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REVIEW ARTICLE

Are oral and dental diseases linked to cancer?

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OBJECTIVE: Infection and inflammation play a role in carcinogenesis, and highly prevalent oral and dental diseases have been significantly linked to some types of cancer. This article reviews current literature in this area.

MATERIALS AND METHODS: Open literature review using the PubMed database and focused on publications from 2000 to 2010.

RESULTS: Numerous potential mechanisms are implicated in the oral disease/carcinogenesis paradigm, including infection- and inflammation-associated cell pathology and microbial carcinogen metabolism. Poor oral hygiene is associated with oral cancer, but there is also evidence of a possible link between oral or dental infections and malignancies in general.

CONCLUSION: Oral infections may trigger malignant transformation in tissues of the mouth and other organs. However, scientific evidence to date remains weak and further well-conducted studies are warranted before cancer can be properly added to the list of oral infection-related systemic diseases.

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Keywords: oral cancer; malignant disease; microbiota; oral hygiene

Introduction

In many industrialized countries, cancer is the number two killer after cardiovascular disease, and smoking is the most frequent single cause of death from cancer (Lancet Editorial, 2010). Smoking is also a risk factor for oral and dental diseases (Warnakulasuriya *et al*, 2010). Tobacco plays a major role in gene methylation, and the earlier the habit starts and the greater its intensity, the higher is the likelihood of aberrant methylation, e.g., of p16 and E-cadherin (Hasegawa *et al*, 2002). Inflammation has also been linked to the development of cancer (Coussens and Werb, 2002), and infections that trigger inflammatory processes have been proposed as major preventable causes of cancer (Kuper *et al*, 2000). The first bacterial species reported to cause cancer was *Helicobacter pylori,* estimated to play a role in around 60% of all stomach cancers worldwide (The EUROGAST Study Group, 1993; Parkin, 2006). It is now well established that gastric cancer risk is reduced by eradication of this microorganism (Fuccio *et al*, 2009).

Carcinogenesis is a multi-step process in which cells accumulate changes in their genetic material, giving rise to alterations of cell function. Some of these changes cannot be attributed to a DNA sequence modification (*e.g.,* deletion or mutation) but are rather designated epigenetic changes, i.e., hereditary changes in gene expression that are not codified in the DNA sequence. For instance, chemical modifications to DNA and associated proteins, e.g., by methylation, can alter gene expression without affecting the DNA sequence (Jones and Baylin, 2002). Cell programs of proliferation, differentiation, senescence, and apoptosis are involved in cell cycle regulation, and changes in cell cycle machinery have been described as a hallmark of cancer development (Lundberg and Weinberg, 1999).

In general, cancer-associated infections and inflammatory processes are characterized by their high prevalence in populations, persistence in the host, and long latency period before cancer onset. Nevertheless, it has been estimated that infection and inflammation play a role in 15–20% of all malignancies. The pathways involved are genetic events that lead to malignant transformation, and tumor-infiltrating leukocytes are the main regulators of cancer inflammation (Allavena *et al*, 2008), although the underlying mechanisms remain largely unknown. The role of bacteria in carcinogenesis and the associated mechanisms were recently reviewed by Chang and Parsonnet (2010). The impact of microbiota on human functions is evident, given that the body contains 10-fold more bacteria than human cells (Savage, 1977), but the mechanisms involved have yet to be fully elucidated.

Oral infections are highly prevalent in populations, leading the World Health Organization (WHO) to develop a specific program for global oral health

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(Petersen, 2005). However, the very wide diversity of oral microbiota makes it difficult to determine whether specific oral microbial species are directly linked to systemic diseases such as cancer (Parahitiyawa *et al*, 2010). Smoking, one of the main culprits in triggering oncogenesis, is also an established risk factor for many oral diseases; therefore, cancer in general and diseases of the mouth share this same risk factor (Warnakulasuriya *et al*, 2010).

