Chapter 11
Oral Infection, Carcinogenesis and Cancer

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Abstract Recent research has shown statistical associations between dental infections and cancer in general but the role of oral microbiota in carcinogenesis is unclear. Oral micro-organisms up-regulate cytokines and other inflammatory mediators that affect the complex metabolic pathways and may thus indeed be involved in carcinogenesis. Microbial populations on mouth mucosa differ between healthy and malignant sites and certain oral bacterial species have been linked with malignancies. Oral microbes also have carcinogenic metabolites, such as acetaldehyde produced from ethanol. In this chapter we briefly review current knowledge about the interaction between oral microorganisms, oral infections and cancer. The focus is both on oral and ear-nose-throat cancer and malignancies in other organs.

Keywords Oral microbiota • Oral bacteria • Cancer • Oral cancer • Carcinogenesis

Abbreviations

EBV	Epstein-Barr virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HPV	human papilloma virus
HTLV-1	human T-cell lymphotropic virus
KSHV	Kaposi's associated sarcoma virus

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Introduction

The best known example of infection-associated malignancy is gastric cancer caused by *Helicobacter pylori* infection (Herrera and Parsonnet 2009). In general, infection-driven inflammations have been estimated to be involved in the pathogenesis of approximately 15–20 % of human tumours (Allavena et al. 2008). Hence, human microbiota may play a role in carcinogenesis (Chang and Parsonnet 2010). The worldwide incidence of cancer also attribute to infections caused by virus. These include hepatitis B virus (HBV), hepatitis C virus (HCV), human papilloma virus (HPV), and Epstein-Barr virus (EBV), human T-cell lymphotropic virus (HTLV-1) and Kaposi's associated sarcoma virus (KSHV), which have estimated to contribute to 10–15 % of the cancers worldwide (Butel 2000; Kuper et al. 2000; Martin and Gutkind 2008; Grinde and Olsen 2010; Rautava and Syrjänen 2012). No such figures exist for bacteria- or yeast-related malignancies. Nevertheless in this chapter the main focus is on oral bacterial and yeast infections.

Inflammation is indeed a key feature in many chronic diseases including cancer (Coussens and Werb 2002; Mantovani et al. 2008). Investigations of gastrointestinal malignancies have shown that the large amount of cytokines and growth factors released during inflammation may influence carcinogenesis (Fantini and Pallone 2008). Characteristic to infections and inflammations linked to cancer is their high prevalence in populations and persistence in the host (Mergaurd et al. 1989). There may be a long latency between the initial infection and tumour appearance. An infected person in fact rarely develops cancer. However, this area of research is difficult and the overall effect of human microbiome on carcinogenesis is not known. This also relates to oral microbiota and cancer. Nevertheless, infections that trigger inflammatory reactions have been suggested as major preventable causes of cancer (Parsonnet 1999; Kuper et al. 2000; Hujoel et al. 2003).

Knowledge about human microbiome is rapidly increasing. Molecular techniques have revealed its vast diversity but, at the same time, individual stability of micro-organisms residing on skin and mucosa has been observed (Turnbaugh et al. 2007; Fritz et al. 2013). Resident micro-organisms seem to play an important role in metabolism in general but it is not known how this diversity relates to function and to the rest of the genes of microbiota (Joyce and Gahan 2014). The gut microbiome is shared among family members but each person's microbial community varies in the specific bacterial lineages with a comparable degree of co-variation. A wide array of shared microbial genes has been observed among individuals comprising an extensive, identifiable core microbiome at the gene level rather than at the microbial lineage (Turnbaugh et al. 2009). Understanding this complex ecosystem will inevitably open new possibilities for diagnosis and prevention of diseases. Corresponding studies on oral microbiota are now on their way, too (Preza et al. 2009; Holgerson et al. 2013; Dimitrov and Hoeng 2013). But certain oral pathogens, such as the periodontal bacterium *Porphyromonas gingivalis*, may nevertheless be responsible for many extra-oral manifestations thus emphasizing the need for also focusing to individual strains (Han and Wang 2013).

Traditionally it has been thought that mouth mucosa (Fiscetti 2003), the tongue (Tachibana et al. 2006) and the pharynx (Brook 2005) harbour characteristic bacterial pathogens causing chronic inflammation and focal infections (Gendron et al. 2000). Many these infections derive from oral biofilms commonly linked with dental diseases, caries and periodontal disease (Desai et al. 1991; Komiyama et al. 1985; Scannapieco 1998). New research techniques have cast more light on the changes in oral microbiota in health and disease (Wade 2013). In particular our knowledge about the number of microbial species harbouring the oral cavity and their function has increased tremendously after introduction of new molecular techniques (Kejser et al. 2008; Olsen et al. 2013).

The association between oral micro-organisms and cancer is a new observation (Meurman 2010). Interestingly this association may even be causal when considering oral and oesophageal cancer, namely mediated by acetaldehyde production of oral micro-organisms (Meurman and Uittamo 2008; Moazzez et al. 2011). This chapter briefly outlines current knowledge about the role of oral microbiota in carcinogenesis with emphasis on oral cancer. Oral microbial changes caused by cancer treatment are also discussed.

Population Studies on the Association of Oral Infections with Cancer

In a Swedish cohort of 1390 subjects followed-up for 24 years missing second molar in the right mandible (odds ratio OR 2.62 (95 % confidence interval CI 1.18–5.78) and age (OR 1.91 [CI 1.06–3.43]), appeared as the principle independent predictors significantly associating with any type of cancer (Virtanen et al. 2014). In the analyses a number of explanatory factors had been taken into account. Furthermore, chronic periodontal disease associated statistically with breast cancer in women. Of the subjects with periodontal disease and any missing molars in the mandible, 5.5 % had breast cancer in comparison to 0.5 % of the subjects who had periodontal disease but no missing molars ($P<0.02$). Female gender (OR 13.08) and missing any molar in the mandible (OR 2.36) were the explanatory variables for breast cancer in this cohort (Söder et al. 2011). The missing molars were used as proxy of long-lasting dental infections because commonly these teeth are extracted due to caries or periodontal disease. In the same cohort, death in cancer was more frequent among patients with poor oral hygiene than in those whose oral hygiene had been better. Dental plaque appeared to be a significant independent predictor associated with 1.79 times the OR of death (Söder et al. 2012).

A 16-year follow-up study on 51,529 male health professionals in the US, showed that when compared with no periodontal disease, history of periodontitis was associated with increased pancreatic cancer risk (RR 1.64,CI 1.19–2.26; $P=0.002$). The crude incidence rates were 61 % versus 25 % per 100,000 person-years, and among never smokers RR was 2.09 (CI 1.18–3.71; $P=0.01$). The baseline number of natural teeth and cumulative tooth loss during follow-up were not associated with pancreatic cancer in this study (Michaud et al. 2007).

