

Oral microbiota in oral cancer patients and healthy individuals: A scoping review

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ABSTRACT

Background: Oral microbiota has been suggested to have a role in the etiopathogenesis of oral cancer; however, the oral microbiota diversity in patients with oral cancer compared to healthy individuals remains unclear. **Purpose:** This scoping review aimed to provide an overview of the current evidence regarding the oral microbiota composition colonized in oral cancer patients and its comparison with healthy individuals. **Reviews:** This study was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. Eligible studies were searched in PubMed, Scopus, Web of Science, and ScienceDirect databases from January 2015 to March 2022. A total of 20 relevant studies were included according to the inclusion and exclusion criteria, including 14 cross-sectional studies and 6 cohort studies. All studies have identified various oral bacteria, but only one study has detected viruses and parasites diversity. A variety of oral microbiota found were 6 phyla of bacteria, 6 phyla of viruses, 7 phyla of fungi, and 7 phyla of parasitic. Seventeen studies proved that oral microbiota compositions were statistically significant differences compared to healthy controls, but not in 3 studies. **Conclusion:** The majority of studies showed various oral bacteria in oral cancer patients which were statistically significant difference compared to healthy controls. This study indicates the need for more research to evaluate viruses and parasites composition and diversity in oral cancer patients. Moreover, future research should focus to clarify whether the changes of oral microbial composition as a community may play a critical role in the etiopathogenesis of oral cancer.

Keywords: microbiota; cancer; oral cavity

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INTRODUCTION

Global Cancer Statistics (GLOBOCAN) data in 2020 showed that there were 19.3 million new cases of cancer and 10 million deaths from 36 types of cancer in 185 countries in the world. Among them, cancer of the lip and oral cavity (oral cancer) is the 11th most common malignancy in various regions of Asia. The number of new cases of oral cancer (ICD-10 codes C00-C06) was 377,713 (2%) and the number of deaths was 177,757 (1.8%). The incidence and mortality rate of oral cancer was higher among men compared to women.^{1–3} Oral cancer is a persistent health issue. Detecting and diagnosis in early stage of oral cancer are essential for patient survival. However, due to diagnostic delay (including the patient, professional and

system delay), diagnosis of this type of cancer at late stage causes poor survival of patients with oral cancer.⁴

Numerous risk factors or possible causative agents have been associated with oral cancer. The most common risk factors include tobacco smoking, consumption of alcohol, betel quid chewing, human papillomavirus (HPV) infection, and nutritional factors.^{5–7} To date, recent studies have shown that the oral microbial community (oral microbiota) may play an important role in the initiation and progression of head and neck cancer, including oral cancer, suggesting that oral microbiota is a new risk factor for cancer development.^{8–10} The oral microbiota plays an essential role within the maintenance of a normal oral physiological environment. They are living in a symbiotic relationship with one another and the host immune system.^{11,12}

However, direct effect of metabolites reaction of chemical carcinogens and inflammatory process caused by oral microbiota may play an important role in cancer patients. The oral microbiota and their metabolites have both direct and indirect effects on the DNA damage causing cell mutations which lead to carcinogenesis. The oral microbial composition changes also result in chronic inflammation that can increase risk of oral cancer. In a chronic inflammatory process, the immune system's host defense activates host cells to produce proinflammatory cytokines, growth factors, chemokines, generating free radicals that can damage DNA, causing cell mutations that lead to the initiation of oral cancer. The generation of reactive oxygen and nitrogen species (RONS) by proinflammatory cytokines during the inflammation process causes cell DNA damage causing cell mutations that lead to the initiation of cancer, and may also contribute in angiogenesis and metastasis. Cell proliferation stimulation and apoptosis resistance can be influenced by growth factors. Chemokines can promote cell migration and invasion by inducing the proliferation of cancer cells and preventing their apoptosis.^{13–16}

Although compelling evidence showed that carcinogenesis can be modulated by microbiota, specifically an association between microbiota in the oral cavity with oral cancer, its composition and diversity in oral cancer patients remain unclear. A big question remains: what are the oral microbiota composition and diversity found in oral cancer patients that may influence an individual's oral cancer risk? Are there any differences with healthy individuals? The aim of this present review is to identify and summarize the existing evidence regarding the oral microbiota composition and diversity colonized in patients with oral cancer and its comparison with healthy

individuals, which may help in the understanding the role of a community microorganism in the oral cavity in the etiopathogenesis of oral cancer.

