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Review

The World of Oral Cancer and Its Risk Factors Viewed from the Aspect of MicroRNA Expression Patterns

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Abstract: Oral cancer is one of the leading causes of death worldwide, with a reported 5-year survival rate of around 50% after treatment. Epigenetic modifications are considered to have a key role in oral carcinogenesis due to histone modifications, aberrant DNA methylation, and altered expression of miRNAs. MicroRNAs (miRNAs) are small non-coding RNAs that have a key role in cancer development by regulating signaling pathways involved in carcinogenesis. MiRNA deregulation identified in oral cancer has led to the idea of using them as potential biomarkers for early diagnosis, prognosis, and the development of novel therapeutic strategies. In recent years, a key role has been observed for risk factors in preventing and treating this malignancy. The purpose of this review is to summarize the recent knowledge about the altered mechanisms of oral cancer due to risk factors and the role of miRNAs in these mechanisms.

Keywords: oral cancer; miRNAs; risk factors; epigenetics

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1. Introduction

Oral cancer is a type of cancer in which tumors develop in the oral cavity, lip, tongue, gingiva, or oropharynx [1,2]. According to the World Health Organization, oral cancer is among the most prevalent cancers worldwide, representing the 16th most common malignancy and the 15th leading cause of death worldwide with an incidence rate higher in men than women; the risk of developing this disease is higher after the age of 45.3 [3,4]. The five-year survival rate can also be correlated with tumor advancement: about 80% for patients with stage I and 20% for patients with stages III or IV [5–7]. The different habits of the population, education, and access to medical services have a powerful influence on oral cancer incidence [8,9]. Oral squamous cell carcinoma (OSCC) is the most common type of oral cancer (approximate 90%); the remaining 10% of oral malignancies involve rare histologic subtypes (minor salivary gland carcinomas, lymphomas, and melanoma) [10–13]. Various risk factors have been notably associated with oral cancer [9,14–17], with the majority of oral cancers being related to the use of cigarettes, alcohol, and betel quids [11] (Figure 1).

Worldwide, tobacco or alcohol was associated with 72% (95% CI 61% to 79%) of HNC cases, of which 35% were attributed to tobacco and alcohol combined [18–21]. Worldwide, in 2018, 38,000 of 900,000 cases were attributable to the human papillomavirus (HPV) [22,23]. The most widely used predictors of survival for oral cancer are tumor stage at the time of presentation, as well as HPV genotypes that are present in the tumor, in conjunction with the tumor site and treatment procedure [24].

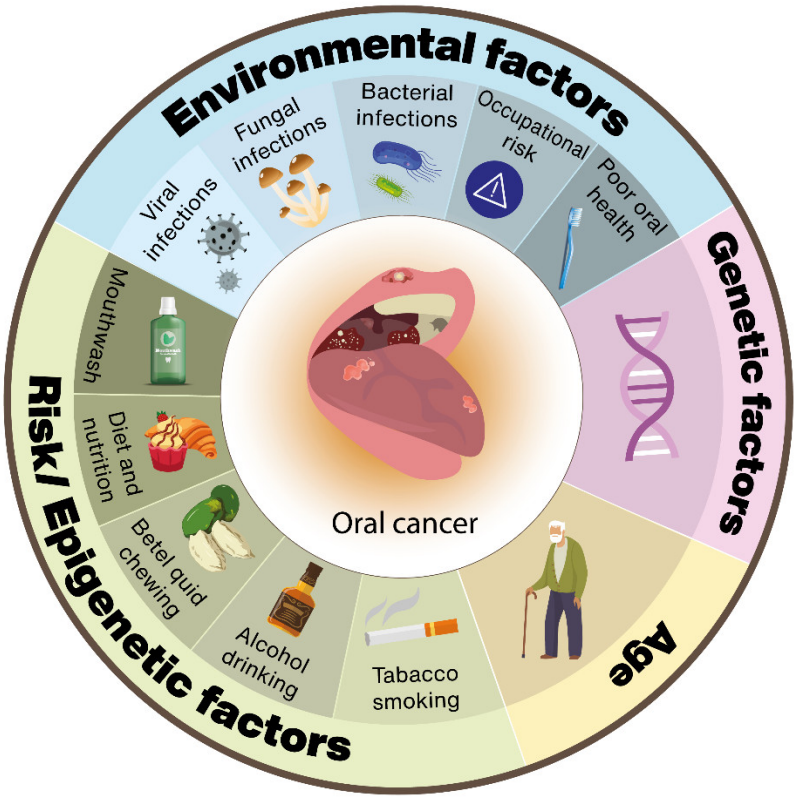

Figure 1. The link between the main factors related to oral carcinogenesis, including environmental, risk/epigenetic factors, genetic background, and age.

Growing evidence supports the role of epigenetic regulation in the process of oral carcinogenesis being considered an early event [25,26]. Epigenetic regulation is evaluated as an early event in the process of oral cancer development, epigenetic modifications including hypermethylation in the promoter region of genes, post-translational histone modifications, and post-transcriptional regulation by microRNAs [27]. In addition, early molecular alterations along with dysregulation of coding and non-coding genes have an important role in modulating the response to the therapy [28].

