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The Effect of *Porphyromonas gingivalis* on Gut Dysbiosis and Its Possible Association with Orodigestive Cancers

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Abbreviations: IBS: Inflammatory Bowel Disease; OSCC: Oral Squamous Cell Carcinoma; HIOEC: Human Immortalized Oral Epithelial Cells; MMP-9: Matrix Metalloproteinase-9; EMT: Epithelial-Mesenchymal Transition; ESCC: Esophageal Squamous Cell Carcinoma; GC: Gastric Cancer; HCC: Hepatocellular Carcinoma; CRC: Colorectal Cancer.

Introduction

The oral microbiota is the microbial community of the oral cavity and is one of the most divergent microbiomes of all the human body. It has an important role in maintaining oral homeostasis [1]. The oral microbiota also plays a part in the pathophysiology of orodigestive cancers [2]. Contributing to the total number of malignancies worldwide, orodigestive cancers include those cancers of the oral cavity and gastrointestinal tract as well as pancreas [3]. The oral microbiome also represents a dynamic biochemical network that is formed by the interaction of proteomes and metabolomes. The hygienic and dietary habits of the host, along with the genetic, behavioral and immunologic host factors also contribute to this formation.

The oral cavity contains a vast variety of flora as opposed to the entire human body. Along with the respiratory system, the oral cavity is also the main entrance of the gastrointestinal system [4]. Different diseases associated with the gastrointestinal system have manifested in the oral cavity. The gastrointestinal tract, along with its accessory organs, comprises the digestive system. In addition to the stomach, small intestine and large intestine, the gastrointestinal tract includes the oral cavity, pharynx and esophagus [5].

The digestive system functions as a mechanical processor that also absorbs foods, secretes all but not limited to water, enzymes and salts as well as excretes waste products. In the same way, the oral cavity conducts mechanical processing with the help of the teeth, tongue and palatal surfaces. The oral cavity also serves as lubrication by combining foods with salivary gland secretion and mucus [5].

Along with the hard and soft pallet, cheeks, gums and teeth, the gingival crevices between the teeth and gums are niches for bacteria colonization of the mouth. Researchers have found that a numerous amount of diseases of the gastrointestinal system involve the mouth. Gastrointestinal tumors, common malignant rumors with a high mortality and morbidity rate, also have low diagnosis rates in the early stages [6].

Accordingly, oral cancer incidence is continuously increasing. There are between 350,000 to 400,000 new cases diagnosed worldwide each year. Bacteria, fungi and viruses are strong etiological factors in these cancers [7]. The cancer sites present a loss of diversity of commensal species, and microbial disturbances enhance the emergence of carcinogenic species to promote cancer development [8].

Moreover, the oral cavity and colon, for example, are in anatomically opposite regions, however, they are both colonized by distinct microbiotas. Oral bacteria have been linked to intestinal dysbiosis in colorectal cancer as well as other orodigestive and gastrointestinal cancers [1]. Dysbiosis refers to the disturbance of the ecosystem of the microbiota [9]. Several oral disorders, including periodontitis, oral cancer and gingivitis, are all associated with dysbiosis of the oral microbiota. Studies indicate that oral bacteria disseminate into the gastrointestinal tract.

Poor oral health has the potential to increase systemic inflammation, as well as result in an overly aggressive and local immune response. Potentially, the gut microbiota can by altered by periodontal disease-causing pathogens. As a chronic inflammatory disease of the tissues supporting the teeth, periodontal disease causes tooth loss. Through the spreading of bacterial infections and gum inflammation to both ligaments and bones that support teeth, it develops over the course of many years. This leads researchers to believe *Porphyromonas gingivalis* could be an important implication for colorectal cancer development [10].

Four defined structures, that constitute the teeth and make up the periodontal tissues, are alveolar bone, cementum, gingiva and the periodontal ligament. Gingivitis is the mildest form of the periodontal disease and is caused by the accumulation of bacterial biofilm that affects the gingiva. The bacterial infection and persistent inflammatory response induces the progressive destruction of the tissues, leading to periodontitis [11]. According to the research paper, Can Oral Bacteria Affect the Microbiome of the Gut?" published by Ingar Olsen, oral bacteria has been shown to translocate to the gut. Diseases associated with periodontal disease have also been linked with gut dysbiosis. This causes changes in its microbiota as well as possible disruption to immune defense [12].

