

The oral cavity microbiota: between health, oral disease, and cancers of the aerodigestive tract

Pierre Le Bars, Sébastien Matamoros, Emmanuel Montassier, Françoise Le Vacon, Gilles Potel, Assem Soueidan, Fabienne Jordana, and Marie-France de La Cochetière

Abstract: Many studies show that the human microbiome plays a critical role in the chronic pathologies of obesity, inflammatory bowel diseases, and diabetes. More recently, the interaction between cancer and the microbiome has been highlighted. Most studies have focused on the gut microbiota because it represents the most extensive bacterial community, and the body of evidence correlating it with gut syndromes is increasing. However, in the strict sense, the gastrointestinal (GI) tract begins in the oral cavity, and special attention should be paid to the specific flora of this cavity. This study reviewed the current knowledge about the various microbial ecosystems of the upper part of the GI tract and discussed their potential link to carcinogenesis. The overall composition of the microbial communities, as well as the presence or absence of “key species”, in relation to carcinogenesis is addressed. Alterations in the oral microbiota can potentially be used to predict the risk of cancer. Molecular advances and the further monitoring of the microbiota will increase our understanding of the role of the microbiota in carcinogenesis and open new perspectives for future therapeutic and prophylactic modalities.

Key words: upper aerodigestive, microbiome, oral cavity, carcinogenesis.

Résumé : Plusieurs études montrent que le microbiome humain joue un rôle essentiel dans les pathologies chroniques que sont l'obésité, les maladies inflammatoires de l'intestin et le diabète. Plus récemment, l'interaction entre le cancer et le microbiome a été soulignée. La plupart des études se sont concentrées sur le microbiote intestinal car il représente la communauté bactérienne la plus étendue, et l'ensemble des preuves le corrélant avec les syndromes de l'intestin est en croissance. Cependant, au sens strict, le tractus gastro-intestinal (GI) commence dans la cavité orale et une attention spéciale devrait être portée à la flore spécifique de cette cavité. Cette étude fait la synthèse des connaissances actuelles relatives à divers écosystèmes microbiens de la partie supérieure du tractus GI et discute de leur lien potentiel à la carcinogenèse. La composition globale des communautés microbiennes, de même que la présence ou l'absence « d'espèces clés » relativement à la carcinogenèse sont soulevées. Des modifications du microbiote oral peuvent potentiellement être utilisées pour prédire les risques de cancer. Les percées moléculaires et la surveillance accrue du microbiote accroîtront notre compréhension du rôle du microbiote dans la carcinogenèse et ouvriront de nouvelles perspectives en vue de modalités thérapeutiques et prophylactiques futures. [Traduit par la Rédaction]

Mots-clés : voie aérodigestives supérieures, microbiome, cavité orale, carcinogenèse.

Introduction

Every year there are 12.7 million new cancer cases worldwide, and an estimated 16.1% are linked to infections. Approximately 15%–20% of human tumors are initiated by inflammation-driven processes (Francescone et al. 2014).

The gastrointestinal (GI) tract can be considered not only a pipeline system from the oral cavity to the anus but also an entry point for nutrients and a point of contact between the immune system and the environment. Various microenvironments are scattered along this tract, each having a specific ecosystem with its own microbiome.

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P. Le Bars, A. Soueidan, and F. Jordana.* UFR d'odontologie, UIC Odontologie, CHU hôtel-Dieu, Université de Nantes, 1, place Alexis Ricordeau, B.P. 84215, 44042 Nantes CEDEX 1, France.

S. Matamoros. Walloon Excellence in Life Sciences and Biotechnology, Louvain Drug Research Institute, Metabolism and Nutrition Research Group, Louvain Drug Research Institute, Université catholique de Louvain, 1, place de l'Université, 1348 Brussels, Belgium.

E. Montassier, G. Potel, and M.-F. de La Cochetière.* EA 3826 Thérapeutiques cliniques et expérimentales des infections, Faculté de médecine, CHU hôtel-Dieu, Université de Nantes, 1, rue G. Veil, 44000 Nantes, France.

F. Le Vacon. Biofortis Innovation Services – Mérieux NutriSciences, 3, route de la Chatterie, 44800 Saint-Herblain, France.

Corresponding author: Assem Soueidan (email: assem.soueidan@univ-nantes.fr).

*Co-last authors.

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The term “gut microbiota” refers to the trillions of microorganisms residing in the intestine. A microbiota can be classified as a planktonic microbiota or a biofilm microbiota. The GI tract is integrated into multiple physiological processes of the host (Haiser and Turnbaugh 2012). The microbial communities of the oral cavity are among the most diverse in the body. The passageways between the oral and nasal cavities and between the oropharynx and nasopharynx are apparent (Bassis et al. 2015). It is possible for bacteria to enter the bloodstream, for example, from periodontitis, untreated carious lesions, or wound healing. Members of the human microbiota community play an active role in carcinogenesis through DNA damage (as is the case with *Escherichia coli*) (Su et al. 2015) and chronic infection (as is the case with *Helicobacter pylori*) (Kipanyula et al. 2013).

To understand the correlation between the human microbiota and health or disease, many sites (such as the skin, mouth, and gut) must be considered. The classical Pasteurian concept of a single microbe causing an infection in a previously sterile tissue is challenged by the demonstration of interrelationships between the host and the microbiota, which can lead to pathogenesis under particular circumstances (Rogers et al. 2013). The diversity of microorganisms involved in these interactions requires a new way of looking at the microbial ecosystem as a whole (Lozupone et al. 2012). Microarray studies (Yu et al. 2014) are proposed to investigate the interactions between the oral microbiome, host proteins, and host cells. Many parameters, such as metabolic interactions and the essential genes of pathogens or commensal communities, are well known and keys to understanding the balance between health and disease (Wade 2013).

We performed a literature search for articles published in PubMed/MEDLINE between 2000 and 2016 using the following keywords: “upper aero digestive”, “microbiome”, “oral cavity”, and “carcinogenesis”. Combinations of the keywords were also used. Article titles and abstracts were examined to exclude irrelevant articles and articles that had already been identified. Finally, additional articles were obtained from a review of the references in selected articles. One hundred and forty-four articles formed the basis of narrative review.

After a brief review of general and major oral diseases, this review aimed to evaluate the impact of the upper aerodigestive tract-specific microbiome on carcinogenesis (Table 1).

The human upper aerodigestive tract microbiota: a complex system

The human microbiota is considered to be a complex system of microorganisms with a metabolic potential rivaling that of the liver (Table 2). The human upper aerodigestive tract (HUAT) is a transition zone that is constantly exposed to both inhaled and ingested microbes from the upper and lower respiratory tracts, as well as to

those contained in the saliva. The HUAT can be divided into 4 areas, which are described below.

