

Review Article

Association between oral pathogens and prostate cancer: building the relationship

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Abstract: Background: Chronic inflammation and infections are associated with increased risk of prostate cancer development. There is considerable evidence that proves the interrelationship between bacterial/viral infections and carcinogenesis. Periodontitis is a chronic inflammatory disease triggered by gram-negative anaerobic bacteria. In this narrative review, we investigate the relationship between periodontal disease and prostate cancer by reviewing previous studies of the association and possible mechanisms that may explain this link. Methods: A comprehensive search for articles published was performed using the key words, “periodontal disease”, “prostate disease”, “prostate cancer”, “prostatic inflammation”. Thorough reviews of each study were conducted and assessed for eligibility, and data was summarized. Results: The role of inflammatory responses in the prostate as drivers of malignancy appears to be predisposed by periodontal pathogens and/or periodontitis inflammatory mediators. Conclusion: Periodontal diseases might be associated with prostate cancer. However, the mechanism(s) explaining this relationship remains unclear and requires further elucidation.

Keywords: Prostate cancer, periodontal diseases, prostatic inflammation, benign prostate hypertrophy

Introduction

Prostate cancer is the most frequent cancer to occur in males and second foremost cause of cancer-related death in the Western world [1]. According to an estimate by GLOBOCAN database, approximately 1.1 million men worldwide were diagnosed with prostate cancer in 2012, accounting for 15% of the cancers diagnosed in men [1, 2]. In the United States, prostate cancer is the second leading cause of cancer-related death in men, behind lung cancer [3]. According to an estimate by the American Cancer Society, in 2019 approximately 164,690 new cases of prostate cancer will be diagnosed, and 29,430 deaths will occur from the disease [4]. In recent years, prostate cancer is of significant concern due to the gradual increase in the number of aging men and the existence of more than 3 million men with the disease. Recent observations suggest that prostate cancer is associated with chronic inflammation [5, 6]. Several factors might be responsible for prostate inflammation, especially the presence of pathogens in the urine, and sexual activity [7].

Recent studies report an association between prostate cancer, periodontal diseases, and tooth loss [8, 9].

Periodontal diseases are inflammatory conditions that have a local effect on the supporting structure of the teeth, which may lead to tooth loss and contribute to systemic inflammation [10]. Chronic periodontitis predominantly affects the tissues surrounding the teeth in response to accumulation of a subgingival biofilm, which consists of over 700 bacterial species [11, 12], many protozoa species [13] and viruses [14]. Of these, the most often recognized periodontal microbes include *Actinobacillus actinomycetemcomitans*, *Prevotella intermedia*, *Porphyromonas gingivalis*, *Bacteroides forsythus*, *Campylobacter rectus*, *Treponema denticola*, *Fusobacterium nucleatum*, *Eubacterium*, and *Spirochetes* (sp) [14, 15]. Additionally, various human herpes viruses, such as Epstein-Barr virus (EBV-1), and cytomegalovirus (HCMV) have also been detected [16]. The subgingival biofilm may induce a host release of pro-inflammatory mediators that elicit a chronic

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Table 1. Studies on the relationship between periodontal disease and prostate cancer

