

Oral microbiota and cancer

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Inflammation caused by infections may be the most important preventable cause of cancer in general. However, in the oral cavity the role of microbiota in carcinogenesis is not known. Microbial populations on mouth mucosa differ between healthy and malignant sites and certain oral bacterial species have been linked with malignancies but the evidence is still weak in this respect. Nevertheless, oral microorganisms inevitably up-regulate cytokines and other inflammatory mediators that affect the complex metabolic pathways and may thus be involved in carcinogenesis. Poor oral health associates statistically with prevalence of many types of cancer, such as pancreatic and gastrointestinal cancer. Furthermore, several oral micro-organisms are capable of converting alcohol to carcinogenic acetaldehyde which also may partly explain the known association between heavy drinking, smoking, poor oral health and the prevalence of oral and upper gastrointestinal cancer. A different problem is the cancer treatment-caused alterations in oral microbiota which may lead to the emergence of potential pathogens and subsequent other systemic health problems to the patients. Hence clinical guidelines and recommendations have been presented to control oral microbiota in patients with malignant disease, but also in this area the scientific evidence is weak. More controlled studies are needed for further conclusion.

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Human microbiota may play a role in carcinogenesis. *Helicobacter pylori* is the best known bacterium causally linked with cancer (1). However, the general concept of human microbiota is changing when molecular techniques have revealed its vast diversity, but, at the same time, individual stability of micro-organisms residing on skin and gastrointestinal tract mucosa (2). Micro-organisms seem to play an important role in metabolism but it is not known how the diversity relates to function and to the rest of the genes in the collective genomes of the microbiota. Extensive studies have shown in the gut that its totality of microbes, the microbiome, is shared among family members, but that each person's microbial community varies in the specific bacterial lineages present, with a comparable degree of co-variation. A wide array of shared microbial genes have been observed among sampled individuals, comprising an extensive, identifiable 'core microbiome' at the gene level rather than at the organismal lineage (3). Corresponding studies on oral microbiota are on their way (4).

Traditionally it has been thought that mouth mucosa (5), the tongue (6), and the pharynx (7) harbor characteristic bacterial pathogens causing chronic inflammation and focal infections (8). Many of these infections derive from oral biofilms commonly linked with the

highly prevalent dental diseases (9–11). For a long time, particularly periodontal disease has been emphasized in this respect (12). Oral microbiota may also associate with the development of cancer. It is a well-known clinical fact that the patients with oral cancer often present with poor oral hygiene. Studies have shown that the association between oral microorganisms and cancer may even be causal (13).

Inflammation is a key feature in many chronic diseases including cancer (14, 15). Investigations of gastrointestinal malignancies have shown that the large amount of cytokines and growth factors released during inflammation by immune and non-immune cells may influence carcinogenesis (16). In general, infection-driven inflammations have been estimated to be involved in the pathogenesis of approximately 15–20% of human tumors (17). Hence inflammation caused by infections might be one of the most important preventable causes of cancer (18).

The worldwide incidence of cancer also attributes to infections caused by virus such as hepatitis viruses, human papilloma virus (HPV), and Epstein-Barr virus (EBV) (19, 20). Characteristic to infections and inflammations linked with malignancies is indeed that they are persistent in the host for a long time and highly prevalent in populations (21). However, there may be a long latency

between the initial infection and tumor appearance, and not at all does every infected person develop cancer. In general this area is difficult for research. The overall effect of the microbiome in these contexts is not known.

This review briefly outlines current knowledge about the role of oral microbiota in carcinogenesis with emphasis on oral cancer and microbial changes caused by cancer treatment. The focus is on bacterial and yeast infections and the reader interested in viral infections is advised to other texts. To put the viral infections in perspective, however, it has been estimated that at least six human viruses, EBV, hepatitis B virus (HBV), hepatitis C virus (HCV), HPV, human T-cell lymphotropic virus (HTLV-1) and Kaposi's associated sarcoma virus (KSHV) contribute to 10–15% of the cancers worldwide (22). No such figures exist for bacteria- or yeast-related malignancies. The role of viruses has recently been reviewed in this journal (23).