(i) The microbiota of the nasal cavity, sinuses, nostrils, and nose

The nares are often colonized predominantly with *Staphylococcus epidermidis*, *Staphylococcus aureus* (20% of the general population), and *Corynebacteriaceae*. *Staphylococcus aureus* is an opportunistic pathogen that maintains a unique, complex relationship with the host immune system (Mulcahy and McLoughlin 2016). The paranasal sinuses are sterile under physiologic conditions (Cho and Blaser 2012). The nasal cavity bacterial communities are dominated by *Actinobacteria*, *Firmicutes*, and *Proteobacteria* (Bassis et al. 2014).

(ii) The microbiota of the nasopharynx

Many bacterial species colonize the nasopharynx (the upper respiratory tract) in a niche-specific manner at discrete anatomical sites (Bogaert et al. 2011). *Staphylococcus aureus* persistently colonizes the anterior nares of approximately one-fifth of the population and maintains a unique, complex relationship with the host immune system. *Streptococcus pneumoniae* is another opportunistic pathogen that inhabits the nasopharyngeal environment (Mulcahy and McLoughlin 2016).

(iii) The microbiota of the oropharynx behind the mouth

The microbiota of the human oral cavity is distinct from that of the colon and stool habitats. The culturable bacterial microbiota of the saliva is dominated by the *Streptococcus*, *Prevotella*, and *Veillonella* genera, which comprise 70% of this microbiota (Nasidze et al. 2009).

The total surface area of the mouth cavity is about 214.7 ± 12.9 cm², and there is no significant difference due to gender in this regard. The teeth, keratinized epithelium, and nonkeratinized epithelium occupy about 20%, 50%, and 30% of the total surface area, respectively (Collins and Dawes 1987). The mouth cavity includes the inner cheeks, hard and soft palates, and tongue, with its connections to the pharynx. Each of these surfaces, along with the saliva and gingival crevices, contain their own microenvironments and harbor site-specific microbiota (Wilson and Nussey 2010).

Another similarity exists between the oropharynx and saliva in relation to *Firmicutes*, *Proteobacteria*, and *Bacteroides*: each site is numerically dominated by distinct families within this phylum.

(iv) The microbiota of the laryngopharynx

The pharynx is normally colonized by members of the *Streptococcaceae* family, but it is sometimes colonized by the pathogens *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Neisseria meningitidis*. The distinction between these 4 areas is purely anatomic. With regard to the human microbiota, communication

Table 1. Epidemiologic studies of the HUAT microbiome and cancer showing principal results.

Author	Cancer localisation	No. of patients	Technique	Results	Oral hygiene	Biomarkers
Michaud et al. 2013	Pancreatic cancers	405	Plasma antibody detection against 25 oral bacteria	Periodontal pathogens are associated with higher risk for pancreatic cancer	Periodontal disease	Very high correlations were observed for the 2 strains of <i>P. gingivalis</i> and <i>A. actinomycetemcomitans</i>
Yu et al. 2014	Esophageal squamous dysplasia precursor lesion of carcinoma	333	HOMIM	Lower microbial richness in HUAT	Poor oral health	ND
Chen et al. 2015	ESCC	171	454 pyrosequencing of oral microbiota of saliva	Comparison between salivary bacterial microbiota and ESCC	Poor oral health	Decreased carriage of genera <i>Lautropia</i> , <i>Bulleidia</i> , <i>Catonella</i> , <i>Corynebacterium</i> , <i>Moryella</i> , <i>Peptococcus</i> , and <i>Cardiobacterium</i> in ESCC subjects compared with non-ESCC subjects
Mima et al. 2015	Colorectal carcinoma	598	qPCR for <i>F. nucleatum</i>	Associations of the amount of <i>F. nucleatum</i> with T-cell densities in tumor tissue	ND	Lower density of T cells in tumor tissue
Fan et al. 2016	Pancreatic cancer	361	Bacterial 16S rRNA gene sequencing	Oral microbiota may play a role in the aetiology of pancreatic cancer	Periodontal disease	Higher risk with <i>P. gingivalis</i> , <i>A. actinomycetemcomitans</i> ; decreased cancer risk with phylum <i>Fusobacteria</i> and genus <i>Leptotrichia</i>
Mitsuhashi et al. 2015	Pancreatic cancers	302	DNA extraction and qPCR for <i>Fusobacterium</i> species	Tumor <i>Fusobacterium</i> status was not associated with any clinical and molecular features	ND	<i>Fusobacterium</i> species are a promising biomarker of pancreatic cancer
Yan et al. 2015	Lung cancer	20	Salivary microbiota qPCR	Association of saliva microbiota with lung cancer	ND	<i>Capnocytophaga</i> and <i>Veillonella</i> were significantly higher in saliva from lung cancer patients
Guerrero-Preston et al. 2016	HNSCC	787	Saliva microbiota (16S rRNA metagenomic sequencing)	Microbiota associated with oral cancer and human papilloma virus infection	ND	HNSCC saliva samples associated with increase in <i>Lactobacillus</i> and <i>Streptococcus</i> and a decrease in <i>Haemophilus</i> , <i>Neisseria</i> , <i>Gemellaceae</i> , and <i>Aggregatibacter</i>
Momen-Heravi et al. 2014	OSCC	34	qPCR	Endogenous control miRNA are discriminatory in OSCC patients	ND	miRNA profiles in OSCC patients and healthy controls were distinctively different
Nosho et al. 2016	Colorectal carcinomas	551	Metagenomic analyses	Association of <i>Fusobacterium</i> with T cells and miRNA expression	ND	<i>F. nucleatum</i> possesses immunosuppressive activities by inhibiting human T-cell responses

Note: HUAT, human upper aerodigestive tract; HOMIM, human oral microbe identification microarray; ESCC, esophageal squamous cell carcinoma; qPCR, quantitative polymerase chain reaction; HNSCC, head and neck squamous cell carcinoma; OSCC, oral squamous cell carcinoma; miRNA, microRNA; ND, not determined; *P. gingivalis*, *Porphyromonas gingivalis*; *F. nucleatum*, *Fusobacterium nucleatum*; *A. actinomycetemcomitans*, *Aggregatibacter actinomycetemcomitans*.

Table 2. Comparative dominant microbiota of different human sites (Ahn et al. 2012; Costello et al. 2009; Kim et al. 2009; Lemon et al. 2010; Nasidze et al. 2009; Takahashi 2015).