METHODS

The method of this review complies with the Preferred Reporting Items Guidelines for Methods of Systematic Review and Meta-Analysis (PRISMA).¹⁷ According to the PICOS schema to construct the literature search, the following criteria were used: (P=Patients) patients diagnosed with oral cancer, (I=Intervention) examination of oral microbiota composition without restriction of the type of microbiological technique used, (C=Comparison) healthy control, (O=Outcome) to summarize the oral microbiota composition. Four electronic databases were searched through PubMed, Scopus, Web of Science, and ScienceDirect from January 2015 to March 2022 for the studies containing data related to “oral microbiota,” “phyla” and “oral cancer.” The inclusion criteria in the present review were no age and gender restrictions, clinical trials and studies in humans. Exclusion criteria are articles are not written in English and not indexed with Scopus.

The relevant articles were as many as 15484 articles. The amount of data after eliminating duplication in the database was 1412 articles, with screened records that full-text articles assessed for eligibility were 102 articles. Articles were excluded because of non-oral cancer (n = 23), non-phyla of microorganism classification (n = 45), articles not published in English (n = 9) and animal studies (n=5). The final number of full text articles that were checked for eligibility was 20 articles (Figure 1).

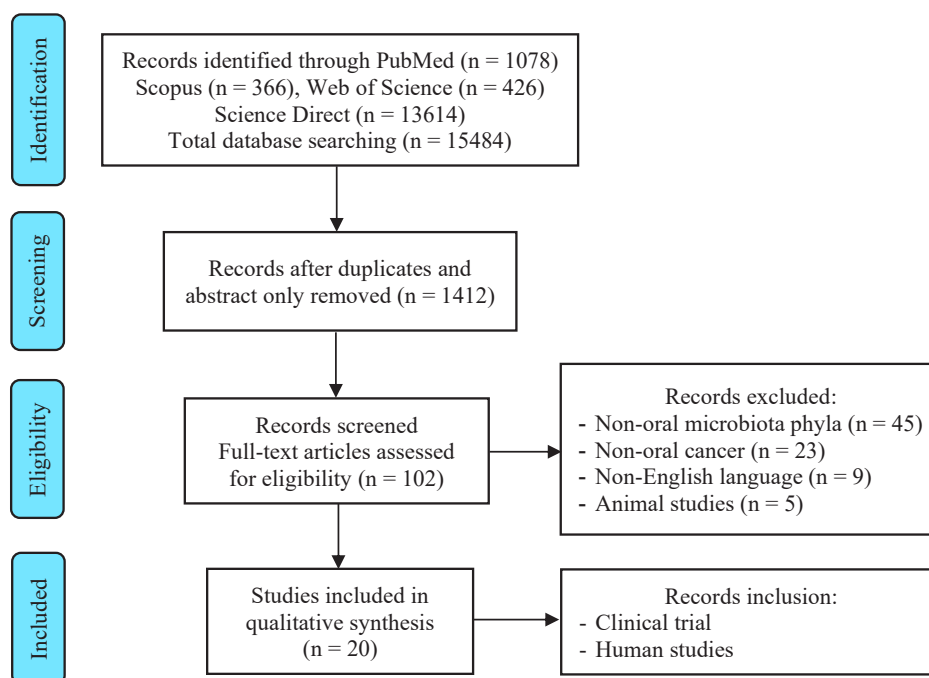


Figure 1. PRISMA flow diagram showing the process of study search, selection, inclusion, and exclusion.

RESULTS

This systematic review obtained 19 studies examining the oral microbiota in oral cancer. The studies were conducted in 10 Asian countries,^{8,18–25} two studies in Australia,^{14,26} and six studies in United States of America (USA),^{9,27–29} and two studies in Europe.^{30,31} The types of studies used were cohort (n=6) and cross-sectional (n=14). From all the studies, a total of 947 oral cancer and 761 healthy controls samples were obtained. The results of this review showed that oral cancer patients have a diversity of microbiota in the oral cavity. Various species of oral microbiota in oral cancer patients that have been identified consist of bacteria, fungi, viruses, and parasites. Six bacterial phyla were identified in oral cancer patients, mostly Firmicutes, Bacteroidetes, Proteobacteria and

