OSHR – Oral Microbiome and Cancer

Introduction, The oral microbiome and cancer, contributed by Dr. Ingrid Glurich, Project Scientist I, Center for Oral and Systemic Health, Marshfield Clinic Research Institute, Marshfield, WI, USA: https://marshfieldresearch.org/profiles/5891:

The hard and soft surfaces in the oral cavity present a spectrum of habitats that are colonized by bacteria representing over 600 taxa with variable density in representation across respective oral niches (1). Collectively, these organisms represent the oral microbiota. A growing body of evidence supports an important role for the oral microbiota as potential contributors to promotion of both local and systemic oncogenesis. Increased oncogenic potential appears to be associated with establishment of dysbiosis in the oral cavity, including establishment of oral pathogens associated with induction of periodontal disease. Moreover, pathogenic mechanisms that support active contribution to oncogenesis by oral bacteria have been delineated. To date contributory mechanisms that promote oncogenesis have been broadly classified into three categories: 1) induction of local and systemic inflammation largely through upregulation of pro-inflammatory cytokines; 2) activation of pathways that disrupt physiologic apoptosis and normal cell cycling while promoting susceptibility to cellular invasion; and 3) release of toxic and/or carcinogenic substances into the environment that promote oncogenesis. (2,3) *Oral* pathogens implicated in more localized cancers such as oral squamous cell carcinomas include: *Streptococcus sp., Peptostreptococcus* sp *Prevotella* sp., *Porphyromonas gingivalis*, and *Capnocytophaga gingivalis (4-10).* Increased carriage of periodontal pathogens including *Porphyromonas gingivalis* and *Fusobacterium nucleatum* among other oral bacteria*,* has also been implicated in oncogenesis of extraoral cancers including colorectal (11-15) orodigestive (16,17) *and* pancreatic cancers (18,19). Higher representation of *Capnocytophaga* and *Veillonella* has also been reported in conjunction with lung cancers (20).

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prospective risk for pancreatic cancer: A population-based nested case-control study. Gut. 2018;67:120–127. doi: 10.1136/gutjnl-2016-312580.

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Oral Microbiome

Borgnakke WS, "The Traveling Oral Microbiome," Chapter 3, Glick M, Ed. (2019) ed., *The Oral-Systemic Health Connection: A Guide to Patient Care,* 2nd ed. (Quintessence, LCCN 2018044816), pp. 38-85.

Michaud DS, "Oral Infections and Cancer," Chapter 11, Glick M, Ed. (2019), *The Oral-Systemic Health Connection: A Guide to Patient Care,* 2nd ed. (Quintessence, LCCN 2018044816), pp. 231-241.

Gao L, Xu T, Huang G, Jiang S, Gu Y, Chen F (2018). Oral microbiomes: more and more importance in oral cavity and whole body. *Protein Cell*. 2018 May; 9(5): 488–50 Published online 2018 May 7. doi: 10.1007/s13238-018-0548-1 At: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5960472/ Abstract: Microbes appear in every corner of human life, and microbes affect every aspect of human life. The human oral cavity contains a number of different habitats. Synergy and interaction of variable oral microorganisms help human body against invasion of undesirable stimulation outside. However, imbalance of microbial flora contributes to oral diseases and systemic diseases. Oral microbiomes play an important role in the human microbial community and human health. The use of recently developed molecular methods has greatly expanded our knowledge of the composition and function of the oral microbiome in health and disease. Studies in oral microbiomes and their interactions with microbiomes in variable body sites and variable health condition are critical in our cognition of our body and how to make effect on human health improvement.

Kilian M, Chapple ILC, Hannig M, Marsh PD, Meuric V, Pedersen AML, Tonetti MS, Wade WG, Zaura E (2016). The oral microbiome – an update for oral healthcare professionals M. Kilian. *Brit Dent J* 221: 657-666. DOI: 10.1038/sj.bdj.2016.865 At: https://www.nature.com/articles/sj.bdj.2016.865.pdf?origin=ppub Abstract: For millions of years, our resident microbes have coevolved and coexisted with us in a mostly harmonious symbiotic relationship. We are not distinct entities from our microbiome, but together we form a 'superorganism' or holobiont, with the microbiome playing a significant role in our physiology and health. The mouth houses the second most diverse microbial community in the body, harbouring over 700 species of bacteria that colonise the hard surfaces of teeth and the soft tissues of the oral mucosa. Through recent advances in technology, we have started to unravel the complexities of the oral microbiome and gained new insights into its role during both health and disease. Perturbations of the oral microbiome through modern-day lifestyles can have detrimental consequences for our general and oral health. In dysbiosis, the finely-tuned equilibrium of the oral ecosystem is disrupted, allowing disease-promoting bacteria to manifest

and cause conditions such as caries, gingivitis and periodontitis. For practitioners and patients alike, promoting a balanced microbiome is therefore important to effectively maintain or restore oral health. This article aims to give an update on our current knowledge of the oral microbiome in health and disease and to discuss implications for modern-day oral healthcare.

Lim Y, Totsika M, Morrison M, Punyadeera C (2017).. Oral Microbiome: A New Biomarker Reservoir for Oral and Oropharyngeal Cancers. *Theranostics* 7(17):4313-4321. doi:10.7150/thno.21804. At: http://www.thno.org/v07p4313.htm Abstract: Current biomarkers (DNA, RNA and protein) for oral cavity and oropharyngeal cancers demonstrate biological variations between individuals, rendering them impractical for clinical translation. Whilst these biomarkers originate from the host, there is not much information in the literature about the influence of oral microbiota on cancer pathogenesis, especially in oral cancers. Oral microbiotas are known to participate in disease initiation and progression not only limited to the oral cavity, but also at other distant sites. Due to the close proximity of oral microbiota and oral cavity and oropharyngeal tumours, abundance changes in oral microbiota may provide useful information on tumourigenesis. This review aims to highlight information on the role of oral microbiota in oral cavity and oropharyngeal cancers. An in-depth analysis into the oral microbiota may provide a new avenue to diagnose and treat these patients. **Keywords**: biomarker, oral and oropharyngeal cancers, oral microbiome.

Slocum C, Kramer C, Genco CA (2016). Immune dysregulation mediated by the oral microbiome: potential link to chronic inflammation and atherosclerosis. *J intern Med* 280(1): 114-128. DOI: 10.1111/joim.12476 At: https://pubmed.ncbi.nlm.nih.gov/26791914/ Abstract. Slocum C, Kramer C, Genco CA (Ora Inc., Andover, MA, USA; and Tufts University School of Medicine, Boston, MA, USA). Immune dysregulation mediated by the oral microbiome: potential link to chronic inflammation and atherosclerosis (Review). J Intern Med 2016; 280: 114–128. Cardiovascular disease is an inflammatory disorder characterized by the progressive formation of plaque in coronary arteries, termed atherosclerosis. It is a multifactorial disease that is one of the leading causes of death worldwide. Although a number of risk factors have been associated with disease progression, the underlying inflammatory mechanisms contributing to atherosclerosis remain to be fully delineated. Within the last decade, the potential role for infection in inflammatory plaque progression has received considerable interest. Microbial pathogens associated with periodontal disease have been of particular interest due to the high levels of bacteremia that are observed after routine dental procedures and every day oral activities, such as tooth brushing. Here, we explore the potential mechanisms that may explain how periodontal pathogens either directly or indirectly elicit immune dysregulation and consequently progressive inflammation manifested as atherosclerosis. Periodontal pathogens have been shown to contribute directly to atherosclerosis by disrupting endothelial cell function, one of the earliest indicators of cardiovascular disease. Oral infection is thought to indirectly induce elevated production of inflammatory mediators in the systemic circulation. Recently, a number of studies have been conducted focusing on how disruption of the gut microbiome influences the systemic production of proinflammatory cytokines and consequently exacerbation of inflammatory diseases such as atherosclerosis. It is clear that the immune mechanisms leading to atherosclerotic plaque progression, by oral infection, are

complex. Understanding the immune pathways leading to disease progression is essential for the future development of anti-inflammatory therapies for this chronic disease.

Glurich I, Acharya A, Brilliant MH, Shukla SK (2015). Progress in oral personalized medicine: contribution of 'omics'. *J Oral Microbiol* 7: 10.3402/jom.v7.28223 DOI: 10.3402/jom.v7.28223 At: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4561229/ Abstract: **Background** Precision medicine (PM), representing clinically applicable personalized medicine, proactively integrates and interprets multidimensional personal health data, including clinical, 'omics', and environmental profiles, into clinical practice. Realization of PM remains in progress. **Objective** The focus of this review is to provide a descriptive narrative overview of: 1) the current status of oral personalized medicine; and 2) recent advances in genomics and related 'omic' and emerging research domains contributing to advancing oral-systemic PM, with special emphasis on current understanding of oral microbiomes. **Design** A scan of peer-reviewed literature describing oral PM or 'omic'-based research conducted on humans/data published in English within the last 5 years in journals indexed in the PubMed database was conducted using mesh search terms. An evidence-based approach was used to report on recent advances with potential to advance PM in the context of historical critical and systematic reviews to delineate current state-of-the-art technologies. Special focus was placed on oral microbiome research associated with health and disease states, emerging research domains, and technological advances, which are positioning realization of PM. **Results** This review summarizes: 1) evolving conceptualization of personalized medicine; 2) emerging insight into roles of oral infectious and inflammatory processes as contributors to both oral and systemic diseases; 3) community shifts in microbiota that may contribute to disease; 4) evidence pointing to new uncharacterized potential oral pathogens; 5) advances in technological approaches to 'omics' research that will accelerate PM; 6) emerging research domains that expand insights into host–microbe interaction including inter-kingdom communication, systems and network analysis, and salivaomics; and 7) advances in informatics and big data analysis capabilities to facilitate interpretation of host and microbiome-associated datasets. Furthermore, progress in clinically applicable screening assays and biomarker definition to inform clinical care are briefly explored. **Conclusion** Advancement of oral PM currently remains in research and discovery phases. Although substantive progress has been made in advancing the understanding of the role of microbiome dynamics in health and disease and is being leveraged to advance early efforts at clinical translation, further research is required to discern interpretable constituency patterns in the complex interactions of these microbial communities in health and disease. Advances in biotechnology and bioinformatics facilitating novel approaches to rapid analysis and interpretation of large datasets are providing new insights into oral health and disease, potentiating clinical application and advancing realization of PM within the next decade. **Keywords:** microbiota, precision medicine, 'omics', big data, biomarkers.