The current text is based on the PubMed literature searching 20 years back and up to the end of May 2010. The keywords used were 'cancer' vs. 'oral microbiota' (20 hits), 'dental hygiene' (981 hits), 'oral micro-organisms' (136 hits); and 'carcinogenesis' vs. 'oral infection' (153 hits), and 'oral infection control' (37 hits). Based on relevance of the abstracts of the publications full texts were then searched and assessed for final inclusion. Because of scarcity of hard data and the descriptive nature of the majority of studies no systematic review could be conducted.

Oral health effects on cancer

The association between poor oral health and tooth loss with increased risk of gastric cancer has been reported in retrospective studies in many countries (24–26). Furthermore, in a prospective study from China, Abnet and co-workers (27) reported that tooth loss increased the risk of developing gastrointestinal cancer. Positive associations between tooth loss and pancreatic cancer have also been reported (28, 29). A prospective cohort study in the US male health professionals showed that when compared with no periodontal disease, the history of periodontitis significantly associated with increased pancreatic cancer risk [risk ratio (RR) 1.64; 95% confidence interval (CI) 1.19–2.26] while the cumulative tooth loss during the 16-year follow-up was not associated with pancreatic cancer (30). There are also anecdotal data to show that oral streptococci may associate with colonic cancer (31). These data, however, rather present systemic complications of the patients than give any evidence for causal effect (32).

In the male health professionals study from the USA, periodontal disease has also been shown to increase the statistical risk for head and neck cancer with an odds ratio (OR) 4.36 (CI 6.01–93.16). The association persisted in subjects who never used alcohol or tobacco (33).

Furthermore, a study from Buffalo, New York, on 51 cases with tongue cancer, showed that chronic periodontitis presented a 5.23-fold increase in the cancer risk when compared with 54 controls (OR 5.23; CI 2.64–10.35) (34). The same group reported that periodontitis patients were also more likely to have poorly differentiated oral squamous cell carcinomas than periodontally healthy patients (35). Interestingly, practicing no regular oral hygiene also conferred OR 2.37 (CI 1.42–3.97) for esophageal cancer when compared with those who undertook daily tooth brushing (36). Recently, in a study on 30,475 individuals also from the USA, the use of dental care was analyzed with respect to oral cancer. After controlling relevant covariates the results showed that when compared with no use of dental care those who had had dental appointments during the past 12 months were 62% less likely to have oral cancer (OR 0.38, CI 0.13–1.10) (37).

Mucocutaneous candidiasis is also known to associate with the development of cancer in particular patients with a rare genetic disease called autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (38). These patients call for frequent follow-up due to markedly increased oral cancer risk with subsequent malignancies presenting in young age of the patients. Recently, however, cases have been presented where chronic mucocutaneous *Candida* infection associated with esophageal cancer in patients with immunoglobulin-A deficiency (39). Thus, it can be speculated that impaired local immunity which renders the patient liable for oral candidiasis increases the risk for cancer. More studies are needed for further evidence, however.

Our unpublished results from a cohort study in Sweden with 16 years of follow-up showed that age, female gender, and periodontitis with loss of the first mandibular molars were the principal independent predictors of cancers in general, and breast cancer in particular, as registered in the Swedish Cancer Registry. From the same database, premature death of young individuals was observed to link statistically with periodontitis and missing molars whether the cause of death was because of cancer, cardiovascular, or gastrointestinal disease (40).

A confounding factor difficult to control in epidemiological studies, however, is the fact that oral health-related variables also link with the use of tobacco and alcohol (41). Furthermore, there are no studies conducted to show if aggressive forms of oral infections affect the incidence or prevalence of cancer compared with milder forms of infections (42). Hence there is a need for further studies in which also the severity of oral infection is taken into account together with encompassing all possible foci of infections and not only periodontitis. However, it is of interest to emphasize that in many studies the associations between periodontal disease and cancer, in particular, persisted after adjustment for major risk factors,

including cigarette smoking and socioeconomic status (43). Thus, taken together the results from studies in this area seem to support the general hypothesis of chronic oral infection-based carcinogenesis (44).

