PERIODONTAL DISEASE AND CANCER: WHAT IS THE RELATIONSHIP?

DOENÇA PERIODONTAL E CÂNCER: QUAL A RELAÇÃO?

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Resumo
A Doença Periodontal (DP), caracterizada por uma inflamação crônica associada a um quadro de disbiose, foi relacionada a diversas patologias no organismo humano. Estudos recentes revelam uma forte associação entre a DP e o câncer. O objetivo deste artigo foi realizar uma revisão narrativa de literatura sobre a relação entre ambas as doenças. Uma pesquisa foi executada nos bancos de dados Biblioteca Virtual em Saúde (BVS), PubMed e Wiley Online Library; com os descritores em saúde (DECs): “Doença Periodontal” e “Carcinogênese” e “Neoplasma”, e seus correspondentes em inglês, “Periodontal Disease” and “Carcinogenesis” and “Neoplasm”. Os critérios de inclusão foram artigos completos publicados em inglês, português e/ou espanhol de 2010 a 2020, resultando em 22 artigos. Verificou-se que, embora o processo inflamatório decorrente da DP ocorra de forma local na cavidade oral, as células inflamatórias e seus produtos, os periodontopatógenos - responsáveis por essa inflamação em conjunto com a resposta imune do hospedeiro - e os componentes bacterianos podem agir no organismo em geral. As consequências são possíveis alterações no ciclo celular, na proliferação celular, na apoptose, nas respostas imunes e inflamatórias. Ademais, os patógenos periodontais são capazes de interagir diretamente com células do organismo e assim, estimular a carcinogênese, progressão tumoral e/ou metástases. Esses fatos estudados em conjunto com a epigenética têm relevado uma associação positiva entre diversos cânceres e a DP. Concluiu-se que, apesar de alguns mecanismos envolvidos na associação permanecerem incertos, os estudos epidemiológicos têm acrescentado um novo panorama para a correlação.


Abstract
Periodontal disease (PD), characterized by chronic inflammation associated with dysbiosis, has been linked to several pathologies in the human body. Recent studies reveal a strong association between PD and cancer. The objective of this article was to carry out a narrative review of the literature on the relationship between both diseases. A search was performed in the Virtual Health Library (BVS), PubMed and Wiley Online Library databases, with the health descriptors (DECs) in Portuguese: “Doença Periodontal” and “Carcinogênese” and “Neoplasma”, and their correspondents in English, “Periodontal Disease” and “Carcinogenesis” and “Neoplasm”. The inclusion criteria were complete articles published in English, Portuguese and/or Spanish from 2010 to 2020, resulting in 22 articles. It was found that, although the inflammatory process resulting from PD occurs locally in the oral cavity, the inflammatory cells and their products, the periodontopathogens — responsible for this inflammation together with the host’s immune response — and the bacterial components can act on the organism in general. Consequences are possible changes in the cell cycle, cell proliferation, apoptosis, immune and inflammatory responses. In addition, periodontal pathogens are able to interact directly with cells in the body and thus stimulate carcinogenesis, tumor progression and/or metastasis. These facts studied in conjunction with epigenetics have revealed a positive association between several cancers and PD. It was concluded that, although some mechanisms involved in the association remain uncertain, epidemiological studies have added a new panorama for the correlation.

Keywords: Neoplasm, Carcinogenesis, Periodontal disease.
INTRODUCTION

Periodontal disease (PD) is characterized by a chronic inflammatory process, produced by a complex interaction between the pathogenic stimulus (a bacterial community) and the host's response, and affects the tissues surrounding and supporting the teeth (1-3). This pathology includes gingivitis and periodontitis, in addition to being highly prevalent in the population (4).

Although inflammation occurs locally in the oral cavity, periodontal pathogens and their components, as well as inflammatory cell products, can spread to the systemic level and contribute to the emergence and progression of various diseases, for example, cardiovascular disease and diabetes (1). Recent studies have pointed to an association of this persistent inflammation and periodontopathogens with premalignant lesions and cancer, both in oral cancer and in other specific cancers (1,3,5). Cancer is characterized by the growth and proliferation of abnormal and undifferentiated cells (6).

The main reported periodontopathogens that are involved in the process of induction and progression of carcinogenesis are Porphyromonas gingivalis (Pg) and Fusobacterium nucleatum (Fn). Both are anaerobic and Gram negative bacteria, often found in oral biofilm, characterized by their virulence factors such as lipopolysaccharide (LPS), fimbria and cell wall. These opportunistic pathogens are mainly comprised in the most aggressive forms of periodontal disease. Recent studies indicate tumorigenic stimulation and pre-tumor cells as an influence of infection (7-10).