Author (Year)	Study Design	Purpose/Criteria	Results/Conclusions
Lee et al. (2017) [34]	Cohort	To investigate the association between PD and PC using records from the National Health Insurance Service-Health Examinee Cohort (NHIS-HEC).	The incidence of PC with PD in men with 40 and above age group was 0.28%. PD was linked with a 14% greater hazard of PC.
Ing-ming Hwang et al. (2014) [32]	Cohort	To assess the effect of treatment of PD and the risks for cancers in Taiwan. Therapy included scaling and root planing, subgingival curettage and periodontal flap surgery.	Treatment of PD reduces the risk of overall cancer and individual cancers. Risk of PC was higher in the treatment cohort group.
Arora et al. (2009) [8]	Prospective co-twin study	Investigation of hereditary risk factors between periodontal disease and cancers. PD measured by questionnaire-recorded tooth mobility.	PD and PC (Hazard ratio 1.47)
Hiraki et al. (2008) [33]	Case-control	To determine the significance of tooth loss on the risk of 14 cancers. The teeth loss was categorized into four groups depending on the number of remaining dentition	An inverse association between the number of teeth loss and risk of PC
Michaud et al. (2008) [31]	Cohort	To determine if PD or teeth loss is associated with cancer risk. Individuals surveyed on the history of PD with bone loss, number of remaining teeth; status and history of smoking; frequency of food intake; any new diagnose of cancer. Survey obtained at baseline and in all subsequent follow-up.	PD was associated with risk of overall cancer and individual cancers. An inverse association between the number of teeth loss and risk of prostate cancer
Hujoel et al. (2003) [9]	Cohort	To investigate PD and cancer relationship. Individuals with PD or gingivitis, a healthy periodontium or edentulous were identified at the commencement of the follow-up. These groups are identified by the teams of dentists and trained recorders evaluated the periodontal status of individual participants. The diagnosis of cancer was determined from death certificates.	Demonstrated a correlation between PC and PD measured by Russell's periodontal index (odds ratio 1.81). Increased risk of PC in individuals with the PD.

Acronyms: PD - periodontal disease, PC - prostate cancer.

inflammatory response, leading to alveolar bone loss [10]. Furthermore, studies have indicated that oral health may influence systemic health [10]. Several reports showed an association between periodontal disease and systemic conditions such as cardiovascular disease [10], type 2 diabetes mellitus [10], preterm low birth weight infants [17-20], osteoporosis [10], rheumatoid arthritis [21, 22], Parkinson's disease [23], Alzheimer's disease [24], psoriasis [25], respiratory functions [26] and several types of human cancers [27]. In particular, individuals with periodontal disease have a greater risk of cancer overall and site-precise malignancies including oral [28], gastrointestinal [29], lung [9], pancreatic [30], hematologic [31] and prostate [8, 9]. It has been reported that chronic inflammatory response to periodontal infection impacts beyond the oral cavity [22] and might increase the risk of various malignancies [23-25]. This association is supported by the effectiveness of anti-inflammatory drugs in reducing the risk of oesophageal, gastric, colorectal, biliary, breast, pancreatic [21], and genitourinary cancers [26, 27]. The aim of this review is to

advance the hypothesis that periodontal diseases may be significant in its contribution to prostate inflammation and cancer.

Materials and methods

An electronic search was carried out in PubMed database until August 2018 for all relevant publications that explored the association between periodontal diseases and/or periodontal microbes in prostate inflammation and malignancy. The following MeSH terms were used, "Periodontal Disease [All Field]", "Prostate disease [MeSH terms]", "Prostate cancer [MeSH terms]", "Prostatic Inflammation [MeSH terms]". Literature published in the English language was included.

Results and discussion

Association between periodontal disease and prostate cancer

A growing number of reports suggest that periodontal disease is significantly associated with an increased risk of prostate cancer [8, 9].

