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Letter to the Editor

Oral microbiota a host in disguise inviting oral cancer

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To the Editor

Oral cancers are one of the leading causes of death in today's world. The development of oral squamous cell carcinoma (OSCC) is mainly recorded due to host-related and lifestyle factors. Out of the several aetiologies that have been attributed to be causing the disease, it includes major consumption of tobacco. Lately, an emerging area of research has focused on the intricate connection between the oral microbiome and cancer risk. The collective genomes of microorganisms inhabiting the oral mucosa are termed microbiota [1]. Several ongoing research studies show that changes in the oral microbiome can result in a shift towards a more pathogenic and pro-inflammatory environment, which may contribute to oral cancer development. Microbiota are complex and are not merely passive inhabitants; they engage in dynamic interactions with the host and each other.

It regulates several functions, such as immune response modulation, its role in the biosynthesis of vitamins, protection from exogenous pathogens, and even the production of antimicrobial substances [1].

While a direct causal relationship has not been definitively established between dysbiosis and oral cancer, there exist several intriguing associations, such as it can give rise to persistent inflammation in the oral cavity, a well-established risk factor for various cancers, including oral cancer. It can modify the local immune response within the oral cavity, affecting the immune system's ability to identify and combat cancerous cells. In some instances, if there is a distortion of homeostasis and the prevalence of the pathogenic bacteria increases, then diseases can occur. It is seen that it can modulate the link between the oral bacteria and the host, leading to diseases [2].

Dysbiosis may interact with other acknowledged risk factors triggering oral cancer, such as tobacco, poor oral hygiene, diet, and alcohol use, as well as human papillomavirus (HPV) infection, which could potentially compound the overall risk. The result is often a disruption in the delicate equilibrium of the oral microbiome. Dysbiosis can primarily be of three forms: firstly, the loss of good bacteria might be due to an increase in pathogenic bacteria or a complete loss of bacterial diversity [3, 4]. There is a dynamic fluctuation of microbiota, which varies from person to person regarding age, gender, geographic variations, diet, already present systemic disease, and many more. Dysbiosis in the oral cavity has been proven to be associated with gingivitis, periodontitis, dental

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caries, and abscesses. Furthermore, cases of osteomyelitis, bacterial endocarditis, aspiration pneumonia, cardiovascular disease, and rheumatoid arthritis have also been reported. Poor oral hygiene and periodontitis have been reported to be an etiologic factor for OSCC [1]. About 15% of OSCCs are reported to be of unknown origin, such as bacterial microbiota [5]. Specific oral bacteria can generate metabolites that may possess carcinogenic properties (**Figure 1**).

Dysbiosis might influence the production of these metabolites, potentially contributing to the development of cancer (**Figure 2**). These advanced gingival diseases caused by bacterial dysbiosis pose a 2-5 times increased risk of developing cancer compared to any healthy individual. *Porphyromonas gingivalis* and *Fusobacterium nucleatum* have been reported to have carcinogenic potential. They can constrain apoptosis, initiate cell proliferation, lead to chronic inflammation, help cellular invasion, and even directly produce carcinogens. There is a high recurrence rate of treated OSCC primarily because of field cancerization, but another theory proposed might be the altered microbiota composition leading to malignant transformation [6]. Associations of increased levels of Fusobacteria and a decrease in *Firmicutes* with OSCC have been previously noted. Higher concentrations of *Peptostreptococcus*, *Fusobacterium*, *Prevotella* (particularly *P. melaninogenica*), *Porphyromonas*, *Veillonella* (primarily *Veillonella parvula*), *Haemophilus*, *Rothia*, and *Streptococcus* have been observed in cases of OSCC [7].

A study found that during the progression of carcinoma, the concentrations of *Streptococcus*, *Haemophilus*, *Porphyromonas*, and *Actinomyces*

declined. In contrast, *F. periodonticum*, *P. micra*, *S. constellatus*, *Haemophilus influenza*, and *Filifactor alocis* were linked to OSCC, and their levels rose in tandem with the severity of the disease as categorized by the TNM classification [8]. In gut microbe dysbiosis, it has been proved that it has a role in gastric carcinoma. However, a scope of research still establishes the link between oral dysbiosis and oral carcinoma. There are several reasons why the relationship has yet to be established, some of which are the complex anatomy of the oral cavity, the varied dynamics of the microbiota varying from individual to individual, etc [9].

