Research Article *Open Access*

Journal of Clinical Oncology & Advanced Therapy

DOI: doi.org/10.63721/25JCOAT0105

Oral Cancer Etiology and Risk Factors

Davit Mathevosyan

Associat Professor, Department of Oral and Maxillofacial Surgery, Yerevan State Medical University after M. Heratsi, Yerevan, Armenia

Citation: Davit Mathevosyan (2025) Oral Cancer Etiology and Risk Factors. J.of Clin Onco & Adv Thpy 1(3), 01-09. WMJ/ JCOAT-105

Abstract

Background: *The GLOBOCAN (Global Cancer Statistics) report shows that oral cancer is in 11th place in terms of frequency of occurrence and has a worse prognosis compared to other cancers. If the oropharynx area is taken into account, this malignant tumor is in 6th place in terms of frequency of occurrence in the world.*

Objective: *The purpose of the study was to analyze the current literature on the etiology and risk factors oral cancer.*

Methods: *A comprehensive electronic literature search was performed in the following databases: PubMed, PMC, ScienceDirect, and Scopus using the Medical Subject Heading (MeSH) terms: oral cancer, carcinogenesis, etiology and risk factors oral cancer.*

Results: *156 articles were found and 88 full-text articles of high methodological quality were selected according to the review method used, the PRISMA.*
As a result, some studies have shown the role general and local factors are involved in the development and progression of oral cancer. These factors which determine the prevalence and nature of the course of oral cancer.

Conclusions: *Research in this field is continuously advancing, leading to ongoing enhancements in diagnostic techniques and treatment methods. Understanding and promptly addressing risk factors can help prevent oral cancer. Controlling risk factors is important in preventing oral cancer. If complete prevention oral cancer isn't possible, managing these factors effectively can minimize the severity of the condition.*

***Corresponding author:** professor Gagik Hakobyan, Head of Department of Oral and Maxillofacial Surgery, Yerevan State Medical University after M. Heratsi, Yerevan, Armenia.

Submitted: 19.08.2025 **Accepted:** 30.08.2025 **Published:** 10.09.2025

Keywords: Oral Cancer, Carcinogenesis, Etiology, Risk Factors Oral Cancer

Introduction

Oral cancer is a malignant tumor originating from the oral mucosa. This group includes cancer of the body of the tongue, the floor of the mouth, cheeks, gums, hard palate and palatoglossal arch, and salivary glands [1].

Average head and neck cancers Oral cancer accounts for 48% of cancer cases and the 5-year survival rate for oral cancer is below 50% in most countries [2].

Research in recent years has shown that in the oral cavity often lead to the development of precancerous lesions, which ultimately lead to the development of squamous cell cancer of the head and neck [3].

The disease manifests itself in long-term non-healing ulcers of the oral cavity or tissue growth.7,8
In the case of the ulcerative form, the lesion is a non-healing ulcer on the oral mucosa; the ulcer quickly increases in size. In the nodular form, dense nodules are formed that have a clear shape and increase in size [4].

In the case of the papillary form, the tumor is a dense growth that hangs down into the oral cavity; this type is more treatable than others because it does not spread to other nearby tissues [5].

The prognosis, metastatic potential, survival and treatment of each histopathological variant are different, which requires an individual approach [6].

Increasing knowledge of molecular genetic alterations in OC has led to a better understanding of molecular pathways in the development of OC.

The use of genetics in recent years has revealed the molecular pathology of OC. An active search is underway to identify genetic alterations in oncogenes or tumor suppressor genes, the role of genomic instability and epigenetic modifications, and to create a gene expression profile in oral oncogenesis. Understanding these genetic alterations and gene expression patterns is key to understanding the molecular pathogenesis of OC, and a full understanding of the molecular pathology of OC and its relationship with the causative agent will require more intensive research.

Methods

A comprehensive electronic literature search was performed in the following databases:PubMed, PMC, ScienceDirect, and Scopus using the Medical Subject Heading (MeSH) terms: oral cancer, carcinogenesis, etiology and risk factors oral cancer.