Skin	Nostril	Oro-pharynx	Mouth	Gastrointestinal tract, gut	Vagina	Saliva	All
<i>Actinobacteria</i> (44.7%) <i>Firmicutes</i> (30.3%) <i>Proteobacteria</i> (11.6%) <i>Bacteroidetes</i> (3.0%) <i>Cyanobacteria</i> (10.5%) — Other	<i>Actinobacteria</i> (47.9%–70.7%) <i>Firmicutes</i> (23.7%–37.2%) <i>Proteobacteria</i> (2.9%–9.6%) <i>Bacteroidetes</i> (1.1%–1.6%) <i>Cyanobacteria</i> (5) <i>Fusobacteria</i> (0.1%) Other	<i>Actinobacteria</i> (7.3%) <i>Firmicutes</i> (52.3%) <i>Proteobacteria</i> (19.7%) <i>Bacteroidetes</i> (15.6%) — <i>Fusobacteria</i> (5.0%) Other	<i>Actinobacteria</i> (7.3%) <i>Firmicutes</i> (52.3%) <i>Proteobacteria</i> (19.7%) <i>Bacteroidetes</i> (15.6%) <i>Cyanobacteria</i> (0.01%) <i>Fusobacteria</i> (5.0%) Other (0.08%)	<i>Firmicutes</i> (35.1%) <i>Proteobacteria</i> (4.9%) <i>Bacteroidetes</i> (59.9%) — — Other	<i>Actinobacteria</i> (14.6%) <i>Firmicutes</i> (60.0%) <i>Proteobacteria</i> (20.6%) <i>Bacteroidetes</i> (1.2%) — <i>Fusobacteria</i> (3.6%) Other	<i>Actinobacteria</i> (7%) <i>Firmicutes</i> (37.8%) <i>Proteobacteria</i> (28.0%) <i>Bacteroidetes</i> (20.0%) — — Other (7.2%)	<i>Actinobacteria</i> (36.7%) <i>Firmicutes</i> (34.0%) <i>Proteobacteria</i> (11.7%) <i>Bacteroidetes</i> (8.5%) <i>Cyanobacteria</i> (7.5%) <i>Fusobacteria</i> (1.0%) Other

and balance exist between various human body niches. Each anatomical site is colonized by a niche-specific microbiota, with a distinct phylum-level distribution. Interpersonal variation exists in the composition of the microbiome community (Flores et al. 2014).

Oral microbiota investigations using next-generation sequencing

We have several ways of studying the oral microbiota. Culture-independent techniques, such as pyrosequencing (Roche 454) and sequencing by synthesis (Illumina), have recently emerged as the methods of choice for the analysis of these complex ecosystems. They are of great value for the investigation of the oral microbiota, which include many microorganism species, some of which are very difficult to culture (Wade 2013). Sequencing of the 16S rRNA gene has shown differences in oral microbiota diversity and composition between patients suffering from oral cavity squamous cell carcinoma and healthy controls (Guerrero-Preston et al. 2016). Similarly, the presence of the pathogens *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* in the oral microbiota was associated with an elevated risk of pancreatic cancer (Fan et al. 2016). It is noteworthy that 16S rRNA sequencing only determines the presence or abundance of bacterial species and thus only allows researchers to draw observational conclusions. Shotgun metagenomic sequencing will also reveal the associated metabolic pathways (F. Zhang et al. 2015), which may shed light on the causal relationship between the HUAT microbiota and carcinogenesis. However, to our knowledge, this is not yet the case.

Factors influencing the stability of the HUAT microbiota

Aging

The human microbiota has evolved over hundreds of thousands of years of microbe–human symbiosis. Several years ago it was shown that the mouth microbiota evolves with age. Colonization begins at birth (Prince et al. 2014) when dynamic microbial colonization of the oral cavity begins (Nelson-Filho et al. 2013). The profile of the predominant phylum evolves during childhood and youth and has almost stabilized by adulthood (Human Microbiome Project Consortium 2012). Nevertheless, in young children, the nasopharyngeal microbiota varies seasonally.

The teeth are colonized by *Streptococcus mutans* and *Streptococcus sanguinis* when they first appear. Some species of *Streptococcaceae* adhere well to the gingival mucosa and cheeks but not to the hard tissues. The structure of the gingival mucosa promotes anaerobic species. The complexity of the oral microbiota increases with age. Around puberty, colonization with *Bacteroidetes* and *Spirochetes* begins (Aas et al. 2005). Additionally, age and pathological conditions may quantitatively modify the microbiota.

For example, the age-related increase in the abundance of *Streptococcus anginosus* in the saliva may be carefully controlled because of its known relationship with diseases such as cancer (Morita et al. 2004).

Location

The human microbiota differs significantly based on anatomical location (Mark Welch et al. 2014). The human GI tract harbors a vast number of microbes, but its microbial diversity at the phylum level is more limited than that of the oral cavity (Park et al. 2015). In the oral cavity, at least 15 phyla have been detected, with the most predominant being *Fusobacteria*, *Actinobacteria*, *Proteobacteria*, *Bacteroidetes*, and *Spirochaeta* (Nadell et al. 2009; Rogers et al. 2013). Most sites are dominated by the *Streptococcus* genus, which is followed in abundance by *Haemophilus* spp. in the buccal mucosa, *Actinomyces* spp. in the supragingival plaque, and *Prevotella* spp. in the subgingival plaque (Cho and Blaser 2012). In contrast, the GI tract microbiota is composed primarily of the *Bacteroidetes* and *Firmicutes* phyla, as well as minor constituents such as *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia* (Lozupone et al. 2012).

Environment

The oral microbial composition is capable of affecting the balance of the oral cavity; the interactions between the resident flora depend on local environmental changes and the host's diet. The presence of nutritious flakes of epithelium and secretions makes the oral cavity a highly favorable environment for various bacteria.

The commensal resident flora, including planktonic bacteria, a product of many microorganisms, and the rests of the apoptotic eukaryotic cells. This flora occupies hard and mucous surface and thus prevent the establishment of exogenous microorganisms. Temperature (33–37 °C), smoking, alcohol use, pH (which is neutral on the tongue and mucosal surfaces and alkaline in gingival crevices), redox potential (which is positive in the major oral sites and negative in gingival crevices), atmospheric pressure, and light affect microbiota composition. It appears that the oral microbiota significantly contributes to the host's immunity because it maintains low levels of antibodies in the saliva and participates in the synthesis of vitamins.

The HUAT microbiota and oral diseases

The oral microbiota is associated with numerous oral diseases. However, in most cases, only correlations or associations, not causality, have been demonstrated. The major infectious pathologies of the buccal tissue (decays, gingivitis, and periodontitis) are all polymicrobial in nature.

Dental procedures can result in the inoculation of microbial germs from the microbiota of the mouth into the bloodstream. Young and Young (2005) isolated Group B

Streptococcus and *Peptostreptococcus* from tumor and peritumoral white matter tissues.

The association between periodontitis and the oral microbiota has been extensively studied for several decades. Although the original culture-based descriptions of the oral microbiota were highly valuable in implicating bacterial species as etiological agents of periodontitis, culture-independent methods, such as polymerase chain reaction (PCR) amplification, have facilitated a much deeper and insightful understanding of these populations' dynamics. More recently, the phylogeny and diversity of the oral microbiota were characterized at an unprecedented level using high-throughput sequencing (Keijser et al. 2008).

