Narrative Review Article

The Converging Contributors to Oral Squamous Cell Carcinoma: Environmental and Molecular Causes and Progressors

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ABSTRACT

Oral squamous cell carcinoma (OSCC) is the most common type of oral cancer, accounting for tens of thousands of diagnoses per year in the United States. Despite various treatment options, the 5-year survival rate of OSCC patients in countries with integrated health systems is approximately 60% with high rates of recurrence and metastasis. This signifies the importance of understanding the multifactorial etiology of OSCC incidence, progression, and mortality. For example, aberrant genetic and epigenetic regulation of tumor suppressor genes in oral epithelial cells contributes to OSCC progression through dysregulated cell proliferation. Tobacco and smoking, alcohol usage, betel nut consumption, and direct contact with environmental pollutants are proven to significantly increase OSCC risk. Due to the heterogeneity of disease, there are a multitude of treatment options available. They are based on Tumor, Node, and Metastasis staging and grading and include independent or conjunctive therapies of radiotherapy, immunotherapy, surgery, and photodynamic therapy. Additionally, clinical trials are currently being completed to evaluate the efficacy of novel treatments such as gene therapy and natural product-based interventions such as black raspberries. Collectively, this review aims to define the molecular, histopathological, and clinical profiles of OSCC to provide novel insight into future therapeutic modalities.

Keywords: Oral Squamous Cell Carcinoma (OSCC); Oral Cancer; Human Papillomavirus (HPV); Environmental toxins; Genetics; Epigenetics; Histopathology

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is the most common type of oral cancer. By the year 2040, its incidence will rise 40% globally, with an associated increase in mortality rate (1). However, this metric may vary with innovations in therapies for OSCC. In the United States, approximately 30,000 individuals are diagnosed with OSCC per year, and globally, OSCC affects more than 400,000 people per year (2). Moreover, OSCC has a five-year survival rate of 68%, depending on time of diagnosis (3). Beyond its rising incidence, OSCC has profound consequences to human health, often impairing essential human body functions. For example, OSCC can cause airway blockages due to aggressive lesion growth (4), leading to an increased risk of cardiovascular and respiratory complications. OSCC has also been linked to lung and esophageal cancer incidence, demonstrating its metastatic potential (4). In addition to bodily impacts on human health, oral cancers increase depression risk 2.2-fold. A study in Taiwan suggests that oral cancer-associated depression is due to treatments causing physical and functional impairments

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and changes in symptom severity (5). Together, these consequences signify the burden OSCC has on affected individuals, establishing it as a global health concern.

In addition to clinical burdens, OSCC poses substantial financial strain. In the United States, first year treatment exceeds $79,000 (6), reflecting OSCC management complexity. Leading up to diagnosis, a dentist or doctor may look for potential signs of oral cancer and order a consultation with an oral surgeon or pathologist who will request a biopsy, take X-rays, or suggest a magnetic resonance imaging (MRI) for evaluation. If a diagnosis is made, patients may be referred to an oral surgeon for surgical resection. Additionally, an oral and maxillofacial prosthodontist may be consulted to restore facial aesthetics and oral function (7). Treatment following diagnosis of carcinoma in situ involves the removal of the affected superficial layer of tissue. In stages I and II, patients are treated with surgery and/or radiation therapy and chemotherapy. In later stages, III and IV (including IVA, IVB, and IVC), tumor resection with possible lymph node dissection is employed to reduce the risk of metastasis. Checkpoint inhibitors are an immunotherapy that doesn't directly kill cancer cells but enables the immune system to restore its normal functioning. The efficacy of these treatments has been proven limited due to the ability of OSCC to evolve and evade treatment methods, illustrating its complex biological nature (8). Moreover, these treatments come with adverse effects, such as xerostomia and dysphagia (9). Failure of early diagnosis contributes to high fatality because later-stage treatments are often ineffective due to distant metastases (1). In this review, we will discuss the biological, genetic and socioeconomic factors driving the incidence and progression of OSCC and will discuss future treatment modalities targeting this multifactorial disease.

