



Breast Cancer and its Treatment: Impact on Oral Health. A Traditional Review

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Abstract

Background: Oral diseases should be considered potentially associated with systemic diseases. Several systemic diseases, including oncological ones, must be taken into consideration by dentists since they can be intercepted early by the dentists themselves and the repercussions of many systemic diseases and their therapies on oral cavity are widely demonstrated.

Objectives: The purpose of this review is to investigate the relationship between the breast cancer and the changes that can occur at the oral level, both alterations of the oral microbiome and pathological conditions. We also want to investigate how breast cancer therapies can affect patients' oral health.

Materials and Methods: The purpose of this review is to investigate the relationship between the breast cancer and the changes that can occur at the oral level, both alterations of the oral microbiome and pathological conditions. We also want to investigate how breast cancer therapies can affect patients' oral health.

Results: The data seem to suggest a correlation between breast cancer and periodontal disease. The effects of therapy for breast cancer on the oral cavity are remarkable: chemotherapy induces an increased risk of caries, dysgeusia, bone loss and mucositis may appear. There was also an important alteration of the oral microbiome in patients receiving chemotherapy.

Conclusions: From this review the importance of dentists is clear in proposing to patients with breast cancer appropriate therapies and dedicated prevention sessions. Appropriate oral hygiene (both professional and domiciliary), a proper diet and the use of artificial saliva may reduce the risk of developing oral complication resulting from breast cancer.

Keywords: Breast Cancer; Impact; Oral Health

Introduction

It is now proven that oral diseases are associated with systemic diseases. The interactions that develop between the oral cavity and the rest of the organism are multiple and very complex. More than 120 medical conditions, some of which are life threatening can be detected and treated in the early stage by dentists [1].

Several studies have shown a close relationship between chronic inflammatory diseases and the development of tumors [2].

Inflammation is a crucial aspect in chronic conditions, such as in periodontal disease [3], but it is also central for tumors, since in these there is an inflammatory microenvironment [4]. Therefore, inflammation is the starting point for understanding the link

between breast cancer and diseases of dental interest such as periodontitis.

In this traditional review we will investigate in particular the link between breast cancer and oral health and microbiome. One of the most common oral disease is periodontitis which is characterized by chronic infection and inflammation in periodontal tissue leading to destruction of the bone surrounding the teeth. Periodontal disease is initiated by a biofilm of bacteria on the teeth which trigger an immune-inflammatory response in the adjacent host tissues [5].

On the other hand, it is also important to investigate the influence of breast cancer therapy on oral health. In fact, there are

several repercussions that these treatments can cause in the oral cavity, so it is essential to know them to adopt a correct treatment plan for post-cancer patients.

Prevalence of breast cancer

Breast cancer is the most common cancer diagnosed among women in the United States, accounting for nearly 1 in 3 cancers. It is also the second leading cause of cancer death among women after lung cancer [6]. Over 200,000 women are diagnosed with breast cancer in the U.S. annually. Breast cancer occurs more frequently in post-menopausal women and the median age at diagnosis is 61 years. The etiology of most breast cancers is unknown. However, some risk factors have been established like gender, age, family history, late menopause, early menarche, ethnicity and genetic risk factors [7].

Breast cancer is by no doubt a very serious and widespread problem, for this reason it is important to evaluate if there is a correlation between oral pathologies and this type of tumor to have a further defense against this pathology. On the other hand, an important decrease in mortality due to breast cancer has been observed in recent years thanks to the development of new adjuvant therapy and screening programs [8]. This involves the need to control possible reactions of the organism to therapy; in the article we analyze this interaction at the level of the oral cavity.

Periodontitis and breast cancer

Periodontal disease is characterized by chronic infection and inflammation in periodontal tissue leading to destruction of the bone surrounding the teeth.

The interaction between breast cancer and periodontitis has been widely investigated by several works.

In 2011, Söder, *et al.* conducted a prospective study of 3273 women randomly selected between the ages of 30 and 40 for a period of about 16 years. The study showed that women with experience in periodontitis and with missing molars have a higher risk of developing breast cancer [9].

