

**IMMUNOHISTOCHEMICAL  
EXPRESSION OF CD44 AND MMP-9  
IN ORAL SQUAMOUS CELL  
CARCINOMA**

Thesis

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**بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ**

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## *Dedications*

*To the spirit of my father*

*Spirit of my mother*

*My dear wife*

*And my lovely children*

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## **List of Abbreviations**

AA: amino acid  
ANOVA: analysis of variance  
CD44: cluster of differentiation  
CD44s: standard CD44  
CD44v: variant CD44  
CNS: central nervous system  
CSCs: cancer stem cells  
DAB: diamino benzidine  
DNA: deoxyribonucleic acid  
ECM: extracellular matrix  
EGF: epidermal growth factor  
EGFR: epidermal growth factor receptor  
EMT: epithelial-mesenchymal transition  
ERM: ezrin,radixin, and moesin  
HA: hyaluronic acid  
HNSCC: head and neck squamous cell carcinoma  
HPV: human papiloma virus  
MAF: mean area fraction  
MDSCC: moderate differentiated SCC  
MMPs: matrix metalloproteinases  
MMP-9: matrix metalloproteinase-9  
MMPIs: matrix metalloproteinase inhibitors  
MT-MMPs: membrane type- MMPs  
OSCC: oral squamous cell carcinoma  
PBS: phosphate buffered saline

PDSCC: poorly differentiated SCC

RNA: ribonucleic acid

SCC: squamous cell carcinoma

SD: standard deviation

TI-MMPs: tissue inhibitors-MMPs

WDSCC: well differentiated SCC



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## **Introduction and review of literature**

Oral cancer is the sixth most common cancer worldwide <sup>(1)</sup>. More than 90% of all oral cancers are squamous cell carcinoma (SCC)<sup>(2, 3)</sup>. The most important risk factors for oral SCC are use of tobacco or betel quid and the regular drinking of alcoholic beverages. However, infection with high-risk human papilloma virus (HPV) genotypes, and a diet low in fresh fruits and vegetables have also recently been implicated in the aetiopathogenesis of oral SCC <sup>(1, 4)</sup>.

The highest incidence and prevalence of oral SCC is found in the Indian subcontinent where the risk of developing oral SCC is increased by the very prevalent habits of chewing tobacco, betel quid and areca-nut<sup>(2)</sup>.

The mutagenic effects of tobacco, alcohol, betel quid or areca-nut are dependent upon dose, upon frequency and upon duration of use, and are accelerated and exaggerated by the concurrent use of two or more of these agents<sup>(4)</sup>.

The survival index continues to be small (50%), as compared to the progress in diagnosis and treatment of other malignant tumors. According to World Health Organization, carcinoma of oral cavity in males in developing countries, is the sixth commonest cancer after lung, prostate, colorectal, stomach and bladder cancer, while in females, it is the tenth commonest site of cancer after breast, colorectal, lung, stomach, uterus, cervix, ovary, bladder and liver<sup>(5)</sup>.

Oral squamous cell carcinoma (OSCC) remains a major public health problem world-wide, with ~275,000 cases annually and little improvement in survival rates<sup>(6)</sup>.

Despite advances in treatment, facial disfigurement, and functional disturbances including mastication, swallowing, and speech remain distressingly common<sup>(7)</sup>.

It is critical to understand key molecular mechanisms in the transformation and spread of OSCC, with a view to designing targeted- or individualized therapies<sup>(8, 9)</sup>.

The stage of oral SCC at the time of diagnosis is the most important prognostic factor<sup>(10)</sup>. OSCC is most frequently diagnosed late in the course of the disease because affected persons fail to seek professional advice timeously, either because they do not understand the significance of early signs and symptoms, or because they are ignorant of the health implications<sup>(11)</sup>.

OSCC arises by malignant transformation of a single precursor cell which by clonal expansion gives rise to a monoclonal cancer cell population. It appears that the precursor cancer cells possess the capacity for relatively unlimited self-renewal but have a limited rate of apoptosis with the outcome of longevity and the ability to initiate and sustain the ongoing growth of the cancerous tissue<sup>(12, 13)</sup>.

The origin of the precursor cell which gives rise to OSCC is uncertain. It is likely that it arises, as is the case in other cancers, from a tissue-specific stem cell or its progenitor cell, which has acquired epigenetic and/or genetic alterations<sup>(14, 15)</sup>. However, it is also possible that the OSCC precursor cell may have arisen from a stem cell which has acquired a precancerous phenotype during embryogenesis and has then differentiated into a tissue-specific cancer stem cell<sup>(16, 17)</sup>.

Another possibility is that the OSCC precursor cell originates from a mature keratinocyte which has undergone cytogenetic alterations resulting in its dedifferentiation into the analogue of an immature progenitor/stem cell which can express the dysregulated intracellular pathways and transcription factors of a tissue-specific cancer stem cell phenotype<sup>(18, 19)</sup>.