There has been research interest in the association between periodontal disease and cancer risk. For example, a study in US male health professionals observed periodontal disease to be associated with a small but significant increase in overall cancer risk, which persisted in never-smokers (Michaud *et al*, 2008). A longitudinal study in Sweden by Söder *et al* (2011) recently showed an association between periodontal disease and breast cancer, with an odds ratio (OR) of 2.36. The role of oral microbiota in oncogenesis in general was recently reviewed by one of the present authors (Meurman, 2010a,b).

Of the many thousands of microbial species in oral biofilms, a number of bacteria, yeasts, and viruses have been detected in oral carcinomas. However, it is not known how many of these are innocent bystanders and how many play a role in the etiology and/or mechanisms of carcinogenesis. In the present article, we discuss the putative mechanisms involved in oral infection-related carcinogenesis, with an emphasis on oral cancer. We mainly searched the more recent literature (PubMed, 2000–2010), focussing on oral bacterial and yeast infections and only briefly addressing viral infections.

Risk factors for oral cancer

In a case–control study in the early 1990s, Marshall *et al* (1992) demonstrated that cigarette smoking and alcohol consumption increase oral cancer risk, finding that poor oral hygiene also raised this risk but to a lesser degree. It was estimated that 25% of oral cancers worldwide are attributable to smoking and/or chewing tobacco, 7–19% to alcohol consumption, 10–15% to micronutrient deficiency, and more than 50% to betel quid chewing in areas where this habit is common (Petti, 2009). Evidence on the association between dietary factors and oral cancer is weak, and results have been controversial. This issue was recently reviewed by one of the present authors and will not be further discussed here (Meurman, 2010a,b).

Viral infections

It has long been known that human papilloma virus (HPV) type-16 infection is a risk factor for oral carcinoma, being implicated in around 24% of one case series (Kreimer *et al*, 2005). Other viruses may also be associated with cancer, including herpes simplex virus (HSV)-1 and HSV-2 and Epstein-Barr virus (EBV). EBV has been implicated in Burkitt's lymphoma, although a direct causal relationship has not been demonstrated, but it has not been related to oral cancer (Cruz *et al*, 2000). DNA of HSV-1 and HSV-2 has been detected in biopsy specimens of oral cancer, but it has not yet been established whether these viruses have malignant potential (Shillitoe, 2009).

In fact, however, the participation of HPV in the etiology of oral cancer remains controversial, and reports on its prevalence in oral cancerous tissue have ranged extremely widely from 0% to 100% over the past 20 years. HPV is also considered a host pathogen of the oral mucosa, although of uncertain origin, but prevalence data have also been highly varied, from 0% to 60% (Zhang *et al*, 2004; Boy *et al*, 2006). Discrepant findings on the presence of HPV in healthy and pathological oral tissue can be at least in part explained by differences in study design. Currently, the most widely used method for HPV detection is polymerase chain reaction (PCR), because of its objectivity. Further research is required to establish the role of HPV in oral cancer, however.

Bacterial infections

Periodontal disease has been shown to increase the risk of head and neck cancer (OR 4.36; 95% confidence interval [CI] 6.01–93.16), and individuals with periodontitis are also more likely to develop poorly differentiated oral squamous cell carcinomas (Tezal *et al*, 2009). Periodontal disease has also been linked with lung cancer (OR 1.55; CI 1.25–1.92) but the evidence is too weak for further conclusions (Hujoel *et al*, 2003). Daily tooth brushing was reported to reduce the risk of esophageal carcinoma in comparison with those without this habit, with an OR of 2.37 (CI 1.42–3.97) (Abnet *et al* (2008), and this risk was not altered when smoking was controlled for, emphasizing the strength of poor oral hygiene as a risk factor for cancer. In a recent systematic review on the relationship between periodontal disease and cancer, Nugent (2010) reported that ten of the twelve articles meeting inclusion criteria evidenced an increased risk, while the results of the other two were mixed or neutral. However, because of the nature of the publications, a meta-analysis was not possible.

