

Correlation between bone mineral density, vitamin D deficiency, and oral health in women with breast cancer

Nicola Marotta^{1,2}, Martina Ferrillo³, Amerigo Giudice³, Lorenzo Lippi^{4,5}, Dario Calafiore⁶, Claudio Curci⁶, Mario Migliario⁷, Marco Invernizzi^{4,5}, Antonio Ammendolia^{2,8}, Alessandro de Sire^{2,8}

¹ Department of Experimental and Clinical Medicine, University of Catanzaro "Magna Graecia", 88100 Catanzaro, Italy; ² Research Center on Musculoskeletal Health, MusculoSkeletalHealth@UMG, University of Catanzaro "Magna Graecia", 88100 Catanzaro, Italy; ³ Dentistry Unit, Department of Health Sciences, University of Catanzaro "Magna Graecia", 88100 Catanzaro, Italy; ⁴ Physical and Rehabilitative Medicine, Department of Health Sciences, University of Eastern Piedmont, 28100 Novara, Italy; ⁵ Translational Medicine, Dipartimento Attività Integrate Ricerca e Innovazione (DAIRI), Azienda Ospedaliera SS. Antonio e Biagio e Cesare Arrigo, 15121 Alessandria, Italy; ⁶ Physical Medicine and Rehabilitation Unit, Department of Neurosciences, ASST Carlo Poma, 46100 Mantua, Italy; ⁷ Dentistry Unit, Department of Translational Medicine, University of Eastern Piedmont, 28100 Novara, Italy; ⁸ Department of Medical and Surgical Sciences, University of Catanzaro "Magna Graecia", 88100 Catanzaro, Italy

ABSTRACT

Breast cancer (BC) survivors treated with aromatase inhibitors (AIs) typically exhibit various pathological issues, including bone loss, poor oral health, and vitamin D deficiency. Nonetheless, chronic oral disorders are even often neglected in women with BC, and explicit indications regarding oral health screening, evaluation, and treatment to prevent cancer treatment-induced bone loss (CTIBL) are lacking. A close link between oral health status and CTIBL might be explained, in part, by the systemic inflammation that characterizes both conditions. In this scenario, the effects of vitamin D (as an inflammation down-regulator) on immune systems are widely acknowledged. Vitamin D might facilitate upregulation of MAP kinases and inhibit the NF- κ B signaling pathway, with crucial implications for cytokine serum levels, the prostaglandin inflammation pathway, and the immune cell system. Vitamin D deficiency, smoking, and insufficient usage of dental floss have been found to harm oral health in women with BC receiving AIs. Consequently, vitamin D deficiency screening and supplementation and an appropriate oral rehabilitation strategy should be advised and implemented in the comprehensive therapeutic approach to women with BC treated with AIs.

KEYWORDS

Vitamin D, vitamin D deficiency, oral health, periodontal diseases, breast cancer.

Introduction

Breast cancer (BC) is the most frequent cause of cancer-related deaths among women; nonetheless, its incidence has tended to decline in recent decades^[1]. The death rate for female BC has halved since its peak, presumably due to a combination of early screening plans and advancements in adjuvant treatments, such as aromatase inhibitors (AIs), which are typically used in hormone-receptor (HR)-positive cancers to prevent recurrences^[2,3]. Aromatase, a cytochrome P450 hemoprotein-containing enzyme, catalyzes the synthesis of estrogens from androgens; it can be found in many peripheral tissues including breast, muscle, soft and adipose tissue^[4]. Third-generation AIs (anastrozole, exemestane and letrozole) are recommended as a component of the therapeutic management of women with BC due to their superior effectiveness in reducing cancer recurrence and their general acceptability compared with tamoxifen^[5]. AIs are used for endocrine treatment of endometriosis, to induce ovulation, and to treat gynecological cancers and BC; hence these medications are extensively used in the sequential or extended adjuvant treatment of BC in postmenopausal women^[4].