As stated in the research paper written by Olsen, *Porphyromonas gingivalis* creates an imbalance or maladaptation, also known as dysbiosis, in the subgingival microbiota. *Porphyromonas gingivalis* is an anaerobic, gram-negative bacterium that is strongly associated with periodontal disease and colonizes in the epithelium [13]. *Porphyromonas gingivalis* has a high genetic capability to develop resistance when an unfavorable interventional condition arises against its proliferation [14]. It has been linked to the development of digestive cancers like primary pancreatic adenocarcinoma [1]. As a result, there is dysregulation in the gut. *Porphyromonas gingivalis* survives and persists in the oral epithelium. After the primary cell of an individual is infected with *Porphyromonas gingivalis*, the possibility of carcinogenesis is significantly increased [6].

As a prime etiological agent in periodontal pathogenesis and progression, *Porphyromonas gingivalis* was found in 85.75 percent of subgingival plaque samples from test subjects diagnosed with chronic periodontitis [15].

When the host cell is infected, *Porphyromonas gingivalis* activates the expression of the B7-H1 receptor. This contributes to apoptosis of the activated T cells and leads to immune evasion, promoting tumorigenesis [13]. Through its involvement with *Porphyromonas gingivalis*, periodontal disease causes the host organism to be in an overall inflammatory state. Independently of periodontitis, the presence of *Porphyromonas gingivalis* also enhances tumorigenic properties. *Porphyromonas gingivalis* has the ability to promote a microbial environment favorable for disease [16]. This pathogen can manipulate the host machinery to facilitate long-term survival once invaded. It inhibits the apoptotic pathway. Moreover, there is a 33 percent higher presence of *Porphyromonas gingivalis* in gingival carcinomas than in normal gingiva [16]. Thus, *Porphyromonas gingivalis* serves as a potential etiological agent inducing tumorigenesis.

Within the Human Microbiome Project, it was discovered that bacteria found in the oral cavity overlapped with those found in stool in 45 percent of the tested subjects [12]. It has been concluded that the transfer of oral bacteria to the gut is common. The oral microbiome and specific subset of *Porphyromonas gingivalis* has been suggested to play an essential role in both anatomically and clinically diseases. These chronic illnesses include periodontal disease, gastrointestinal cancers and orodigestive cancers [17].

As one of the hundreds of bacterial species originating from the oral cavity, *Porphyromonas gingivalis* also plays a role in the dental plaque composition. *Porphyromonas gingivalis* also destroys the homeostasis of its host, leading to biological disorders and diseases [13]. The colonization of *Porphyromonas gingivalis* also causes toxicity as it secretes hemin- binding proteins, proteinases and protein adhesions- all factors leading to such toxicity. Due to periodontitis causing systemic diseases, *Porphyromonas gingivalis* has been extensively linked with intestinal dysbiosis because of its effect on oral immunity [1].

In reference to research published by Olsen, through swallowed saliva, nutrients and drinks, oral as well as oropharyngeal microbiota are able to reach the stomach. Ingested saliva contains an immense number of oral bacteria that are poor colonizers of the intestine. It was documented that in severe diseases, an increased amount of the oral bacteria was found in the intestine. These diseases included inflammatory bowel disease (IBS), gastroesophageal reflux disease and liver cirrhosis [12]. The periodontal pathogen Porphyromonas gingivali was swallowed daily by patients with periodontitis, a severe gum infection [18].

Although the pH of the stomach varies, its natural state is between pH levels of 1.5 and 3.5 [19]. Oral bacteria were found to tolerate the harsh pH levels of the stomach, leading researchers to suggest that the oral bacteria can proliferate in the gastrointestinal tract [12]. Specifically, *Porphyromonas gingivalis* is acid-resistant allowing migration to the colon to occur and leading to changes in colonic functions. In correlation with this, *Porphyromonas gingivalis* may have a possible association with orodigestive cancers [12].

In the oral cavity, *Porphyromonas gingivalis* seize and takes over leukocytes by altering the defense functions and migration. *Porphyromonas gingivalis* also elicits inflammation so that it can obtain the nutrients from the tissue breakdown [20]. As an anaerobe, *Porphyromonas gingivalis* locates itself within the sub-gingival pocket. At this position, the bacterium encounters a neutrophil. From studies involving periodontitis in mice, it was confirmed that *Porphyromonas gingivalis* inhibits the expression of neutrophil-recruiting chemokines.