Periodontal disease in particular has been found to link statistically with oral cancer. From Taiwan from an insurance database of one million people, a study showed that in patients with periodontal disease the hazard ratio (HR) for oral cancer was 1.79 (CI 1.42–2.25) (Wen et al. 2013). A study from Germany showed a mean alveolar bone loss 4.3 mm in 178 oral cancer patients vs. 2.9 mm in their 123 controls ($P<0.001$) and the regression model resulted in OR 2.4 (CI 1.5–3.8) in this regard (Moergel et al. 2013). In this study a history of periodontal treatment was associated with significantly reduced cancer risk ($p<0.001$; OR 0.2, CI 0.1–0.5).

In the US the national health and nutrition study including13,798 subjects clinical attachment loss (CAL) was related to the presence of tumour in the mouth (OR 4.57, CI 2.25–9.30) and precancerous lesions in oral mucosa (OR 1.55, CI 1.06–2.27), respectively (Tezal et al. 2005). Similarly, OR was 5.23 (CI 2.64–10.35) for each millimeter of alveolar bone loss vs. tongue cancer (Tezal et al. 2007). Another study by the same group on 266 cases with head and neck cancer and 207 controls showed OR 4.36 (CI 3.16–6.01) for each millimeter of alveolar bone loss after adjustment for age, gender, race/ethnicity, marital status, smoking status, alcohol use, and missing teeth. The association persisted in subjects who never used tobacco and alcohol. There was a significant interaction between smoking and alveolar bone loss ($P=0.03$). Patients with periodontitis were more likely to have poorly differentiated oral cancer than those without periodontitis (32.8 % versus 11.5 %; $P=0.038$) (Tezal et al. 2009). HPVinfection also seems to play a significant role in these connections (Tezal 2012). Interestingly, an inverse association between head and neck cancer and dental caries was observed in this US patient material (Tezal et al. 2013). This unexpected result was explained by interactions between the commensal microbiota, such as oral streptococci and the host which was thought to be important for stimulating local mucosal and systemic immunity, tolerance and fine-tuning of T-cell receptor function, epithelial turnover, mucosal vascularity, and lymphoid tissue mass.

From national data from the US periodontitis was also associated with increased orodigestive cancer mortality (relative risks [RR] 2.28, CI 1.17–4.45) and the association seemed dependent on the increasing severity of periodontitis (P for trend 0.01). Mortality was in excess for colorectal (RR 3.58, CI 1.15–11.16) and possibly for pancreatic cancer (RR 4.56, CI 0.93–22.29). Greater serum *P. gingivalis* IgG values tended to be associated with the increased orodigestive cancer mortality (P for trend 0.06). It also associated with mortality in subjects with no periodontal disease (RR 2.25,CI 1.23–4.14) (Ahn et al. 2012). Interestingly, practicing no regular oral hygiene also conferred OR 2.37 (CI 1.42–3.97) for oesophageal cancer when compared with those who undertook daily tooth brushing (Abnet et al. 2008).

A German population-based study on 4233 subjects with oral leukoplakia showed OR 1.7 (0.6–5.0), 3.3 (0.8–13.1) and 5.3 (1.2–22.7), respectively, for second, third and fourth quartiles of CAL, respectively. For bleeding on probing the respective ORs were 2.0 (0.8–4.90), 2.9 (1.1–7.8) and 3.8 (1.5–9.8) (Meisel et al. 2012). Oral leukoplakia is regarded a potentially precancerous state.

Thus, the oral infections, especially periodontitis, have been clearly associated with cancer (Gondiykar et al. 2013).

Bacteria, Oral Cancer and the Effect of Treatment on Oral Microbiota

Principally, the role of bacteria in oral cancer is not known (Rajeev et al. 2012). Microbial populations on mouth mucosa differ between healthy and malignant sites, however. For example, *Streptococcus anginosus* and *Treponema denticola* seem to associate with various upper gastrointestinal tract carcinomas and also syphilis has been mentioned to be associated with cancer (Narikiyo et al. 2004). *S. anginosus*infection might be implicated in the carcinogenesis of head and neck squamous cell carcinoma in general (Shiga et al. 2001). *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 (Sasaki et al. 2005). Hooper et al. (2007) studied with molecular technique oral carcinoma specimens and observed 70 distinct taxa with 52 different phylotypes isolated from tumour tissues, and 37 taxa from within non-tumorous specimens. Differences between the composition of the microbiotas within the tumorous and non-tumorous mucosae were apparent, possibly indicating selective growth of bacteria within carcinoma tissue. Most taxa isolated from within the tumour tissue represented saccharolytic and aciduric species and studies were called for to investigate if these aspects have any link to carcinogenesis (Hooper et al. 2009).

Treatment of cancer, such as radiotherapy and chemotherapy, obviously modifies oral microbial composition leading to a major imbalance of the ecosystem (Sixou et al. 1998; Pushalkar et al. 2012; Xu et al. 2014). For example, in a study from Sweden, the patients harboured enterococci in 38 % of mouth samples *vs.* none of the controls. *Lactobacillus* spp. were detected in 92 % of the subjects and the proportion of these species was high compared with the controls. Mutans streptococci were also detected in high numbers; 31 % in the patients *vs.* 23 % in controls (Almståhl et al. 2008). On the other hand in a study from China mutans streptococci were not isolated in radiotherapy patients while lactobacilli, *S. mitis* and *S. salivarius* were the predominant caries-related oral bacteria following radiotherapy (Tong et al. 2003).

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 subgingival 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. These species included micro-organisms such as *Gemella*, *Peptostreptococcus, Staphylococcus, Stomatococcus, Streptococcus, Actinomyces, Eubacterium, Lactobacillus, Propionibacterium, Neisseria, Veillonella, Bacteroides, Campylobacter, Capnocytophaga, Fusobacterium, Kingella, Porphyromona*s 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 (Leung et al. 1998). The new molecular techniques have revealed patterns of

microbial shifts providing data for better understanding the impact of cancer treatment in this regard (Hu et al. 2013a, b). However, it the practical importance of the bacterial diversity observed remains to be seen.

How permanent are the shifts in oral microbiota after treatment of cancer is another interesting question. Radiotherapy or cytostatic treatment caused changes in bacterial composition in oral microbiota need not be permanent. For example, in child allogenic 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 between baseline and the end of a 119-day study, or between patients and controls (Lucas et al. 1997). However, caries risk may still be increased in particular in paediatric patients surviving a malignant disease (Dens et al. 1996). Furthermore pathogens such as *Capnocytophaga* may pose a systemic risk in these patients and call for continuous attention in order to prevent bacteraemia and also to overcome problems of developing antibiotic resistance (Sixou et al. 1998). Risk for dental caries remains high after radiotherapy while periodontitis does not seem to pose corresponding problem (Al-Nawas and Grötz 2006).