BIOLOGICAL OVERVIEW OF OSCC

Histological Characterization of OSCC

Over 90% of malignant tumors of the head and neck region are located on the tongue (10). To understand the development and progression of OSCC, it is essential to compare the histological features of a normal tongue and OSCC tongue. Like skin, the tongue has superficial protective layers, such as the stratified squamous epithelium (11, 12), which is the primary surface layer of the oral mucosa of the tongue and is comprised of 4 layers: the stratum corneum, stratum granulosum, stratum spinosum, and the stratum basale. These layers provide structural integrity to the skin and protect deeper tissues from damage. In healthy tongue epithelium, cells are organized and follow a regulated division pattern, while basal cells divide and gradually migrate to the tongue surface, where they are shed (Figure 1) (11). This shedding cycle, which occurs every 14 to 21 days, ensures proper barrier tongue function (13). Of note, 50% of OSCC lesions are found on the posterior lateral border of the tongue (14, 15), associated with alcohol and tobacco buildup. Moreover, frictional irritation from adjacent teeth is associated with lesion formation. The basal layer, where epithelial stem cells are located, is the most common origin of OSCC (16, 17).

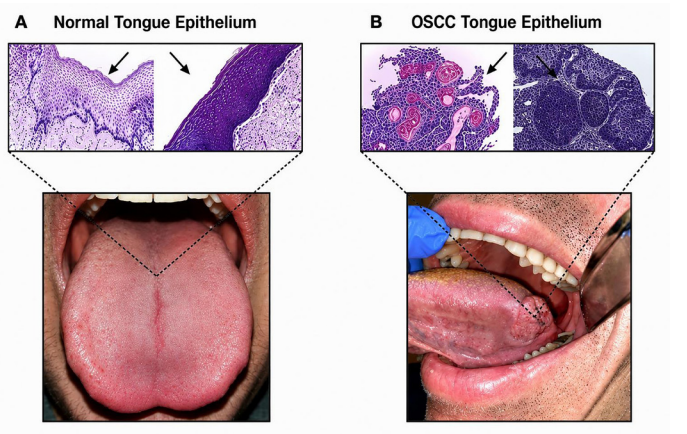

***Figure 1.* Clinical and Histological Characterization of OSCC Pathogenesis.** *A. Normal midline tongue morphology and associated histology, denoted by organized layers of epithelium. B. Clinical pathology of oral squamous cell carcinoma in posterior lateral border of the tongue with associated histology, denoted by arrows indicating epithelial layer disorganization and including epithelial pearl invasion and immune cell infiltration (17–19).*

OSCC Progression is Associated with Changes in Epithelial Histopathology

Genetic abnormalities and molecular disruptions translate into a series of structural and cellular changes that define OSCC's histopathologic stage. When these mutations build up in basal epithelial cells, they progress from normal oral epithelium to invasive OSCC (18). The earliest observable change is epithelial hyperplasia, which is denoted by an increase in epithelial cell production resulting in epithelial thickening (17). Consequently, abnormal cells have not invaded deeper

tissues, such as the basal membrane. If carcinogenesis progresses, epithelial dysplasia occurs, denoted by epithelial layer disorganization. Epithelial dysplasia is characterized into 3 tiers: mild, moderate, and severe, each associated with how deeply these changes have affected deeper tissues (19). In terms of clinical staging, the Tumor, Node, Metastasis (TNM) system is used to stage OSCC progression through 4 stages established by the American Joint Committee on Cancer (Figure 2) (10, 18). Stages are determined by the following: tumor size (T1-4), lymph node involvement (N1-3), and distant metastases (M). The TNM system indicates treatment evaluation, recurrence risk, and survival (18). Overall, TNM staging dictates the clinical classification of OSCC stages as it relates to the histopathological changes within the tongue and directs individualized therapeutic strategies. Beyond observable histopathological changes, OSCC progression is also shaped by epigenetic dysregulation, which contributes to abnormal gene expression and tumor development.