The work of Virtanen, *et al.* 10 of 2013 examined the association between periodontitis and breast cancer risk by recruiting 286 subjects with periodontal disease in 1985: in 2009, 6.3% of these had cancer. Moreover, it was observed that the risk is greater if the first mandibular molar was missing, compared to the second mandibular molar.

This association also seems to be confirmed by a study by Freudenheim, *et al.* [11], in which the risk of breast cancer among more than 93,000 postmenopausal women with a history of periodontitis has been increased, especially in former smokers who quit in the previous 20 years. But periodontal disease increases the risk of breast cancer regardless of smoking [12].

Sfreddo, *et al.* [13] wanted to evaluate the linkage between periodontitis and breast cancer in a sample of adult Brazilian women. They observed that cases had significantly greater clinical attachment loss than controls. Women diagnosed with periodontitis had two to three times higher odds of breast cancer than women without periodontitis. They conclude that a significant association was observed between periodontitis and breast cancer.

Meanwhile Taichman, *et al.* [14] conducted a population-based analysis, that examined the prevalence of periodontal diseases along with the self-perceived oral health and patterns of dental care utilization of breast cancer survivors in the United States.

They observed in this sample that a history of breast cancer does not significantly impact periodontal health, self-perceived oral health, and dental care utilization.

We report two systematic reviews researched on PubMed by writing the key words 'periodontitis breast cancer'.

Shi, *et al.* [15] in a Meta-analysis of Eight studies, with 168,111 individuals, explored the connection between periodontal disease and breast cancer. They showed that periodontal disease did increase susceptibility to breast cancer (RR = 1.18, CI 95%: 1.11–1.26) with robust results confirmed by sensitivity analysis.

In this other systematic review, Corbella, *et al.* initially examined just under 500 articles to understand the role of periodontitis in cancer development in various sites, including breast cancer. There was an association between periodontal disease and the breast neoplasm (RR = 1.11; CI 95%: 1.00-1.23).

Amodio, *et al.* [16], unlike the studies previously taken into consideration, conducted a matched case-control study in which they assessed the prevalence of periodontal disease in 48 postmenopausal patients after cancer treatment, compared to 48 controls without cancer. They detected a high prevalence of periodontitis in postmenopausal survivors: 98% in breast cancer survivors and 87% in controls. However, we report that there are limitations in the design of the study as claimed by the authors themselves.

The results found are therefore oriented in two directions: on the one hand, periodontitis, in affected patients, leads to an increased risk of developing breast cancer; on the other hand, in patients suffering from cancer, after the treatment of cancer itself, a greater prevalence of periodontitis has been observed.

A possible explanation is that Periodontal disease is associated with an increased production of reactive oxygen species which cause damage to the host cells and tissues. The byproducts of the oral inflammation enter the bloodstream, which may enhance cellular proliferation and mutagenesis, allowing for the development and spread of cancer [17]. Some studies have also described that some polymorphisms of the TLRs (toll-like receptors) genes are associated with greater susceptibility to periodontitis [18,19], but also to several types of cancer [20,21].

It is opportune to observe how the lowering of the immune defenses, due to the tumor and its treatments, can be a factor favoring the development of periodontal disease, since this has bacterial etiology

Vargas-Villafuerte., *et al.* [22] evaluated the influence of tumor therapy on periodontal therapy: they have seen that patients who receive breast cancer chemotherapy respond less to non-surgical periodontal treatment compared to patients without cancer and therefore require further treatment. As said before, the effects of breast cancer therapy have a huge impact on the patient's oral health; therefore, an evaluation of oral health before, during and at the end of the treatment should be included in the breast cancer management protocols, so as to intercept the initial lesions and favor the patient's adhesion to the treatment.

Breast cancer treatment option

The selection of breast cancer treatments are based on many prognostic and predictive factors including tumor histology, lymph node involvement, tumor hormone receptor content, tumor HER2 status, age, patient preference and others [23]. The choice of the treatment normally depends on two main factors: menopausal status and estrogen receptor status.

Following PDQ Adult Treatment Editorial Board [24] breast cancer therapies are: Surgery, Radiation therapy, Chemotherapy, Hormone therapy, Targeted therapy.