In immunosuppressed patients treated with cytostatic drugs pathogenic and opportunistic micro-organisms colonizing the mouth may be dangerous. Enterobacteria and species such as *Pseudomonas, Neisseria*, and *Veillonella* have been observed in oral samples from granulocytopenic patients with leukaemia (Peterson et al.1990). It appears that the pre-treatment oral health status is important in this respect. For example, in a study on non-lymphocytic leukaemia patients in Baltimore periodontal disease status and attachment loss were positively correlated with increase in the proportional recovery of *Staphylococcus* sp. from supragingival sites and total yeasts from supra- and subgingival sites (Reynolds et al. 1989). The authors suggested that host factors such as periodontal disease may contribute to patterns of oral microbial changes during cancer chemotherapy. However, it should also be kept in mind that sampling site as such may influence the results and in oral cancer patients optimal sampling may be difficult (Rautemaa et al. 2006). Consequently, proper sampling technique for both conventional cultivation and novel molecular methods needs to be emphasized (Rusanen et al. 2009). Table 11.1 gives examples of oral microbial strains which are often isolated from cancer patients.

Table 11.1 Micro-organisms which are frequently detected in mouth samples from cancer patients.

Candida albicans
Enterococci
Lactobacilli
Viridans streptococci
Staphylococci
Enterobacteria (*Pseudomonas, Neisseria, Veillonella*)
Capnocytophaga
Fusobacteria

Oral Cancer and Yeasts

Immunosuppression enhances the selection and outgrowth of yeasts in oral microbiota (Bensadoun et al. 2011). Hence cancer patients are at risk for invasive yeast infections and life-threatening candidemias (Pompej et al. 1993). For example, *Candida albicans* was found in 54 % of subjects who received radiotherapy to the head and neck in comparison to 15 % of controls (Almstål et al. 2008). Particularly non-*albicans Candida* strains may become a problem since these yeasts often are resistant to commonly used antifungal drugs (Redding et al. 2004). Oral yeasts also convert ethanol to carcinogenic acetaldehyde, a mechanism which may play even causal role in the development of cancer (Nieminen et al. 2009). However, more studies are needed in this area.

Local antifungal first-line therapy is recommended for oral cancer patients with mucosal *Candida* infections but severe systemic infections obviously call for intravenous medication.

Pathogenic Mechanisms in Oral Infection-Linked Carcinogenesis

Infection caused inflammation may induce cellular proliferation, inhibit apoptosis, interfere with cellular signaling mechanisms, and act as tumor promoters (Lax and Thomas 2002). Up-regulation of cytokines and other inflammatory mediators affect complex metabolic pathways. 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 (Katz et al. 2010). Oral infection may also directly reflect in endothelial dysfunction (Janket et al. 2008). The cytokine reactions involved have been shown to play a role in the immune-related mechanisms of cancer development (Sheu et al. 2008). Figure 11.1 shows the complex pathways thought a play a role in infection driven carcinogenesis.

Another mechanism suggested is mediated via salivary factors. Poor oral health has been shown to associate with the genotoxic salivary activity. Bloching et al. (2007) studied dental status and saliva of 100 subjects relating their oral health to in vitro salivary mutagenicity, using the *Salmonella* test, and observed a significant association ($p<0.05$) between high plaque index and high number of carious teeth with genotoxic activity in saliva. Hence 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 tumour genesis.

Several bacteria and *Candida* strains in the mouth convert ethanol to carcinogenic acetaldehyde thus explaining the epidemiological evidence between heavy

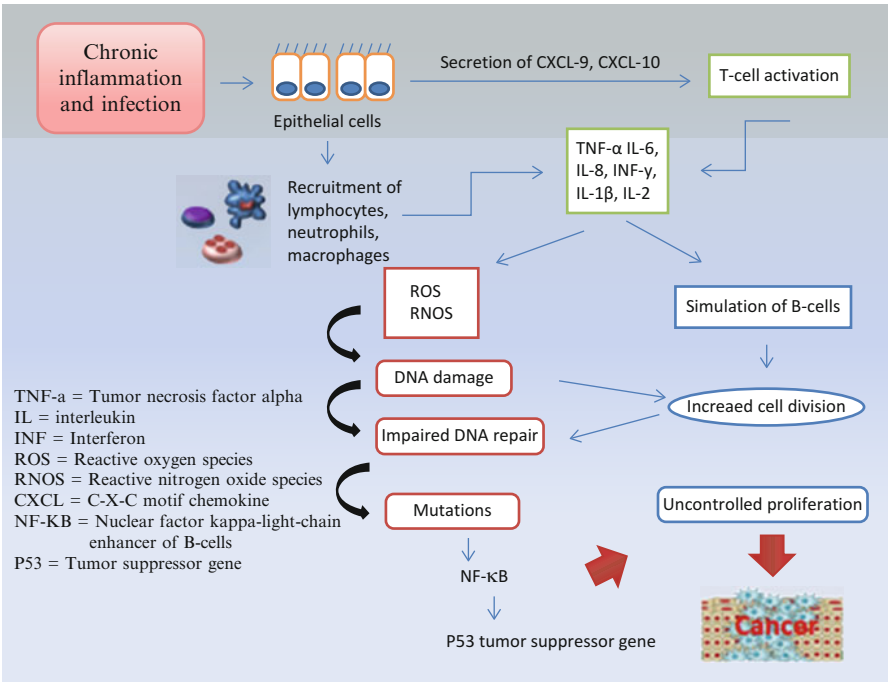

Fig. 11.1 The chronic infection and inflammation activate the T lymphocytes and release proinflammatory cytokines leading to DNA damage increased cell division and uncontrolled proliferation.

drinking, smoking and development of cancer (Homann et al. 2000a, b). Both the commonly encountered oral streptococci and yeasts possess metabolic pathways for this conversion (Kurkivuori et al. 2007; Uittamo et al. 2009; Nieminen et al. 2009). 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 about higher or lower metabolic activities involved in alcohol metabolism (Marichalar-Mendia et al. 2010). Nevertheless, there is a significant dose-response relationship between intake frequency, duration and oral cancer risk (Cancela Mde et al. 2009). Similarly, smoking associates with cancer risk and smoking also causes an increase in salivary acetaldehyde concentrations thus adding to the risk related to alcohol (Morse et al. 2007). The effect of smoking and alcohol is synergistic (Salaspuro and Salaspuro 2004). Figure 11.2 depicts the ethanol acetaldehyde pathway.