Given the increasing use of AIs in adjuvant treatment and

Article history

Received 13 May 2023 – Accepted 19 Dec 2023

Contact

Nicola Marotta; nicola.marotta@unicz.it
Physical and Rehabilitative Medicine, Experimental and Clinical Medicine,
University of Catanzaro "Magna Graecia", Via Tommaso Campanella, 115
88100 Catanzaro, Italy – Phone: +39 0961712316

as preventive agents, their potential oral toxicities need to be properly understood^[6]. Periodontal disorders, alveolar bone loss, and tooth loss correlate with downstream levels of estrogens both in menopause and in osteoporosis^[7,8]. The estrogen insufficiency observed in postmenopausal women is often related to skeletal and alveolar bone loss; in fact, an association of reduced skeletal and mandibular bone mineral density (BMD) with bone resorption features has been reported^[9]. With low skeletal BMD values found to be coupled with alveolar bone loss, osteoporotic postmenopausal women are at high risk for low oral health; although site-specific divergences have been found, osteoporosis is a systemic state resulting in loss of bone mass and microarchitecture^[10,11]. Women with HR+ BC

should be provided with adjuvant endocrine treatment for at least 5 years after surgical intervention ^[2,3]. Adjuvant endocrine therapy for BC reduces estrogen levels and alters the progress of periodontal disease; in fact, low estrogens decrease bone density, leading to osteoporosis and stimulating bone loss ^[10,11].

Similarly, vitamin D plays a key role in different fields of medicine, including dentistry; it acts through several mechanisms, including cellular proliferation and differentiation, cell maturation, and innate immune system response; in addition, high serum vitamin D3 levels may be strongly associated with an increase in the overall survival rate of BC patients ^[12].

The correlation between oral health, bone health, and vitamin D status has already been investigated in different conditions ^[13,14]. However, to date, the pathophysiological mechanisms underlying this link in BC survivors has not been widely investigated.

In the light of these considerations, the aim of this concise review was to evaluate the state of the art with regard to scientific evidence on the correlation between oral hygiene and vitamin D status in BC survivors treated with AIs.

The relationship between bone health and breast cancer

The clinical risk factors between female BC and osteoporosis/fractures are mutual. Vitamin D insufficiency or deficiency has been described in more than half of BC survivors worldwide ^[15]. The current evidence suggests that women receiving adjuvant AIs and pre-menopausal women treated with tamoxifen have accelerated bone loss, and that women receiving adjuvant AIs have an increased fracture risk ^[6]. Both bisphosphonates and denosumab (a monoclonal antibody for the receptor activator of *nfk-B* ligand [RANKL]) prevent bone loss ^[15-17]; additionally, denosumab has a proven anti-fracture benefit in post-menopausal women receiving AIs for HR+ BC ^[18]. Recently, some authors have explored the use of antiresorptive agents, such as bisphosphonates and denosumab, in the management or prevention of AI-associated bone loss (AIBL) ^[19,20]. Longitudinal studies suggest that oral bisphosphonate therapy for postmenopausal osteoporosis can decrease the incidence of invasive BC ^[18,21-23]. Furthermore, clinical trials have verified direct anticancer properties of zoledronate on advanced cancer cells in the bone marrow of patients with early BC, and subset analyses from ongoing trials show that adding zoledronate to neo-adjuvant chemotherapy can reduce residual tumor size and improve pathologic response rates compared with chemotherapy alone ^[24-27]. Unfortunately, adjuvant bisphosphonates for the inhibition of bone metastases in early BC, having seemed favorable, provided indecisive evidence ^[21]. This was probably due to the broad inclusion criteria of the trials in question ^[28-30]; in this setting, bisphosphonates seem to have a low impact on BC recurrence in premenopausal women, with all the benefits recorded in women who are either postmenopausal or have had an induced menopause. Nevertheless, Coleman *et al.*, in a meta-analysis, suggested an antitumor effect of bisphosphonates, emphasizing their ability to reduce the incidence of bone recurrence by one third, and BC-specific mortality by nearly one fifth ^[31].