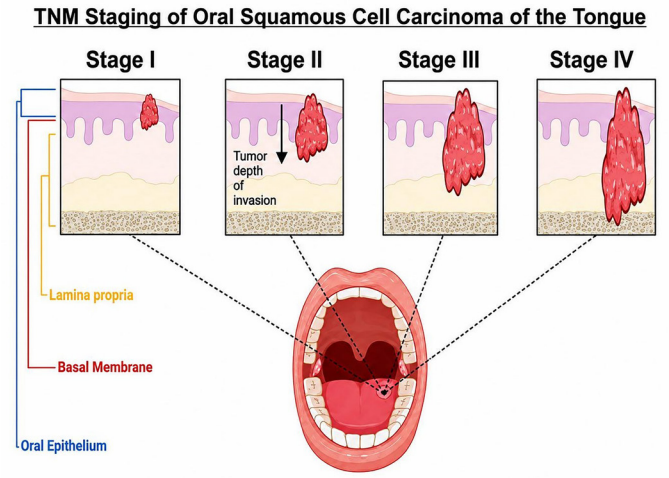

Figure 2. TMN Staging (I-IV) of OSCC Invasion. *Cartoon illustration of anatomical tumor progression harvested from OSCC on dorsal surface of tongue. Stage I: the tumor penetrates the basal membrane but has not entered much deeper tissues (≤ 5 mm). Stage II: the tumor extends deeper into the lamina propria (5-10 mm). Stage III: invasion depth has extended into the lamina propria (> 10 mm) with or without lymph node involvement. Stage IV (A-C): the tumor has disrupted the entire oral epithelium, basement membrane, lamina propria, and beyond deeper structures. Stage IV also involves significant invasion of nearby structures, possible lymph node involvement and may have present distant metastases (IVA IVB, IVC).*

GENETIC DYSFUNCTION IS ASSOCIATED WITH OSCC INCIDENCE

Mutations in Tumor Suppressor Genes are Associated with OSCC Incidence and Progression

OSCC incidence is associated with genetic mutations in cancer stem cells that cause increased proliferation. For example, loss of p53, Smad4, PTEN, and TGF-βR1, activation of K-ras, and deregulation of NOTCH signaling are associated with aberrant cell proliferation leading to cellular carcinogenesis (20, 21) In mice, basal epithelial stem cells become carcinogenic when exposed to carcinogens (16). This signifies the role of the basal layer in cancer development, most notably OSCC. Basal epithelial stem cells have been identified as the origin of carcinogen-induced OSCC in murine 4-NQO models, mimicking the progression of dysplasia to invasive carcinoma (16). Genetic disruptions in TGF-β signaling (including loss of Smad4) prompt epithelial proliferation and instability and contribute to carcinogenesis (21–23). Additionally, inactivation of transforming growth factor beta receptor 1 (Tgfβr1) and phosphatase and TENsin homolog deleted on chromosome 10 (Pten). causes tumor formation. Overall, these molecular alterations show a central role in the incidence and progression of OSCC. Loss of p53, encoded by TP53, is another pathway of interest. 78% of OSCC patients possess irregular p53 expressions associated with a higher risk of regional lymph node metastasis, demonstrating that disruption of the p53 pathway contributes to the progression and metastatic potential of OSCC (24). Additionally, TP53 mutations are also associated with drug resistance, highlighting its crucial role in treatment resistance (25). As genetic mutations accumulate within basal epithelial cells, the signaling pathways that control cell growth and survival are affected. Among the most significant are epidermal growth factor receptor (EGFR) and canonical Wnt/β-catenin pathways: rat sarcoma virus (RAS), rapidly accelerated fibrosarcoma (RAF), mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase (ERK) (14, 26). EGFR regulates cellular proliferation, migration, differentiation, and survival (27, 28). However, EGFR overexpression causes uncontrolled cell growth and contributes to tumor proliferation, metastasis, invasion, apoptosis resistance, and resistance to OSCC therapies (27). Additionally, EGFR interacts with other receptors such as Axl, enhancing carcinogenic potential within the oral mucosa (14). RAS/RAF/MAPK is downstream of EGFR and promotes cell proliferation and survival

in OSCC upon activation (Figure 3A) (29). Within this cascade, activation of extracellular signal-regulated kinase (ERK) promotes proliferation through G1 cycle progression, meaning it is also involved in carcinogenesis (30). Furthermore, canonical Wnt/β catenin signaling is upregulated in oral epithelial metaplasia and OSCC (31, 32). WNT7B, a Wnt ligand, facilitates OSCC tumorigenesis through modulation of Wnt/β-catenin signaling (26). Thus, the dynamic regulation of numerous cell cycle and transduction pathways contributes to OSCC incidence and progression.