Inflammation is a critical component of tumor progression (e.g., reflux esophagitis/esophageal cancer; inflammatory bowel disease/colorectal cancer) (Coussens and Werb 2002). This can also happen in the oral environment, such as in the periodontal pocket as a weak point for tumor invasion. Increasing evidence indicates that the inflammation may result from persistent mucosal or epithelial cell colonization

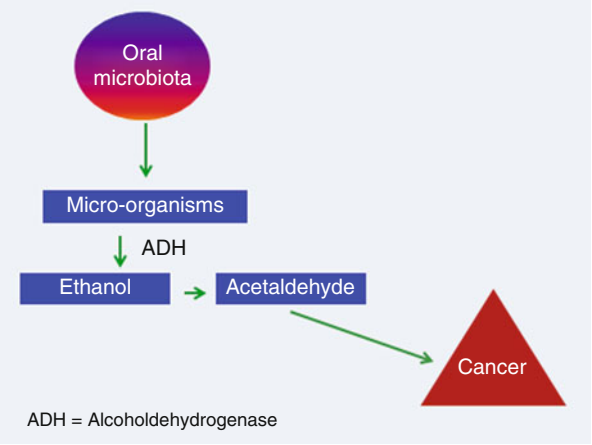

Fig. 11.2 Microorganisms metabolize ethanol to acetaldehyde leading to cancer. The alcohol dehydrogenase (ADH) play a major role in the pathway.

by microorganisms. Persistent inflammation leads to increased cellular turnover, especially in the epithelium, and provides selection pressure that results in the emergence of cells that are at high risk for malignant transformation (Moss and Blaser 2005). Meisel et al. (2012) explained how chronic periodontitis may affect the pathogenesis of precancerous lesions by showing that chronic periodontitis was a risk factor for the development of leukoplakia predisposing for oral cancer. In periodontitis, the inflammatory response caused by bacteria colonizing periodontal pockets leads to significant interleukin-8 (IL-8) and IL-6 mRNA levels induced in response to exposure to the bacteria (Yumoto et al. 1999).

Chronic inflammation causes epithelial cells to secrete CXCL 9 and CXCL 10 through the action of various inflammatory mediators, including TNF-α, IL-6, and IL-17, leading to eradication of antitumor immunity and accelerated tumor progression (Lin and Karin 2007). Tumor endothelial cells (ECs) secrete high levels of CXCL9 in all, and CXCL10 in most melanoma metastases (Amatschek et al. 2011). In the combination of the secretion of CXCL 9 and CXCL 10 with the recruitment of lymphocytes, neutrophils and macrophages which are sources of cytotoxic and genotoxic reactive nitrogen oxygen species (RNOS) the process of tumour genesis goes on. Genetic instability is a common feature of solid tumors and we and others have proposed that mutagenic RNOS generated by these tumor-infiltrating cells are, in some measure, responsible for the accumulation of mutations associated with tumour progression (Haqqani et al. 2000) (Fig. 11.1).

IL-6 is a potent pleiotropic inflammatory cytokine that is considered a key growth promoting and antiapoptotic factor (Lin and Karin 2007). Malignant transformation of oral epithelium would then be a consequence of the immune response due to macrophage and T-cell activation and cytokine release (e.g., IL-1, IL-8, and TNF-α) (Mantovani et al. 2008).

Production of interleukin-8 (IL-8) by oral epithelial cells can be expected to play a major role in the recruitment and activation of phagocytes at the infected site (Dongari-Bagtzoglou et al. 2003). IL-8 is a human CXC chemokine for neutrophils

and an angiogenic factor. This proinflammatory cytokine is expressed in many human tumors (Haqqani et al. 2000).

TNF-α also appears to be essential for skin carcinogenesis, however, as genetically engineered mice deficient in TNF-α were shown to be resistant to skin carcinogenesis (Moore et al. 1999). Oral infections and sepsis promote the degradation cascade of IL-6, TNF-α, IL-8, INF-Y, important cytokines causing DNA damage This, in turn, causes impaired DNA repair and subsequent mutation; most carcinogens activate NF-κB and STAT3 pathways. These lines of evidence strongly support the hypothesis that carcinogen-induced NF-κB activation could lead carcinogenesis (Aggarwal et al. 2009). The key molecular link is provided by the inhibitor of NF-kB kinase/ NF-kB (IKK/NF-kB) signaling pathway, which is activated by many proinflammatory cytokines (Lin and Karin 2007) (Fig. 11.2).

P53 is known to be recruited in response to DNA damaging genotoxic stress and it plays an important role in maintaining the integrity of the genome. We therefore conclude that BP transcriptionally activates the human p53 gene through the induction of NF-κB activity (Pei et al. 1999). These mechanisms are anticipated to play a role in the mutations leading to oral cancer. Table 11.2 summarizes the principal mechanisms by which oral micro-organisms may enhance the development of cancer.

Prevention of Oral Microbiota-Associated Carcinogenesis

The simple answer to the question how to prevent oral microbiota-associated carcinogenesis would be avoidance of any infections and inflammations in the mouth. This, however, is not possible in practice due to the complex nature of oral biofilms. However, maintaining good level of oral hygiene can be anticipated to reduce cancer risk by the mechanisms here discussed. But there is only indirect evidence to support this (Abnet et al. 2008).

The nonessential amino acid cysteine which effectively binds acetaldehyde by forming a thiazole-carboxylic acid compound and thus eliminates the local carcinogenic effect may be one means of future prevention of oral cancer (De Vries and De Flora 1993; Van Schouten et al.2002; Salaspuro et al. 2002, 2006; Salaspuro 2007).

Table 11.2 Carcinogenic mechanisms where oral microbiota may play a role.

Induction of cell proliferation
Inhibition of apoptosis
Interference with signalling mechanisms
Tumor promoter activity
Up-regulation of cytokines and other inflammatory mediators
Effect on cellular sugar metabolism
Enhancing mutagenic activity in saliva
Metabolizing ethanol to acetaldehyde

In an animal model, cysteine was shown to reduce metastases by inhibiting the gelatinolytic activity of matrix metalloproteinases (Morini et al. 1999). Here, however, clinical studies are called for final conclusion.

Other chemicals studied in this respect are retinoids (King et al. 1982), antioxidant vitamins E and A, and carotenoids (Krisnky 1989; Tengerdy 1990), but there is no true scientific evidence. Liede et al. (1998a, b) for example could not show any effect of beta-carotene on the prevalence of oral mucosal dysplasia in their 7-year study on men.

Furthermore, many herbs and other natural remedies have been suggested to provide protection from carcinogenesis. These include garlic, cumin, cloves, cinnamon, thyme, mustard, rosemary and green tea (Lai and Roy 2004; Taylor et al. 2005). The expected effect is thought to be mediated by phytochemicals of the plants, also tested in animal models (Miller et al. 2008). Here it is interesting to cite results from a 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) (Ide et al. 2007). However, scientific evidence in general is weak of the topic and properly powered, controlled long-term studies are called for further conclusions.

Another future approach might be bacteriotherapy with probiotics, health beneficial bacteria shown to inhibit mutagenicity and provide adjuvant effect by modulation of cell-mediated immunity (Kumar et al. 2010). Probiotics may also help in preventing mucositis caused by cancer treatment, but scientific evidence still is very weak (Maria-Aggeliki et al. 2009).

Clinical Aspects of Controlling Oral Microbiota in Cancer Patients

Maintaining proper oral hygiene during treatment of cancer is of utmost importance. Life-threatening complications may arise if this is neglected (Meurman et al. 1997). Systemic infection and sepsis remains the leading causes of morbidity and mortality in immunosuppressed patients. Therefore practical guidelines have been given for the oral health care of these patients (Meurman and Scully 2012).

