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*ОБЗОР*
*REVIEW*

# Oral microbiota importance in the development and prognosis of oropharyngeal region oncological diseases

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**Annotation.** *Relevance.* Despite many years of scientific research and clinical results, cancer remains a global health problem. In recent years, there has been an increased interest in studying the role of microorganisms in the occurrence, prognosis and progression of cancer. The probability of isolating carcinogenic microorganisms in the oral microbiota is quite high. In this regard, understanding the role of microorganisms in the occurrence and course of cancer pathology in the future can contribute to the development of innovative strategies for the prevention, treatment of malignant neoplasms and minimization of complications of antitumor treatment. The purpose of this review is a literature analysis of the relationship between representatives of the human oral microbiota in the occurrence and prognosis of cancer. Collection and analysis of 1050 scientific papers using PubMed, Google Scholar and eLIBRARY search engines, published from 2003 to 2024, of which 47 papers are included in this literature review. According to the literature analysis, prevention, diagnostics and treatment of oncological diseases can and should be supplemented by dental approaches aimed at normalizing the microflora. Understanding that oral sanitation significantly reduces its bacterial contamination and, as a result, reduces the number of pathogenic and oncogenic microorganisms can improve the quality of antitumor treatment without significant material and social costs. *Conclusion*. The use of modern methods of diagnostics and monitoring of oral microbiota in dentistry can become the basis for the development of new strategies for the prevention and treatment of malignant neoplasms of the oral mucosa. Integration of these data into clinical practice requires interdisciplinary cooperation between oncologists, microbiologists and dentists to improve the prognosis of patient treatment.

**Keywords:** Microbiota oral cavity; malignant neoplasms; carcinogenesis; oncogenic bacteria; chronic inflammation

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## Introduction

Despite many years of research and significant advances in clinical practice, cancer continues to be one of the most serious global health problems. Currently, there is an active search for new tools and methods aimed at improving the treatment of this pathology. Among them: new methods of chemotherapy, radiation therapy, improved surgical treatment techniques. Particular attention is paid to accompanying dental therapy of cancer patients, since they have an increased risk of developing complications in the oral cavity during antitumor treatment and during rehabilitation. To date, there are insufficient etiopathogenetically substantiated methods for the prevention and treatment of cancer. In this regard, significant attention of scientists is attracted by the oral microflora, which is considered a potential trigger in the development of cancer not only in the oral cavity, but also in many organs and systems of the body. Understanding the interactions between the oral microbiota and the development of cancer can contribute to the development of innovative approaches to the prevention and treatment of this pathology, as well as to reducing complications that arise during and after antitumor therapy.

The aim of this review is a literary analysis of the relationship between representatives of the human oral microbiota in the occurrence and prognosis of oncological diseases.

Collection and analysis of 1050 scientific papers using PubMed, Google Scholar and eLIBRARY search engines, published from 2003 to 2024, by the keywords: «Oral microbiota», «malignant neoplasms», «carcinogenesis», «oncogenic bacteria», «chronic inflammation», «oncogenic bacteria», «the effect of oral microbiota on the development of cancer», of which 47 papers are included in this literature review. The conducted systematic review made it possible to evaluate and study the effect of oral microbiota on the development of malignant neoplasms in the oropharyngeal region, as well as in other organs and systems of the body.

The oral cavity is an ecosystem inhabited by diverse microbial communities collectively referred to as the oral microbiota. Recent advances in technology have significantly deepened our understanding of the microbial ecosystem. Over millions of years of co-evolution, dynamic relationships have developed between humans and microorganisms, which can be pathogenic (causing disease), commensal (natural inhabitants), or symbiotic (based on mutual benefit) [1]. Understanding the oral microbial ecosystem may open up new opportunities for developing interdisciplinary approaches to maintaining homeostasis and microbial

balance in the oral cavity to enhance mucosal immunity, which is a pressing issue for practicing physicians and healthcare researchers worldwide [2]. Tumor tissues contain a large number of microorganisms. These microorganisms, located within tumor tissue, influence the processes of oncogenesis by colonizing the tumor and changing its biological behavior [3]. The mechanisms by which intratumoral microbiota can contribute to the development and progression of cancer are very diverse: they include genomic instability, mutations, epigenetic modifications, inflammatory reactions, avoidance of the destructive effects of the immune system, and influence on the metabolism of tumor cells [4]. That is, the more diverse the quantitative and qualitative composition of the oral microflora, the higher the risk of tumor development and its negative prognosis.

