Association between oral microflora and gastrointestinal tumors (Review)

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Abstract. The oral cavity contains the highest density and the most species of microorganisms compared with other parts of the body. Recent studies have determined that the species and abundance of oral microflora are closely associated with the development of upper gastrointestinal tumors, including oral, esophageal and gastric cancer. Additionally, differential abundant microbiota in patients with cancer and abnormal microorganisms inside the tumor tissue have been identified as critical markers of tumorigenesis. There is evidence to suggest that certain genera, including *Firmicutes*, along with various species, such as *Porphyromonas*, can increase the risk of oral cancer. Furthermore, *Porphyromonas gingivalis* is a risk factor for esophageal carcinoma, while *Helicobacter pylori* infections are a main cause of gastric cancer. Currently, as far as carcinogenic mechanisms of oral microorganisms are concerned, it has been hypothesized that the production of carcinogenic substances, chronic inflammation and altered cell metabolisms may be mechanisms by which oral microorganisms influence the development of upper gastrointestinal cancer. Certain phrases, including 'oral microbes', 'oral microorganism', 'oral microbiology', 'oral microflora', 'oral cancer', 'oral carcinoma', 'carcinoma of mouth', 'esophagus cancer', 'esophageal cancer', 'esophageal carcinoma', 'carcinoma of esophagus', 'gastric cancer', 'gastric carcinoma', 'stomach cancer', 'cancer of the stomach', 'carcinogenic mechanism' and 'carcinogenesis', were searched as key words in PubMed and Web of Science for articles published between 1975 to 2020. A total of 1,512 studies were obtained. After further searching the abstracts for key words, such as oral microorganisms, oral cancer, esophagus cancer, gastric cancer and carcinogenic mechanisms, 137 studies were selected. The current review systematically and comprehensively summarized the association between the oral microbiota and oral, esophageal and gastric cancer. Additionally, the current review described the carcinogenic mechanisms of oral microbes and attempted to identify common molecular mechanisms among different types of tumor. The association between upper gastrointestinal cancer therapy and oral microflora was also assessed. The present review may be used as a reference for future diagnosis and therapeutics for upper gastrointestinal tumors.

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Contents

1. Introduction
2. Basic features and oral microflora characteristics of three types of tumor
3. Possible mechanisms of oral microorganisms affecting the three types of gastrointestinal tumors
4. Association between therapy and microflora
5. Summary and outlook

1. Introduction

The incidence and mortality rates of upper gastrointestinal cancer are high, particularly in gastric and esophageal cancer (1). According to statistics produced by the World Health Organization (WHO), cancer is the first or second leading cause of death among individuals <70 years old in 91 countries, ranking third or fourth in an additional 22 countries (1). Most types of cancer have clear causes, such as smoking for lung cancer (2) and alcohol consumption (3) or occupational hazards (4) for upper gastrointestinal cancer. The human mouth is colonized by a set of microorganisms, including bacteria, archaea, fungi and viruses (5). Additionally, the bacterial colonies of the oral cavity are significantly less variable and more diverse than all other environments of the body, including the gut or skin (6). Currently, a large

number of studies have demonstrated that oral microorganisms are closely associated with gastrointestinal tumors (7,8). Mechanisms of carcinogenesis mediated by oral microorganisms may include the production of carcinogenic substances, chronic inflammation and altered cell metabolisms (9). The current review summarized the association between the oral microbiota and oral, esophageal and gastric cancer, providing discussion regarding the carcinogenic mechanisms of oral microbes and attempting to identify common molecular mechanisms among different tumors. The regulation of the oral microbiota from the perspective of diet, probiotics and prebiotics was also assessed to improve gastrointestinal cancer prevention and treatment.

2. Basic features and oral microflora characteristics of three types of tumor

Stomach cancer. Stomach cancer (gastric cancer) is one of the most common malignancies as indicated by International Agency for Research on Cancer data collected in 2018 (1). The incidence of stomach cancer was 5.7% worldwide, ranking fifth among all types of cancer in the same year (1). Additionally, the mortality rate was 8.2%, ranking third worldwide (1). In China, stomach cancer is one of the most common types of malignancy. A 2017 survey revealed that the incidence and mortality rates of stomach cancer among the Chinese population was 1.5 times higher than those of the world standard population who died of stomach cancer (10). As a result, stomach cancer has been the focus of national cancer prevention and treatment (10).

The human stomach has a pH of 1-2, whereas the gastric mucus layer establishes a pH gradient from 6-7 at the surface of the mucosa (11). The stomach can therefore support a bacterial community with hundreds of phylotypes (12). Additionally, pH values <4 prevent bacterial overgrowth, which is important as the acidic milieu is not capable of sterilizing the stomach (13). However, *Helicobacter (H.) pylori* influences gastric colonization dynamics (14). During the development of chronic gastric disease, pH values increase, resulting in bacterial overgrowth, particularly of Gram-negative bacilli in diarrheic infants (15).

