PCNA*	38	
Mallick (12)	2010	English	India	55±10.2	High *PCNA*	20	1998 to 2003
					Low *PCNA*	19	
Monteiro (13)	2012	English	Spain	59±12.6	High *PCNA*	42	1995 to 2003
					Low *PCNA*	34	
Myoung (14)	2006	English	Korea	58.2±10.2	High *PCNA*	59	1996 to 2001
					Low *PCNA*	54	
Stenner (15)	2012	English	Germany	59.4±1.3	High *PCNA*	12	1986 to 2006
					Low *PCNA*	12	
Watanabe (16)	2010	English	Brazil	60.5±8.3	High *PCNA*	19	1996 to 2002
					Low *PCNA*	20	

PCNA, proliferating cell nuclear antigen.

exclusion (including reasons) process.

Characteristics of included studies

Detailed characteristics of the included studies are presented in *Table 1*. All of the included studies were published between 2005 and 2020. The sample size ranged from 20 to 113. In total, 223 patients were in the high *PCNA* group and 257 patients were in the low *PCNA* group.

Quality assessment

Since the included articles were case-control studies, we used the Newcastle-Ottawa Scale (NOS) table to evaluate the risk of patient selection problems in nine trials (*Table 2*). Four of the nine included articles had 9 stars, and the other five had 8 stars, which demonstrated that included papers were good quality (>6 stars was considered to indicate good research quality).

Heterogeneity analysis

Heterogeneity analysis of the prognostic value of *PCNA* and *p53* in OSCC

Since five of the nine included studies did not report on *PCNA* level, comprehensive analysis was performed on the other four articles. As shown in *Figure 2A*, I^2=0%, and thus a fixed effects model was adopted. The results showed high *PCNA* expression (event/total: 61/87) was significantly more prevalent than low *PCNA* expression (33/86) in OSCC [odds ratio (OR) =3.88; 95% confidential interval (CI): 2.04–7.37; P<0.0001; I^2=0%, *Figure 2A*]. However, only two studies reported on *p53* expression in OSCC. As shown in *Figure 2B*, I^2=86%, and therefore a random effects model was used. The result suggested that there was no significant difference between *p53* positive (33/55) and *p53* negative (22/55) in OSCC (OR =1.60; 95% CI: 0.18–14.63; P=0.68; I^2=86%, *Figure 2B*).

Table 2 Newcastle-Ottawa Scale table of included studies

Study	Definition adequate	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	Total quality scores
Fernanda 2005	☆	☆	☆	☆	☆	☆	☆	☆	8
Kato 2011	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Keum 2006	☆	☆	☆	☆	☆	☆☆	☆	☆	9
Lee 2005	☆	☆	☆	☆	☆	☆	☆	☆	8
Mallick 2010	☆	☆	☆	☆	☆	☆	☆	☆	8
Monteiro 2012	☆	☆	☆	☆	☆	☆☆	☆	☆	9
Myoung 2006	☆	☆	☆	☆	☆	☆	☆	☆	8
Stenner 2012	☆	☆	☆	☆	☆	☆	☆	☆	8
Watanabe 2010	☆	☆	☆	☆	☆☆	☆	☆	☆	9

☆ , medium quality ; ☆☆ , high quality. The higher the quality score is, the better quality of article is.

