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Review Article

Dentistry Section

Role of Bacterial Flora in Oral Cancer- An Insight

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ABSTRACT

The human body contains about 10^{14} bacteria which usually colonise different parts of the body. The bacterial flora is important for a person's health as well as normal functioning of tissue and organ systems. Bacteria are single celled organisms and are found on almost all surfaces of human body. They act in synergy with host immune mechanism and provide protection against various undesirable foreign invasions, especially in the oral cavity, where they exist in a diversified form which survive in a symbiotic relationship with the host. When there is a disturbance in this equilibrium due to various factors like trauma or tobacco smoking, betel nut chewing and alcohol intake, which makes the mucous membrane more permeable to invading microorganisms, these commensal bacterial species can become virulent and give rise to oral diseases ranging from dental caries to oral carcinoma. The effects of these bacteria can be either direct or indirect initiation of chronic inflammation, formation of procarcinogens that contribute to the development of oral carcinoma. This article focuses on the role of oral bacterial flora in initiation and progression of oral carcinogenesis. Various bacterial and fungal species associated with oral carcinoma and predominant bacterial species in oral cavity and oropharyngeal region along with measures to prevent their adverse effects are described.

Keywords: Carcinogens, Chronic inflammation, Literature review, Mucous membrane, Oral carcinogenesis

INTRODUCTION

Bacteria are biological cells which constitute a major domain of prokaryotic microorganisms. They lack nuclear membrane, are metabolically active and multiply by the process of binary fission. They are simple life forms and are highly adaptable and sophisticated. They are present on almost all the surfaces of human body including skin, oral mucosa, gut mucosa and cervical region [1].

The microorganisms found in the oral cavity in human beings are referred to as oral microflora or oral microbiome. The oral cavity consists of plethora of bacterial species that are implicated in various oral diseases [2]. The oral cavity is considered as a major entry point into the human body and the bacterial flora colonising on the oral mucosal surface has the highest possibility of entering systemic circulation. Bacterial colonisation on the surface of oral mucosa is shown to produce various oral infections ranging from dental caries to periodontitis and even lead to oral carcinoma [3].

Over the past few decades, various epidemiological studies have defined various risk factors for carcinogenesis which includes age, genetics, dietary pattern, long term usage of tobacco products, chronic viral infection and inflammation. Previous research has proved that a bacterial infection could possibly lead to cancer development in an individual [4-6]. The first evidence of bacteria causing cancer was proven in 1994, when *H. Pylori* was accepted as a potential carcinogen causing gastric cancer by World Health Organization (WHO) [4]. Since then, there has been a lot of research regarding the pivotal role of bacteria in causing carcinoma, especially in oral cavity, which comprises of diversified community of bacterial species [4].

The multifactorial aetiology of the development of oral cancer is attributed to the use of tobacco products, alcohol consumption along with betel nut chewing. In addition to the environmental factors mentioned, dietary factor along with poor oral hygiene has also been found to have a role in the initiation of oral cancer [7]. Apart from the above-mentioned aetiological factors, recent findings from various studies [6-8] suggest that the individual's oral microbial flora can act as an aetiological component for the development of oral cancer. It has been studied that, both the commensal and pathologic strains of bacteria present in the oral cavity offers significant contribution to the process of oral carcinogenesis [9].

Thus, a shift in the normal oral microflora indicates a dysbiosis in the oral cavity and act as an early diagnostic tool for the detection of underlying pathology. To detect the shift from the normal microflora, saliva has been used as a potential diagnostic tool for many years owing to its non invasive nature, ease of collection and more patient compliance method [10].

Variety of bacterial species have been thought to initiate carcinogenesis through induction of chronic inflammation and by directly or indirectly interfering with the eukaryotic cell cycle and cell signaling pathways leading to mutation and abnormal cellular proliferation [8]. This review attempts to reveal the various bacterial species involved in oral carcinogenesis along with the difference between the salivary microbiota of patients suffering from Oral Squamous Cell Carcinoma (OSCC) with that of the healthy individuals.