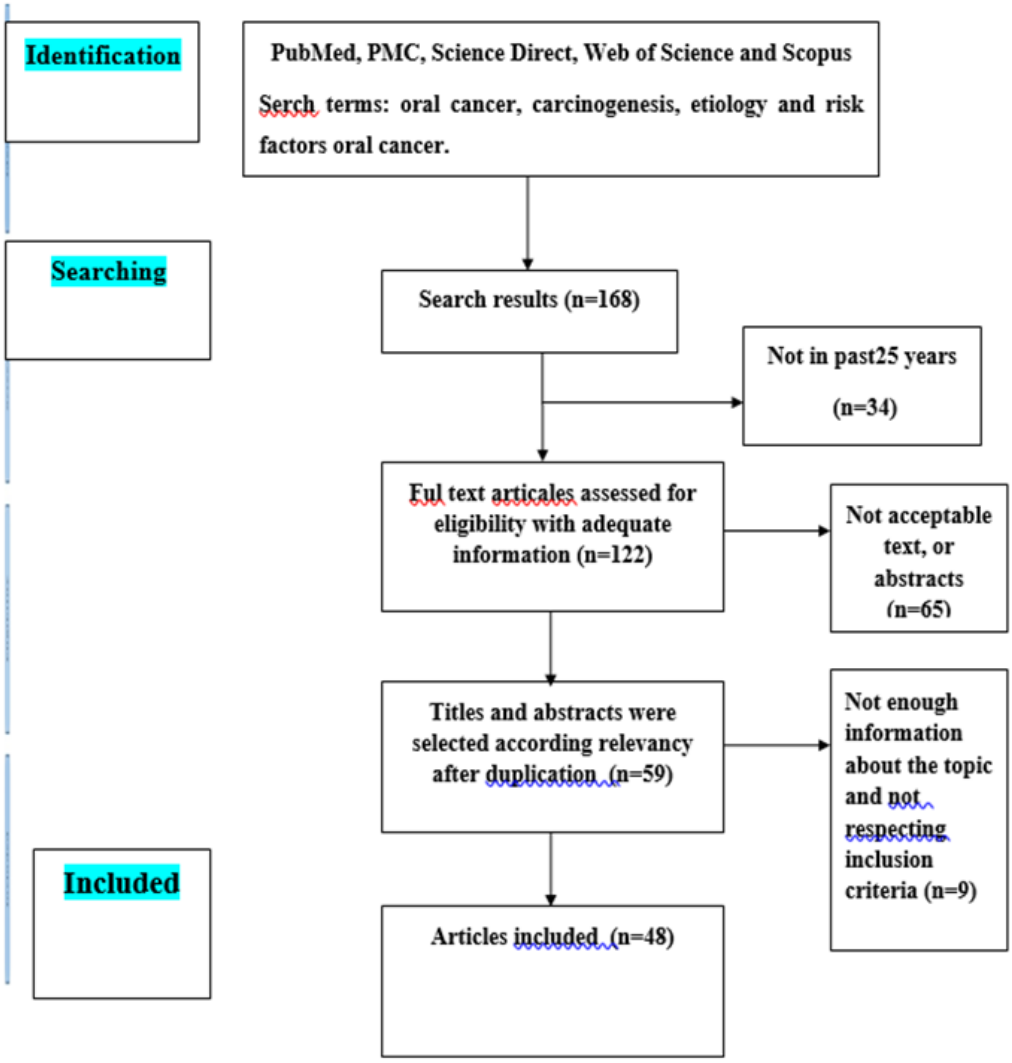
Inclusion Criteria: Included clinical trials that evaluated the current literature on the etiology and risk factors oral cancer written in English.

Exclusion Criteria: original primary studies, due to language limitations, abstracts, letters to the editor, book chapters, case reports, conference abstracts, duplicate publications, and in vitro and in vivo animal experimental studies.

Results

156 articles were found and 88 full-text articles of high methodological quality were selected. The selection of articles is demonstrated in the PRISMA flow chart (table1).

Table1. The selection of articles is demonstrated in the PRISMA flow chart



Oral cancer is a multifactorial disease, its etiology involves environmental, genetic and/or epigenetic factors [7].

These factors which determine the prevalence and nature of the course of oral cancer.
The main risk factors are:

- Bad habits (smoking, chewing various mixtures, including betel and nas, drinking alcohol);
- Occupational hazards;
- Chronic infection in the oral cavity;
- Chronic trauma to the oral mucosa (destroyed teeth and their roots, poorly made dentures);
- Precancerous processes (Bowen's disease, warty leukoplakia, papillomatosis, leukokeratosis);
- Biological carcinogens
- Chronic Inflammation,
- Ultraviolet (UV) Radiation (for lip cancer),
- Human papillomavirus (HPV) or Candida infections,
- Immunosuppression,
- Genetic predisposition,
- Diet.