the rest were Actinobacteria, Fusobacteria, Spirochaetes and Tenericutes. Six phyla of viruses found in a study, they were Reoviridae, Herpesviridae, Poxviridae, Orthomyxoviridae, Retroviridae and Polyomaviridae. Seven phyla of fungi that were identified include Fonsecaea, Malassezia, Pleistophora, Rhodotorula, Cladophialophora, Cladosporium, and Glomeromycotan. A study found seven phyla of parasitic Hymenolepis, Centrocestus, Dipylidium, Prosthodendrium, Trichinella, Contraecaecum and Toxocara. The majority of studies (17 studies) proved that oral microbiota composition were statistically significant differences compare to healthy control. However, three studies found no statistically significant differences. A summary of the oral microbiota composition and diversity identified in oral cancer patients compared to healthy controls can be seen in Table 1.

Table 1. Summary of oral microbiota identified in oral cancer patients.

Authors	Country	Sample	Type of Study	Methods	Oral Microbiota in Oral Cancer Patients	Oral Microbiota in Healthy Controls	Results
Zixuan Li et al. (2021)	China	10 oral squamous cell carcinoma (OSCC), 10 healthy controls	Cross-sectional	16S rRNA gene sequencing	Bacteria: Bacteroidetes 24.02% Firmicutes 19.47% Actinobacteria 2.60% Proteobacteria 2.06%	Bacteria: Bacteroidetes 9.69% Firmicutes 39.82% Actinobacteria 6.98% Proteobacteria 4.56%	Statistically significant difference (p < 0.05)
Hezi Li et al. (2021)	China	33 OSCC, 35 healthy controls	Cross-sectional	16S rRNA gene sequencing	Bacteria: Firmicutes 34.0% Bacteroidetes 25.3% Proteobacteria 17.0% Fusobacteria 10.9%	Bacteria: Firmicutes 31.1% Bacteroidetes 24.9% Proteobacteria 20.1% Fusobacteria 10.3%	Statistically significant difference (p < 0.05)
Ling Zhang et al. (2020)	China	50 OSCC, 50 healthy controls	Cross-sectional	16S rRNA gene sequencing	Bacteria: Firmicutes 12.13% Bacteroidetes 17.85% Proteobacteria, 12.57% Fusobacteria 11.03% Actinobacteria 1.32%	Bacteria: Firmicutes 25.54% Bacteroidetes 11.99% Proteobacteria 12.55% Fusobacteria 3.29% Actinobacteria 3.73%	Statistically significant difference (p < 0.05)
Madhusmita Panda et al. (2020)	India	8 oropharyngeal (OP) and hypopharyngeal squamous cell carcinoma Patients (HP), 10 healthy controls	Cross-sectional	16S rRNA gene sequencing	Bacteria: Actinobacteria Bacteroidetes Proteobacteria Firmicutes Spirochaetes	Bacteria: Actinobacteria Bacteroidetes Proteobacteria Firmicutes Spirochaetes	Statistically significant difference (p < 0.05)