2. Major Risk Factors for Oral Cancer

2.1. Epigenetic Alteration Associated with Risk Factors

Epigenetics refers to modifications in DNA expression that do not involve alterations in the DNA sequence. The mechanisms responsible for these changes are DNA methylation, histone modification, and post-transcriptional gene downregulation by microRNAs (miRNA), which are able to induce overexpression of oncogenes but also the silencing of tumor suppressor genes [29,30]. The epigenetic mechanism of DNA methylation can lead to gene silencing in neoplasms; the process of DNA methylation consists of a covalent insertion of a methyl group into the 5 carbon (C5) position of cytosine to generate 5-methylcytosine (5-mC) in cytosine/guanine dinucleotide islands (CpGIs) [31]. CpGIs are often discovered in the promoter of some genes, including tumor suppressor genes and proto-oncogenes [31]. Epigenetic alterations are related to chromosomal instability and modifications in transcriptional control, affecting the gene expression differences that are found in human cancers [31]. Recent evidence has shown that promoter hypermethylation, especially in CpG islands, can enhance the downregulation of tumor suppressor genes, while the downstream signaling pathways are dysregulated [32].

In the DNA methylation event, a series of enzymes named DNA methyltransferases (DNMTs) with a role in the covalent addition of a methyl group to a CpG dinucleotide were found [33,34]. DNA methylation was observed in 28–58% of precancerous oral tissues,

while in oral cancer a progressive increase in oral cancers has been found [35,36]. The use of DNA methylation should be mentioned as a highly predictive blood biomarker to detect heavy alcohol drinking [37]. Moreover, the hypermethylation of p16 is an early event found in patients with long-term tobacco use and premalignant lesions [35]. DNA methylation was demonstrated to be present in adjacent normal tissues as an early event and/or process of field cancerization occurring in the oral cavity [38]. An imbalance in tumor suppressor gene methylation status is related to multiple risk factors or environmental agents [39].

2.1.1. Tobacco Consumption

Worldwide, tobacco is responsible for nearly 6.4 million deaths and hundreds of billions of dollars of economic damage each year; in 2012, the total economic cost of smoking was estimated to be PPP $1852 billion (US$1436 billion), representing 1.8% of the world's annual gross domestic product (GDP) [40]. According to specialists' estimates, by 2030, tobacco consumption will lead to the death of more than 8 million people each year, with most cases estimated to occur in developing countries with a lower income, low levels of education, and prevention programs [41]. The concentration and potency of carcinogens from tobacco depend on the type of tobacco product and its method of consumption [40]. Thus, more than 60 known carcinogens in smoking tobacco and about 16 in unburned tobacco have been identified [42]. A stronger association of smoking with larynx and pharynx cancer has been observed due to a higher exposure of the larynx and pharynx to smoke than the oral cavity [43,44]. Cigar smoking and smokeless tobacco use were associated with an increased risk for premalignant and malignant lesions of the oral cavity, as well as with periodontal diseases, tooth loss, and dental implant failures [45,46]. In recent years, smokeless tobacco has become more and more popular in developing countries. Smokeless tobacco consumption consists of direct contact with mucous membranes commonly in nasal snuff or placed in the oral vestibule, thus leading to a significant increase in the risk for squamous cell carcinoma [47]. Chewing tobacco is popular in Western Europe and North America, with the main types being plug, loose-leaf, and twist [48]. Additionally, moist snuff (ground tobacco) has become common in North America and Scandinavia, and the habit of oral snuff was associated with the so-called 'snuff dipper's cancer' that is classically described as verrucous carcinoma [49]. The principle of duration, more important than frequency, has been demonstrated for smoking. Thus, smoking fewer cigarettes per day over a longer period proves to be more harmful to oral cancer risk than smoking more cigarettes per day over a shorter period [50]. The nicotine levels for heat-not-burn cigarettes are considered to be lower, and as a result, the health risks are unclear [51]. At the same time, carcinogens have been found in the heat-not-burn (HNB) tobacco aerosol, with the levels being lower than the smoke from ordinary cigarettes, but no current data are available regarding the risk of HNB cigarettes for the development of oral cancer [52]. Additionally, in vitro studies identified a lower effect of aerosol from HNB tobacco products compared to cigarette smoke [53–55]. Regarding snus use, an association with the presence of non-neoplastic oral mucosal lesions has been reported. Once the user has been stopped, the lesions are rapidly healed, and the health risks associated with snus are considerably lower than those associated with cigarette smoking [56].

The interaction between smoking and carcinogen metabolizing gene polymorphisms by modulating promoter methylation of tumor suppressor genes has been revealed [57]. Oxidative stress and persistent reactive species in tissues produce the occurrence of cell cycle-regulated mutations, disruption of the immune system [58], and abnormal expression of different epigenetic genes, such as p53, P13K, DAPK, GLUT-1, MGMT, and p16, in oral epithelium [41]. Several frequently mutated genes, including TP53, CASP8, and CDKN2A have been identified in OSCC tumors from subjects with different tobacco consumption habits. Furthermore, TP53 and HRAS revealed mutually exclusive mutation patterns [59].

Dibenzo [def,p] chrysene (DBP) has been found in tobacco and can be a potential biomarker for early detection of OSCC, with an important role in oral carcinogenesis due to the epigenetic alteration that occurred due to tobacco use [60,61]. In patients with an early

history of smoking, a significant correlation was observed between promoter methylation of CDKN2a and tobacco carcinogens, smoking exposure influencing the promoter methylation in a gene-specific manner in HNSCC. Thus, the link between promoter methylation and an increase in tobacco carcinogen exposure may be a clue for the presence of cells resistant to gene alteration that is induced via mutations [61]. Chronic smoking and drinking can induce aberrant methylation in the P15 gene, an effector of transforming growth factor (TGF-β)-induced cell cycle arrest. The downregulation of P15 is essential in the oral carcinogenesis process and was also methylated in 64% of OSCC heavy smokers [62].

