Elevated Matrix Metalloproteinase-9 Expression Correlates With Advanced Stages of Oral Cancer and Is Linked to Poor Clinical Outcomes

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Purpose: Using a meta-analytic approach, the relation between increased matrix metalloproteinase-9 (MMP-9) expression, tumor stage, and clinical outcomes in oral cancers was investigated.

Materials and Methods: Multiple English- and Chinese-language electronic databases were searched to identify high-quality case-and-control studies relevant to this meta-analysis. Methodologic quality of the included trials was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology statement to ensure consistency in reviewing and reporting the results. Statistical analyses were carried out with STATA 12.0 statistical software.

Results: Nine case-and-control studies containing a combined total of 419 patients with oral cancer were included in the present meta-analysis. Results showed that patients who were positive for MMP-9 expression had a significantly poorer overall survival compared with those negative for MMP-9 (effect size = 2.10; 95% confidence interval, 0.98 to 3.22; $P < .001$). MMP-9 expression also positively correlated with lymph node metastasis and advanced T-stage groups ($P < .05$ for all comparisons). Further, high MMP-9 expression level correlated with increased oral cancer risk in Asians ($P < .05$ for all comparisons) as shown by method-stratified subgroup analysis.

Conclusion: The present results strongly suggest that MMP-9 expression level influences tumor invasion and metastasis in oral cancers. Based on these results, MMP-9 can be an excellent therapeutic target in patients with oral cancer.

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Oral cancer refers to a group of head and neck malignancies that develop on the lip, oral cavity, oropharynx, middle ear, nasal cavity, and salivary gland. Many mutations in oncogenes and tumor suppressor genes found in other cancers also are seen in oral cancers, and these mutations confer oral cancers the ability to escape immune surveillance, suppress apoptosis, and hyperactivate cell signaling pathways involved in proliferation and metastasis.[1] Approximately 90% of oral cancers are oral squamous cell carcinoma (OSCC).[2] Oral cancer is the 11th most common cancer globally and the 10th leading cancer in Asia.[3] Approximately 405,000 new cases of oral cancer are diagnosed each year, and the incidence of the disease continues to rise in many countries. In Asian countries, oral and oropharyngeal cancers constitute more than half of all malignancies. Particularly in South Korea, its annual incidence rate is 2.2% in women and 5.9% in men

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according to the National Cancer Center in Korea.[4] Oral cancer accounts for more than 6 million deaths annually in the world.[5] The major risk factors for oral cancer include chewing betel quid, alcohol consumption, tobacco use, smoking, poor oral hygiene, diet, viral infection, and intrinsic genetic factors.[6] Despite focused efforts to promote healthy lifestyles to lower oral cancer risks and recent advances in clinical diagnostics for early intervention, the survival rate for patients with OSCC remains poor.[2] Surgical resection or radiation therapy is often recommended as a curative therapy in early-stage oral cancers when the tumors are small,[7] and radiation therapy with or without chemotherapy also is frequently adopted, especially in inoperable tumors.[8,9] In this context, oral cancer biomarkers are important in selecting treatment options and in disease management. Recent evidence suggests that increased focal adhesion kinase activity leads to enhanced cell motility through elevating matrix metalloproteinase-9 (MMP-9) expression; therefore, the role of MMP-9 in oral cancers merits further investigation.[10-12]

MMP-9, also known as gelatinase B, is the main member of the MMP family that exhibits zinc-independent endopeptidase activity against substrates, such as type IV collagen, gelation, and elastin.[6] The *MMP* gene family is classified into 5 groups, including collagenases, gelatinases, stromelysin, matrilysin, and membrane-type MMPs.[13] MMP-9 is secreted by macrophages with a normal role in tissue remodeling.[14] MMP-9 expression is highly restricted to specific tissues, is used multiple times in fetal and adult development, and is prominently involved in branching morphogenesis during kidney morphogenesis and in axonal outgrowth in postnatal development in humans. However, ectopic or excess MMP-9 activity degrades various components of the extracellular matrix, especially type IV collagen of the basement membranes.[15] Not surprisingly, overexpression of MMP-9 is observed in many cancers and is the leading cause of tumor progression, promoting tumor invasion and metastasis.[16] MMP-9 also is involved in the pathogenesis of inflammatory disorders, such as arthritis. Therefore, MMP-9 is a useful biomarker in several disease settings.[17] Increased expression of MMP-9, resulting in extracellular matrix degradation and remodeling, is a major factor in gastric cancers and cardiovascular and respiratory diseases.[18] MMP-9 overexpression has been shown to influence the aggressiveness of OSCC,[12] and MMP-9 has been shown to indirectly promote differentiation and proliferation of OSCC.[19] The authors suspected a link between abnormal MMP-9 expression, advanced tumor stage, and poor prognosis in patients with oral cancer. Previous studies have associated MMP-9 overexpression with oral cancer progression and poor prognosis in patients with OSCC.[20,21] However, other studies have reported contradictory results.[22,23] In light of the conflicting results, the authors performed a meta-analysis of high-quality cohort studies to investigate the correlation between MMP-9 expression, tumor stage, and prognosis in oral cancer to identify potential novel therapeutic approaches for oral cancer treatment.

Materials and Methods

SEARCH STRATEGY

Topic-relevant studies were extracted through a comprehensive electronic search followed by a manual search using the following databases: MEDLINE, Cochrane Library, PubMed, Embase, CINAHL, and Current Contents Index for studies published before 2014. Three Chinese-language databases—Chinese Biomedical, the Chinese Journal Full-Text, and Weipu—also were searched to identify additional articles relevant to this meta-analysis. The authors used combinations of the following Medical Subject Headings and free language terms in a highly sensitive search strategy: *mouth neoplasms* or *oral neoplasm* or *oral cancer* or *mouth cancer* or *cancer of the mouth* or *oral carcinoma* or *mouth carcinoma* or *oral squamous cell carcinoma* or *OSCC* and *matrix metalloproteinase 9* or *MMP-9* or *matrix metalloproteinase-9* or *MMP9 metalloproteinase* or *92-kDa gelatinase* or *gelatinase B*. In addition, cross-reference lists of topic-relevant studies selected from the electronic databases were manually searched to identify related studies.

INCLUSION AND EXCLUSION CRITERIA

Retrieved studies were evaluated for their eligibility using the following criteria: *1)* human studies; *2)* case-and-control or cohort studies investigating the role of MMP-9 levels in tumorigenesis and progression and prognosis of oral cancer; *3)* patients with histologic confirmation of oral cancer; *4)* clinicopathologic staging consistent with the TNM system[24]; *5)* current original data on MMP-9 levels, clinicopathologic stages, and prognosis of oral cancer; and *6)* the study with the largest sample number was included in case of overlapping data. The exclusion criteria were: *1)* did not meet the inclusion criteria; *2)* letters, abstracts, and summaries; *3)* unpublished studies; and *4)* duplicate publications. Based on the inclusion criteria, 2 investigators independently assessed the eligibility of the studies for inclusion in the present meta-analysis.

STUDY QUALITY AND DATA EXTRACTION

Two experienced reviewers independently assessed the methodologic quality of the included case-and-