Review

Oral Squamous Cell Carcinoma: A Comprehensive Review of Risk Factors, Molecular Pathogenesis, and Prevention Strategies

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Oral Squamous Cell Carcinoma: A Comprehensive Review of Risk Factors, Molecular Pathogenesis, and Prevention Strategies

Jean Baptiste Lamango [1], Elizabeth Mazzio [1], Renee Reams [1], Diana J. Wilkie [2], Ramesh Badisa [1], Ebenezer Oriaku [1] and Karam F. A. Soliman [1,*]

[1] Florida Agricultural and Mechanical University, College of Pharmacy and Pharmaceutical Sciences, Tallahassee, FL 32307

[2] University of Florida, College of Nursing, Gainesville, FL 32608-9235

* Correspondence: karam.soliman@famu.edu

Abstract

Oral squamous cell carcinoma (OSCC) remains a major contributor to global head and neck cancer morbidity and mortality. This review examines the epidemiological aspects of OSCC and the biological mechanisms through which established exposures (e.g., tobacco, alcohol, betel/areca nut, socioeconomic and selected viral infections etc.) and emerging determinants (oral microbiome dysbiosis, host genetics/epigenetics, and immune dysfunction) converge to initiate and promote malignant transformation. We emphasize that OSCC risk is probabilistic and multifactorial: incidence rises markedly with age and cumulative exposures, yet the majority of individuals risk exposed to these risk factors will not develop disease. Mechanistically, carcinogen-driven DNA damages intersects with dysbiosis characterized by enrichment of periodontal pathobionts (notably Porphyromonas gingivalis and Fusobacterium nucleatum), which can sustain chronic inflammation, increase local generation of acetaldehyde and nitrosamines, and promote immune evasion via expansion of immunosuppressive cell populations and checkpoint signaling. We summarize recurrent molecular and genetic alterations in OSCC and highlight progress in early detection, including adjunctive visualization, optical and vibrational spectroscopy, and liquid-biopsy approaches using salivary and blood-based biomarkers. Finally, we discuss prevention opportunities spanning risk-factor modification, historical cultural practices, oral hygiene to mitigate dysbiosis (pH modulation and probiotics), and dietary/nutritional strategies. Integrating exposure history with microbial and molecular profiling may enable risk-stratified screening and prevention paradigms for OSCC.

Keywords: oral squamous cell carcinoma; oral microbiome; risk factors; acetaldehyde; biomarkers; prevention

1. Introduction

Oral squamous cell carcinoma (OSCC) accounts for the majority of malignancies arising within the oral cavity and remains a leading cause of morbidity and mortality worldwide. Despite advances in surgery, radiotherapy, and systemic therapy, outcomes remain strongly dependent on stage at diagnosis, and survivorship is frequently complicated by functional impairment. These realities underscore the need for improved risk stratification, earlier detection, and prevention-oriented strategies that can be deployed in clinical and public health settings. Toward this need, this narrative review maps and synthesizes evidence across epidemiology, established and emerging risk determinants, microbial mechanisms, and the molecular landscape of OSCC, with an emphasis on potentially actionable pathways for screening and prevention. We focus on human evidence where available and incorporate mechanistic and translational studies to contextualize how exposures and

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oral ecology may converge on carcinogen metabolism, immune remodeling, and genomic/epigenomic change. The aims are to *(i)* summarize major risk domains and mechanistic links, *(ii)* catalog candidate biomarkers and technology platforms for early detection, and *(iii)* identify prospective preventative approaches.

2. Epidemiology

Oral cancer is the most common cancer in the head-and-neck, commonly presenting as oral OSCC. According to SEER (Surveillance, Epidemiology, and End Results Program), oral cavity and pharynx cancer incidence rates by sex and age at diagnosis from 2000–2022 show an average age-adjusted incidence in the U.S. of ~ 20–25 cases per 100,000 per year in males and ~8–12 cases per 100,000 per year in females. Moreover, data show that this is a disease predominantly of aging, reflecting cumulative exposures (tobacco, alcohol, microbiome dysbiosis) + declining immune surveillance [immune senescence] viral factors, or underlying genetic vulnerability, which begins to rise noticeably around ages 45–50, is predominant in males and is followed by a sharp and sustained increase with advancing age **[Figure 1].** The greater incidence in males is reportedly associated with habitual carcinogenic lifestyle factors, including smoking habits, betel nut chewing, and alcohol consumption, with an earlier age of diagnosis, whereas females are often diagnosed at an older age even with low-risk behavior [1,2] The highest combined incidence rates are observed between approximately 70 and 85 years, where rates can reach up to ~55–60 cases per 100,000 [3–5] .