Arora et al. (2010), in a prospective co-twin study, reported an association of prostate cancer and periodontal disease measured by questionnaire-recorded tooth mobility and prostate cancer (hazard ratio 1.47) [8]. In another investigation, Hujoel et al. (2003), in a prospective cohort study, evaluated data from 11,328 individuals and verified a correlation between prostate cancer and periodontal disease (odds ratio 1.81) [9]. Despite the small sample size of (20 cases) of prostate cancer, this study was the only one to include a direct evaluation of the periodontal condition and establish a positive association between both diseases [9]. A study in Taiwan, by Hwang et al. (2014) showed that periodontal treatment consisting of scaling and root planing, subgingival curettage and periodontal flap surgery decreased the risk of cancer of the gastrointestinal tract, lungs, brain, and female reproductive organs [32]. However, the risk of prostate and thyroid cancers was significantly greater even after periodontal treatment [32]. Michaud and Hiraki (2008) reported an inverse association between the number of teeth lost and the risk of prostate cancer [31, 33]. However, the tooth loss is not necessarily representative of periodontal disease; for instance, an individual may lose teeth due to caries or fracture. Furthermore, in a more recent study it was found that periodontal disease was associated with a 14% higher risk of prostate cancer [34]. Overall, these studies indicate that, an association probably exists between periodontal diseases and prostate cancer, see **Table 1**. Joshi et al. (2010) from Case Western Reserve University evaluated serum prostate-specific antigen (PSA) levels as a marker of inflammation in patients with prostatitis and periodontitis and showed that subjects with both diseases have greater levels of PSA compared with either disease alone [35]. Furthermore, Alwithanani et al. (2015) reported the impact of treatment of periodontal disease on clinical symptoms of prostatitis showing that periodontal treatment improves prostate symptoms and lowered serum PSA levels in patients having both periodontitis and prostatitis [36]. Estemalik et al. (2017) further substantiated the association between periodontitis and prostatitis, as evidenced by the presence of similar oral bacteria such as *P. gingivalis* and *T. denticola* DNA in both the expressed prostatic secretion (EPS) and dental plaque of the same patient [37]. This finding support the hypothe-

sis that periodontal pathogens may be migrating through the systemic circulation to initiate an infection and inflammatory response in the prostate. The prostate inflammatory responses may in turn induce neoplastic transformations.

Chronic inflammation and prostate cancer

Grading and types of prostate inflammation

Several studies have suggested that inflammation is common within the prostate [5]. The National Institutes of Health (NIH) consensus classification refers chronic intraprostatic inflammation as chronic prostatitis (CP)/chronic pelvic pain syndrome (CPPS) [38]. According to NIH, prostatitis is classified into four categories: (1) acute bacterial prostatitis (category I); (2) chronic bacterial prostatitis (category II); (3) CP/CPPS (category III); and (4) asymptomatic inflammatory prostatitis (category IV) [38]. CP/CPPS (category III) is the most common prostatitis syndrome, covering approximately 95% of prostatitis cases [38]. This condition is extremely common in adults: 2-10% of adults suffer from symptoms compatible with chronic prostatitis, and approximately 15% of men suffer from symptoms of prostatitis [39]. Subgroup IIIA of this category consists of individuals with white blood cells in their prostatic fluid, post-prostate massage urine/or seminal fluid [39], and subgroup IIIB consist of individuals without leukocytes in any fluid [38]. It has been reported that genitourinary tract pathogens such as *Chlamydia trachomatis*, *Ureaplasma urealyticum*, protozoan pathogen *Trichomonas vaginalis*, *Neisseria gonorrhoea*, herpes simplex types I and II, and cytomegalovirus may be playing a role in CP/CPPS [40-44]. Category IV, asymptomatic inflammatory prostatitis, is present in patients undertaking examination for other urogenital conditions, such as increased PSA [38]. The estimated prevalence of category IV prostatitis is 11.2-32.3% in patients with elevated PSA [45]. It has been reported by Roberts et al. (2004) that prostatitis category III was associated with prostate malignancy whereas category I, II, IV was not [46, 47].

Chronic inflammation-mediated histological changes in the prostate

Epidemiological, histopathological, and in vivo investigations have determined an association