There is an association between the development of gastric cancer and the oral microbiota. The first gastric tumor-associated bacteria to be identified was *Streptococcus salivarius* (16). Yamamura *et al* (17) revealed that *Fusobacterium (F.) nucleatum* in the oral cavity may be involved in the development of esophageal and gastric cancer. Additionally, *Lactobacillus* colonization increases during the process from gastritis to gastric cancer (18). In the saliva or plaque of patients with gastric cancer, the relative abundance of certain bacteria (*Veillonella, Prevotella*, *Aggregatibacter* and *Megasphaera*) increases, while that of others (*Leptotrichia, Rothia, Capnocytophaga, Campylobacter, Tannerella* and *Granulicatella*) decreases (19). Compared with healthy controls with no gastric diseases, the coating of patient tongues has a higher relative abundance of *Firmicutes* and a lower relative abundance of *Bacteroidetes* at the phylum level (20). Additionally, higher *Streptococcus* and lower *Neisseria, Prevotella*, *Prevotella* and *Porphyromonas* levels have been demonstrated at the genus level (20). Sun *et al* (21) revealed that the increased colonization of periodontal pathogens in the oral cavities of patients with gastric cancer, specifically *Treponema denticola*, *Tannerella forsythia* and *Actinobacillus actinomycetemcomitans*, decreased bacterial diversity in dental plaques. Furthermore, not regularly flossing teeth has been identified as a significant predictor of increased risk of precancerous lesions in gastric cancer (21). Therefore, importance should be placed on daily cleaning for the purposes of oral hygiene. The occurrence of gastric cancer may also be associated with certain viruses, such as the Epstein-Barr virus (22).

Esophageal cancer. The incidence rate of esophageal cancer is the 7th highest in the world (1). Additionally, it is one of the deadliest tumors, with the 6th highest mortality rate of any type of cancer worldwide (1). In China, esophageal cancer is the fourth most common cause of cancer-associated death (23). It is also the most highly publicized and researched type of cancer in China, indicating that it causes serious harm to human health (24). Esophageal cancer is regionally aggregated in China, demonstrating a high incidence in Linxian (Henan province) (25), Cixian and Shexian (Hebei province) (26) and Taixing (Jiangsu Province) (27). In total, >90% of esophageal cancer cases are of the esophageal squamous cell cancer (ESCC) and esophageal adenocarcinoma (EAC) type (28). Esophageal cancer is a genetically diverse disease with a high frequency of somatic copy number alterations in oncogenic driver genes due to large-scale rearrangements (29). The development of esophageal cancer also involves various external factors, such as drinking excessive quantities of hot tea (30), smoking, alcohol consumption (31) and the interaction between alcohol intake and genetic polymorphisms (32). The prognosis of patients with esophageal cancer is dependent on their pathological stage and the treatment available, as early detection and suitable therapy can significantly improve the prognosis of individuals (33). Li *et al* (34) demonstrated that CD147 was an important prognostic factor that was highly expressed in patients with esophageal cancer, which was associated with decreased patient survival.

From the perspective of the microbiota, the development of esophageal cancer is also associated with oral microorganisms. Peters *et al* (35) revealed that the periodontal pathogen, *Tannerella forsythia*, was associated with an increased risk of EAC, and that the depletion of the commensal genus *Neisseria,* as well as the species *Streptococcus pneumoniae,* was associated with decreased EAC risk. Finally, the abundance of *Porphyromonas (P.) gingivalis* in the oral cavity has been associated with an increased risk of ESCC (35), which is in agreement with another study (36). *Treponema denticola*, *Streptococcus mitis* and *Streptococcus anginosus* may have significant roles in the carcinogenic process of esophageal cancer by causing inflammation and by promoting the carcinogenic process (37). Eradication of these bacteria may therefore decrease the risk of recurrence (37). Chen *et al* (38) demonstrated that patients with ESCC exhibited significantly decreased microbial diversity and a significant decrease in *Lautropia, Bulleidia, Catonella, Corynebacterium, Moryella, Peptococcus* and *Cardiobacterium* abundance compared with those of healthy controls and patients with dysplasia. In terms of fungi, the participation of nitrosamine compounds produced by chronic *Candida* infections has been revealed to

be a risk factor for esophageal cancer (39), which is consistent with the fact that oral *Candida* colonization is significantly more common in patients with esophageal cancer than in healthy controls (40). Professional dental care, such as teeth and tongue cleaning, may reduce 'bad' microbiota abundance in the oral cavity, thereby decreasing the risk of esophageal cancer (41,42).