Periodontal disease, characterized by its chronic inflammation, is a significant risk for orodigestive carcinogenesis [21]. The increasing evidence leads to a strong association between periodontitis and oral, gastrointestinal and pancreatic cancers. In oral squamous cell carcinoma (OSCC), *Porphyromonas gingivalis* has been recovered in abundance. There have also been tumorigenesis models recently established that shows a direct relationship between carcinogenesis and *Porphyromonas gingivalis* [21]. The bacterium upregulates certain OSCC cell receptors and transitions normal oral epithelial cells in cultures of the carcinoma cells. *Porphyromonas gingivalis* was also proven to suppress apoptosis in the oral epithelial cell cultures as well as accelerate cell cycling. In oral cancer cells, the cell cycle is arrested and apoptosis is not affected. However, macro autophagy was found to be increased.

To observe the underlying effect of *Porphyromonas gingivalis*, researchers established a novel model that exposed human immortalized oral epithelial cells (HIOEC) to *Porphyromonas gingivalis*. The exposure was at low multiplicity of infection, between five to 23 weeks in duration. The cells were monitored for tumor alteration. Microarray analysis was performed on HIOEC. The results of the study showed that constant exposure to *Porphyromonas gingivalis* caused morphological changes in the cell and the S phase fraction of the cell cycle was higher. The invasive properties of the cell were also promoted as well as the ability for the cell to migrate [22].

Research conducted in 2016 shows oral cancer, globally, was the sixth most common type of carcinoma [13]. *Porphyromonas gingivalis* contribute to deoxyribonucleic acid (DNA) damage as well as mutational and excessive proliferation of the epithelium. It was also discovered that the concentration rate of *Porphyromonas gingivalis* among cancer cells were significantly higher than normal tissues of the mouth. Patients with chronic infection of *Porphyromonas gingivalis* expressed CD44 and CD133, both which are cancer stem cell markers. This led to the promotion of tumorigenic properties, originating because of Porphyromonas gingivali [13]. Patients who were infected with *Porphyromonas gingivalis* also had an increase in matrix metalloproteinase-9 (MMP-9), a class of enzymes involved in the degradation of extracellular matrix [23]. Activated MMP-9 promotes the invasion of tumor cells.

Amongst several digestive cancers, *Porphyromonas gingivalis* has been reported to be responsible for the destruction of periodontal tissues as well as the evasion of immune defense [13]. Furthermore, *Porphyromonas gingivalis* increases the risk of metastasis and promotes chemoresistance to anti-cancer agents. It also accelerates the proliferation of oral tumor cells, resulting in altered gene expression of defensins.

According to Olsen, *Porphyromonas gingivalis* also converts ethanol to acetaldehyde, a carcinogenic intermediate [21]. In addition to being the first metabolite of alcohol, acetaldehyde is considered a group one carcinogen to humans when associated with alcoholic beverages. At levels capable of inducing DNA damage and mutagenesis, *Porphyromonas gingivalis* converts ethanol to acetaldehyde, leading researchers to believe that heavy drinking and gastrointestinal cancers are related [21].

Likewise, *Porphyromonas gingivalis* has been implicated in not only pancreatic cancer, but also precancerous gastric lesions as well as colon and esophageal squamous cell carcinoma. *Porphyromonas gingivalis* also shows systemic tumorigenic effects because distant organs can be involved, in addition to its native territory- the oral cavity. There is also a possible association of *Porphyromonas gingivalis* and orodigestive cancers because it relates to cancer even in the absence of periodontitis [21].

In a mouse experimental model, *Porphyromonas gingivalis* was orally administered to the test subjects. The purpose of this was to mimic patients with periodontitis who swallow the bacterium. After examining the mice, it was found that the gut microbiome was changed. Inflammatory markers were increased as well as serum endotoxin. Lastly, the function of the gut barrier was also found to be impaired [12]. The demonstration proved a direct relationship between the gut microbiota and the oral microbiota. Researchers also reported that the suspected role of *Porphyromonas gingivalis* affects the gut immune system by causing composition shifts in the gut microbiota.

Secondary research studies show that in patients diagnosed with liver cirrhosis, there was a change in gut microbiota that was caused by massive invasion of the gut by oral bacteria [12]. Fifty-four percent of the assigned bacterial species originated in the oral cavity. This statistic suggested that bacteria from the mouth that transported to the gut had taken place in these patients diagnosed with liver cirrhosis. It was also concluded that in addition to *Porphyromonas*

gingivalis, other oral bacteria can also play a role in the pathology of liver cirrhosis [12].