To understand the role of infectious bacterial assemblages in periodontitis pathogenesis, it is essential to consider the interrelationships among the selected niche, the microbiota composition, and the host. These relationships modify the pathologies of oral diseases, and gaining insight into them requires time.

The archaea are different from other microorganisms. Archaea are present in dental calculus; this dietary residue consists of harmless organisms and pathogens associated with local and systemic infections (Huynh et al. 2016). Recently, studies have revealed the structure, role, and genetic composition of the Archaea. It is known that they may be involved in the onset of disease, although not directly. The methanogens (*Methanobrevibacter smithii*, *Methanobrevibacter oralis*, and *Methanosphaera stadtmanae*), the only archaea identified in humans, appear to aid in the development of bacteria that play direct roles in pathogenesis. Members of this domain can colonize the intestine, oral cavity, and skin (Kanady et al. 2012). Archaea may affect oral health through interspecies hydrogen transfer and by favoring the growth of fermenting bacteria. For example, methanogens are often found in infected periodontal pockets and dental canals. *Methanobrevibacter oralis* has been found in periodontal pockets. Furthermore, methanogens and sulfate-reducing bacteria have been found in association with colorectal cancer (Horz and Conrads 2011). Finally, methanogens are able to transform heavy metals and metalloids (such as bismuth and amalgamated mercury) into methylated derivatives, which are more toxic (Zahnd et al. 2012). This transformation of heavy metals and metalloids in the oral cavity has not yet been investigated.

Periodontal diseases and poor plaque control in the biofilm are related to many general diseases

Periodontal disease, a form of chronic inflammation, affects more than 80% of human adults (Kim et al. 2013). It is a polymicrobial attack that destroys the periodontal ligament and supporting marrow that surrounds the teeth. The 3 main microbial pathogenic agents involved are known as the red complex (*Porphyromonas gingivalis*, *Tannerella forsythensis*, *Treponema denticola*). Other pathogens

involved in periodontal diseases include *Fusobacterium nucleatum*, *Prevotella intermedia*, and *Treponema socranskii* (Nasidze et al. 2009). *Porphyromonas gingivalis* is an anaerobic, Gram-negative bacillus (Love et al. 1992). It can invade eukaryotic cells via the action of several virulence mechanisms, such as adhesion to epithelial cells, the inhibition of the host's immune system (for example, by decreased phagocytosis and the inhibition of leukocytes and immunoglobulin proteases), the inhibition of anti-oxidative systems, and enhanced inflammation (Steffen et al. 2000). *Tannerella forsythensis*, previously known as *Bacteroides forsythus*, is a Gram-negative, strictly anaerobic bacterium that is frequently found in periodontal pockets (Sakamoto et al. 2002).

The HUAT microbiota and general disorders

Many correlations exist between oral infections and diseases. Among these, we can list generalized diseases, such as rheumatoid arthritis (Zheng et al. 2015), cardiovascular disease (Ordovas and Mooser 2006), and pulmonary diseases (Scannapieco and Genco 1999), as well as brain and liver abscesses (Wagner et al. 2006). Other such illnesses include gastrointestinal cancer (Meurman and Grönroos 2010), breast cancer (Laidi et al. 2016), cirrhosis (Bajaj et al. 2015), and diabetes (Maruyama et al. 2007; Deshpande et al. 2010; Farag and Gaballa 2011). More recently, links with pregnancy (Digiulio et al. 2015), the human immunodeficiency virus (HIV) (Kistler et al. 2015), and acquired immune deficiency syndrome (AIDS) have also been described (Zheng et al. 2015).

Among human pathogens of the *Spirochetes* order, Gram-negative bacteria are pathogenic factors for several human diseases, such as syphilis (*Treponema pallidum*), Lyme disease (*Borrelia burgdorferi*), and pinta (*Treponema carateum*). *Treponema denticola* is strictly anaerobic, rapidly motile, and has a great ability to adhere to host cells and tissues via certain proteins expressed on outer cell membranes and adhesions (Holt and Ebersole 2005).

Recently, it was shown that polymicrobial oral disease, if systematically distributed, favors various pathologies, such as bacteremia, pulmonary bacterial diseases, and preterm birth. For example, during dental hygiene procedures, wounds may be inoculated with oral streptococci, which can travel via the bloodstream and cause bacterial endocarditis. Patients with cardiovascular disease, numerous subgingival infections of *Porphyromonas gingivalis* and *Tannerella forsythia*, and modestly higher levels of anti-hHSP60 (anti-human heat shock protein 60) antibodies have been described (Leishman et al. 2012).

The HUAT microbiota and cancers

Patients with oral cancer often have inflammation and poor oral hygiene. Oral microbiota may play a role in carcinogenesis. Many clinical and epidemiological studies have suggested the existence of relationships between chronic inflammation and infectious diseases. Chronic inflammation is often studied in the context of the mech-

anisms at work behind the development of cancer. Specifically, pro-inflammatory cytokine interleukin-20 is involved in rheumatoid arthritis, atherosclerosis, osteoporosis, and oral cancer (Hsu et al. 2012). The mucosal microenvironment is a specific ecological niche. In this system, bacteria can genetically influence epithelial cells. In the saliva, poor dental status increases carcinogenic acetaldehyde production using ethanol (Homann et al. 2001). The imbalance of the microbiome, followed by translocation via blood circulation, is a major vector for disease progression. In the gut, at the mucosal level, microbial translocation can be explained by the following events, in order: mucosal CD4+ depletion, chronic inflammation, the alteration of the enterocytes in the epithelium, and penetration by microorganisms. The mechanism by which microbial translocation causes immune activation is still not well understood, although the authors have concluded that the translocation of periodontopathic bacteria occurs via lymphatic drainage (Amodini Rajakaruna et al. 2012).

Cancer and oral viruses

A majority of HIV-1 (human immunodeficiency virus) infections worldwide are acquired via mucosal surfaces. The oral transmission of HIV is dependent on the ability of the virus to efficiently cross from one host to the next by traversing mucosal membranes (Wood et al. 2013).

Human papillomaviruses (HPVs) have been found in various types of oral mucosal lesions and are linked to the risk of malignant lesions. Mucosal human papillomaviruses, mostly of the HPV-16 and HPV-18 genotypes, cause head and neck cancers (Kreimer et al. 2005). HPV-16 has been identified in cancers of the tongue.

HPV-16 has also been identified in nonsmokers, non-drinkers (Pintos et al. 2008), oropharyngeal squamous cell carcinoma patients, and specifically in young individuals (González-Ramírez et al. 2013). Lin et al. (2010) demonstrated the presence of HPV-11 during the malignant transformation of recurrent respiratory papillomatosis. However, the virus is rarely found in the saliva given a healthy oral mucosa. Many theories have proposed pathways for virus transmission, including perinatal transmission, manual contact, and sexual transmission by oral-genital contact (Stanko et al. 2013). Contradictory results have been shown in pediatric acute lymphoblastic leukemia with chemotherapy complications (such as oral mucositis). The presence of HSV and *Candida* spp. was found to be associated with mucositis in acute lymphoblastic leukemia, but no relationship was found between the number of bacterial colony-forming units and the intensity of oral mucositis. The type of chemotherapy used could explain these results (de Mendonça et al. 2012).