Tobacco and its metabolites can change the methylation profiles in oral cancer by altering the expression of DNA methyltransferase expression [63]. In oral cancers, the methylation profile of genes evidences a differential methylation pattern, involving global hypomethylation in the genome's repeat sequences and hypermethylation of specific genes [64]. DNA methylation was also observed in the normal-appearing surgical margins of OSCC patients in which the incidence of local recurrences was highlighted. DAPK promoter hypermethylation was revealed in surgical margins to be linked to a decrease in overall survival [65]. An inverse significant association was demonstrated between tobacco consumption and DNA methylation, while the smoking effect is amplified, the overall methylation index is reduced, and cigarette smoke causes hypomethylation [39].

2.1.2. Betel Quid/Nut Chewing

In many parts of South Asia, the high preponderance of oral cancer has been linked to the habit of betel quid chewing, one of the dominant etiological factors for the development of this malignancy and an important menace to public health [66,67]. Multiple factors were linked to malignant transformation in the oral mucosa of betel quid chewers; the involvement of each component in betel quid was individually, synergistically, and coordinately found in the carcinogenesis process [67]. Thus, the carcinogens from alcohol and tobacco can act synergistically in this process besides betel quid; an increase in the duration for the habit of betel quid chewing can generate chronic inflammation of the oral cavity with numerous ulcerations and microbiome dysbiosis [67]. Furthermore, these multiple factors intertwine and can cause malignant transformation in the oral mucosa of betel quid chewers [67]. Approximately 10% of the world's population chews betel nuts regularly, being the fourth most commonly used psychoactive substance in the world [68,69]. Recent evidence showed the association of oral cancer with betel quid-areca nut habit, but also with oral premalignant lesions, such as oral submucous fibrosis and leukoplakia, both with the capacity to develop malignant transformation [70]. The RARB gene was hypermethylated in the OSCC tongue tissues from a mouse model cotreated with arecoline and 4-nitroquinoline-1-oxide (4-NQO). Moreover, in the human oral cancer cells, gene reexpression was identified by 5′-aza-2′-deoxycytidine (5-aza-dC) at 2 μM. Thus, de novo DNA methyltransferases proved to be associated with the gene epigenetic alternations of OSCC [71]. Areca nut components play key roles in the pathogenesis of betel quid-induced oral cancer via induction of ROS, IL-1α, EGF/EGFR, JAK, and COX signaling pathways. In addition, these components cause aberration in cell cycle- and differentiation-related proteins of oral keratinocytes [72].

2.1.3. Alcohol Consumption

Alcohol consumption turned out to be the leading risk factor for disease burden worldwide, responsible for nearly 10% of global deaths among populations aged 15–49 years [73]. Nowadays, the role of alcohol in the development of oral cancer has been proven due to its potential to cause malignancies of the oral cavity, esophagus, larynx, pharynx, and liver [49]. The risk of oral cancer is considerably increased by the association of alcohol consumption with tobacco [49]. Alcohol has a major role in the DNA methylation process and histone modifications that increase carcinogenesis due to the two major components—ethanol and its metabolite, acetaldehyde. DNA methylation can also be affected by alterations in folate metabolism and transmethylation reactions [74].

Alcohol can be directly related to 4.2% of cancer deaths [75] and 26.4% of all lip and oral cavity cancers worldwide [76], with the main metabolites of ethanol being considered a class 1 carcinogen [77]. These metabolites are directly involved in the carcinogenesis process by the occurrence of the disturbance of DNA synthesis and repair, the development of DNA adducts, and DNA hypomethylation that leads to the alteration of oncogene expression [78]. Furthermore, alcohol metabolites have an indirect solvent role, causing more mucosa permeability to other carcinogens, such as those from tobacco [79]. The effect of drinking alcohol was associated with a higher risk for oropharyngeal and hypopharyngeal cancer than for laryngeal cancer among those that have never smoked [80].

In a study conducted by Lubin, using the INHANCE dataset, it was found that higher alcohol drinks/day over a shorter period can be more harmful than fewer alcohol drinks/day over a longer period [50]. Studies regarding the interaction between genetic polymorphisms in genes that code for alcohol metabolizing enzymes and alcohol consumption have revealed that the prevalence of these genetic polymorphisms varies by ethnicity [81,82]. Smoking cigarettes has been linked to a two-fold increased risk of oral cancer among those that have never consumed alcohol, with the risk being observed to increase with prevalence, persistence, and pack-years of cigarette smoking [83]. The combined effects of tobacco and alcohol use lead to a higher risk for the development of oral cancer compared to multiple individual effects [18,84]. It is well known that ethanol from wine is oxidized to form acetaldehyde in the oral cavity [85]. Acetaldehyde is a metabolite with genotoxic properties that leads to the overexpression of oncogenes but can also cause the silencing of tumor suppressor genes [86]. Moreover, ethanol and acetaldehyde cause alteration of methyl transfer during carcinogenesis, generating DNA hypomethylation with alteration in the expression of oncogenes and tumor-suppressor genes and stimulating tumor cell dissemination [85]. In oral keratinocytes exposed to alcohol and acetaldehyde, the dysregulation of lncPSD4-1 and in-NETO1-1, two key long non-coding RNAs strongly linked to the development of head and neck squamous cell carcinoma, has been observed [87]. Oral cancer cell proliferation was also increased by the expression of miR-30a and miR-934, which promote the induction of anti-apoptotic gene Bcl-2 [88].