Oral cancer. Oral cancer is a general term for tumors of the oral cavity, and is one of the most common malignancies of the head and neck. The 5-year overall survival rate of patients with oral cancer is 68%, and the 5-year disease-specific survival rate is 78%, and the cancer stage and invasion depth are important factors affecting prognosis (43). The latest global cancer statistics report revealed that new cases and deaths associated with oral cancer were ranked 18th and 15th, respectively, among all tumors in 2018 (1). According to the WHO definition, >80% of oral cancer cases are squamous cell carcinoma, followed by glandular carcinoma, basal cell carcinoma, undifferentiated carcinoma and lymphatic carcinoma (ICD-10 rubrics C01-C06) (44). Oral cancer treatment strategies include surgery (45), radiation therapy (45), chemotherapy (46) and traditional Chinese medicine (47). Additionally, oral cancer may be treated via diet therapy. Lee *et al* (48) determined that a diet low in n-6/n-3 polyunsaturated fatty acids may prevent oral cancer.

The development of oral cancer is closely associated with oral microorganisms. Takahashi *et al* (49), Schmidt *et al* (50) and Zhao *et al* (51) reported significantly greater bacterial diversity in oral cancer samples than in normal samples. However, other studies have indicated that bacterial diversity is decreased in oral cancer (52-54). Patients with oral cancer have an increased richness of *Peptostreptococcus, Fusobacterium, Alloprevotella* and *Capnocytophaga,* whilst also demonstrating a lower richness of *Rothia* and *Haemophilus* (49). This is consistent with the conclusion of Yost *et al* (55), which indicated that *Fusobacteria* contained a significantly higher number of transcripts in patients with cancer than in healthy controls at tumor sites and tumor-adjacent sites. Three species of periodontopathogenic bacteria, including *Prevotella tannerae*, *F. nucleatum* and *Prevotella intermedia*, have been associated with an increased risk of oral squamous cell carcinoma (OSCC) (56). Experiments in mice have revealed that *P. gingivalis* infection-induced periodontitis increases the tongue lesion size and multiplicity of each mouse, promoting oral cancer development (57). In particular, a group of periodontitis-associated taxa, including *Fusobacterium, Dialister, Peptostreptococcus, Filifactor, Peptococcus, Catonella* and *Parvimonas,* are significantly enriched in OSCC samples (51). Additionally, a case-control study in Mexico has revealed that the prevalence of human papillomavirus (HPV) infection is significantly increased in patients with oral cancer, indicating that without risk factors such as smoking and alcohol consumption, high risk-HPV may be a risk factor for oral mucosa carcinogenesis (58) (Table I).

In summary, a decrease in diversity of oral bacteria and *Neisseria* abundance occurs in all of the three aforementioned types of cancer. *Rothia, Proteobacteria, Haemophilus* and *Bacteroidetes* diversity is decreased in stomach and oral cancer, while the diversity of *Treponema denticola* and *Tannerella forsythia* increases in stomach and esophageal cancer. Furthermore, *Prevotella* and *Firmicutes* diversity is enriched in stomach and oral cancer, while *P. gingivalis* is enriched in esophageal and oral cancer.

The differences between the cancer and normal paracancer tissues of the same patients with oral, esophageal and gastric cancer were compared in the current review (Table II). Compared with normal tissues, an enriched microflora was identified in oral cancer tissues, exhibiting bacteria such as *Veillonella*, *Fusobacterium*, *Prevotella, Porphyromonas*, *Actinomyces* and *Clostridium* (anaerobes); *Haemophilus*, *Enterobacteriaceae* and *Streptococcus* (aerobes); *Candida albicans* (59); *Streptococcus* species, *Staphylococcus* species, *Moraxella* species, *Enterococcus faecalis,* aerobic spore formers, *Klebsiella* species, *Citrobacter* species, *Proteus* species and *Pseudomonas* species (60). Similar patterns were observed in esophageal and gastric cancer (Table II).

3. Possible mechanisms of oral microorganisms affecting the three types of gastrointestinal tumors

Gastrointestinal tumors may affect the density and diversity of oral microorganisms. For patients with cancer exhibiting low immunities, harmful microbes may take advantage and disrupt the normal distribution of human oral flora. Conversely, alterations in oral microorganisms may also be a risk or protective factor for the tumorigenesis of various types of cancer, including gastrointestinal cancer. The possible mechanisms by which this occurs are described in the current review. Currently, the carcinogenic mechanisms of oral microorganisms include the production of carcinogenic substances, chronic inflammation (61) and altered cell metabolism, through which oral microorganisms influence the development of upper gastrointestinal cancer (62).