Livingston was the first physician who proposed that bacterial species can cause cancer and bacterial organisms which are capable of causing various carcinomas exhibits intracellular parasitism during different phases of its life cycle [11]. Elicited findings from important studies related to oral microflora associated with oral carcinoma have been summarised [Table/Fig-1] [6,12-22].

DEFINING BACTERIAL FLORA OF A HEALTHY INDIVIDUAL

Oral cavity is densely populated and hosts the largest ecosystem of microbes in human body. The normal microflora of the oral cavity can be broadly classified into resident flora and transient flora. Resident flora is always present and represents the normal microbial community. In case of disturbance in the normal resident flora, transient flora proliferates and gains the capability to cause diseases.

The resident flora is again divided into indigenous and supplement flora. Indigenous flora comprised of >1% in the particular site of oral cavity implying that they are in a symbiotic relationship with the host [16]. The supplement flora are organisms which are present in <1% and they have the potential to become indigenous when the environmental conditions are disturbed [23].

Year	Authours	Discovery
1993	Rawlinson A et al., [12]	Determined the most important bacterial species responsible for adult periodontal lesions which are frequently isolated from tumour sites in oral cavity.
1998	Nagy KN et al., [6]	Determined that samples from carcinoma lesion harbor increased number of aerobes and anaerobes when compared with healthy mucosa.
2002	Lax AJ and Thomas W, [13]	Explained bacteria could cause cancer and chronic infection when there is disturbance in the cell signaling and they also facilitate tumour initiation and promotion.
2005	Takahashi N, [14]	Microbial metabolic activity modifies the microbial physiological activity, initiating a shift from healthy to pathologic condition of oral cavity.
2006	Mager DL, [15]	Stated that certain bacteria evade immune system and contribute to carcinogenic changes through stimulatory effects of cytokines released by inflammatory cells.
2006	Hoper SJ et al., [16]	Analysed bacteria within oral squamous cell carcinoma tissues.
2009	Kang M et al., [17]	Revealed significant increase in number of *Porphyromonas gingivalis, Tannerella forsythia and Candida albicans* in cancer group.
2011	Pushalkar S et al., [18]	Concluded that most prevalent genera in oral squamous cell carcinoma library were *Streptococcus, Gemella, Rothia, Peptostreptococcus, Porphyromonas and Lactobacillus.*
2014	Bolz J et al., [19]	Concluded from their study that the prominent pathogens of the normal healthy oral mucosa were aerobes such as Streptococcus species, Staphylococcus species *Haemophilus parainfluenza, Neisseria species, Escherichia coli.*
2018	Banerjee S et al., [20]	Used pan-pathogen array technology coupled with next-generation technology to determine microbial signature unique to human oral and oropharyngeal squamous cell carcinomas.
2020	Zhang L et al., [21]	Analysed patients' samples using 16 rDNA sequencing and compared the microbial composition between tumour sites and normal tissues and revealed that genes involved in bacterial chemotaxis, flagellar assembly and Lipopolysaccharide (LPS) biosynthesis which are associated with various pathological processes, were significantly increased in the oral squamous cell carcinoma group.
2020	Sami A et al., [22]	Highlighted the role of oral as well as gut microbiome in development and progression of oral squamous cell carcinoma along with the potential side effects with the management of the same.

[Table/Fig-1]: Findings from various studies related to oral microflora associated with oral carcinoma [6,12-22].

Bacteria can also be classified as aerobes (oxygen-dependent) and anaerobes. These aerobic bacteria interact with oxygen and create a localised ideal environment for anaerobes to colonise and thrive expressing co-aggregation. Thus, efficiently maintaining the homeostasis within the oral cavity [16].

Oral microflora represents various genomes of microorganisms in the oral cavity. Both the pathogenic and mutagenic organisms co-exist in oral cavity and saliva provides the essential nutrients required for the growth and development of organisms and keeps them hydrated. The oral microbial population varies with saliva and different habitats like buccal mucosa, supragingival and subgingival plaque. There exists other microbial habitats such as periodontal pocket area, surface of teeth and tongue in oral cavity [9]. Among the various habitats, tongue shows the highest diversity of microorganisms, and these organisms on the tongue can reach other regions of oral cavity through saliva [16].