The possible bacterial mechanisms related to PD emphasize microbial colonization itself, systemic dissemination throughout the organism and induction of host inflammatory responses, which are the main factors of the positive association with cancer. Thus, recent studies involving epigenetics have been explored to fill this gap in the understanding of mechanisms that govern this association (6,10).

Malignant neoplasms of the oral cavity and oropharynx are the most widely explored in relation to associations with PD. However, the influence of periodontal disease at the systemic level was also observed, as in cancers of the digestive tract (esophageal cancer, gastric cancer, pancreatic cancer and colorectal cancer), breast, lung, gallbladder, bladder, hematologic and melanoma (1,3,5,11).

The aim of this study was to conduct a review of the existing literature on the relationship between periodontal disease and cancer, both in the oral cavity and in the systemic scope.

LITERATURE REVIEW

An advanced bibliographic search was performed in the Virtual Health Library (BVS), PubMed and Wiley Online Library databases. Complete articles related to the theme of cancer and Periodontal Disease, published between 2010 and 2020, in English, Portuguese and/or Spanish were selected. The health descriptors (DECs): “Doença Periodontal” and “Carcinogênese” and “Neoplasm”, and their correspondents in English, “Periodontal Disease” and “Carcinogenesis” and “Neoplasm”. The search resulted in 49 articles read in full, 22 of which were included in this review. Of the selected articles, there were 12 reviews of narrative literature, 3 systematic reviews, 4 experimental studies and 3 cross-sectional studies. The 27 excluded articles did not cover all the inclusion criteria previously established. In addition to the selected articles, data available on the platform of the National Cancer Institute José Alencar Gomes da Silva (INCA) were used.

The factors related to the association between cancer and periodontal disease are:

Epigenetics and Carcinogenesis

Epigenetics is described as pathological or behavioral factors that modify the activity of the gene without changing its DNA sequence, and that are capable of transmitting these characteristics to daughter cells. The main epigenetic mechanisms are methylation and acetylation of histones and DNA methylation (6,12,13).
Epigenetic events occur naturally in the body and can act on cancers and autoimmune/inflammatory diseases, favoring them. The action of periodontopathogens can promote the increase of epigenetic factors and their consequences, such as hypermethylation of interleukin 12A, toll-like receptor 2, MALT1, TNF-α, COX-2 and hypomethylation of STAT5, ELA2, IL-8 and IL-6. Thus, they directly impact the host’s innate and adaptive immune response, which makes it more susceptible to the severity and progression of PD and to the induction and/or progression of malignancy (6,12,13).

Carcinogenesis or oncogenesis is the process of cancer formation that occurs due to changes in the genetic material, which results in changes in cellular functioning. Epigenetics is directly related to carcinogenesis because it is involved in the expression and suppression of some genes. This process consists of three stages: Initiation Stage, Promotion Stage and Progression Stage, which occur slowly and gradually, allowing for adequate control through early diagnosis and treatment. Oncoaccelerating agents stimulate the mutated cell growth rate and oncogenesis progression. Among these, we can highlight alcohol, lack of healthy food, viruses and bacteria, in addition to smoking, considered a complete carcinogen because it acts in the three carcinogenesis stages (13-15).

The pathogenesis of cancer is the result of the deregulation of signaling of pathways that act directly on oncogenesis, by inactivating the tumor suppressor gene. These are genes whose products control cellular functions, suppressing tumorigenic effects, and changes in the loss of function that can contribute to the cancer formation (11,15). One of the possible pathways for cancer induction is chromosomal instability, due to the accumulation of modifications in the gene performance, or structural, which lead to the loss of suppressor genes and the activation of oncogenes (10,15). The inactivation of tumor suppressors P53 and CDK-N2A and molecular dysregulation as a result of carcinogens play a significant role and are often found in oral cancer. In addition, there is an increase in the expression of pro-inflammatory cytokines such as TNF-α, IL-6, IL-1β, Rank-I and IL-1 that act in immune defense, initiation of immune responses, osteoclastogenesis and activation of other immune cells as neutrophils and B cells (11,16).