Chlorhexidine-containing preparations have been the standard in controlling oral microbiota in patients with cancer and other malignancies (Meurman et al. 1997; Wahlin 1989). Chlorhexidine may also prevent oral mucositis during cancer chemotherapy (Sorensen et al. 2008). However, antifungal agents must be used when yeast infections need to be controlled (Madan et al. 2008).

Proper hands-on counseling of cancer patients is often needed. Nurses, dental hygienist and auxiliary personnel at the wards must all be advised of the importance of daily oral hygiene of cancer patients. Here the oral health care personnel is in a key position in advising both the patients and hospital personnel (Chandu et al. 2002; Meurman and Grönroos 2010). Electric toothbrush may be of help (Fjeld

Table 11.3 Practical aspects in controlling oral microbiota of patients with cancer.

Diagnosing and eradication of dental infection foci is of high importance.
Importance of good oral hygiene throughout the treatment of cancer and follow-up need to be emphasized.
The patient, nurses and auxiliary personnel must be advised in how to clean the mouth and dental prostheses.
The hospital personnel must be advised how to help the patient in maintaining satisfactory oral hygiene.
Electric toothbrush with soft brush tip might be recommended.
Dental prostheses need to be checked in order to avoid mucosal damage.
Use of chlorhexidine preparations recommended in particular during immunosuppression due to cancer treatment.
Use of antifungal agents need to be prescribed in cases with oral yeast infections.
Regular dental check-ups are needed even though no subjective symptoms arise.

et al. 2014). Particular attention must also be focused on daily hygiene of dental prostheses to avoid fungal infections of the mouth (Davies et al. 2006). Worthington et al. (2007) have reviewed the prevention of oral mucositis due to treatment of cancer based on Cochrane database. Table 11.3 gives some practical guidelines for maintaining good oral health in cancer patients.

Conclusion

The mouth is a habitat of billions of micro-organisms. In cancer patients controlling oral microbiota is of utmost importance in order to avoid life-threatening systemic infections. Oral microbes may also have a role in carcinogenesis via a number of mechanisms. These include carcinogenic metabolites of oral bacteria and yeasts and chronic inflammation-mediated pathogenic cascade reactions. Hospital personnel should be advised about the importance of the mouth, both as regards the quality of life of the patient and preventing hematogenic spread of infections of the mouth. Dentists and other oral health professionals have a key role in counseling nurses, auxiliary and the medical profession, in addition to providing oral health treatment to the patients.

References

Abnet CC, Kamangar F, Islami F, Nasrollahzadeh D, Brennan P, Aghcheli K et al (2008) Tooth loss and lack of regular oral hygiene are associated with higher risk of esophageal squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev 17:3062–3068

Aggarwal BB, Vijayalekshmi RV, Sung B (2009) Targeting inflammatory pathways for prevention and therapy of cancer: short-term friend, long-term foe. Clin Cancer Res 15:425–430

Ahn J, Segers S, Hayes RB (2012) Periodontal disease, Porphyromonas gingivalis serum antibody levels and orodigestive cancer mortality. Carcinogenesis 33:1055–1058
Allavena P, Garlanda C, Borrello MG, Sica A, Mantovani A (2008) Pathways connecting inflammation and cancer. Curr Opin Genet Dev 18:3–10
Almståhl A, Wikström M, Fagerberg-Mohlin B (2008) Microflora in oral ecosystems in subjects with radiation-induced hyposalivation. Oral Dis 14:541–549
Al-Nawas B, Grötz KA (2006) Prospective study of the long term change of the oral flora after radiation therapy. Support Care Cancer 14:291–296
Amatschek S, Lucas R, Eger A, Pflueger M, Hundsberger H, Knoll C, Grosse-Kracht S, Schuett W, Koszik F, Maurer D, Wiesner C (2011) CXCL9 induces chemotaxis, chemorepulsion and endothelial barrier disruption through CXCR3-mediated activation of melanoma cells. Br J Cancer 104:469–479
Bensadoun RJ, Patton LL, Lalla RV, Epstein JB (2011) Oropharyngeal candidiasis in head and neck cancer patients treated with radiation: update 2011. Support Care Cancer 19:737–744
Bloching M, Reich W, Schubert J, Grummt T, Sandner A (2007) The influence of oral hygiene on salivary quality in the Ames Test, as a marker for genotoxic effects. Oral Oncol 43:933–939
Brook I (2005) The role of bacterial interference in otitis, sinusitis and tonsillitis. Otolaryngol Head Neck Surg 33:139–146
Butel JS (2000) Viral carcinogenesis: revelation of molecular mechanisms and etiology of human disease. Carcinogenesis 21:405–426
Cancela Mde C, Ramadas K, Fayette JM, Thomas G, Muwonge R, Chapuis F, Thara S, Sankaranarayanan R, Sauvaget C (2009) Alcohol intake and oral cavity cancer risk among men in a prospective study in Kerala, India. Community Dent Oral Epidemiol 37:342–349
Chandu A, Stulner C, Bridgeman AM, Smith AC (2002) Maintenance of mouth hygiene in patients with oral cancer in the immediate post-operative period. Aust Dent J 47:170–173
Chang AH, Parsonnet J (2010) Role of bacteria in oncogenesis. Clin Microbiol Rev 23:837–857
Coussens LM, Werb Z (2002) Inflammation and cancer. Nature 420:860–867
Davies AN, Brailsford SR, Beighton D (2006) Oral candidosis in patients with advanced cancer. Oral Oncol 42:698–702
De Vries N, De Flora S (1993) N-acetyl-l-cysteine. J Cell Biochem Suppl 17F:270–277
Dens FL, Boute P, Vinckier F, Declerck D (1996) Salivary caries risk factors in long-term event-free survivors of pediatric malignant diseases. J Clin Pediatr Dent 20:241–245
Desai HG, Gill HH, Shankaran K, Mehta PR, Prabhu SR (1991) Dental plaque: a permanent reservoir of Helicobacter pylori? Scand J Gastroenterol 26:1205–1208
Dimitrov DV, Hoeng J (2013) Systems approaches to computational modeling of the oral microbiome. Front Physiol 4:172. doi:10.3389/fphys.2013.00172
Dongari-Bagtzoglou A, Kashleva H (2003) Candida albicans triggers interleukin-8 secretion by oral epithelial cells. Microb Pathog 34:169–177
Fantini MC, Pallone F (2008) Cytokines: from gut inflammation to colorectal cancer. Curr Drug Targets 9:375–380
Fischetti VA (2003) Novel method to control pathogenic bacteria on human mucous membranes. Ann N Y Acad Sci 987:207–214
Fjeld KG, Mowe M, Eide H, Willumsen T (2014) Effect of electric toothbrush on residents' oral hygiene: a randomized clinical trial in nursing homes. Eur J Oral Sci 122:142–148
Fritz JV, Desai MS, Shah P, Schneider JG, Wilmes P (2013) From meta-omics to causality: experimental models for human microbiome research. Microbiome 3:14
Gendron R, Grenier D, Maheu-Robert L (2000) The oral cavity as a reservoir of bacterial pathogens for focal infections. Microbes Infect 2:897–906
Gondivkar SM, Gondivkar RS, Gadbail AR, Chole R, Mankar M, Yuwanati M (2013) Chronic periodontitis and the risk of head and neck squamous cell carcinoma: facts and figures. Exp Oncol 35:163–167
Grinde B, Olsen I (2010) The role of viruses in oral disease. J Oral Microbiol 2:2127. doi:10.3402/jom.v2iO.2127