Along with cell apoptosis and tumorigenesis, the signaling pathways that are activated by *Porphyromonas gingivalis* are also involved in cell invasion of tumor cells and immune evasion [13]. Increased aggressiveness of OSCC cells were found in a study that showed the cells were chronically infected with *Porphyromonas gingivalis* [24]. The cells not infected with *Porphyromonas gingivalis* did not exhibit aggressiveness. The OSCC cells were also resistant to paclitaxel when treated with *Porphyromonas gingivalis*. The serum values of *Porphyromonas gingivalis* immunoglobulin G (IgG) were also higher in stage IV cancers than of cancers of lower grades. This result also supported the statement that *Porphyromonas gingivalis* is closely associated with OSCC [24].

The serum values of *Porphyromonas gingivalis* IgG were also higher in OSCC patients as opposed to the healthy controls. The mortality rate of individuals with periodontitis increases with an increase in *Porphyromonas gingivalis* IgG levels [6]. The study also demonstrated that *Porphyromonas gingivalis* contributed to overall aggressiveness of oral cancer because it promoted epithelial-mesenchymal transition (EMT) and accelerated cell invasions. The findings suggested that metastasis involved in OSCC is strongly associated with periodontitis, which leads to *Porphyromonas gingivalis* being a biomarker for OSCC.

During EMT, cell-to-cell adhesion of epithelial cells is lost as well as cellular polarity. However, the epithelial cells do gain migratory and invasive properties. *Porphyromonas gingivalis* not only enhances this aggressiveness previously mentioned, but also metastatic potential as well as mortality [16]. The canonical EMT markers are induced. EMT changes include downregulation of E-cadherin and β-catenin that have a positive correlation with OSCC prognosis [16].

In a cohort study regarding pancreatic cancer, *Porphyromonas gingivalis* antibodies were found in high levels and were determined to be correlated as a risk factor for pancreatic cancer. A European study also found that the elevated antibodies could possibly triple the risks of pancreatic carcinoma in patients [13]. Oral bacterial flora changes were also found to increase pancreatic cancer morbidity [6].

A study conducted in 2017 showed gastrointestinal disorders, whether infectious, genetic or inflammatory, produced alterations in oral tissues- both hard and soft. It was reported that of all test subjects, a considerable amount of the patients was affected by oral manifestations prior to the onset of any and all gastrointestinal symptoms [25]. *Porphyromonas gingivalis*, along with increased autophagy, induces cell cycle arrest. An experimental study conducted by Olsen showed that when *Porphyromonas gingivalis* invaded oral cancer cells, cell proliferation was inhibited through arrest of the G1 phase of the cell cycle [21]. In anti-cancer agents, *Porphyromonas gingivalis* was found to promote distant metastasis and chemoresistance. It was suggested that *Porphyromonas gingivalis* could have a possible role in the chemoresistance towards OSCC. The OSCC cells were repeatedly exposed to *Porphyromonas gingivalis* over the course of five weeks for the experiment, and showed resistance to the chemotherapeutic agent, Taxol.

Peptidyl-arginine deiminase (PAD), an enzyme that modifies bacterial and host proteins, is currently known to be produced by *Porphyromonas gingivalis*. The host of PDAs have been linked to human cancers. It has been shown that PAD is overexpressed in several invasive carcinoma types and play important roles in tumor progression [21].

Although esophageal cancer is one of the top ten most frequent cancers globally, as well as being the sixth leading cause of death in reference to cancers worldwide, there have never been any prior evidence of specific microbiological agents in esophageal squamous cell carcinoma (ESCC). However, statistical studies in 2016 detected high levels of *Porphyromonas gingivalis* in ESCC. *Porphyromonas gingivalis* was undetected in normal esophageal mucosa [26]. The IgG levels against *Porphyromonas gingivalis* were also higher in patients with ESCC as opposed to the healthy controls. This correlated with a worse prognosis of those patients with ESCC between stages zero and two, or essentially metastasis of lymph nodes. Individuals with high levels of periodontal disease had periodontal pathogens detected in plaque, which is a risk factor for precancerous gastric lesions. In other words, *Porphyromonas gingivalis* found in the oral cavity is a contributing factor to the development of precancerous gastric cancer [27].