Carcinogenic substances. Carcinogens produced by oral microorganisms in the process of upper digestive tract tumor development include acetaldehyde, reactive oxygen species (ROS), organic acids and n-nitrotrimethylamine (63-65).

Oral cancer may develop from certain Gram-negative bacteria, such as *Stomatococcus*, which convert ethanol into acetaldehyde via alcohol dehydrogenase (66). Among bacteria, the genus *Neisseria* exhibits extremely high alcohol dehydrogenase activity and can produce a large quantity of acetaldehyde (100 times that of other strains) when cocultured with ethanol *in vitro*, promoting the development of upper aerodigestive tract tumors (63). Carcinogenic substances are produced after long-term alcohol consumption (67). Furthermore, drinking alcohol affects the distribution of oral bacteria, leading to an increased abundance of *Neisseria*, which further leads to an increase in carcinogen production (63). This interaction suggests that *Neisseria* may be a primary source of the oral carcinogen, acetaldehyde, and that oral microbial disorders may serve an important role in the occurrence of upper gastrointestinal tumors induced by drinking alcohol (63). The concentration of acetaldehyde in the oral cavity of healthy adults is positively correlated with the abundance and diversity of lingual dorsal bacteria and the relative abundance of *Gemella sanguinis*, *Veillonella parvula* and *Neisseria flavescens* (64).

Table I. Characteristics of the oral flora in patients with upper gastrointestinal tumors compared with in healthy controls.

Type of cancer	Diversity of oral bacteria	Enriched oral bacteria	Reduced oral bacteria	Other enriched microorganisms in the oral cavity
Stomach cancer	↓ (21)	*Veillonella, Prevotella, Aggregatibacter,* *Megasphaera* and other 25 types of bacteria (19); *Actinobacteria* (125); *Firmicutes, Streptococcus* (20); *Treponema denticola, Tannerella forsythia* and *Actinobacillus actinomycetemcomitans* (21)	*Leptotrichia, Rothia,* *Capnocytophaga, Campylobacter, Tannerella* and *Granulicatella* (19); *Proteobacteria, Fusobacterium, Haemophilus, Porphyromonas* (125); *Neisseria* (20,57,125), *Prevotella, Bacteroidetes* (20)	Epstein-Barr virus (22)
Esophageal cancer	↓ (38)	*Tannerella forsythia, Porphyromonas gingivalis* (35,36); *Treponema denticola, Streptococcus mitis, Streptococcus anginosus* (37)	*Neisseria* and *Streptococcus pneumoniae* (35), *Lautropia, Bulleidia, Catonella, Corynebacterium, Moryella, Peptococcus,* and *Cardiobacterium* (38)	Chronic candidiasis (39,40)
Oral cancer	↑ (49-51) ↓ (52,54)	*Alloprevotella,* and *Capnocytophaga* (49); *Prevotella tannerae* and *Prevotella intermedia* (56); *Porphyromonas gingivalis* (57); *Peptostreptococcus* (49,51), *Fusobacterium* (49,51,55,56), *Dialister, Filifactor, Peptococcus, Catonella* (51); *Fusobacteria* (55), *Firmicutes, Lactobacillus, Streptococcus, Staphylococcus* and *Parvimonas* (52)	*Rothia* (49) and *Haemophilus* (49,52), *Bacteroidetes, Proteobacteria, Aggregatibacter, Lautropia, Leptotricha, Neisseria, Gemellaceae* (52)	High-risk-human papillomavirus (58)

The arrows (↓ and ↑) indicate decrease and increase of oral bacteria diversity, respectively.

Oral bacteria, such as streptococci, are involved in the formation of certain ROS, including peroxide (68). ROS participate in cell metabolism and serve an important role in the occurrence and development of eukaryotic periodontitis by participating in signal transduction, cell differentiation and apoptosis (69). Additionally, ROS can damage DNA, serving an important role in carcinogenesis (69).

Compared with non-tumor oral tissues, bacteria isolated from oral squamous cell carcinoma tissue demonstrate acid resistance (65). Additionally, various oral bacteria, such as *Streptococcus mutans*, can ferment nutrients to produce lactic acid, among other organic acids (70). Therefore, these oral microorganisms may cause oral cancer by producing organic acids. Furthermore, specific *Candida* fungi can produce N-nitrosobenzylmethylamine (NBMA), a potent carcinogen (39).

Therefore, oral microorganisms may cause esophageal cancer by producing carcinogens. Bacteria that colonize the dorsum of the tongue convert ~30% of dietary nitrate to nitrite (71), which can be converted into carcinogenic N-nitroso-compounds in the acidic environment of the distal esophagus, resulting in gastroesophageal reflux disease and potentially cancer (72). Professional oral care can reduce the amount of acetaldehyde in the oral cavity and decrease the risk of esophageal cancer by reducing the density of certain microorganisms (41).