2.1.4. Diet and Nutrition

An important role in the development of oral cancer has been assigned to dietary and nutritional habits, increased consumption of citrus fruits and raw vegetables (especially yellow, green, and cruciferous vegetables), which are involved in the decrease of oral cancer risk [89–92] due to their regulation of the activity and the expression of transcription factors, growth factors, mediators of the inflammatory process, and intermediates of the cell cycle [93]. The International Head and Neck Cancer Epidemiology (INHANCE) Consortium, according to the results from 22 case-control studies, reported an odds ratio (OR) of 0.52 for high fruit consumption and 0.66 for high vegetable consumption [91]. The risk for oral cancer can increase with the consumption of red meat more than once a week compared to white meat (chicken, fish) [89]. Low consumption of fruit and vegetables or high consumption of meat along with increased exposure to tobacco and alcohol has been associated with a 10- to 20-fold increase in risk for development of oral cavity and pharyngeal cancer [90,94]. A case-control study from Italy reported a 50% decrease in oral carcinogenesis due to the dietary consumption of flavonoids [95]. Epigallocatechin-3-gallate (EGCG) inhibited cell proliferation and promoted apoptosis and autophagy in OSCC cells by inhibiting TP53, CASP8, and MYC [96]. Glucoraphanin and its bioactive metabolite sulforaphane promoted the detoxification of carcinogenic chemical agents found in tobacco smoke and NRF2-independent dephosphorylation/inactivation of pSTAT3, which is a crucial oncogenic factor in head and neck squamous cell carcinoma [97]. Consumption of minimally processed foods has been reported as a protective factor in the development of squamous cell carcinoma of the head and neck [98]. An in vivo mouse model demonstrated that a high-fat diet and male sex contribute to the pathology of 4-nitroquinoline-1-oxide-induced oral cancer [99]. An important dietary risk factor for the development of OSCC

is the high intake of iron linked to the involvement of this element in major cellular processes, such as metabolism, cell growth, and proliferation, with the generation of nitrogen compounds and free radicals, which cause cell damage [100]. Obesity is also an important risk factor for OSCC; a high-fat diet (HFD) significantly accelerated oral carcinogenesis by recruitment and functional enhancement of myeloid-derived suppressor cells (MDSCs) [101].

2.1.5. Mouthwash

A possible association between the use of mouthwash with alcohol and the risk of oral cancer is supported by a few epidemiological studies with contradictory results [102,103]. However, the development of oral cancer can be influenced by the use of mouthwash with alcohol simultaneously with other risk factors, such as tobacco or alcohol [104].

2.2. Environmental Factors

2.2.1. Viral Infections

Persistent infections with human papillomavirus (HPV) lead to the development of cancer, with the majority of HPV-induced carcinomas being related to type 16 [105]. HPV infection is a major risk factor for HNSCC [106]. A worrying increase has been observed in the worldwide incidence of HPV-positive oropharyngeal cancer, especially among younger men in the United States and other Western countries [107,108]. Head and neck squamous cell carcinoma (HNSCC) and oral squamous cell carcinoma (OSCC) represent 3% and 2% of all malignant neoplasms in men and women, respectively [107,109]. Furthermore, HPV infection has been associated with other risk factors, such as open mouth (deep) kissing, number of sexual partners, number of oral sex partners, alcohol, and tobacco [110]. HPV infection has also been especially observed in wild-type TP53 tumors [59]. HPV-16 is the most common HPV type, responsible for ~90% of HPV-associated OSCCs, the other HPV types being HPV-18, HPV-33, and HPV-35 [111–113]. 84% and 61.5% of patients with OSCC were found to be positive for HPV and HPV-16 [114]. "High-risk" HPV (HR HPV), such as HPV-16 and 18, have been discovered in up to 99% of cervical carcinomas [115]. It has been reported that approximately 4% of patients with cervical HPV infection are co-infected with the same HPV types in the oral region [116].

Epstein-Barr virus was found to be associated with the development of nasopharyngeal carcinoma and oral squamous cell carcinoma [117,118], a meta-analysis of 53 studies reported a 2.5 increased risk for developing OSCC in patients with EBV infection [119]. Latent membrane protein-1 (LMP-1) is an important marker of most EBV-related malignancies, including for OSCC [120], LMP-1 activates multiple signaling pathways, such as NF-κB, JAK-STAT, JNK–p38, and PI3K–AKT [121].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is more threatening in cancer patients, mainly due to the aggressiveness of the tumor type but also due to the side effects of the cancer treatment [122,123]. In the case of this infection, the oral mucous membrane may be targeted by the virus due to the highly expressed angiotensin-converting enzyme 2 (ACE2), the main host cell receptor of the SARS-CoV-2 [124]. Aphthous-like and superficial necrosis are oral ulcerations that occur in patients diagnosed with COVID-19 [125]. However, additional studies are needed to investigate whether oral ulcerations are directly caused by SARS-CoV-2 infection or whether oral lesions are a coincidental event, as well as the progression of the lesions.

2.2.2. Fungal Infections

Candida albicans is an opportunistic fungus that becomes pathogenic in immunocompromised individuals [126], is found to be an independent risk factor in the development of oral carcinoma [127]. Oral cancer occurrence was significantly associated with *Candida* oral colonization. Furthermore, the genotypic diversity of *C. albicans* strains is directly involved in oral carcinogenesis [127].

2.2.3. Bacterial Infections

Porphyromonas gingivalis promoted the invasion and metastasis of highly invasive oral cavity cancers [128,129] by stimulation of matrix metalloproteinase and by apoptosis of activated T cells [128,130,131]. *Streptococcus anginosus* has also been associated with the carcinogenesis of oral cancer [132]. A positive association has been discovered between the capacity of oral *Candida* to metabolize alcohol to acetaldehyde and, thus, to promote oral cancer development [133].

2.2.4. Occupational Risks

Socioeconomic status (SES), including educational level, income, and occupation, was linked to oral cancer incidence in many studies [10,134,135]. Commonly, the risk of the development of oral cancer is lower in persons with higher education and income levels. However, the risk for the development of oral cancer has been remarkably reduced by the progress made in the last period [136]. Multiple exposures to asbestos and polycyclic aromatic hydrocarbons have been strongly associated with the risk of oral and pharyngeal cancer [137]. One of the most common occupational and carcinogenic agents for oral cancer pathogenesis is wood dust [138]. Exposure to excessive solar radiation/ultraviolet (UV) light can cause lip cancers and may also produce actinic cheilitis, which may transform to OSCCs [49]. In medium-low-income countries, occupational exposures are less controlled and more frequent due to the lack of automatic monitoring equipment and self-protection in the work [139]. Access to dentists and oral cancer screening services was also associated with delays in establishing a diagnosis and poorer survival [140].