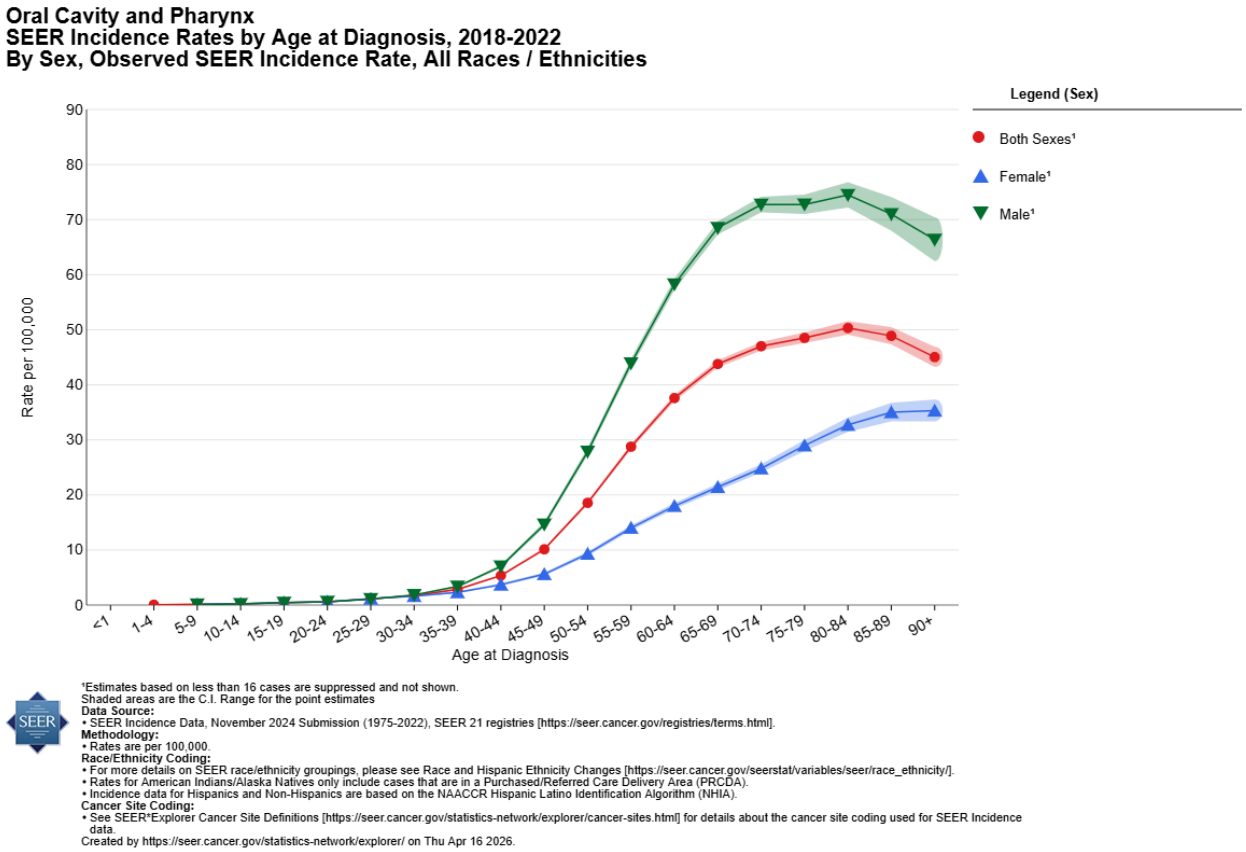

Figure 1. SEER*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program, National Cancer Institute; [updated: 2026 Jan 8; cited 2026 Apr 11]. Available from: https://seer.cancer.gov/statistics-network/explorer/. Data source(s): SEER Incidence Data, Oral Cavity and Pharynx SEER Incidence Rates by Age at Diagnosis, 2018-2022 By Sex, Observed SEER Incidence Rate, All Races / Ethnicities.

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However, the reality is that this also indicates that approximately 99,940 to 99,995 per 100,000 individuals do not develop oral cavities or pharynx cancer; many of them are exposed to the same environmental and genetic risk factors, underscoring the probabilistic and multifactorial nature of disease risk **[Figure 2].** Yet at the same time, the individual case numbers reaching up to 17,150 (age 60-64) between 2018-2022 reflect a significant public health challenge and present a need to understand risk factors and preventative measures **[Figure 3].**

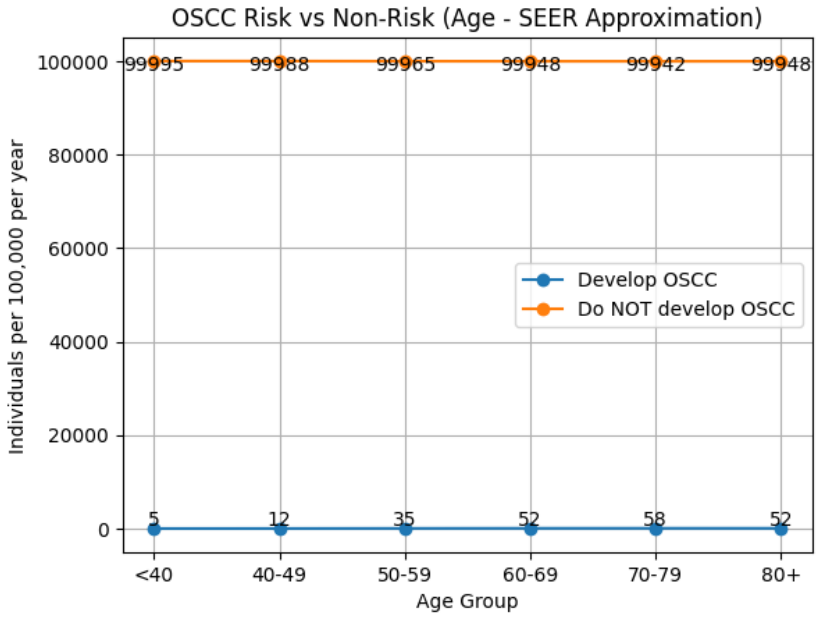

Figure 2. Oral Cancer Risk vs. Non-Risk (Age Effect); age-stratified incidence of oral cancer per 100,000 individuals per year based on SEER data. Incidence increases with age, rising from approximately ~5 per 100,000 in individuals under 40 to ~50–60 per 100,000 in individuals aged 70–79. Despite this increase, the overwhelming majority of individuals in all age groups do not develop OSCC, with approximately 99,940–99,995 per 100,000 remaining unaffected.

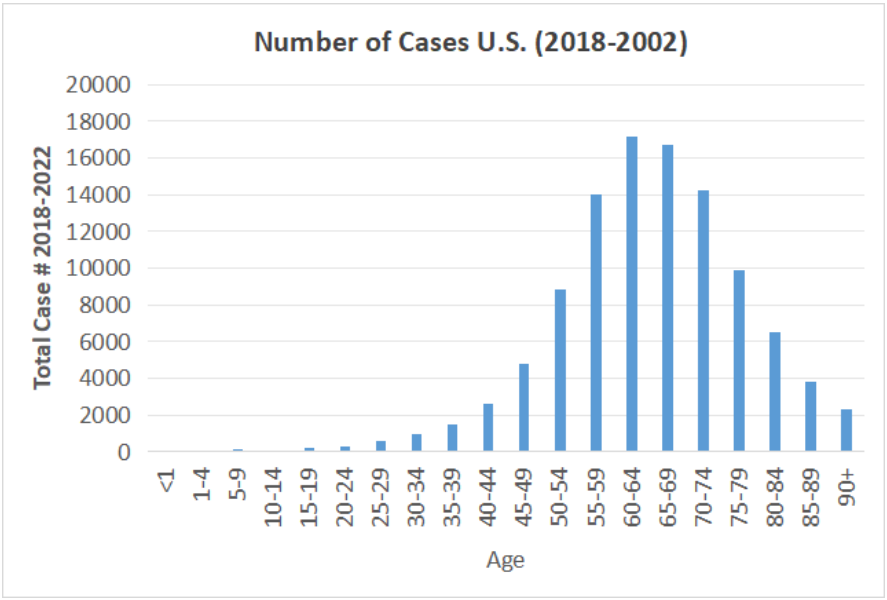

Figure 3. Age-specific number of oral cavity and pharyngeal cancer cases in the United States (2018–2022). Total number of cases stratified by age group, demonstrating a marked increase in incidence beginning in midlife, with peak case burden observed between ages 60–74, followed by a gradual decline in older populations. Data derived from the Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute.

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3. Risk Factors for Oscc

3.1. Environmental and Behavior – Cumulative

While the baseline lifetime risk of oral cavity and pharyngeal cancer in the United States is approximately 1–1.5% (≈1 in 70–100 individuals) , these cases are associated with elevated environmental risk factors. These include the use of areca or betel quid, tobacco (cigarettes, cigars, vaping, pipes, and smokeless) alcohol or opium [6–8] exposure to acrolein and various occupational hazards such as asbestos [9–11], viral infection (e.g.; type 16 human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), herpes simplex virus (HSV) and human papillomavirus (HPV) [12–14], the latter associated with oral sex [15,16] dominant in oropharyngeal cancers [17]) and chronic mechanical irritation (CMI) in the mouth, from sources like jagged teeth, ill-fitting dentures, or constant cheek biting [18,19]. All of these risks are intensified with age, concomitant with oral frailty, tooth loss, xerostomia/dehydration [20–23] and sleep deprivation [24]. Moreover, risks are compounded by socio-economic barriers that delay early diagnosis [25] or hamper HPV vaccination in adolescents and young adults [26] otherwise 90% to 100% effective in preventing precancerous lesions [27]. While the oral cavity is somewhat protected from sunlight, ultraviolet radiation can lead to lip squamous cell carcinoma originating from actinic cheilitis; a premalignant state known as "sailor's lip" or "farmer's lip" [28] , also aggravated by tobacco and alcohol, with capacity to invade the oral mucosa, nerves, jawbone, and lymph nodes [29,30]. Lastly, in terms of the environment, oral potentially malignant disorder (OPMD) is now linked to the use of immunosuppressive drugs [31] corticosteroids, chemotherapy drugs [32] penicillamine, TNF-α inhibitors, and certain medications for type 2 diabetes [33,34] .

