LETTER TO THE EDITOR

Bone health, vitamin D status and oral hygiene screening in breast cancer women before starting osteoporosis treatment: a cross-sectional study

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To the Editor,

Breast cancer (BC) is the most common malignancy and cause of mortality in women, presenting also with several treatment-related disabling complications (e.g. breast cancer-related lymphedema, BC-related fatigue, axillary web syndrome, physiological disorders) (1-4). In this scenario, an increased survival rate of women affected by BC with estrogen receptor-positive (ER) tumors has been observed after the introduction of adjuvant therapies, such as tamoxifen and aromatase inhibitors (AIs), aimed at reducing the proliferative effects of estrogens on breast tissue in ER-positive BC patients (5). However, these anti-hormonal pharmacological interventions, promoting bone resorption through aromatase blockade at bone tissue level might lower bone mineral density (BMD) with a resulting pathological condition, defined as cancer treatment-induced bone loss (CTIBL) (5-6).

Moreover, BC women undergoing cancer treatments and anti-osteoporotic drugs might experience osteonecrosis of the jaw and periodontal tissue diseases, including gingivitis, and infections (7). Nevertheless, chronic oral diseases are still frequently neglected in BC patients, and detailed indications about oral health screening, evaluation and treatment before CTIBL treatment initiation are missing.

In this cross-sectional study we therefore assessed bone health and oral hygiene status in BC women before CTIBL treatment initiation. The aim is twofold: to provide new data on oral health status in BC survivors undergoing CTIBL treatment, and to propose a feasible clinical pathway in order to better define a patient-oriented multidisciplinary management of these women.

Key words: oral health; bone health; osteoporosis; vitamin D deficiency; breast cancer

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DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

MATERIALS AND METHODS

Participants

In this observational cross-sectional study, we recruited women referred to the Outpatient Service for Oncological Rehabilitation of the Physical Medicine and Rehabilitation Unit of the University Hospital "Maggiore della Carità", Novara, Italy. Patients were recruited over a 6-month period, from January to June, 2020.

The inclusion criteria were the following: women with a diagnosis of invasive BC surgery performed at least 12 months earlier; tamoxifen or AI adjuvant hormone therapy; post-menopausal status. Exclusion criteria were the following: psychiatric or neurological diseases; evidence of major concurrent diseases; patients undergoing treatment with corticosteroids, immunoglobulin, or immunosuppressive drugs; fully edentulous patients; patients suffering or having suffered in the past from major oral infections; dental elements less than 10; patients unable to understand the informed consent.

The study was approved by the Local Ethics Committee (CE 61/10, prot.392 CE). All the participants were asked to carefully read and sign an informed consent, and the researchers provided to protect the privacy and the study procedures according to the Declaration of Helsinki, with pertinent National and International regulatory requirements. Moreover, the study was performed in accordance with the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) Guidelines (https://www.equator-network.org/wp-content/uploads/2015/10/STROBE_checklist_v4_cross-sectional.pdf).

All the included patients underwent a bone and functional screening and were then referred to the Dental Clinic of the University Hospital 'Maggiore della Carità' of Novara to undergo a clinical assessment of their oral health status before initiating anti-osteoporotic treatment (Fig. 1). The following demographic and anamnestic data were collected: sex, age, Body Mass Index (BMI), smoking habit, BC situs (right/left), BC type (lobular/ductal), histological type (in situ/infiltrative), type of breast surgery (conservative/mastectomy), sentinel lymph node biopsy (SLNB), axillary lymph node dissection (ALND), adjuvant hormone therapy (tamoxifen or aromatase inhibitors). The following data regarding bone health were also collected: previous femur fragility fractures, previous vertebral fragility fractures, lumbar spine (LS) bone mineral density (BMD), LS Tscore, LS Zscore, femoral neck (FN) BMD, FN Tscore, FN Zscore, osteoporosis, osteopenia, Fracture Risk Assessment tool (FRAX®) major osteoporotic fractures, FRAX® hip fractures, serum 25-hydroxy-vitamin D (25(OH)vit. D) (ng/ml), serum 25(OH)vit. D $\geq$30 ng/ml, serum 25(OH)vit. D $\geq$20 and <30 ng/ml, serum 25(OH)vit. D <20 ng/ml, serum calcium (mg/dl), serum parathyroid hormone (PTH) (pg/ml), serum alkaline phosphatase (ALP) (U/l).