2.2.5. Poor Oral Health

Poor oral hygiene is strongly associated with oral cancer, especially in association with other risk factors, such as tobacco and alcohol. A case-control study of Indian patients aged 18–45 years reported poor hygiene for 79% of the patients with oral cavity and oropharynx cancer [141]. The risk for the development of oral cancer is decreased by 26% by dental visits [142]. The Chinese population has observed a positive association between the number of missing teeth due to poor hygiene and head and neck cancer risk [143]. Detection of oral cancer cases at early stages can be accomplished by oral cavity screening, with the survival rates being improved if the disease is treated in early stages [144].

2.3. Genetic Factors

The role of Family History of Cancer (FHC) in oral cancer incidence led to contradictory opinions. Thus, some researchers believe that there is no evidence of a clear hereditary trait for oral cancers, except for Cowden syndrome (correlated with a few reported cases of head and neck cancer) and dyskeratosis congenital, a rare genetic disorder characterized by oral white lesions in young people, and with risk of transformation to cancer [145]. However, the familial risk for oral cancer has been assessed in several epidemiological studies suggesting a possible correlation between FHC and oral cancer [146–149]. The Utah Population Database resource, including about 1 million individuals, has been used for a unique comprehensive population-based study of familial cancer, with a standardized incidence ratio of oral cancer of 1.8 (95%) for patients with a first-degree relative with the same cancer type [149].

2.4. Age

Young age is known to be an independent factor for survival. Regarding oral malignancies, in young adults, oral cancer is a rare disease that is increasing in women [150]. In the United States, the incidence rate was found to increase in patients aged 55–64 years, with a median age of 63 years, and most of them being diagnosed at age 45 and above https://seer.cancer.gov/statfacts/html/oralcav.html (accessed on 19 December 2021). A population-based study in Taiwan reported that oral cancer patients with an age less than

45 years had a lower risk of mortality compared to middle age (45–65 years) or old age (>65 years) patients [3].

3. Oxidative Stress and Chronic Inflammation Associated with Risk Factors in Oral Cancer

Common risk factors, such as tobacco, alcohol, and betel nut/areca quid chewing, promote carcinogenesis via ROS-based mechanisms by the increase of oxidative DNA damage that is secondary to ROS generation [151]. The link between increased ROS levels and oral cancer development has been observed in tobacco chewers and smokers [41,152]. Tobacco smoke supports the production of ROS via the production of NO, superoxide, and hydrogen peroxide in different types of head and neck cancer [153]. Tobacco chewing and smoking can increase oxidative stress along with the increase of lipid peroxidation and oxidative DNA alteration, which can disturb antioxidant protection inducing the malignant process [154]. Chewing areca nuts is another risk factor for oral carcinogenesis by ROS generation; the increase in ROS levels leads to oxidative DNA damage [155]. Areca nut extract decreased cisplatin toxicity of OSCC cells by inducing autophagy through the AMPK/mTOR pathway and with remarkable increases in ROS levels [156]. The upregulation of MKP-1, increases in autophagy, and defense against apoptosis are also processes observed as pathogenesis-promoting mechanisms [157]. For betel quid, the major component is arecoline, which can promote the generation of reactive oxygen species (ROS) [68]. Patients with a history of areca quid chewing have been observed a ROS-induced overexpression of the Snail family of transcription factors, which can also be linked to metastasized lymph nodes [158,159]. In both normal and malignant cells, autophagy induction by the 30–100 kDa fraction of areca nut occurred through the production of reactive oxygen species [160]. The high levels of ROS, which leads to lipid peroxidation and binds to DNA to form mutagenic adducts, were correlated with chronic alcohol consumption and can generate single nucleotide polymorphisms in Cytochrome P450 2E1 (CYP2E1) CYP2E1 [161]. Studies regarding the effects of the EBNA1 protein of the Epstein–Barr virus on the redox pathway found that overexpression of EBNA1 is linked to the presence of increased levels of ROS and NADPH oxidases NOX1 and NOX2, which can generate ROS, being directly involved in the development of NPC [162]. Changes in cellular metabolism by high-risk HPV E2 proteins are important in carcinogenesis by inducing the Warburg effect, the localization of HPV-18 E2 at mitochondrial membranes promoting ROS release, and an increase in glycolysis [163]. Human papillomavirus type 16 E6 * is involved in the oral mutagenesis process by increasing oxidative stress due to a decrease in cellular antioxidant activity through the production of high levels of ROS and DNA damage [164]. HPV16 E6 and E7 proteins generated a chronic oxidative stress response via NOX2, promoting genomic instability and increased sensitivity to DNA damage in head and neck cancer cells [165]. The increased levels of ROS are generated by circCDR1as upregulation, which plays a major role in the activation of autophagy under a hypoxic microenvironment in OSCC, also supporting the role of ROS as a cellular autophagy regulator by suppression of mTOR pathway activation [166]. Furthermore, the inhibition of autophagy in combination with circCDR1as can be considered a potential therapeutic strategy for oral cancer [167].