Finally, it is interesting that malignancies in the periodontal tissue seem rare. Hence, for example in an epidemiological study from Spain, benign tumors predominated at the gingiva (Sortino and Milici, 1998). However, in a cumulative 40-year material from Brazil, gingiva was the most affected site of oral squamous cell carcinoma (Marocchio *et al*, 2010). Nevertheless, we agree with the conclusion by Tezal *et al* (2005) who discussed that to confirm the hypothesis about a possible relationship between periodontal disease and oral cancer, prospective or well-designed case–control studies are needed. As pointed out by Meyer *et al* (2008), in studies, it is not easy to control all the possible confounding factors. This fact might partly explain the lack of hard data in this area.

Cancer treatment affects dental health, as reported by Hong *et al* (2010) in their systematic review. Specifically, patients undergoing radiation therapy were found to be susceptible to dental diseases, as evaluated by the WHO Diseased Missing Filled Tooth Index, Plaque Index, and

Gingival Bleeding Index. There appear to be no reports on the association between dental caries and oral carcinogenesis as such, although the frequent clinical observation of a poor level of oral hygiene in patients with cancer may indicate an indirect association. In a study by López-Galindo *et al* (2006), poor oral hygiene was reported in 22.7% of patients examined before anticancer therapy *vs* 3.3% of a healthy control population.

Yeast infections

Candida in general is more prevalent on carcinoma lesions than on healthy mouth mucosas (Nagy *et al*, 1998). McCullough *et al* (2002) observed significantly more prevalent *Candida* colonization in larger numbers of colony forming units in patients with oral epithelial dysplasia or carcinoma than in controls. The role of *Candida* in carcinogenesis is particularly evident among patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), an autosomal recessive disorder. It has been suggested that the chronic oral candidosis found in most APECED patients may be carcinogenic (Rautemaa *et al*, 2007). Yeasts may invade the oral epithelium and may also be causally implicated in oral leukoplakia and dysplastic changes. The mechanisms involved are probably related to the proteolytic activity of *Candida, i.e.,* degradation of basal membrane components and disruption of epithelial cell-to-cell contacts (Pärnänen *et al*, 2008, 2010). *Candida* leukoplakias have been estimated to develop into carcinomas in 9–40% of cases (Hooper *et al*, 2009). Animal studies previously confirmed the potential of *Candida* to produce malignant transformation in oral mucosa (O'Grady and Reade, 1992). We highlight the detection of non-*albicans Candida* strains in an increasing number of patients with oral carcinoma (Davies *et al*, 2002). These strains pose a future therapeutic challenge, given their greater resistance to antifungal drugs in comparison with *C. albicans* (Meurman *et al*, 2010).

Pathological mechanisms in oral carcinogenesis

Figure 1 outlines the mechanisms and pathways involved in infection-derived carcinogenesis. According to Chang and Parsonnet (2010), these mechanisms include the following: (i) alteration by bacterial infection of physiologic host processes, e.g., inflammation; (ii) infection-induced modification of antigen-driven lymphoproliferation; (iii) infection-induced upregulation of hormones that increase epithelial cell proliferation; (iv) direct effect of infection on cell transformation; and (v) production of toxic and carcinogenic metabolites by bacteria.

Human oral infections are frequently chronic, and oral biofilms are characterized by microbial species stability. Hence, specific bacteria can reside in the mouth for many years and may continuously trigger and upregulate pro-inflammatory cytokines, creating an environment of persistent inflammation. Periodontal disease is a good example of this state. Chronic inflammation may in turn promote carcinogenesis by damaging cells and interfering with cellular and tissue repair mechanisms (Coussens and Werb, 2002).