Environmental risk factors interact in a multiplicative and often synergistic manner rather than simple addition. For example, tobacco and alcohol exposure together are associated with approximately 75–90% of cases at the population level and correspond to an estimated incidence of approximately 50+ cases per 100,000 individuals per year in heavily exposed populations, compared with a baseline of ~15 per 100,000. Given that approximately 50,000–60,000 out of 100,000 adults consume alcohol and ~13,000 out of 100,000 smoke in the United States, with only a subset engaging in both behaviors, these data further emphasize that even among commonly exposed populations, the absolute risk remains low at the individual level. Most individuals do not develop oral cancer, with approximately 54,984 per 100,000 remaining unaffected among those who drink alcohol and approximately 12,995 per 100,000 remaining unaffected among those who smoke, underscoring the probabilistic and multifactorial nature of disease risk. **[Figure 4]**

This is also the case for oral hygiene. Poor oral hygiene and chronic periodontal disease alone are associated with a modest increase in oral cancer risk (approximately 1.5–3-fold), corresponding to an incidence of ~ 20–45 cases per 100,000 individuals per year; however, approximately 42,000–47,000 out of 100,000 adults in the United States have some form of periodontal disease [CDC], suggesting ~ 44,980–45,995 per 100,000 with some form of periodontal disease remain unaffected-again underscoring the probabilistic and multifactorial nature of disease risk. **[Figure 5]**

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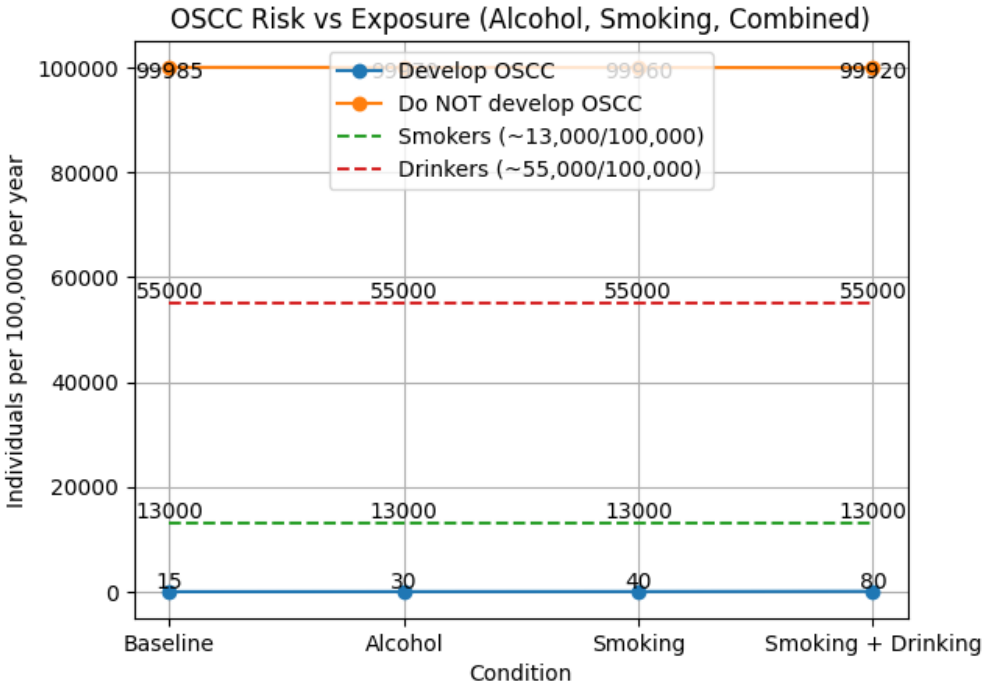

Figure 4. Oral Cancer Risk vs. Non-Risk (Smoking and Alcohol) . Variable alcohol use and habitual cigarette smoking are evident in approximately 55-60,000 and 12-13,000 per 100,000 Americans ([2024 National Survey on Drug Use and Health (NSDUH)]/ CDC) respectively, which are associated with an increase in risk corresponding to ~15 cases per 100,000 at baseline to ~30 cases per 100,000 with alcohol exposure, ~40 cases per 100,000 with smoking, and ~80 cases per 100,000 with combined smoking and alcohol exposure. Most individuals exposed will not develop oral cancer, with approximately 54,984 per 100,000 remaining unaffected among those who drink alcohol and approximately 12,995 per 100,000 remaining unaffected among those who smoke, underscoring the probabilistic and multifactorial nature of disease risk.

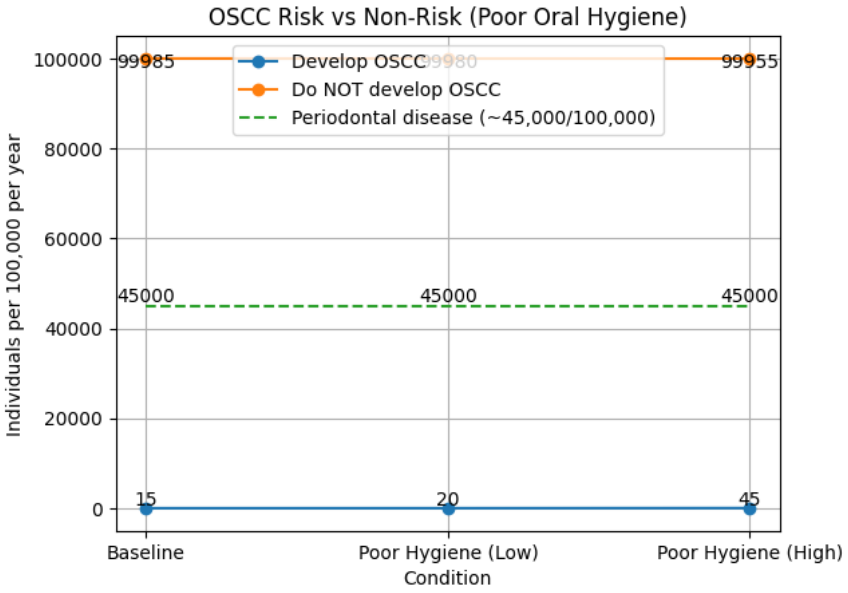

Figure 5. Oral Cancer Risk vs Non-Risk (Poor Oral Hygiene) Estimated incidence per 100,000 individuals per year under conditions of baseline risk and poor oral hygiene. Poor oral hygiene and periodontal disease are evidenced in approximately 45% of Americans [CDC], which is associated with a modest increase in risk (approximately 1.5–3-fold), corresponding to an increase from ~15 to ~20–45 cases per 100,000. Most individuals exposed, however, do not develop oral cancer, with approximately 44,980–45,995 per 100,000 remaining

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unaffected, and those with periodontal disease . Values are derived from SEER baseline incidence data and published relative risk estimates for periodontal disease.