The role of oral sanitation is often underestimated by both healthcare professionals and society as a whole, despite the fact that the oral microbiota plays an important role in maintaining the patient's health [5]. It is known that an unsanitized oral cavity and the presence of foci of chronic odontogenic infection can significantly disrupt the balance of microflora, which, in turn, can lead to the development of various diseases, including cancer both in the oral cavity and in other organs and systems of the body [5]. When performing oral sanitation, microbial contamination is significantly reduced, which helps to reduce the number of pathogenic microorganisms, and thereby reduces the activity of foci of chronic infection, which are often sources of pathological processes. Due to this, the normal microbial balance is restored, which plays an important role in the prevention of various diseases and maintaining the general health of the patient [3–5].

## Oral microbiota and its role in carcinogenesis

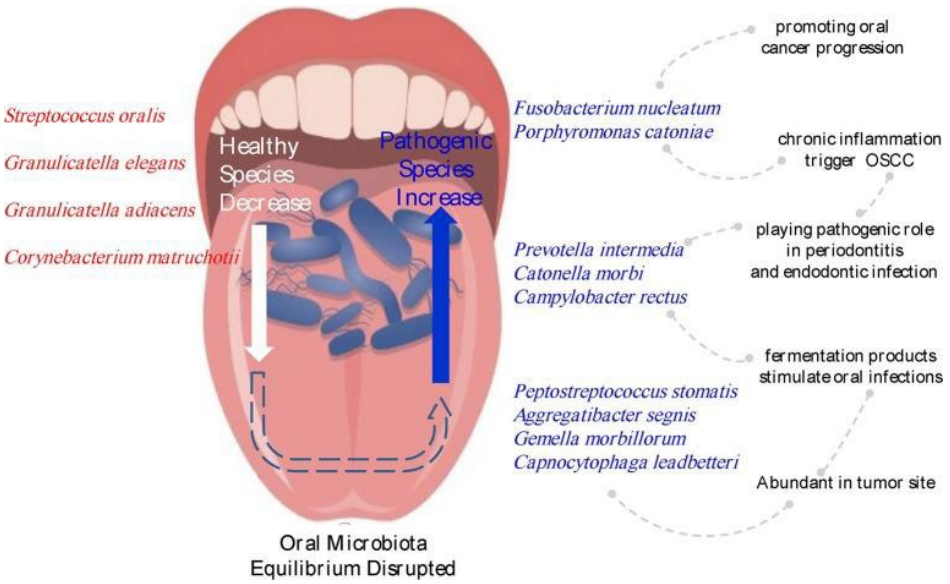
Over the past two decades, the scientific community has recognized the presence of specific characteristics inherent in malignant neoplasms. In 2000, Hanahan D. identified six key properties of cancer cells: support of proliferative signals, avoidance of growth suppression mechanisms, resistance to apoptosis, unlimited replication capabilities, induction of angiogenesis, and predisposition to invasion and metastasis [6]. A decade later, two more characteristics were added to the above-mentioned: changes in metabolic activity and the ability to resist immune defense [6]. Modern studies indicate that carcinogenesis associated with oral microbiota may not only correspond to these characteristics, but also contribute to their implementation [6]. In this regard, it is obvious that microorganisms living in the oral cavity significantly affect the occurrence of oncological diseases, which emphasizes the importance of preventive dental measures and control of the quantitative and qualitative composition of oral microbiota [7]. Providing dental care not only improves the overall health of patients, but also has a positive effect on antitumor treatment. This can reduce the risk of complications during therapy and speed up the rehabilitation of patients [8].

