

## Original Article

# Zinc dependent endopeptidases of matrix metalloproteinases-9 expressions is associated with tumor metastases of oral squamous cell carcinoma in Chinese population: a meta-analysis

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**Abstract:** Matrix metalloproteinase-9 (MMP-9) is an important member of zinc dependent endopeptidases family and is considered to be involved in the invasion and metastasis of cancer cells. Many studies were published to assess the prognostic role of MMP-9 expression in patients with oral squamous cell Carcinoma, but the findings from those studies were inconsistent in Chinese population. We searched eligible studies in Pubmed, Embase, and Web of Science databases. Six studies with a total of 556 patients were finally included into the meta-analysis. The pooled odds ratios (OR) with the corresponding 95% confidence interval (95% CIs) for positive rate of MMP-9 were calculated by using meta-analysis. Overall, MMP-9 positive expression was associated with tumor metastases in patients with oral squamous cell Carcinoma (fixed-effects OR 4.24, 95% CI 2.25-7.99,  $P < 0.001$ ; random-effects OR 4.35, 95% CI 2.31-8.21,  $P < 0.001$ ). Our results indicated that MMP-9 expression is associated with tumor metastases in patients with oral squamous cell carcinoma, and patients with higher MMP-9 expression have less tumor metastases.

**Keywords:** MMP-9, tumor metastases, oral squamous cell carcinoma

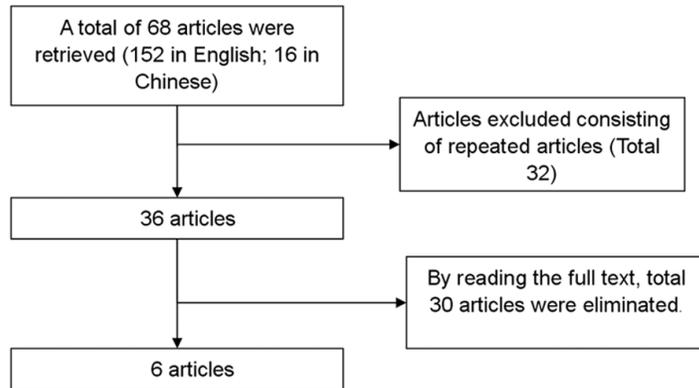
## Introduction

Head and neck squamous cell carcinoma (HNSCC) ranks sixth among the most common cancers worldwide with an incidence of over 500,000 new cases each year [1]. Oral squamous cell carcinoma (OSCC) is the most prevalent malignant cancer in oral cavity [2], which is a disease found particularly in low income communities and mainly a problem of older men, 90% being in the > 45 year age group who are exposed to the known risk factors of tobacco and/or alcohol (IARC 2004) [3]. However, there are changing pattern in both lip and intraoral cancer with a decrease in male incidence of lip cancer over about a 30-year period, but several studies have shown an increase in OSCC, particularly in younger patients, currently attributed to smoking and drinking among young people [4, 5]. Patients with OSCC have a poor

prognosis, and typically, more than one-third of the patients die within 5 years of diagnosis [6].

Matrix metalloproteinases (MMP) are enzymes that are able to degrade collagen, fibronectin, elastin and laminin, which are all components of the extracellular matrix. The proteolytic activity of MMPs is counteracted by tissue inhibitors of matrix metalloproteinases (TIMPs). MMPs function in growth and vascular remodeling during wound healing and inflammation [7]. The MMPs expression in oral cancer tissue is an important tool in cancer prognosis. However, MMP expression only became substantial if the tests are performed after cancer initiation. Due to this fact, this methodology might be used for therapeutic purposes, but not as a preventive tool, which is the idea of new medicine. MMP-9 is associated with the aggressive nature of many cancers, including OSCC [8-10], and this

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**Figure 1.** Flow diagram: publications documenting the association between matrix metalloproteinases-9 expressions and tumor metastases of oral squamous cell carcinoma.

aggressive nature was thought to cause type IV collagen degradation, a main component of basement membranes [11]. To date, the spectrum of MMP-9 matrix substrates has significantly increased, and aside from substrates, which originate in the matrix, MMP-9 has other bioactive substrates that independently modulate carcinogenesis, such as the pro-transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1) and the pro-tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) [10]. MMP-9 has traditionally been associated with the aggressive nature of OSCC. However, in spite of increased MMP-9 expression levels, many researchers have presented contradictory results [12-14]. For example, Guttman et al [15] did not find a correlation between MMP-9 expression and the size of the primary tumor or the neck metastasis in tongue SCC patients. Meanwhile, another study reported that high levels of MMP-9 expression in OSCC patients were correlated with regional lymph node and/or distant metastases and a poor prognosis [16]. In addition, De Vicente et al. [17] showed that MMP-9 expression was not associated with clinical variables, such as tumor stage or recurrence rate. In a study conducted by Ikebe et al, gelatinolytic activity and increased expression of MMP-9 in OSCC tumors were related to the invasiveness, but not to the metastatic potential of OSCC tumors [18].