between chronic inflammation and an increased risk of prostate cancer [5, 48, 49]. However, the significance of inflammation of the prostate gland, and the mechanisms that lead to the development of prostate cancer are still unclear. Numerous meta-analysis and case-control studies have shown that men with prostatitis have a considerable increase risk of having prostate cancer. Daniels et al. (2005) conducted a prospective cohort study of 5821 men, and showed an association between a history of prostatitis and a history of prostate cancer (OR 5.4, 95% CI 4.4-6.6) [50]. Dennis et al. (2002) reported in a meta-analysis of 11 case-control studies that there is an increased risk of prostate malignancy among men with a history of prostatitis (odds ratio = 1.6) [48]. The presence of inflammatory cell infiltrates and proliferative inflammatory atrophy (PIA) are often detected in histologic samples of benign and malignant prostates [51-54]. PIA consists of lesions that might include epithelial atrophy [51, 52, 55, 56] low apoptotic index, and an increased proliferative index [51, 55], typically with inflammation characterized by mononuclear infiltrates in the periglandular stroma or by macrophages and neutrophils in the glandular lumina or epithelium. PIA is an inflammatory lesion emerging as a result of infection or cell injury subsequent from free radical toxicity, hypoxia, infection or autoimmunity. These lesions may lead to malignancy through an accumulation of transmutation in rapidly dividing cells. PIA is probably a precursor lesion to cancer and frequently exist near to high-grade prostatic intraepithelial neoplasia (HGPIN) or early cancer. It has been determined that a genetic association between PIA, HGPIN, and cancer exists [51]. MacLennan et al. (2006), in a five years follow-up study, examined prostate biopsy specimens of men with clinically abnormal findings and reported that the majority had chronic inflammation of prostate gland and that 6% of these patients had adenocarcinomas [5]. These studies suggest that the history of chronic inflammation is associated with an increased risk for prostate cancer. Elkahwaji et al. (2009), in a 25 weeks follow-up study, using an animal model of chronic prostatitis induced by *E. coli* infection, detected the development of prostate hyperplasia and dysplasia [56]. Furthermore, the prostate epithelium exhibited positive nuclear staining for 8-hydroxy-20-deoxyguanosine, a biomarker of DNA injury due to free radical tox-

icity [56]. This study provides evidence that prostatitis may trigger the development of prostate cancer.

Role of infectious organisms in prostatic cancer

Periodontal microorganisms

Dental biofilm is an organized mass, consisting mainly of microorganisms, that adheres to teeth [57, 58]. In the gingival crevice and periodontal pocket, a dysbiotic biofilm is one of the main factors contributing to periodontal diseases [59]. Nearly 50% of the American populations have chronic periodontitis as manifested by alveolar bone resorption [61]. There is an association between periodontal diseases and systemic diseases [10, 62, 63]. This link may be due to a metastatic, spreading/diffusion of periodontal bacteria and/or bacterial toxins [63] to other parts of the body. Many authors have provided a comprehensible correlation among two or more systemic diseases with periodontitis [62-66].

For instance, oral microbial pathogens are associated with undesirable pregnancy outcomes [67, 68]. Periodontal pathogens *P. gingivalis*, *F. nucleatum* [68, 70, 71] and *A. actinomycetemcomitans* [69, 70] have the ability to cross the placental barrier and have been detected in the amniotic fluid of women with preterm low-birth-weight infants [71-73]. Additionally, *F. nucleatum* DNA is identified in the synovial fluid of individuals who have rheumatoid arthritis [75]. Recent studies link periodontal bacteria to prostate inflammation and cancers [76, 77]. In a study conducted in the Department of Periodontics at CWRU, Estemalik et al. (2017) detected DNA of the periodontitis pathogens *P. gingivalis*, *T. denticola*, and *E. coli* in prostatic secretions of men with both periodontal and prostate diseases [37]. Oral microbes migrate to other parts of the body via the bloodstream, causing chronic inflammation that may initiate neoplastic transformation, the first step towards malignancy [71]. A series of studies showed the association of *F. nucleatum* species to colorectal carcinomas [78-80]. Also, Hwang mentioned that studies showed the presence of fusobacteria in normal tissue next to colon cancer [32]. According to Jacob et al. (2016) individuals with *P. gingivalis* in their oral cavity had a 59% increased risk of pancreatic cancer

