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Chronic periodontitis as a risk factor for breast cancer: An update

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Abstract

Breast cancer is the second-most common malignancy affecting one in every eight women worldwide. Common risk factors for breast cancer include endogenous hormone levels, immune factors, genetic susceptibility, lifestyle, chronic infection, and inflammation. Periodontitis is a chronic infecto-inflammatory disease of tooth-supporting tissues which, if not treated, ultimately results in loss of the tooth. It is a well-known fact that the inflammatory component present in periodontitis can be involved in the initiation or progression of many systemic diseases, including cancer. There is less evidence to confirm the fact that periodontitis can also lead to breast cancer also. This evidence-based short review presents a brief note on the mechanisms of links between chronic periodontitis and breast cancer.

Keywords: Breast cancer, periodontitis, inflammation, poor oral hygiene

1. Introduction

Cancer is one of the most common causes of human mortality worldwide. In developed countries, fifty-five percent of the disease burden is associated with cancer^[1, 2]. Breast cancer is the most common malignancy in women affecting more than 1.3 million people every year globally. According to a report by World Health Organization, the incidence of breast cancer varies from 19.4 to 89.7 per 1,00,000 women^[3]. Common risk factors for breast cancer include endogenous hormone levels, immune factors, genetic susceptibility, lifestyle habits, chronic infections, and inflammation. Periodontal disease or gum disease, more specifically periodontitis, on the other hand, is the sixth-most prevalent disease worldwide. It is a chronic condition that is considered as a complex, multifactorial, infecto-inflammatory disease of the tooth-supporting tissues which, if left untreated, results in loss of connective tissue and alveolar bone surrounding the teeth ultimately causing loss of teeth. It has been found that chronic periodontitis is associated with an increased risk of many systemic diseases like cardiovascular diseases, cerebrovascular attacks, diabetes, respiratory disorders, etc. While there has been less study on the association of the periodontal disease with cancer, there is evidence that those with periodontal disease are at increased risk of developing cancer^[4]. Recently, periodontal health status has been identified as a risk factor for breast cancer too. In a meta-analysis, Shao *et al.* have concluded that periodontitis can be an important risk factor for the initiation, development or progression of breast cancer^[5]. Sfreddo *et al.* conducted a case-control study and concluded that the women diagnosed with periodontitis had two to three times higher odds of breast cancer than those without periodontitis^[6]. Therefore the purpose of this evidence-based minireview was to present a brief note on the possible mechanisms of links between chronic periodontitis and breast cancer.

2. Inflammation as a key-factor

Multiple possible mechanisms behind the association between periodontal disease and cancers have been proposed, and the most widely accepted theory is the alteration of the oral flora and subsequent influx of the inflammatory components into the systemic circulation, which could act as a procarcinogen at distant sites. Chronic periodontitis is characterized by polymicrobial infection and inflammation of the periodontium that results in loss of connective tissue and

Alveolar bone surrounding the teeth. Periodontal inflammation promotes systemic inflammation via translocation of oral bacteria, bacterial toxins, and inflammatory mediators like Prostaglandins, Cytokines, Interleukins. This transient bacteremia could promote cellular differentiation seen in the process of oncogenesis [7]. The subgingival biofilm of breast cancer patients were found to be colonized predominantly by Gram-negative species like *Porphyromonas gingivalis*, *Tannerella forsythia*, *Fusobacterium*, *Prevotella*, *Actinomyces*, etc. and few of Gram-positive bacterial species like *Streptococcus*, *Staphylococcus*. All of these microorganisms are considered as potent periodontopathogens. Therefore, an indirect pathway from periodontitis and breast cancer could be hypothesized and the chronic inflammation resulting from this periodontal infection can be one of the risk factors for the development and/or progression of breast cancer. The presence of lipopolysaccharides (LPS) in Gram-negative bacteria can cause chronic inflammation which may be a potential candidate to connect periodontitis with breast cancer. According to Mager *et al.* [8], estimates have indicated that over 15% of malignancies worldwide could be related to infections. Therefore, this oral bacterial dysbiosis can increase the expression of virulence factors leading to an inflammatory status in the host and produce chronic inflammation through different pathways. Activation of the Caspase-1 Inflammasome is an example of such a pathway. Inflammasomes are multiprotein complexes localized within the cytoplasm of the cell [9]. According to Karki *et al.* [10], excessive inflammation driven by the Inflammasome or the interleukin-1 (IL-1) signaling pathway can promote breast cancer, gastric carcinoma, fibrosarcoma, and lung metastasis. Kolb *et al.* [11] also reported that Inflammasomes mediate the expression of adipocyte-mediated vascular endothelial growth factor A (VEGF-A), and accelerates the progression of breast cancer. Recently, it was found that *P. gingivalis* and *F. nucleatum* [9] have the ability to develop different mechanisms in Inflammasome activation and function, and therefore this systemic inflammation could indirectly contribute to chronic diseases, including breast cancer. Moreover, existing data revealed a significant increase in the prevalence of periodontal diseases among females during different stages

like puberty, menstruation, pregnancy, menopause, etc. [5] and periodontal disease in women has been found to be positively associated with autoimmune diseases, infertility disorders, adverse pregnancy outcomes, preterm birth, and low birth weight and breast cancer [5]. Interestingly, since the breast is made up of fatty tissue with extensive vasculature and lymphatic drainage, the concept that it can be a favorable environment for the growth of disease-associated bacteria cannot be denied [12].