Yasuharu Takahashi et al. (2019)	Japan	60 OSCC, 80 healthy controls	Cross-sectional	16S rRNA gene sequencing	Bacteria: Bacteroidetes 0.87% Firmicutes 1.31% Proteobacteria 1.54%	Bacteria: Bacteroidetes 0.81% Firmicutes 0.98% Proteobacteria 1.40%	Statistically significant difference (p < 0.05)
Jenn-Ren Hsiao et al. (2018)	Taiwan	138 OSCC, 151 healthy controls	Cross-sectional	16S rRNA gene sequencing	Bacteria: Bacteroides 1.20% Fusobacterium 1.05%	Bacteria: Bacteroides 0.49% Fusobacterium 0.57%	Statistically significant difference (p < 0.05)
Chia-Yu Yang et al. (2018)	Taiwan	197 OSCC, 51 healthy controls	Cross-sectional	16S rRNA Gene sequencing	Bacteria: Firmicutes 59.76% Proteobacteria 35.57% Actinobacteria 11.56% Bacteroidetes 8.39% Fusobacteria 7.92%	Bacteria: Firmicutes 58.40% Proteobacteria 23,22% Actinobacteria 8.36% Bacteroidetes 5.65% Fusobacteria 2.98%	Statistically significant difference (p < 0.0001)
Susan Yost et al. (2018)	USA	4 OSCC, 4 healthy controls	Cohort	16S rRNA gene sequencing	Bacteria: Fusobacteria Firmicutes Bacteroidetes	Bacteria: Firmicutes Proteobacteria	Statistically significant difference (p < 0.05)
Yenkai Lim et al. (2018)	Australia	11 OCC and OPC, 10 healthy controls	Cohort	16S rRNA gene sequencing	Bacteria: Firmicutes Proteobacteria Actinobacteria Bacteroidetes Fusobacteria	Bacteria: Firmicutes Proteobacteria Actinobacteria Bacteroidetes Fusobacteria	Statistically significant difference (p < 0.01)
M. Perera et al. (2018)	Australia	25 OSCC, 27 healthy controls	Cohort	16S rRNA gene sequencing	Bacteria: Firmicutes 37% Proteobacteria 20% Bacteroidetes 15% Fusobacteria 17% Actinobacteria 11%	Bacteria: Firmicutes 41% Proteobacteria 19% Bacteroidetes 9% Fusobacteria 13% Actinobacteria 11%	Not statistically significant difference (p > 0.05)
Zhao H et al. (2017)	China	80 OSCC, 80 healthy controls	Cross-sectional	16S rRNA gene sequencing	Bacteria: Bacteroidetes 37.6% Proteobacteria Firmicutes Fusobacteria Actinobacteria	Bacteria: Bacteroidetes Proteobacteria Firmicutes Fusobacteria Actinobacteria	Statistically significant difference (p < 0.05)
Nezar Noor Al-Hebshi et al. (2017)	Saudi Arabia	20 OSCC, 20 healthy controls	Cross-sectional	16S rRNA gene sequencing	Bacteria: Fusobacteria 30% Proteobacteria 28% Bacteroidetes 19% Firmicutes 17% Actinobacteria 6%	Bacteria: Fusobacteria 20% Proteobacteria 19% Bacteroidetes 21% Firmicutes 24% Actinobacteria 16%	Statistically significant difference (p < 0.01)
Wei-Hsiang Lee et al. (2017)	Taiwan	125 OSCC, 127 healthy controls	Cross-sectional	16S ribosomal DNA (rDNA) sequencing	Bacteria: Firmicutes Bacteroidetes, Proteobacteria, Actinobacteria, Fusobacteria.	Bacteria: Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, Fusobacteria.	Statistically significant difference (p < 0.01)

Axel Wolf et al. (2017)	Austria	11 OSCC, 11 healthy controls	Cross-sectional	16S rRNA gene sequencing	Bacteria: Firmicutes 48% Bacteroidetes 17% Actinobacteria 15% Proteobacteria 12% Fusobacteria 5%	Bacteria: Firmicutes Bacteroidetes Actinobacteria Proteobacteria Fusobacteria	Statistically significant difference (p < 0.05)
Abdrzak Amer et al. (2017)	Ireland	36 OSCC, 36 healthy controls	Cross-sectional	16S rRNA gene sequencing	Bacteria: Bacteroidetes Proteobacteria Fusobacteria Firmicutes	Bacteria: Bacteroidetes Proteobacteria Fusobacteria Firmicutes	Statistically significant difference (p < 0.007).
Sagarika Banerjee et al. (2017)	USA	100 OSCC, 20 healthy controls	Cross-sectional	16S rRNA gene sequencing	Bacteria: Proteobacteria 41% Firmicutes 35% Actinobacteria 31% Bacteroides 27% Virus: Reoviridae, Herpesviridae, Poxviridae, Orthomyxoviridae, Retroviridae and Polyomaviridae. Fungi: Fonsecaea, Malassezia, Pleistophora, Rhodotorula, Cladophialophora and Cladosporium. Parasites: Hymenolepis, Centrocestus, Dipylidium, Prosthodendrium, Trichinella, Contraecaecum and Toxocara	Bacteria: Proteobacteria 25% Firmicutes 24% Actinobacteria 36% Bacteroides 5% Virus: Reoviridae, Herpesviridae, Poxviridae, Orthomyxoviridae, Retroviridae and Polyomaviridae. Fungi: Fonsecaea, Malassezia, Pleistophora, Rhodotorula, Cladophialophora and Cladosporium. Parasites: Hymenolepis, Centrocestus, Dipylidium, Prosthodendrium, Trichinella, Contraecaecum and Toxocara	Statistically significant difference (p < 0.05)
Pranab K. Mukherjee et al. (2017)	USA	39 OSCC, 39 healthy controls	Cross-sectional	16S rRNA gene sequencing	Bacteria: Firmicutes 48% Actinobacteria 20% Fungi: Glomeromycota 2.2%	Bacteria: Firmicutes 40% Actinobacteria 11%, Fungi: Glomeromycota 2.7%,	Not statistically significant difference (p > 0.05)
Daniela Börnigen et al. (2017)	USA	121 Oral Cancer, 242 healthy controls	Cohort	16S rRNA gene sequencing	Bacteria: Firmicutes Actinobacteria Bacteroidetes	Bacteria: Firmicutes Actinobacteria Bacteroidetes	Statistically significant difference (p < 0.01)
Rafael Guerrero-Preston et al. (2017)	USA	17 HNSCC, 25 healthy controls	Cohort	16S rRNA gene sequencing	Bacteria: Firmicutes, Proteobacteria, Bacteroidetes, Fusobacteria, Actinobacteria	Bacteria: Firmicutes, Proteobacteria, Bacteroidetes, Fusobacteria, Actinobacteria	Statistically significant difference (p < 0.05)
Rafael Guerrero-Preston et al. (2016)	USA	25 OSCC, 25 healthy controls	Cohort	16S rRNA gene sequencing	Bacteria: Firmicutes 67% Bacteroidetes 13.4% Proteobacteria 10.24%	Bacteria: Firmicutes 47.1% Bacteroidetes 21.2% Proteobacteria 22.7%	Statistically significant difference (p < 0.05)