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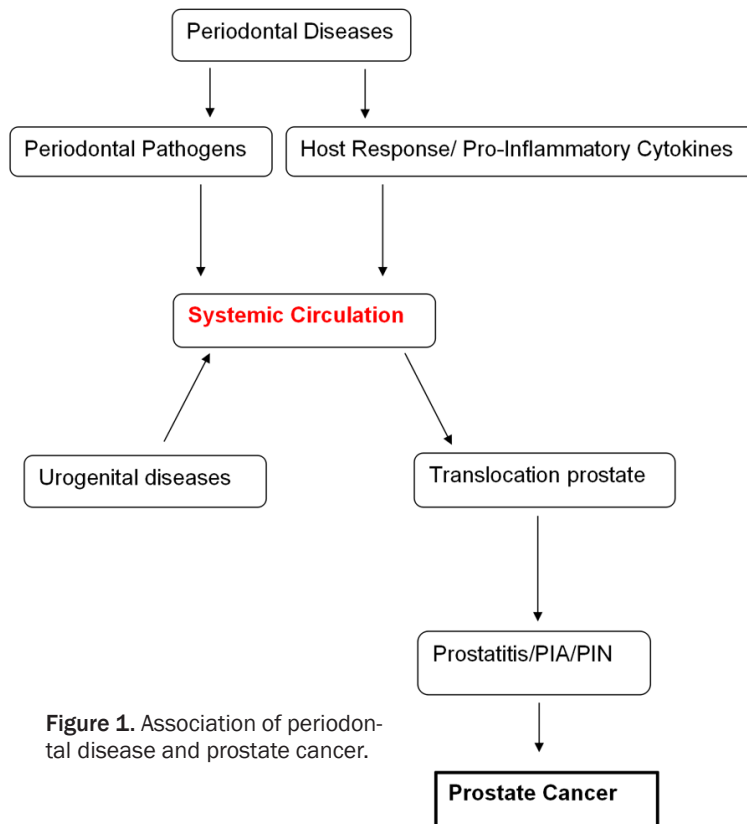


Figure 1. Association of periodontal disease and prostate cancer.

than those who did not harbor this microbe [81]. The authors also reported that individuals with *A. actinomycetemcomitans* in their oral cavity had a 50% greater chance of developing pancreatic cancer [81]. Furthermore, Michaud et al. (2012) showed that individuals with increased levels of antibodies to *P. gingivalis* are at significant increased risk of pancreatic cancer [82]. Fan et al. (2018) demonstrated that *P. gingivalis* and *A. actinomycetemcomitans* were associated to a higher threat of pancreatic cancer [83]. *P. gingivalis* and *A. actinomycetemcomitans* are capable of commencing the Toll-like receptor (TLR) signaling pathways, which are significant for the progression of pancreatic carcinogenesis [84]. Overall, the information presented provides a strong association between periodontal microorganism and the risk of development of several human cancers.

Sexually transmitted microorganisms

Pathogens of venereal diseases may affect the prostate by eliciting an inflammatory response. The prostate, like other organs, produces a normal immune response after exposure to an antigen. The etiology of prostatic inflammation

may involve an infectious component [48]. The microbial pathogens in urinary tract infections are similar to bacterial prostatitis in category and distribution [85]. Bacterial prostatitis may be an outcome of ascending urinary tract infections, resulting from urethral inoculation during sexual intercourse [85]. In addition, sexually transmitted agents have been identified in the prostate, such as the human papillomavirus, human herpes simplex virus type 2, cytomegalovirus, *Neisseria gonorrhoea*, *Chlamydia trachomatis*, *Treponema pallidum*, *Trichomonas vaginalis*, and some Gram-negative pathogens, such as *Escherichia coli* [49, 86]. Epstein-Barr virus (EBV) and cytomegalovirus's (CMV) may cause mononucleosis, well-known as 'kissing disease' by spreading through direct mouth-to-mouth contact [87, 88]. Interestingly,

these organisms are risk factors for the development of periodontitis [16, 89]. Patients with periodontal conditions associated with the subgingival viruses recover upon antiviral therapy (500 mg valaciclovir, Valtrex, orally twice daily over 10 days), which suggests a clinical role for these viruses in periodontitis [90, 91]. Therefore, these organisms may be involved in the development of both diseases.