4. Oral Microbiome

4.1. Microbiome Dysbiosis and Periodontal Inflammation

The largest host symbiotic risk factor for oral cancer involves the composition of the oral microbiota and its transition to a state of dysbiosis, linked to periodontal disease [35]. The human oral cavity hosts hundreds of bacterial strains that occupy specific micro-niches, within the tongue, tooth surfaces, oropharynx, saliva, tonsils, and gingival crevices, where pathogenic strains originate [36]. Pathogenic periodontal strains are gram-negative obligate anaerobes that dwell in low-oxygen-tension (e.g subgingival pockets, interdental spaces, back of the tongue) being enriched in phyla *Bacteroidetes, Fusobacteriata and Spirochaetes* [37]. Among these are the key pathogens: *Fusobacterium nucleatum, Fusobacterium periodonticum* and *Porphyromonas gingivalis* , which synergize biofilm maturation into hardened plaque [38,39].

The architectural maturation of hardened plaque is built in layers, where early colonizers first anchor direct to the dental pellicle (gram-positive facultative anaerobes, including *Streptococcus mutans, S. sanguinis, S. mitis, and Actinomyces* species). These become the structural scaffold for the next layer, being pathogen *Fusobacterium nucleatum* , which then *recruits* and stabilizes the oncogenic "red complex" (*Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola*) within the subgingival niche [40]. This hijacked niche becomes a risk factor for developing OSCC, where, by sustaining chronic inflammation, it evokes a negative feedback response with expansion of tumor immune-suppressive subpopulations of tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs),regulatory T cells (Tregs) and reduced NK CD8(+) T cell infiltration [41–49]. *Porphyromonas gingivalis* exhibits its unique main virulence factors as proteases (e.g gingipains (cysteine proteases RgpA, RgpB, and Kgp) matrix metalloproteinases (MMPs)) and sticky fimbriae, which enable dual attachment to other bacteria such as *Capnocytophaga gingivalis* a Gram-negative, capnophilic, facultative anaerobe. [50] *P. and C. gingivalis* synergize by enabling gliding motility to enable colonization in deep areas of the subgingival pocket, with elevated levels in saliva now being used as a biomarker for early detection of OSCC [51,52] . *Fusobacterium nucleatum's* unique main virulence factors are adhesive (e.g. Fap2, FadA, FomA and the sugar Gal-GalNAc adhesins) allowing for intense colonization, invasion and docking, not only to the subgingival gum line but also to the surface of tumor cells and cancer-associated fibroblasts (CAFs), directly linked to immune evasion [41–44]. In OSCC, this is not random dysbiosis, but rather a specific pathogenic consortium enriched with tumor-associated bacteria that also correlates with known gene expression and epigenetic alterations, including CpG methylation silencing of tumor suppressor genes and the activation of oncogenes [53]. This dysbiosis, in particular for *P. gingivalis* and *Fusobacterium nucleatum is* not only involved with oral cancer but can migrate to other areas of the body, contributing to distal cancers [50,54] including gastric, esophagus, colon, bladder, breast, lung, genitourinary and pancreas, where it thrives in the tumor microenvironment (TME) and subverts host tumor immune surveillance [55–61]. Without proper preventative dental care and cleaning throughout life, periodontitis can become a driving force for cancer risk further aggravated by environmental insults and aging [52,62,63]. However, this is not only cancer risk; *F. nucleatum* and *P. Gingivalis* originating from the oral cavity are now linked to a growing list of non-malignant chronic diseases; as a component of atherosclerotic plaque contributing to heart disease as well as respiratory infections, pulmonary disease, sleep apnea, asthma, inflammatory bowel disease, ulcerative colitis, Crohn's disease, appendicitis, irritable bowel syndrome, Alzheimer's disease, Parkinson's disease, diabetes, multiple sclerosis, and adverse pregnancy outcomes [64–72]. The ability of periodontopathogens and oral commensals to dislodge to other areas of the body, such as the brain, is believed to be a function of aging [73].

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4.2. Acidity to Acetaldehyde

Prior to the development of pathogenic-induced periodontal subgingival pockets, acidity involving lactic and acetic acids first creates these niches most often associated sugar-fermenting bacteria, such as *Streptococcus mutans* , *Streptococcus sobrinus* and *Lactobacillus species* [74,75] many of which thrive in high sugar diets, and produce adhesions that enable direct binding to the enamel surface of the tooth. These changes alter the oral microbiome to environmental changes that are now enriched in acidogenic and acid-tolerant species. [76] Once established, localized acidity can be come destructive, as it can evoke enamel demineralization, cavity formation, and erosion of the gum, underlying bone, and ligaments, allowing for deep, anaerobic periodontal pockets that then become breeding grounds for these pathogenic strains [37]. In addition, anaerobic and sugar fermenters can create dysbiosis on the upper surface of the back 1/3 of the tongue and the hard palate [3,14,75,77] , which can release volatile sulfur compounds (hydrogen sulfate, methyl mercaptan , dimethyl sulfide), medium short chain fatty acids, and metabolites associated with halitosis [39,78–80] . In these locations, a high sugar/alcohol diet can drive the overgrowth of *Streptococcus mitis, S. salivarius, Neisseria subflava, and Rothia mucilaginosa* which express alcohol dehydrogenase (ADH) [14,75,77], converting alcohol to acetaldehyde, a Group 1 human carcinogen ; a DNA-damaging toxin [81,82]. Moreover, acetaldehyde can concentrate at even higher levels if combined with an inadequate detoxification and clearance capacity from acetaldehyde dehydrogenases (ALDH1, 2) arising from either an oral acidic pH [74,75] or ALDH genetic polymorphisms [3,83–85]. Acetaldehyde generated in the oral cavity is normally rapidly detoxified to acetate by aldehyde dehydrogenase and cleared by saliva, but accumulation under certain conditions can contribute to carcinogenic risk. Under the selective pressures of the high acetaldehyde and acidic environment, *Candida* species—typically harmless commensals found in 40% to 60% of healthy adults—can now undergo a virulent phenotypic transition. In this dysbiosis, *Candida* and other members of the oral mycobiome further produce and amplify acetaldehyde and nitrosamines and create fungal hyphae, tunnels by which microbes can travel [86,87] enabling the invasion of red complex and orange complex (*Fusobacterium, Prevotella,* and *Campylobacter species*) organisms [38]. The association between these complex microbial consortia and the development of oral cancer is well-documented across numerous epidemiological [88,89] and clinical studies [14,90].

Acetaldehyde in the mouth can also arise from dietary intake of fermented, ripe, and processed foods, notably fortified wines, spirits, vinegar, and tobacco/ areca nut; the latter two, which concentrate along with carcinogenic nitrosamines [91] and polycyclic aromatic hydrocarbons in cigarette smoke [92–95]. Nitrosamines in the mouth can also arise from dietary intake of cured meats, processed fish, beer, and seasonings [96–98]. In addition, nitrosamine-contaminated medicines are now being linked to dysbiosis and increased oral cancer rates involving various antihypertensive drugs, (bisoprolol, nebivolol, metoprolol), calcium antagonists (amlodipine, felodipine), diuretics, SSRIs, and ACE inhibitors such as lisinopril [99,100].

The synergy between chemical carcinogens (nitrosamines, acetaldehyde) and oncogenic periodontal pathogens creates a combined risk for oral cancer. While carcinogens provide the initial genotoxic insult by mutating the cellular DNA, onco-pathogens such as *Fusobacterium nucleatum* and *Porphyromonas gingivalis* ensure these damaged cells survive by undergoing immune-evasive state transformation in the oral environment [101] .