Mechanisms involved in oral infection-linked carcinogenesis

In general, the association between periodontal disease and various systemic diseases has been intensively studied during the past two decades, but the exact mechanisms involved are still not known. Most studies have focused on the development of atherosclerosis; periodontal microorganisms have been detected in atheroma plaques (45). The large potential wound area of inflamed periodontium in dentate subjects, the rich oral microbiota and the frequent transient bacteremia episodes in normal life, maintain a low-grade chronic inflammation which triggers a variety of systemic reactions. These in turn may lead to carcinogenic mechanisms which, however, are not clear. Irrespective of the focus of infection bacteria may induce cellular proliferation, inhibit apoptosis, interfere with cellular signaling mechanisms, and act as tumor promoters (46).

Up-regulation of cytokines and other inflammatory mediators affect complex metabolic pathways and there also seems to be a link between chronic infections and sugar metabolism. For example, the receptor for advanced glycation end products (RAGE), a multi-ligand receptor expressed on various cell membranes, has been suggested to play a role also in carcinogenesis. RAGE is activated by ligands in a variety of cell types and tissues, and may play a role in the oral infection-systemic health associations (47). This receptor is associated with pro-inflammatory responses and may underlie in diverse pathologies including periodontal disease (48). Oral infection may also directly reflect in endothelial dysfunction with systemic consequences (49). The cytokine reactions involved have been shown to play a role in the immune-related mechanisms of cancer development (50).

Another mechanism suggested to be involved in oral carcinogenesis is mediated via salivary factors. Poor oral health has been shown to associate with the genotoxic salivary activity. Bloching et al. (51) studied dental status and saliva of 100 subjects relating their oral health to *in vitro* salivary mutagenicity, using the *Salmonella* test. The authors reported a significant association ($p < 0.05$) between high-plaque index and high number of carious teeth with the genotoxic activity in saliva. Studies on this field indicate, however, that salivary mutagenicity is the result of external chemicals and carcinogens introduced into the system. Thus, for example, the use of tobacco and areca nuts associates with the development of oral cancer (52). The polymicrobial burden caused by oral biofilms may also possess mutagenic interactions with saliva which may act as co-factors in

carcinogenesis. These examples illustrate the complexity of tumor genesis.

Recently, a possible causal link between micro-organisms and oral cancer has been suggested. Several bacteria and *Candida* strains in the mouth convert ethanol to carcinogenic acetaldehyde thus explaining the epidemiological evidence between heavy drinking, smoking, and development of cancer (53, 54). Both the commonly encountered oral streptococci and yeasts possess metabolic pathways for this conversion (55–57). Alcohol-related carcinogenesis is well-known and the enzymes involved have been characterized. Polymorphism in these genes may partly explain why subjects differ in their liability for the development of cancer; it may be a question of higher or lower metabolic activities involved in alcohol metabolism (58). Nevertheless, there is a significant dose–response relationship between alcohol intake frequency, duration of use, and oral cancer risk (59). Similarly, smoking associates with cancer and smoking also causes an increase in salivary acetaldehyde concentrations thus adding to the risk related to alcohol (60). The effect of smoking and alcohol is thus synergistic (61).

Differences in oral microbiota in patients with and without cancer

Microbial populations on mouth mucosa seem to differ between healthy and malignant sites. For example, *Streptococcus anginosus* and *Treponema denticola* associate with various upper gastrointestinal tract carcinomas (62). Shiga et al. (63) suggested that *S. anginosus* infection might be implicated in the carcinogenesis of head and neck squamous cell carcinoma in general. *S. anginosus* DNA has been detected in carcinoma tissue samples but not in lymphoma, rhabdomyosarcoma, or leukoplakia samples. Dental plaque could be a dominant reservoir of this bacterium (64). As a curiosity, syphilis has also been mentioned in textbooks to be associated with cancer, but there are no data found to support this statement.