Saliva Exosomics

Nonaka T, Wong DTW (2017). Saliva-exosomics in cancer. *Enzymes* 42: 125-151. DOI: 10.1016/bs.enz.2017.08.002 At: https://pubmed.ncbi.nlm.nih.gov/29054268/ /Abstract: Exosomes are small membrane vesicles of endocytic origin that are secreted by most cells and detected in saliva. Pathophysiological roles for salivary exosomes are beginning to be

recognized in diseases including cancer, highlighting potential biomarkers and biological functions. Since early detection of cancer is vital for successful treatment, salivary exosomes would be advantageous in achieving a better survival rate due to their ready availability and noninvasiveness. The use of salivary exosomes may therefore be promising in the accurate detection of premalignant lesions and early-stage cancers, also for better our understanding of the molecular basis of tumorigenesis. In this chapter, we review our current knowledge of salivaomics, focusing on nucleic acids and proteins in saliva as potential cancer biomarkers. Since salivaomics is a rapidly evolving field, we hope to expand frameworks toward salivary exosomes, integrate new and existing information, and bridge salivaomics with other biomedical researches. Furthermore, we would like to coin the term "saliva-exosomics" as the next-generation salivaomics. Our goal in this chapter is to provide the most updated information on cancer-derived exosomes in the saliva as natural carriers of biomarkers and signaling molecules. Major advances include definitive structure analysis and molecular characterization of salivary exosomes. We also highlight the exosome biogenesis and cargo trafficking mechanisms in which recent animal studies have expanded our understanding of exosome-mediated transfer of cancer-derived products from distal tumor to salivary gland. The potential roles of the salivary exosomes in cancer progression and immune surveillance are also addressed.

Oral Virome

Gao L, Kang M, Zhang MJ, Sailani MR, Kuraji R, Martinez A, Ye C, Kamarjan P, Le C, Zhan L, Rangé H, Ho SP, Kapila YL (2020). Polymicrobial periodontal disease triggers a wide radius of effect and unique virome. *npj Biofilms Microbiomes* 6(10). DOI: https://doi.org/10.1038/s41522-020-0120-7 At: https://www.nature.com/articles/s41522-020-0120-7# **Abstract:** Periodontal disease is a microbially-mediated inflammatory disease of tooth-supporting tissues that leads to bone and tissue loss around teeth. Although bacterially-mediated mechanisms of alveolar bone destruction have been widely studied, the effects of a polymicrobial infection on the periodontal ligament and microbiome/virome have not been well explored. Therefore, the current investigation introduced a new mouse model of periodontal disease to examine the effects of a polymicrobial infection on periodontal ligament (PDL) properties, changes in bone loss, the host immune response, and the microbiome/virome using shotgun sequencing. Periodontal pathogens, namely Porphyromonas gingivalis, Treponema denticola, Tannerella forsythia, and Fusobacterium nucleatum were used as the polymicrobial oral inoculum in BALB/cByJ mice. The polymicrobial infection triggered significant alveolar bone loss, a heightened antibody response, an elevated cytokine immune response, a significant shift in viral diversity and virome composition, and a widening of the PDL space; the latter two findings have not been previously reported in periodontal disease models. Changes in the PDL space were present at sites far away from the site of insult, indicating that the polymicrobial radius of effect extends beyond the bone loss areas and site of initial infection and wider than previously appreciated. Associations were found between bone loss, specific viral and bacterial species, immune genes, and PDL space changes. These findings may have significant implications for the pathogenesis of periodontal disease and biomechanical

properties of the periodontium. This new polymicrobial mouse model of periodontal disease in a common mouse strain is useful for evaluating the features of periodontal disease.

Pérez-Brocal V (2018). The analysis of the oral DNA virome reveals which viruses are widespread and rare among healthy young adults in Valencia (Spain). *PLoS One 13(2): e0191867* DOI: 10.1371/journal.pone.0191867 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5805259/ Abstract: We have analysed oral wash samples from 72 healthy young adults in Valencia (Spain) for a metagenomic analysis through the construction of shotgun libraries and high-throughput-sequencing. The oral viral communities have been taxonomically characterised as well as and the gene content from the latter. The majority of viruses are found in few individuals, with single occurrences being the most widespread ones, whereas universally distributed viruses, while present, are relatively rare, with bacteriophages from families *Siphoviridae* and *Myoviridae*, and *Streptococcus* phages, as well as the eukaryotic viral family *Herpesviridae* amongst the most widespread viruses. No significant differences were found between females and males for either viruses and bacteria in abundance and alpha and beta diversity. The virome show similarities with other oral viromes previously reported for healthy individuals, suggesting the existence of a universal core of oral viruses, at least in the Western society, regardless of the geographical location.

Ly M, Abeles SR, Boehm TK, Sikisaka RR, Naidu M, Santiago-Rodriguez T, Pride DT (2014). Altered Oral Viral Ecology in Association with Periodontal Disease. *mBio Commumity.* DOI: 10.1128/mBio.01133-14 At: https://mbio.asm.org/content/5/3/e01133-14 Abstract: The human oral cavity is home to a large and diverse community of viruses that have yet to be characterized in patients with periodontal disease. We recruited and sampled saliva and oral biofilm from a cohort of humans either periodontally healthy or with mild or significant periodontal disease to discern whether there are differences in viral communities that reflect their oral health status. We found communities of viruses inhabiting saliva and the subgingival and supragingival biofilms of each subject that were composed largely of bacteriophage. While there were homologous viruses common to different subjects and biogeographic sites, for most of the subjects, virome compositions were significantly associated with the oral sites from which they were derived. The largest distinctions between virome compositions were found when comparing the subgingival and supragingival biofilms to those of planktonic saliva. Differences in virome composition were significantly associated with oral health status for both subgingival and supragingival biofilm viruses but not for salivary viruses. Among the differences identified in virome compositions was a significant expansion of myoviruses in subgingival biofilm, suggesting that periodontal disease favors lytic phage. We also characterized the bacterial communities in each subject at each biogeographic site by using the V3 hypervariable segment of the 16S rRNA and did not identify distinctions between oral health and disease similar to those found in viral communities. The significantly altered ecology of viruses of oral biofilm in subjects with periodontal disease compared to that of relatively periodontally healthy ones The significantly altered ecology of viruses of oral biofilm in subjects with periodontal disease compared to that of relatively periodontally healthy ones suggests that viruses may serve as useful indicators of oral health status.

Extaroral Cancer (Pancreatic, Breast, Colon/Colorectal, Esophogeal, Lung, Renal, Liver)

Wallis C (2020). New Player in Cancer's Spread: A commonplace mouth bacterium now is tied to metastasis of some tumors. *Sci Am* 323(4): 28. See also: https://www.scientificamerican.com/article/deadly-spread-of-some-cancers-may-be-driven-by-a-common-mouth-microbe/

Casasanta MA, Yoo CC, Udayasuryan B, Sanders BE, Umaña A, Zhang Y, Peng H, Duncan AJ, Li L, Verbridge SS, Slade DJ (2020). *Fusobacterium nucleatum* host-cell binding and invasion induces IL-8 and CXCL1 secretion that drives colorectal cancer cell migration. Sci Signaling 641: eaba9157 DOI: 10.1126/scisignal.aba9157 At: https://stke.sciencemag.org/content/13/641/eaba9157 Abstract: *Fusobacterium nucleatum* is implicated in accelerating colorectal cancer (CRC) and is found within metastatic CRC cells in patient biopsies. Here, we found that bacterial invasion of CRC cells and cocultured immune cells induced a differential cytokine secretion that may contribute to CRC metastasis. We used a modified galactose kinase markerless gene deletion approach and found that *F. nucleatum* invaded cultured HCT116 CRC cells through the bacterial surface adhesin Fap2. In turn, Fap2-dependent invasion induced the secretion of the proinflammatory cytokines IL-8 and CXCL1, which are associated with CRC progression and promoted HCT116 cell migration. Conditioned medium from *F. nucleatum*–infected HCT116 cells caused naïve cells to migrate, which was blocked by depleting CXCL1 and IL-8 from the conditioned medium. Cytokine secretion from HCT116 cells and cellular migration were attenuated by inhibiting *F. nucleatum* host-cell binding and entry using galactose sugars, L-arginine, neutralizing membrane protein antibodies, or *fap2* deletion. *F. nucleatum* also induces the mobilization of immune cells in the tumor microenvironment. However, in neutrophils and macrophages, the bacterial-induced secretion of cytokines was Fap2 independent. Thus, our findings show that *F. nucleatum* both directly and indirectly modulates immune and cancer cell signaling and migration. Because increased IL-8 and CXCL1 production in tumors is associated with increased metastatic potential and cell seeding, poor prognosis, and enhanced recruitment of tumor-associated macrophages and fibroblasts, we propose that inhibition of host-cell binding and invasion, potentially through vaccination or novel galactoside compounds, could be an effective strategy for reducing *F. nucleatum*–associated CRC metastasis.