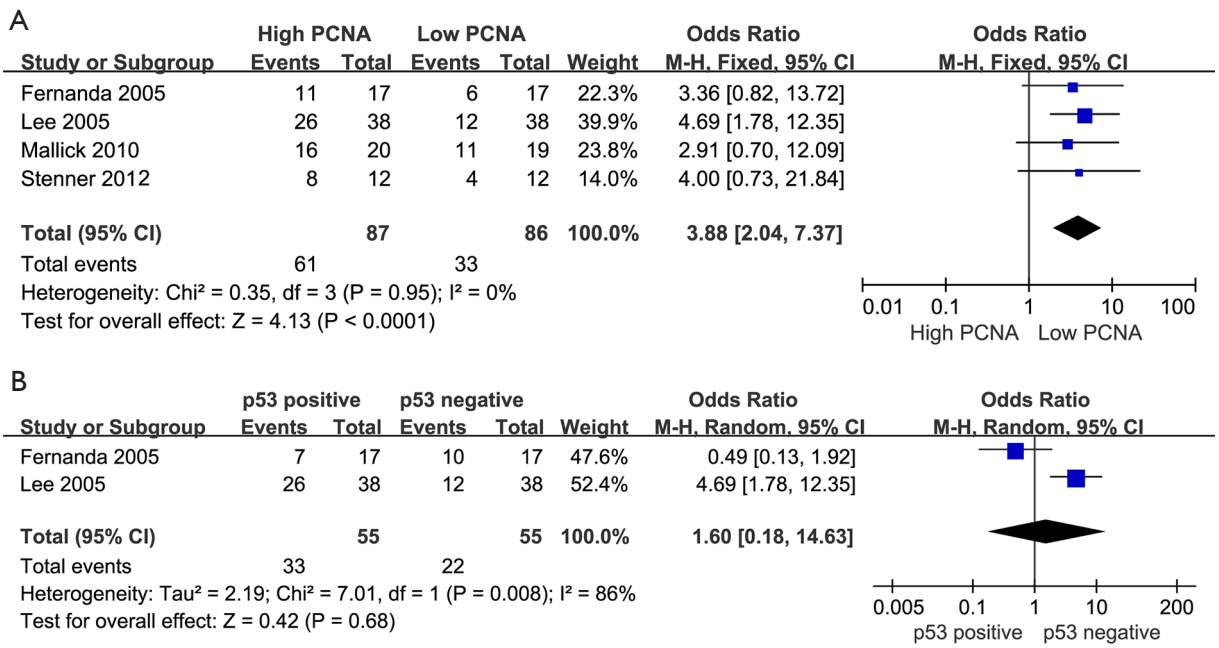

Figure 2 Forest plots of the prognostic value of *PCNA* and *p53* in OSCC. (A) OSCC patients' *PCNA* was compared; (B) OSCC patients' *p53* was contrasted. *PCNA*, proliferating cell nuclear antigen; *p53*, *p53* gene; OSCC, oral squamous cell carcinoma.