Mager et al. (65) investigated the relationship of 40 common salivary bacteria counts between 45 patients with oral cancer compared with counts from 229 healthy controls. They observed that *Capnocytophaga gingivalis*, *Prevotella melaninogenica*, and *Streptococcus mitis* counts were significantly increased among the oral cancer patients. The authors further analyzed if these species could be used as diagnostic markers for oral cancer and found 80% sensitivity and 82% specificity, respectively. In oral cancer patients mutated salivary DNA at the 53p gene was observed in 62.5% of 10 patients when compared with 18.5% among 27 healthy controls in a study from Taiwan (66). In another study salivary mitochondrial DNA was found to be increased in patients with head and neck cancer directly in proportion to the degree of malignancy of the tissue, i.e. from mild to severe

dysplasia (67). Again, however, further studies are needed to confirm these findings.

Several researchers have observed viral or pro-viral DNA in saliva or gingival crevicular fluid samples of patients with malignancies (68, 69). These and other biomarkers of oral cancer have been recently reviewed by Seoane Lestón and Diz Dios (70) and Wu et al. (71). In the future laboratory methods such as microarray analyses and gene expression profiling might be applicable for investigating changes in oral microbiota on malignant sites. For example, pyrosequencing of the oral cavity and salivary samples has greatly improved our understanding in the wider perspective of the complex microbiota of the mouth (72).

In general, novel approaches to map oral cancer lesions are based on molecular techniques (73, 74). It has been shown that genes express differently on malignant vs. healthy sites and that more accurately than conventional histology certain gene profiles can be used to assess the disease course. It remains to be shown how specifically these changes possibly affect oral microbiota, however. Further, studies are called for to investigate whether combined molecular techniques such as genomics, transcriptomics, and proteomics could be used to profile both the host tissue and the microbiota for accurate diagnostics (75).

Finally, it should also be kept in mind that the sampling site as such may influence the results. In oral cancer patients optimal sampling may be difficult (76). Consequently, proper sampling technique for both the conventional cultivation and the new molecular methods needs to be emphasized (77). There is a need for standardized guidelines in this area.

Effect of cancer treatment on oral microbiota

Microbiological studies have been conducted in particular in patients undergoing treatment for cancer. Radiotherapy-caused hyposalivation may affect the oral microbiota. Variations in quantity, complexity, and quality of the oral microbiota also occur during chemotherapy, leading to a major imbalance of the ecosystem (78). For example, in a study from Sweden, *Candida albicans* was found in one or more sites in 54% of the subjects who had received radiotherapy to the head and neck in comparison to 15% of the controls. These patients also harbored enterococci in 38% vs. none of the controls. *Lactobacillus* spp. were detected in 92% of the subjects and the proportion of the species was high compared with the controls. Mutants streptococci were also detected in high numbers; 31% in the patients vs. 23% in controls (79). On the other hand, in a study from China mutants streptococci were not isolated in radiotherapy patients while lactobacilli, *S. mitis* and *S. salivarius* were the predominant caries-related oral bacteria following radiotherapy (80).

Bacteria in gingival pockets in head- and neck-irradiated patients have also been investigated. A comprehensive study from Hong Kong showed that the major components of sub-gingival microbiota appear similar to that of gingivitis sites in the normal population although among the radiotherapy patients bacterial or fungal species uncommon in normal subjects were also detected (81). These species included micro-organisms such as *Gemella*, *Peptostreptococcus*, *Staphylococcus*, *Stomatococcus*, *Streptococcus*, *Actinomyces*, *Eubacterium*, *Lactobacillus*, *Propionibacterium*, *Neisseria*, *Veillonella*, *Bacteroides*, *Campylobacter*, *Capnocytophaga*, *Fusobacterium*, *Kingella*, *Porphyromonas*, and *Prevotella*. Also species of microbes that are characteristic to the normal microbiota of skin (*Peptostreptococcus prevotii* and *Propionibacterium granulosum*) and gut (*Eubacterium aerofaciens*, *Fusobacterium mortiferum*, and *Fusobacterium varium*) were detected in this material (81).