In this scenario, patients receiving a hormonal treatment should receive an adequate fracture risk evaluation, covering clinical and biochemical risk factors, as well as BMD measurement through dual X-ray absorptiometry (DXA) ^[32,33]. Rehabilitation evaluation, weight-bearing exercise, and vitamin D and calcium adequacy are routinely suggested ^[34]. Anti-resorptive therapy is specified in patients with the occurrence of fragility fractures, which should be not underestimated in women with a DXA T score (or Z score in women aged < 50 years) of < - 2.0 at any site, or if annual bone loss is $\geq 5\%$, considering baseline BMD and other fracture risk factors ^[6]. Duration of anti-resorptive treatment can be tailored on the basis of absolute fracture risk. Relative to their skeletal benefits, the risk of adverse events with anti-resorptive therapies is small ^[6].

The role of oral health assessment in breast cancer patients

Women with HR+ BC might receive an adjuvant endocrine intervention for at least 5 years after surgical intervention ^[35]. In this scenario, adjuvant endocrine therapy moderates estrogen levels and might increase the risk of a periodontal disorder ^[36-38]; in parallel, lower bone density levels could induce an osteoporotic process, promoting alveolar bone loss ^[39]. Furthermore, gingival fibroblasts are a target tissue for estrogens, and tamoxifen may decrease the stimulatory effect of estrogens on the proliferation of fibroblasts ^[38]. In this scenario, AIs might result in increased periodontal probing depth, dental plaque accumulation, bone loss and alveolar bone loss ^[40]. Anti-estrogen therapy impacts personal mental status, with effects including fatigue and depression, resulting in misdiagnosis and under-treatment of oral diseases ^[41]. However, an appropriate calcium supplementation is necessary in BC patients with a risk of bone metastases ^[42]. Bisphosphonates appear to be related to the development of osteonecrosis of the jaw, but in clinical studies, lowering bisphosphonate doses did not negatively impact BC metastases ^[43]. Such bone-targeted treatment adjustments may benefit oral health ^[34]. Oestradiol is important for breast cancer development and progression. Endocrine therapy prevents the deleterious effects of oestradiol in breast tissue by systemically depleting oestradiol concentration (aromatase inhibitors). In conclusion, Ferrillo *et al.* ^[7] recently reported that vitamin D deficiency, insufficient use of dental floss, and smoking had a damaging impact on oral health in BC women treated with AIs. Consequently, vitamin D deficiency screening and supplementation, and properly designed oral rehabilitation strategies might be advised and employed in the complex therapeutic framework of BC survivors undergoing treatment with AIs ^[7].

The role of oral health and vitamin D status in women with breast cancer receiving aromatase inhibitors

Bisphosphonate-related osteonecrosis of the jaws, dental problems, and periodontal tissue diseases ^[36-38] (e.g., gingivitis and periodontitis) may occur more frequently in women

with BC receiving cancer and anti-osteoporotic therapies ^[42]. Vitamin D plays a pleiotropic role in different fields of medicine, including dentistry, and acts with numerous mechanisms, through stimulation cell proliferation and differentiation ^[112]. Elevated serum vitamin D3 levels might be related to an increased overall survival rate in BC, and this could be due to the reciprocal role of both vitamin D3 and vitamin D receptors (VDRs) in BC pathogenesis; since, vitamin D immunomodulatory and anti-inflammatory potential seems to resemble the activity of many nature-derived molecules (e.g., flavonoids) ^[44,45]. The VDR, which is expressed at a systemic level, acts as a negative tumor suppressor moderator in physiological circumstances, and might be decreased in women with cancer, thus failing to inhibit cancer proliferation and other cancer-related consequences, as well as impaired bone health ^[46].

In this scenario, previous studies advised that vitamin D might promote the production of antimicrobial peptides and prevent antigen-induced T-cell proliferation, as well as synthesis of cytokines (e.g., IL-2 IFN- γ), resulting in a significant anti-inflammatory effect. Likewise, vitamin D supplementation appears to augment serum levels of the anti-inflammatory cytokine IL-10, and reduce pro-inflammatory cytokines like tumor necrosis factor- α ^[46]. These anti-inflammatory and an-

timicrobial features might underlie an association between deficient vitamin D serum levels and periodontal disorder (PD), but further research is needed further clarify the relationship ^[8,13]. *In vitro* studies have demonstrated that vitamin D3 could influence the presentation of the antimicrobial peptide LL-37 in cultivated cells of the gingival epithelium, and that vitamin D supplementation may decrease, upstream, the periodontal pathogen, e.g., *Aggregatibacter actinomycetemcomitans* ^[46]. Moreover, similar *in vitro* studies indicated that vitamin D-induced LL-37 displays antimicrobial activity against *Porphyromonas gingivalis* and other pathogens related to PD pathogenesis ^[47-49]. In this scenario, Freudenheim *et al.* ^[50] established that PD could significantly raise BC risk, and proposed a possible role for the oral microbiome in BC pathogenesis and prevention.