Surgery

Most of the patients with advanced breast cancer are treated with surgery. The choice in the type of surgery depends on the stage and the spread of the tumor. The main options are:

- **Breast conserving surgery:** It consists in removing the tumor and normal tissue around it while maintaining the structure of the breast.
- **Total mastectomy:** The removal of the whole breast.

Radiation therapy

Radiotherapy is a treatment that uses high intensity x-rays to neutralize rapidly proliferating cells, thus strongly affecting the cancer cells. The radiation therapy for breast cancer is usually external with machines specialized in the emission of these rays toward the cancer. Prolonged radiotherapy can lead to the development of important lesions in the oral cavity that must be monitored and treated.

Chemotherapy

Chemotherapy consists of taking drugs that can kill or block cell proliferation. Therapy can be systemic with an oral, intravenous or intramuscular intake or regionally with local injections. Systemic therapy is the most used for breast cancer

Hormone therapy

Hormones synthesized by our body can induce a proliferation of the tumor itself. Hormone therapy aims precisely at the inhibition of these processes by acting on the endocrine system. The most used treatments are:

Ovarian ablation: It is a treatment which stops the production of estrogen by ovaries.

Tamoxifen: It is a drug which blocks the effects of the hormone estrogen in breast tissue, which reduces the growing of breast cancer cells.

Aromatase inhibitor: Used on postmenopausal women which blocks aromatase enzyme from turning androgen into estrogen.

All these therapies are fundamental and allow in many cases to greatly increase life expectancy in patients with breast cancer, but they often have important side effects, many of them in the oral cavity. It is therefore the dentist's and dental hygienist's duty to be informed about the possible side effects of these therapies in order to recognize and treat them correctly.

Oral disease induced by breast cancer therapy

Many breast cancer therapies, exerting a non-specific action on the organism, can lead to the development of oral diseases.

Surgery is a regional treatment only concerning breast, for this reason it has no relationship with possible oral lesions.

Meanwhile Chemotherapy and Radiation therapy are not tissue-specific; these therapies are therefore able to hit the cancer cells, but they also damage normal cells. Oral tissues are particularly susceptible to these therapies. In fact, there are approximately 400,000 cases of treatment-induced damage to the oral cavity [25]. Oral complications that arise with chemotherapy and/or radiation therapy include mucositis; xerostomia; bacterial, fungal, or viral infection; dental caries; dysgeusia; and osteonecrosis [26]. Chemotherapy for breast cancer is certainly more related to these lesions than Radiation therapy which is normally limited to the tumor area.

Oral mucositis

Oral mucositis is a lesion characterized by inflammation and ulceration of the mucosa with the possibility of pseudomembrane formation [27].

It is estimated that about 40% of patients treated with standard chemotherapy develop mucositis [28].

Adamietz, *et al* [29], have also reported that mucositis may be seen in nearly every patient when chemotherapy and radiation therapy are used simultaneously.

This entails an increase in hospital admittance, a higher use of parenteral nutrition and very often there is an interruption of therapy that compromises the control of the tumor. Mucositis causes 9% to 19% of chemotherapy and radiation therapy interruption [30].

Oral mucositis is a result of two major mechanisms: direct toxicity on the mucosa and myelosuppression due to the treatment. In fact, despite the pathogenesis of mucositis is not completely known it's thought to have two possible mechanisms related to cancer therapies: direct and indirect [31].

Direct mucositis

Oral mucosa cells are in rapid turnover, for this reason they are susceptible to effect of cytotoxic therapy like chemotherapy and radiation therapy.

Indirect mucositis

This mucositis is caused by myelosuppression caused by therapy, which leads to the invasion of bacterial and fungal species due to neutropenia. Chemotherapy in particular also changes the oral microbial flora, the epithelial maturation and composition of saliva, all factors that cause the development of these lesions [32].

Xerostomia and dental caries. Salivary glands are very susceptible to irradiation and chemotherapy. According to Epstein, *et al.* [33] after 1 week of RT both stimulated and resting saliva productions are decreased by 36.67% and 47.9%. Even low doses like 20 Gy can result in changes in the amount of saliva and its consistency [34].

The effect on salivary glands also depends on tumor location and technique.

The radiation therapy used for breast cancer can induce only a transient xerostomia, meanwhile the effect of chemotherapy on salivation are more severe. In addition to the changes in clearance, RT and chemotherapy cause significant changes in the oral flora with an increase in cariogenic microorganisms (Streptococcus mutans, Lactobacillus, and Candida species) [35].