Aberrant Epigenetic Modifications Are Associated with OSCC Progression

Epigenetic regulation plays a significant role in the incidence and progression of OSCC by altering gene expression without directly modifying DNA sequences (14). Histone modifications, which are chemical alterations that occur on histone proteins, can activate or repress gene expression and have been associated with OSCC incidence and progression (33, 34). Acetylation, methylation, phosphorylation, and ubiquitination modify chromatin structure and subsequently alter gene expression (34). For example, DNA methylation silences tumor suppressor genes in OSCC, causing cell cycle deregulation. DNA methylation is the addition of a methyl group (CH3) to a DNA sequence without altering the DNA itself (35). DNA methylation typically targets CpG motifs, Cytosine nucleotides adjacent to Guanine (36). The accumulation of CpG sites within gene promoters control gene regulation and are commonly known as a CpG island (37). Typically, CpG islands are unmethylated, allowing for proper gene transcription; however, CpG islands in OSCC-derived epithelial cells become hypermethylated, leading to tumor suppressor silencing (38). For example, the tumor suppressor, p16, is silenced by promoter hypermethylation, leading to OSCC (Figure 3B).

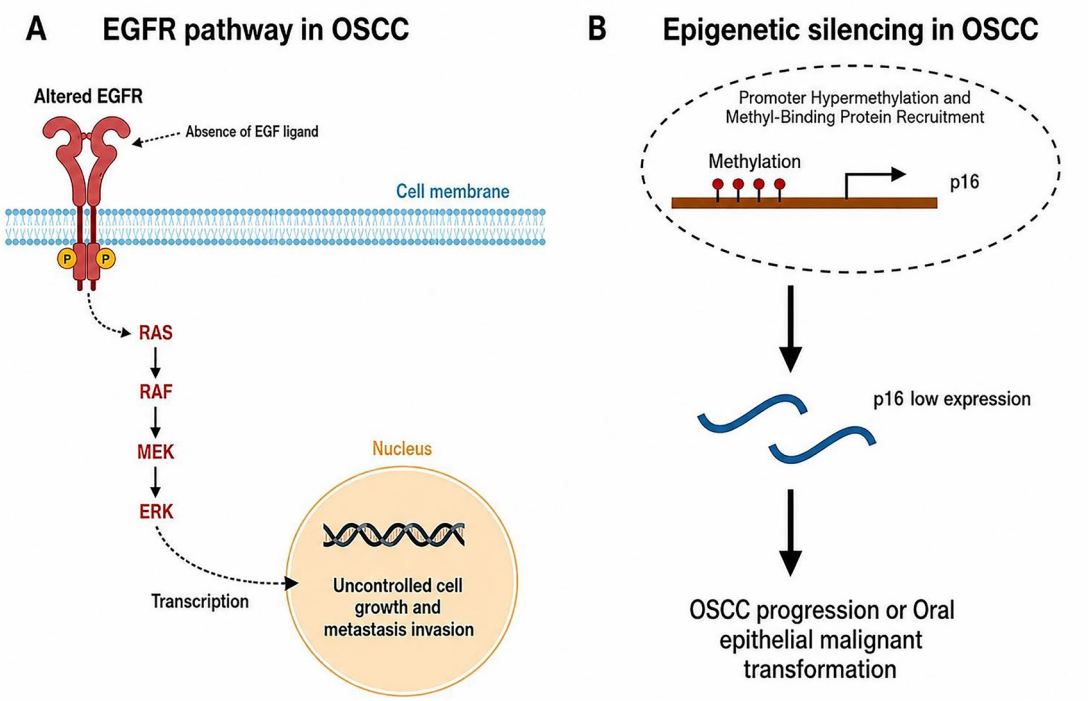

Figure 3. *Epigenetic/Genetic EGFR Pathway in OSCC. A. Constitutive activation of EGFR causes uncontrolled cell growth, metastasis invasion, and apoptosis resistance via dysregulated intracellular RAS/RAF/MAPK/ERK signaling resulting in cell cycle dysregulation and carcinogenesis. B. Epigenetic mechanism of oral epithelial malignant transformation involves hypermethylation resulting in low p16 expression. RAS: rat sarcoma virus, RAF: rapidly accelerated fibrosarcoma, MAPK: mitogen-activated protein kinase, ERK: extracellular signal-regulated kinase.*