Bacterial species in oral cavity exhibit specific attachment modality to different biological surfaces such as teeth, tongue and mucosa [16]. The different types of receptors and adhesion molecules present on the microorganisms ensures colonisation of bacteria to various non shedding and continually shedding surface of the oral mucosa through a specialised mechanism known as 'Lock and Key' mechanism by which bacteria attaches itself with the complementary receptors present on the host mucosal surface [16].

Abundant anaerobic species including Spirochetes and Bacteroidaceae subspecies are commonly found in the subgingival area with less oxygen tension [9]. [Table/Fig-2] summarises the predominant bacterial species found in oral cavity and oropharyngeal region [9].

Fungal organisms present in oral cavity can be divided into candida and non candida organisms and they have been listed in [Table/Fig-3] [23].

ORAL ONCOGENIC BACTERIAL SPECIES

Among the diversified group of microflora present in oral cavity certain bacterial species are considered to be highly selective and present in abundance in malignant conditions [24]. Species belonging to *Streptococcus anginous* most commonly infect patients with OSCC and are considered as a potential diagnostic marker for the same [24]. Other species such as *Capnocytophaga gingivalis*, *Prevotella melaninogenica*, *Streptococcus mitis* was elevated in saliva of patients with OSCC. Among all the species mentioned above streptococcus species were highly associated with OSCC tumour site. Species belonging to *Veillonella*, *Fusobacterium, Prevotella, Porphyromonas, Actinomyces, Clostridium, Haemophilus, Streptococcus* and *Enterobacteriaceae* were present in higher number in case of oral keratinising squamous cell carcinoma [24].

Oral bacteria such as *Streptococcus mitis*, *S. sanguinis* and *Treponema denticola and* certain fungal species like *Candida albicans* were found to play a significant role in the carcinogenesis process [24]. [Table/Fig-4] enumerates various bacterial species associated with different kinds of carcinomas [25-28].

ORAL MICROBIOME IN CARCINOGENESIS

The mechanism by which oral bacterial species and Candida species bring about carcinogenesis can be divided into direct and indirect mechanism [29]. The occurrence of OSCC involves multifactorial events that take place in a sequential manner which includes genetic damage caused by exogenous carcinogens which are acted upon by environmental factors and chronic inflammation [29].

Deoxyribonucleic Acid (DNA) damage brings about mutation and also promotes overexpression of oncogenes. Tumour suppressor genes act on the normal cell cycle and produces a stem cell which develops and proliferates, escaping apoptosis process [29].

The various processes by which oral bacterial flora induce carcinogenesis are discussed below:

1. Process of Chronic Inflammation

Infection due to bacteria is mainly attributed to the chronic inflammatory mediators which are released during chronic inflammatory process and can activate cell proliferation, oncogenic activity mutagenesis and angiogenesis, all of which leads to loss of normal function and growth [30]. [Table/Fig-5] shows the role of oral bacteria in the pathogenesis of cancer [30].

Nuclear Factor-kappa B (NF-kB) plays a major connective role between inflammatory process and carcinogenic process [29]. When activated, nuclear factor kappa B initiate cytokines to recruit phagocytes to the inflammatory site. It has also been studied that the abundance of reactive oxygen species which are released from neutrophils to destroy the pathogen will also damage the host DNA, which in turn leads to genetic mutation and initiate carcinogenic process [29].

2. Induction of Procarcinogens

Alcohol consumption has been considered as one of the major risk factors for development of oral cancer. The pure ethanol found in alcohol is not considered to be carcinogenic, however, the acetaldehyde which is the first metabolite, is a proven carcinogen in humans [29]. [Table/Fig-6] provides a summary of risk factors associated with development of oral cancer [31].