Lo C-H, Nguyen LH, Wu K, Ogino S, Chan AT, Giovannuci EL, Song M (2020). Periodontal Disease, Tooth Loss, and Risk of Serrated Polyps and Conventional Adenomas. *Cancer Prev Res* 13(8): 699-706. DOI: 10.1158/1940-6207.CAPR-20-0090 At: https://cancerpreventionresearch.aacrjournals.org/content/13/8/699.abstract Abstract: Growing data indicate an association between periodontal disease and the development of cancer. However, the evidence for colorectal cancer has been inconsistent and longitudinal study examining its precursor lesions is lacking. We prospectively collected information on periodontal disease and number of tooth loss in the Nurses' Health Study (1992–2002) and the Health Professionals Follow-up Study (1992–2010). Polyp diagnosis was acquired via self-reported questionnaires and confirmed through review of medical records. We used logistic regression to calculate the multivariate-adjusted ORs and 95% confidence intervals (CI) with adjustment for smoking and other known risk factors for periodontal disease and colorectal cancer. In this study, we included 17,904 women and 24,582 men. We documented 2,336 cases

of serrated polyps and 4,102 cases of conventional adenomas among 84,714 person-endoscopies throughout follow-up. The ORs of serrated polyps and conventional adenomas comparing individuals with and without periodontal disease were 1.17 (95% CI, 1.06–1.29) and 1.11 (95% CI, 1.02–1.19), respectively. Compared with participants without tooth loss, those who lost ≥4 teeth had 20% (OR, 1.20; 95% CI, 1.03–1.39) greater risk of serrated polyps (P_{trend} 0.01). Among never smokers, similar associations with periodontal disease were observed for both serrated polyps (OR, 1.20; 95% CI, 1.02–1.41) and conventional adenomas (OR, 1.12; 95% CI, 1.00–1.26). History of periodontal disease and possibly higher number of tooth loss may modestly increase the risk of developing colorectal precursor lesions. Our findings advance our understanding of the interplay between oral health, microbiome, and early colorectal carcinogenesis. [In terms of disease rather than microbiome.]

Sun J, Tang Q, Yu S, Xie M, Yanling X, Chen G, Chen L (2020). Role of the oral microbiota in cancer evolution and progression. DOI: https://doi.org/10.1002/cam4.3206 At: https://onlinelibrary.wiley.com/doi/full/10.1002/cam4.3206 Abstract: Bacteria identified in the oral cavity are highly complicated. They include approximately 1000 species with a diverse variety of commensal microbes that play crucial roles in the health status of individuals. Epidemiological studies related to molecular pathology have revealed that there is a close relationship between oral microbiota and tumor occurrence. Oral microbiota has attracted considerable attention for its role in in-situ or distant tumor progression. Anaerobic oral bacteria with potential pathogenic abilities, especially *Fusobacterium nucleatum* and *Porphyromonas gingivalis*, are well studied and have close relationships with various types of carcinomas. Some aerobic bacteria such as *Parvimonas* are also linked to tumorigenesis. Moreover, human papillomavirus, oral fungi, and parasites are closely associated with oropharyngeal carcinoma. Microbial dysbiosis, colonization, and translocation of oral microbiota are necessary for implementation of carcinogenic functions. Various underlying mechanisms of oral microbiota-induced carcinogenesis have been reported including excessive inflammatory reaction, immunosuppression of host, promotion of malignant transformation, antiapoptotic activity, and secretion of carcinogens. In this review, we have systemically described the impact of oral microbial abnormalities on carcinogenesis and the future directions in this field for bringing in new ideas for effective prevention of tumors.

Robayo DAG, Hernandez RF, Erira AT, Kandaurova L, Juarez CL, Juarez CL, Juarez V, Cid-Arregui A (2020). Oral Microbiota Associated with Oral and Gastroenteric Cancer. *The Open Microbiol J* 14. D**OI:** 10.2174/1874285802014010001 At: https://openmicrobiologyjournal.com/VOLUME/14/PAGE/1/FULLTEXT/ Abstract: When the normal microbiota-host interactions are altered, the commensal microbial community evolves to a dysbiotic status resulting in some species becoming pathogenic and acting synergistically in the development of local and systemic diseases, including cancer. Advances in genetics, immunology and microbiology during the last years have made it possible to gather information on the oral and gastrointestinal microbiome and its interaction with the host, which has led to a better understanding of the interrelationship between microbiota and cancer. There is growing evidence in support for the role of some species in the development, progression and responses to treatment of various types of cancer. Accordingly, the number of studies investigating the association between oral microbiota and oral and gastrointestinal cancers has

increased significantly during the last years. Here, we review the literature documenting associations of oral microbiota with oral and gastroenteric cancers

Teles FRF, Alawi F, Castilho RM, Wang Y (2020). Association or Causation? Exploring the Oral Microbiome and Cancer Links. *J Dent Res* (Online ahead of print.) At: https://pubmed.ncbi.nlm.nih.gov/32811287/ DOI: 10.1177/0022034520945242 Abstract: The oral microbiota plays an important role in the human microbiome and human health, and imbalances between microbes and their hosts can lead to oral and systemic diseases and chronic inflammation, which is usually caused by bacteria and contributes to cancer. There may be a relationship between oral bacteria and oral squamous cell carcinoma (OSCC); however, this relationship has not been thoroughly characterized. Therefore, in this study, we compared the microbiota compositions between tumor sites and opposite normal tissues in buccal mucosal of 50 patients with OSCC using the 16S rDNA sequencing. Richness and diversity of bacteria were significantly higher in tumor sites than in the control tissues. Cancer tissues were enriched in six families (*Prevotellaceae, Fusobacteriaceae, Flavobacteriaceae, Lachnospiraceae, Peptostreptococcaceae*, and *Campylobacteraceae*) and 13 genera, including *Fusobacterium, Alloprevotella* and *Porphyromonas*. At the species level, the abundances of *Fusobacterium nucleatum, Prevotella intermedia, Aggregatibacter segnis, Capnocytophaga leadbetteri, Peptostreptococcus stomatis*, and another five species were significantly increased, suggesting a potential association between these bacteria and OSCC. Furthermore, the functional prediction revealed that genes involved in bacterial chemotaxis, flagellar assembly and lipopolysaccharide (LPS) biosynthesis which are associated with various pathological processes, were significantly increased in the OSCC group. Overall, oral bacterial profiles showed significant difference between cancer sites and normal tissue of OSCC patients, which might be considered diagnostic markers and treatment targets. Our study has been registered in the Chinese clinical trial registry (ChiCTR1900025253, http://www.chictr.org.cn/index.aspx). **Keywords:** oral microbiota, oral squamous cell carcinoma, *Fusobacterium nucleatum*, *Prevotella intermedia*, *Peptostreptococcus stomatis*, 16S rDNA sequencing.

Robayo DAG, Hernandez RF, Erira AT, Kandaurova L, Juarez CL, Juarez CL, Juarez CL, Juarez V, Cid-Arregui A (2020). Oral Microbiota Associated with Oral and Gastroenteric Cancer. *Open Microbiol J* 14: 1-17. DOI: 10.2174/1874285802014010001 At: https://openmicrobiologyjournal.com/VOLUME/14/PAGE/1/FULLTEXT/ Abstract: When the normal microbiota-host interactions are altered, the commensal microbial community evolves to a dysbiotic status resulting in some species becoming pathogenic and acting synergistically in the development of local and systemic diseases, including cancer. Advances in genetics, immunology and microbiology during the last years have made it possible to gather information on the oral and gastrointestinal microbiome and its interaction with the host, which has led to a better understanding of the interrelationship between microbiota and cancer. There is growing evidence in support for the role of some species in the development, progression and responses to treatment of various types of cancer. Accordingly, the number of studies investigating the association between oral microbiota and oral and gastrointestinal cancers has

increased significantly during the last years. Here, we review the literature documenting associations of oral microbiota with oral and gastroenteric cancers.

Nonaka T, Kaczor-Urbanowicz KE, Wong DTW, "Oral-Systemic Connection: The Salivanomics and Exosomics Connection," Chapter 17, Glick M, Ed. (2019), *The Oral-Systemic Health Connection: A Guide to Patient Care,* 2nd ed. (Quintessence, LCCN 2018044816), pp. 342-356.

https://www.dental.columbia.edu/news/how-common-oral-bacteria-makes-colon-cancer-more-deadly New York, NY (March 4, 2019) – Researchers at the Columbia University College of Dental Medicine have determined how *F. nucleatum* — a common oral bacteria often implicated in tooth decay — accelerates the growth of colon cancer. The study was published online in the journal *EMBO Reports*. The findings could make it easier to identify and treat more aggressive colon cancers. It also helps explain why some cases advance far more quickly than others, thanks to the same bacteria found in dental plaque. Colon cancer is the second leading cause of cancer death in the U.S. Researchers have long known that the disease is caused by genetic mutations that typically accumulate over the course of a decade. "Mutations are just part of the story," says study leader Yiping W. Han, PhD, professor of microbial sciences at Columbia University's College of Dental Medicine and Vagelos College of Physicians & Surgeons." Other factors, including microbes, can also play a role." At: Rubinstein MR, Baik JE, Lagana SM, Han RP, Raab WJ, Sahoo D, Dalerba P, Wang TC, Han YW (2019). Fusobacterium nucleatum promotes colorectal cancer by inducing Wnt/β-catenin modulator Annexin A1. *EMBO Rep* (2019)20:e47638 https://doi.org/10.15252/embr.201847638 At: https://www.embopress.org/doi/10.15252/embr.201847638

Peterson DE, "Oral Complications in the Immunocompromised Patient: The Oncology Prototype," Chapter 13, Glick M, Ed. (2019), *The Oral-Systemic Health Connection: A Guide to Patient Care,* 2nd ed. (Quintessence, LCCN 2018044816), pp. 271-291.