4.3. Immune Suppressive Tumor Microenvironment

The immune-evasive state transformation in the oral environment has a distinct signature, characterized not only by the infiltration and expansion of TAMs and MDSCs but a coordinating cascade of reinforcing cytokines such as interleukin-1β (IL-1β), IL-18 [102], IL-1RA [103] CXCR2 [104], SERPINA1 [105], CCL22 [106] , a high IL-6/IFIT2 ratio [107] and active toll-like receptor (TLR) signaling which drives CXCL8, CCL5, CXCL10, STAT1, and key signaling pathways [108] propelling ITGA3 /ITGA5 and immune checkpoint expression [109]. Moreover, metabolic and degradative products released from oral microbes, including cell-free nucleic acids (cfNAs) such as

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cfDNA and cfRNA—can further contribute to immune dysregulation by chronic activation of specialized nucleic acid-sensing pathways within host cells. This activation also influences macrophage polarization, often shifting the balance toward a pro-tumorigenic, immunosuppressive phenotype that favors malignant progression rather than clearance [110]. These profound shifts in the local immune and cytokine profiles are also reflected in saliva, establishing opportunities for the development of validated noninvasive biomarkers that are growing in number and now include tests for IL-8, CCL20, CCR7, CXCL1, CCL2, CXCR4/CXCL12 axis (lymph node metastasis) [111] TNF-α, IL-17, IL-1α, IL-1β, and cyclooxygenase-2 (COX-2) [112–114].

In addition, this immune-evasive transformation also involves cancer-associated fibroblasts (CAFs) which contribute to pro-tumorigenic secretion of transforming growth factor-β (TGF-β), platelet-derived growth factor-BB (PDGF-BB), and angiopoietin-like 3, in addition to cytokines such as IL-6/ 10) [115,116]. This secretome actively remodels the local TME by altering critical checkpoint pathways, specifically upregulating PD-L1 and PD-1 expression [117] while simultaneously modulating CXCR2 signaling and autophagy [104,118]. Likewise, immune-driven changes in fibroblasts and osteoblasts contribute to this effort, with aberrant activation of extracellular matrix (ECM) proteins, such as periostin, and the overexpression of MMPs that catalyze the digestion of the collagen-rich basement membrane, facilitating epithelial–mesenchymal transition (EMT) [119] These risks can be compounded by systemic comorbidities such as obesity and release of adipokines which effectively re-engineer visceral adipocytes, creating a fertile ground for malignant transformation [120–123]. While local immune suppression within the oral cavity is a risk factor for OSCC, whole-host immune suppression is also an aggravating factor, with elevated incidences of immunosuppressive disorders [124] such as HIV, Graft-versus-Host Disease or the process of aging [125,126].

4.4. Ph Modulation and Oxidizing / Ionizing Rinses (Sodium Bicarbonate, Hydrogen Peroxide, Salt and Fluoride)

Given the fundamental role of the acid– acetaldehyde cycle in driving oral dysbiosis, the use of sodium bicarbonate (baking soda) as a powerful alkalizing agent offers a robust mechanism to disrupt the pathogenic microenvironment at the start. In both clinical and research settings, as well as historical ones, sodium bicarbonate has been shown to immediately elevate the pH of dental plaque from the critical pH of 5.5 back toward a neutral or alkaline range [127,128]. Moreover, saliva itself contains HCO_3^- (bicarbonate) when the flow rate is increased (eating , gum chewing), which can remain low in conditions of dehydration, aging/medications (dry mouth :xerostomia) and dysbiosis - favoring acid producing bacterial (Streptococcus mutans, Lactobacillus) where saliva mail fail local buffering. Exogenous baking soda- can induce a rapid alkalization effectively negating the environmental advantage of acid-tolerant (aciduric) pathogens, which struggle to survive and adapt thereby breaking the cycle of dysbiosis, while preventing the initial pitting and pocket formation where the red-complex pathogens (like *P. gingivalis*) hide, prevent enamel demineralization, cavity formation, and erosion of the gum, underlying bone, and ligaments . Furthermore, while fluoride can be employed to help mitigate structural damage by promoting remineralization, its efficacy is significantly attenuated by the presence of a mature biofilm, which acts as a barrier to mineral penetration; underscores the necessity of pH-neutralizing agents like sodium bicarbonate to first disrupt the pathogenic microenvironment [129].

Beyond simple pH neutralization, the high solubility of baking soda allows it to penetrate the dental biofilm rapidly, which may increase the solubility of plaque proteins and facilitate the penetration of the host's innate antimicrobial enzymes, such as lysozymes, into previously shielded areas [127,130]. Moreover, when combined with hydrogen peroxide, this alkalizing and oxygenating strategy creates a dual-threat environment inhospitable to both obligate oncogenic anaerobes and *Candida* species. Crucially, this treatment inhibits *Candida*'s ability to undergo phenotypic transition into invasive hyphae, effectively sealing the physical conduits that pathogenic bacteria otherwise use to infiltrate deeper tissue layers and facilitate the spread of malignancy. This intervention is generally

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deemed safe, effective, and vital for individuals with hyposalivation, whose diminished natural bicarbonate buffering capacity leads to protracted periods of biofilm acidification following sugar exposure [127,131]. The addition of vitamin C to baking soda, (sodium ascorbate) could protect the mouth because it would inactivate nitrosamines, ensure ALDH2 clearance of acetaldehyde, loosen plaque, restore healthy flora, and foster collagen synthesis [132–134]. In addition to alkalizing the oral cavity, a 2% saline rinse is commonly recommended to promote oral wound healing and reduce inflammation of the gums.[135]

4.5. Protective Commensals and Oral Probiotics

The oral cavity can also be guarded to protect healthy commensal species that thrive in neutral to alkaline PH , and actively prevent and suppress Red Complex dominance: S. This beneficial microbial community is composed of *Streptococcus salivarius, S. mitis, S. sanguinis, and Streptococcus gordonii* (noted for its ability to produce endogenous hydrogen peroxide) and that work in tandem with *Rothia mucilaginosa, Neisseria, Veillonella, Leptotrichia, and Capnocytophaga* to maintain oral homeostasis [136,137]. These species, along with various *Actinomyces*, serve as critical markers of a healthy ecosystem; conversely, where their depletion is a primary symptom of dysbiosis [52,138].

To effectively reseed the microbiome environment, emerging dental therapeutics and over the counter oral probiotics are now available. Key strains such as *Streptococcus salivarius* (K12 and M18), *S. dentisani* (7746), and various Lactobacillus species (including *L. fermentum, L. casei, L. reuteri*, and *L. rhamnosus* strains ATCC 55730 and PTA 5289) have demonstrated a profound ability to inhibit periodontal pathogens [139,140]. Oral probiotics are now available in various commercial formats specifically designed for oral health, including over-the-counter (OTC) lozenges, chewable tablets, and powders, alongside advanced "dentist-formulated" oral products [141]. These serve as multi-modal therapeutic agents to reverse dysbiosis by restoring a neutral pH, destroying existing biofilms, providing capacity to detoxify mutagens such as acetaldehyde (AcH) and nitrosamines [142] and used to manage radiation-induced oral mucositis [143]. Beyond these attributes, they can also reduce the production of volatile sulfur compounds (VSCs) associated with halitosis [144,145] virulence factors such as gingipain A (RgpA), utilized by the red complex and *Candida* [140,146–150] and significantly reduce dental plaque, caries, and periodontal disease [151–153]. In doing so, by reducing pathogenic strains, this can also enhance local immunity by fostering expansion of natural killer cell cytotoxicity, CD8(+) T-cell activity, and inducing TRAIL-mediated apoptosis [149].