Bacterial colonisation site in oral and oropharyngeal region	Name of the bacterial species	Name of the phylum	Aerobic/Anaerobic	Commensol/Pathogenic
Teeth Surface	*Streptococcus mutans* *Eubacterium* *Peptostreptococcus* *Actinomyces*	Firmicutes Firmicutes Firmicutes High GC gram +	Facultative anaerobic Anaerobic Anaerobic Anaerobic	Commensal Pathogenic Commensal Commensal
Tongue	*Capnocytophaga* *Veillonella atypica* *Selenomonas subspecies* *Aggregatibacter actinomycetemcomitans* *Porphyromonas gingivalis* *Prevotella intermedia* *Eikenella corrodens*	Bacteroidetes Firmicutes Firmicutes Proteobacteria Bacteroidetes Bacteroidetes Proteobacteria	Facultative anaerobic Anaerobic Obligately anaerobic Facultative anaerobic Anaerobic Anaerobic Anaerobic	Pathogenic Commensal Pathogenic Pathogenic Pathogenic Pathogenic Commensal
Gingival Crevice	*Fusobacterium* *Prevotella* *Porphyromonas* *Streptococcus mitis* *Streptococcus sanguinis* *Propionibacterium acnes* *Leptotrichia buccalis* *Actinomyces odontolyticus* *Veillonella pravula*	Fusobacteria Bacteroidetes Bacteroidetes Firmicutes Firmicutes Actinobacteria Fusobacterium Actinobacteria Firmicutes	Anaerobic Anaerobic Anaerobic Anaerobic Anaerobic Anaerobic Anaerobic Anaerobic Anaerobic	Commensal & pathogenic Pathogenic Pathogenic Commensal Commensal Commensal Commensal Pathogen Commensal
Dental Plaque	*Actinomyces* *Rothia* *Microbacterium* *Mycobacterium* *Propionibacterium* *Corynebacterium* *Bifidobacterium*	Actinobacteria High GC gram + High GC gram + High GC gram + High GC gram + High GC gram + High GC gram +	Anaerobic Facultative anaerobic Aerobic Aerobic Anaerobic Aerobic/facultatively anaerobic Anaerobic	Pathogenic Commensal Commensal Pathogenic Commensal Pathogenic Commensal
Tonsil	*Staphylococcus* *H influenzae* *Streptococcus viridans* *Neisseria species*	Firmicutes Proteobacteria Firmicutes Proteobacteria	Facultative aerobic Facultative anaerobic Facultative anaerobes Aerobic	Pathogenic Commensal Commensal Commensal
Oropharynx	*Streptococcus pyogenes* *Streptococcus pneumoniae* *Haemophilus influenzae* *Haemophilus* *Parainfluenzae* *Streptococcus mutans* *Streptococcus salivarius* *Streptococcus anginosus*	Firmicutes Firmicutes Proteobacteria Proteobacteria Proteobacteria Firmicutes Firmicutes Firmicutes	Facultative anaerobic Facultative anaerobic Aerobic Aerobic/Facultative anaerobe Aerobic/Facultative anaerobic Facultative anaerobic Facultative anaerobic Facultative anaerobic	Pathogenic Pathogenic Commensal Commensal & pathogenic Commensal & pathogenic Commensal Commensal Pathogenic

[Table/Fig-2]: Predominant bacterial species and their phylum in oral cavity and oropharyngeal region [9].
The major phylum of bacteria inhabiting normal oral mucosa belongs to Firmicutes, Proteobacteria, Actinobacteria, High GC gram +, Bacteroidetes; GC: Guanine cytosine

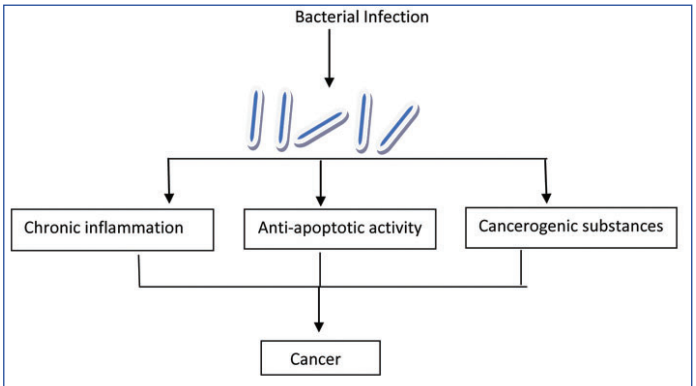
Candida species	Non candida organisms
C.albicans, C. tropicalis, C. glabrata, C. parapsilosis, C. krusei, C. kyfer	*Aspergillus fumigatus, Cryptococcus neoformans, Histoplasma capsulatum, Blastomyces dermatitidis, Coccidiodes Paracoccodioidesbrasiliensis.*

[Table/Fig-3]: List of fungal organisms present in oral cavity [24].