It is now known that caries disease is multifactorial and closely related to the quantity and quality of saliva. In fact, saliva has a washing power and a capacity to buffer the acids produced by the cariogenic species of bacteria.

For this reason, patients undergoing chemotherapy and radiation therapy have a greater risk of caries development.

Dysgeusia

Dysgeusia is an alteration or reduction of the sense of taste. Dysgeusia or taste disorder is a common complaint among cancer patients undergoing chemotherapy. Pathophysiological mechanisms of dysgeusia during chemotherapy are explained by factors such as neurological damage in cranial nerves (VII, IX, and X) and taste buds and mucosal damage [36].

According to Ishikawa, *et al.* 43.8% of the patient included in the study undergoing cancer chemotherapy experienced dysgeusia [37].

Another study from Imai, *et al.* Dysgeusia developed in 38.8% (14/38) of chemotherapy patients [38].

Bone alterations

Breast cancer therapies deeply influence bone metabolism. This can lead to the development of bone loss or structural changes like modification to the BMD (bone mineral density).

Hormone therapy is the most related to these bone lesions. As stated by Juozaitytė, *et al.* Tamoxifen increases bone density in

post-menopausal patients but cause bone loss in premenopausal women [39].

According to Reid, *et al.* in postmenopausal women, the use of aromatase inhibitors increases bone turnover and induces bone loss at an average rate of 1-3% per year leading to an increase in fracture incidence compared to that seen during tamoxifen use [40].

Taichman, *et al.* also indicated a secondary effect of tamoxifen and aromatase inhibitors on oral mucosa like gingival inflammation, gingival bleeding, and burning sensations [41].

However, chemotherapy and ovarian ablation cause the highest levels of bone loss. For this reason, osteoporotic treatment should be associated with these therapies [39].

The changes in bone density must therefore be taken into consideration also in the case of implant and bone-regeneration dentistry by dentists.

The impact of cancer chemotherapy on the oral bacterial flora

Napenas, *et al* [42]. determined the profile of the oral bacterial flora in an outpatient cancer population before and after chemotherapy using molecular techniques.

They recruited 9 newly diagnosed breast cancer patients scheduled for induction chemotherapy. All were seen immediately before chemotherapy, and 7 to 14 days later.

They found species not previously identified in chemotherapy patients. From pre- and post- chemotherapy samples, 41 species were detected, with a predominance of *Gemella haemolysans* and *Streptococcus mitis*.

Their results suggest a shift to a more complex oral bacterial profile in patients undergoing cancer chemotherapy.

Conclusions

The carcinoma of the breast, although it affects a district other than the mouth, causes several problems at the oral level. Some of these acting in a direct way, for example through a lowering of the immune system: the risk of developing periodontal disease increases.

Breast cancer therapy also has different effects on the oral cavity that the dentists must know.

From this review, the importance of the dentist is clear in proposing to patients with breast cancer appropriate therapies and dedicated prevention sessions.

Close professional hygiene sessions can reduce the risk of developing periodontitis as the use of artificial saliva and a diet low in fermentable sugars reduces the risk of caries.

For oral mucositis, well-structured trials are needed to define the standard treatment in order to reduce pain and increase the quality of life of the patient [28].

For dysgeusia caused by cancer therapy has not yet been established a standard therapy, more studies are needed also in this field [43].

As regards periodontitis, most of the authors who have investigated the correlation with breast cancer have also said that better conducted studies would be needed, with comparable and standardized protocols and with more accurate sampling methods. This requirement is also motivated by the fact that the ODDs obtained in the various studies show a correlation, which although statistically significant, is weak.

Patients undergoing hormone therapy have the risk of developing bone loss; the dentist must know this possibility and keep the situation monitored by assessing the possible need for anti-osteoporosis therapy [39].

Chemotherapy modifies the oral microbiome of the patient: an assessment of the cariogenic species through appropriate instrumental tests can be performed periodically to investigate these bacteria early before the sign of caries can appear.

Dentist should be aware of these disorders resulting from the therapy of breast cancer, to inform patients about the alterations they might have.

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