Carcinogenesis has common characteristics (of molecular basis) in all its cells, regardless of the origin and type of cancer, which are called the fundamental points of cancer. Currently, there are eight characteristics described: self-sufficiency capacity, insensitivity to signs of stopping proliferation, avoidance of apoptosis, unlimited replicative potential, sustained angio-
genesis, invasion and metastasis capacity, cellular energy metabolism dysregulation and the immune system escape. In addition, two more characteristics are pointed out that allow the formation of the fundamental points of cancer: genomic instability and mutation; and inflammation. Cytokines lead to the formation of an inflammatory microenvironment (it can also be formed by periodontopathogens) that promotes changes in gene expression and, consequently, changes in tumor and oncogene suppressor pathways (10,11,15). In situations of poor oral hygiene, in addition to favoring PD and the inflammatory state, there may be an increase in the production of carcinogenic compounds, such as nitrosamine, which has been associated with stomach and esophageal cancer (5).

**Inflammatory process**

Since the 19th century, it has been possible to associate inflammation with cancer, based on the findings of the physician Rudolf Virchow, who noticed an infiltration of leukocytes in the tumor microenvironment and thus proposed that the chronic inflammatory process could boost the cancer development (16).

Inflammation is a defense mechanism of the organism triggered by tissue damage or an infectious agent (4). The inflammatory response can be divided into four stages: innate inflammatory response, initial inflammatory response, acute inflammatory response and chronic inflammatory response (13). The innate inflammatory response is responsible for recognizing pathogen-associated molecular patterns (PAMPs). This response has the presence of macrophages, neutrophils, dendritic cells and natural killer cells (NK), and Toll-like receptors (TLRs) and nucleotide-binding oligomerization are also involved. During the initial inflammatory response, molecules such as prostaglandins and cytokines act by regulating vascular permeability, which facilitates the recruitment and arrival of inflammatory cells to the site. In contrast, when the acute inflammatory response reaches a chronic inflammatory stage, more severe tissue damage is promoted (13).

The chronic inflammatory process in the oral cavity, generated by PD, allows the creation of the chronic inflammatory microenvironment, which is responsible for causing a disturbance of the cell cycle and, thus, a continuous stimulation of cell proliferation and rapid cell division, which can cause errors in the DNA replication and repair process (8,11). In addition, inflammation can generate free radicals and active intermediates that, from oxidative and nitrosative stress, can cause several mutations in DNA, in addition to DNA repair (3). The damage caused to DNA has the ability to consequently damage genes that control normal cell division and apoptosis (9). In this way, a modulatory cycle that favors the abnormal proliferation of undifferentiated cells is created. In addition, there are several other mechanisms, including the activation of infiltrating immune cells, inducing damage to genetic material through reactive and toxic products of inflammatory cells and increased levels of bioactives derived from immunocompetent lymphocytes (8). Inflammatory activity and therapy can be modulated by genetic polymorphisms and epigenetic changes, as they promote disturbances in the innate and adaptive immune response (13).

Periodontopathogens associated with periodontitis contribute to the inflammatory process by activating pathways and releasing specific factors (1). In the most severe forms of PD, a significant inflammatory load is established in the body, mainly in the blood and saliva. There is an increase in systemic markers of inflammation, such as C-reactive protein, interleukins (IL-6) and tumor necrosis factor-alpha (TNF-α) in plasma (17). Thus, the instability generated by constant cell renewal, the presence of inflammatory cells themselves, mediators (cytokines, chemokines and prostaglandins) and free radicals contribute to carcinogenesis and tumor development (4,5). Inflammatory mediators are capable of stimulating transcription factors, such as STAT-3, AP-1 and NF-κB (nuclear transcription factor kappa-B). These proteins can activate oncogenesis and new inflammation products, such as cytokines (4). In addition, myeloperoxidase and superoxide dismutase, which participate in the regulation of inflammation, are found in a high form in periodontitis. Phenotypic variations in the genes encoding these enzymes have been associated
with an increased risk of pancreatic and gastric cancer. The pro-inflammatory expression of receptors for advanced glycation end-products (RAGE) is associated with esophagus, stomach, colon, biliary, pancreatic and prostate cancers (5).

**Pathogenic microbiota**

Naturally, the mouth is inhabited by a complex and highly variable microbial community that is in an immune-inflammatory state balanced between itself and the host. However, certain bacterial species can disturb the balance and thus result in dysbiosis. The imbalance generated in conjunction with the host’s unregulated immune response causes PD (5,8).

Among the main species known for involvement in PD, *P. g* and *F. n* have been studied in the pathogenesis of several chronic diseases, as well as several types of malignancies (8). These opportunistic, invasive, anaerobic, gram-negative and pro-inflammatory bacteria are largely directly related to oral, oropharyngeal, esophageal, gastric, pancreatic and colorectal cancer (5,9,10,17-19). It is important to note that the risks are higher in certain anatomical sites than others, in particular those closest to the oral cavity (3).