A recent study ^[7] performed by our research group included 41 post-menopausal women with BC receiving IAs; a regression machine learning model suggested a close correlation of high Decayed, Missing, and Filled Permanent Teeth Index (DMFT) scores with poor use of dental floss and smoking habits. Moreover, further model analysis highlighted that vitamin D serum levels have been associated with higher DMFT scores. In the last few decades, the nutritional consequences of vitamin D deficiency on periodontal health have been a topic of interest.

Table I Main characteristics of studies included in the present review.

AUTHORS	NATIONALITY	DESIGN	POPULATION	AGE (YEARS)	OUTCOMES	MAIN FINDINGS
Taichman <i>et al.</i> 2015	United States	Cross-sectional	58 postmenopausal women; 29 with BC on Als and 29 controls without BC	BC: 61.6 \pm 5.4 / Control: 61.7 \pm 7.6	(1) periodontal pocket depth (PD); (2) bleeding on probing (BOP); and (3) attachment loss (AL).	Oral health is an important component of BC survivorship care. Authors reported that adjuvant AI use is associated with increased attachment loss and gingival bleeding in early stage estrogen receptor + BC survivors
Eagle <i>et al.</i> 2015	United States	Longitudinal study	58 postmenopausal women (29 receiving AI therapy; 29 women without BC)	BC: 61.7 \pm 7.6 / Control: 61.6 \pm 5.4	Comprehensive periodontal examinations including alveolar bone height (ABH) were conducted at baseline, 6, 12 and 18 months. Bisphosphonate, vitamin D, and calcium supplementation	Aromatase inhibitor therapy has a negative impact on the periodontal health of postmenopausal BC patients. Calcium supplementation appears to mitigate alveolar bone height loss in women on Als
de Sire <i>et al.</i> 2021	Italy	Cross-sectional	122 postmenopausal BC women	BC: 55.6 \pm 10.4	Previous fragility fractures, previous lumbar spine (LS) bone mineral density (BMD), femoral neck (FN) BMD, osteoporosis, osteopenia, serum 25-hydroxyvitamin D (25(OH)vit. D) (ng/ml)	Authors showed that BC women had high prevalence of osteopenia/osteoporosis, hypovitaminosis D, and a very high prevalence of mild/moderate periodontitis and low oro-dental care
Kizub <i>et al.</i> 2021	United States	Longitudinal study	6018 eligible women, 48 women with bisphosphonate-related osteonecrosis of the jaw were analyzed	BC: 63.5 \pm 6.1	Dental plaque levels, calculus, gingivitis, periodontitis, overall dental disease, presence of dentures, and number of teeth with deep caries, failing root canals, fractures/restorations, or endodontic treatment.	Advanced dental disease led to increased BRONJ risk; with a trend toward additive risk when in combination with more potent bisphosphonates such as zoledronate.
Ferrillo <i>et al.</i> 2023	Italy	Cross-sectional	41 post-menopausal BC women with Vitamin D	BC: 66.10 \pm 8.47	Oral health indexes as the Decayed, Missing, and Filled Permanent Teeth Index (DMFT); serum levels of 25(OH)D3; Bone Mineral Density (BMD); and the diagnosis of osteoporosis	Vitamin D deficiency, inadequate use of dental floss, and smoking had a negative impact on oral health in BC women. Thus, vitamin D deficiency screening and supplementation and a prompt oral rehabilitation plan should be suggested and implemented

Conclusions

In conclusion, the impact of AIs on oral health could be a neglected issue, particularly in the glare of their systemic consequences on bone remodeling in post-menopausal women. In this scenario, vitamin D deficiency seems to be correlated with poor oral health in women with BC receiving AIs.