External carcinogenic factors interacting with the pathways of expression of the genetic code (tobacco, HPV) damage DNA, causing activation of proto-oncogenes, (Ras,) inactivation of tumor suppressor genes, (p53) and lead to cancer in patients with a genetic predisposition [8]. Epigenetic changes include changes in gene expression that are not associated with changes in the bases in the DNA sequence, but are associated with changes in chromatin complex histone proteins and other non-sequence-related changes in DNA.

Most carcinogenic "risk factors" exert their action through epigenetic conditions, and not through mechanisms of DNA sequence mutagenicity. in the pathogenesis of cancer Epigenetic changes can be transmitted through the replication of a clonal cell line (tumor) and play an important role of oral cavity cancer(fig1) [9].

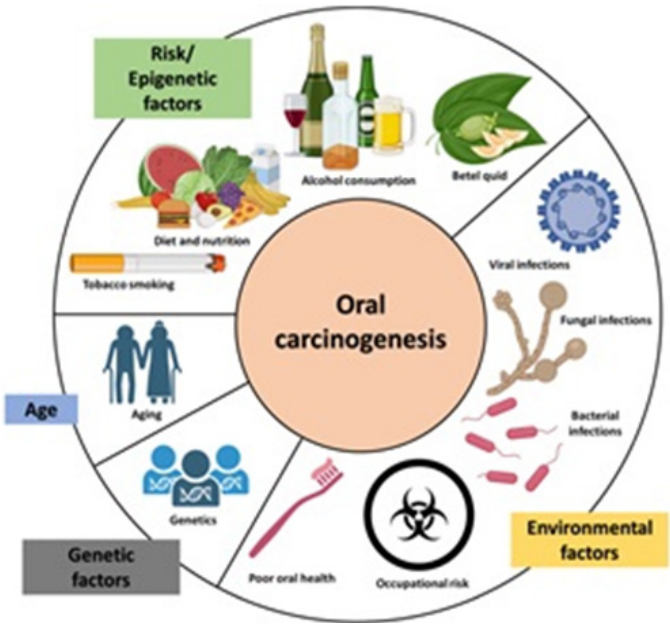


Figure 1: Scheme Risk Factors Oral Cancer

Carcinogenesis involves

Cancer is a disease of the genome [10]. Genetic changes (mutations) in the somatic cell line.

- Epigenetic changes (altered DNA, histone protein, and mediated RNA-silencing complexes).
- Inherited genetic susceptibility

One of the main epigenetic processes is DNA methylation, which is altered in virtually all types of cancer and is a common feature of neoplasia and leads to changes in the correct packaging of DNA and increased genomic instability [11].

Genetic predisposition is an important risk factor for oral cancer. Some individuals inherit susceptibility to an inability to metabolize carcinogens or procarcinogens and/or an impaired ability to repair DNA damage. Genetic polymorphisms in genes encoding enzymes (P450 and XME enzymes) play a key role in genetic predisposition to oral cancer head and neck cancer. A complete understanding of these key regulatory events is vital to approach more rational drug therapy for a variety of malignancies [12].

Risk Factors Oral Cancer

Smoking

Data from the World Health Organization confirm that hookah smoking is also potentially dangerous and is not a harmless alternative to smoking [13].

Inhaled hookah vapor can damage organs and tissues due to the content of toxic substances. Nicotine, contained in the blood of smokers in high concentrations, affects the central nervous system and quickly causes tobacco addiction.

The addictive effects of the alkaloid have been carefully studied, and the effect on oncogenesis continues to be studied. Thus, in a study on the effect of nicotine on the proliferation of oral cancer cells through the α7 subunit of the nicotinic acetylcholine receptor, it was shown that nicotine promotes cell growth and migration through epidermal growth factor signaling and plays an important role in the progression of oral cancer. Smoking cessation leads to a decrease in the risk of developing cancer, 10 years after complete cessation, the relative risk of developing malignant neoplasms reaches the level of risk of a non-smoker [14].

Betel Quid

Betel quid (also called pan or paan) typically contains betel quid (Piper's betel leaf), areca nut, slaked lime, and tobacco. Chewing is the most common habit in Southeast Asia [15].