Many studies were published to assess the prognostic role of MMP-9 expression in patients with oral squamous cell Carcinoma, but the findings from those studies also were inconsistent in Chinese population. This study examines the relationship between MMP-9 expression in patients and oral squamous cell carcinoma

metastases. The aims of this study were to compare MMP-9 levels in oral squamous cell carcinoma patients with and without lymph node metastasis.

### Data and methods

#### Data sources and search strategy

We searched PubMed, Embase, and Cochrane for English-language articles published subsequent to 20 February 2014 using a search strategy that included terms related to the relationship between MMP-9 levels and lymph node metastasis among oral squamous cell carcinoma patients. The search strategy targeted peer reviewed, published and non-published literature. Only published intervention studies are reported in this paper. We also reviewed reference lists of relevant primary research and review articles for additional publications.

#### Initial inclusion criteria and data abstraction

Studies had to (1) the relationship between MMP-9 levels and lymph node metastasis among oral squamous cell carcinoma t; (2) on MMP-9 levels and lymph node metastasis (3) report findings for all-cause mortality. We excluded studies of patients not on Chinese oral squamous cell Carcinoma.

Relevant data from each study were abstracted into an evidence table by one investigator and were verified by the study statistician prior to use in the meta-analysis. Data elements included study characteristics, patient characteristics, (eg, Age, Area), and data.

#### Literature assessment

For each manuscript that presented a correlation of MMP-9 levels with lymph node metastasis among oral squamous cell carcinoma of interest, We also noted if figures were plotted showing the relationship between MMP-9 levels with lymph node metastasis among oral squamous cell carcinoma .

#### Statistical methods

The association between the MMP-9 levels and lymph node metastasis among oral squamous

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**Table 1.** Summary of studies included in meta-analysis

First author	Age (year)		Year	Province of China	male	female
	< 55	≥ 55				
Hai Liu [1]	-	-	2003	Anhui	-	-
Xuanping Cao [2]	38	38	2003	Zhenzhou	43	33
Hong Xu [3]	9	42	2006	Jiangxi	34	17
Hongji Li [4]	12	28	2002	Tianjin	24	16
Caiwang Chang [5]	12	38	2007	Jiangsu	27	23
HaiXia Fan [6]	20	28	2008	Northeast	36	12

cell carcinoma was assessed by OR and 95% CI. Heterogeneity between studies was evaluated by Cochran's  $\chi^2$  based Q statistic test. If the *P*-value for heterogeneity was 0.05 suggesting that there was obvious heterogeneity of the data, a random-effects model was used; otherwise, we used a fixed effects model to pool the results. In present study we used both above model. The significance of pooled ORs was detected by the Z test (*P* < 0.05 was considered significant). Publication bias was evaluated by the funnel plot. All *P* values < 0.05 were two-sided.

### Results

#### Overview of studies

The interim search strategy identified 168 publications. We ultimately identified 6 studies among patients with oral squamous cell Carcinoma correlated with MMP-9 (see **Figure 1** and **Table 1**).

#### Overview of accepted publications

As noted in **Table 1**, most studies found a significant relationship between metalloproteinases-9 expressions and tumor metastases of oral squamous cell carcinoma.

#### Primary meta-analysis findings

Six studies with a total of 556 patients were finally included into the meta-analysis (see **Table 1**). The pooled odds ratios (OR) with the corresponding 95% confidence interval (95% CIs) for positive rate of MMP-9 were calculated by using meta-analysis (**Figures 2** and **3**). Overall, MMP-9 positive expression was associated with tumor metastases in patients with oral squamous cell carcinoma (fixed-effects OR 4.24, 95% CI 2.25-7.99, *P* < 0.001; random-effects OR 4.35, 95% CI 2.31-8.21, *P* < 0.001).

The funnel plot was used to evaluate the Publication bias (**Figure 4**).

### Discussion

Our literature review shows that most studies found a significant relationship between MMP-9 positive expression and tumor metastases in patients with oral squamous cell Car-

