



## REVIEW ARTICLE

# On the Search to Elucidate the Role of the Microbiota in the Genesis of Cancer: The Cases of Gastrointestinal and Cervical Cancer

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The microbiota that inhabits the human body plays an important role in health and disease, by their fundamental role in food digestion, training of the immune system or protection against pathogen colonization. However, when the equilibrium with its host is altered, some diseases like cancer might be promoted. In this review we describe the information collected in recent studies between the microbiota and its association with cancer. We conducted the review of the relation of microbiome and cancer etiology focusing on the gastrointestinal and cervical cancer. The MEDLINE database was used for the search. The gastrointestinal tract harbours a diverse and site specific microbiota, and several studies have demonstrated that perturbation of these microbial communities might be associated with different types of cancer. In particular, alteration of the colorectal, gastric and oesophageal microbiota have been reported associated with cancer development. Likewise, cervical microbiome studies suggest that some members of the cervical microbiota are possible modifiers of the cytokine profile of the cervical micro-environment during the development of cervical lesions and cervical cancer. Larger prospective studies are needed to examine whether microbiome dysbiosis could cause cancer, and to evaluate the utility of microbiome profiles as biomarkers for prevention and early diagnosis. This is an important area of research if we consider that microbiota may be a modifiable factor by the use of pre- and probiotics, in order to prevent cancer evolution or even to potentiate cancer treatment. © 2017 IMSS. Published by Elsevier Inc.

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## Introduction

The human body is the natural habitat for a highly diverse community of microorganisms including bacteria, fungus and virus. The microbial community also referred as microbiota, resides across a wide range of human body sites and shows site-specific composition and structure in both taxa and function. The microbiota in oral cavity and distal gut are especially diverse compared to the microbiota in

other sites such as skin, vagina, lung, or nasal cavity. In addition, microbiota shows high inter-personal variation in community structure (composition of microbes), but less variation in community function.

Human microbiota play an important role in health as well as in an expanding list of disease through modulating human nutrients, immunity and pathogen infection dynamics. Certain microbes (e. g. *Helicobacter pylori* for gastric cancer, *Fusobacterium nucleatum* for colorectal cancer) or the dysbiosis of the microbial community have been shown linked with diseased state, even cancer. Dysbiosis refers to the state where microbial community of a certain habitat is inbalance and deviated from the states that

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microbiota and human benefit each other. Several mechanisms have been proposed for the links. These include inflammation promoted by the interaction of microbiota and host, genotoxic effect by microbial genotoxins or microbial metabolic actions (1). The connection of human microbiota and cancer, especially the gastrointestinal cancer have been suggested by numerous studies. In this chapter, we will review the evidence on the link of microbiota (mainly bacteria) and gastrointestinal tract cancer.

### Oral Cancer (OSCC)

Oral squamous cell carcinoma (OSCC) belongs to the group of head and neck tumors (HNSCC) that affects the oral cavity including the areas of the lips, tongue, gingiva, floor of mouth and palate. Globally, it ranked 15th place in frequency of all types of cancer in 2012, with a higher incidence in men. It is estimated that two thirds of the cases occur in developing countries and represent a serious health problem in South-East and South-Central Asia (2). However, in recent years the incidence of this cancer has increased mainly among young population (<40 years old) and women. It is estimated that there are between 350,000–400,000 new cases every year worldwide, with age, ethnic group, culture, life-style, and level of country development as important risk factors.

The main risk factor to develop OSCC is the abuse of alcohol and tobacco, although it has recently been proposed that oral microbiota may play a relevant role in the development of OSCC as a consequence of the emergence of diseases such as periodontal disease and tooth loss. The proposed mechanisms are the induction of a chronic inflammatory process and/or as a result of the metabolism of carcinogenic compounds. Moreover, infection with human papilloma virus (HPV types 16 and 18) has been identified as possible factor for the development of OSCC, with a poor prognosis (five year survival rate of 60%) (3). In addition, host genetics, epigenetic defects or environmental factors (obesity, smoking, diabetes, aging, and stress) may have an influence on oral diseases.

The oral cavity is the niche that houses more than 700 species of microorganisms including fungi, bacteria and yeasts. In healthy conditions, the oral microbiota is composed by the phyla Firmicutes, Proteobacteria, Bacteroidetes, Actinobacteria, and Fusobacteria, with a predominance of the genus *Streptococcus* followed by *Prevotella*, *Veillonella*, *Neisseria*, and *Haemophilus*.

The initial attempts to identify the microorganisms involved in OSCC by molecular methods, indicated that common *streptococci* had an increased abundance in oral and esophageal cancer lesions (4). Subsequently, using DNA-DNA hybridization, it was possible to show that in the saliva of patients with OSCC there were significantly increased counts of *Capnocytophaga gingivalis*, *Prevotella melaninogenica* and *Streptococcus mitis*, compared to a

cancer-free control group (5). In 2012, one study reported a high frequency of *E. faecalis* in oral cancer samples. The authors of the study proposed that the interaction of *E. faecalis* with host cells and the production of H<sub>2</sub>O<sub>2</sub> favors the onset and progression of oral cancer by the activation of the epidermal growth factor receptor (EGFR) (6). Schmidt and cols., observed differences in the abundance of microbiota in oral cancer samples compared to anatomically matched normal tissue by sequencing the 16S rRNA hypervariable region. In this study, a reduction in abundance of *Streptococcus* and *Rothia* was observed in oral cancer (7). Another study, aimed to identify differences in the microbioma of saliva between OSCC and normal epithelium controls using the 16S rRNA V3-V5 marker gene approach. In this study, the most abundant genera in OSCC were *Streptococcus*, *Prevotella*, *Haemophilus*, *Lactobacillus* and *Veillonella*, with lower numbers of *Citrobacter* and *Neisseraceae* genus *Kingella* (8). More recently, the oral microbiota of normal, potentially malignant disorders and cancer lesions was analysed by 16S rRNA sequencing, using swab samples. A core microbiota was defined with *Firmicutes* and *Streptococcus* as the most prevalent phylum and genus respectively, and a significant difference was observed between normal and cancer microbiota. In contrast, the microbiota in the potentially malignant disorders was found to overlap between the normal and cancer samples (9).

The studies in oral cancer microbiota are scarce, although suggesting the link of oral microbiota and OSCC development. More studies are needed to examine the possible role of certain bacterial groups in pre-malignant and cancer lesions, as well as its utility as early cancer markers.

### Esophagus Adenocarcinoma (EAC)

Esophageal cancer ranks the eighth most common cancer and the sixth leading cause of cancer death worldwide (10). It is estimated that in 2017 in the United States, the number of new cases of EAC will be 16,940 and 15,690 deaths (11). It also represents the sixth most common cancer death in the United Kingdom (12). The two main risk factors for the development of EAC are gastroesophageal reflux disease (GERD) and Barrett's esophagus (BE). In addition, epidemiologic studies emphasize the role of obesity as a contributing factor to carcinogenesis (13). GERD is considered to represent the first stage for the development of EAC, where, as in other regions of the digestive system, the inflammatory process plays a very important role in the development of cancer.

The esophagus is the conduit of the digestive tract that transfers food to the stomach and its surface is a mucous layer covered by a stratified squamous epithelium. The content of the esophagus is controlled by a valve mechanism that prevents the return of the bolus from the stomach;

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