How permanent are the shifts in oral microbiota after the treatment of cancer is another question of interest. Radiotherapy or cytostatic treatment-caused changes in bacterial composition need not be permanent. For example, in child allogeneic bone marrow transplantation patients in the UK no differences were seen in the total anaerobic counts or in the proportion of the *S. oralis* group bacteria between the baseline and end of a 119-day study or between the patients and controls (82). However, caries risk may still be increased in particular in pediatric patients surviving a malignant disease (83).

In immunosuppressed patients treated with cytostatic drugs pathogenic and opportunistic micro-organisms colonizing the mouth may indeed be dangerous. *Enterobacteria* and genera such as *Pseudomonas*, *Neisseria*, and *Veillonella* have been observed in oral samples from granulocytopenic patients with leukemia (84). Yeasts can also be predominant but not always (85). It appears that the pre-treatment oral health status is important in this respect. For example, in a study on non-lymphocytic leukemia patients in Baltimore periodontal disease status and attachment loss were positively correlated with increase in the proportional recovery of *Staphylococcus* spp. from supra-gingival sites and total yeasts from supra- and sub-gingival sites (86). The authors suggested that host factors such as periodontal disease may contribute to the patterns of oral microbial successions during cancer chemotherapy. Finally, pathogens such as *Capnocytophaga* may pose a systemic risk in patients with cancer. Hence continuous attention is called for in order to prevent bacteremia and also to overcome problems of developing antibiotic resistance as pointed out by Sixou et al. (87). Above all, however, studies are lacking to show how different cancer treatments affect oral microbiota as a whole. It can be anticipated that all the oral cancer treatment modes, include surgery, radiotherapy, and cytostatic drugs, affect oral micro-organisms differently

with possible characteristic shifts in biofilm composition. Hence more studies are needed in this area which is important in order to get evidence-based guidelines to the maintaining satisfactory dental health of an individual with cancer (88). These are briefly discussed below.

Controlling oral microbiota in cancer patients

Potential oral infection foci need to be diagnosed and treated before starting immunosuppressive therapy (89). To avoid complications antiseptic oral rinses have been recommended. Chlorhexidine has been the golden standard in controlling oral microbiota in cancer patients. Oncologic units and wards have guidelines explaining how and at what phase of the treatment the mouthwashes should be administered to the patients. Chlorhexidine in general has shown effective in preventing dentogenic bacteremia. For example, in a study by Tomás et al. (90), the prevalence of bacteremia after dental extraction by using chlorhexidine and control groups were 79% vs. 96%, respectively, at 30 s ($p < 0.01$), 30% vs. 64% at 15 min ($p < 0.001$), and 2% vs. 20% at 1 h ($p < 0.01$) after the treatment. In their study the most frequently identified bacteria were *Streptococcus* spp., particularly of the viridans group. These were detected from blood cultures of both the chlorhexidine and control groups (64% and 68% of the subjects, respectively).

Chlorhexidine mouthwash has also shown effective in preventing oral mucositis during cancer chemotherapy. In a randomized double-blind study on 206 patients receiving fluorouracil-based chemotherapy in gastrointestinal cancer mucositis occurred more frequently (33%) if the patients did not receive chlorhexidine in comparison to the study phase when three daily chlorhexidine mouth rinses were administered (13%, $p < 0.01$) (91). Similarly in a study on head and neck cancer patients undergoing radiotherapy using either 0.12% chlorhexidine or 1% povidone-iodine mouthwash was efficient in reducing oral mucositis episodes when compared with saline or soda rinses (92).