Gastric, pancreatic, and lung cancers and the oral microbiota (Table 3)

The upper aerodigestive tract is an area of high risk for multiple primary cancers. Periodontal diseases and tooth

Table 3. Associations between oral microbiome and carcinogenesis.

Reference	Study design	Cancer	Study population(s)	Population data			Main findings
				Age	Sex	Ethnic group or country	
Shiga et al. 2001	Evaluation of the diversity of bacteria in the saliva of subjects with OSCC	Oral squamous carcinoma head and neck cancer	4 subjects 3 subjects	—	—	Japan	Using 454 parallel DNA sequencing, 58 000 PCR amplicons that span the V4–V5 hypervariable region of rRNA from subjects; 15 unique phylotypes were present in all subjects
Narikiyo et al. 2004	Evaluation of bacterial diversity in saliva and in esophageal cancer	Esophageal cancer	20 esophageal cancers tissues	45–69 (mean 57)	—	Japan (Tokyo)	Three periodontitis bacteria (<i>T. denticola</i> , <i>S. mitis</i> and <i>S. anginosus</i>) are present in esophageal cancer causing inflammation and promoting carcinogenic process.
			20 healthy esophageal tissues			Japan	
			20 healthy patients for saliva			Japan	
			58 esophageal cancer tissue			Japan	PCR: 69% are positive for <i>S. anginosus</i> , 38% for <i>T. denticola</i>
			4 esophageal cancer tissue			China	PCR: 91% are positive for <i>S. anginosus</i> , 46% for <i>T. denticola</i>
			2 esophageal cancer			France	PCR: 100% are positive for <i>S. anginosus</i> , and 100% for <i>T. denticola</i>
Morita et al. 2004	Molecular analysis of age related changes of <i>S. anginosus</i> and <i>S. mitis</i> in saliva	Healthy patients (aging)	—	—	—	Japan	Increase in <i>S. anginosus</i> with age because of its association with diseases, including cancer
Sasaki et al. 2005	<i>S. anginosus</i> in oral cancer	Oral cancer	46 subjects (oral cancer) and 3 precancerous leukoplakia	—	—	Japan	Infection of <i>S. anginosus</i> could occur frequently in OSCC and that dental plaque could be a dominant reservoir of <i>S. anginosus</i>

Table 3 (concluded).

Reference	Study design	Cancer	Study population(s)	Population data			Main findings
				Age	Sex	Ethnic group or country	
Sixou et al. 2006	<i>Capnocytophaga</i> in the dental plaque of children with cancer	Lymphoma	31 children with cancer and 30 healthy control children	—	—	France	<i>Capnocytophaga</i> decreased in prevalence in the dental plaque of cancer patients during chemotherapy but became predominant in some cases
Souto and Colombo 2008	Detection of <i>H. pylori</i> in saliva	—	56 periodontally healthy subjects and 169 with chronic periodontitis	—	—	—	<i>H. pylori</i> was frequently detected in the oral microbiota of subjects with periodontitis
Söder et al. 2011	Periodontal disease and breast cancer	Breast	3273 subjects — 1676 were clinically orally examined, 1597 were not clinically examined	30–40	Women	Sweden	Chronic periodontal disease indicated by missing molars seemed to associate statistically with breast cancer
Wang and Li 2015 (a Review paper)	Infections that have been linked to pancreatic cancer	Pancreatic carcinogenesis	Review	—	—	China	<i>H. pylori</i> infection may be a risk factor for pancreatic cancer; chronic hepatitis virus and oral microbiota may also play a role in pancreatic carcinogenesis
Galvão-Moreira and da Cruz 2016 (a Review paper)	Relationship between the oral microbiome, periodontitis, and head and neck cancer	Head and neck cancer	Review	—	—	—	Evidence has implicated <i>P. gingivalis</i> and periodontitis in head and neck rates
Park et al. 2016	The risk factors and microbiological etiologies	Head and neck cancer (radical neck dissection)	370 patients		Male and female	South Korea	The most common pathogen was methicillin-resistant <i>S. aureus</i>

Note: OSCC, oral squamous cell carcinoma; *T. denticola*, *Treponema denticola*; *P. gingivalis*, *Porphyromonas gingivalis*; *H. pylori*, *Helicobacter pylori*; *S. anginosus*, *Streptococcus anginosus*; *S. mitis*, *Streptococcus mitis*; *S. aureus*, *Staphylococcus aureus*.

loss conditions caused by oral bacteria greatly contribute to this risk (Meyer et al. 2008; Chen et al. 2017). Chronic inflammation, in the presence of alcohol and tobacco, is an established risk factor for upper aerodigestive cancer. The microorganisms that compose the oral microbiota greatly differ in abundance, and some have been associated with oral cancer.

Some bacteria (*Streptococcus* and *Treponema*) have been linked to various kinds of head and neck cancers (Narikiyo et al. 2004; Shiga et al. 2011). Dental plaque seems to be a reservoir of these pathogens (Sasaki et al. 2005). Several studies based on the pyrosequencing analysis of 16S rRNA genes from the bacterial communities of cancer patients and healthy subjects showed significant differences in their microbiota profiles (Gong et al. 2013; Guerrero-Preston et al. 2016; Hu et al. 2016). The levels of the *Streptococcus*, *Fusobacterium*, *Abiotrophia*, *Haemophilus*, *Prevotella*, *Tannerella*, *Aggregatibacter*, *Leptotrichia*, and *Neisseria* genera have been shown to vary between patients suffering from oral cancers and healthy controls (Gong et al. 2013; Guerrero-Preston et al. 2016; Hu et al. 2016). However, the results between studies are often contradictory, highlighting the need to improve knowledge about the causal relationship between tumor development and oral microbiota.

An association between periodontal diseases and serum albumin concentration was found in head and neck cancers (Maruyama et al. 2012). These results support the presence of an altered oral microbiota in cancer, although longitudinal studies are necessary to determine whether there is a causal relationship.

Typically, oral and esophageal cancers are concomitant with periodontal diseases (Galvão-Moreira and da Cruz 2016). The high salivary counts of *Capnocytophaga gingivalis*, *Prevotella melaninogenica*, *Streptococcus mitis*, and *Porphyromonas gingivalis* may be diagnostic indicators of oral squamous cell carcinoma (Galvão-Moreira and da Cruz 2016), and *Streptococcus mitis* is a biomarker for pancreatic cancer (Farrell et al. 2012). The percentage of gastric and pancreatic cancers associated with periodontal diseases seems to be low (Kim et al. 2009). Other types of cancers (e.g., lung, prostate, and hematological) appear to be less consistently associated with periodontal diseases, although the number of studies on this topic remains limited. Nevertheless, a positive link between periodontal diseases and some forms of cancer should be considered (Nugent 2010).