Furthermore, all the participants underwent a specialistic oral health evaluation, including the following outcome measures: the Decayed, Missing and Filled Permanent Teeth Index (DMFT), to assess dental caries prevalence as well as dental treatment needs; the Oral Hygiene Index (OHI), for the presence of debris/stain and calculus on the dental elements; the Plaque Control and Record Index (PCR), to assess the presence of plaque on the dental elements; Gingival Bleeding Index (GBI), to evaluate gingival inflammation; the Periodontal Screening and Recording Index (PSR), to assess periodontal status; the Winkel Tongue Coating Index (WTCI), to evaluate the amount of tongue coating.

Statistical analysis

Data management and analyses were conducted according to a pre-specified statistical analytical plan. Statistical analysis was performed using STATA v. 12 (StataCorp LP, College Station, TX). The continuous variables are presented as means ± standard deviations, or median and interquartile range. The Shapiro–Wilk test was performed to assess the distribution of all continuous data; as the data did not follow a normal distribution, Wilcoxon rank sum test was used to compare continuous variables between the two groups; Fisher exact test was performed to compare categorical variables between the two groups. Pearson correlation coefficients and regression analyses assessed associations and correlations among oral health status of study participants, analyzing a correlation with clinical and demographic features. A p-value of 0.05 was considered statistically significant.

RESULTS

Of 128 subjects recruited, 6 did not match the inclusion/exclusion criteria and were excluded, thus, 122 postmenopausal BC women (mean aged

55.6±10.4 years) were included in the final analysis. Demographic and clinical characteristics of the patients enrolled are summarized in Table I.

Regarding bone health assessment, the mean LS BMD was 1.049±0.147g/cm2, whereas the mean FN BMD was 0.747±0.109 g/cm2; 23% of BC women had osteoporosis and 52.5% had osteopenia. The FRAX® major osteoporotic fractures score was 7.7±4.4% and the FRAX® hip fractures score was 1.7±2.0%, testifying a mild risk of fractures in the subsequent 10 years. Furthermore, the mean serum level of 25(OH) vit. D was 23.9±16. ng/ml, and 89 patients (72.9%) reported hypovitaminosis D ([25(OH)vit. D] <30 ng/ml). Lastly, mean serum calcium level was 9.2±0.5 mg/dl. Further details on bone health status in our sample of BC women are depicted by Table II.