Loss of histone lysine methyltransferase KMT2D results in failure to remove the repressive H3K27me3 mark, causing tumor suppressor silencing and increased tumor growth (33, 34). Abnormalities in histone lysine methyltransferase KMT2D, KDM5C, and KDM6A are significant drivers of cancer. Histone modifications can be reversed by the reactivation of tumor-suppressing genes through pharmaceutical inhibitors that target histone-modifying enzymes, offering therapeutic potential (36, 39). Additionally, many differentially methylated regions are linked to immune system pathways, primarily those involving CTLA4 and IL-9 signaling (40). CTLA4 and IL-9 signaling are necessary to maintain immune tolerance; however, cancer cells can alter these pathways to evade the immune system. This suggests that abnormal DNA methylation in OSCC affects tumor suppressor genes as well as how the immune system interacts with the tumor. Thus, DNA methylation represents one of the major epigenetic aspects of OSCC, along with other mechanisms such as histone modification and non-coding RNA. Non-coding RNA is another epigenetic modification of interest. OSCC is most often associated with the downregulation of tumor-suppressing proteins such as miRNA (14). To note, miRNAs are not reliable biomarkers for therapeutic avenues due to their ability to possess dual functions, such as a tumor suppressor in one cancer type but also promoting tumor growth in another (41). For example, miR-21 and miR-424 overexpression led to OSCC development. miR-21 expression in tumor samples was found to be related to lower survival associated with OSCC progression (42). A 2025 study identified four miRNA salivary signatures (miR-21, miR-31, miR-146a, miR-424) to be strongly upregulated in OSCC, highlighting their possible diagnostic capability (42). These findings signify individual miRNAs may be inconsistent across contexts, while multi-marker panels may have better diagnostic utility. Emerging research suggests that exosomal miRNA networks play a large role in regulating epithelial-mesenchymal transition (EMT), a key process driving OSCC metastasis (41). For example, TGFβ1-induced EMT displayed 43-gene signatures from exosomal miRNA targets associated with patient prognosis (41). Overall, these recent findings suggest that while single miRNAs may lack therapeutic reliability, their collective regulatory influence on EMT may provide diagnostic utility, resulting in more accurate and precise OSCC staging and grading. In addition to intrinsic molecular and epigenetic abnormalities, external environmental and behavioral exposures can significantly contribute to OSCC initiation and progression.

CULTURAL/SOCIETAL INFLUENCES ON OSCC INCIDENCE, PROGRESSION, AND MORTALITY

Socioeconomic Factors Influencing OSCC

Socioeconomic factors, including income, race/ethnicity, education, age, and sex, play a role in shaping OSCC knowledge and access to treatment. These factors can contribute to potential increases in OSCC incidence, progression, and mortality. Research on diagnostic delays in OSCC indicates that treatment delays in low-income-level patients are substantially higher than those of wealthier individuals (43). Individuals from lower wealth indexes are also less likely to seek treatment due to the costs of consultations, surgery, as well as time off work, causing losses in income. Beyond income, race and ethnicity have also shown correlation to OSCC survival; African Americans are diagnosed at later stages and display higher mortality rates (9). In addition, those with higher education are more likely to be knowledgeable about early symptoms, while those with lower education levels are not. A study in North Germany explains how the time of diagnosis of those with a higher education was significantly earlier than those with a lower education level (44). Moreover, African Americans with higher levels of education were far less likely to smoke and present with OSCC (45). Collectively, race, education, and income factors intersect and lead to significant variances in OSCC risk, diagnosis, and survival. Age, income (rural geography) and sex were found to interlink to shape OSCC risk, diagnosis, and survival as well. Older rural males are the least likely to receive radiation treatment, despite being told to do so (46,47). Together, the interplay of income, race/ethnicity, education, age, and sex highlights the role of socioeconomic disparities in OSCC and general oral cancer development and progression.

