

Oral Bacterial Microbiota in Digestive Cancer Patients

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Oral microbiota dysbiosis and specific bacteria, such as *Fusobacterium nucleatum* and *Porphyromonas gingivalis*, appeared to be associated with colorectal cancers.

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digestive cancer

1. Introduction

Digestive cancers include cancers located in the esophagus, stomach, liver, pancreas, colon, and rectum. Their incidence and related mortality are increasing worldwide, but with some characteristic geographical differences ^[1]. According to the GLOBOCAN, i.e., Cancer Incidence in Five Continents, and the World Health Organization (WHO) mortality databases in 2018, the majority of new cases of digestive cancers (63%) and related deaths (65%) occurred in Asia, followed by Europe and North America. Moreover, esophageal, gastric, and liver cancers appear to be more prevalent in Asia, whereas colorectal and pancreatic cancers are more common in Europe and North America ^[2]. Most of these cancers are considered sporadic and are influenced by several potentially modifiable environmental factors, such as tobacco smoking, diet, alcohol consumption, physical inactivity, obesity, and immunosuppressive drugs ^[1]. Some recent evidence suggested a role of the human microbiota in the development of digestive cancers, not only related to the composition and changes in relative abundance of microbes of the gut microbiota ^{[3][4][5]} but also linked to a state of dysbiosis of the oral microbiota ^{[6][7]}. In this review, we define “dysbiosis” as any change to the composition of resident bacterial communities relative to the community found in healthy individuals ^[8].

The oral cavity is a reservoir of more 700 species or phylotypes of bacteria, of which approximately 35% have not been cultured yet ^[9]. The equilibrium of this complex ecosystem is essential for oral health and influences host responses to disease ^[10]. The disruption in the homeostasis, i.e., dysbiosis, can result in significant metabolic and immunologic effects on the host, ultimately leading to local and systemic diseases ^{[11][12]}. These mechanisms are well documented in the pathogenesis of periodontitis, a chronic multifactorial inflammatory disease of the tooth-supporting tissues including the gums, the periodontal ligament, and the alveolar bone ^[13], but it has also been observed for cardiovascular, neurological, and metabolic disorders as well as digestive cancers and inflammatory bowel diseases ^{[7][13][14][15]}.

In particular, specific oral bacteria that are typically found in the oral cavity of individuals suffering from periodontal diseases, such as *Fusobacterium nucleatum* ^[16] and *Porphyromonas gingivalis* ^[17], have been found in

significantly high abundance in tumoral tissues and fecal samples of patients affected by colorectal cancer (CRC) [18][19], supporting the ability of these bacteria to migrate through the gastrointestinal tract where they can induce inflammation, alter the host immune response, and create an environment that may eventually favor tumor growth [20][21][22][23]. Specifically, data from a mouse model of intestinal tumorigenesis suggest that fusobacteria generate a proinflammatory microenvironment that is conducive to CRC progression through recruitment of tumor-infiltrating immune cells [24][25][26]. This was confirmed in clinical studies analyzing *Fusobacterium nucleatum* abundance by quantitative real-time polymerase chain reaction of DNA extracted from colorectal tissue biopsies and surgical resection specimens and observing that *Fusobacterium nucleatum* was more abundant in stool samples from CRC patients compared with adenomas or controls [27][28][29]. Some authors concluded that *Fusobacterium nucleatum* could be a novel risk factor for disease progression from adenoma to cancer, possibly affecting patient survival outcomes [27].

2. Oral Microbiota and Esophageal Cancer (EC)

Five articles investigated the association between oral microbiota and EC [6][30][31][32][33].

Chen et al. [30] demonstrated that patients with esophageal squamous cell carcinoma (ESCC) have a decreased oral microbiota diversity when compared with non-ESCC controls. The authors described a decreased salivary carriage of genera *Lautropia*, *Bulleidia*, *Catonella*, *Corynebacterium*, *Moryella*, *Peptococcus*, and *Cardiobacterium* and higher relative abundance of *Prevotella*, *Streptococcus*, and *Porphyromonas* in the ESCC group [30]. Wang et al. [31] showed that *Actinomyces* and *Antopobium* were related to a higher risk of ESCC, whereas the healthy group of the study was closely related to *Fusobacterium* and *Porphyromonas*. Zhao et al. [32] showed that ESCC is associated with an increased salivary carriage of *Firmicutes*, *Negativicutes*, *Selenomonadales*, *Prevotellaceae*, *Prevotella*, and *Veillonellaceae* and with a decreased taxa of *Proteobacteria*, *Betaproteobacteria*, *Neisseriales*, *Neisseriaceae*, and *Neisseria*.

Kawasaky et al. and Peters et al. concluded that differences in microbiota compositions between cases and controls could be used as a possible biomarker for cancer screening [6][33]. Only one study investigated the microbiota in relation to an esophageal adenocarcinoma, showing an association with an increased oral rinse carriage of *Tannarella forsythia* and a depletion of the commensal genus *Neisseria* and *Streptococcus Pneumoniae* [6].

3. Oral Microbiota and Liver Cancer (LC)

Only two articles investigated the association between oral microbiota dysbiosis, and LC. Lu et al. [34] identified *Oribacterium* and *Fusobacterium* as possible biomarkers to identify LC patients, showing a significant difference in their relative abundance between healthy controls and LC patients [34]. Li et al. compared the oral microbiota of patients with LC with healthy controls and patients with cirrhosis in different stages, finding an association between cancer and *Haemophilus*, *Porphyromonas*, and *Filifactor*.

4. Oral Microbiota and Pancreatic Cancer (PC)

In the seven studies dealing with PC, the microbiota analysis was conducted on salivary samples in five studies [35][36][37][38][39], on tongue coating in one study [40], and on oral rinse [41] in the remaining study. Results were heterogeneous. Lu et al. as well as Fan et al. observed an increased risk of cancer linked to *Porphyromonas gingivalis*, but contrasting findings were reported in relation to *Fusobacterium*, which was respectively linked to an increased and decreased risk of cancer [41][40]. The remaining studies found different bacteria linked to PC risk, without highlighting the predominance of a specific microbiota.

5. Oral Microbiota and Gastric Cancer (GC)

The microbiota analysis was conducted on tongue coating in four studies [42][43][44][45] and on salivary sample in two studies [46][47]. Hu et al. [43], Xu et al. [45], and Han et al. [42] reported that tongue coating characteristics significantly differ between cases and controls, with thicker tongue coating associated with an increased risk of GC. Xu et al. [45] divided the sample of GC patients into five subgroups based on the tongue coating characteristics, reporting different microbial associations in the different groups. However, also for this type of cancer there was no evidence of a specific microbiota being related to the development of GC.

6. Oral Microbiota and Colorectal Cancer (CRC)

Microbial samples were collected by oral swab in three studies [3][16][48], oral rinse in one study [41], saliva in three studies [49][50][51], subgingival plaque in one study [52], and tongue coating in one study [42]. Overall, these studies showed the most consistent results. *Fusobacterium nucleatum* was found to be linked to an increased risk of CRC in five studies [52][49][42][48][51]. Four studies agreed on the association of different species of *Prevotella* and CRC risk [3][52][53][48], while a borderline association was found in one study [42].

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