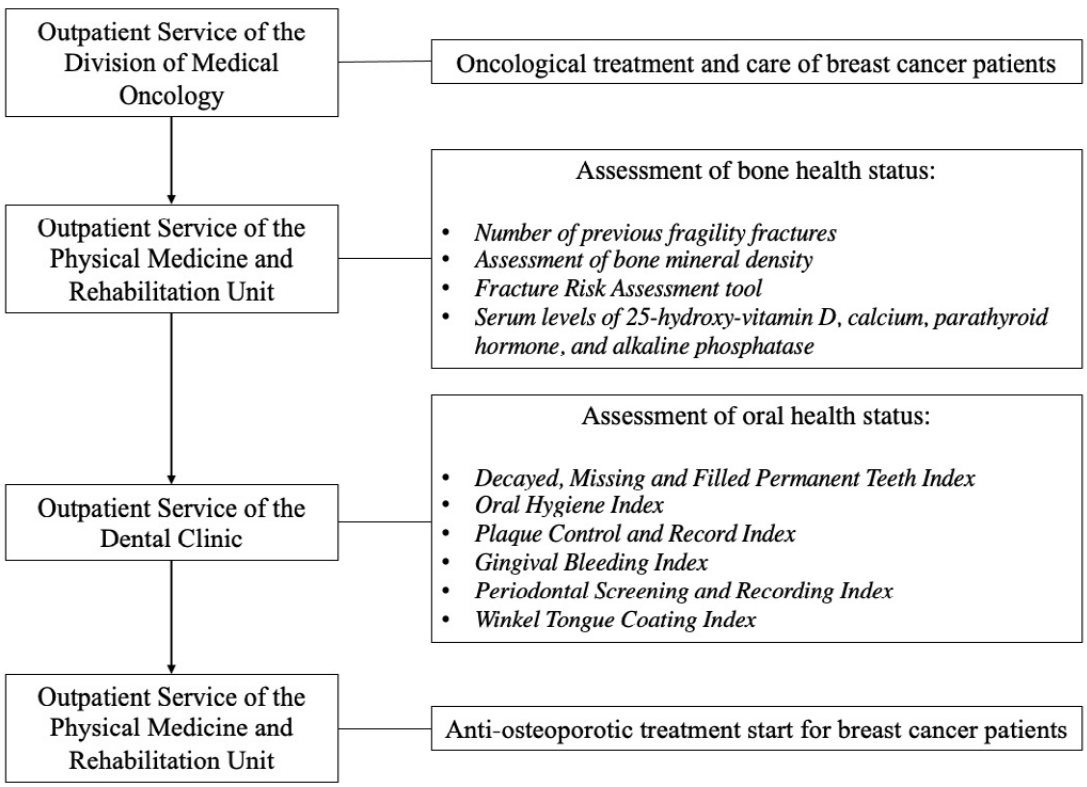

Fig. 1. *Flow chart of a feasible multidisciplinary bone and oral health management of breast cancer patients.*

Table I. *Anamnestic characteristics of breast cancer women included in the study (n=122).*

Age (years)	55.6±10.4
BMI (kg/m^2)	23.9±5.4
Smokers	22 (18.0%)
Laterality (right/left)	52/70
Type of breast cancer (lobular/ductal)	38/84
Histological type (in situ/infiltrative)	60/62
Type of breast surgery (conservative/mastectomy)	36/86
SLNB	104 (85.2%)
ALND	18 (14.8%)
Tamoxifen	48 (39.3%)
Aromatase inhibitors	74 (60.7%)

Continuous variables are expressed as means ± standard deviations; categorical variables are expressed as counts (percentages); ratios are expressed as x/y. Abbreviations: BMI: body mass index; SLNB: sentinel lymph node biopsy; ALND: axillary lymph node dissection.

DMFT index had a high average value of 16.07±7.05 and similarly, OHI showed that only 11.5% (n=14) had good oral hygiene while 35.3% had a sufficient oral health and 53.2% (n=65) had an insufficient status. PCR index showed that in 33.6% (n=41) the plaque was present from 50% and 75% of the sites investigated and in 18.0% (n=22) of BC women in more than 75%. From PSR index assessment, it emerges that only 2.5% (n=3) had good oral health while 18.9% (n=23) had gingivitis, 63.1% (n=77) had a moderate periodontitis and 15.6% (n=19) had serious periodontitis. Further details on the results obtained are reported in Table III. There were no statically significant correlations ($p>0.05$) among oral health indexes and BMD or vitamin D status.

DISCUSSION

This cross-sectional study aimed to assess bone health status and oral hygiene in a wide cohort (n=122) of BC patients, thus showing a possible correlation between bone health, vitamin D status, and oral health in BC women undergoing tamoxifen or AI treatment. These findings might provide more information to the body of knowledge surrounding the correlation between osteoporosis, BC, and oro-dental diseases (e.g. periodontitis, poor oral health, jaw osteonecrosis).

A recent metanalysis, performed by Hadji et al. (8), investigated the potential effect of endocrine therapies on bone metabolism in postmenopausal women, confirming that the use of AIs is associated with an average bone loss of 2.6% after 12 months of treatment and of 3.5% after 24 months.