Periodontal pathogens migrate from the oral cavity to distant locations and can adversely affect general health (11). The dissemination of these oral bacteria to the circulation occurs after simple daily activities, such as brushing teeth, flossing and chewing, and also through therapeutic procedures performed by the dentist. Ingestion of saliva is the main explanation for the involvement in the oro-digestive tract and the presence of a distinct microbiome in the lungs originating from oral microorganisms sown through the oral fluid microaspiration (1,2). *P. g* is able to survive in the host’s blood and tissue, which has already been found in the heart, liver, kidney and spleen (5). In comparison, *F. n* has been described as present in the intestine and pancreas (8,9,11).

The toxic effects and carcinogenic metabolic by-products of periodontal disease are the main links with the process of carcinogenesis and tumor progression (11). The main virulence factors of these periodontal pathogens are LPS, proteases, fimbriae and nucleoside diphosphate kinase (NDK) (5,7). In addition, there is a unique virulence factor and potential diagnostic marker expressed in *F. n* - FadA adhesin -, which is responsible for allowing *F. n* to bind with epithelial cells and their subsequent invasion of endothelial cells (10,11).

Recently, *F. n* has been directly related to colorectal cancer by increasing the signaling of the WNT pathway, pro-inflammatory cytokines, oncogenes and stimulating the proliferation of cells responsible for this type of cancer (10,11). It has been reported that *F. n* can act in two possible ways: by attracting tumor-infiltrating myeloid cells and thus creating a pro-inflammatory environment; another route is through the modulation of the anti-tumor immune system. *F. n* showed the ability to expand myeloid cells derived from the immune system, such as Treg cells that promote tumor progression (3).

In addition, these periodontopathogens can stimulate carcinogenesis via direct interaction with cells, activating the innate immune response through the activation of TLRs - via TLR2 and TLR4. TLRs correspond to a group of receptors that are part of Pattern Recognition Receptors (PRRs), which recognize PAMPs and damage-associated molecular patterns (DAMPs). TLRs play an important role in innate immune signaling in response to microbial infection, and these receptors are expressed in different parts of the body, such as epithelial cells in the oral cavity, and also appear to be expressed in tumor cells. LPS - a PAMP - of these pathogens can specifically activate the host’s response through TLRs, which are able to inhibit apoptosis and promote tumor growth and angiogenesis (1,5,8,18). The recent role of epithelial TLR2 has been demonstrated in the progression of non-oral carcinomas - in bowel and breast cancer (1).

*P. g* and *F. n* can activate the NLRP3 inflammasome through the recognition of PAMPs by TLRs and then induce DAMPs as the adaptation protein ASC and HMGB1 (high mobility group 1 protein) which is an inflammatory me-
Diactor. This protein can activate cells through TLRs and RAGE. Overexpression of HMGB1 is noticeable in colorectal, pancreatic, breast, melanoma and even prostate cancer. The activation of the NLRP3 inflammasome culminates in the cleavage of pro-caspase 1 into caspase 1, which in turn cleaves Gasdermin D which promotes the formation of pores in the cell membrane, consequently the extracellular release of IL-1β and pyroptosis, and cleavage of pro-IL-1β in active IL-1β, which induces pyroptosis. Through the release of extracellular IL-1β, TNF-α levels are high, being one of those responsible for alveolar bone resorption, this damage to bone tissue can be highlighted (1,8,9,20,21).

Pg acts in anti-apoptotic pathways, which reduces the expression of pro-apoptotic proteins and blocks apoptosis through its LPS, modulating the intrinsic cell death pathway. This mechanism is strongly associated with gastroesophageal cancer. In addition, NDK, Fim A fimbria and Pg membrane LPS act in the early stages of carcinogenesis, while proteases (gingipains) and the "GroEL" protein are associated with later stages. NDK acts to inhibit apoptosis in cells by inhibiting ATP/P2X7 cell death signaling, while FimA is able to attenuate host p53-mediated tumor suppression and cell cycle progression. The joint action of these virulence factors is capable of controlling the epithelial-mesenchymal transition (1,21,22).