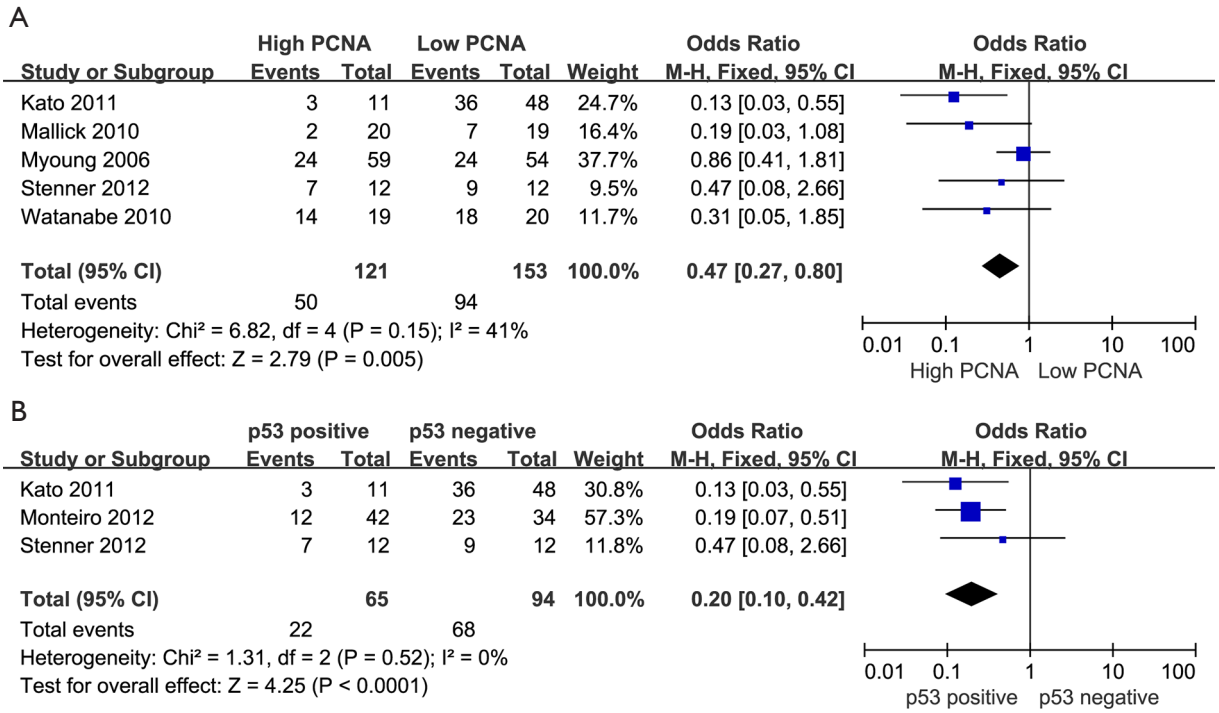

Figure 3 Forest plots of the value of *PCNA* and *p53* on the 5-year overall survival among patients with OSCC. (A) OSCC patients' 5-year overall survival with different *PCNA* levels was compared; (B) OSCC patients' 5-year overall survival with different *p53* was contrasted. *PCNA*, proliferating cell nuclear antigen; *p53*, *p53* gene; OSCC, oral squamous cell carcinoma.

Heterogeneity analysis regarding the value of *PCNA* and *p53* on the 5-year overall survival among patients with OSCC

As shown in *Figure 3A*, five of the nine studies reported on *PCNA* and the 5-year overall survival of OSCC patients. Since the I^2 value was low, the fixed effects model was used. The results showed that low *PCNA* expression had a higher 5-year overall survival in OSCC patients (94/153) than high *PCNA* expression (50/121) (OR =0.47; 95% CI: 0.27–0.80; P=0.005; I^2=41%, *Figure 3A*). As for *p53*, a fixed effects model was used for heterogeneity analysis, which showed that *p53* negative (68/94) had a higher 5-year overall survival than *p53* positive (22/65) (OR =0.20; 95% CI: 0.10–0.42; P<0.0001; I^2=0%, *Figure 3B*).

Heterogeneity analysis on the role of *PCNA* and *p53* in metastasis

We used three articles (3/9) for *PCNA* and two articles (2/9) for *p53* to conduct heterogeneity analysis. The heterogeneity test results showed that we needed a random effects model to analyze the data (OR =0.80 with 95% CI: 0.18–3.45, P of heterogeneity =0.07, I^2=63%, Z=0.30, P of over effect =0.76, *Figure 4A*). There was no difference in the overall effect of high (18/38) and low (28/51) *PCNA* on metastasis (*Figure 4A*). A fixed effects model was used to evaluate *p53*, and also showed no difference between *p53* and metastasis (OR =0.38 with 95% CI: 0.13–1.10, P of heterogeneity =0.71, I^2=0%, Z=1.79, P of over effect =0.07, *Figure 4B*).

Sensitivity analysis and publication bias

According to heterogeneity analysis, the heterogeneity of *PCNA* in OSCC was low (I^2=0%, P<0.0001). This might be attributed to the different results of each study. When Lee *et al.* (11) from 2005 was excluded, the I^2 did not change, while the P value of heterogeneity changed from 0.95 to 0.96 (*Figure 5*). The sensitivity analysis indicated that the results in this article were robust.

We performed a funnel plot for *PCNA* in OSCC. Four studies were included in the plot. The standard error of or logarithm is ordinate, and the image symmetry is the