Accordingly, it is plausible to hypothesize that the loss of estrogen pathways associated with AIs could lead to a more significant risk of periodontal diseases and high alveolar bone loss in postmenopausal women with BC.

This review offers interesting insights for a comprehensive counseling model, and concludes that vitamin D status screening and a proper oral rehabilitation strategy might be advisable and therefore worth incorporating in the treatment framework of BC survivors undergoing treatment with AIs.

Therefore, it is mandatory to improve awareness, among women with BC, of the significance of lifestyle medicine for an appropriate quality of life, promoting both better oral health status and bone health.

References

- Mubarik S, Yu Y, Wang F, et al. Epidemiological and sociodemographic transitions of female breast cancer incidence, death, case fatality and DALYs in 21 world regions and globally, from 1990 to 2017: an Age-Period-Cohort Analysis. *J Adv Res.* 2021;37:185-96.
- Keim-Malpass J, Doede A, Showalter SL. Does patient health literacy impact adherence to adjuvant endocrine therapy in breast cancer patients? *Patient Prefer Adherence.* 2018;13:47-51.
- Rosso R, D'Alonzo M, Bounous VE, et al. Adherence to adjuvant endocrine therapy in breast cancer patients. *Curr Oncol.* 2023;30(2):1461-72.
- Ustaoglu G, Goller Bulut D, Uyeturk U, Uysal O. Evaluation of periodontal health in breast cancer patients undergoing tamoxifen or aromatase inhibitors drugs therapy: A cross-sectional study. *Spec Care Dentist.* 2021;41(1):41-8.
- Kaklamani VG, Gradishar WJ. Endocrine Therapy in the current management of postmenopausal estrogen receptor-positive metastatic breast cancer. *Oncologist.* 2017;22(5):507-17.
- Grossmann M, Ramchand SK, Milat F, et al. Assessment and management of bone health in women with oestrogen receptor-positive breast cancer receiving endocrine therapy: position statement summary. *Med J Aust.* 2019;211(5):224-9.
- Ferrillo M, Migliario M, Marotta N, et al. Oral health in breast cancer women with vitamin D deficiency: a machine learning study. *J Clin Med.* 2022;11(16):4662.
- de Sire A, Ferrillo M, Gennari A, et al. Bone health, vitamin D status and oral hygiene screening in breast cancer women before starting osteoporosis treatment: a cross-sectional study. *J Biol Regul Homeost Agents.* 2021;35(1):397-402.
- Jayusman PA, Nasruddin NS, Baharin B, Ibrahim NI, Ahmad Hairi H, Shuid AN. Overview on postmenopausal osteoporosis and periodontitis: the therapeutic potential of phytoestrogens against alveolar bone loss. *Front Pharmacol.* 2023;14:1120457.
- Mashalkar VN, Suragimath G, Zope SA, Varma SA. A cross-sectional study to assess and correlate osteoporosis and periodontitis among postmenopausal women: a dual energy X-ray absorptiometry study. *J Midlife Health.* 2018;9(1):2-7.
- Lee Y. Association between osteoporosis and periodontal disease among menopausal women: the 2013-2015 Korea National Health and Nutrition Examination Survey. *PLoS One.* 2022;17(3):e0265631.
- Calafiore D, Fortunato L, Migliario M. Vitamin D for clinical diseases in women: an indispensable factor in medicine and dentistry. *J Clin Med.* 2022;11(11):3104.
- Ferrillo M, Migliario M, Rocuzzo A, et al. Periodontal disease and vitamin D deficiency in pregnant women: Which correlation with preterm and low-weight birth? *J Clin Med.* 2021;10(19):4578.