However, scientific evidence for the practise of recommending chlorhexidine (or any other chemical) during cancer treatment is weak and the results are partly controversial. For example, in a study on leukemia patients one group rinsed with a 0.2% of chlorhexidine solution twice daily while the other group did not. The results showed that chlorhexidine had no significant effect on any clinical parameters such as the number of days with fever, number of oral lesions, plaque score, gingival bleeding score, or the occurrence of candidiasis (93). Recently, Antunes et al. (94) confirmed in their study on hematopoietic stem cell transplantation patients that using extra soft toothbrush and toothpaste was enough during immunosuppression to prevent systemic spread of alpha-hemolytic *Streptococcus viridans* and *C. albicans*. Using 0.12% chlorhexidine mouthrinse thrice

daily in addition to the mechanical cleaning did not add anything in preventing streptococcal bacteremia (94). Nevertheless chlorhexidine has been routinely used since the early 1970s when, for example, oral application of 0.2% chlorhexidine was found to reduce the suffering of leukemic children and prevented spread of thrush from the oral cavity (95).

Other chemicals except chlorhexidine may, however, also have some value in controlling oral bacteria during cancer chemotherapy. A 1-year randomized trial from our clinic on 79 Hodgkin and non-Hodgkin lymphoma patients showed that using mouthwash containing 0.025% amine fluoride-stannous-fluoride caused a significant decrease in visible plaque, gingival bleeding, and salivary *S. mutans* counts while an increase was found in the group using 0.05% sodium fluoride rinses (96). However, also in this study a short-term use of 0.12% chlorhexidine at the induction phase of chemotherapy was most efficient in reducing dental plaque scores in both the fluoride-rinsing groups (97).

In a meta-analysis, Stokman et al. (98) concluded that of the several chemicals reported in controlled trials for preventing oral mucositis the combined use of polymyxin E, tobramycin, and amphotericin B showed an OR 0.61 (CI 0.39–0.96) and amifostine OR 0.37 (CI 0.15–0.89). The authors concluded that ‘to date, no single intervention completely prevents oral mucositis, so combined preventive therapy strategies seem to be required to ensure more successful outcomes’. The important issue of anticancer therapy-related oral mucositis has also been recently assessed in the Cochrane collaboration. The systematic review was based on trials meeting the following criteria: design was random allocation of participants; participants were anyone with cancer receiving chemotherapy or radiotherapy; interventions with agents prescribed to prevent oral mucositis; and the outcomes were prevention of mucositis, pain, amount of analgesia, dysphagia, systemic infection, length of hospitalization, costs incurred, and patient quality-of-life. The authors conclude their meta-analysis stating that ‘there is a need for well-designed and -conducted trials with sufficient numbers of participants to perform subgroup analyses by type of disease and chemotherapeutic agent’ (99). There is nothing to add to this conclusion.

In addition to preventing oral bacteremia complications due to the direct spread of micro-organisms is of further concern among immunosuppressed and cancer patients. For example, pneumonia may follow and the risk increases if the level of oral hygiene is poor (100). Akutsu et al. (101) observed that pathogens in preoperative dental plaque are risk factors for postoperative pneumonia in patients with esophageal cancer.

Taken into consideration the weak scientific evidence and partly controversial results from studies investigating the control of oral microbiota in cancer patients there

nevertheless is agreement that oral health care is important during and after the treatment of cancer. The oral health care personnel are in a key position in advising the patients (102). We have recently reviewed this topic more thoroughly (88).

Prevention of oral microbiota-linked carcinogenesis

If there is indeed a causal link between oral microbiota and cancer then the ultimate goal would be to prevent the development of cancer by interfering with the putative carcinogenic potential of the microbiome. Intervention of acetaldehyde-related carcinogenesis has been investigated using cysteine (103, 104). This non-essential amino acid binds effectively acetaldehyde by forming a stable thiazolidine-carboxylic acid compound hence eliminating the local carcinogenic effect (105–107). Cysteine has also been shown to exert inhibitory effect on the gelatinolytic activity of matrix metalloproteinases and to reduce metastases in animal models (108). Studies are now in progress for assessing the local effect of orally administered cysteine on oral microbiota in this perspective. In general, this compound is widely available in a number of dietary supplements.