Gastric carcinoma

Several studies have explored the association between the oral microbiome and gastrointestinal cancers. Chen et al. (2015) analyzed the saliva samples of 87 patients with esophageal squamous cell carcinoma, 63 patients with dysplasia, and 85 healthy controls. Using 16S rRNA gene sequencing, they showed that patients diagnosed with esophageal squamous cell carcinoma exhibited significantly decreased microbial diversity as compared with healthy controls and dysplasia patients. Moreover,

taxonomic analyses revealed that patients with esophageal squamous cell carcinoma presented a significant decrease in *Lautropia*, *Bulleidia*, *Catonella*, *Corynebacterium*, *Moryella*, *Peptococcus*, and *Cardiobacterium* as compared with healthy controls and patients with dysplasia (Chen et al. 2015).

A small study evaluated the relationship between the salivary microbiota and pancreatic cancer. Farrell et al. (2012) analyzed samples from 10 patients with pancreatic cancer and 10 matched healthy controls using a human oral microbe identification microarray. They showed that 16 taxa changed significantly between cancer patients and controls. However, only 6 were confirmed using qPCR. Moreover, in an independent validation using new saliva samples from 28 pancreatic cancer patients and 28 healthy controls, only *Neisseria elongata* and *Streptococcus mitis* were useful in distinguishing patients with pancreatic cancer from healthy subjects, with an area under the curve value of 0.90 (95% CI: 0.78–0.96, $p < 0.0001$), a 96.4% sensitivity and a 82.1% specificity (Farrell et al. 2012). Moreover, using an immunoblot array, Michaud et al. (2013) evaluated antibodies detected against 25 oral bacteria in the serum of 405 pancreatic cancer patients and 416 healthy controls. They observed that 6% of the patients with high antibody titres against *Porphyromonas gingivalis* (>200 ng/mL) had an adjusted odds ratio (OR) of 2.14 (95% CI: 1.05–4.36) for pancreatic cancer as compared with those with undetectable or lower levels. Furthermore, in a recent case-control study, Fan et al. (2016) assessed the association between the oral microbiome and pancreatic cancer. They analyzed prediagnostic oral wash samples were taken from 361 cases of adenocarcinoma of the pancreas and 371 matched controls collected from 2 prospective cohort studies. Using 16S rRNA gene sequencing, they found that *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* were positively associated with pancreatic cancer, with adjusted ORs of 1.60 (95% CI: 1.15–2.22) and 2.20 (95% CI: 1.16–4.18), respectively. Moreover, they showed that *Fusobacteria* and *Leptotrichia* were negatively associated with pancreatic cancer, with ORs of 0.94 (95% CI: 0.89–0.99) and 0.87 (95% CI: 0.79–0.95), respectively (Fan et al. 2016).

Helicobacter pylori is often associated with peptic and gastric cancers. This species is associated with esophageal adenocarcinoma and esophageal squamous cell carcinoma. *Helicobacter* infection favors apoptosis, activates cyclooxygenase, and inhibits heat shock protein (Targosz et al. 2012). *Streptococcus anginosus* may be associated with esophageal cancer, as well as head and neck cancers. Periodontitis often represents a permanent reservoir of this bacterium (Souto and Colombo 2008).

Pancreatic cancer

Several studies have reported a link between oral infection and an increased risk of pancreatic cancer. Variations in the biomarkers of the salivary microbiota may play a role in pancreatic pathologies (Torres et al. 2015).

Several potential bacterial biomarkers have been identified: *Neisseria elongata*, *Streptococcus mitis*, *Porphyromonas gingivalis*, and *Aggregatibacter actinomycetemcomitans* (Fan et al. 2016). More recently, *Fusobacterium* species of the oral bacterial group were detected in pancreatic cancer tissue and may be a prognostic biomarker of this pathology (Mitsuhashi et al. 2015). *Fusobacterium* spp. are pleomorphic and seem to be a symptom of clinically significant acute or chronic illnesses, rather than implying pathogen-specific therapeutic challenges for clinicians (Johannesen et al. 2016).

Lung cancer

Lung cancer is the greatest cause of mortality worldwide. A study on the salivary transcriptomes of lung cancer patients prevalidated 7 biomarkers of the disease. Instead of the lung, the buccal (cheek) mucosa has been suggested as an excellent surrogate site in the field of injury (Radosevich et al. 2014). Among bacteria, the relationships between *Neisseria*, *Streptococcus*, and *Porphyromonas* and lung cancer have been established, along with clearly significant associations between salivary *Capnocytophaga* and *Veillonella* and lung cancer (including squamous cell carcinoma and adenocarcinoma) (Yan et al. 2015).

Host side

The normal healthy state of the oral mucosal cavity is a state of balance between various organisms and the host. The oral microbiota is now understood as an organ whose mechanisms closely match those of the gut microbiota ecosystem. The stability of the microbiota increases with probiotics and prebiotics (Zaura et al. 2014).

Many antimicrobial peptides are expressed by epithelial cells, helping to preserve the equilibrium between the constituents of the microbiota. In addition, these molecules have specific properties and play a role in the immune system (Bowdish et al. 2005). For example, epithelial antimicrobial peptides (AMPs) have targets within the microbiota and in cancer neck tissues. In healthy patients, the homeostasis of the constituents of the microbiota prevents aggression on the part of pathogens. Several families of antimicrobial peptides are described, and they are specifically designed to kill or inactivate microorganisms that come in contact with epithelial surfaces (Zasloff 2002). AMPs are present on the mucosa and in saliva and are the front line of defense against bacteria, viruses, and fungi (Lai and Gallo 2009). Furthermore, the innate immune receptors identify bacterially conserved microbe-associated molecular patterns (Medzhitov and Janeway 2000). This mechanism is used by the innate immune system to differentiate pathogenic and non-pathogenic bacteria. This distinction between pathogenic and innocuous bacteria remains the main concern of many research teams. Parameters such as structure, expression, virulence factors, and invasive properties are being investigated. Furthermore, the infection can be influenced by the genetic variations of the host, which

can result in defective peptides (Kalus et al. 2009). In the intestine, AMPs are produced by epithelial cells.

A constant cross-talk takes place between epithelial cells, which are present in the saliva, and the commensal microorganisms to maintain the homeostasis of the gut. The perturbation of AMP production plays a major role in the etiology of the inflammatory GI tract, underscoring the importance of gut microbial homeostasis (Guaní-Guerra et al. 2010).

Biomarkers for early cancer detection (Table 4)

Multiple studies have shown that the oral microbiota overlaps with the GI tract microbiota and that there are many avenues for the dissemination of bacteria within the body (Aviles-Jimenez et al. 2014; Prasad et al. 2016). Lamster et al. (1994) reported on the potential relationships among periodontal pathologies, the oral microbiota, and host response.