Mascitti M, Togni L, Troiano G, Alberto-Caponio VC, Gissi DB, Montebugnoli L, Procaccini M, Muzio LL, Santarelli A (2019). Beyond Head and Neck Cancer: The Relationship Between Oral Microbiota and Tumour Development in Distant Organs. *Front Cell Infect Microbiol* 9: 232. DOI: 10.3389/fcimb.2019.00232 At: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6607058/ Abstract: An altered oral microbiota has been linked with the development of several oral diseases, such as dental caries, periodontal disease, and oral stomatitis. Moreover, poor oral health has been linked to head and neck cancer, particularly oral cancer. In recent years a growing number of studies indicate that oral microbiota could be involved in the development of primary tumours outside of head and neck region. The aim of this article is to review the recent studies based on high-throughput technology to present evidences of a relationship between oral microbiota and "non-head and neck tumours." Oral dysbiosis seem to be more pronounced in patients with tumours of gastrointestinal tract, in particular oesophageal, gastric, pancreatic, and colorectal cancers, paving the way for developing specific oral microbiota test to allow early cancer detection. Regarding other tumour types, the results are promising but highly preliminary and still debated. Currently, there are several factors that limit the generalization of the results, such as the small sample size, the lack of adequate clinical

information about patients, the different sequencing techniques used, and biological sample heterogeneity. Although only at the beginning, the analysis of oral microbiota could be the next step in the evolution of cancer therapy and will help clinicians to develop individualised approaches to cancer prevention and treatment. **Keywords:** oral microbiota, oral microbiome, pancreatic cancer, gastrointestinal tract cancer, high-throughput sequencing.

Maddi A, Sabharwal A, Violante T, Manuballa S, Genco R, Patnaik S, Yendamuri S (2019). The microbiome and lung cancer. *J Thorc Dis* 11(1): 280-291. DOI: 10.21037/jtd.2018.12.88 At: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6384374/ Abstract: It has become increasingly clear that we live in a symbiotic relationship with microbes within us. We are just beginning to unravel the nature and strength of this relationship and its impact on both physiology and by extension, pathology. While microorganisms have long been known to have carcinogenic potential, their role may have been underestimated. The knowledge of the role of the microbiome in carcinogenesis is rapidly evolving. This evolution has reached a tipping point with current omics technologies used for cataloguing the microbiome. The lung is an organ constantly exposed to the environment. It is now clear that the lung has a distinct microbiome and that this may influence the development of lung cancer. In addition, evidence suggests that this microbiome originates from the oral microbiome. This review summarizes current knowledge about the role of microbiome, especially the oral and lung microbiome in human lung cancer. The goal of the manuscript is to provide a summary of this rapidly evolving field while providing a context of the general role of the microbiome in carcinogenesis. In addition, a primer of the current technology used in evaluating the microbiome is provided to familiarize the practicing clinician with the experimental methods used to generate the information that will likely impact the field of lung cancer.

Gerlovin H, Michaud DS, Cozier YC, Palmer JR (2019). Oral Health in Relation to Pancreatic Cancer Risk in African American Women. Downloaded from cebp.aacrjournals.org on March 29, 2019 *Cancer Epidemiol Biomarkers Prev*; 28(4), April 2019, At: https://pubmed.ncbi.nlm.nih.gov/30923045/ DOI: 10.1158/1055-9965.EPI-18-1053 Abstract: **Background:** Incidence of pancreatic cancer is higher in African Americans than in U.S. whites. We hypothesized that poor oral health, disproportionately common in African Americans and associated with increased risk of pancreatic cancer in several studies of predominantly white populations, may play a role in this disparity. **Methods:** We examined the relation of self-reported measures of oral health (periodontal disease and adult tooth loss) in relation to pancreatic cancer incidence in the prospective Black Women's Health Study (BWHS). Cox proportional hazard analyses were used to calculate HRs of pancreatic cancer for women with periodontal disease, tooth loss, or both, relative to women who reported neither. Multivariable models adjusted for age, cigarette smoking, body mass index (BMI), type 2 diabetes, and alcohol consumption. **Results:** Participants aged 33 to 81 were followed for an average of 9.85 years from 2007 through 2016, with occurrence of 78 incidence cases of pancreatic cancer. Multivariable HRs for pancreatic cancer incidence were 1.77 [95% confidence interval (CI) 0.57-5.49] for periodontal disease with no tooth loss, 2.05 (95% CI, 1.08-3.88) for tooth loss without

report of periodontal disease, and 1.58 (95% CI, 0.70-3.57) for both tooth loss and periodontal disease. The HR for loss of at least five teeth, regardless of whether periodontal disease was reported, was 2.20 (95% CI, 1.11-4.33). **Conclusions:** The poor oral health experienced by many African Americans may contribute to their higher incidence of pancreatic cancer. **Impact:** Future research will assess associations between the oral microbiome and pancreatic cancer risk in this population.

Al-Hebshi, N. N., Borgnakke, W. S., and Johnson, N. W. (2019). The microbiome of oral squamous cell carcinomas: a functional perspective. *Curr. Oral Health Rep.* 6, 145–160. doi: 10.1007/s40496-019-0215-5 At: https://www.researchgate.net/publication/344876587_Screening_of_Health-Associated_Oral_Bacteria_for_Anticancer_Properties_in_vitro/references

Jordão HW, McKenna G, McMenamin, Kunzmann AT, Murray LJ, Coleman HG (2019). The Association Between Self-Reported Poor Oral Health and Gastrointestinal Cancer Risk in the UK Biobank: A Large Prospective Cohort Study. *United European Gastroenterol J* 7(9): 1241-1249. doi: 10.1177/2050640619858043. Epub 2019 Jun 8. At: https://pubmed.ncbi.nlm.nih.gov/31700637/ **Background:** Controversy remains as to whether poor oral health is independently associated with gastrointestinal cancers, due to potential confounding by smoking, alcohol and poor nutrition. The aim of this study was to investigate the association between oral health conditions and gastrointestinal cancer risk. **Methods:** Data from the large, prospective UK Biobank cohort, which includes *n* = 475,766 participants, were analysed. Cox proportional hazard models were applied to estimate the relationship between gastrointestinal cancer risk and self-reported poor oral health (defined as painful gums, bleeding gums and/or having loose teeth), adjusting for confounders. **Results:** During an average six years of follow-up, *n* = 4069 gastrointestinal cancer cases were detected, of which 13% self-reported poor oral health. Overall, there was no association between self-reported poor oral health and risk of gastrointestinal cancer detected (hazard ratio 0.97, 95% confidence interval 0.88-1.07). In site-specific analysis, an increased risk of hepatobiliary cancers was observed in those with self-reported poor oral health (hazard ratio 1.32, 95% confidence interval 0.95-1.80), which was stronger for hepatocellular carcinoma (hazard ratio 1.75, 95% confidence interval 1.04-2.92). **Conclusion:** Overall there was no association between self-reported poor oral health and gastrointestinal cancer risk. However, there was a suggestion of an increased risk of hepatobiliary cancer, specifically hepatocellular carcinoma.

Lu H, Ren Z, Li A, Zheng HJ, Zhang CP (2019). Tongue Coating Microbiome Data Distinguish Patients With Pancreatic Head Cancer From Healthy Controls. *J Oral Microbiol* 9: 476. DOI: 10.1080/20002297.2018.1563409 .At: https://pubmed.ncbi.nlm.nih.gov/30728915/ Abstract: **Background:** The microbiota plays a critical role in the process of human carcinogenesis. Pancreatic head carcinoma (PHC)-associated tongue coating microbiome dysbiosis has not yet been clearly defined. **Objective:** Our aim is to reveal the bacterial composition shifts in the microbiota of the tongue coat of PHC patients. **Design:** The tongue coating microbiota was analyzed in 30 PHC patients and 25 healthy controls using 16S rRNA gene sequencing

technology. **Results:** The microbiome diversity of the tongue coat in PHC patients was significantly increased, as shown by the Shannon, Simpson, inverse Simpson, Obs and incidence-based coverage estimators. Principal component analysis revealed that PHC patients were colonized by remarkably different tongue coating microbiota than healthy controls and liver cancer patients. Linear discriminant analysis effect size revealed that *Leptotrichia*, *Fusobacterium*,*Rothia*, *Actinomyces*, *Corynebacterium*, *Atopobium*, *Peptostreptococcus*, *Catonella*, *Oribacterium*, *Filifactor*, *Campylobacter*, *Moraxella* and *Tannerella* were overrepresented in the tongue coating of PHC patients, and *Haemophilus*, *Porphyromonas* and *Paraprevotella* were enriched in the tongue coating microbiota of healthy controls. Strikingly, *Haemophilus*, *Porphyromonas*, *Leptotrichia* and *Fusobacterium* could distinguish PHC patients from healthy subjects, and *Streptococcus* and SR1 could distinguish PHC patients from liver cancer patients. **Conclusions:** These findings identified the microbiota dysbiosis of the tongue coat in PHC patients, and provide insight into the association between the human microbiome and pancreatic cancer. **Keywords:** Miseq sequencing; Pancreatic head carcinoma; microbiome dysbiosis; tongue coat.