Several other compounds have been introduced for the prevention of oral cancer. The main target, however, has been interfering with the cellular carcinogenic mechanisms rather than addressing oral microbiota. Nevertheless, many such compounds also exert antimicrobial activity. These include retinoids (109), anti-oxidant vitamins E and A, and carotenoids (110, 111). However, data are sparse on their effect in preventing oral carcinogenesis. Liede et al. (112, 113) could not show any effect of beta-carotene on the prevalence of oral mucosal lesions and buccal cell dysplasia in a controlled 5–7-year study in men in Finland.

Many naturally occurring spices and herbs have been used from the early history of mankind in foods and to treat ailments. These include spices such as garlic, cumin, cloves, cinnamon, thyme, mustard, and rosemary, which possess antimicrobial properties (114). Green tea has been particularly investigated in this perspective (115). The common nominators in many of these items are the potent phytochemicals the plants contain; several compounds have been tested in animal models (116). It is of interest in this context to cite results from a recent study from Japan where in women the hazard ratios of oral cancer for green tea consumption of 1–2, 3–4, and 5 or more cups per day were 0.51 (CI 0.10–2.68), 0.60 (CI 0.17–2.10), and 0.31 (CI 0.09–1.07), respectively, compared with those who daily drank less than one cup of green tea (*p* for trend was 0.08) (117). However, scientific evidence is weak of the topic and more controlled long-term studies are called for further conclusions. In the future the development of anti-carcinogenic products

from naturally occurring compounds is fascinating but certainly a big challenge.

Finally, during the past two decades probiotic or health-beneficial bacteria have been re-introduced for strengthening immune function. The early discovery in the turn of the nineteenth century by Nobel laureate Ilya Metchnikoff was long forgotten until the globally increased antibiotic drug resistance problem and functional food concept brought these bacteria again into daylight (118, 119). It has been suggested that consuming of dairy products with probiotic lactic acid bacteria may have anti-tumor effects. The mechanisms involved are attributed to the inhibition of mutagenic activity, the decrease in several enzymes implicated in the generation of carcinogens, mutagens, or tumor-promoting agents, suppression of tumors, adjuvant effects including modulation of cell-mediated immune responses, activation of the reticuloendothelial system, augmentation of cytokine pathways, and regulation of interleukins and tumor necrosis factors (120). However, these findings are mainly based on laboratory or animal studies. Evidence regarding probiotic effect on human carcinogenesis is weak or non-existent. These bacteria seem to have some effect on preventing oral mucositis caused by treatment of cancer, however (121). But there are no studies on the effect of probiotics on oral cancer. It can be anticipated, however, that the same mechanisms are involved here as in the lower parts of the gastrointestinal tract. This certainly is an area of interest in future studies.

Conclusion

Oral microbiota with its hundreds of microbial species mainly residing in biofilms pose a threat to immunosuppressed cancer patients if microbes gain access to blood circulation or spread locally to adjacent tissues. Therefore a number of clinical guidelines and protocols have been introduced to control oral infections. However, the protocols are not evidence based, but rather derive from long-time clinical practice. Since bacteremia complications are life-threatening to patients whose defense systems are weakened obviously every effort should be taken to prevent such complications. All cancer patients, including patients with oral cancer, must therefore maintain satisfactory oral health which often calls for regular professional treatment given by the oral health care team. Another question is the role of oral microbiota in carcinogenesis. Certain bacteria and yeasts may trigger carcinogenic mechanisms at the cellular level. They may also participate in metabolizing substances to carcinogens. An example to this is the microbial metabolism of alcohol to carcinogenic acetaldehyde. Poor oral hygiene has been associated with increased risk of oral cancer where the known risk factors are heavy use of alcohol and tobacco. Modern molecular methods are anticipated to cast new light on the role of oral microbiome in

carcinogenesis in general. It is noteworthy that some epidemiological studies have linked poor oral health with overall prevalence of malignancies.

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