Studies have shown the carcinogenic, mutagenic, and genotoxic potential of betel quid ingredients, and

chewing Betel quid has been linked to oral cancer and precancerous conditions (namely leukoplakia, erythroplakia, and oral submucous fibrosis) [16].

Some of the main ingredients in betel quid have been shown to be genotoxic, cytotoxic, and to stimulate cell proliferation. Methylating agents and reactive metabolic intermediates from betel quid cause various types of DNA damage [17].

Smokeless tobacco is also widely used worldwide as chewing or snuff. In this form, it also leads to the development of GERD, but some studies (the effect of Swedish snuff) have shown that there is no risk of malignancy. Betel nut and/or tobacco are often mixed with other substances: slaked lime, betel nut inflorescences, sweeteners, spices. Betel increases the risk of developing GERD regardless of whether tobacco is added to it or not. It is known that exposure to sunlight is a risk factor for lip cancer. In Western Australia, lip cancer accounts for the same number of cases as oral cancer.

Alcohol

Alcohol abuse increases the negative effects of nicotine. Those who consume more than 100 g of alcohol per day have a 30-fold higher risk of developing gastroesophageal reflux disease (GERD), while those who consume alcohol less frequently have a 3-9-fold higher risk.

Drinking alcoholic beverages also increases the relative risk of developing oncopathology and is one of the main risk factors.

There is not much data in the scientific literature on the influence of the professional factor on the incidence of oral cancer. There are data on the relationship between malignant neoplasms of the oral cavity and frequent contact with asbestos and polycyclic organic compounds [18].

Work associated with prolonged exposure to the open air (ultraviolet irradiation) is considered a risk factor for developing lip cancer.

The impact of occupational hazards on the occurrence of malignant neoplasms is more pronounced in men, apparently due to the fact that men work in more difficult working conditions and have bad habits (smoking, alcohol).

Oral Hygiene Related Factors

Has been linked to oral hygiene and periodontal disease with an increased risk oral cancer [19].
Poor oral hygiene also leads to the development of PR SOR, but it has not been proven that this fact is an independent risk factor.

Diet and Nutrition

The International Agency for Research on Cancer (IARC) has confirmed the relationship between diet and nutrition and cancer risk.

Low intake of fruits and vegetables is associated with an increased risk of cancer. Frequent consumption of fruits and vegetables, especially carrots, fresh tomatoes, and green peppers, fish, vegetable oil, olive oil, bread, cereals, legumes, protein, fat, fresh meat, chicken, liver, shrimp, lobster, and fiber are associated with a decreased risk of oral cancer [20].

Certain micronutrients have been shown to reduce the risk of oral cancer. These include vitamins A (retinol), C (AA), and E (α-tocopherol); carotenoids (β-carotene); potassium; and selenium. β-carotene, retinol, retinoids, vitamin C (AA) and vitamin E (α-tocopherol) which are antioxidants, reduce free radical reactions that can cause DNA mutations, changes in enzymatic activity and lipid peroxidation of cell membranes [21].

carotenoids serve as antioxidants, prooxidants, enhance the immune response, suppress mutagenesis, reduce induced nuclear damage (micronuclei), prevent sister chromatid exchanges, protect against various neoplastic events and protect against photoinduced tissue damage [22].

α-tocopherol antioxidant, has shown promising results in oral cancer and precancerous conditions. α-Tocopherol also affects the activity of leukocytes and macrophages, and is involved in the activity of cytochrome P450, which is important for the inactivation of potent carcinogens and the metabolic activation of procarcinogens.

Chang, Jeffrey S., et al. “Investigating the association

between oral hygiene and head and neck cancer".

Vitamins and antioxidants can counteract the formation of PR. Thus, eating a large amount of fruits and vegetables helps prevent the development of PR SOR [23].

Biological Carcinogens

At present, much attention is paid to biological carcinogens. These include a number of microorganisms that are facultatively or obligately pathogenic for humans: yeast-like fungi that cause increased keratinization of the mucous membrane of the tongue, pale spirochetes, and mycobacteria tuberculosis. The influence of viruses on the development of oropharyngeal cancer is generally recognized. Recent epidemiological studies confirm that infection with human papillomaviruses is one of the main causes of malignant neoplasms of the oral cavity [24].

Human papillomavirus (HPV) is closely associated with benign and malignant lesions of the oral cavity [25].