- de Sire A, Ferrillo M, Lippi L, et al. Sarcopenic dysphagia, malnutrition, and oral frailty in elderly: a comprehensive review. *Nutrients.* 2022;14(5):982.
- Neuhouser ML, Sorensen B, Hollis BW, et al. Vitamin D insufficiency in a multiethnic cohort of breast cancer survivors. *Am J Clin Nutr.* 2008;88(1):133-9.
- Scaturro D, De Sire A, Terrana P, et al. Early Denosumab for the prevention of osteoporotic fractures in breast cancer women undergoing aromatase inhibitors: a case-control retrospective study. *J Back Musculoskelet Rehabil.* 2022;35(1):207-12.
- Rossini A, Frigerio S, Dozio E, Trevisan R, Perseghin G, Corbetta S. Effect of denosumab on glucose homeostasis in postmenopausal women with breast cancer treated with aromatase inhibitors: a pilot study. *Int J Endocrinol.* 2020;2020:1809150.
- Chukir T, Liu Y, Farooki A. Antiresorptive agents' bone-protective and adjuvant effects in postmenopausal women with early breast cancer. *Br J Clin Pharmacol.* 2019;85(6):1125-35.
- McAndrew NP, Finn RS. Clinical Review on the Management of Hormone Receptor-Positive Metastatic Breast Cancer. *JCO Oncol Pract.* 2022;18(5):319-27.
- Gaudio A, Xourafa A, Rapisarda R, Castellino P. Therapeutic options for the management of aromatase inhibitor-associated bone loss. *Endocr Metab Immune Disord Drug Targets.* 2022;22(3):259-73.
- Hadji P, Aapro MS, Body JJ, et al. Management of Aromatase Inhibitor-Associated Bone Loss (AIBL) in postmenopausal women with hormone sensitive breast cancer: Joint position statement of the IOF, CABS, ECTS, IEG, ESCEO IMS, and SIOG. *J Bone Oncol.* 2017;7:1-12.
- Trémollières FA. Screening for osteoporosis after breast cancer: for whom, why and when. *Maturitas.* 2014;79(3):343-8.
- de Sire A, Di Capua L, Amico ID, Pinto M. Bone health and quality of life in breast cancer patients treated by aromatase inhibitors. *Ann Phys Rehabil Med.* 2018;61S:e285.
- Aft R, Naughton M, Trinkaus K, et al. Effect of zoledronic acid on disseminated tumour cells in women with locally advanced breast cancer: an open label, randomised, phase 2 trial. *Lancet Oncol.* 2010;11(5):421-8.
- Vidula N, Hwang J, Greenberg S, et al. Long-term follow-up (LTFU) of adjuvant zoledronic acid (ZOL) in high risk early stage breast cancer (ESBC) defined by bone marrow (BM) disseminated tumor cells (DTC). *J Clin Oncol.* 2017;35(15_suppl):e12001-e12001.
- Rack B, Schindlbeck C, Strobl B, Sommer H, Friese K, Janni W. [Efficacy of zoledronate in treating persisting isolated tumor cells in bone marrow in patients with breast cancer. A phase II pilot study]. *Dtsch Med Wochenschr.* 2008;133(7):285-9.
- Coleman RE, Winter MC, Cameron D, et al. The effects of adding zoledronic acid to neoadjuvant chemotherapy on tumour response: Exploratory evidence for direct anti-tumour activity in breast cancer. *Br J Cancer.* 2010;102(7):1099-105.
- Clézardin P. Can bisphosphonates really reduce the risk of recurrences in early breast cancer? *IBMS Bonekey.* 2011;8(3):159-64.
- Takahashi S, Iwase T, Kohno N, et al. Efficacy of zoledronic acid in postmenopausal Japanese women with early breast cancer receiving adjuvant letrozole: 12-month results. *Breast Cancer Res Treat.* 2012;133(2):685-93.
- Eidtmann H, de Boer R, Bundred N, et al. Efficacy of zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: 36-month results of the ZO-FAST Study. *Ann Oncol.* 2010;21(11):2188-94.
- Coleman R, Gray R, Powles T, et al. Adjuvant bisphosphonate treat-