5. Molecular Landscape (Genetic and Epigenetic Alterations)

5.1. Inherited Predisposition

OSCC inherited genetic risk factors create a field cancerization effect in which the entire oral lining becomes a high-risk zone for malignant transformation [11]. These include Fanconi anemia, xeroderma pigmentosum, Bloom syndrome, and ataxia telangiectasia, often leading to early-onset oral malignancies [154–156]. Another rare condition is Dyskeratosis Congenita, an X-linked recessive disorder primarily affecting males due to a defect in the DKC1 gene. This gene encodes the dyskerin protein, which plays a critical role in telomere maintenance. Approximately 80% of affected patients present with oral leukoplakia, which are white lesions being significantly more prone to progress into oral squamous cell carcinoma [157,158] Chromosomal instability is also a significant factor, with reports identifying the loss of the Y chromosome (LOY) and the extreme downregulation of Y-linked genes (EDY) in oral epithelial cells. These also serve as predictive biomarkers for the malignant transformation of OPMDs [159].

In Fanconi anemia, defective DNA cross-link repair leads to profound genomic instability, consistent with alterations in DNA damage response genes such as BRCA1, BRCA2, FANCD2, and FANCG, contributing to a 500–800 fold increased risk of oral cancers [160–162]. Early detection strategies are being developed using liquid biopsies to detect early low-frequency mutations or noninvasive oral brush biopsy cytology, especially when combined with DNA ploidy analysis for the

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detection of dysplasia [162,163]. Furthermore, familial aggregation studies indicate a 3–4× increased risk in first-degree relatives and up to a 14× increased risk in siblings, confirming a strong genetic susceptibility component that operates independently of environmental factors [155,164].

5.2. Polymorphisms

Genetic susceptibility to OSCC is compounded by common single-nucleotide polymorphisms (SNPs) in genes, most of which govern xenobiotic metabolism, DNA repair, and inflammatory pathways. For example, polymorphisms in detoxification genes can impair the oral mucosa's ability to metabolize carcinogens such as acetaldehyde and tobacco-derived toxins, with notable variants in CYP1A1, GSTM1, ADH1B, GPX4 and ALDH2. Additional polymorphisms in promoter or regulatory regions may further heighten susceptibility when combined with environmental stressors such as tobacco, betel quid, or HIV-associated risks. These include PD-1 rs36084323, which may impair tumor immune surveillance; ABCA1 rs2230806, which can disrupt lipid homeostasis; and EBI3-related variants involving the IL-27/IL-35 cytokine axis. Some of these proposed as markers for identifying high-risk tobacco users [165–167].

5.3. Somatic Mutations

Transition to malignancy is primarily driven by the accumulation of somatic mutations in oral epithelial cells, which disrupt key regulatory pathways and facilitate clonal expansion. The most frequent are the loss of tumor suppressors such as TP53 (mutated in ~60–70% of cases) and CDKN2A (p16), linked to changes induced by carcinogens such as acetaldehyde or nitrosamines. Additionally, FAT1 loss-of-function mutations contribute to the dysregulation of Wnt signaling, EMT, stemness, and invasiveness [168,169] and histopathologic features such as the worst pattern of invasion-5 (WPOI-5) associated with reduced E-cadherin and increased N-cadherin expression, reflect this enhanced invasive and metastatic potential [170].

5.4. Over/Under Expression

Beyond primary drivers, the literature is filled with a plethora of differentially expressed genes (DEGs) as risk factors for OSCC, including overexpressed protein-coding mRNAs, long non-coding RNAs (lncRNAs) and microRNAs. Some are specific to activating mutations (gain-of-function), whereas others are frequently characterized by overexpression (too many copies) rather than a point mutation. For example, OSCC is associated with overexpression of oncogenes such as PIK3CA, HRAS, and various EGFR pathway genes [171,172]. In addition, a plethora of overexpressed oncogenic transcriptional regulators linked to oral cancer risk involves basic cell proliferation, bioenergetics, matrix remodeling, adhesion, invasion, and intracellular transport. These include HOXD10[173], HOXA10/RUNX2 isoform II/PRDX2 [174], HOXD10 [173], ENOX2, SIRT1 [175], NCOA7 [176], PFN2 [177], CIAPIN1 [178], YAP1 [179], SYPL1 [180], FN1 [181], BMI1 [182], PDGF-BB [183], NMT1 [184], HK2 [185], HDC [186], ZG16B [187], GLUT-1/SLC48A1 [188], STAT3 and ITGB6 [189], SFXN1 [190], TRIB3 [191], Panx3 [192], integrin $\alpha v\beta 3$ [193], NCAPD2 [194] and N4BP1 [195]. There are also reports of overexpressed autophagy-related genes such as LC3, an enrichment of cancer stem cell markers including CD44, CD133, and ALCAM (CD166 [118,196,197] and overexpression of transient receptor potential (TRP) channels such as TRPA1, TRPV1–4, TRPM2, and TRPM6 [198,199] and HOMER3, which acts as a scaffold to regulate calcium release through the formation of functional complexes like HOMER3–CAMKK1–TRPV6 [200]. Many of these are now being prioritized as potential diagnostic biomarkers for either OSCC risk or clinical stage, including CD44, Snail1 [201], ANAPC10 [202] DPM1 [203], RSAD2 [204], Chemerin/CMKLR1 [205], MCTP2 [206], BUB1 (prognostic biomarker and a driver of immune evasion) [207].

In contrast, a plethora of studies also report the underexpression of key tumor suppressors, such as ZC3H12A [208], ATG16L1 [209], OSR1 [210], TFAP2E [211], ELF3 (E74-like factor 3) and m6A

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(N6-methyladenosine) linked to advanced-stage tumors (Stage III/IV) and lymph node metastasis [212].

Lastly, epigenetic signatures are often detectable in premalignant lesions readily captured by non-invasive liquid biopsies (e.g., blood and saliva) [213] . These include hypermethylation of key tumor suppressor genes, such as CDKN2A (p16) and GABRB2 [214] as well as ZNF382, HOXA9, DAPK, and MGMT [215,216]. Other changes include downregulation of tumor-suppressive microRNAs (miRNAs) such as the loss of miR-34b-3p which leads to the aberrant elevation of the SOX5 axis, a molecular shift that is highly predictive of advanced clinical stages and lymph node metastasis [217–219]. The clinical utility of these non-coding RNAs is promising due to enhanced stability in saliva, their release by a variety of tissues [220] and selective packaging into exosomes such as miR-21, miR-155, miR-34a, miR-200 [221]. Histone modifications also play a central role in this process; for instance, H3K27ac acetylation is associated with the downregulation of critical tumor suppressors, such as HOXD10 [173] along with DNA methylation that disrupts the HOX gene clusters, specifically HOXA1, HOXA11, HOXB5, HOXB6, HOXB9, HOXC5, HOXC10, and HOXC11 [222,223] . Furthermore, the integrity of these expression patterns is maintained by chromatin remodeling complexes, where alterations in genes like CDK2AP1 and imbalances in the NuRD/SWI-SNF ratio serve as a pivotal diagnostic axis [224].