3. Role of viruses

Human cytomegalovirus (HCMV), Human papillomavirus (HPV), Herpes Simplex Virus (HSV), Epstein-Barr virus (EBV), and HCMV-EBV co-infection seems to be closely associated with disease-active periodontitis. Infection by HCMV or EBV or HSV seems to inhibit the macrophages, which respond to the microbial challenges, and thus have a pathogenic role in the development of periodontal disease [13]. Though the exact mechanism of how viral infections can initiate breast cancer is still unknown, infections originating from HPV or HCMV seem to be closely associated with breast cancer as well, as shown in a recent meta-analysis [14].

4. Role of poor oral hygiene

Poor oral hygiene may not be a direct causative agent for carcinogenesis, but it certainly catalyzes the process by increasing the carcinogenicity of known carcinogens. Lack of oral hygiene maintenance leads to the accumulation of microorganisms which, with time, shifts the commensal oral microflora towards a pathogenic one, ultimately initiating the process of chronic periodontitis. Translocation of microorganisms from this local subgingival area to distant sites can initiate or promote carcinogenesis. Factors contributing to poor oral hygiene include irregular teeth brushing habits, less number of dental visits, poor socioeconomic status, lower level of education, tobacco chewing and alcohol consumption, etc. [15].

5. Common microbiological profile

Common microbiological profile between breast cancer and periodontitis [16] is shown in Table 1.

Table 1: Microbiological profile in Breast cancer and Periodontitis. BRER- Endocrine Receptor (Estrogen, Progesterone) positive, BRHR- Human Epidermal Growth Factor Receptor-2 (HER-2) positive, B RTP- Triple positive (Estrogen, Progesterone, HER-2), BRTN- Triple Negative.

Type of microorganism	Name of the species	Type of breast cancer	Association with Periodontitis (+ = Positive association)
Bacterial signature	<i>Bifidobacterium</i>	BRER	+
	<i>Streptococcus</i>	BRHR	+
	<i>Bordetella</i> ,	BRHR	+
	<i>Mycoplasma</i>	BRTN+BRER	+
	<i>Legionella</i>	B RTP	+
	<i>Chlamydia</i>	B RTP	+
	<i>Campylobacter</i>	B RTP	+
	<i>Fusobacterium</i>	BRER+BRHR	+
	<i>Escherichia</i>	BRHR	+
	<i>Staphylococcus</i>	BRHR+B RTP+BRER	+
	<i>Actinomyces</i>	BRER+BRHR+B RTP+BRTN	+
Viral signature	<i>Papillomaviridae</i>	BRER+BRHR+B RTP+BRTN	+
	<i>Herpesviridae</i>	BRER+BRHR+B RTP+BRTN	+

6. What does the evidence say? (Table 2)^[4, 5]

Table 2: Studies on the association of breast cancer and periodontitis. (OR= Odd's Ratio, RR= Relative Risk, HR= Hazard ratio)

Author	Year	Type of study	Result
Hujoel	2003	Epidemiologic follow-up	Significantly increased risk of Breast cancer (OR= 1.32) in the patients clinically diagnosed with periodontitis
Arora M	2010	Prospective co-twin	Significantly increased risk of Breast cancer (HR= 1.12) in patients with self-reported periodontal disease
Soder B	2011	Prospective	Significantly increased risk of Breast cancer (OR= 13.08) in the patients clinically diagnosed with periodontitis
Freudenheim	2015	Prospective cohort	Significantly increased risk of Breast cancer (HR= 1.14) in patients with self-reported periodontal disease
Chung SD	2016	Retrospective cohort	Significantly increased risk of Breast cancer (HR= 1.23) in the patients clinically diagnosed with periodontitis
Mai X	2016	Prospective cohort	Significantly increased risk of Breast cancer (HR= 1.15) with increasing loss of height of crest of alveolar bone
Dizdar O	2017	Retrospective cohort	Significantly increased risk of Breast cancer (RR= 2.40) in the patients clinico-radiographically diagnosed with periodontitis
Nwizo NN	2017	Prospective cohort	Significantly increased risk of Breast cancer (HR= 1.13) in patients with self-reported periodontal disease
Sfreddo	2017	Case-control	Significantly increased risk of Breast cancer (OR= 2.72) in the patients clinically diagnosed with periodontitis
Michaud DS	2018	Prospective cohort	Significantly increased risk of Breast cancer (HR= 1.32) in the patients clinically diagnosed with periodontitis
Heikkila P	2018	Prospective cohort	Significantly increased risk of Breast cancer (RR= 1.19) with increasing Periodontal Pocket depth (PPD)

7. Conclusion

In summary, the current literature shows a strong degree of evidence of association with periodontal disease with breast cancer. It also proves that women with periodontitis are at higher risk for breast cancer than women without it. Given the evidence to date, it would be beneficial to the dental provider to be aware of the real potential that periodontal disease may exist as a risk factor for many forms of malignancy. Thus it may be of real benefit to patients exhibiting periodontal disease to consider several steps to reduce the risk levels for cancer. This may include a more frequent periodontal recall schedule to keep the level of disease and inflammation to a minimum and stressing the importance of maintaining regular dental visits and meticulous oral hygiene. However, additional studies are needed to explore these suggested associations. Consistent and standardized criteria periodontal disease and consistent rigorous control of the confounding factors such as smoking and alcohol use will be helpful in establishing a definitive link between periodontal disease and cancer. Nonetheless, this review could be helpful in increasing awareness regarding the importance of oral health maintenance, which may lead to reduced risk, morbidity or mortality of breast cancer.

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