- ment in early breast cancer: Meta-analyses of individual patient data from randomised trials. *Lancet* 2015; 386(10001): 1353–1361.
32. Hadji P. Cancer treatment-induced bone loss in women with breast cancer. *Bonekey Rep.* 2015;4:692.
 33. Rizzoli R, Body JJ, Brandi ML, et al; International Osteoporosis Foundation Committee of Scientific Advisors Working Group on Cancer-Induced Bone Disease. Cancer-associated bone disease. *Osteoporos Int.* 2013;24(12):2929-53.
 34. Ramchand SK, Cheung YM, Yeo B, Grossmann M. The effects of adjuvant endocrine therapy on bone health in women with breast cancer. *J Endocrinol.* 2019;241(3):R111-R124.
 35. van Hellemond IEG, Geurts SME, Tjan-Heijnen VCG. Current status of extended adjuvant endocrine therapy in early stage breast cancer. *Curr Treat Options Oncol.* 2018;19(5):26.
 36. Gaba FI, Gonzalez RC, Martínez RG. The role of oral *Fusobacterium nucleatum* in Female Breast Cancer: A Systematic Review and Meta-Analysis. *Int J Dent.* 2022;2022:1876275.
 37. Hao Y, Peng X, Zhou X, Cheng L. [Research progress on the relationship between periodontal disease and common malignancies]. *Hua Xi Kou Qiang Yi Xue Za Zhi.* 2019;37(3):320-4.
 38. Taichman LS, Havens AM, Van Poznak CH. Potential implications of adjuvant endocrine therapy for the oral health of postmenopausal women with breast cancer. *Breast Cancer Res Treat.* 2013;137(1):23-32.
 39. Diana A, Carlino F, Giunta EF, et al. Cancer Treatment-Induced Bone Loss (CTIBL): state of the art and proper management in breast cancer patients on endocrine therapy. *Curr Treat Options Oncol.* 2021;22(5):45.
 40. Eagle I, Benavides E, Eber R, et al. Periodontal health in breast cancer patients on aromatase inhibitors versus postmenopausal controls: a longitudinal analysis. *J Clin Periodontol.* 2016;43(8):659-67.
 41. Hlatky MA, Boothroyd D, Vittinghoff E, Sharp P, Whooley MA; Heart and Estrogen/Progestin Replacement Study (HERS) Research Group. Quality-of-life and depressive symptoms in postmenopausal women after receiving hormone therapy: Results from the Heart and Estrogen/Progestin Replacement Study (HERS) trial. *JAMA.* 2002;287(5):591-7.
 42. Zhang Y, Ren X, Hu T, Cheng R, Bhowmick NA. The relationship between periodontal disease and breast cancer: from basic mechanism to clinical management and prevention. *Oral Health Prev Dent.* 2023;21:49-60.
 43. Fehm T, Felsenberg D, Krimmel M, Solomayer E, Wallwiener D, Hadji P. Bisphosphonate-associated osteonecrosis of the jaw in breast cancer patients: Recommendations for prevention and treatment. *Breast.* 2009;18(4):213-7.
 44. Sîrbe C, Rednic S, Grama A, Pop TL. An update on the effects of vitamin D on the immune system and autoimmune diseases. *Int J Mol Sci.* 2022;23(17):9784.
 45. Kim Y, Je Y. Vitamin D intake, blood 25(OH)D levels, and breast cancer risk or mortality: a meta-analysis. *Br Br J Cancer.* 2014;110(11):2772-84.
 46. Kamen DL, Tangpricha V. Vitamin D and molecular actions on the immune system: modulation of innate and autoimmunity. *J Mol Med (Berl).* 2010;88(5):441-50.
 47. McMahon L, Schwartz K, Yilmaz O, Brown E, Ryan LK, Diamond G. Vitamin D-mediated induction of innate immunity in gingival epithelial cells. *Infect Immun.* 2011;79(6):2250-6.
 48. Pahar B, Madonna S, Das A, Albanesi C, Girolomoni G. Immunomodulatory role of the antimicrobial LL-37 peptide in autoimmune diseases and viral infections. *Vaccines (Basel).* 2020;8(3):517.
 49. Ridyard KE, Overhage J. The potential of human peptide LL-37 as an antimicrobial and anti-biofilm agent. *Antibiotics (Basel).* 2021;10(6):650.
 50. Freudenheim JL, Genco RJ, LaMonte MJ, et al. Periodontal disease and breast cancer: Prospective cohort study of postmenopausal women. *Cancer Epidemiol Biomarkers Prev.* 2016;25(1):43-50.