Han YW, Wang X (2013) Mobile microbiome: oral bacteria in extra-oral infections and inflammation. J Dent Res 92:485–491

Haqqani AS, Sandhu JK, Birnboim HC (2000) Expression of interleukin-8 promotes neutrophil infiltration and genetic instability in mutatect tumors. Neoplasia 2:561–568

Herrera V, Parsonnet J (2009) Helicobacter pylori and gastric adenocarcinoma. Clin Microbiol Infect 15:971–976

Holgerson PL, Vestman NR, Claesson R, Ohman C, Domellöf M, Tanner AC, Hernell O, Johansson I (2013) Oral microbial profile discriminates breast-fed from formula-fed infants. J Pediatr Gastroenterol Nutr 56:127–136

Homann N, Tillonen J, Salaspuro M (2000a) Microbially produced acetaldehyde from ethanol may increase the risk of colon cancer via folate deficiency. Int J Cancer 86:169–173

Homann N, Tillonen J, Meurman JH, Rintamäki H, Lindqvist C, Rautio M, Jousimies-Somer H, Salaspuro M (2000b) Increased salivary acetaldehyde levels in heavy drinkers and smokers: a microbiological approach to oral cavity cancer. Carcinogenesis 21:663–668

Hooper SJ, Crean SJ, Fardy MJ, Lewis MA, Spratt DA, Wade WG, Wilson MJ (2007) A molecular analysis of the bacteria present within oral squamous cell carcinoma. J Med Microbiol 56:1651–1659

Hooper SJ, Wilson MJ, Crean SJ (2009) Exploring the link between microorganisms and oral cancer: a systematic review of the literature. Head Neck 31:1228–1239

Hu YJ, Wang Q, Jiang YT, Ma R, Xia WW, Tang ZS, Liu Z, Liang JP, Huang ZW (2013a) Characterization of oral bacterial diversity of irradiated patients by high-throughput sequencing. Int J Oral Sci 5:21–25

Hu YJ, Shao ZY, Wang Q, Jiang YT, Ma R, Tang ZS, Liu Z, Liang JP, Huang ZW (2013b) Exploring the dynamic core microbiome of plaque microbiota during head-and-neck radiotherapy using pyrosequencing. PLoS One 8(2):e56343. doi:10.1371/journal.pone.0056343

Hujoel PP, Drangsholt M, Spiekerman C, Weiss NS (2003) An exploration of the periodontitis-cancer association. Ann Epidemiol 13:312–316

Ide R, Fujino Y, Hoshiyama Y, Mizoue T, Kubo T, Pham TM, Shirane K, Tokui N, Sakata K, Tamakoshi A, Yoshimura T, JACC Study Group (2007) A prospective study of green tea consumption and oral cancer incidence in Japan. Ann Epidemiol 17:821–826

Janket SJ, Jones JA, Meurman JH, Baird AE, Van Dyke TE (2008) Oral infection, hyperglycemia, and endothelial dysfunction. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 105:173–179

Joyce SA, Gahan CG (2014) The gut microbiota and the metabolic health of the host. Curr Opin Gastroenterol 30:120–127

Katz J, Wallet S, Cha S (2010) Periodontal disease and the oral-systemic connection: is it all the RAGE? Quintessence Int 41:229–237

Keijser BJ, Zaura E, Huse SM, van der Vossen JM, Schuren FH, Montijn RC, ten Cate JM, Crielaard W (2008) Pyrosequencing analysis of the oral microflora of healthy adults. J Dent Res 87:1016–1020

King K, Jones DH, Daltrey DC, Cunliffe WJ (1982) A double-blind study of the effects of 13-cis-retinoic acid on acne, sebum excretion rate and microbial population. Br J Dermatol 107:583–590

Komiyama K, Tynan JJ, Habbick BF, Duncan DE, Liepert DJ (1985) Pseudomonas aeruginosa in the oral cavity and sputum of patients with cystic fibrosis. Oral Surg Oral Med Oral Pathol 59:590–594

Krinsky NI (1989) Antioxidant functions of carotenoids. Free Radic Biol Med 7:617–635

Kumar M, Kumar A, Nagpal R, Mohania D, Behare P, Verma V, Kumar P, Poddar D, Aggarwal PK, Henry CJ, Jain S, Yadav H (2010) Cancer-preventing attributes of probiotics: an update. Int J Food Sci Nutr 61(5):473–496

Kuper H, Adami HO, Trichopoulos D (2000) Infections as a major preventable cause of human cancer. J Intern Med 248:171–183