DISCUSSION

The oral cavity host complex communities of microbial, called oral microbiota, are comprised of a wide variety of bacteria, fungi, viruses, archaea, and protozoa.^{11,32} The oral microbiota has a symbiotic relationship with the host. The oral microbiota contributes to critical metabolic, physiological, and immunological functions.³³ Disruption in the symbiotic microbiota compositions (dysbiosis) can have significant consequences on the development of oral health and disease.^{34–36} Oral dysbiosis, a shift in the oral microbiota composition, can be predisposed by many factors. Poor oral hygiene is a major factor cause of dysbiosis of oral microbiota. Poor oral hygiene is frequently seen in oral cancer patients and potentially oral dysbiosis leads to the emergence of potential pathogens that can promote the progression of oral cancers. Other factors such as inflammation of gingival/periodontal, genetic variation, salivary dysfunction, dietary habits, and smoking can also lead to oral dysbiosis.^{35–37}

This review identified the various oral microbiota among oral cancer patients. The three major phyla (Firmicutes, Bacteroidetes, and Proteobacteria) were the most prevalent bacterial found in oral cancer patients. The high levels of bacteria have been known to be related to infection and inflammation in the oral cavity. Accordingly, the mechanisms of how bacteria may contribute in carcinogenesis of oral cancer are by chronic inflammation induction and carcinogenic bacterial metabolites production.³⁸ A prior study reported that the microecological composition of bacteria in saliva was different from the tumor site. Firmicutes were predominant in saliva of oral cancer patients followed by Bacteroidetes, while Proteobacteria were found more in tumor site followed by Bacteroidetes, Firmicutes, and others such as Fusobacteria and Actinobacteria. Based on the location of OSCC, both phyla Bacteroidetes and Fusobacteria were more found at the site of the tongue, while Firmicutes was detected more in gingiva and Proteobacteria in oropharynges. The bacteria composition was also different in the various stages of OSCC. Bacteroidetes and Fusobacteria were more found in the early stage, while Firmicutes and Proteobacteria were more identified in the late stage.³⁹