Role of periodontal and prostate inflammatory mediators on prostate cancer

Periodontitis inflammatory mediators and its expression

Periodontal pathogens and/or microbes harboring LPS endotoxins induce innate immune pathways such as toll-like receptors (TLR). Activation of these pathways causes downstream synthesis and release of pro-inflammatory mediators such as IL-1 β , IL-6, TNF- α , PGE2, and matrix metalloproteinases [92-95]. These molecules may enter into systemic circulation leading to an increase in systemic inflammatory markers [94]. The presence of IL-6 in the systemic circulation is associated with the severity

of disease [94]. IL-6 is the major procoagulant cytokine that may stimulate cells of the liver to produce acute-phase proteins such as C-reactive protein (CRP), fibrinogen and plasminogen activator inhibitor 1 [94]. The chronic and elevated levels of CRP in the systemic circulation may indicate risk for myocardial infarction, stroke, and peripheral arterial disease even in healthy individuals [96]. In the periodontium, the control of infection/inflammation may inhibit markers of systemic inflammation and dysfunction of endothelial cells within 2-6 months [97]. Locally chronic inflammation results in hypoxia, which leads to the release of nitric oxide and other reactive oxygen species (ROS) [6]. This leads to the conversion of arachidonic acid by cyclooxygenases into prostaglandin, which acts on the regulation of cell proliferation [6]. Also, hypoxia activates the discharge of vascular endothelial growth factors (VEGF), triggering neoangiogenesis and fibroblast differentiation, which are developmental factors in prostatic hyperplasia or neoplasm [98]. Therefore, the pro-inflammatory cells and mediators in periodontal disease result in cellular proliferation, angiogenesis, mutagenesis, decrease adaptation to oxidative stress, and suppression of apoptosis [99].

Inflammatory cytokines induction in neoplastic tissue

Inflammatory mediators generated during prostatitis or in chronic inflammatory diseases in other parts of the body such as in periodontitis may promote neoplastic tissue development [5, 27, 46, 48, 50, 56, 60, 100]. These mediators may be involved in the communication between inflammatory cells and prostate tumor cells [100]. For instance, interleukin-1 (IL-1) promotes proliferation [101], growth, and progression of the prostate epithelium and connective tissue stroma [102, 103]. IL-6 is capable of manipulating neoplastic developments such as reduction of apoptosis and upturn of angiogenesis [104]. In addition, IL-6 and TNF-alpha enhance proliferation and promote survival signal for different cancer cell types, including neoplastic prostate cell lines [51]. Nelson et al. (2004) suggested that these cells may influence the development of neoplasm [105]. In prostate cancer, both TNF-alpha and IL-6 serum levels are elevated and correlate to advanced-stage disease and decreased patient survival [106].

Conclusions and future directions

Periodontal disease appears to be associated with prostate cancer. To date, there is no definite mechanism(s) that can explain this relationship. It is hypothesized that this association might be influenced by periodontal pathogens and/or periodontitis inflammatory mediators. The host response to periodontal pathogens and/or any infectious agents could contribute to an exacerbated inflammatory response and PIA/PIN in the prostate that may progress to cancer. In addition, certain periodontal pathogens are associated with prostatitis. These pathogens may be migrating from the periodontium to the prostate gland through the bloodstream and contributing to prostatic inflammation and cancer development (**Figure 1**). Further studies are warranted to better characterize the role of periodontal pathogens in initiating malignancy in the prostate gland.

Disclosure of conflict of interest

None.

Abbreviations

PD, Periodontal Disease, Prostate disease; PIA, Proliferative Inflammatory Atrophy; PC, Prostate cancer.

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