The β -glucuronidase level in the saliva may be a quantitative marker of oral inflammation (Lamster et al. 2003). Other biomarkers exist for rheumatoid arthritis (Mirrieles et al. 2010).

Saliva is an abundant and accessible biofluid (Sivadasan et al. 2015; Javaid et al. 2016). However, recently, a new approach integrating both saliva and tumor tissue metabolomics will be useful in understanding the origin of salivary metabolites in oral cancer patients. Oral cancer can be detected via 4 mRNA markers of cell-free saliva using microarray technology (Li et al. 2004). Despite the ability of the identified biomarkers to discriminate oral cancers from controls, no significant difference in disease stages and histological types were identified, which prevents the use of these markers as screening tools with which to evaluate all oral cancers (Ishikawa et al. 2016).

Recent advances in salivary cancer diagnostics have enabled wearable bioelectronics, with in vivo monitoring detection of target analytes. Two types of wearable mouth-guard biosensors have been developed for the continuous monitoring of cancer biomarkers, such as lactate and uric acid, in the saliva. This mouth-guard biosensor, used for the real-time detection of salivary metabolite via Bluetooth wireless transmission, has opened a new era of in vivo salivary diagnostic devices (Kim et al. 2015). However, no established publication in this area describes methods and techniques with which to detect DNA and RNA in real time (Mishra et al. 2016).

The oral complications of cancer treatment may have selective effects related to oral care, and these effects may be important for health maintenance. The control of biofilms via hygienic procedures is necessary to limit the installation and development of the oral microbiome. However, predicting the risk of adverse oral outcomes is difficult. In this regard, periodontal treatments have been shown to induce systemic changes in several inflammatory markers.

Table 4. Potential biomarkers for early cancer detection.

References	Study design	Cancer	Study population(s)	Population date			Main findings
				Age (years)	Ethnic group	Sex	
Aas et al. 2005	Defining normal human microflora	—	5 subjects	—	—	—	Specificity of subjects and 9 sites; specificity of periodontal and carie diseases
Fabian and Pachev 2008 (a Review paper)	Salivary genomics, transcriptomics, proteomics	Early diagnosis of cancer	Review	—	—	—	The identification of biomarkers with a proper and definite sensitivity and specificity to as many disorders and conditions as possible is also a prerequisite
Jimenez et al. 2009	Periodontitis and cerebrovascular disease	Cerebrovascular disease	1137 dentate men in Veterans Affairs	27–84	White, USA	Men	Periodontal probing depth was not associated with a significantly increased rate of cerebrovascular disease in the combined or age-stratified analyses
Farrell et al. 2012	Oral microbiota and cancer risks	Pancreatic cancers	10 pancreatic cancers, 10 controls 28 healthy, 27 chronic pancreatitis salivary biomarkers: qPCR	—	USA	—	Thirty-one bacteria species are increased in saliva of patients with pancreatic cancer and 25 bacteria decreased; 2 bacterial (<i>G. adiacens</i> and <i>S. mitis</i>) showed significant variation ($p < 0.05$) between chronic pancreatitis samples and controls; this report provides proof of salivary microbiota as an informative source for discovering noninvasive biomarkers of systemic disease
Monteiro et al. 2012	Cardiovascular risk marker with periodontal disease; measure of LDL	—	40 patients with chronic periodontitis	—	—	—	Change in several inflammatory markers show that the periodontal treatment induces systemic changes
Michelet and Legouis 2012 (a Review paper)	Study selection before and after radiotherapy and chemotherapy	Head and neck cancers	24 cohort, 8 case control, 14 cross-sectional; how many participants are included is unclear	—	—	—	Patients who were post-radiotherapy had the highest DMFT compared with those who were post-chemotherapy and the healthy controls
Leishman et al. 2012	Periodontal pathogen and cardiovascular disease composition of human gut microbiota	Myocardial infarction	74 patients	—	—	—	Periodontal pathogens (<i>P. gingivalis</i> , <i>F. nucleatum</i> , <i>T. forsythia</i> , <i>A. actinomycetemcomitans</i>); serum antibodies to these pathogens GroEL and hHSP60 antibody; in cardiovascular patients, a greater burden of subgingival infection with increased levels of <i>P. gingivalis</i> and <i>T. forsythia</i> is associated.

Table 4 (concluded).

References	Study design	Cancer	Study population(s)	Population date			Main findings
				Age (years)	Ethnic group	Sex	
Chen et al. 2012	Association between periodontal pathogens and preterm	—	110 cases	—	—	—	<i>P. gingivalis</i> , <i>T. forsythia</i> , <i>T. denticola</i> in saliva; <i>P. gingivalis</i> may be related to preterm low birth weight
Ahn et al. 2012	<i>P. gingivalis</i> serum antibody levels and orodigestive cancer morbidity	—	105 patients	—	—	—	<i>P. gingivalis</i> is a biomarker for microbe associated risk of death due to orodigestive cancer; independently of periodontal disease, <i>P. gingivalis</i> is a biomarker of orodigestive cancer
de Freitas et al. 2013	Oral <i>Candida</i> in head and neck cancers	Head and neck cancers	Saliva from 29 patients with head and neck cancers — 34 noninstitutionalized, 29 institutionalized	—	—	—	Diversification and non-albicans species were observed in irradiated patients on head and neck treatment associated fungus positiveness
Momen-Heravi et al. 2014	Human salivary miRNAs	Oral cancer	34 subjects	—	USA	—	Overexpression of miRNA-27b appeared to be a promising OSCC salivary biomarker
Sivadasan et al. 2015	Human salivary proteome; biomarkers	Oral cancer	Meta-analysis	20–50	—	Equality Men/women	139 proteins which may serve as secretory markers in oral malignancies
Zahran et al. 2015	Markers for malignant transformation in oral mucosal lesions	OSCC	100 subjects	—	—	—	miRNA-84 tested might furnish a rapid, noninvasive aid for revealing malignant transformation in oral mucosal lesions
Sinha et al. 2015	Immunohistochemical expression of P63	Oral carcinogenesis	45 subjects	—	India	—	p63 expression in oral premalignant and malignant lesions as compared with the normal oral mucosa

Note: qPCR, quantitative polymerase chain reaction; LDL, low density lipoprotein; DMFT, decayed, missing, or filled teeth; OSCC, oral squamous cell carcinoma; miRNA, microRNA; *G. adiacens*, *Granulicatella adiacens*; *F. nucleatum*, *Fusobacterium nucleatum*; *T. forsythia*, *Tannerella forsythia*; *A. actinomycetemcomitans*, *Aggregatibacter actinomycetemcomitans*; *P. gingivalis*, *Porphyromonas gingivalis*; *T. denticola*, *Treponema denticola*.