Campbell MJ, McCune E, Johnson B, O'Meara, Heditsian D, Brain S, Esserman L (2019). Breast cancer and the human oral and gut microbiomes [abstract]. In: *Proceedings of the American Association for Cancer Research Annual Meeting 2019*; 2019 Mar 29-Apr 3; Atlanta, GA. Philadelphia (PA): AACR; *Cancer Res* 2019;79(13 Suppl): Abstract nr 2830. At: https://cancerres.aacrjournals.org/content/79/13_Supplement/2830

Vasilyeva D, Peters SM, Philipone EM, Yoon AJ (2018). Renal cell carcinoma metastatic to the maxillary gingiva: A case report and review of the literature. *J Oral Maxillofac Pathol* 22(Suppl 1): S102-S107.DOI: 10.4103/jomfp.JOMFP_69_17 At: https://pubmed.ncbi.nlm.nih.gov/29491617/ Abstract: Tumor metastasis to the oral cavity is rare and is usually an indication of late-stage disease and poor prognosis. While, there are reports of renal cell carcinoma (RCC) metastatic to oral cavity, vast majority of them are to the jaw. Herein, we present a case of a 78-year-old woman with RCC metastasis limited to the oral soft tissue without any bone involvement. As the lesion solely involved maxillary gingiva, it clinically mimicked that of a pyogenic granuloma, which is a reactive, nonneoplastic condition. This case was further complicated as the patient was unaware of primary cancer and appeared to be in good physical health. Her oral metastasis marked the initial manifestation of an otherwise silent primary renal cancer.

McKernan SC, Kuthy RA, Reynolds JC, Tuggle L, García DT (2018). Medical-Dental Integration in Public Health Settings: An Environmental Scan. At: http://ppc.uiowa.edu/sites/default/files/ced_environmental_scan.pdf Executive Summary: Noncommunicable chronic diseases (NCDs) account for almost 90% of total deaths in the United States. The four most common NCDs—cardiovascular diseases, diabetes, cancers, and chronic respiratory diseases—share common risk factors, including cigarette use, alcohol use, and dietary behaviors associated with obesity and elevated blood sugar. The most common oral

diseases—dental caries, periodontal disease, and oral cancer—also share these same risk factors. A coordinated approach to primary prevention, the “common risk factor approach,” argues that coordinated primary prevention of oral and systemic diseases will reduce programmatic costs, and increase efficiency and effectiveness. However, use and evaluation of this coordinated approach in primary prevention activities in the United States has not been well documented. This report describes the results of an environmental scan to identify, categorize, and describe examples of medical-dental integration in US public health settings. Findings are intended to inform public health officials and other stakeholders about existing programs and policies that encourage coordination and integration. Conclusion: Public health activities targeting oral health and chronic diseases operate at multiple levels, including public policy, community-level campaigns, health care delivery systems, and clinical interventions. Well-developed efforts were especially noted for environmental approaches targeting sugar-sweetened beverage consumption, state-level efforts targeting tobacco use and oral cancer, and co-location of medical and dental services. The lack of robust evaluation and effectiveness data surrounding most of the activities described in this report may hamper widespread implementation, sustainability, and stakeholder support

Flemer B, Warren RD, Barrett MP, Cisek K, Das A, Jeffrey IB, Hurley E, O’Riordan M, Shanahan F, O’Toole PW (2018). The oral microbiota in colorectal cancer is distinctive and predictive. *Gut* 67(8): 1454-1463. DOI: 10.1136/gutjnl-2017-314814 At: https://pubmed.ncbi.nlm.nih.gov/28988196/ Abstract: **Background and aims:** Microbiota alterations are linked with colorectal cancer (CRC) and notably higher abundance of putative oral bacteria on colonic tumours. However, it is not known if colonic mucosa-associated taxa are indeed orally derived, if such cases are a distinct subset of patients or if the oral microbiome is generally suitable for screening for CRC. **Methods:** We profiled the microbiota in oral swabs, colonic mucosae and stool from individuals with CRC (99 subjects), colorectal polyps (32) or controls (103). **Results:** Several oral taxa were differentially abundant in CRC compared with controls, for example, *Streptococcus* and *Prevotella*s pp. A classification model of oral swab microbiota distinguished individuals with CRC or polyps from controls (sensitivity: 53% (CRC)/67% (polyps); specificity: 96%). Combining the data from faecal microbiota and oral swab microbiota increased the sensitivity of this model to 76% (CRC)/88% (polyps). We detected similar bacterial networks in colonic microbiota and oral microbiota datasets comprising putative oral biofilm forming bacteria. While these taxa were more abundant in CRC, core networks between pathogenic, CRC-associated oral bacteria such as *Peptostreptococcus*, *Parvimonas* and *Fusobacterium* were also detected in healthy controls. High abundance of Lachnospiraceae was negatively associated with the colonisation of colonic tissue with oral-like bacterial networks suggesting a protective role for certain microbiota types against CRC, possibly by conferring colonisation resistance to CRC-associated oral taxa and possibly mediated through habitual diet. **Conclusion:** The heterogeneity of CRC may relate to microbiota types that either predispose or provide resistance to the disease, and profiling the oral

microbiome may offer an alternative screen for detecting CRC. Ke**ywords:** colonic bacteria; colorectal cancer; colorectal cancer screening; diet; tumour markers.

Peters BA, Wu J, Pei Z, Yang L, Purdue MP, Freedman ND, Jacobs EJ, Gapstur SM, Hayhes RB, Ahn J (2017). Oral microbiome composition reflects prospective risk for esophageal cancers. *Cancer Res* 77(23): 6777-6787. DOI: 10.1158/0008-5472.CAN-17-1296 At: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5726431/ Abstract: Bacteria may play a role in esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC), although evidence is limited to cross-sectional studies. In this study, we examined the relationship of oral microbiota with EAC and ESCC risk in a prospective study nested in two cohorts. Oral bacteria were assessed using 16S rRNA gene sequencing in pre-diagnostic mouthwash samples from n=81/160 EAC and n=25/50 ESCC cases/matched controls. Findings were largely consistent across both cohorts. Metagenome content was predicted using PiCRUST. We examined associations between centered log-ratio transformed taxon or functional pathway abundances and risk using conditional logistic regression adjusting for BMI, smoking, and alcohol. We found the periodontal pathogen Tannerella forsythia to be associated with higher risk of EAC. Further, we found that depletion of the commensal genus Neisseria and the species Streptococcus pneumoniae were associated with lower EAC risk. Bacterial biosynthesis of carotenoids was also associated with protection against EAC. Lastly, the abundance of the periodontal pathogen Porphyromonas gingivalis trended with higher risk of ESCC. Overall, our findings have potential implications for the early detection and prevention of EAC and ESCC. **Keywords:** oral microbiome, esophageal cancer, esophageal adenocarcinoma, esophageal squamous cell carcinoma, bacteria.

Ramos A, Hemann MT (2017). Drugs, Bugs, and Cancer: *Fusobacterium nucleatum* Promotes Chemoresistance in Colorectal Cancer. *Cell* 170(3): 411-413. At: https://www.sciencedirect.com/science/article/pii/S0092867417308255

Yu TC, Guo F, Yu Y, Sun T, Ma D, Han J, Qian Y, Krycek I, Sun D, Nagarsheth N, Chen Y, Chen H, Hong J, Zou W, Fang JY (2017). *Fusobacterium nucleatum* Promotes Chemoresistance to Colorectal Cancer by Modulating Autophagy. *Cell* 170(3): 548-563.e16 At: https://www.sciencedirect.com/science/article/pii/S0092867417308152 Summary: Gut microbiota are linked to chronic inflammation and carcinogenesis. Chemotherapy failure is the major cause of recurrence and poor prognosis in colorectal cancer patients. Here, we investigated the contribution of gut microbiota to chemoresistance in patients with colorectal cancer. We found that *Fusobacterium* (*F.*) *nucleatum* was abundant in colorectal cancer tissues in patients with recurrence post chemotherapy, and was associated with patient clinicopathological characterisitcs. Furthermore, our bioinformatic and functional studies demonstrated that *F. nucleatum* promoted colorectal cancer resistance to chemotherapy. Mechanistically, *F. nucleatum* targeted TLR4 and MYD88 innate immune signaling and specific microRNAs to activate the autophagy pathway and alter colorectal cancer chemotherapeutic response. Thus, *F. nucleatum* orchestrates a molecular network of the Toll-like receptor,

microRNAs, and autophagy to clinically, biologically, and mechanistically control colorectal cancer chemoresistance. Measuring and targeting *F. nucleatum* and its associated pathway will yield valuable insight into clinical management and may ameliorate colorectal cancer patient outcomes.