## The influence of oral microbiota on oncoprogression in different organs and systems of the body

Prevention, diagnosis and treatment of squamous cell carcinoma of the oral cavity (squamous cell carcinoma) require a multidisciplinary approach [9]. Research shows an increasingly clear link between the condition of the oral cavity and the risk of developing cancer. Preventive measures such as oral hygiene and maintaining normal microbiota play a particularly important role [10].

This type of cancer, which is the most common type of malignant tumors of the head and neck, accounts for about 2 % of all cancers worldwide [10]. Traditionally, squamous cell carcinoma is associated with tobacco and alcohol use, but recent studies suggest that certain components of the oral microbiota may also be involved in the etiology of squamous cell carcinoma [10].

According to studies [11,12], some bacteria that belong to the genera Lactobacillus, Lactococcus, Bifidobacterium, Streptococcus, Leuconostoc and Pediococcus can produce lactic acid and belong to the group of saccharolytic and aciduric streptococci. Due to this, they are capable of acidogenesis, leading to a decrease in pH [13]. Some of them can also synthesize




Changes in the microbiota composition associated with squamous cell carcinoma of the oral cavity. Species names labeled with red indicate bacteria enriched in normal sites, and species names labeled with blue indicate bacteria increased in tumor sites [17]

other acids, such as acetic, butyric, isobutyric, isovaleric and isocaproic, for example, Peptostreptococcus stomatis [14]. These microorganisms can create an acidic and hypoxic microenvironment in tumors, which, with a high degree of probability, can enhance the ability of tumors to metastasize [15, 16]. The microorganism Porphyromonas gingivalis is known for its association with the occurrence and progression of squamous cell carcinoma of the oral mucosa [16]. In a study conducted by Zhang L. et al. [17,18] involving 50 patients, it was found that tumor tissue samples were characterized by an increased content of Porphyromonas bacteria compared to healthy tissue samples (Figure), these data coincide with the results of other studies by Katz J. et al. and Sayehmiri et al. [19–21].

At the same time, Porphyromonas gingivalis is one of the most common periodontogenic microorganisms that contribute to the development of inflammatory periodontal diseases. According to WHO data, more than 95 % of patients over 50 years of age suffer from periodontitis, and in studies aimed at studying the etiology and pathogenesis of periodontitis, Porphyromonas gingivalis remains the most frequently detected microorganism [17–21].

Other types of opportunistic and pathogenic microbiota in the oral cavity also contribute to the development of malignant neoplasms of the mucous membrane. In a study by Rai et al. [21], elevated levels of Porphyromonas endodontalis bacteria were detected in the saliva of patients with oral squamous cell carcinoma [22]. Ye C. et al [23], who used modern sequencing methods, showed that Fusobacterium nucleatum predominates in oral squamous cell carcinoma samples compared to normal tissues in the same patients [24]. These data are supported by the work of Al-Hebshi NN et al [25], who also found a higher abundance of F. nucleatum in oral carcinoma biopsies compared to healthy samples [26]. Analytical data by Perera M. et al. [27] in 2018 indicate that the presence and concentration of Fusobacterium periodonticum can serve as a prognostic marker of the severity and progression of oral cancers. In a study by Takahashi et al. [27] in Japanese patients with oral squamous cell carcinoma and healthy controls, Alloprevotella was found to be significantly more common in patients with cancer. Alloprevotella may promote cancer development by producing metabolites or toxins that cause chronic inflammation of the oral mucosa, which in turn may

lead to malignant changes in cells. This inflammatory effect is confirmed for other Prevotella bacteria, which can also cause reactive changes in tissues and promote carcinogenesis. Recent studies by Zhang [17] and colleagues have shown that oral squamous cell carcinoma contains elevated levels of Prevotella intermedia, and Torralba [28] and colleagues have noted that some patients with oral squamous cell carcinoma have an overall increase in Prevotella bacteria.