Oral Squamous Cell Carcinoma (SCC) is a malignant neoplasm that affects the oral cavity, and may occur on the tongue, buccal mucosa, retromolar area, buccal floor, palate, lip and gums (1,9). Infection with Pg and Fn directly affects the progression of this type of cancer through signaling in the TLR, resulting in increased signaling of the IL-6-STAT3 axis (pro-inflammatory cytokines) and thus inducing factors capable of directing SCC invasiveness and growth. In addition, the proteases of these periodontal pathogens activate NF-κB in oral squamous cell carcinoma, being important for metastatic cases (1,9,11,23). From a metatranscriptomic analysis cited by Hoare et al. (2019), although both Pg and Fn were active in sites with oral squamous cell cancer, only Fn showed a significant difference in transcription activity (1). Thus, the indication is that the species have different roles in the stages of tumorigenesis, or that the interactions that occur close between the species of pathogens in the tumor tissues are capable of modifying the expression of genes from each other (1).

Other pathogens, such as Prevotella intermedia, Campylobacter rectus and Tannerella forsythia, have been associated with the carcinogenesis process. However, this association still needs further studies (10).

**DISCUSSION**

This study showed that there is a relationship between PD and both oral and systemic cancer. The general understanding of this association remains evolving, that is, the mechanisms of cancer induction and progression due to periodontal disease have not yet been fully elucidated. From the epidemiological results together with the epigenetic understanding, it was observed that the periodontopathogens and the inflammatory state directly contribute to the strengthening of this association.

Although PD has been linked to cancer in several studies, some authors remain with uncertain results for the relationship of PD with some specific types of cancers, such as breast and lung cancer (3,4). According to studies cited in Güven et al. (2019), PD was responsible for an increase ranging from 13% to 23% in the total risk of cancer (17). Studies related to the association with head and neck cancer - including cancer of the mouth and oropharynx - and digestive tract (esophageal, gastric, pancreatic and colorectal cancer) provide consistent support in individuals with PD (3-5,7, 8,16). The main evidence comes from researches that evaluated periodontopathogens that play a key role in cancers of the digestive system (5,9,10,17-19). With the control of relevant confounding factors in PD, a three times greater risk of esophageal cancer was observed in individuals participating in the Women’s Health Initiative-Observational Study (3). Furthermore, a European study by Michaud et al. (2013) cited
by Michaud et al. (2017) showed that high levels of antibody to Pg were associated with a 2-fold higher risk of pancreatic cancer (4). In addition, the association between pancreatic cancer and PD was observed in individuals who never smoked, which may be an indication that, regardless of smoker status, the correlation is positive (3). However, when assessing the correlation through tooth loss, these associations were not consistent (5). Nwizu; Wactawski-Wende; Genco (2020) point to the absence of any association between PD and colorectal cancer (3). However, two other studies report Fn as being associated with colorectal cancer (10,11).

Regarding lung cancer, the correlation with PD was significant, but because smoking and alcoholism are risk factors for both pathologies, there are still many doubts about the action of these factors in the relationship, which may be residual confounding factors. However, it is biologically acceptable that both smoking and PD can act together to increase the risk of this cancer (2-4,16,17).

In the case of breast cancer, there is a scarcity of studies related to PD and very varied and conflicting results (3,4,17). Although PD has been linked to breast cancer through evidence - the risk of breast cancer in patients with PD has increased more than twice -, some authors indicate that the results showed no significant correlation with the prevalence of this cancer (3,5,8,16,17).

The fact that PD manifests in different ways, depending on the stage, degree and extent/distribution, and the heterogeneity of the PD evaluation parameters creates a complex study scenario, since the most relevant measures to relate to the risk of cancer (4,5). Some articles took into account...
tooth loss - number of teeth lost - and its association with certain types of cancer, such as oral cancer (3-5). Given that people can lose teeth for reasons other than PD, it is likely that the evaluation using only this data can be considered incomplete (4). In addition, smoking and alcohol consumption can be factors of residual confusion, or capable of generating modification of effects in the association of PD with cancers (3,4). Methodological differences, such as sample size, sociodemographic differences and the classification of periodontitis, could explain the discrepancies and the varied results.

In short, further studies are needed to explore other mechanisms of pathogenic action and new parameters for carrying out the analyses (3-5,17). Therefore, there is a clear need for additional efforts to clarify the correlation in all cancers mentioned above.

CONCLUSION

Epidemiological studies point to an association between periodontal disease and cancer, showing places of greater possibility, especially closer to the oral cavity. Although many mechanisms remain uncertain, epigenetic events, the inflammatory process and the action of periodontal bacteria seem to influence carcinogenesis, cell transformation and tumor progression.

The authors declare no conflict of interest.

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