Nwizu NN, Marshall JR, Moysich K, Genco RJ, Hovey KM, Xiodan M, LaMonte JL, Wactawski-Wende J (2017). Periodontal Disease and Incident Cancer Risk among Postmenopausal Women: Results from the Women's Health Initiative Observational Cohort. *Cancer Epidemiol Biomarkers Prev 26(8):1255-65.* DOI: 10.1158/1055-9965.EPI-17-0212 At: https://cebp.aacrjournals.org/content/26/8/1255

Freudenheim JL, Genco RJ, LaMonte MJ, Millen AE, Hovey KM, Mai X, Nwizu N, Andrews CA, Wactawski-Wende J (2016). Periodontal Disease and Breast Cancer: Prospective Cohort Study of Postmenopausal Women. *Cancer Epidemiol Biomarkers Prev* 25(1): 43-50. DOI: 10.1158/1055-9965.EPI-15-0750 At: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4713270/ Abstract: **Background** Periodontal disease (PD) has been consistently associated with chronic disease; there are no large studies of breast cancer although oral-associated microbes are present in breast tumors. **Methods** In the Women's Health Initiative Observational Study, a prospective cohort of postmenopausal women, 73,737 women without previous breast cancer were followed. Incident, primary, invasive breast tumors were verified by physician adjudication. PD was by self-report. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated by Cox proportional hazards, adjusted for breast cancer risk factors. Because the oral microbiome of those with PD differs with smoking status, we examined associations stratified by smoking. **Results** 2,124 incident, invasive breast cancer cases were identified after mean follow-up of 6.7 years. PD, reported by 26.1% of women, was associated with increased breast cancer risk (HR 1.14, 95% CI 1.03 to 1.26), particularly among former smokers who quit within 20 years (HR 1.36; 95% CI 1.05 to 1.77). Among current smokers, the trend was similar (HR 1.32; 95% CI 0.83 to 2.11); there were few cases (n=74) and the CI included the null. The population attributable fraction was 12.06% (95% CI 1.12 to 21.79) and 10.90% (95% CI 10.31 to 28.94) for PD among former smokers quitting within 20 years and current smokers, respectively. **Conclusion** PD, a common chronic inflammatory disorder, was associated with increased risk of postmenopausal breast cancer, particularly among former smokers who quit in the past 20 years. **Impact** Understanding a possible role of the oral microbiome in breast carcinogenesis could impact prevention. **Keywords:** Breast neoplasms, periodontal disease, postmenopausal women, inflammation, microbiome, epidemiology.

Han P, Sun D, Yang J (2016). Interaction between periodontitis and liver diseases. *Biomed Rep* 5(3): 267-276. Published online 2016 Jul 18. doi: 10.3892/br.2016.718 At: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4998044/ Abstract:Periodontitis is an oral disease that is highly prevalent worldwide, with a prevalence of 30–50% of the population in developed countries, but only ~10% present with severe forms. It is also estimated that periodontitis results in worldwide productivity losses amounting to ~54 billion USD yearly. In

addition to the damage it causes to oral health, periodontitis also affects other types of disease. Numerous studies have confirmed the association between periodontitis and systemic diseases, such as diabetes, respiratory disease, osteoporosis and cardiovascular disease. Increasing evidence also indicated that periodontitis may participate in the progression of liver diseases, such as non-alcoholic fatty liver disease, cirrhosis and hepatocellular carcinoma, as well as affecting liver transplantation. However, to the best of our knowledge, there are currently no reviews elaborating upon the possible links between periodontitis and liver diseases. Therefore, the current review summarizes the human trials and animal experiments that have been conducted to investigate the correlation between periodontitis and liver diseases. Furthermore, in the present review, certain mechanisms that have been postulated to be responsible for the role of periodontitis in liver diseases (such as bacteria, pro-inflammatory mediators and oxidative stress) are considered. The aim of the review is to introduce the hypothesis that periodontitis may be important in the progression of liver disease, thus providing dentists and physicians with an improved understanding of this issue.

Whitmore SE, Lamont RJ; Goldman WE, ed. (2014). Oral Bacteria and Cancer. *PLoS Pathog* 10(3): e1003933. DOI: 10.1371/journal.ppat.1003933 At: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3968118/

Fan X, Alekseyenko AV, Wu J, Peters BA, Jacobs EJ, Gapstur SM, Purdue MP, Abnet CC, Solomon RS, Miller G, Ravel J, Hayes RB, Ahn J (2000). Human oral microbiome and prospective risk for pancreatic cancer: a population-based nested case-control study. *Gut* 67: 120-127. doi:10.1136/gutjnl-2016-312580 At: https://gut.bmj.com/content/67/1/120.abstract Abstract: **Objective** A history of periodontal disease and the presence of circulating antibodies to selected oral pathogens have been associated with increased risk of pancreatic cancer; however, direct relationships of oral microbes with pancreatic cancer have not been evaluated in prospective studies. We examine the relationship of oral microbiota with subsequent risk of pancreatic cancer in a large nested case–control study. **Design** We selected 361 incident adenocarcinoma of pancreas and 371 matched controls from two prospective cohort studies, the American Cancer Society Cancer Prevention Study II and the National Cancer Institute Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. From pre-diagnostic oral wash samples, we characterised the composition of the oral microbiota using bacterial 16S ribosomal RNA (16S rRNA) gene sequencing. The associations between oral microbiota and risk of pancreatic cancer, controlling for the random effect of cohorts and other covariates, were examined using traditional and L1-penalised least absolute shrinkage and selection operator logistic regression. **Results** Carriage of oral pathogens, *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*, were associated with higher risk of pancreatic cancer (adjusted OR for presence vs absence=1.60 and 95% CI 1.15 to 2.22; OR=2.20 and 95% CI 1.16 to 4.18, respectively). Phylum *Fusobacteria* and its genus *Leptotrichia* were associated with decreased pancreatic cancer risk (OR per per cent increase of relative abundance=0.94 and 95% CI 0.89 to 0.99; OR=0.87 and 95% CI 0.79 to 0.95, respectively). Risks related to these phylotypes remained after exclusion of cases that developed within 2 years of sample

collection, reducing the likelihood of reverse causation in this prospective study. **Conclusions** This study provides supportive evidence that oral microbiota may play a role in the aetiology of pancreatic cancer.

Oral Cancer, Head and Neck Cancer

Fitzsimonds Z, Rodriguez,-Hernandez CJ, Bagaitkar J, Lamont RJ (2020). From Beyond the Pale to the Pale Riders: The Emerging Association of Bacteria with Oral Cancer. *J Dent Res* 99(6): 604-612. DOI: 10.1177/0022034520907341 At: https://pubmed.ncbi.nlm.nih.gov/32091956/ Abstract : Oral cancer, predominantly oral squamous cell carcinoma (OSCC), is the eighth-most common cancer worldwide, with a 5-y survival rate <50%. There are numerous risk factors for oral cancer, among which periodontal disease is gaining increasing recognition. The creation of a sustained dysbiotic proinflammatory environment by periodontal bacteria may serve to functionally link periodontal disease and oral cancer. Moreover, traditional periodontal pathogens, such as Porphyromonas gingivalis, Fusobacterium nucleatum, and Treponema denticola, are among the species most frequently identified as being enriched in OSCC, and they possess a number of oncogenic properties. These organisms share the ability to attach and invade oral epithelial cells, and from there each undergoes its own unique molecular dialogue with the host epithelium, which ultimately converges on acquired phenotypes associated with cancer, including inhibition of apoptosis, increased proliferation, and activation of epithelial-to-mesenchymal transition leading to increased migration of epithelial cells. Additionally, emerging properties of structured bacterial communities may increase oncogenic potential, and consortia of P. gingivalis and F. nucleatum are synergistically pathogenic within in vivo oral cancer models. Interestingly, however, some species of oral streptococci can antagonize the phenotypes induced by P. gingivalis, indicating functionally specialized roles for bacteria in oncogenic communities. Transcriptomic data support the concept that functional, rather than compositional, properties of oral bacterial communities have more relevance to cancer development. Collectively, the evidence is consistent with a modified polymicrobial synergy and dysbiosis model for bacterial involvement in OSCC, with driver mutations generating a conducive microenvironment on the epithelial boundary, which becomes further dysbiotic by the synergistic action of bacterial communities. **Keywords***: F. nucleatum*; OSCC; *P. gingivalis; S. gordonii; T. denticola;* polymicrobial synergy and dysbiosis.

Zhang L, Liu Y, Zheng HJ, Zhang CP (2020). The Oral Microbiota May Have Influence on Oral Cancer. *Front Cell Infect Microbiol* 9: 476. DOI: 10.3389/fcimb.2019.00476 At: https://pubmed.ncbi.nlm.nih.gov/32010645/ Abstract: The oral microbiota plays an important role in the human microbiome and human health, and imbalances between microbes and their hosts can lead to oral and systemic diseases and chronic inflammation, which is usually caused by bacteria and contributes to cancer. There may be a relationship between oral bacteria and oral squamous cell carcinoma (OSCC); however, this relationship has not been thoroughly characterized. Therefore, in this study, we compared the microbiota compositions between tumor sites and opposite normal tissues in buccal mucosal of 50 patients with OSCC using the 16S rDNA sequencing. Richness and diversity of bacteria were significantly higher in tumor sites than in the control tissues. Cancer tissues were enriched in six families (*Prevotellaceae, Fusobacteriaceae, Flavobacteriaceae, Lachnospiraceae, Peptostreptococcaceae*, and

Campylobacteraceae) and 13 genera, including *Fusobacterium, Alloprevotella* and *Porphyromonas*. At the species level, the abundances of *Fusobacterium nucleatum, Prevotella intermedia, Aggregatibacter segnis, Capnocytophaga leadbetteri, Peptostreptococcus stomatis*, and another five species were significantly increased, suggesting a potential association between these bacteria and OSCC. Furthermore, the functional prediction revealed that genes involved in bacterial chemotaxis, flagellar assembly and lipopolysaccharide (LPS) biosynthesis which are associated with various pathological processes, were significantly increased in the OSCC group. Overall, oral bacterial profiles showed significant difference between cancer sites and normal tissue of OSCC patients, which might be onsidered diagnostic markers and treatment targets. Our study has been registered in the Chinese clinical trial registry (ChiCTR1900025253, http://www.chictr.org.cn/index.aspx). **Keywords:** 16S rDNA sequencing; Fusobacterium nucleatum; Peptostreptococcus stomatis; Prevotella intermedia; oral microbiota; oral squamous cell carcinoma.