Bacterial species	Carcinoma associated
Exiguobacterium oxidotolerans, Prevotella melaninogenica, Staphylococcus aureus	Oral squamous cell carcinoma
Bifidobacteria *Fusobacterium necrophorum*	Colorectal cancer
Actinomycetes	Lung cancer
Lactobacillus	Cervical cancer
S. anginosus	Esophageal, gastric, and pharyngeal cancer

[Table/Fig-4]: Bacterial species associated with various types of carcinomas [25-28].

This acetaldehyde promotes chromosomal mutation leading to DNA adducts, aneuploidy, DNA cross-linking and chromosomal aberration. This reaction is carried out by the alcohol dehydrogenase enzyme present in the oral cavity of host and also by the other oral microflora. This hypothesis is supported by various studies [31-33] and till date it has been shown that Streptococci, gram-positive aerobic bacteria and yeast have been related to the production of acetaldehyde along with the organisms mentioned in [Table/Fig-6]. *Neisseria* species is also demonstrated to release increased levels of acetaldehyde in the presence of ethanol. Salivary analysis of patients with both alcohol and tobacco usage shows higher level of microbial acetaldehyde, thus proving the role of oral microbial flora in the pathogenesis of OSCC in patients with alcohol and tobacco chewing habit [31].



[Table/Fig-5]: The role of oral bacteria in the pathogenesis of cancer [31].

Risk factors for development of oral cancer	
1) Chemical factors	Tobacco, alcohol
2) Biological factors	Human papilloma virus, syphilis
3) Oro-dental factors	Poor oral hygiene (in case of poor oral hygiene there is reduction in the diversity of bacterial species present in the oral cavity, which facilitates growth of certain bacteria becoming more dominant that can result in bacterial dysbiosis), dental sepsis promotes carcinogenic action of tobacco.
4) Nutritional intake	Lower risk of developing oral cancer with high intake of vegetables and fruits.

[Table/Fig-6]: Risk factors for development of oral cancer [31].

3. Effect of Bacteria on Cell Signaling

Various species of bacteria interfere directly with normal cell signaling pathway which is characteristic of tumour promoters [29].

Activation of the Mitogen-Activated Protein Kinase (MAPK) and cyclin D1 pathways stimulates proliferation and Deoxyribonucleic Acid (DNA) replication in a variety of infections. BCL-2 family protein expression mediates pathogens which are capable of intracellular entry and is linked to suppression of apoptosis. Ras-mediated activation of cyclin-dependent kinases also supress apoptosis by tumour suppressive effects of Retinoblastoma protein (Rb). By blocking these apoptosis mechanisms, the partially transformed cell infected with bacteria escapes destruction and attains higher level of transformation eventually resulting in carcinogenesis. Focal Adhesion Kinase (FAK) and SRC are signalling molecules related to cell adhesion particularly related to focal adhesion complex plays a role in tumourigenesis. Toxins secreted by bacteria targets small GTPases of Rho family which regulates focal adhesion. Disruption of Rho family proteins disrupts the signalling pathway and are interconnected which are responsible for cellular responses. Rho proteins play a major role in cellular control and their disruption by toxins from bacteria needs to be fully investigated [34].

Commensal microflora of oral cavity has a potential to promote host cell proliferation, this property is exhibited by a periodontal pathogen *Porphyromonas gingivalis,* which contains proteins and Lipopolysaccharides (LPSs) on its outer surface which has the ability to induce human fibroblast proliferation [29].