Aside from being the 11th most common cancer globally, pancreatic cancer has the highest incidence and mortality rates of developed countries. *Porphyromonas gingivalis* and its association with periodontal disease is essential to the development of pancreatic cancer [28]. There is a positive association between salivary microbiota found in the oral cavity of patients with pancreatic cancer as well as chronic pancreatitis.

For nearly a decade, approximately 800 men and women with incident adenocarcinoma of pancreas were assessed and monitored to see who developed pancreatic cancer. Accumulating data suggests that oral dysbiosis has a higher associated risk for pancreatic cancer. A higher ratio of *Porphyromonas gingivalis* was found in the test subjects'

saliva [8]. It was founded that patients with *Porphyromonas gingivalis* had a higher risk of about 59 percent of developing cancer than those patients without. Thus, oral microbial dysbiosis of *Porphyromonas gingivalis* precedes cancer development [29]. *Porphyromonas gingivalis* was proven to reach the pancreas and be of contribution in pancreatic carcinogenesis. *Porphyromonas gingivalis* is an independent risk factor of pancreatic cancer [17].

A study established in 2012 measured plasma antibodies in pre-diagnostic blood samples, and revealed that *Porphyromonas gingivalis* was at a higher increase of being a risk of pancreatic cancer. Two strains of *Porphyromonas gingivalis*, ATCC 53978 and ATCC 33277, were demonstrated in high correlations. Participants with a higher level of antibodies against *Porphyromonas gingivalis* 53978 expressed a two-fold higher risk of pancreatic cancer than those with lower levels of antibodies [3].

Shegan Gao, a researcher at the Henan University of Science and technology in China, reported that *Porphyromonas gingivalis* was detected in 61 percent of cancerous tissues as well as 12 percent of adjacent tissues. *Porphyromonas gingivalis* was reported to be undetected by Gao in normal esophageal mucosa [26]. Gao also reported that *Porphyromonas gingivalis* infection had a positive correlation and association to differentiation status, metastasis and overall survival rate. The findings demonstrated that *Porphyromonas gingivalis* infects the epithelium of the esophagus of patients with ESCC. It also is strongly associated with the progression of ESCC, resulting in *Porphyromonas gingivalis* being considered a possible biomarker for orodigestive cancers.

In reference to gastric cancer (GC), there have been many inconsistent findings. However, an analysis has showed that tooth loss is a potential risk factor of GC. In other words, precancerous lesions of GC are associated with periodontal pathogen colonization. The colonization has the possibility of consisting of *Porphyromonas gingivalis* [6].

As the third leading cause of cancer death globally, hepatocellular carcinoma (HCC) is a common malignancy. Toxic metabolites and viruses are known to cause chronic damage and inflammation. Although the correlation between periodontitis and liver diseases is unclear, Japanese researchers have found that individuals diagnosed with HCC and periodontitis simultaneously have higher integrated stages [6].

Yearly, OSCC claims close to 8,000 lives in the United States as part of the top five types of cancer mortalities-orodigestive cancers. Two common risk factors of other well-known cancers are tobacco and alcohol consumption. However, OSCC does not correlate with these risk factors. Instead, OSCC is strongly tied to *Porphyromonas gingivalis*. As a well-observed oral colonizer and periodontal pathogen, *Porphyromonas gingivalis* is a microbial species located in the oral cavity that has the highest association with OSCC [17]. The microorganism also has propensity for colonization of the lower gastrointestinal tract.

Accordingly, *Porphyromonas gingivalis* is the only known cultivable constituent of the oral microbiota and is listed as the most highly associated organism of orodigestive tract cancers [17]. Current research continuously show that *Porphyromonas gingivalis* detection in OSCC tissues progressively increase.

In a European cohort study, patients with high levels of *Porphyromonas gingivalis* antibodies had a 2-fold higher risk of developing pancreatic cancer. The results of the study were compared to those with lower levels of antibodies [30]. Emerging evidence suggest a possible correlation between the bacterium and orodigestive cancers.

Mayuka Nakajima, a research scholar from the Niigata University Graduate School of Medical and Dental Sciences in Japan, orally administered *Porphyromonas gingivalis* to mice and analyzed the phylogenetic structure of the microbial communities in the gut and liver. The gut microbiota was significantly altered with increased serum endotoxin levels. Within the liver of infected mice, higher levels of bacterial DNA were found. These findings showed that *Porphyromonas gingivalis* has a negative effect on gut dysbiosis [31].