Environmental Etiologies of OSCC

Exposure to tobacco/smoking, alcohol, betel nut, and certain environmental pollutants (carcinogens) are linked to the development and progression of OSCC (8). A study in Finland revealed that 57% of patients with OSCC were exposed to smoking/tobacco and alcohol (48). Exposure to alcohol and tobacco are linked to double-strand breaks, mutations, and miscoding in DNA as replication, which results in errors in DNA repair and signifies the role of environmental exposures in oral cancer development. Of note, 51% of OSCC tumors were in the tongue (48). Moreover, in Sichuan Cancer Hospital, both

smoking and alcohol had relatively the same influence on OSCC development (49). The simultaneous use of alcohol and tobacco increased OSCC risk 15-fold (48). Interestingly, ethanol was found to break down cell membranes in vitro, increasing the permeability of other cancer-causing agents such as those found in tobacco smoke (50). Recent analysis of vaping and oral cancers shows a notable correlation. E-cigarette vapor (EVE) exposure, along with other ingredients in vapes, is linked to OSCC, thereby countering arguments that vapes are a safer alternative to smoking (51). Red Hot EVE, a spicy flavor containing cinnamaldehyde, had the most notable effect on OSCC development due to its cause of Ca9-22 cell (gingival squamous cell carcinoma cell) invasion, contributing to cancer development (50). Altogether, eliminating smoking/tobacco use and reducing alcohol consumption can possibly prevent 75% or more of oral cancers (52). While smoking/tobacco and alcohol consumption account for a large proportion of OSCC cases, betel nuts are another contributor. The betel nut, a highly addictive seed of the areca palm, is commonly chewed in Asia and known to cause mutations in the TP53 gene (53, 54). Mutation of TP53 may be a way betel nut causes the development of OSCC, as demonstrated by in vivo evidence (50). Moreover, food exposure to harmful environmental agents such as Acetyl Tributyl Citrate (ATBC), a plasticizer that is becoming a crucial additive for plastic manufacturing industries, is associated with OSCC pathogenesis (55). Although current research does not confirm a direct relationship of ATBC to oral cancer incidence, some research suggests that exposure to specific plasticizers may elevate the risk of developing cancers, including OSCC (55). Overall, multiple behavioral and environmental exposures, including smoking/tobacco, alcohol, vaping, betel nut chewing, and emerging plasticizers, collectively contribute to OSCC risk and development through their carcinogenic effects (Figure 4).

HPV16/18 Infection and How it Relates to OSCC Incidence

Human papillomavirus (HPV), most notably high-risk types such as HPV16 and HPV18, are strongly associated with OSCC development (56, 57). Epidemiological findings demonstrate that HPV16 is positively associated with a 6.8-fold increase in OSCC risk (58). In an evaluation of OSCC patient tissue samples, HPV16 was discovered in 12 out of 40 samples, and HPV18 was found in 6 out of 40 (59). In a similar study, HPV16 was suggested to lead to cancer incidence, including OSCC (60). As a preventative treatment, HPV vaccines can be implemented to reduce the risk of developing OSCC. HPV-associated OSCC risk development varies based on cultural lifestyles and sexual behaviors by region, influencing the prevalence of related OSCC development. The rise in HPV incidence, particularly in the United States, is due to societal norms in terms of sexual activity (61). To highlight the increase of HPV relevance in OSCC development, a 2014 case study in China predicted a future increase of oropharynx cancer–which is distinct but often related to OSCC incidence (62). Closely following the 2014 prediction, HPV accounted for over 90% of oropharyngeal squamous cell carcinomas (63). This signifies the role of HPV in OSCC and closely related squamous cell carcinomas. Current incidence rates indicate, in the United States, 20,000 HPV cases are diagnosed, and 30,000 annual cases are predicted by the year 2029 (61). Of note, HPV