Radiotherapy

During radiation therapy with only 20 Gy, approximately 80% of salivary function is lost, and above 30 Gy, permanent damages are sustained. Changes occur in antibacterial properties, with consequent alterations in the oral microbiome, and the pH of the saliva decreases to about 5. The levels of acidogenic and cariogenic bacterial species, such as *Streptococcus mutans*, *Actinomyces*, and *Lactobacillus*, increase, while the concentrations of *Neisseria*, *Fusobacterium*, and *Streptococcus sanguinis* decrease (de Barros da Cunha et al. 2015).

In 2013, another study was performed on 8 irradiated patients with head and neck cancers. The variety of organisms in the oral microbiota was assessed using 16S rDNA 454 pyrosequencing (V1–V3) and UniFrac metrics studies. In these irradiated patients, there was an increase in the occurrence of caries, which was related to 3 genera (*Streptococcus*, *Veillonella*, and *Actinomyces*) (Hu et al. 2013). After irradiation (head and neck radiotherapy), the level of *Streptococcus sanguinis* decreased, whereas those of *Streptococcus mitis* and *Streptococcus salivarius* increased. Furthermore, the impact of conventional radiotherapy differs from that of intensity modulated radiotherapy (IMRT), which limits the negative effect of irradiation on the tissue near the tumor. Thus, in IMRT patients, a reduction in the severity of hyposalivation was observed, and in this situation, the temporal stability of the oral ecosystem was found to be significantly beneficial (Shao et al. 2011).

When patients with head and neck cancer undergo radiotherapy, the proliferation of oral yeast (genus *Candida*) is induced. A study of 92 patients showed that this proliferation involved a diversity of *Candida*, with the non-albicans species prevailing (Basu et al. 2012). Another study that examined 36 patients with tongue carcinoma previous to antitumor therapy revealed oral dysbiosis. The same patients, after preoperative radiotherapy and before surgery, saw an increase in the pathogenic potential of selected microflora. As a precautionary measure, patients must establish and maintain oral hygiene before and after treatments to prevent postoperative complications (Lebedev et al. 2015).

The differential diagnosis of osteoradionecrosis, separating it from a relapse of malignancy or an inflammation-driven infection, is necessary. There is a significant overlap in the standard uptake values among patients with osteoradionecrosis and those with tumor recurrence.

Oral mucositis

Mucositis is a medical condition characterized by inflammatory lesions located within the oral and gastrointestinal mucosa. Many etiologies are attributed to mucositis, including infectious disease, immune deficiency, medications and high-dose cancer therapy. In addition, one study suggests a potential relationship between coagulase-negative staphylococci and OM in

patients with acute lymphoblastic leukemia undergoing antineoplastic chemotherapy (Soares et al. 2011).

The risks associated with a combination of chemotherapy and radiotherapy may influence the gravity of OM. In these conditions, the management of OM is an important challenge, with the risk of bloodstream inoculation being associated with the degree of degradation of the epithelial and connective tissue and with marrow suppression. Mouthwash has been recommended to prevent OM in patients receiving more than 50 Gy of radiotherapy without concomitant chemotherapy (Vasconcelos et al. 2016).

Among methods used to prevent chemotherapy- and (or) radiotherapy-induced mucositis, maintaining oral hygiene is of utmost importance, including an oral care protocol (brushing, flossing, dental visits before and during the treatment, and the usage of bland mouthwashes) (Hashemi et al. 2015). Using chlorhexidine digluconate (0.05%–0.2%) as an antimicrobial rinse may be beneficial in reducing the oral microbial load and the chances of secondary infection. However, chlorhexidine is not recommended for the prevention of OM in patients with solid tumors of the head and neck and those who are undergoing radiotherapy (Zhu et al. 2016).

For the prevention and relief of OM, a palliative effect is sought to reduce the pain, duration, and severity of the pathology. All experts advise the use of frequent mouthwashes, in addition to 0.9% saline and sodium bicarbonate rinses; the patient should rinse with at least 8–12 fluid ounces in mouthful-sized portions, with expectoration until completion (Turner et al. 2013). It was also mentioned that honey, which is used in some parts of the world for this purpose, may be an effective and feasible option for preventing mucositis (Zhu et al. 2016).

Many studies have proposed various predictive biomarkers for the severity of OM in patients after radiotherapy (Loo et al. 2013). Early results suggest that a marker of blood lymphocytes, gamma-H2AX, correlates with the degree of OM severity before radiotherapy. In an interesting study on the consequences of breast cancer, patients were shown to experience long-term elevation of serum T4 (thyroxine) and serum T3 (triiodothyronine) levels. The findings support the idea that thyroid function is damaged in breast cancer patients with post-traumatic stress disorder; elevated T3 and T4 levels, together with ulcerative OM, could be indicative of the emotional status of these patients (Loo et al. 2013).

The use of palifermin, cryotherapy, and low-power lasers (Peterson et al. 2013; Chaveli-López and Bagán-Sebastián 2016) was also tested as a possible method of preventing OM in patients receiving specific types of chemotherapy. This technique is also used as a treatment to reduce inflammation in patients treated with edatrexate. However, based on the information gathered in this review of the literature, the current topical treatment of mucositis-related pain is based on empiricism and not on

scientific evidence. One significant problem is the risk of malnutrition after a high dose of chemoradiotherapy due to problems with swallowing as a result of OM. This problem can be avoided via early enteral nutrition. The use of mouth rinses, such as Caphosol R (supersaturated $\text{Ca}^{2+}/\text{PO}_4$ oral rinse), in patients with high-dose cancer therapy has been deemed efficacious in reducing the pain and grade of mucositis. However, it is not evident that Caphosol use can counter the debilitating effects of OM (Lambrecht et al. 2013). Specific adjuvant treatments, such as irsogladine maleate treatment, have been successfully tested for use in OM (Nomura et al. 2013).

Oral management is necessary to reduce the occurrence of OM resulting from allogenic or autologous hematopoietic stem cell therapy, radiotherapy, and chemotherapy. Twice-daily brushing can be used in limiting the accumulation of plaque. Control over the initial stage of accumulation, that is, the formation of biofilm, is the basis of therapy.

Conclusion

The accumulated evidence suggests physiologic relationships between inflammatory and immune diseases via the oral cavity. Species-level identification may be insufficient to understand the link between microbiota and cancer.

Nevertheless, the genes and proteins of all the microbial species that colonize the digestive tract constitute an area of research in the field of evolutionary biology. The analysis of these genes sends us back to an unknown universe: in total, 3 million genes in microbial species remain to be identified, making the collective microbial genome much more complex than the human genome. The knowledge of these microbial species is rapidly developing, and further understanding will require metagenomic and proteomic studies. These discoveries in the microbiology of infectious diseases will have an impact on the identification of known and new microorganisms involved in chronic diseases such as cancer (Kipanyula et al. 2013).

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