In a similarly recent study, scientists administered *Porphyromonas gingivalis* to mice orally as well and found the intestinal microbiota differed significantly from untreated mice. *Porphyromonas gingivalis* indeed disrupted gut dysbiosis and caused elevated Bacteriodetes phyla [1]. Clostridiales decreased and Prevotella increased. The dysbiotic profile seen in the test subject mice are also detected in colitis. The presence of *Porphyromonas gingivalis* impaired the host microbiota balance in the fecal samples of the mice.

Another retrospective study, conducted by Fatemeh Momen-Heravi from Harvard Medical School in 2016, demonstrated that patients with chronic periodontitis, with associated tooth loss, were at a higher risk of developing colorectal cancer (CRC) with poorer prognosis. Proximal tumors were mostly associated with the findings. Momen-Heravi also researched that *Porphyromonas gingivalis* synergistically initiated oral tumorigenesis [10]. It was also concluded that women who had fewer teeth, whether from moderate or severe periodontal disease, were at a higher risk of developing CRC. This suggested that oral health, more

specifically *Porphyromonas gingivalis*, played a potential role in colorectal carcinogenesis.

Jie Chen, from John Hopkins University, conducted research between 2017-18 and found that polymicrobial entities were associated with CRC and colonic biofilms. The mechanisms of microbiota-driven CRC are in relation to the bacterial organization and function of the biofilms from CRC patients at the strain level [8]. Bacterial biofilms altered cancer colonic mucosal metabolome by the upregulation of polyamine metabolism, leading to cancer progression and colonic epithelial proliferation.

In an eight-week study, 14 mice were the test subjects of a periodontal pathogen-associated oral tumorigenesis model. Half of the mice were infected and the other half were the control group. Oral carcinogen was administered in the drinking water. It was hypothesized, and proved, that infection may enhance tumorigenesis. Tongue carcinoma was observed in six out of the seven infected mice. Five of the seven non-infected mice also showed tongue carcinoma. Immunohistochemical analysis revealed that *Porphyromonas gingivalis* enhanced the severity of the tongue tumors. Although both infected and non-infected mice showed tongue carcinoma, the tumors from the infected mice were 2.5 times larger than those of non-infected mice. These tumors were also more invasive. It was noted that the oral cavity of OSCC cell proliferation was affected [32].

Researcher Kalina Atanasova, from the University of Florida, found that the highest association of periodontitis was from CRC and pancreatic cancer. Atanasova also reported that higher serum levels of *Porphyromonas gingivalis* IgG was more commonly linked with increased orodigestive cancer mortality [3]. In healthy individuals not showing signs of periodontal disease, *Porphyromonas gingivalis* was found to be associated with a 2.25-fold higher likelihood for orodigestive mortality.

In a study consisting of 711 participants who were infected with *Porphyromonas gingivalis*, the prevalence of the bacterium was 40.7 percent. The results showed that *Porphyromonas gingivalis* increased the chance of cancer development and periodontal disease by 1.36 times [14]. It is important to note, that *Porphyromonas gingivalis* does not always lead to periodontal disease. This bacterium rather signifies a risk factor to the disease [20]. Given the connectivity of the digestive tract, *Porphyromonas gingivalis* is possibly involved in other gastrointestinal disorders aside from orodigestive cancers. Although research from previous decades have led scientists to strongly suggest *Porphyromonas gingivalis* and overall oral health has a possible role in colorectal carcinogenesis, there are not enough epidemiological studies to support this. Thus, there have not been any definitive conclusions [10]. Significantly more research is a necessity to fill the gap regarding the effect *Porphyromonas gingivalis* has on gut dysbiosis and well as its effect on orodigestive cancers. The result of more recent research can clarify the detailed mechanisms that orodigestive cancers and gut dysbiosis are orally-driven, and especially focus more on the role of *Porphyromonas gingivalis* and its potential being as a biomarker.

The only research available now, regarding the plausible role of *Porphyromonas gingivalis* in orodigestive cancers, does not include extensive in vitro studies. In fact, as of 2015, there were only several in vitro reports worldwide that directly studied the correlation between *Porphyromonas gingivalis* and carcinogenesis [3]. Today's times provides more advanced technologies, allowing the scientific community to further investigate the emerging role of *Porphyromonas gingivalis* in cancer development.