6. Early Detection

Early diagnosis of premalignant conditions requires assessment of oral leukoplakia, erythroplakia, oral submucous fibrosis (OSMF), and oral lichen planus, each exhibiting varying potentials for malignant transformation [12,225,226]**.** Current developments in oral cancer screening emphasize early detection of these conditions in high-risk populations, particularly elderly patients [227] [228] with a focus on high-risk anatomical sites including the floor of the mouth, ventrolateral tongue, and soft palate [229]. While punch tissue biopsy, clinical examination, and histopathology remain the gold standard for lesion assessment [12,230–232] non-invasive diagnostic approaches are increasingly utilized in particular with availability of biomarkers as previously discussed. None invasive sampling methods include the use of buccal swabs (for viral, genetic, epigenetic, DNA / RNA , microbiome-associated alterations, or micronuclei formation) [233] or exfoliative brush cytology [234,235] cytobrush, OralCDx, and Orcellex [236] (for dysplasia on suspect lesions).

Moreover, dysplasia is also being identified by extensive imaging and adjunctive diagnostic technology, including the use of toluidine blue (TB) (mouthrinse or swab) [231] , light-based detection such as Vizilite Plus with TBlue system, LED based systems such as the Microlux/DL® and the Orascoptic DK or use of fluorescence (VELscope®) all of which aid , but are limited by major methodological and real-world constraints and as of now suited only to assist with conventional visual examination [237,238]. While these devices still have limited specificity, the use of narrow band imaging (NBI) with intrapapillary capillary loop (IPCL) classification has emerged as a more promising modality owing to its ability to enhance subepithelial vascular patterns, providing a standardized, vascular-pattern–based framework that objectively distinguishes low- from high-risk lesions [239,240]. More advanced, highly predictive tools include spectroscopy-based approaches such as Raman, which can provide a highly sensitive, noninvasive molecular fingerprint of tissue. This technique relies on inelastic scattering of light, where incident photons interact with molecular vibrations, producing distinct spectral peaks that reflect the biochemical composition of the tissue, offering high diagnostic accuracy and potential for early cancer detection [241]. Additionally, deep learning–integrated Surface-Enhanced Raman Spectroscopy allows for the high-sensitivity analysis of gaseous and liquid biomarkers and has demonstrated diagnostic accuracy reaching up to 98% [242]. Meanwhile, imaging examinations, including X-rays, CT scans, MRI, and PET-CT, can help evaluate the size, location, and presence of lymph node or distant metastasis of tumors [243].

Noninvasive liquid biopsy (blood saliva) the latter using transform infrared (ATR-FTIR) spectroscopy is a rapid, noninvasive method for staging OSCC, with an overall sensitivity of 98.6% and a specificity of 93.3% [244,245]. Liquid biopsies also allow for detection of OSCC indicators such

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as circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), or extracellular vesicles, some surveying for podoplanin (PDPN) [246] , microRNAs, circular RNAs , lncRNAs [247] exosomal mRNAs [248] , osteopontin [249], HPV [250], PrP(C) [251] ,MMP-9 [252] , gingival crevicular fluid (GCF) , cytokines (eg. IL- 1, IL- 2, IL- 4, IL- 6, IFN-γ and TNF-α) [253–255] ,serum bone turnover markers [256], S100P [257], or salivary concentration of N(1)-acetylspermidine and N(1)-acetylspermine [258], leptin [259] or lactic acid dehydrogenase [260].

7. Prevention

Preventive strategies for oral cancer rely heavily on behavior modification, including quitting smoking, avoiding smokeless tobacco and betel quid, limiting alcohol, reducing sun exposure, improving oral hygiene, maintaining regular dental visits, and consuming a diet rich in fruits and vegetables, low in meat consumption, and high in polyunsaturated fatty acids (omega 3, EPA, DHA) and mono-unsaturated fatty acids [261,262] such as consumption of fish oils [263] salmon, mackerel, or sardines [263,264]. In addition, preventive strategies include greater physical activity and various complementary and alternative medicine (CAMs) modalities [265–269]. OSCC risk reduction involves CAMS including routine intake of vitamins/ minerals (zinc, copper, selenium, and vitamins A, β-carotene D, E, C, folate/B complex) [270] , green tea, curcumin, lycopene, blueberry extracts (anthocyanins), resveratrol, ellagic acid (pomegranate), chios mastic gum, holy basil/Tulsi (*Ocimum sanctum*) [271], N-acetyl cysteine, quercetin, shikonin (*Lithospermum erythrorhizon*) [11,12,272–278], aged garlic extract [279] and triphala [280].

Ancient and traditional cultural medicines used as preventative approaches for oral conditions include *Potentilla fulgens* roots (Bajradanti) used by indigenous tribes in Northeast [281], *Terminalia chebula* (used in India and China) [282], *Asarum sieboldii,* a species of wild ginger (used in East Asia) [283] oil pulling (swishing, holding sesame or coconut oil in the mouth) [284] and use of herbal sticks/pastes and jivha lekhana (cleaning tongue) (India) [284]. In Greece and Spain, practices involve resin from the Mastic tree (*Pistacia lentiscus*) as chewing gum, Egyptians used honey and gum from Acacia trees high in tannins [285,286] and for generations in Mexico, traditional healers and families have utilized a diverse pharmacopeia of native plants to treat oral conditions such as gingivitis, periodontitis, systemic mouth infections, and tooth discoloration. These include: *Aloe vera* (aloe), *Capsicum frutescens* (chili pepper/Tabasco pepper), *Chenopodium ambrosioides* (epazote), *Opuntia ficus-indica* (prickly pear/nopal), *Persea americana* (avocado), *Polygonum aviculare* (knotgrass/common knotweed), *Punica granatum* (pomegranate), *Theobroma cacao* (cacao/cocoa), *Uncaria tomentosa* (cat's claw), *Acacia cornigera* (bullhorn acacia), *Acacia farnesiana* (sweet acacia/huisache), *Amphipterygium adstringens* (cuachalalate), *Asclepias curassavica* (tropical milkweed/bloodflower), *Bidens odorata* (Spanish needles/beggar's ticks), *Byrsonima crassifolia* (nance/nanche), *Caesalpinia pulcherrima* (pride of Barbados/peacock flower), *Carica papaya* (papaya), *Chenopodium graveolens* (strong-scented goosefoot), *Chiranthodendron pentadactylon* (devil's hand tree), *Dorstenia contrajerva* (contrajerva), Heterotheca inuloides (Mexican arnica), *Heliopsis longipes* (Aztec root/chilcuague), *Jatropha gaumeri* (jatropha), *Lobelia laxiflora* (Mexican lobelia), and *Sida rhombifolia* (arrowleaf sida/Cuban jute)[287] . Together, these integrative approaches—combining lifestyle modification, nutrition, and traditional medicinal practices—highlight a comprehensive, multi-layered strategy for reducing oral cancer risk, supporting mucosal health, and maintaining overall oral homeostasis.