Homann *et al* (1997, 2000) were the first to implicate the highly carcinogenic acetaldehyde, metabolised from alcohol by several oral micro-organisms, in mechanisms underlying the bacteria–oral carcinogenesis interaction. This activity of oral bacteria may explain the frequent association between poor oral hygiene and oral cancer in heavy drinkers and smokers, given that salivary acetaldehyde concentrations are significantly increased under poor oral hygiene conditions (Homann *et al*, 2000). Oral streptococci (Kurkivuori *et al*, 2007) and *Candida* spp. (Nieminen *et al*, 2009, Uittamo *et al,* 2009) proved able to convert ethanol into acetaldehyde *in vitro*. Interestingly, xylitol, a widely used non-cariogenic polyol sweetener, markedly reduced (by 84%) the production of acetaldehyde by *Candida* when incubated

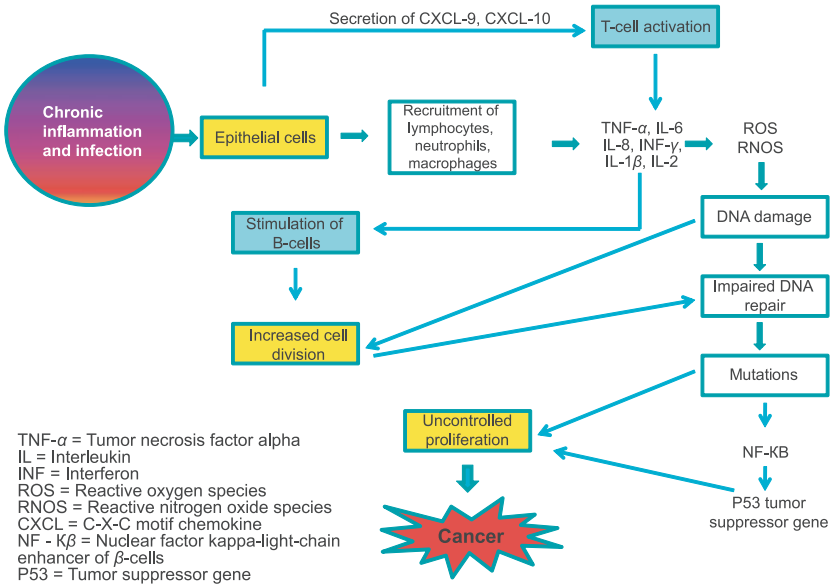

Figure 1 Mechanisms and pathways associated with the development of infection-linked cancer. Partly modified from Chang and Parsonnett (Clin Microbiol Rev 2010; 23:837)

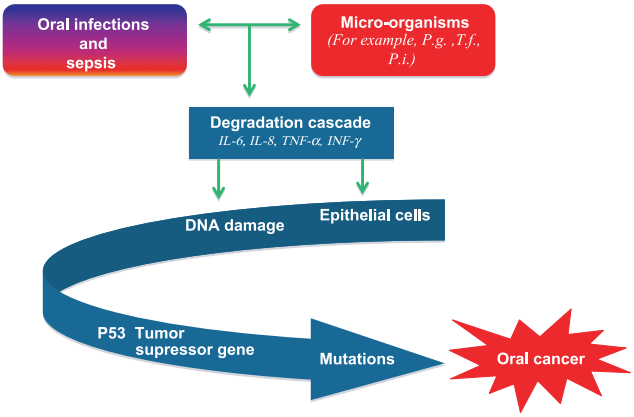

Figure 2 Putative pathway in the oral infection–oral cancer relationship. P.g., Porphyromonas gingvalis, T.f., Tannerella forsythia; P.i., Prevotella intermedia. For the other abbreviations please see Figure 1

Table 1 Areas in which further research is warranted to clarify links between oral/dental diseases and cancer

Research area	*Research topic*
Epidemiology	Oral infections and oral cancer
	Oral infections and malignancies in general
Oral microbiota	Role of specific micro-organisms (bacteria, yeasts, and viruses) in carcinogenesis
	Carcinogenic metabolites
	Direct effect on host cells and tissue reactions known to be associated with the development of cancer
Saliva	Innate mutagenicity
	Mechanisms affecting dietary and other external components with carcinogenic potential
	Defensive and protective factors in patients with and without cancer

with or without ethanol (Uittamo *et al*, 2010). However, it remains to be seen whether these findings will lead to novel strategies against oral cancer.