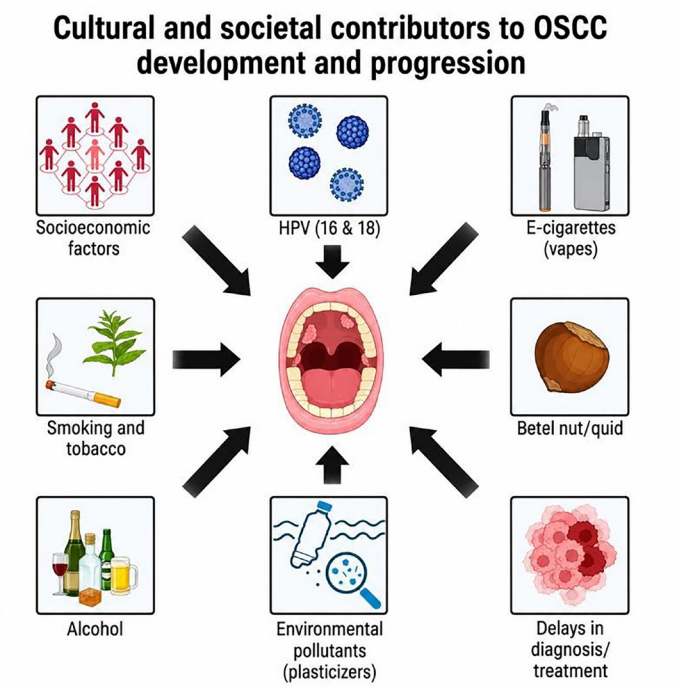

Figure 4. Multifactorial Etiology of OSCC. *Factors such as socioeconomics (income, race/ethnicity, education, age, and sex), Human papillomavirus 16 (HPV16/ HPV18), e cigarettes, betel nut/quid chewing, delays in treatment and diagnosis, environmental pollutants (plasticizers), alcohol, and smoking/tobacco contribute to the development and progression of oral squamous cell carcinoma.*

participants with low exposure to tobacco still developed OSCC, suggesting that HPV is directly related to OSCC incidence (58). The carcinogenesis of HPV is due to E6 and E7 oncoprotein encoding. Oncoprotein E6 causes cell cycle deregulation, leading to an inactivation of tumor-suppressing proteins such as p53 and pRB, causing uncontrolled cell proliferation, genome instability, and cancer incidence (57, 59). Oncoprotein E7 binds to and inactivates retinoblastoma tumor suppressor pRB, leading the cell cycle to enter the S-phase, replicating its entire genome, and consequently leading to cancer development (59). Interestingly, inhibiting the expression of HPV16-related proteins E6 and E7 can result in the restoration of regular p53 and pRB function associated with apoptosis of cancer cells (64). Collectively, deregulation of p53 and pRB due to oncogenic activity of E6 and E7 proteins in HPV underscores their central role in OSCC. As understanding of the molecular and viral mechanisms underlying OSCC have advanced, these discoveries have contributed to the development of targeted therapeutic and immunotherapeutic approaches.

THERAPEUTIC AVENUES FOR OSCC TREATMENT

Current Clinical Treatment for OSCC

The primary treatment for OSCC is tumor excision to prevent recurrence (65). In many cases, especially when metastasis to nearby lymph nodes is suspected or present, neck dissection is performed to remove the affected tissue (65). Photodynamic therapy serves as an alternative treatment that uses light-activated photosensitizers to cause targeted cell damage and tissue death (66). Radiation therapy may also be used as a primary treatment option when surgery is not feasible. Clinical studies examining OSCC treatment outcomes have demonstrated that surgery is the primary treatment method in conjunction with radiation or chemotherapy to improve treatment efficacy and reduce recurrence (Figure 5) (65, 67). In a clinical study of 1,316 patients treated for OSCC, 51% received surgery alone, 41% underwent surgery in conjunction with radiotherapy, with or without chemotherapy, and 8% were treated with radiotherapy or chemotherapy when surgery was not possible (67). This highlights the diversity of current OSCC treatments. These treatment strategies heavily depend on tumor stage. Early-stage treatments are most often surgery alone, with possible addition of radiation therapy. Later stages of OSCC require more advanced treatments, such as the combination of surgery, radiotherapy, and chemotherapy to control tumor progression (65). Although there are various treatments for OSCC, the 5-year survival rate is 68% (68). Despite their efficacy, OSCC treatments can lead to significant function and aesthetic complications, including difficulty with speech, paresthesia, swallowing, and facial asymmetry. This highlights the need for a more targeted and less invasive approach to OSCC treatment for the betterment of patient life and well-being.