8. Treatment

Therapeutic strategies for oral cancer predominantly OSCC are rapidly evolving toward integrated, multi-modal frameworks that combine conventional treatments with emerging molecular, microbiome, and nanotechnology-driven approaches. Standard care remains centered on surgery, radiotherapy, and chemotherapy (e.g., platinum-based chemotherapies (cisplatin) 5-fluorouracil often combined with taxanes (docetaxel/paclitaxel), with additional local modalities such as cryoablation, boron neutron capture therapy, and Au-198 mold therapy, expanding options for

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early, advanced, recurrent, or metastatic disease, and various gene, photodynamic, and EGFR inhibitors/immunotherapies [243,288–292]. Current developments in nanotechnologies enable targeted drug delivery, gene silencing, and multimodal therapy integrating hydrogens, stem cells, photothermal and photodynamic therapy, also used in pain management [293–299]. Collectively, these developments reflect a shift toward precision oncology, where conventional cytotoxic therapies are increasingly complemented by biologically informed, targeted, and technologically enabled strategies to improve efficacy, reduce toxicity, and personalize treatment outcomes.

9. Future Directions and Conclusion

OSCC is increasingly understood not as a linear consequence of genetic mutations alone, but as a complex, multicellular systems-level failure involving coordinated interactions between the microbiome, host metabolism, immune regulation, and epigenetic reprogramming. Central to this paradigm is the role of the oral microbiome as an active carcinogenic driver, where dysbiosis marked by enrichment of pro-inflammatory pathogens such as *Fusobacterium nucleatum* and *Porphyromonas gingivalis*, alongside depletion of protective commensals like *Rothia* and *Streptococcus mitis* contributes to tumor initiation and progression. This microbial imbalance is further compounded by metabolic and toxic synergies, particularly the microbial conversion of ethanol into acetaldehyde, which creates a localized genotoxic environment and amplifies carcinogenic risk in the context of smoking and alcohol exposure. Concurrently, the tumor microenvironment evolves into a permissive, immunosuppressive niche characterized by the recruitment of myeloid-derived suppressor cells and tumor-associated macrophages, driven by a complex cytokine network including IL-6, IL-1β, and TGF-β. These processes intersect with widespread genetic and epigenetic dysregulation, in which inherited susceptibilities such as Fanconi anemia coexist with coordinated epigenetic silencing and oncogenic activation; suppressor inactivation collectively sustains tumor growth and resistance.

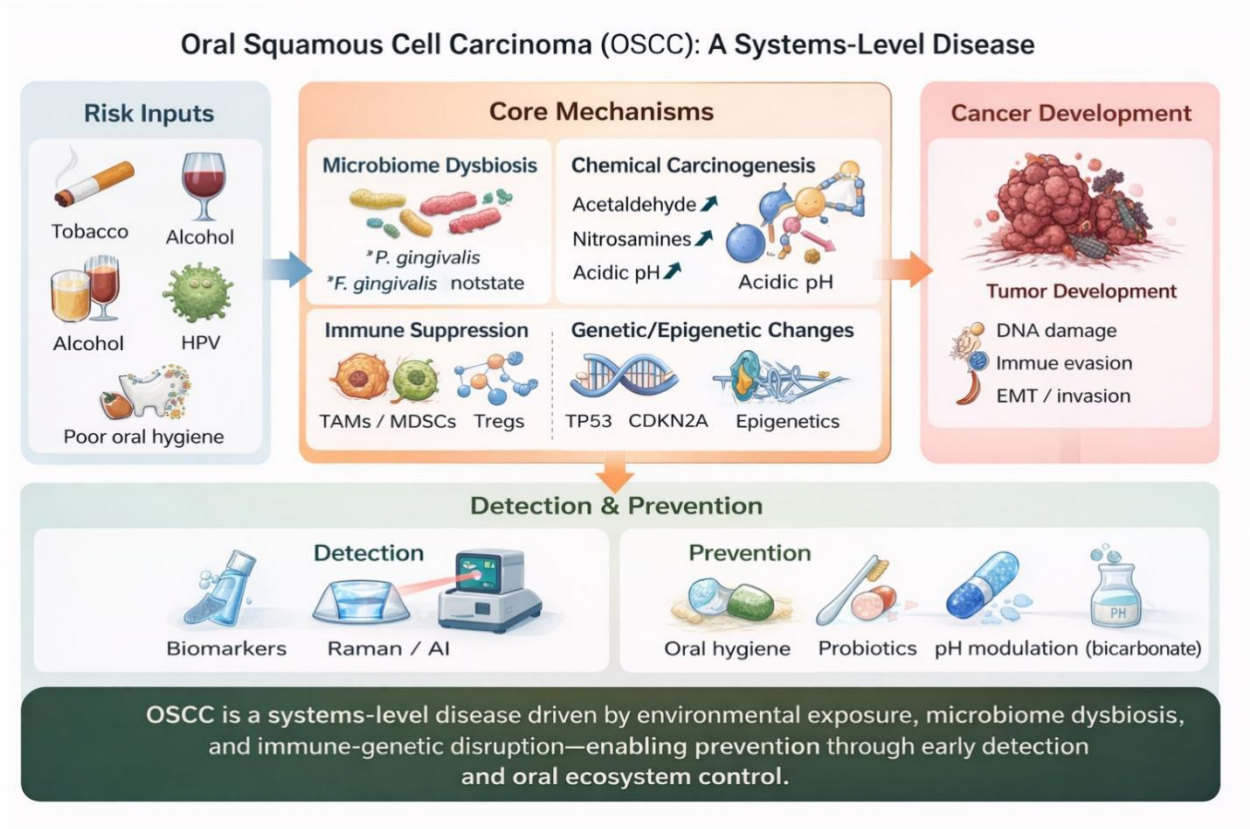

Figure 6. Systems-level model of oral squamous cell carcinoma (OSCC) pathogenesis, detection, and prevention. OSCC arises from the convergence of environmental and behavioral risk factors, including tobacco, alcohol, viral

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infections, and poor oral hygiene, which drive oral microbiome dysbiosis. This dysbiotic state, enriched with pathogenic species such as Porphyromonas gingivalis and Fusobacterium nucleatum, promotes carcinogenesis through chronic inflammation, carcinogen production (e.g., acetaldehyde, nitrosamines), and immune suppression involving tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs). These processes interact with genetic and epigenetic alterations (e.g., TP53, CDKN2A) to drive tumor initiation and progression. Intervention opportunities include early detection via salivary biomarkers and AI-based diagnostics, alongside prevention strategies targeting risk factors, oral hygiene, and microbiome modulation. This framework defines OSCC as a multifactorial, systems-level disease amenable to precision prevention.

Looking forward, the field is shifting from reactive intervention toward a precision-based, preventive framework. Multi-omics diagnostic platforms integrating salivary, serum, and buccal biomarkers with microbial, epigenetic, and imaging data enhanced by artificial intelligence offer the potential to detect disease at a preclinical stage, before visible lesions emerge. In parallel, ecological restoration strategies aimed at rebalancing the oral microbiome through targeted probiotics and pH modulation represent a novel approach to disrupting carcinogenic biofilms and restoring host–microbe homeostasis. Advances in nanotechnology further support this transition, enabling highly targeted drug delivery and theranostic systems capable of simultaneous tumor imaging and treatment through gene silencing, photothermal, and photodynamic modalities. Together, these developments define a new precision oncology framework for OSCC, emphasizing early detection, systems-level intervention, and biologically informed therapeutic strategies.

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