According to A.M. Avanesov and E.N. Gvozdikova, the presence of carious teeth, chronic infectious processes, outdated dental prostheses, and inadequate oral hygiene contribute to alterations in the normal microbiome of the mucosal membrane [29]. These factors exacerbate tissue damage during antitumor therapy. Although the direct influence of microflora on the pathogenesis of oral mucositis was not specifically examined in this study, the authors emphasize that compromised local immunity combined with impaired microcirculation creates favorable conditions for the activation of opportunistic microorganisms. This process leads to intensified inflammatory responses and progression of erosive-ulcerative lesions of the mucosal membrane [29].

It should be emphasized that bacterial degradation products of the oral microbiota, particularly muramyl peptides, can induce the production of pro-inflammatory cytokines. Chronic maintenance of such an inflammatory microenvironment may contribute to oncogenic transformation by promoting genomic instability, inhibiting apoptosis, and activating proliferative signaling pathways in epithelial cells [30].

In 2000, Tateda et al. [31] detected Streptococcus anginosus in cancer samples obtained from the oral and pharyngeal regions. Subsequently, in 2005, Sasaki et al. [30–32] confirmed that S. anginosus is significantly elevated in patients with squamous cell carcinoma, but not in other cancers. Importantly, the bacterium was detected exclusively in plaque and not in the saliva of patients. Rai et al. [28–32] emphasize the importance of S. anginosus in the carcinogenesis of oral cancer. And in 2020, a number of researchers proposed the use of S. anginosus as a non-invasive biomarker for oropharyngeal cancer [33,34]. Other studies, including the work of Mager et al., indicate elevated levels of Streptococcus mitis in patients with oral squamous cell carcinoma. However, the results vary: in a study by Yang et al. involving 197 patients, an inverse relationship was found between Streptococcus abundance and tumor progression. Perera et al. found that S. mitis was frequently found in fibroepithelial polyp samples, which were used as a control group in their study. However, Streptococcus bacteria are cariogenic microorganisms and are found in 100 % of the world population, as dental caries and its complications remain the most common dental diseases in both childhood and adulthood [34].

The state of the oral microbiota can also influence the development of oncological diseases of other organs and systems of the body. Morita E. et al. and Narikiyo M. et al. [35,36] proved that Streptococcus anginosus and Streptococcus mitis bacteria are often found in patients with malignant neoplasms of the esophagus, these data coincide with the data of Kawasaki M. et al. and Gao S. et al. [37,38], who established a connection between this type of microorganism and the risk of developing gastrointestinal neoplasms. Porphyromonas gingivalis, as shown by the studies of Chen MF et al. [39], is detected in the tissues of malignant neoplasms of the esophagus. In the works of X. Fan et al, AV Alekseyenko et al, Mitsuhashi K. et al., Hu J. et al. and Wu J. et al., Huang K. et al. [40–42] showed a connection between pathogenic microorganisms of the oral cavity, such as P. gingivalis and Fusobacterium nucleatum, and the risk of developing pancreatic cancer [43,44]. Also, according to the studies of Hosgood HD and Yang J. et al. [45], low diversity of microbiota in the oral cavity is associated with an increased risk of lung cancer. A number of authors [40–46] note the influence of oral microbiota on the pathogenesis of breast cancer. A meta-analysis conducted by Shao et al. [46] revealed a significant relationship between periodontal diseases and the risk of developing this disease. The work of Parhi L. et al. [47] confirms that F. nucleatum can spread through the bloodstream and colonize breast tissue, which leads to suppression of antitumor immunity and acceleration of cancer progression, these data correlate with the data of Van der Merwe et al. [45–48].

The most convincing evidence for the carcinogenic effects of oral microorganisms is that of Fusobacterium nucleatum and Porphyromonas gingivalis. In addition, bacteria of the genera Streptococcus, Prevotella, and Capnocytophaga gingivalis also play an important role in the process of carcinogenesis. The proposed mechanisms of the oncogenic effects of these microorganisms on human cells include the induction of chronic inflammation, antiapoptotic effects, and the synthesis of carcinogenic metabolites. However, further studies are needed to more accurately identify specific oral bacteria as carcinogenic agents (Table) [49].