Teles FRF, Alawi F, Castilho RM, Wang Y (2020). Association or Causation? Exploring the Oral Microbiome and Cancer Links. *J Dent Res* (Online ahead of print.) At: https://pubmed.ncbi.nlm.nih.gov/32811287/ DOI: 10.1177/0022034520945242 Abstract: The oral microbiota plays an important role in the human microbiome and human health, and imbalances between microbes and their hosts can lead to oral and systemic diseases and chronic inflammation, which is usually caused by bacteria and contributes to cancer. There may be a relationship between oral bacteria and oral squamous cell carcinoma (OSCC); however, this relationship has not been thoroughly characterized. Therefore, in this study, we compared the microbiota compositions between tumor sites and opposite normal tissues in buccal mucosal of 50 patients with OSCC using the 16S rDNA sequencing. Richness and diversity of bacteria were significantly higher in tumor sites than in the control tissues. Cancer tissues were enriched in six families (*Prevotellaceae, Fusobacteriaceae, Flavobacteriaceae, Lachnospiraceae, Peptostreptococcaceae*, and *Campylobacteraceae*) and 13 genera, including *Fusobacterium, Alloprevotella* and *Porphyromonas*. At the species level, the abundances of *Fusobacterium nucleatum, Prevotella intermedia, Aggregatibacter segnis, Capnocytophaga leadbetteri, Peptostreptococcus stomatis*, and another five species were significantly increased, suggesting a potential association between these bacteria and OSCC. Furthermore, the functional prediction revealed that genes involved in bacterial chemotaxis, flagellar assembly and lipopolysaccharide (LPS) biosynthesis which are associated with various pathological processes, were significantly increased in the OSCC group. Overall, oral bacterial profiles showed significant difference between cancer sites and normal tissue of OSCC patients, which might be considered diagnostic markers and treatment targets. Our study has been registered in the Chinese clinical trial registry (ChiCTR1900025253, http://www.chictr.org.cn/index.aspx). **Keywords:** oral microbiota, oral squamous cell carcinoma, *Fusobacterium nucleatum*, *Prevotella intermedia*, *Peptostreptococcus stomatis*, 16S rDNA sequencing.

Amit M, Takahashi H, Dragomir MP *et al.* (2020) Loss of p53 drives neuron reprogramming in head and neck cancer. *Nature* 578, 449–454. https://doi.org/10.1038/s41586-020-1996-3 At: https://www.nature.com/articles/s41586-020-1996-3?WT.ec_id=NATURE-202002&sap-

outbound-id=E51ED5B1AAA3724B421F5D9BD6FA5A09D7BFD3CF&mkt-key=005056B0331B1EE7A9F0A8C9FD77F02A#citeas

Zhang L, Liu Y, Zheng HJ, Zhang CP (2019). The Oral Microbiota May Have Influence on Oral Cancer. *Front Cell Infect Microbiol* 9 : 476. DOI: 10.3389/fcimb.2019.00476 At: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6974454/ Abstract: The oral microbiota plays an important role in the human microbiome and human health, and imbalances between microbes and their hosts can lead to oral and systemic diseases and chronic inflammation, which is usually caused by bacteria and contributes to cancer. There may be a relationship between oral bacteria and oral squamous cell carcinoma (OSCC); however, this relationship has not been thoroughly characterized. Therefore, in this study, we compared the microbiota compositions between tumor sites and opposite normal tissues in buccal mucosal of 50 patients with OSCC using the 16S rDNA sequencing. Richness and diversity of bacteria were significantly higher in tumor sites than in the control tissues. Cancer tissues were enriched in six families (*Prevotellaceae, Fusobacteriaceae, Flavobacteriaceae, Lachnospiraceae, Peptostreptococcaceae*, and *Campylobacteraceae*) and 13 genera, including *Fusobacterium, Alloprevotella* and *Porphyromonas*. At the species level, the abundances of *Fusobacterium nucleatum, Prevotella intermedia, Aggregatibacter segnis, Capnocytophaga leadbetteri, Peptostreptococcus stomatis*, and another five species were significantly increased, suggesting a potential association between these bacteria and OSCC. Furthermore, the functional prediction revealed that genes involved in bacterial chemotaxis, flagellar assembly and lipopolysaccharide (LPS) biosynthesis which are associated with various pathological processes, were significantly increased in the OSCC group. Overall, oral bacterial profiles showed significant difference between cancer sites and normal tissue of OSCC patients, which might be onsidered diagnostic markers and treatment targets. Our study has been registered in the Chinese clinical trial registry (ChiCTR1900025253, http://www.chictr.org.cn/index.aspx). **Keywords:** oral microbiota, oral squamous cell carcinoma, *Fusobacterium nucleatum*, *Prevotella intermedia*, *Peptostreptococcus stomatis*, 16S rDNA sequencing

Karpinski TM (2019). Role of Oral Microbiota in Cancer Development. *Microorganisms* 7(1) 20. doi: 10.3390/microorganisms7010020 At: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6352272/ Abstract: Nowadays cancer is the second main cause of death in the world. The most known bacterial carcinogen is *Helicobacter pylori*. Pathogens that can have an impact on cancer development in the gastrointestinal tract are also found in the oral cavity. Some specific species have been identified that correlate strongly with oral cancer, such as *Streptococcus* sp., *Peptostreptococcus* sp., *Prevotella* sp., *Fusobacterium* sp., *Porphyromonas gingivalis*, and *Capnocytophaga gingivalis*. Many works have also shown that the oral periopathogens *Fusobacterium nucleatum* and *Porphyromonas gingivalis* play an important role in the development of colorectal and pancreatic cancer. Three mechanisms of action have been suggested in regard to the role of oral microbiota in the pathogenesis of cancer. The first is bacterial stimulation of chronic inflammation. Inflammatory mediators produced in this process cause or facilitate cell proliferation, mutagenesis, oncogene activation, and angiogenesis. The second mechanism attributed to bacteria that may influence the pathogenesis of cancers by affecting cell proliferation is the activation of NF-κB and inhibition of cellular apoptosis. In the third mechanism, bacteria produce some substances that

act in a carcinogenic manner. This review presents potentially oncogenic oral bacteria and possible mechanisms of their action on the carcinogenesis of human cells.

Chattopadhyay I, Verma M, Panda M (2019). Role of Oral Microbiome Signatures in Diagnosis and Prognosis of Oral Cancer. *Technol Cancer Res Treat* 18: 1533033819867354. DOI: 10.1177/1533033819867354 At: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6676258/ Abstract: Despite advancement in cancer treatment, oral cancer has a poor prognosis and is often detected at late stage. To overcome these challenges, investigators should search for early diagnostic and prognostic biomarkers. More than 700 bacterial species reside in the oral cavity. The oral microbiome population varies by saliva and different habitats of oral cavity. Tobacco, alcohol, and betel nut, which are causative factors of oral cancer, may alter the oral microbiome composition. Both pathogenic and commensal strains of bacteria have significantly contributed to oral cancer. Numerous bacterial species in the oral cavity are involved in chronic inflammation that lead to development of oral carcinogenesis. Bacterial products and its metabolic by-products may induce permanent genetic alterations in epithelial cells of the host that drive proliferation and/or survival of epithelial cells. *Porphyromonas gingivalis* and *Fusobacterium nucleatum* induce production of inflammatory cytokines, cell proliferation, and inhibition of apoptosis, cellular invasion, and migration thorough host cell genomic alterations. Recent advancement in metagenomic technologies may be useful in identifying oral cancer–related microbiome, their genomes, virulence properties, and their interaction with host immunity. It is very important to address which bacterial species is responsible for driving oral carcinogenesis. Alteration in the oral commensal microbial communities have potential application as a diagnostic tool to predict oral squamous cell carcinoma. Clinicians should be aware that the protective properties of the resident microflora are beneficial to define treatment strategies. To develop highly precise and effective therapeutic approaches, identification of specific oral microbiomes may be required. In this review, we narrate the role of microbiome in the progression of oral cancer and its role as an early diagnostic and prognostic biomarker for oral cancer. **Keywords:** oral microbiome, biofilm, oral cancer, inflammation, biomarker.