Kurkivuori J, Salaspuro V, Kaihovaara P, Kari K, Rautemaa R, Grönroos L, Meurman JH, Salaspuro M (2007) Acetaldehyde production from ethanol by oral streptococci. Oral Oncol 43:181–186
Lai PK, Roy J (2004) Antimicrobial and chemopreventive properties of herbs and spices. Curr Med Chem 11:1451–1460
Lax AJ, Thomas W (2002) How bacteria could cause cancer: one step at a time. Trends Microbiol 10:293–299
Leung WK, Jin LJ, Samaranayake LP, Chiu GK (1998) Subgingival microbiota of shallow periodontal pockets in individuals after head and neck irradiation. Oral Microbiol Immunol 13:1–10
Liede K, Hietanen J, Saxen L, Haukka J, Timonen T, Häyrinen-Immonen R, Heinonen OP (1998a) Long-term supplementation with alpha-tocopherol and beta-carotene and prevalence of oral mucosal lesions in smokers. Oral Dis 4:78–83
Liede KE, Alfthan G, Hietanen JH, Haukka JK, Saxen LM, Heinonen OP (1998b) Beta-carotene concentration in buccal mucosal cells with and without dysplastic oral leukoplakia after long-term beta-carotene supplementation in male smokers. Eur J Clin Nutr 52:872–876
Lin WW, Karin M (2007) A cytokine-mediated link between innate immunity, inflammation, and cancer. J Clin Invest 117:1175–1183
Lucas VS, Beighton D, Roberts GJ, Challacombe SJ (1997) Changes in the oral streptococcal flora of children undergoing allogeneic bone marrow transplantation. J Infect 35:135–141
Madan PD, Sequeira PS, Shenoy K, Shetty J (2008) The effect of three mouthwashes on radiation-induced oral mucositis in patients with head and neck malignancies: a randomized control trial. J Cancer Res Ther 4:3–8
Mantovani A, Allavena P, Sica A, Balkwill F (2008) Cancer-related inflammation. Nature 454:436–444
Maria-Aggeliki KS, Nikolaos KL, George KM, Vassilis KE (2009) The potential clinical impact of probiotic treatment for the prevention and/or anti-inflammatory therapeutic effect against radiation induced intestinal mucositis. A review. Recent Pat Inflamm Allergy Drug Discov 3:195–200
Marichalar-Mendia X, Rodriguez-Tojo MJ, Acha-Sagredo A, Rey-Barja N, Aguirre-Urizar JM (2010) Oral cancer and polymorphism of ethanol metabolising genes. Oral Oncol 46:9–13
Martin D, Gutkind JS (2008) Human tumor-associated viruses and new insights into the molecular mechanisms of cancer. Oncogene 27(Suppl 2):S31–S42
Megraud F, Brassens-Rabbe MP, Denis F, Belbouri A, Hoa DQ (1989) Seroepidemiology of Campylobacter pylori infection in various populations. J Clin Microbiol 27:1870–1873
Meisel P, Holtfreter B, Biffar R, Suemnig W, Kocher T (2012) Association of periodontitis with the risk of oral leukoplakia. Oral Oncol 48:859–863
Meurman JH (2010) Oral microbiota and cancer. J Oral Microbiol 10:2. doi:10.3402/jom.v2i0.5195
Meurman JH, Grönroos L (2010) Oral and dental health care of oral cancer patients: hyposalivation, caries and infections. Oral Oncol 46:464–467
Meurman JH, Scully C (2012) Oral cancer: comprehending the condition, causes, controversies, control and consequences: infections. Dent Update 39:298–299
Meurman JH, Uittamo J (2008) Oral micro-organisms in the etiology of cancer. Acta Odontol Scand 66:321–326
Meurman JH, Pyrhönen S, Teerenhovi L, Lindqvist C (1997) Oral sources of septicaemia in patients with malignancies. Oral Oncol 33:389–397
Michaud DS, Joshipura K, Giovannucci E, Fuchs CS (2007) A prospective study of periodontal disease and pancreatic cancer in US male health professionals. J Natl Cancer Inst 99:171–175
Miller EG, Peacock JJ, Bourland TC, Taylor SE, Wright JM, Patil BS, Miller EG (2008) Inhibition of oral carcinogenesis by citrus flavonoids. Nutr Cancer 60:69–74
Moazzez R, Thompson H, Palmer RM, Wilson RF, Proctor GB, Wade WG (2011) Effect of rinsing with ethanol-containing mouthrinses on the production of salivary acetaldehyde. Eur J Oral Sci 119:441–446

Moergel M, Kämmerer P, Kasaj A, Armouti E, Alshihri A, Weyer V, Al-Nawas B (2013) Chronic periodontitis and its possible association with oral squamous cell carcinoma – a retrospective case control study. Head Face Med 9:39. doi:10.1186/1746-160X-9-39

Moore RJ, Owens DM, Stamp G, Arnott C, Burke F, East N, Holdsworth H, Turner L, Rollins B, Pasparakis M, Kollias G, Balkwill F (1999) Mice deficient in tumor necrosis factor-alpha are resistant to skin carcinogenesis. Nat Med 5:828–831

Morini M, Cai T, Aluigi MG, Noonan DM, Masiello L, De Flora S, D'Agostini F, Albini A, Fassina G (1999) The role of the thiol N-acetylcysteine in the prevention of tumor invasion and angiogenesis. Int J Biol Markers 14:268–271

Morse DE, Psoter WJ, Cleveland D, Cohen D, Mohit-Tabatabai M, Kosis DL, Eisenberg E (2007) Smoking and drinking in relation to oral cancer and oral epithelial dysplasia. Cancer Causes Control 18:919–929

Moss SF, Blaser MJ (2005) Mechanisms of disease: inflammation and the origins of cancer. Nat Clin Pract Oncol 2:90–97

Narikiyo M, Tanabe C, Yamada Y, Igaki H, Tachimori Y, Kato H et al (2004) Frequent and preferential infection of Treponema denticola, Streptococcus mitis, and Streptococcus anginosus in esophageal cancers. Cancer Sci 95:569–574

Nieminen MT, Uittamo J, Salaspuro M, Rautemaa R (2009) Acetaldehyde production from ethanol and glucose by non-Candida albicans yeasts in vitro. Oral Oncol 45:e245–e248

Olsen I, Tribble GD, Fiehn NE, Wang BY (2013) Bacterial sex in dental plaque. J Oral Microbiol 3:5. doi:10.3402/jom.v5i0.20736

Parsonnet J (1999) Microbes and malignancy. Oxford University Press, New York, pp 3–15

Pei XH, Nakanishi Y, Takayama K, Bai F, Hara N (1999) Benzo[a]pyrene activates the human p53 gene through induction of nuclear factor kappaB activity. J Biol Chem 274:35240–35246

Peterson DE, Minah GE, Reynolds MA, Weikel DS, Overholser CD, DePaola LG, Wade JC, Suzuki JB (1990) Effect of granulocytopenia on oral microbial relationships in patients with acute leukemia. Oral Surg Oral Med Oral Pathol 70:720–723

Pompei R, Ingianni A, Cagetti MG, Rizzo A, Cotti S (1993) Evaluation of the opportunistic microbial flora and of some antimicrobial factors in the oral cavity of leukaemic patients. Microbios 75:149–157

Preza D, Olsen I, Willumsen T, Grinde B, Paster BJ (2009) Diversity and site-specificity of the oral microflora in the elderly. Eur J Clin Microbiol Infect Dis 28:1033–1040

Pushalkar S, Ji X, Li Y, Estilo C, Yegnanarayana R, Singh B, Li X, Saxena D (2012) Comparison of oral microbiota in tumor and non-tumor tissues of patients with oral squamous cell carcinoma. BMC Microbiol 12:144. doi:10.1186/1471-2180-12-144

Rajeev R, Choudhary K, Panda S, Gandhi N (2012) Role of bacteria in oral carcinogenesis. South Asian J Cancer 1:78–83

Rautava J, Syrjänen S (2012) Biology of human papillomavirus infections in head and neck carcinogenesis. Head Neck Pathol 6(Suppl 1):S3–S15

Rautemaa R, Rusanen P, Richardson M, Meurman JH (2006) Optimal sampling site for mucosal candidosis in oral cancer patients is the labial sulcus. J Med Microbiol 55:1447–1451

Redding SW, Dahiya MC, Kirkpatrick WR, Coco BJ, Patterson TF, Fothergill AW, Rinaldi MG, Thomas CR (2004) Candida glabrata is an emerging cause of oropharyngeal candidiasis in patients receiving radiation for head and neck cancer. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 97:47–52

Reynolds MA, Minah GE, Peterson DE, Weikel DS, Williams LT, Overholser CD, DePaola LG, Suzuki JB (1989) Periodontal disease and oral microbial successions during myelosuppressive cancer chemotherapy. J Clin Periodontol 16:185–189

Rusanen P, Siikala E, Uittamo J, Richardson M, Rautemaa R (2009) A novel method for sampling the microbiota from the oral mucosa. Clin Oral Invest 13:243–246