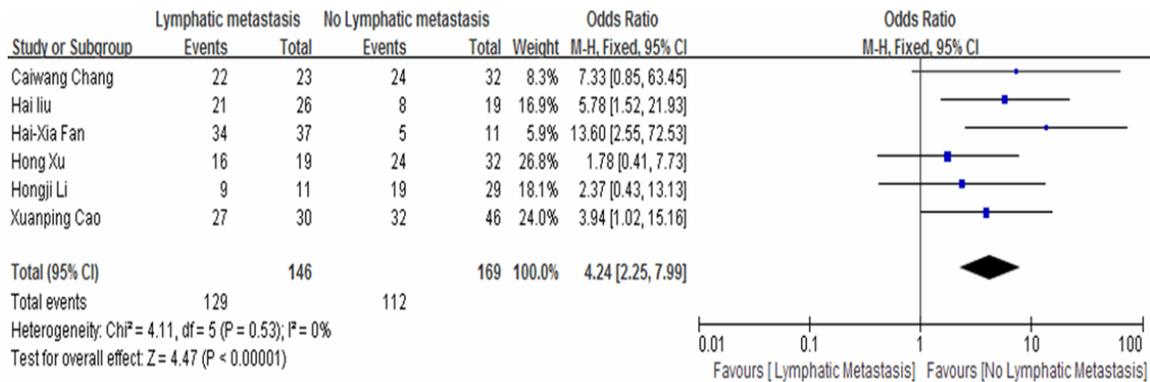
cinoma. One hallmark of cancer is the degradation of the extracellular matrix (ECM), which is caused by proteinases. In oral cancers, matrix metalloproteinases (MMPs), especially MMP-9, are associated with this degradation. MMPs break down the ECM allowing cancer to spread; they also release various factors from their cryptic sites, including cytokines. These factors modulate cell behavior and enhance cancer progression by regulating angiogenesis, migration, proliferation, and invasion. The development of early metastases is typical for oral cancer, and increased MMP-9 expression is associated with a poor disease prognosis. However, many studies fail to relate MMP-9 expression with metastasis formation. Contrary to earlier models, recent studies show that MMP-9 plays a protective role in oral cancers. Therefore, the role of MMP-9 is complicated and may fluctuate throughout the different types and stages of oral cancer [25].

We also rarely encountered a paper that reported explicit power calculations, which is important given that categorizing a variable reduces power. Thus, it is important to acknowledge that the statistical methods used in the literature may be insufficient and the results should be cautiously interpreted.

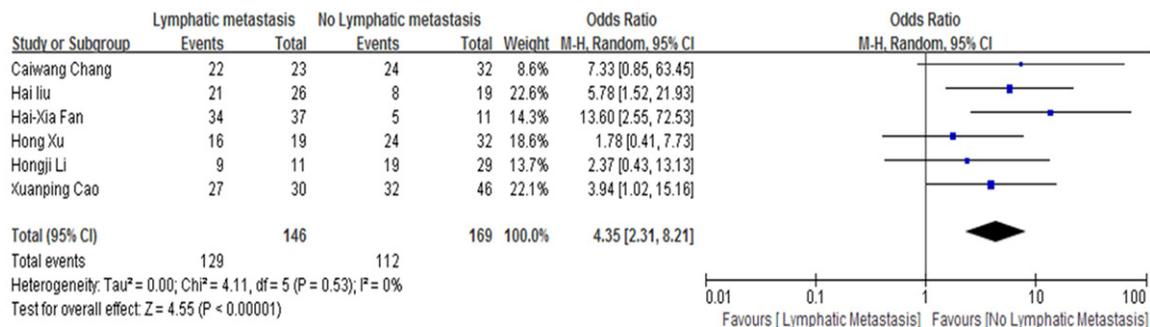
Our meta-analysis has specific limitations. Although we did not perform independent, dual data abstraction (the gold standard for systematic reviews), we employed a rigorous quality review of abstracted data, and we do not believe that this approach compromised the accuracy of our results. Additionally, while statistically significant associations between MMP-9 expression and tumor metastases in patients with oral squamous cell carcinoma were found, we stress that association alone does not necessitate a causal relationship.

In addition, we excluded several studies because their results could not be synthesized in

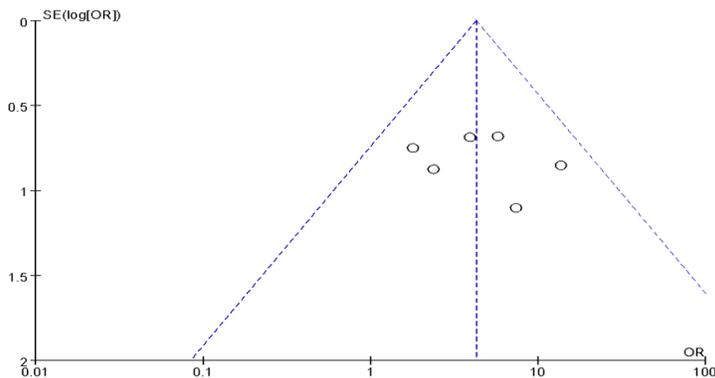
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**Figure 2.** Forest plot for association between MMP-9 positive expression and tumor metastases in patients with oral squamous cell carcinoma in fixed effects model.



**Figure 3.** Forest plot for association between MMP-9 positive expression and tumor metastases in patients with oral squamous cell carcinoma in random effects model.



**Figure 4.** Funnel plot for publication bias in selection of studies.

our meta-analysis due to the population were not Chinese. All meta-analyses are limited by the availability of pertinent data in relevant publications, nevertheless, our analysis of abnormally low values may have been underpowered and we encourage future studies to look at this clinically uncommon subset of patients in more detail.

### Conclusions

In summary, we conclude that MMP-9 expression is associated with tumor metastases in patients with oral squamous cell carcinoma, and patients with higher MMP-9 expression have less tumor metastases.

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### Disclosure of conflict of interest

None.

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