Osteoporosis is a systemic condition that might also affect the jawbones, the structure of which may be also impaired by periodontitis, a chronic infection-mediated condition resulting in a loss of clinical attack level of the soft tissue to teeth and resorption of alveolar bone (9). The association between

Table II. *Bone health in breast cancer women included in the study (n=122).*

Previous femur fragility fractures	4 (3.3%)
Previous vertebral fragility fractures	5 (4.1%)
LS BMD (g/cm^2)	1.049 ± 0.147
LS Tscore	-1.0 ± 1.2
LS Zscore	0.0 ± 1.0
FN BMD (g/cm^2)	0.747 ± 0.109
FN Tscore	-1.5 ± 1.0
FN Zscore	-0.3 ± 0.6
Osteoporosis	28 (23.0%)
Osteopenia	64 (52.5%)
FRAX® major osteoporotic fractures (%)	7.7 ± 4.4
FRAX® hip fractures (%)	1.7 ± 2.0
Serum 25(OH)vit. D (ng/ml)	23.9 ± 16.2
Serum 25(OH)vit. D ≥30 ng/ml	33 (27.1%)
Serum 25(OH)vit. D ≥20 and <30 ng/ml	48 (39.3%)
Serum 25(OH)vit. D <20 ng/ml	41 (33.6%)
Serum calcium (mg/dl)	9.2 ± 0.5
Serum PTH (pg/ml)	21.8 ± 7.9
Serum ALP (U/l)	134.3 ± 73.1

Continuous variables are expressed as means ± standard deviations; categorical variables are expressed as counts (percentages). Abbreviations: LS: lumbar spine; BMD: bone mineral density; FN: femoral neck; FRAX®: Fracture Risk Assessment tool; 25(OH)vit. D: 25-hydroxy-vitamin D; PTH: parathyroid hormone; ALP: alkaline phosphatase.

Table III. *Oral hygiene status in breast cancer women included in the study (n=122).*

DMFT	16.07±7.05
OHI	
Optimal	*0 (0.0%)*
Good	*14 (11.5%)*
Sufficient	*43 (35.3%)*
Insufficient	*65 (53.2%)*
PCR	
From 0% to 25%	*13 (10.7%)*
>25% and ≤50%	*46 (37.7%)*
>50% and ≤75%	*41 (33.6%)*
>75%	*22 (18.0%)*
GBI	
From 0% to 25%	*114 (93.44%)*
>25% and ≤50%	*8 (6.56%)*
>50% and ≤75%	*0 (0.0%)*
>75%	*0 (0.0%)*
PSR	
Normal periodontal health status	*3 (2.5%)*
Gingivitis	*23 (18.9%)*
Mild/moderate periodontitis	*77 (63.1%)*
Severe periodontitis	*19 (15.6%)*
WTCI	
Grade 0	*10 (7.8%)*
Grade 1	*81 (63.3%)*
Grade 2	*37 (28.9%)*

Continuous variables are expressed as means ± standard deviations; categorical data are expressed as counts (%). Abbreviations: DMFT: Decayed, Missing and Filled Permanent Teeth; OHI: Oral Hygiene Index; PCR: Plaque Control and Record; GBI: Gingival Bleeding Index; PSR: Periodontal Screening and Recording; WTCI: Winkel Tongue Coating Index.

periodontitis and osteoporosis has been investigated by Lin et al. (10) in a large-scale population-based cohort study (1,878,401 individuals) showing a significant correlation in women.

Oral hygiene assessment might be considered as crucial in BC women and could be implemented and screened in the clinical practice even in other disabling conditions, as shown by our group in recent observational studies performed on right stroke survivors (11) and on subjects with amyotrophic lateral sclerosis (12). In this context, rehabilitation and oral health interventions could be included within the quality-of-life interventions for an adequate management of BC survivors (4).

The main limitation of this study the cross-sectional design that hinders any potential causality relationship and long-term follow-up evaluation. However, this is the first study that assessed oral health status with several specific oral hygiene indexes, and the largest case history evaluating a possible correlation between oral health and bone health in BC women undergoing tamoxifen or AIs treatment.

Taken together, our findings 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. This study might be a starting point for future works investigating the correlation between BC, osteoporosis and oral health to define a patient-oriented multidisciplinary management.

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