The use of bacteriophages for the treatment of infectious diseases is one of the promising areas of dentistry and medicine in general

The search for new promising, effective, but at the same time non-toxic methods of treating diseases of the oral mucosa, including chronic inflammatory processes, as well as precancerous conditions and possible reactions arising against the background of various types of antitumor treatment, remains an urgent problem. In this direction, methods using some microorganisms to suppress and control the reproduction of other microorganisms are actively developing. Such drugs include bacteriophages [50].

Bacteriophages are viruses that infect bacteria, causing changes in the structure and functionality of the oral microbiome. However, the role of bacteriophages in maintaining oral health and developing diseases has not been adequately studied. Phages are effective against planktonic bacteria and bacteria that form biofilms, which provide protection for microbes. These viruses are adapted to destroy biofilms by lysing bacterial cells and penetrating bacterial capsules or biofilm matrices. The high therapeutic potential of phages is explained by their ability to be used together with antibiofilm agents, which makes it possible to combat resistant bacteria. The human immune system is adapted to bacteriophages, which ensures their safety and non-toxicity confirmed by clinical studies. The key advantage of phage therapy is the lack of resistance to phages, which makes them effective in combating resistant infections. They have a narrow specificity for certain types of bacteria, preventing dysbiosis. However, in case of polyclonal infections or to minimize the risk of resistance, it is necessary to use a mixture of different types of phages, i.e., for the effective use of bacteriophages in the prevention and treatment of oral infections, as well as possible reactions that occur during antitumor treatment, an interdisciplinary approach is needed that combines the knowledge and methods of dentistry and oncology. Such an approach will allow achieving the best therapeutic results, improving the overall health and quality of life of patients [42–50].

**Influence of oral microbiome representatives on oncogenesis**

| Microorganism | Association with Cancer Types | Mechanisms of Influence | Clinical Significance |
|---|---|---|---|
| Porphyromonas gingivalis | Oral squamous cell carcinoma, pancreatic cancer, esophageal cancer | Chronic inflammation induction, apoptosis suppression, angiogenesis stimulation | Risk biomarker, prevention target |
| Fusobacterium nucleatum | Colorectal cancer, breast cancer | Acidic microenvironment creation, antitumor immunity suppression | Prognostic marker |
| Streptococcus anginosus | Oropharyngeal cancer, esophageal cancer | Carcinogenic metabolite production | Potential non-invasive biomarker |
| Prevotella intermedia | Oral squamous cell carcinoma | Chronic inflammation induction | Diagnostic potential |
| Cariogenic streptococci | GI tract cancer, pancreatic cancer | Acidic hypoxic microenvironment creation | Importance of oral sanitation |

Since their discovery a century ago, bacteriophages have been the subject of scientific research as a potential therapeutic agent. In a number of countries, the use of phages in medical practice has long been proven. However, a significant part of the Western world has expressed skepticism regarding phage therapy, arguing that there are no sufficient clinical trials confirming its effectiveness. Currently, Russian scientists are demonstrating an increased interest in bacteriophages, which opens up new horizons for further research and practical application of this treatment method. In particular, studies conducted by Volkov E.A. and co-authors [50] demonstrated that local application of a gel containing bacteriophages can relieve exacerbations in patients with chronic recurrent aphthous stomatitis [51]. The work of Uryadnikova V.A. and colleagues [52] emphasizes that bacteriophages have a positive effect on the hygienic condition of the oral cavity, which is expressed in a decrease in inflammatory processes and a specific effect on pathogenic microorganisms. One of the key advantages of bacteriophages is their ability to act selectively on certain bacterial strains, which allows preserving the integrity of the natural human microbiota. These results substantiate the feasibility of using bacteriophages in the treatment of infectious and inflammatory periodontal diseases and other diseases of the oral mucosa. Modern treatment approaches consider the influence of oral microbiota on the results of cancer treatment, where the use of bacteriophages can be an effective method for correcting microbiota during antitumor therapy. Changes in the composition of oral microbiota can also complicate the course of the disease and the rehabilitation process of patients, which emphasizes the need for dentists to pay close attention to the condition of the oral cavity of patients. Thus, an important aspect of the prevention of malignant neoplasms is associated with maintaining oral health, where high-quality individual and regular professional hygiene, treatment of inflammatory diseases of the oral mucosa and gums can reduce the risk of carcinogenesis. From the point of view of early diagnostics of oncological pathology, the oral microbiota is of great interest. Studies show that the presence of specific types of bacteria can signal the initial stages of the oncological process. Changes in the composition of the microbiota can serve as potential biomarkers, which opens up new prospects for dentists in determining the predisposition of patients to cancer and early preventive measures. The interaction of dentists and oncologists opens up new opportunities for prevention, early diagnosis and comprehensive treatment of cancer. Effective treatment of patients with cancer requires an interdisciplinary approach and close interaction between specialists in different fields of medicine.