Homann *et al* (1997) had previously reported that oral chlorhexidine rinsing reduces salivary acetaldehyde production and suggested that antiseptic agents may indirectly reduce the development of oral cancer by inhibiting dental plaque bacteria, but there is no supporting clinical evidence. Acetaldehyde was also successfully removed from saliva by the administration of tablets containing l-cysteine (Salaspuro *et al*, 2002), finding a 58% reduction in salivary acetaldehyde concentrations *vs* placebo administration (Salaspuro *et al*, 2006). This amino acid binds covalently to acetaldehyde, resulting in an inactive sulfur compound. In general, the pharmacological treatments for reducing acetaldehyde contents of the mouth and upper gastrointestinal track have been discussed in detail by Salaspuro (2007). Acetaldehyde-associated oral carcinogenesis has been more thoroughly reviewed by Meurman and Uittamo (2008). So far, there is no clinical evidence to support the hypothesis that inhibiting oral acetaldehyde metabolism and/or reducing acetaldehyde concentration diminishes cancer frequency.

In this context, it should also be pointed out that alcohol used as a solvent in many commercial mouthwashes may be considered risky in the perspective of oral carcinogenesis. However, there is no evidence to show that alcohol-containing mouthwashes would increase cancer risk (Werner and Seymour, 2009). Alcohol in the oral hygiene preparations does not seem to offer any particular benefit, however, and thus alcohol-free mouthwash products are to be recommended (Carretero Peláez *et al*, 2004).

Saliva may also contain mutagenic compounds. Bloching *et al* (2007a,b) reported that a high dental plaque index and large number of decayed teeth were significantly correlated with *Salmonella typhimurium* genotoxicity (Ames test). The authors concluded that polymicrobial supragingival plaque may be a co-factor in the development of oral carcinomas. The same authors, using a cell culture model, observed that saliva from patients with head and neck tumors had a higher cytotoxic effect on fibroblasts in comparison with saliva from healthy controls (Bloching *et al*, 2007a,b). Hence, the mutagenicity of saliva needs to be taken into account when considering the mechanisms involved in oral carcinomas. Oral bacteria may also metabolize dietary components into carcinogenic substances, such as nitrates and nitrites, which can be converted by intestinal microflora into carcinogenic nitrosamines (Lijinsky, 1988). In this context, it should be borne in mind that carcinogenic nitrosamines are also essential components and play a role in all tobacco-associated malignancies (Boffetta *et al*, 2008).

Conclusion

Table 1 indicates the main areas in which further research is warranted on the role of oral and dental diseases in carcinogenesis. Evidence in the literature remains inadequate to allow final conclusions to be drawn on whether infectious diseases of the mouth are a true risk factor for the development of malignancies. Some epidemiological data indicate an association but no causal relationship has been established. It can, however, be assumed that general inflammatory mechanisms linked to carcinogenesis also play a role in the oral cavity, where numerous resident micro-organisms trigger harmful cell and tissue reactions (Figure 2). Importantly, poor oral hygiene is associated with oral cancer in particular and plays a significant role in malignancies in other organs. Consequently, carcinogenesis can be included in the oral infection–systemic health paradigm. Further research is required to explore whether the likelihood of cancer could be reduced by good oral hygiene and/or modification of the oral biofilm composition by specific chemicals in oral hygiene products, among other measures. Finally, the relationship between oral and dental diseases and different forms of cancer should be investigated especially in countries where reliable nation-based cancer registries are available. The studies from Sweden by Söder *et al* (2007, 2011) are examples of this approach.

Author contributions

The authors contributed equally to the research and manuscript handling.

Declaration of interests

There are none.

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