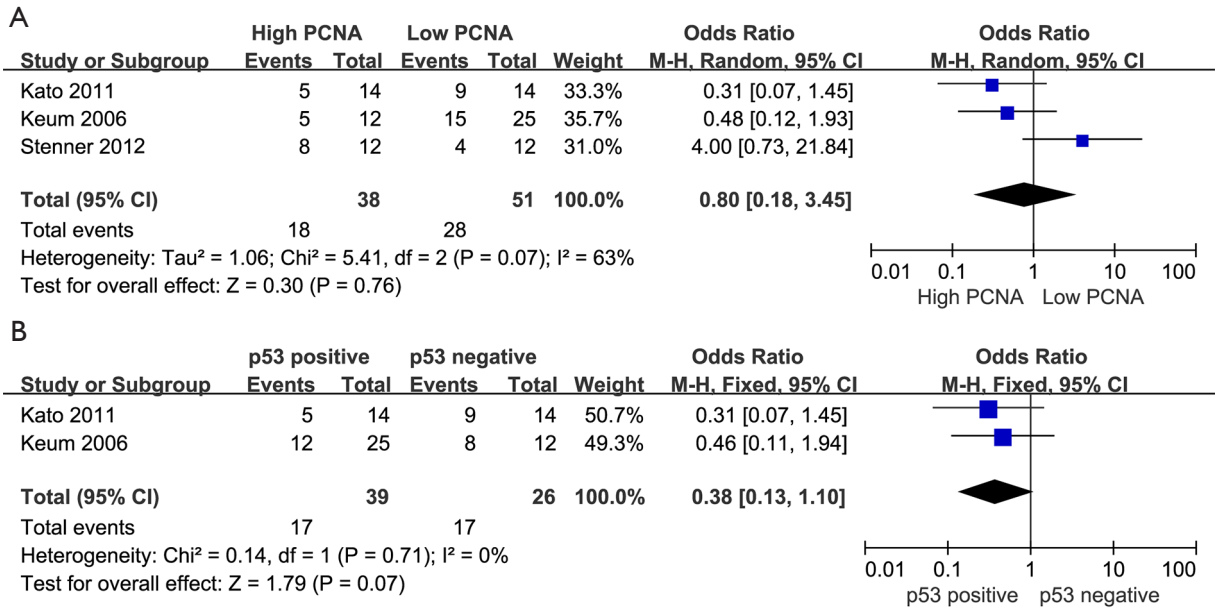

Figure 4 Forest plots of the role of *PCNA* and *p53* on metastasis. (A) OSCC patients' metastasis with different *PCNA* levels was compared; (B) OSCC patients' metastasis with different *p53* was contrasted. *PCNA*, proliferating cell nuclear antigen; *p53*, *p53* gene; OSCC, oral squamous cell carcinoma.

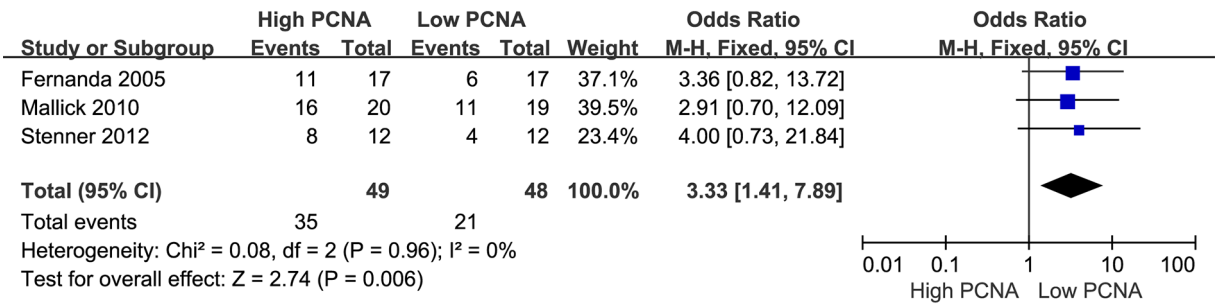

Figure 5 Sensitivity analysis forest plots of the prognostic value of *PCNA* in OSCC. *PCNA*, proliferating cell nuclear antigen; OSCC, oral squamous cell carcinoma.

basis of judging publication bias. When it is symmetrical, publication bias is slight; when it is asymmetrical, publication bias is significant (7). To some extent, the result indicated that there existed slight publication bias, since the symmetrical characteristic of the funnel plot was good (*Figure 6*). The result of Begger's test suggested that no significant evidence of potential publication bias existed (z=1.15, P=0.101), and Egger's test also indicated that no significant evidence of possible publication bias existed (t=1.27, P=0.215).

Discussion

Our results showed that high *PCNA* expression was significantly more prevalent in OSCC than low *PCNA* expression, which indicated that *PCNA* might have predictive value for OSCC. Sajeevan (17) stated that the functional change of *PCNA* activity is a joint genetic event in various cancers and an effective marker of cell proliferation. It could be used to determine the histological grade, recurrence rate, and prognosis of head and neck

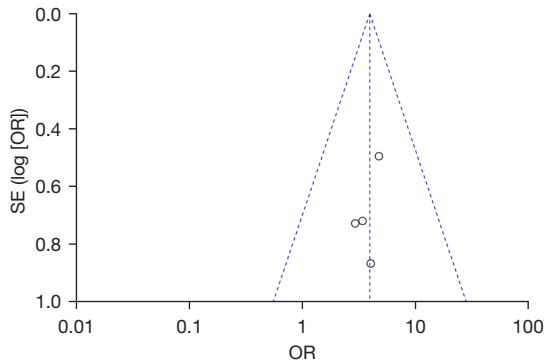

Figure 6 Funnel plot of the prognostic value of *PCNA* and *p53* in OSCC. *PCNA*, proliferating cell nuclear antigen; *p53*, *p53* gene; OSCC, oral squamous cell carcinoma.

