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A Mini-Review of the Relationship between Periodontal Disease and Various Types of Less Common Cancers

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Abstract

Previous research has investigated the possible role of periodontal disease (PD) as a risk factor for systemic diseases and disorders such as diabetes mellitus, cardiovascular disease, arterial hypertension, respiratory diseases, rheumatoid arthritis, endocrine disorders, osteoporosis, and cancer. Recently, many investigators have focused on the possible role of PD in carcinogenesis, using several PD indices, such as depth of the periodontal pockets (PPD), clinical attachment loss (CAL), Community Periodontal Index of Treatment Needs (CPITN), bleeding on probing (BOP), the number of existing or lost teeth, gingivitis indices, whereas periodontal tissue condition has also been assessed by radiographic examinations. Associations have been observed between PD indices and an increased risk of cancer development in organs such as tongue, oropharynx, breast, esophagus, stomach, lung, kidney, pancreas, hematopoietic, colon, prostate and uterus. However, those studies are characterized by differences in design and methods, whereas possible influences caused by unknown confounders could lead to secondary biases associations. The aim of the current review was to refer the possible association between PD and various types of less common cancers in organs such as breast, gall bladder, liver, prostate and hematological/hematopoietic malignancies.

Keywords: Epidemiology; Cancer; Periodontal disease

Introduction

Several studies have investigated the possible role of periodontal disease (PD) as a risk factor for systemic diseases and disorders such as cardiovascular disease, arterial hypertension, diabetes mellitus, respiratory diseases, rheumatoid arthritis, endocrine disorders, osteoporosis, and cancer [1,2]. It has also recorded that the association between oral cavities diseases with some systemic diseases are possible bi-directional as PD is correlated with an intense local and systemic immune response [3]. Especially the association between PD and diabetes mellitus has been investigated and is considered to be bi-directional [4].

Associations have been observed between PD indices and an increased risk of cancer development in various organs and locations such as tongue [5], oropharynx [6-9], breast [10], esophagus [11], stomach [11,12], lung, kidney, pancreas, hematopoietic [13-15], colon, prostate and uterus [14,16,17]. However, a few amounts of studies have explored the association between PD and less common malignancies. The aim of the present review was to examine the possible association between PD and various types of less common cancers in organs such as breast, gall bladder, liver, prostate and hematological/hematopoietic malignancies.

Periodontal Disease and Carcinogenesis

It has been shown that chronic inflammation is able to promote tumor development and progression [18], and that tumors can arise from infectious locations in human organs such as liver, colon, stomach, urinary bladder, uterine cervix, ovaries and lung [19,20]. Host's persistent infections induce chronic inflammation,

in which leukocytes and other immune cells are responsible for DNA damage in proliferating cells due to secretion of reactive oxygen species (ROS) and reactive nitrogen species (RNI). Those species are normally produced by immune cells for the treatment of infection. ROS are produced through a variety of intracellular and extracellular actions, as act as signal mediators which are implicated in growth, differentiation, progression, and death of the cell. RNI act as both positive and negative regulators of cell death. Moreover, ROS and RNI react and form peroxy-nitrate (PN), a mutagenic agent, and in case of a repeated tissue damage in the presence of ROS and RNI high levels which are released by inflammatory cells, leads to interactions with DNA in the proliferating epithelium, and consequently to permanent genomic alterations such as point mutations, chromosomal rearrangements or deletions [21]. The mentioned mechanism is the endogenous mechanism in which those genetic aberrations and alterations trigger tumor development, whereas the exogenous one is the presence of a chronic inflammation which increases the risk of carcinogenesis [20].

A chronic infection can stimulate epithelial malignancies through an indirect mechanism implicating an inflammatory activation of cellular environment, condition that can expose those epithelial cells to mutagenic factors. Moreover, inflammatory cells, fibroblasts and epithelial cells can be activated by bacteria and their products, and can produce and release a wide variety of cytokines, chemokines, growth factors, and other biological mediators which can cause damage to epithelial cells DNA. Chronic inflammations can produce an inflammatory environment which is associated with cell functions such as survival, proliferation, migration, angiogenesis, and apoptosis. This environment can induce the epithelial cells to accumulate mutations and lead those mutant cells to proliferation, migration and provide growth benefits [10].

The possible association between PD as a chronic inflammation and carcinogenesis was based on the observation that individuals with chronic inflammatory conditions showed a higher incidence of cancer development [22].

PD as a chronic inflammation increases the risk for cancer development in various organs [13,16,22,26], is caused by the colonization of Gram-negative bacteria mainly that stimulate an inflammatory response, which in some individuals leads to destruction of the connective tissue [27]. Moreover, that inflammatory response to periodontal infection spreads beyond the oral tissues and leads to increased levels of circulating inflammatory biomarkers [28]. This link, as has already been stated, is supported by the higher incidence of cancer cases in individuals with chronic inflammatory conditions [22] and the effectiveness of anti-inflammatory medication in prevention of some cancers, such as colorectal cancer [29], however this observation has not been confirmed in all surveys [30,31].

The appearance of a chronic and systemic inflammation due to PD may lead to signaling pathways which increase the risk of cancer development in various organs. Moreover, other mechanisms have been proposed and concern the deflection of the immune system and the production of carcinogenic products by the periodontal tissues pathogens [32].