This virus is found in condyloma, focal epithelial hyperplasia, squamous cell papilloma, and malignant lesions of the oral cavity. A neoplasm is usually associated with an excess of tissue due to increased proliferation and/or decreased apoptosis of cells; the malignancy of a tumor is determined by its negative impact on adjacent and distant tissues [26,27].

These cancers have the HPV16 virus found in the tumor.The number of HPV-positive cancers of the tonsils and the base of the tongue (cancer of the oropharynx) is growing rapidly.

HPV are the most common viruses involved in oral cancer.

Certain types of HPV (HPVs 16, 18, 31, 33, 35, and 39). Q gene products can interfere with the cell cycle machinery [28-31].

Chronic inflammation in the oral cavity creates favorable conditions for the persistence of papilloma viruses in the human body. In cancer diseases, human papilloma viruses of the 16th type are most often detected.

The use of a vaccine against human papillomaviruses can become an effective method of preventing cancer diseases. Tertiary syphilis is known to predispose to the development of oral cancer along with other risk factors. However, tertiary syphilis is now rare in clinical practice because the infection is diagnosed and treated before the tertiary stage [32].

Fungal Infections

Chronic hyperplastic candidiasis potentially malignant oral epithelial lesions may cause epithelial proliferation and may produce carcinogens from procarcinogens [33]. Candida species are commensals in the oral cavity that become opportunistic during host immunosuppression due to systemic diseases or drug therapy in immunocompromised individuals [34].

Oral Candida may coexist with or be associated with iron deficiency, which may be synergistic in the development of oral cancer. There is evidence that Candida produces nitrosamines and chemicals that are carcinogenic [35,36].

Immune Deficiency

Immune deficiency may predispose to cancer. Oral cancer of the oral cavity is more common in transplant recipients receiving immunosuppressive therapy [37,38]. Immune deficiency in HIV-infected patients may predispose to oral cancer naprimer Kaposi's sarcoma, Lymphoma [39,40]. In oral cancer, there is activation of oncogenes such as myc, erbB-2, epidermal growth factor receptor (EGFR), cyclin D1, as well as mutations, deletions and hypermethylation, and inactivation of tumor suppressor genes, inactivation of tumor suppressor genes such as p16 and p53, plays an important role in cell cycle control and induction of apoptosis [41-45]. Inactivation of tumor suppressor genes leads to deregulation of cell proliferation and death, can cause cell growth defects, promoting the oncogenic process.

Professional Risks

There are certain occupations that have an increased risk of developing oral cancer.
These occupations include manufacturing of rubber products, exposure to metals, and woodworking in the automobile industry [46-48].

Increased risk of developing oral cancer as well as exposure to excessive ultraviolet (UV) light from the sun, causing lip cancer. UV rays also cause actinic cheilitis, which can progress to OSCC.

Sulfur dioxide, asbestos, pesticides, inorganic acids, and fossil fuel combustion cause cancer of the back of the mouth, pharynx, and larynx.

To prevent the high morbidity and mortality rates associated with this disease a public awareness program that emphasizes the importance of at least one annual dental examination to detect warning signs of oral cancer and to recognize the dangers of tobacco and alcohol use Research is ongoing to develop reliable screening programs. Medical examinations and preventive check-ups are mandatory for people regardless of their health. Malignant neoplasms can be prevented by timely treatment of precancerous diseases.

To do this, it is necessary to undergo regular preventive check-ups, not to refuse medical check-ups offered by the doctor, especially for elderly people, in whom tumors are more common. Prevention A healthy diet, good oral and sexual hygiene, and awareness of the signs and symptoms of disease are important. Success depends on culturally sensitive public health messages disseminated through educational campaigns.

Declaration of Competing Interest: No competing financial interests.

Authors' Contributions

DM: Conceptualization, Methodology, Investigation, Validation, Funding acquisition, Writing – original draft, Writing – review & editing.

GV: Writing – Review & editing.

Acknowledgement: N/A

Statements Relating to our Ethics and Integrity Policies : N/A

Funding Statement

The work was not funded.

Conflict of Interest Disclosure

The author declares that he has no Conflict Interest. None of the authors have relevant financial relations with a commercial interest.

Ethics Approval Statement

The study was reviewed and approved by University Ethical Committee and in accordance with those of the World Medical Association and the Helsinki Declaration.

Patient Consent Statement : N/A

Permission to Reproduce Material from Other Sources (if needed) : N/A

Data Availability Statement : N/A

Funding No Funding

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