Chronic inflammation induces epigenetic and transcriptomic modifications, and the chronic inflammation associated with reactive oxygen species represents an important source of DNA damage that is involved both in the development of oral carcinogenesis and in cancer treatment [41]. Tobacco and alcohol consumption, along with chronic inflammation, are important risk factors associated with dysregulations in the epigenetic pattern [168,169]. The chronic exposure of human mucosal epithelial cells to carcinogens from tobacco is related to the hypermethylation of different tumor suppressor genes [41,170]. Epigenetic alterations of key genes linked to the regulation of the DNA methylation feedback process were identified to maintain normal cell division in oral cell lines. In addition, a significant upregulation of CTLA4 was observed. In addition, the expression or pro-

moter DNA methylation of CD28, a T cell activation promoter, did not suffer significant alterations [171].

4. The Functions of miRNAs Associated with Risk Factors in Oral Cancer

MicroRNA (miRNAs) are small non-coding RNA molecules with 18–25 nucleotides in length, playing important roles in biological processes, such as cell growth, proliferation, and apoptosis. The role in cancer progression is defined through post-transcriptional modification of gene expression and/or translational repression [172–175]. Furthermore, alteration of miRNA expression is crucial in cancer for clinically prognostic cancer, influencing the expression of many protein-coding genes [176–178]. A key role in the field of drug development is played by the detection of toxicity-related biomarkers and by the influence-related transcriptomics signals [179]. MiRNAs were highlighted in OSCC, making them potential candidates for screening and diagnosis, the association of these markers with OSCC being studied in primary tumors, but also in biopsies, serum, and saliva [180–183].

Studies regarding the discovery of new prognostic biomarkers for oral cancer to improve patient stratification accuracy revealed that increased miR-155 expression is a positive predictor of survival; this effect was strongly correlated with high CD8+ TIL numbers. Moreover, miR-185 was independently associated with decreased survival [184].

miRNAs are associated with multiple aspects of oral cancer, and epigenetic and alteration of the expression levels being emphasized [185]. miR-21 and miR-155 were the most studied miRNAs in OSCC; miR-155e-5p facilitated tumor progression and was found to be significantly upregulated in OSCC tissues and cell lines [186]. The overexpression of miR-21 in OSCC has been demonstrated in several studies [187–189]. MiR-770 was identified as an oncomiR, leading to a more prominent OSCC metastasis [190]. miR-1237 was found to be significantly overexpressed in OSCC tumor samples, especially in the early stages (stages I and II), and was associated with poor prognosis of OSCC patients [191]. miR-205 was found to be significantly downregulated in oral cancer, its overexpression reducing cell viability and inducing cell apoptosis by activation of caspase-3/caspase-7 [192].

The miRNA altered pattern was linked to risk factors of oral carcinoma (Table 1, Figure 2).

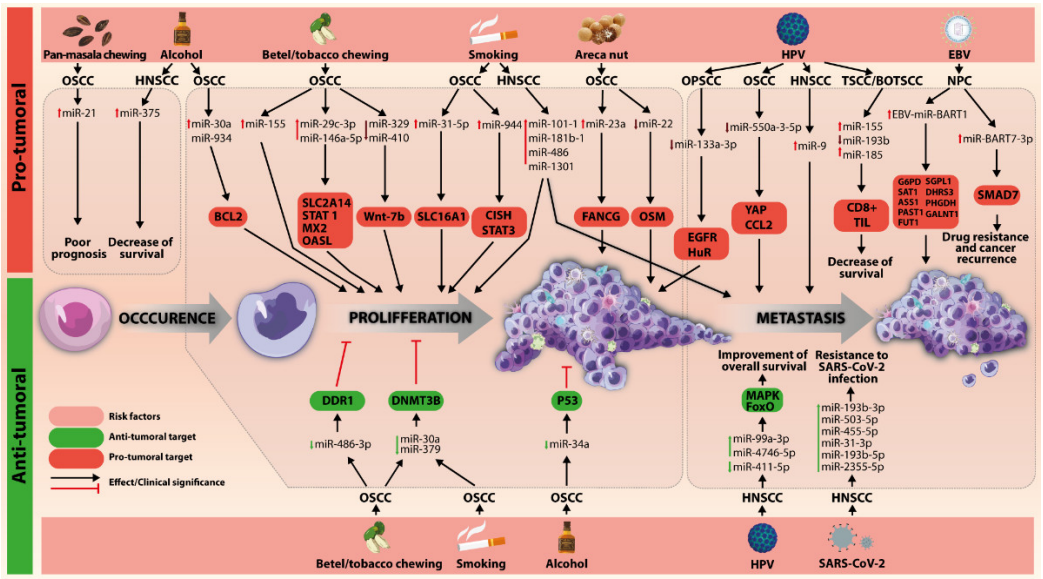

Figure 2. The connection between miRNAs and the main risk factors in oral cancer.

In oral cancer, miRNA expression was found to be closely related to DNA methylation and hypermethylation, and CpG hypermethylation is associated with the downregulated expression of miR-203, miR-34b, miR-193a, and miR-137 in oral cancer cell lines [193]. Additionally, DNA hypermethylation is associated with a decrease in the expression of miR-218

and miR-585, and it is known that miR-218 can act as a suppressor of the mechanistic target of the rapamycin (mTOR)–Akt signaling pathway and independently of the phosphoinositide 3-kinase (PI3K)–Akt signaling pathway. Rictor is a possible target of miR-218 and was found to be upregulated in OSCC, which supports oral carcinogenesis by the epigenetic alteration of miR-218 and activation of the mTOR–Akt signaling pathway [194]. The proliferation and invasion of OSCC are promoted by the epigenetic alteration of miR-329 and miR-410, contributing to Wnt-7b overexpression and triggering the Wnt-β-catenin signaling pathway [195]. miR-200/miR-205 are miRNAs suppressed in disease with poor prognosis, being activated by epigenetic DNA hypermethylation in CD44 high OSCCs [196]. The presence of miR-31-mediated post-transcriptional regulation of SIRT3 in OSCC has been associated with OSCC progression, the oxidative stress in oral cancer being increased by SIRT3-miR-31 targeted to suppress mitochondrial activity. Additionally, the disturbance of the miR-31-SIRT3 cascade and the occurrence of metabolic aberrances are related to the development of OSCC [197]. The methylation in the p16 promoter was significantly higher in tobacco and maras powder users compared to those that have never used [35].

miR-218, miR-137e, miR-596, and miR-193a expression are significantly influenced by DNA methylation and loss of tumor suppressor activity and are downregulated in oral cancer [193,194,198].