Causing chronic inflammation. Chronic irritation and inflammation are important factors in tumorigenesis. Various important cytokines serve key roles in the development of chronic inflammation, including TNF-α, IL-6, IL-1, IL-17 and IL-23 (73). Additionally, IL-6 activates numerous important immune cells, including macrophages and T cells (74), serving an important role in the acute inflammatory response. Moreover, IL-1 mediates a key inflammatory pathway in rare genetic syndromes and gout, which is a chronic inflammatory disease (75).

Generally, oral microorganisms may cause oral cancer by inducing chronic inflammation and periodontal disease, which is harmful to parenchymal cells (9). These cells influence the concentration of various cytokines, including TNF-α, leading to tumor development (9). For example, *P. gingivalis* infections can induce periodontitis in mice, increasing the area and type of oral lesions and promoting the occurrence and development of oral cancer (57).

Chronic inflammation has been revealed to promote genetic and epigenetic abnormalities that result in cancer (76). In the process of inflammation leading to cancer, the NF-κB family of transcription factors are important for the mediation of inflammation, cell proliferation, differentiation and cell death (77). NF-κB cooperates with several other signaling pathways to regulate a large number of target genes and produce a complex feedback loop, serving a vital role in inflammation and innate

Table II. Microorganism composition of tumor tissues compared with normal tissues.

Type of cancer	Diversity	Enriched bacteria	Reduced bacteria
Stomach cancer	↑ (117) ↓ (126) (Serum-derived samples)	*Streptococcus salivarius* (16), *Fusobacterium nucleatum* (17), *Peptostreptococcus, Streptococcus* (117)	Lactic acid-producing bacteria, such as *Lactococcus lactis* and *Lactobacillus brevis* (117)
Esophageal cancer	↓ (127) (Esophageal disease)	*Porphyromonas gingivalis* (36), *Enterobacteriaceae* (83), chronic candida (39,40)	NA
Oral cancer	NA	*Veillonella, Fusobacterium, Prevotella, Porphyromonas, Actinomyces* and *Clostridium* (anaerobes), and *Haemophilus, Enterobacteriaceae* (59), *Streptococcus* species (aerobes), *Candida albicans* (59,60), *Staphylococcus* species, *Moraxella* species, *Enterococcus feacalis*, aerobic spore bearers, *Klebsiella* species, *Citrobacter* species, *Proteus* species, *Pseudomonas* species (60)	NA

The arrows (↓ and ↑) indicate decrease and increase of oral bacteria diversity, respectively. NA, not applicable.

immunity, and certain Gram-negative bacteria can activate NF-κB, and thereby interfere with the Toll-like receptor 4 (TLR4) signaling pathway, causing carcinogenesis in the colon, liver, pancreas and skin (77). In view of the role of NF-κB in the development of cancer, the NF-κB signaling pathway may be an effective target for clinical intervention (78). In addition, inflammatory cells and cytokines, such as TNF-α, have been found to decrease the number of fibroblasts and osteoblasts in the tumor microenvironment during bacterial-associated chronic inflammation (79), which can also lead to the production of ROS and nitrogen, inducing DNA mutations that lead to cancer (80,81). In terms of viruses, infection with HPV can cause p53 inactivation, immunodeficiency or suppression of the immune response, increased DNA fragility and increased sensitivity to carcinogens (82).

Oral microorganisms may potentially cause esophageal cancer by inducing chronic mild inflammation. Distal esophageal colonies are composed of oral bacteria, in which Gram-negative bacterial-specific antigens, such as lipopolysaccharides, promote tissue inflammation (83). In addition, oral esophageal bacteria are altered in Barrett's esophagus and reflux esophagitis, and the known risk factors, combined with the chronic mild inflammation or direct carcinogenesis caused by the altered microbiota, promote Barrett's esophagus metaplasia, progressing to EAC (83).

Oral microorganisms may cause gastric cancer through distal effects. For example, they can cause periodontal disease, and periodontal infection can lead to systemic chronic inflammation, which is a risk factor for gastric cancer (19,84).