cancers. Overexpression of *PCNA* is also associated with chemotherapy or radiation therapy (17). However, the relationship between *PCNA* changes and cervical lymph node metastasis of oral tongue cancer remains unclear. In the analysis of the 5-year overall survival and *PCNA*, low *PCNA* expression had a higher 5-year overall survival in OSCC patients than high *PCNA* expression. These findings demonstrated that low *PCNA* might be an influencing factor for OSCC patients' 5-year overall survival. Furthermore, the results regarding the role of *PCNA* in the metastasis of OSCC patients suggested that *PCNA* is not valuable for determining metastasis.

The analysis also showed that *p53* could be a potential indicator for the 5-year overall survival of OSCC patients, but does not appear to have predictive value for OSCC. Zhong *et al.* (5) reported that *p53* gene mutations and overexpression of mutant p53 proteins play an essential role in the occurrence and loss of apoptosis in various human cancers. Simultaneously, *p53* gene mutations have been increasingly found in several poorly differentiated head and neck cancers, including oral cancer (18). There are also changes in *p53* that are associated with aggressive laryngeal and pharyngeal phenotype tumor recurrence (19). Overexpression of *p53* is associated with a higher risk of oral lymph node metastasis, and is a marker of poor prognosis for oral squamous cell cancer (20). However, these correlations have not been further confirmed by other studies. The results about the role of *p53* in metastasis among OSCC patients showed that *p53* might not have any value for indicating metastasis.

Mestrinho *et al.* (18) reported that the data of 159 patients with OSCC showed that *PCNA* was expressed in different degrees in all histological subtypes examined. Expression was related to the ages of patients and the stages of pathological lymph nodes. Most importantly, the high expression of *PCNA* was a significant prognostic indicator for poor overall prognosis and disease-free survival of OSCC (21). In the acinar cell carcinoma subgroup, *PCNA* expression was found to be the only negative prognostic factor affecting the 5-year tumor-free survival rate and overall survival (22). Simultaneously, the stability and overexpression of the *p53* gene might be related to *p53* gene mutation or genotoxic stress, and *p53* gene alterations are the most common gene abnormality in numerous cancers (23). Overexpression of *p53* plays an essential role in the development of OSCC (24).

Generally, mutation of the *p53* gene and overexpression of the mutant protein plays an important role in carcinogenesis and apoptosis in many human cancers. Simultaneously, *p53* mutations have been increasingly found in some poorly differentiated head and neck cancers, including an oral cavity in breast cancer (20,21). Moreover, *p53* changes are related to the invasive phenotype and recurrence of laryngeal and pharyngeal carcinomas. Overexpression of *p53* has been shown to be associated with a high risk of lymph node metastasis and is a marker of poor prognosis in oral cancer (22). The functional change of *PCNA* activity is a joint genetic event (23). *p53* is an effective marker of cell proliferation and could be used as an indicator to predict head and neck cancer. The overexpression of *PCNA* is also related to chemotherapy or the response to chemotherapy (24).

Since OSCC remains one of the most challenging cancers to control, with only slight improvement in survival over the past 50 years, prevention, treatment, and prognosis are crucial for OSCC. To improve the prognosis, survival biomarkers are needed. As our analysis demonstrated, *PCNA* and *p53* might be suitable for prognostic and survival evaluation of OSCC. It was reported that expression of PCNA and P53 had association with some other kinds of carcinoma like skin cancer, colorectal cancer and lung cancer. There is need to analyze the other relationships in the future (20-23). It was also reported that PCNA and Ki-67 were related to the abnormal proliferation of oral mucosa, and their proliferation index was parallel to the degree of proliferation, and they were linearly correlated (25,26). So, we can conduct a further analysis between Ki-67 and proliferation of OSCC in the next step.

However, there were some limitations in this study that should be noted. Firstly, more indicators evaluating other

aspects between biomarkers and OSCC could be included, which should be conducted in the future. Secondly, comparisons between different subgroups, like age or area, could also be analyzed in future research.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://dx.doi.org/10.21037/atm-21-6133

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/atm-21-6133). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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