Alternatively, underlying genetic factors may increase the sensitivity or susceptibility to both diseases or may alter the relationship of known environmental risk factors, such as smoking, with PD and cancer. However, the accurate role of the common genetic risk factors between both conditions remains unknown, whereas it is not clear whether systemic inflammation, pathogenic invasion in blood circulation or immune response to PD could affect the overall risk of cancer development at various locations [33].

PD and Risk of Less Common Cancer Development

A previous case-control study by Hiraki et al. [34], in which PD status was assessed by numbers of loss and remaining teeth, after matched for age and gender, no association was recorded between PD and risk of liver cancer. Similarly, no association was identified in another study between PD, which was based on self-reported data and liver cancer risk in a female study sample [35]. On the contrary, other researchers in a prospective study observed a higher risk of liver cancer in individuals who had lost many permanent teeth or were completely edentulous when compared with those reporting a lower number of teeth loss [36]. However, after adjusting for *Helicobacter pylori* infection and known risk factors of liver cancer, such as hepatitis B, and hepatitis C, the risk insisted but was not significant. A recent register-based Swedish cohort report showed that the loss of many teeth did not lead to an increased risk of liver cancer mortality [37]. In another Japanese cohort survey was found that the risk of death from liver cancer was almost significance [38]. Only one survey has examined the possible association between PD and gall bladder risk cancer, and showed a significantly higher risk of gall bladder cancer among females with a history of PD compared with those with no history of PD. However, after limitation to never-smokers only, the association reduced significantly [35].

A few amounts of studies have investigated the possible association between PD and breast cancer development, and in some cases the outcomes were inconsistent. A previous study by Hiraki et al. [34] in which tooth loss was used as a PD index showed no associations between both diseases. Similar results were observed in another survey by Arora et al. [17]. Mai X et al. [39] used radiographic analyses of alveolar crestal height for assessing PD status and found that the risk of breast cancer was not associated to either mild/moderate or severe PD after adjusting for age and smoking. Moreover, the sample size for breast cancer cases was small and thus, the outcomes could not be

reliable. Similarly, Michaud et al. [40] in a recent study observed that breast cancer risk was not associated with varying clinical measures of severe periodontitis when restricted to never-smokers.

On the contrary, a Swedish study showed that more breast cancer cases were observed among females who had PD accompanied by missing molars compared with those with PD and remaining molars [10]. However, that study had some endogenous limitations as many participants did not undergo a clinical examination. The NHANES (National Health and Nutrition Examination Survey) survey recorded an increased risk of breast cancer mortality among those with periodontitis, however that risk was not statistically significant [23]. A larger research to date was carried out by Freudenheim et al. [41]. Self-reported PD history was found to be associated with an increased risk of breast cancer after adjustment for known breast cancer risk factors, such as body mass index (BMI), age at menarche, parity, age at first birth, and age at menopause. However, that risk was substantially reduced after additional adjustment for smoking status and pack years. It is possible that residual confounding from smoking may have played a role in the positive associations observed. Chung et al. [42], in one retrospective cohort study with equal numbers of cases and matched controls was observed that the rate of breast cancer was significantly higher among females with chronic periodontitis than those without periodontitis, despite the fact that known risk factors for breast cancer and smoking status were not controlled for, in logistic regression analyses. In another study in Turkey, individuals with moderate/severe periodontitis had a greater than 2-fold increase in breast cancer comparative to the expected risk for a similar age-matched group [43]. Limitations of that study was the small sample size of breast cancer cases and the fact that smoking and other important risk factors were not adjusted for, leading to unreliable outcomes. A recent case-control study in Brazil used four different case definitions for periodontitis and found that the odds of having breast cancer in all cases varied from 2- to 3-fold based on the case definition carried out [44]. In case of a possible association between PD and breast cancer risk, smoking status, and other factors, may play a contributory role.

Lee et al. [45] examined the association between PD and prostate cancer risk over a 12-year period, in Korean adults aged over than 40 years. PD was determined by clinical and radiographic findings. The outcomes showed an increased risk of prostate cancer among those with PD after adjustment for known confounders, smoking, alcohol, and sociodemographic factors.

Similarly, Arora et al. [17] reported a 47% higher risk of prostate cancer among individuals with PD, in which tooth mobility was used as PD index, compared with those with no evidence of PD. On the contrary Michaud et al. [40] found no association between severe periodontitis with risk of prostate cancer. Similarly, in a previous study in male health professionals Michaud et al. [13] examined history of PD in relation to risk of advanced prostate cancer and observed a negative association after adjustment for relevant factors such as smoking. In another more recent study, the outcomes when restricted to never-smokers revealed no association between both diseases [46]. Similarly, Hiraki et al. [34] examined that association using categories of tooth loss, as a PD index and found no association between that index and prostate cancer risk.

Few surveys have examined the possible association between PD with increased risks of hematological cancers [42] and of lymphoid/hematopoietic malignancies in never-smokers [35] and have recorded such associations. Michaud et al. [13] in a prospective e cohort study revealed increased risks with hematopoietic malignancies, whereas in a recent one [40] observed that PD was not associated with hematopoietic and lymphatic cancers. Similar surveys have shown an association between PD and non-Hodgkin lymphomas [47], but not lymphomas in general [34] or leukemias [35].

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