Regulation of host cell metabolism. Through murine experiments, Wu *et al* (57) revealed that *P. gingivalis* infection enhanced the carcinogenesis induced by 4-nitroquinoline-1-oxide. Additionally, immunohistochemical analysis and reverse transcription-quantitative PCR results revealed that the expression levels of fatty acid synthase and acetyl-CoA carboxylase I in the tongue and liver tissues of mice increased after animals were infected with *P. gingivalis*, indicating that the fatty acid synthesis pathway may be activated during oral carcinogenesis, and that the pathway may be further upregulated by *P. gingivalis* infection (57). The possible mechanism by which this may occur is via *P. gingivalis* infection significantly increasing the level of free fatty acids in the mouse tongue and serum, therefore changing the fatty acid spectrum, aggravating fatty acid metabolism disorder and eventually promoting oral carcinogenesis (57). Oral bacteria may also secrete bacterial effector proteins through type three or type four secretory systems, directly affecting the development of cancer (85), while normal tissues are still regulated by oral microorganisms after they become cancerous. Cho *et al* (86) determined that *P. gingivalis* inhibited the proliferation of oral cancer cells by blocking the G_1 phase of the cell cycle. The results also demonstrated that compared with uninfected control cells, the expression levels of cyclin D1 and CDK4 in oral cancer cells were decreased, while the expression levels of the CDK inhibitor p21 were increased after infection with *P. gingivalis*, suggesting that autophagy was significantly enhanced in infected cells, aiding the inhibition of proliferation (86). Yamamura *et al* (17) first detected the oral microorganism *F. nucleatum* in esophageal and gastric cancer. It was determined that the involvement of *F. nucleatum* in the formation of gastrointestinal tumors may be associated with nucleation (17). *H. pylori*, commonly found in the oral cavity, is a strong inducer of gastric cancer and precancerous lesions (87). Increased PI3K/AKT/GSK3β mRNA and protein expression in gastric cancer tissues may indicate that *H. pylori* infection can activate the PI3K/AKT/GSK3β signaling pathway in gastric cancer (88), promoting the proliferation of tumor cells (89).

The aforementioned carcinogenic mechanisms are summarized in Fig. 1, representing the three main carcinogenic mechanisms of oral cancer caused by oral microorganisms. In the first carcinogenic mechanism, oral microorganisms contribute to the formation of acetaldehyde, ROS, organic

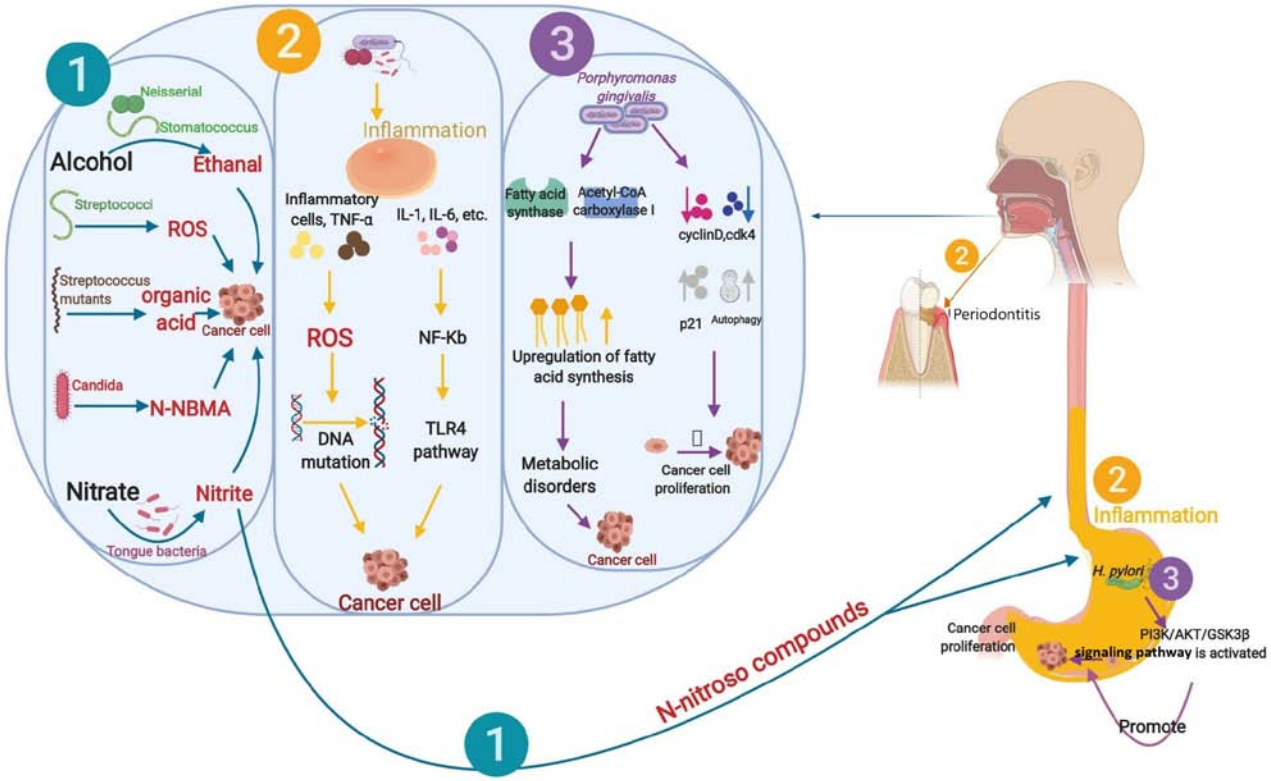

Figure 1. Three main mechanisms by which oral microorganisms may affect the three types of gastrointestinal tumors (gastric, esophageal and oral cancer). The figure was drawn using BioRender. ROS, reactive oxygen species; N-NBMA, N-nitrosobenzylmethylamine; TLR4, Toll-like receptor 4.