Table 1. The main miRNAs related to risk factors in oral carcinogenesis.

Risk Factor	Tumor Type	miR	Targets	Effects/Clinical Significance	References
smoking	OSCC	miR-31-5p↑	SLC16A1	Cancer cell proliferation	[199]
	OSCC	miR-30a↓ miR-379↓	DNMT3B	Growth inhibition in oral cancer cells	[200]
	OSCC	miR-944↑	CISH STAT3	Maintaining a pro-carcinogenic microenvironment in oral cancer	[201]
	OSCC	miR-200a, miR-200b, miR-200c, miR-141 and miR-429, ↓	ZEB2-AS1 and ZEB2	No significant effect on treatment outcome	[202]
	HNSCC	miR-101-1, miR-181b-1, miR-486, and miR-1301↑		Increase of cell proliferation, metastasis, and decrease in survival	[203]
alcohol	HNSCC	miR-375↑		Decrease in survival	[204]
	OSCC	miR-34a↓	P53	Inhibition of tumor growth	[205]
		miR-30a↑miR-934↑	BCL-2	Increase in cellular proliferation	[88]
betel/tobacco chewing	OSCC	miR-155↑		Increase in cellular proliferation	[187]
	OSCC	miR-486-3p↓	DDR1	Growth inhibition and apoptosis induction	[206]
	OSCC	miR-30a↓ miR-379↓	DNMT3B	Growth inhibition in oral cancer cells	[200]

Table 1. *Cont.*

Risk Factor	Tumor Type	miR	Targets	Effects/Clinical Significance	References
	OSCC	miR-29c-3p miR-146a-5p↑	SLC2A14 STAT 1, MX2, OASL	Cancer cells proliferation	[199]
	OSCC	miR329 and miR410↓	Wnt-7b	Proliferation and invasion of cells	[195]
Areca nut	OSCC	miR-23a↑	FANCG	Induction of cell proliferation	[207]
	OSCC	miR-22↓	OSM	Promote cell proliferation and cell-cycle progression	[208]
pan-masala chewing	OSCC	miR-21↑		Poor prognosis	[209]
HPV	TSCC/BOTSCC	miR-155↑ miR-193b↓ miR-185↑	CD8+ TIL	Decreased survival	[184]
	OSCC	miR-550a-3-5p↓	YAP CCL2	Larger tumor size and nodal metastasis	[210]
	HNSCC	miR-9↑		Proliferation and migration of the cells	[211]
	HNSCC	miR-99a-3p and miR-4746-5p↑ miR-411-5p↓	MAPK FoxO	Improvement of overall survival	[212]
	OPSCC	miR-133a-3p↓	EGFR and HuR	Promote cell proliferation	[213]
	OSCC	let-7e↑	βCatenin	Induction of stem-like traits in tobacco-related OSCCs	[214]
SARS-CoV-2	HNSCC	miR-193b-3p; miR-503-5p; miR-455-5p; miR-31-3p; miR-193b-5p; miR-2355-5p↑	TMPRSS2	Resistance to SARS-CoV-2 infection	[215]
EBV	NPC	EBV-miR-BART1↑	G6PD, SAT1, ASS1, PAST1, FUT1, SGPL1, DHRS3, PHGDH, GALNT1	Tumor metastasis	[216]
	NPC	miR-BART7-3p↑	SMAD7	Drug resistance and cancer recurrence	[217]

Abbreviations: TSCC/BOTSCC, tonsillar and base of tongue cancer; OSCC, oral squamous cell carcinoma; HNSCCs, head, and neck squamous cell carcinomas; OSM, oncostatin M; oropharyngeal squamous cell carcinoma (OPSCC); DNMT3B, DNA Methyltransferase 3 β; CISH, Cytokine Inducible SH2 Containing Protein; STAT3, Signal Transducer And Activator Of Transcription 3; ZEB2, Zinc Finger E-Box Binding Homeobox 2; ZEB2-AS1, ZEB2 Antisense RNA 1; BCL2, BCL2 Apoptosis Regulator; DDR1, Discoidin Domain Receptor Tyrosine Kinase 1; epidermal growth factor receptor (EGFR); SLC2A14, Solute Carrier Family 2 Member 14; MX2, MX Dynamin Like GTPase 2; OASL, 2′-5′-oligoadenylate synthase-like protein; YAP, Yes1 Associated Transcriptional Regulator HuR; FOXO1, Forkhead Box O1; TMPRSS2, Transmembrane Serine Protease 2; ASS1,Argininosuccinate Synthase 1; FUT1, Fucosyltransferase 1 (H Blood Group); SGPL1 (Sphingosine-1-Phosphate Lyase 1); DHRS3, dehydrogenase/reductase 3; PHGDH, Phosphoglycerate Dehydrogenase; RBP Hu-antigen R; GALNT1, Polypeptide N-Acetylgalactosaminyltransferase 1; NPC, nasopharyngeal carcinoma.