We support the hypothesis that dysbiosis leads to the disease. In dysbiosis, the bacteria living and sustaining within a biofilm possess much bacterial resistance. In this biofilm environment, horizontal gene transfer occurs due to its closeness to bacterial cells and stable structural properties, spreading antibiotic-resistant genes among the biofilm inhabitants. The structural and physiological changes in the biofilm-forming bacteria aid them to tolerate antibiotics and eventually become antibiotic-resistant. This leads to the entry of antibiotic-resistant (ABR) bacteria, resulting in the formation of oral biofilm with a mix of normal flora and ABR bacteria, leading to various infections (challenging to remove pathogenic bacteria as antibiotics do not work), leading to chronic inflammations and release of oncogenic metabolites, eventually resulting to oral carcinoma.

Conflict of interests

None

Figure 1. Flowchart depicting the causal association of dysbiosis with oral squamous cell carcinoma.

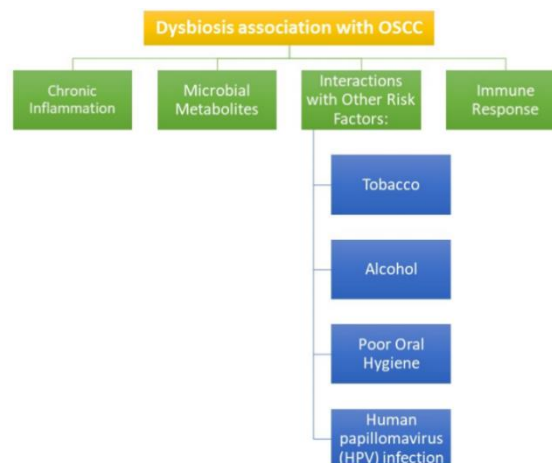
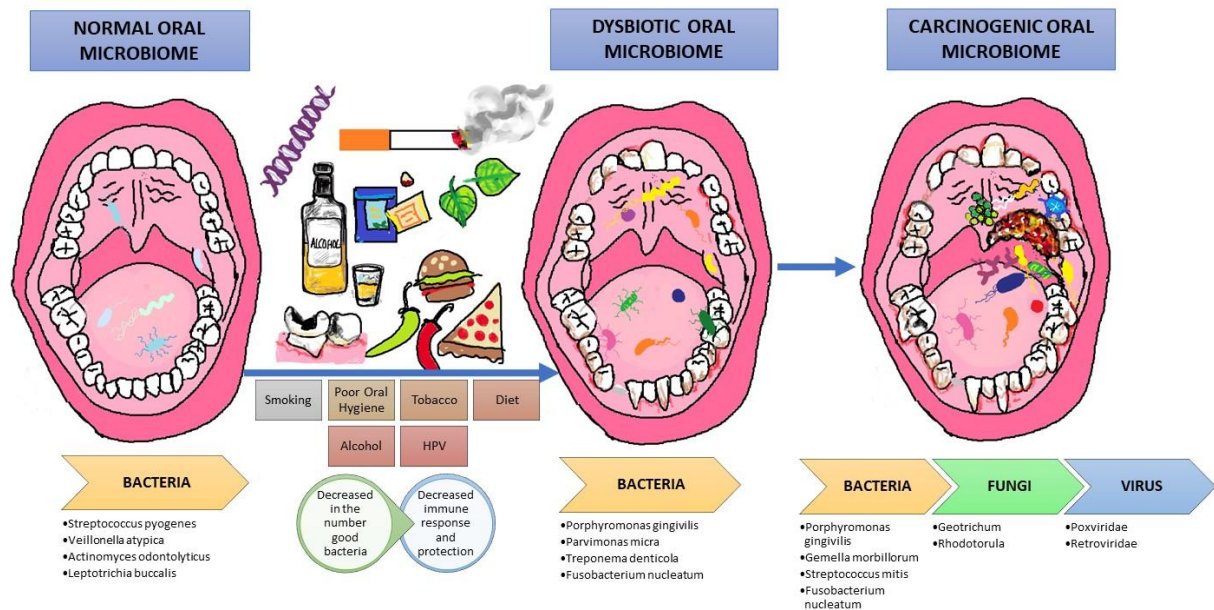


Figure 2. Pictorial representation of a standard oral microbiome converting into oral squamous cell carcinoma due to dysbiosis.

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