acids, N-NBMA, nitrite and other carcinogenic substances in the body to promote cancer cell proliferation. In addition, after the conversion of nitrate to nitrite, nitrite is further converted into the carcinogens N-nitroso-compounds in the acidic environment of the distal esophagus and stomach cardia, resulting in gastroesophageal reflux disease and potentially cancer. In the second carcinogenic mechanism, microorganisms directly or indirectly cause chronic inflammation, which leads to DNA mutations or causes cell carcinogenesis through TLR4 and other metabolic pathways. Additionally, oral microorganisms can induce periodontitis and chronic inflammation of the esophagus and stomach, which encourages Barrett's esophagus and Reflux esophagitis to esophageal and gastric cancer. In the third carcinogenic mechanism, microorganisms regulate host cell metabolism to induce metabolic disorders that lead to cell carcinogenesis and proliferation. *H. pylori* infection can activate the PI3K/AKT/GSK3β signaling pathway in gastric cancer, promoting the proliferation of tumor cells.

4. Association between therapy and microflora

Thus far, the association between oral microbes and three types of upper gastrointestinal cancer has been described in the present review, as well as their related mechanisms. As a result, from the perspective of regulating oral microorganisms, upper gastrointestinal cancer types may be protected in the future. There are numerous ways to regulate oral microorganisms: Physical removal, antibiotic use, diet control, probiotics and prebiotics (90). More novel interventions, such as diet, probiotics and prebiotics, will be discussed henceforth.

There is sufficient evidence to indicate that diet affects numerous types of cancer (91). For example, a pro-inflammatory diet may be a risk factor for oral cancer (92). One of the reasons why diet is relevant to cancer may be that diet can affect the composition of oral microbes (93). Diet can also affect the gut microbiota, serving a fundamental role in the prevention of gastric (94) and colorectal cancer (95,96). Therefore, it may be possible to effectively prevent oral and other types of cancer by controlling certain dietary aspects, such as eating more fruit and vegetables, and less meat and animal products (97).

Prebiotics are ingredients capable of stimulating the growth of beneficial gut microorganisms, while probiotics provide benefits to the host when taken in sufficient quantities (98,99). The probiotic *E. coli* Nissle 1917 can be used as a targeting vector to transfer P53 and the tum5 protein to the tumor region, enhancing targeted therapeutic effects and reducing tumor volume (100). *Propionibacterium freudenreichii* is able to induce tumor cell death in the human colon and stomach (101). Moreover, *Lactobacillus acidophilus* and *Lactobacillus casei* can enhance 5-fluorouracil-induced apoptosis in colon cancer cells (102), improving the efficacy of chemotherapy. Furthermore, probiotics and prebiotics have chemoprophylactic effects on colon cancer (103). Research has demonstrated that gut microbes can influence the efficacy of chemotherapy for pancreatic cancer (104). For melanoma, probiotics enhance immunity and the antitumor immune response by increasing antigen presentation and improving T cell function (105). In a previous study assessing lung cancer, tumor volumes increased and survival rates were significantly decreased when patients were treated with cisplatin and a combination

of antibiotics compared with those that received cisplatin alone (106). This indicated that a balanced commensal flora improved anticancer chemotherapy. Additionally, the flora of the human body can affect the efficacy of radiotherapy, gene therapy, immunotherapy and other tumor treatments (106).

Prebiotics (107) and probiotics (108,109) enhance the immunity of the body through the intestinal flora, reducing gastrointestinal inflammation and preventing cancer (110). For example, Guglielmetti *et al* (111) demonstrated that certain types of oral *Streptococci* exhibited good adaptability to the host and had potential immune regulatory and anti-inflammatory effects, making them potential candidates for pharyngeal probiotics. Conversely, probiotics can also affect oral microorganisms. Cortes-Dorantes *et al* (112) revealed that probiotics can decrease the levels of *Streptococcus mutans*.