Species like *E. coli* secretes variety of virulence factors which includes Cytotoxic Necrotising Factor type-1 (CNF1), which activates a cell signaling process and initiate the expression of antiapoptotic members of BCL-2 gene family which prevents the apoptosis [29]. Similarly, *C. pneumoniae* initiates the expression of Interleukin-10 (IL-10) which suppresses the expression of Major Histocompatibility Complex (MHC) Class 1 molecules and the cells infected with *Chlamydia pneumoniea* show high resistance to apoptosis process [29].

DETECTION AND PREVENTIVE MEASURES TO REDUCE PATHOLOGIC BACTERIAL FLORA IN ORAL CARCINOMA PATIENTS

The various techniques involved in diagnosis of oral cancer includes vital staining method (5% Acetic acid, Toluidine Blue), Light-Based detection system (velscope, Vizilite), Histological techniques (incisional biopsy, excisional biopsy), Cytological technique (Oral brush biopsy, liquid-based cytology), Molecular analysis (Gene alteration), Imaging techniques such as- Fluorodeoxyglucose (FDG)-Positron Emission Tomography (PET), Optical Coherence Tomography (OCT), other techniques (Onco Chip) [35].

The first stage of prevention is to educate patient regarding harmful effects of consuming alcohol and tobacco products, and advise patient to discontinue the deleterious habits. Encourage patient to maintain adequate oral hygiene, prescribing oral mouth rinses which have antibacterial effect to reduce the bacterial load. Advise patient to consume more fruits and vegetables which have a potential to reduce risk of oral cancer [36].

The ultimate goal of preventing bacterial flora causing oral cancer is by interfering in the development of carcinogenic potential of these microbes. Cysteine is a non essential amino acid when administered orally, binds to acetaldehyde and creates a stable thiazolidine-carboxylic acid molecule, preventing the carcinogenic process caused by acetaldehyde. Various other compounds have also been employed to prevent oral cancer which primarily interfere with the cellular carcinogenic mechanism. They also possess antimicrobial components which includes antioxidant, retinoids, vitamin A and E, carotenoids. Apart from the chemical compounds, naturally occurring herbs and spices have also been employed in prevention of oral cancer and also possess antimicrobial property. These spices include cumin, garlic, cloves, thyme, cinnamon, rosemary and also mustard. Green tea has also been investigated extensively. Finally, probiotic or bacteria which provide 'health benefits' have been studied extensively for empowering ones own immune function [37].

It has been reported that consumption of dairy products with higher levels of probiotics, which are defined as living bacteria, when administered in adequate amounts, confer a health benefit on the host (FAO/WHO 2001) [38]. The commonly used probiotic strains are Lactobacillus acid bacteria, which is a gram-positive microbe, along with its members Lactococcus and Streptococcus, constitutes the endogenous gut microbiota of humans. The absence of LPSs and secreted proteases make them ideal for usage as a probiotic. *Escherichia coli*, commonly used as a Gram-negative probiotic may have antitumour effects [39]. Sources of probiotics includes yogurt [40], Kefir, a milk drink with kefir grains added to cow's and goat's milk, Kimchi, a fermented spicy Korean sides dish [41].

Lactic acid bacteria's anticancer mechanism is attributed to the inhibition of mutagenic activity, reduction in the level of enzymes that are involved in generation of various carcinogens, tumour promoting agents or mutagens suppression of tumours and supplementary actions like modulation of cell mediated immune response, activation of reticuloendothelial system and regulation of cytokine pathway. They also regulate interleukin and tumour necrosis factors [37].

All the above-mentioned findings have to be extensively researched and to be adapted for future usage.

CONCLUSION(S)

The link for the bacterial infection and oral carcinogenesis has been extensively studied and the various mechanisms by which bacterial cell induce carcinoma have been proposed. Chronic inflammation, direct or indirect activation of eukaryotic cell cycle and signaling pathways and metabolism of potentially carcinogenic substances were considered as important factors for inducing carcinogenesis. The shift in the oral commensal microflora can serve as a potential diagnostic indicator for the early diagnosis of the OSCC which cannot be completely explained by the traditional risk factors. The microflora associated with carcinomatous conditions and various interactions between the host cell and microbes at cellular level are the concept which still needs further studies which can result in appropriate treatment planning leading to better prognosis.

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