Al-Hebshi, N. N., Borgnakke, W. S., and Johnson, N. W. (2019). The microbiome of oral squamous cell carcinomas: a functional perspective. *Curr. Oral Health Rep.* 6, 145–160. doi: 10.1007/s40496-019-0215-5 At: https://www.researchgate.net/publication/344876587_Screening_of_Health-Associated_Oral_Bacteria_for_Anticancer_Properties_in_vitro/references

Michaud DS, Fu Z, Shi J, Chung M (2017). Periodontal Disease, Tooth Loss, and Cancer Risk. *Epidemiol Rev* 39(1): 49-58. DOI: 10.1093/epirev/mxx006 At: https://pubmed.ncbi.nlm.nih.gov/28449041/ Abstract: Periodontal disease, which includes gingivitis and periodontitis, is highly prevalent in adults and disease severity increases with age. The relationship between periodontal disease and oral cancer has been examined for several decades, but there is increasing interest in the link between periodontal disease and overall cancer risk, with systemic inflammation serving as the main focus for biological plausibility. Numerous case-control studies have addressed the role of oral health in head and neck cancer, and several cohort studies have examined associations with other types of cancers over the

past decade. For this review, we included studies that were identified from either 11 published reviews on this topic or an updated literature search on PubMed (between 2011 and July 2016). A total of 50 studies from 46 publications were included in this review. Meta-analyses were conducted on cohort and case-control studies separately when at least 4 studies could be included to determine summary estimates of the risk of cancer in relation to 1) periodontal disease or 2) tooth number (a surrogate marker of periodontal disease) with adjustment for smoking. Existing data provide support for a positive association between periodontal disease and risk of oral, lung, and pancreatic cancers; however, additional prospective studies are needed to better inform on the strength of these associations and to determine whether other cancers are associated with periodontal disease. Future studies should include sufficiently large sample sizes, improved measurements for periodontal disease, and thorough adjustment for smoking and other risk factors. **Keywords:** cancer; meta-analysis; periodontal disease; periodontitis; review.

Parera M, Speicher DJ, Al-Hebshi N, Parera I (2016). Emerging Role of bacteria in oral carcinogenesis: A review with special reference to perio-pathogenic bacteria. *J Oral Microbiol* 8: 10.3402/jom.v8.32762 DOI: 10.3402/jom.v8.32762 At: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5039235/ Abstract: Oral cancer, primarily oral squamous cell carcinoma (OSCC), continues to be a major global health problem with high incidence and low survival rates. While the major risk factors for this malignancy, mostly lifestyle related, have been identified, around 15% of oral cancer cases remain unexplained. In light of evidence implicating bacteria in the aetiology of some cancer types, several epidemiological studies have been conducted in the last decade, employing methodologies ranging from traditional culture techniques to 16S rRNA metagenomics, to assess the possible role of bacteria in OSCC. While these studies have demonstrated differences in microbial composition between cancerous and healthy tissues, they have failed to agree on specific bacteria or patterns of oral microbial dysbiosis to implicate in OSCC. On the contrary, some oral taxa, particularly *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, show strong oral carcinogenic potential in vitro and in animal studies. Bacteria are thought to contribute to oral carcinogenesis via inhibition of apoptosis, activation of cell proliferation, promotion of cellular invasion, induction of chronic inflammation, and production of carcinogens. This narrative review provides a critical analysis of and an update on the association between bacteria and oral carcinogenesis and the possible mechanisms underlying it. **Keywords:** bacteria, carcinoma, dysbiosis, inflammation, microbiome, mouth, squamous cell

Al-Hebshi N, Borgnakke WS, Johnson N (2019). The Microbiome of Oral Squamous Cell Carcinomas: a Functional Perspective. Curr Oral Health Rep DOI: 10.1007/s40496-019-0215-5 At: https://www.semanticscholar.org/paper/The-Microbiome-of-Oral-Squamous-Cell-Carcinomas%3A-a-Al-Hebshi-Borgnakke/243eb1b62648e367b9136a7f02e25db0a279947e Abstract: Purpose of Review This decade has witnessed increasing interest in the potential role of the oral microbiome in head and neck cancers, particularly oral squamous cell carcinoma (OSCC). Most studies have focused on the bacterial component of the microbiome

(bacteriome), but the fungal component (mycobiome) is also receiving attention. In this review, we provide an overview of mechanisms by which the microbiome can contribute to oral carcinogenesis, and summarize results from clinical studies, especially focusing on those reporting functional microbiome analysis. Synthesizing and illustrating the evidence, we also suggest a new “passenger-turning-driver” functional model for the role of the microbiome in oral cancer. Recent Findings In vitro studies provide convincing evidence for the carcinogenicity of the periodontal bacteria Fusobacterium nucleatum and Porphyromonas gingivalis. However, results from clinical studies are inconsistent, with significant variations in composition of the microbiome associated with oral cancer. Methodological differences may partially explain the differing conclusion. However, variations observed may also reflect functional redundancy: the phenomenon that different species may be enriched in different samples, but still serve the same functions. Indeed, functional analyses of the bacteriome associated with oral cancer have revealed more consistent results, namely enrichment of a virulent, inflammatory bacteriome in the tumors. Summary Apart from oncoviruses associated with a special entity of oral cancer, no consistent evidence implicates specific microbial species in OSCC etiology. Instead, the disturbed function of an initially “passenger” microbiome within the tumor microenvironment likely contributes to tumor progression by sustaining chronic inflammation.

Vasilyeva D, Peters S M, Philipone E M, Yoon A J (2018). Renal cell carcinoma metastatic to the maxillary gingiva: A case report and review of the literature. *J Oral Maxillofac Pathol* **22:** 102-107.

Oral Complications of Cancer Treatment

NIDCR (2009). *Oral Complications of Cancer Treatment: What the Dental Team Can Do.* https://www.nidcr.nih.gov/sites/default/files/2017-09/oral-complications-cancer-dental-team.pdf With over 1.4 million new cases of cancer diagnosed each year and a shift to outpatient management, you will likely see some of these patients in your practice. Because cancer treatment can affect the oral tissues, you need to know about potential oral side effects. Preexisting or untreated oral disease can also complicate cancer treatment. Your role in patient management can extend benefits beyond the oral cavity. Oral complications from radiation to the head and neck or chemotherapy for any malignancy can compromise patients’ health and quality of life, and affect their ability to complete planned cancer treatment. For some patients, the complications can be so debilitating that they may tolerate only lower doses of therapy, postpone scheduled treatments, or discontinue treatment entirely. Oral complications can also lead to serious systemic infections. Medically necessary oral care before, during, and after cancer treatment can prevent or reduce the incidence and severity of oral complications, enhancing both patient survival and quality of life.

Cancer Risk

Rajesh KS, Thomas D, Hegde S, Kumar MSA (2013). Poor periodontal health: A cancer risk? *J Indian Soc Periodotol* 17(6): 706-710. DOI: 10.4103/0972-124X.124470 At: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3917197/ Abstract: Evidence indicates that chronic infections and inflammation are associated with increased risk of cancer development. There has also been considerable evidence that proves the interrelationship between bacterial

and viral infections and carcinogenesis. Periodontitis is a chronic oral infection thought to be caused by gram-negative anaerobic bacteria in the dental biofilm. Periodontal bacteria and viruses may act synergistically to cause periodontitis. Many studies have shown that periodontal pockets may act as reservoirs for human papilloma virus, cytomegalovirus, Epstein Barr virus, and suspected agents associated with oral cancer. Periodontitis, characterized by epithelial proliferation and migration, results in a chronic release of inflammatory cytokines, chemokines, growth factors, prostaglandins, and enzymes, all of which are associated with cancer development. This review article intends to shed light on the association between periodontal health and carcinogenesis. **Keywords:** Carcinoma, inflammation, microorganisms, poor oral hygiene, virus.

Anticancer Properties, Oral Bacteria

Baraniva D, Jain D, Lucarelli R, Tam V, Vanderveer L, Puri , Yang M, Al-Hehshu NN (2020). Screening of Health-Associated Oral Bacteria for Anticancer Properties in vitro. *Front Cell Infect Microbiol* DOI: 10.3389/fcimb.2020.575656 At: https://www.frontiersin.org/articles/10.3389/fcimb.2020.575656/full Abstract: While extensive literature exists about the role of oral bacterial pathogens like *Porphyromonas gingivalis* and *Fusobacterium nucleatum* in oral squamous cell carcinoma (OSCC), the role of health-associated species has been largely unexplored. In this study, we assessed the effect of *Streptococcus mitis, Rothia mucilaginosa, Neisseria flavescens, Haemophilus parainfluenzae, Lautropia mirabilis*, and *Veillonella parvula* on proliferation and expression of marker genes (IL-6, TNF-α, MMP3, CD36, CCD1, and NANOG) in OSCC cell lines CAL27, SCC25, and SCC4. *Porphyromonas gingivalis* was included as a pathogenic control. Both bacterial lysates (3 concentrations) and live cells (3 MOIs) were tested. *S. mitis, H. parainfluenzae*, and *N. flavescens* resulted in substantial, dose-dependent reduction of proliferation, which was found to be mediated by H_2O_2 for the former and intracellular infection in the latter two species. However, only *H. parainfluenzae* showed differential antiproliferative effect against the cancer cell lines vs. the normal control (TIGKs). In the gene expression assays, the health-associated species mostly downregulated CD36, a gene that plays an important role in tumor growth and metastasis, while *P. gingivalis* upregulated it. IL6 and TNF expression, on the other hand, was upregulated by almost all species, particularly the Gram-negatives including *P. gingivalis*. The effect on other genes was less evident and varied significantly by cell line. This exploratory study is the first insight into how health-associated bacteria may interact with OSCC. Further studies to explore whether the observed effects may have implications for the prevention or treatment of oral cancer are warranted.

The compilation of this bibliographic resource was contributed by Dr. Valerie J. H. Powell, Project on Clinical Data Integration, Department of Computer and Information Systems, Robert Morris University (RMU), Moon Township. Pennsylvania (2020).

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