## Conclusion

According to the data of the presented studies, the prevention, diagnosis and treatment of oncological diseases can and should be supplemented by dental approaches aimed at normalizing the microflora. Understanding that oral sanitation significantly reduces contamination and, as a result, reduces the number of pathogenic and oncogenic microorganisms can improve the quality of antitumor treatment without significant material and social costs. Regular oral sanitation and monitoring of the microbiotaplay an important role in the prevention of oncological diseases. Timely detection and treatment of oral diseases not only improve the general health of the patient, but can also significantly increase the chances of successful treatment and a good prognosis for cancer patients. The use of modern methods of diagnostics and monitoring of oral microbiota in dentistry can become the basis for the development of new strategies for the prevention and treatment of squamous cell carcinoma of the mucous membrane. Integration of these data into clinical practice requires interdisciplinary collaboration between oncologists, microbiologists and dentists to improve patient outcomes.

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# Значение микробиоты полости рта в возникновении и прогнозе онкологических заболеваний орофарингеальной области

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**Аннотация.** *Актуальность.* Несмотря на многолетние научные исследования и клинические результаты, онкологические заболевания остаются глобальной проблемой здравоохранения. В последние годы возрос интерес к изучению роли микроорганизмов в возникновении, прогнозе и прогрессировании онкологических заболеваний. Вероятность выделения в составе ротовой микробиоты канцерогенных микроорганизмов достаточно велика. В связи с этим, понимание роли микроорганизмов в возникновении и течении онкологической патологии в дальнейшем может способствовать разработке инновационных стратегий профилактики, лечения злокачественных новообразований и минимизации осложнений противоопухолевого лечения. Целью данного обзора является литературный анализ роли представителей микробиоты

полости рта человека в возникновении и прогнозе онкологических заболеваний. В ходе исследования проведены сбор и анализ 1050 научных работ с помощью поисковых систем PubMed, Google Scholar и eLIBRARY, опубликованных с 2003 по 2024 гг., среди которых 47 работ включены в данный литературный обзор. Согласно данным проведенного литературного анализа, профилактика, диагностика и лечение онкологических заболеваний могут и должны быть дополнены стоматологическими подходами, направленными на нормализацию микробиоты полости рта. Понимание того, что санация полости рта существенно снижает ее бактериальную обсемененность и как следствие сокращает количество патогенных и онкогенных микроорганизмов, может повысить качество противоопухолевого лечения без существенных материальных и социальных затрат. *Выводы.* Применение современных методов диагностики и мониторинга микробиоты полости рта в стоматологии может стать основой для разработки новых стратегий профилактики и лечения злокачественных новообразований слизистой оболочки полости рта. Интеграция этих данных в клиническую практику требует междисциплинарного сотрудничества между онкологами, микробиологами и стоматологами для улучшения прогноза лечения пациентов.

**Ключевые слова:** микробиота полости рта; злокачественные новообразования; канцерогенез; онкогенные бактерии; хроническое воспаление

**Информация о финансировании.** Работа выполнена без спонсорской поддержки.

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