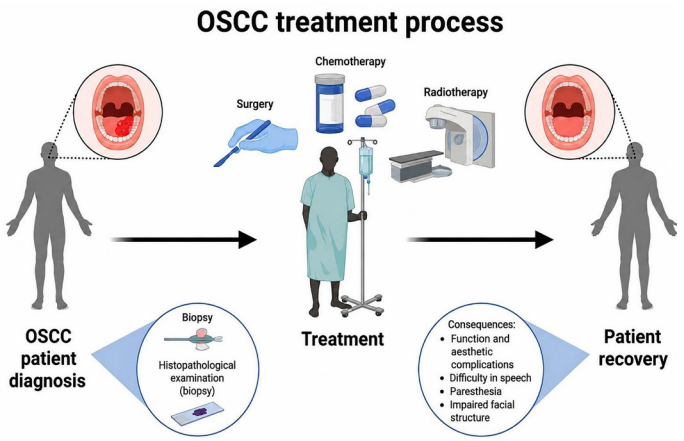

Figure 5. OSCC Treatment Regimen. *Oral squamous cell carcinoma treatment involves initial diagnosis through biopsy or histopathological examinations. Following diagnosis, treatment options include surgery, chemotherapy, and radiotherapy. Once in remission, patients may experience several post-operative complications, such as impaired facial structure, dysarthria, and facial paresthesia.*

Immunotherapy and Small-Molecule Clinical Trials

Immunotherapy has become a promising therapy for OSCC, especially in advanced or recurrent cases (65). The most studied approaches involve immune checkpoint inhibitors that target the programmed cell death protein-1 (PD-1) and programmed death-ligand-1 (PD-L1) (69). Immunotherapy enhances the body's response against tumor cells by blocking the pathway cancer cells use to escape the immune system. Many cancer cells evade immune detection by activating immune checkpoint pathways such as PD-1/PD-L1 signaling pathway (69). Immune checkpoint inhibitors work by blocking these pathways, enabling immune cells to detect and destroy tumor cells (14). High PD-L1 expression in OSCC tumors facilitates therapeutic targeting (69). Recent studies demonstrate drugs targeting the PD-1 receptors,

pembrolizumab and nivolumab, improve patient survival outcomes (14). Additionally, other studies have demonstrated improved survival rates in patients with recurrent or metastatic OSCC treated with PD-1 inhibitors (70). Additionally, ongoing clinical trials are investigating small molecule therapies targeting EGFR, PI3K/AKT/mTOR, which are commonly aberrantly regulated in association with OSCC incidence and progression (14). These emerging therapies represent a shift towards personalized treatment options for OSCC, based on tumor heterogeneity and patient genetics.

CONCLUSION

This review highlights the multifactorial etiology underlying OSCC incidence, progression, and mortality, emphasizing the increasingly recognized interplay between environmental and genetic factors in OSCC progression and development. The combination of environmental contributions (e.g., smoking, alcohol, betel nut chewing, socioeconomic factors, e-cigarettes, and HPV 16 and 18) and molecular factors (genetics and epigenetics) pose significant risk for OSCC progression and tumorigenesis overall. Importantly, these factors can collectively interact to influence OSCC's development and progression. OSCC is a global health concern due to these diverse contributors and progressors pointing to the disease's low survival rate. While the current therapeutic regimen for OSCC is robust, it is not perfect. Interestingly, phytochemical-based therapies are beginning to emerge as possible therapies for OSCC due to their anti-inflammatory effects. For example, freeze-dried black raspberries have been shown to reduce harmful gene activity linked to tumor growth (70). Recent evidence highlights the ability for blackberry isolates to lower pro-inflammatory and pro-survival gene expression, suggesting that black raspberries in conjunction with surgical, immunotherapeutic, and radiotherapy, may be possible future treatment options for OSCC patients (70). Ultimately, advancing research on OSCC heterogeneity is essential to overcoming therapeutic resistance and achieving more precise, effective, and patient-centered care. Ongoing clinical trials are investigating gene therapy as a new method of treatment (71). This process involves modifying a living cell's genetic material and is composed of two types: somatic gene therapy and germ-line gene therapy. Gene therapy is being explored as a promising avenue but still requires more clinical validation. As of now, it shows low mortality rate, high effectiveness, low toxicity, and generally being a promising treatment for oral cancer and pre-cancerous lesions (71). Moreover, evaluating tumor biopsy heterogeneity using spatial transcriptomics is also a critical area for future research as it may inform the development of targeted, personalized treatment options for patients, thereby minimizing unnecessary toxicity and enabling more accurate prognoses for patients (72). Collectively, this review has highlighted the vast complexity of OSCC pathogenesis, (epi)genetic and environmental etiologies. Innovations in clinical medicine and translational research highlight the great promise of personalized treatment modalities, such as gene therapy, for OSCC management and offer a glimmer of hope for the treatment of this devastating disease.

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CONFLICT OF INTEREST

The author declares that there are no conflicts of interest related to this work.

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