The studies must also include a more variety of people, from different regions of the world. Most of the research available have been conducted in the eastern hemisphere. The research presented in this paper have been from experiments with small sample sizes as opposed to the possibility of using more individuals worldwide. For more solid results, larger study samples are a necessity to ensure accuracy and validity. Patients of all ages and sex should be selected at random.

To explore the potential, long-term effect of *Porphyromonas gingivalis*, those infected with the bacterium should be examined closely for expression and localization of canonical EMT markers and shifts. This way, the importance of molecular signaling pathway of *Porphyromonas gingivalis* associated with EMT can help researchers identify future therapeutic targets.

With more extensively conducted research, treatments targeting the microbiota, and *Porphyromonas gingivalis* in specific, can modulate immune response. This can allow physicians to take better preventative measures as well as have exclusive treatments for gut dysbiosis as well as orodigestive cancers.

The results of future research can help reduce the number of patients who are deceased from such conditions. However, to have the most accurate results, test subjects should be analyzed for years, and possibly decades. For example, CRC takes more than 10 years to develop. This is because of the accumulation of genetic mutations in colonic epithelial cells as well as the development of histopathological stages- polyp, adenomas and carcinomas [8]. *Porphyromonas gingivalis* has been strongly linked to CRC cases. To see the effect the bacterium has on chronic conditions, the research study

cannot be for a short period of time. Lengthy observational studies are needed to produce more accurate and precise data.

Due to the time frame of orodigestive cancer development being long, it is critical to identify any bacterial community and disease-inducing host so that these interactions are not missed earlier on during the onset of initial symptoms.

It should be noted that possible challenges not only include the time frame, but also the potential for incomplete data within the sample. Future studies should follow participants based off of their genetic disposition to develop gastrointestinal and digestive cancers. Of those individuals, their oral health should be observed and closely studied. The willingness of individuals to participate in long-term research studies can be a hardship. Specifically finding immunocompromised individuals meeting specific bacterium and orodigestive conditions will be the biggest challenge of them all.

To reduce the incidence rate, more research is needed. Studies previously conducted show that the incidence rate of patients with oral cancer is on the rise for ages 45 and above [16]. Improving therapeutic measures as well as attempting to increase the five-year survival rate of cancers, such as oral and pancreatic cancer, should be of priority.

Additionally, scientists should use other bacterium, aside from *Porphyromonas gingivalis*, that are associated with periodontal disease to further one's knowledge about oral bacteria and its involvement with intestinal dysbiosis. *Porphyromonas gingivalis* is an opportunistic oral pathogen and shows signs of being a promising potential risk modifier in oral cancer research. However, closely related bacterium should also be used as constants and controls for comparative analysis. Studies have shown that profiling of gut microbiota in CRC, for instance, have diverse results in regards to bacterial communities and patters enriched in tumor regions. However, it is not clear whether or not bacterial dysbiosis is secondary to tumor development of the colon or if it is a causative exposure just prior to the colon carcinogenesis onset [8]. Different strains of the same species type can cause different phenotypes. Genome sequencing can reveal the evolution of different bacterium along the course of disease, and more importantly among diverse individuals and populations.

For prevention and enhanced prognosis of gut dysbiosis and orodigestive cancers, understanding the pathophysiological mechanisms and interactions with bacterium such as *Porphyromonas gingivalis* and the host is much needed. There is a strong linkage that the same oral microbes detected in gastrointestinal organs represent the same strains or species that inhabit the oral cavity.

Both prospective and longitudinal epidemiological studies are necessities to determine the effect and role microbial communities have in the onset initiation and progression of orodigestive cancers. If the oral bacteria residing in the gastrointestinal tract originated from the oral cavity, the mechanisms of these bacterium to adapt to the environment must be researched more to understand the carcinogenesis effect.

Conclusion

As there are no recommended screening tests available for certain orodigestive cancers, for example pancreatic cancer, understanding microbiota science can help establish a screening lab test perhaps. This can help significantly reduce the number of patients diagnosed with aggressive and deadly cancer types yearly. Until further research can be done, practicing good oral hygiene can improve overall oral health. Less dental plaque means a less risk of developing *Porphyromonas gingivalis*, and from the studies currently available, less of this bacterium can decrease one's risk of gut dysbiosis and developing orodigestive cancers. The pathogenic mechanism of *Porphyromonas gingivalis* must be studied further to provide new data for orodigestive cancer prevention and treatment.

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