In addition to bacteria, fungi were also detected in two studies with different results. It is well known that fungi are a small part of the oral microbiota; however, these opportunistic pathogens have been linked to carcinogenesis.^{40,41} *Candida albicans* (*C. albicans*) is well-known as the predominant species in the oral cavity and involved in oral cancer development. The mechanisms by which *C. albicans* may initiate or promote oral carcinogenesis are still not well-established. However, it has been suggested that it can occur through several mechanisms. First, it was proposed that *C. albicans* produce carcinogenic substances such as acetaldehyde that promote DNA damage-induced apoptosis and contribute

to carcinogenesis. The production of endogenous nitrosamines through hyphal invasion may also induce *C. albicans* in the development of oral cancer. Second, candidalysin secreted during the infection by *Candida* is able to cause epithelial damage and immune activation via mitogen-activated protein kinase (MAPK) signaling pathways. Third, *C. albicans* infection could enhance the production of several inflammatory cytokines. These immune responses may affect metabolic pathways and promote oral cancer development. Fourth, reducing the antimicrobial peptide β -defensin caused by chronic cigarette smoking and heavy alcohol consumption may also be associated with the development of oral cancer. Human β -defensin is a broad spectrum of antimicrobial activity that also has an important component of innate host defense against microbial colonization. Fifth, the influence of *Candida* infection on the tumor suppressor gene p53, cell proliferation nuclear antigen Ki-67, and (COX-2) expression that is related to malignant transformation through the upregulation of inflammatory and epithelial proliferation.^{40,42–44} These possible mechanisms may provide our understanding of the oral cancer development associated with fungal dysbiosis.

The viruses and parasites in the oral cavity among oral cancer patients were found only in a study conducted by Banerjee et al. (2017). Several viruses have been strongly associated with oral cancer, particularly Papilloma Virus (HPV), and other viruses include herpes simplex virus (HSV), Epstein-Barr virus (EBV), and Hepatitis C virus (HCV). The possible mechanisms by which viruses are responsible for the development of oral cancer are through both direct mechanism (genomic instability, increased cell proliferation, altered cell and tissue differentiation, apoptosis resistance, accumulation of DNA damage and defect), and indirect mechanism (through immunosuppression, chronic inflammation, or chronic antigenic stimulation).^{45–47} Unlike bacteria and viruses, there are few studies showing an association between parasites and oral cancer. Similar mechanisms has been suggested to underlie parasite infections in modulating carcinogenesis, including the modulation of immune system, genomic instability and mutation, insufficient proliferation, chronic inflammation, stimulation of angiogenesis, deregulation of apoptosis, and activation of cancer invasion and metastasis.⁴⁸ However, future studies are needed to confirm the association between parasites and oral cancer.

The different results obtained on the oral microbiota composition and diversity may be related to different types of samples used and different sample collection methods. However, the present review showed that the majority of studies proved that the oral microbiota in cancer patients were statistically significant difference compared to healthy controls. The findings suggest that the oral microbiota may undergo distortions that lead to imbalance and promote the development and progression of cancer. The effect of oral dysbiosis in the etiopathogenesis of oral cancers has not been completely elucidated.⁴⁹ Recently, four possible

mechanisms of oral microbiota dysbiosis have been found to contribute to the etiopathogenesis of oral cancer as proposed by La Rosa et al. (2020), including (1) stimulate chronic inflammatory responses; (2) genetic damage in oral mucosa epithelial cells induced by oxygen and nitrogen reactive species, also oncogenic metabolites produced by bacteria; (3) changes in the integrity of epithelial barrier that can lead to irreversible damage of genomic DNA; and (4) epigenetic alterations.⁵⁰ It has also been elucidated another mechanism in the process of carcinogenesis called a tightly interdependent triangle; they are dysbiosis of microbiota, dysfunction of epithelial barrier, and dysregulation of immune responses/inflammation.⁵¹

This study has a limitation. Assessment of the quality of studies is beyond scoping review parameters; therefore, we couldn't assess the quality of each study included in this review. However, the present review provides a comprehensive map of the studies on the oral microbiota composition and diversity. The significant differences in the composition of the oral microbiota between oral cancer patients and healthy individuals may emerge the potential of oral microbiota as potential biomarkers associated with the progression of the cancer and therapeutic target in the management of the disease. Identification of the oral microbiota allows the diagnosis of oral cancer to be possible and even allows early treatment intervention to occur before the onset of oral cancer.

In conclusion, the majority of studies in this review showed various oral bacteria in oral cancer patients (dominated by Firmicutes, Bacteroidetes, Proteobacteria, and Fusobacteria), and statistical analysis revealed significant differences compared to healthy controls. This study indicates the need for more research to evaluate viruses and parasites composition and diversity in oral cancer patients. Moreover, future research should focus to determine whether the changes of oral microbial composition as a community may contribute to oral cancer development and progression.

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