In terms of the oral cavity, increasing numbers of studies have demonstrated that probiotics can decrease the incidence of dental caries (113), oral inflammation and periodontal disease when properly applied (90). Krasse *et al* (114) determined that the probiotic *Lactobacillus reuteri* can decrease gingivitis and gum bleeding. Therefore, it can be assumed that probiotics or prebiotics can be used to control periodontal disease and oral inflammation to prevent and treat oral cancer. Xie *et al* (115) and Zheng *et al* (110) hypothesized that probiotics can regulate intestinal microorganisms by increasing the number of beneficial bacteria, such as *Bacteroides*, *Faecalibacterium* and *Akkermansia*, decreasing the density of harmful bacteria, such as *Streptococcus*, and finally reducing the degree of inflammation and enhancing the immunity of patients with gastric cancer. *Faecalibacterium* and *Akkermansia* are highly abundant human gut microbes in healthy people, and their decreased levels are associated with inflammation and alterations of metabolic processes (116). At the genus level, the probiotic combination treatment greatly enhances the richness of *Faecalibacterium* (6.50 vs. 0.32%, richness with probiotic combination treatment versus richness without probiotic combination treatment) and *Akkermansia* (2.42 vs. 0.01%, richness with probiotic combination treatment versus richness without probiotic combination treatment), indicating an improved balance of the intestinal microflora, thereby decreasing the severity of physiological and microbial disorders, and as a result, impeding the development and progression of gastric cancer (110). Although the mechanism by which oral microorganisms cause oral cancer has been relatively well-studied, the mechanism by which oral microorganisms cause gastric and esophageal cancer has not been fully elucidated. Therefore, further studies are required.

5. Summary and outlook

The current review summarized the association between oral, esophageal and gastric cancer and oral microbial abundance and diversity. It also compared the microbial differences between cancer tissues of patients with upper gastrointestinal tumors and normal adjacent tissues. The analysis revealed that certain microorganisms are enriched in the oral cavity and in tumor tissues. For example, *Streptococcus* is enriched in the stomach and oral cavity of patients with gastric cancer (20,117). Therefore, the present review suggested that the high abundance of *Streptococcus* and other microorganisms in the oral cavity may be important to promote the occurrence and development of gastric, esophageal and oral cancer.

The possible mechanisms of oral microbial carcinogenesis can be roughly divided into three types. First, oral microorganisms participate in material metabolism to produce carcinogens (66) or greatly increase the production of carcinogenic substances (63). Second, oral bacteria can cause periodontitis (57), esophageal (83) or gastric inflammation by producing distal effects (84). Third, oral microorganisms regulate host metabolism, participating in important signaling pathways and even directly interacting with parenchymal cells (57). As a result, the incidence of cancer may be inhibited and decreased by regulating the distribution of oral microorganisms through physical removal, antibiotics, specific diet, prebiotics and probiotics (90).

Previous studies have focused on 16S ribosomal RNA (rRNA) (118,119). Although 16S rRNA profiling is an effective and straightforward technique to study microbial communities, it only provides the taxonomic composition. Due to complex variations among oral microbiota, characterization at the species level may not be sufficient to evaluate their pathogenic potential. Metagenomic whole-genome shotgun sequencing data can provide taxonomy information and determine the biological functional profiles of microbial communities (120). Furthermore, as bacteria contain plasmids, there may be cross-species conjugation and transfer (from one bacterium to another), which cannot be determined via 16S rRNA evaluation. The recent discovery that genotoxic polyketide-non-ribosomal peptide synthase operon (also referred to as clb) *E. coli* promotes colorectal cancer may suggest that genes are dominant and that bacteria are only a vehicle (121). The function of the bacterial spectrum may be considered the resting state, while genomics involves counting and quantification. Metatranscriptomic (122) and metaproteomic (123) techniques can further describe the promotive function of bacterial spectrums on esophageal cancer.

Probiotics may decrease inflammation in gastrointestinal illness and oral cancer. Bacteriotherapies (probiotics and symbiotics) may potentially be efficacious in reducing complications associated with chemotherapy, radiotherapy and surgery in patients with cancer (124). However, further research is required to determine whether probiotics can treat cancer, improve survival rates and influence time to progression. Future basic or clinical studies should be performed to enhance therapy or synergize with other oncology treatments to analyze their effects. Assessing changes in immunity, the tumor microenvironment and the tumor cell survival cycle will be important to future work.

Carcinogenic substances, inflammation and the regulation of host cell metabolism are oncogenic factors; however, it is not known which factors dominate and whether there are interactions between them. Future studies should determine the additive or multiplicative effects of these factors in animal models or in epidemiological studies.

The current review provided a comprehensive reference for future research. For example, oral microbes may be used as new biomarkers for disease diagnosis and surveillance. The particular targets of oral microorganisms in the process of tumorigenesis may also be used for precise targeted therapy.

Additionally, it may be possible to control oral microbes in a variety of ways to prevent cancer.

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Availability of data and materials

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Authors' contributions

XL wrote and revised the article. SZ provided the article idea and revised the article. TZ and XC revised the article and edited part of the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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