Salaspuro V (2007) Pharmacological treatments and strategies for reducing oral and intestinal acetaldehyde. Novartis Found Symp 285:145–153

Salaspuro V, Salaspuro M (2004) Synergistic effect of alcohol drinking and smoking on in vivo acetaldehyde concentration in saliva. Int J Cancer 111:480–483
Salaspuro V, Hietala J, Kaihovaara P, Pihlajarinne L, Marvola M, Salaspuro M (2002) Removal of acetaldehyde from saliva by a slow-release buccal tablet of L-cysteine. Int J Cancer 97:361–364
Salaspuro VJ, Hietala JM, Marvola ML, Salaspuro MP (2006) Eliminating carcinogenic acetaldehyde by cysteine from saliva during smoking. Cancer Epidemiol Biomarkers Prev 15:146–149
Sasaki M, Yamaura C, Ohara-Nemoto Y, Tajika S, Kodama Y, Ohya T, Harada R, Kimura S (2005) Streptococcus anginosus infection in oral cancer and its infection route. Oral Dis 11:151–156
Scannapieco FA (1998) Position paper of The American Academy of Periodontology: periodontal disease as a potential risk factor for systemic diseases. J Periodontol 69:841–850
Sheu BC, Chang WC, Cheng CY, Lin HH, Chang DY, Huang SC (2008) Cytokine regulation networks in the cancer microenvironment. Front Biosci 13:6255–6268
Shiga K, Tateda M, Saijo S, Hori T, Sato I, Tateno H, Matsuura K, Takasaka T, Miyagi T (2001) Presence of Streptococcus infection in extra-oropharyngeal head and neck squamous cell carcinoma and its implication in carcinogenesis. Oncol Rep 18:245–248
Sixou JL, De Medeiros-Batista O, Gandemer V, Bonnaure-Mallet M (1998) The effect of chemotherapy on the supragingival plaque of pediatric cancer patients. Oral Oncol 34:476–483
Söder B, Yakob M, Meurman JH, Andersson LC, Klinge B, Söder PÖ (2011) Periodontal disease may associate with breast cancer. Breast Cancer Res Treat 127:497–502
Söder B, Yakob M, Meurman JH, Andersson LC, Söder PÖ (2012) The association of dental plaque with cancer mortality in Sweden. A longitudinal study. BMJ Open 2:pii: e001083. doi:10.1136/bmjopen-2012-001083
Sorensen JB, Skovsgaard T, Bork E, Damstrup L, Ingeberg S (2008) Double-blind, placebo-controlled, randomized study of chlorhexidine prophylaxis for 5-fluorouracil-based chemotherapy-induced oral mucositis with nonblinded randomized comparison to oral cooling (cryotherapy) in gastrointestinal malignancies. Cancer 112:1600–1606
Tachibana M, Yoshida A, Ansai T, Takata Y, Akifusa S, Fukuhara M et al (2006) Prevalence of periodontopathic bacteria on the tongue dorsum of elderly people. Gerodontology 23:123–126
Taylor PW, Hamilton-Miller JM, Stapleton PD (2005) Antimicrobial properties of green tea catechins. Food Sci Technol Bull 2:71–81
Tengerdy RP (1990) The role of vitamin E in immune response and disease resistance. Ann N Y Acad Sci 587:24–33
Tezal M (2012) Interaction between chronic inflammation and oral HPV infection in the etiology of head and neck cancers. Int J Otolaryngol 2012:575242. doi:10.1155/2012/575242
Tezal M, Grossi SG, Genco RJ (2005) Is periodontitis associated with oral neoplasms? J Periodontol 76:406–410
Tezal M, Sullivan MA, Reid ME, Marshall JR, Hyland A, Loree T, Lillis C, Hauck L, Wactawski-Wende J, Scannapieco FA (2007) Chronic periodontitis and the risk of tongue cancer. Arch Otolaryngol Head Neck Surg 133:450–454
Tezal M, Sullivan MA, Hyland A, Marshall JR, Stoler D, Reid ME, Loree TR, Rigual NR, Merzianu M, Hauck L, Lillis C, Wactawski-Wende J, Scannapieco FA (2009) Chronic periodontitis and the incidence of head and neck squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev 18:2406–2412
Tezal M, Scannapieco FA, Wactawski-Wende J, Meurman JH, Marshall JR, Rojas IG, Stoler DL, Genco RJ (2013) Dental caries and head and neck cancers. JAMA Otolaryngol Head Neck Surg 139:1054–1060
Tong HC, Gao XJ, Dong XZ (2003) Non-mutans streptococci in patients receiving radiotherapy in the head and neck area. Caries Res 37:261–266
Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI (2007) The human microbiome project. Nature 449:804–810

Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, Ley RE, Sogin ML, Jones WJ, Roe BA, Affourtit JP, Egholm M, Henrissat B, Heath AC, Knight R, Gordon JI (2009) A core gut microbiome in obese and lean twins. Nature 457:480–484

Uittamo J, Siikala E, Kaihovaara P, Salaspuro M, Rautemaa R (2009) Chronic candidosis and oral cancer in APECED-patients: production of carcinogenic acetaldehyde from glucose and ethanol by Candida albicans. Int J Cancer 124:754–756

Van Schooten FJ, Besaratinia A, De Flora S, D'Agostini F, Izzotti A, Camoirano A, Balm AJ, Dallinga JW, Bast A, Haenen GR, Van't Veer L, Baas P, Sakai H, Van Zandwijk N (2002) Effects of oral administration of N-acetyl-L-cysteine: a multi-biomarker study in smokers. Cancer Epidemiol Biomarkers Prev 11:167–175

Virtanen E, Söder B, Andersson LC, Meurman JH, Söder PÖ (2014) History of dental infections associates with cancer in periodontally healthy subjects: a 24-year follow-up study from Sweden. J Cancer 5:79–85. doi:10.7150/jca.7402

Wade WG (2013) The oral microbiome in health and disease. Pharmacol Res 69:137–143

Wahlin YB (1989) Effects of chlorhexidine mouthrinse on oral health in patients with acute leukemia. Oral Surg Oral Med Oral Pathol 68:279–287

Wen BW, Tsai CS, Lin CL, Chang YJ, Lee CF, Hsu CH, Kao CH (2013) Cancer risk among gingivitis and periodontitis patients: a nationwide cohort study. QJM 107(4):283–290

Worthington HV, Clarkson JE, Eden OB (2007) Interventions for preventing oral mucositis for patients with cancer receiving treatment. Cochrane Database Syst Rev 4:CD000978

Xu Y, Teng F, Huang S, Lin Z, Yuan X, Zeng X, Yang F (2014) Changes of saliva microbiota in nasopharyngeal carcinoma patients under chemoradiation therapy. Arch Oral Biol 59:176–186

Yumoto H, Nakae H, Fujinaka K, Ebisu S, Matsuo T (1999) Interleukin-6 (IL-6) and IL-8 are induced in human oral epithelial cells in response to exposure to periodontopathic Eikenella corrodens. Infect Immun 67:384–394