4.1. miRNAs Altered by Epigenetic Risk Factors

The use of smokeless tobacco-like maras powder proved to increase the expression of miR-138 and miR-31 and decreased expression of miR-200b, miR-145, miR-375, miR-10b, miR-372, miR-92a, and miR-378a [218]. Tobacco chewing has been associated with an increase in miR-155 and a decrease in miR-542 expression, while tobacco smoking was linked to a decrease in miR-375, miR-23a, miR-203a, miR-23b, and miR-200b expression [199]. In pan-masala chewers, overexpression of miR-21 has been found; the increase in miR-23a and miR-155 expression was correlated with areca nut chewing, and alcohol consumption with overexpression of miR-375, miR-34a, and miR-183 [68,219]. miR-155 was found to have high levels in the tumor samples obtained from tobacco/betel quid chewers compared to those from individuals without this habit, with aberrant expression being due to exposure of oral mucosa to environmental factors, such as tobacco [187]. The overexpression of miR-23a was associated with the areca nut-chewing habit in oral cancer patients, and it is known that areca nut extract (ANE)-induced miR-23a was significantly associated with human malignancies [207].

Alcohol consumption in OSCC patients has been associated with high levels of miR-34a; downregulation of miR-34a and miR-143 may indirectly inhibit p53, revealing an indirect mode of p53 suppression in oral cancer [205]. Regarding miR-21 expression, an important relationship has been found between pan-masala chewers in OSCC patients, acting as a potential biomarker for early diagnosis, treatment, and prognosis [209]. An important upregulation of miR-31-5p and overexpression of miR-29c-3p and miR-146a-5p were observed in chewing tobacco-treated cells [199]. Recent evidence reported the dysregulation of miRNAs, such as miR-30a and miR-379, in oral cancer as a result of exposure to tobacco smoking and betel quid chewing; these miRNAs can regulate the retinoic acid pathway by targeting DNA methyltransferase B [200].

Chou et al. investigated the role of discoid domain receptor-1 (DDR1) tyrosine kinase and miR-486-3p as potential therapeutic targets of oral cancer as a result of exposure to betel nut alkaloids. Thus, a low level of miR486-3p is involved in OSCC tumorigenesis through DDR1 upregulation [206]. The link between cigarette smoking and the inflammatory microenvironment has been identified as a possible mechanism for cigarette smoking-induced oral carcinogenesis, tobacco extract (NNK) promoting miR-944 induction, activation of STAT3, and tumor malignancy through suppression of cytokine-inducible Src homology 2-containing (CISH) protein [201].

Dysregulation of miR-200 family miRNAs has been related to tobacco chewing/smoking, the cellular differentiation status of oral tumors, and upregulation of EMT-inducer genes in OSCC [202]. A potential role in the early development of smoking-related HNSCCs has been assigned to miR-1301, miR-101, miR-486, and miR-181b, miRNAs reported to be differentially expressed in cigarette-treated epithelial cell lines [203]. The involvement of alcohol in the early events of oral carcinogenesis was demonstrated in oral keratinocytes exposed to ethanol and acetaldehyde; thus, miR-3178, miR-934, miR-30a, and miR-3164 were upregulated, and the expression of miR-30a and miR-934 stimulated the induction of the anti-apoptotic gene BCL-2 in head and neck squamous cell carcinoma [88].

4.2. miRNAs Altered by Environmental Factors

TMPRSS2, a SARS-CoV-2 internalization protease, was identified as downregulated in HNSCC patients positive for SARS-CoV-2 infection, related to selective targeting of microRNAs, supporting the idea that tumor tissue from SARS-CoV-2 target organs is more resistant to SARS-CoV-2 infection [215]. The importance of miR-9 in human papillomavirus-associated with oral and oropharyngeal head and neck cancer was highlighted, with miR-9 being identified as the most important miRNA for HNSCC with HPV etiology and being upregulated in recurrent HNSCC [211]. In HPV16+ HNSCC tissues, a significant upregulation of miR-99a-3p and miR-4746-5p, and downregulation of miR-411-5p were observed; both miRNAs are involved in cancer progression through EMT-related pathways. The target genes are involved in cell growth and differentiation, MAPK, and FoxO signaling

pathways [212]. Between the miR329/miR410 and the Wnt–β-catenin pathway, a strong relationship may be involved in oral carcinogenesis; dysregulation is associated with exposure to betel quid chewing [220]. miR-22 was downregulated via arecoline-induced c-Myc upregulation in arecoline-treated OSCC cells. Moreover, miR-22 inhibited proliferation, migration, and cell-cycle progression in OSCC cell lines [208]. In HPV (+) patients, miR-133a-3p is a target of smoking-induced modifications and was observed to be also significantly downregulated in OPSCC smokers and E6/E7 overexpressing HPV (−) cells that were treated with cigarette smoke extract [213].

HPV-positive oral carcinoma cells from smoking patients revealed a low activity of the Wnt/βCatenin pathway that can be related to the differential expression of miRNA let7e [214]. RNA deep sequencing was used to analyze the EBV-miR-BART1 involvement in the regulation of the cell's metabolism-associated genes in nasopharyngeal carcinoma, demonstrating that EBV-miR-BART1, a virus-encoded miRNA, can be involved in cancer metabolism [221]. EBV-miR-BART7-3p was discovered to suppress SMAD7 in NPC stemness, leading to activated TGF-β signaling and drug resistance and cancer recurrence [217].

5. Conclusions

Most oral cancers are due to risk factors. Different altered miRNAs have been proven to play key roles in the initiation and progression of oral cancer due to their roles either as oncogenes or as tumor suppressors; they also have considerable potential to be excellent biomarkers and new therapeutic tools for this pathology. Furthermore, many studies have demonstrated a strong relation between altered miRNA expression and the main risk factors for the development of oral cancer, promoting early diagnosis and novel anticancer treatments to disturb the process of oral carcinogenesis. However, these studies require supplementation and validation in large cohorts of patients.

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