JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Original Article DOI: https://doi.org/10.23950/jcmk/15703

The Effect of Breast Cancer History on Bone Mineral Density in the Treatment of Postmenopausal Osteoporosis: One-Year Follow-Up Results

Yasemin Tombak[1], Ebru Karaca Umay[1], Fatma Nazli Unkazan[2], Ozgur Zeliha Karaahmet[1], Methiye Kubra Sezer[1], Ece Unlu Akyuz[1], Eda Gurcay[3]

[1]Physical Medicine and Rehabilitation, Ankara Etlik City Hospital, Ankara, Turkey
[2]Physical Medicine and Rehabilitation, Kirklareli University Faculty of Medicine, Kirklareli, Turkey
[3]Physical Medicine and Rehabilitation, University of Health Sciences, Gaziler Physical and Rehabilitation Medicine Education and Research Hospital, Ankara, Turkey

Received: 2024-10-12.
Accepted: 2024-12-09.

This work is licensed under a Creative Commons Attribution 4.0 International License

J Clin Med Kaz 2024; 21(6): 85–90

Corresponding author:
Yasemin Tombak.
Email: yasemintombak@hotmail.com.
ORCID: 0000-0003-0065-5376.

Abstract

Aim: Breast cancer patients who get certain chemotherapeutic agents are more likely to experience early menopause and to suffer osteoporotic fractures at a younger age. This study investigated the impact of breast cancer history on bone mineral density (BMD) levels in postmenopausal osteoporosis (OP) treatment.

Materials and Methods: This is a retrospective case-control study analyzed 65 female cases diagnosed with OP, including 32 patients with stable breast cancer who had undergone chemotherapy and/or radiotherapy but not within the last 5 years, and 33 matched controls. Demographic characteristics, total lumbar and femoral neck BMD levels and biochemical parameters were recorded for both groups.

Results: Before treatment, femoral neck T-score and serum Ca levels were lower in the patient group than in the control group (p=0.038, p=0.007, respectively). There was no difference between groups for the first year (p>0.05), but when the change within a group was examined, only the patient group showed a significant increase in femoral neck T-score and serum Ca levels (p=0.027, p=0.001, respectively). Patients who received radiotherapy had lower femoral neck BMD levels before and after treatment than those who did not receive radiotherapy (p=0.021, p=0.024, respectively), and the post-treatment recovery was not different (p>0.05).

Conclusion: This study demonstrated the success of osteoporosis treatment in patients with a previous diagnosis of breast cancer. Patients with breast cancer must be screened for osteoporosis and treated accordingly.

Keywords: bone mineral density; breast cancer; osteoporotic fractures; postmenopausal osteoporosis, screening

Introduction

In osteoporosis (OP), a systemic skeletal disorder, decreased bone density and degradation within the bone micro-architecture contribute to an increased fragile nature and a higher risk of fractures [1]. Based on the cause, it is divided into primary and secondary OP.

Primary OP consists of type 1 (postmenopausal) and type 2 (senile) OP. The biochemical phenomenon known as postmenopausal osteoporosis (OP) is typified by low bone mass and weakened microarchitecture as a result of the estrogens' no longer having a direct influence on osteoclasts [2]. Secondary OP is caused by a variety of disorders or medication use. Changes in lifestyle, genetic diseases, hypogonadal conditions, endocrine diseases, gastrointestinal diseases, hematological diseases, rheumatological and autoimmune diseases, neurological and musculoskeletal system difficulties, smoking and alcohol use, weight loss, and drugs (aromatase inhibitors, chemotherapeutics, etc.) are all potential causes [3].

Menopause causes rapid bone loss. Women may experience a loss up to 30% of their bone density over the first five years after menopause if estrogen is not present. Some chemotherapy agents used in breast cancer patients develop premature menopauses as well as elevate the possibility of osteoporotic fractures in these patients at early ages [4,5].

Bone mineral density (BMD), Z- and T-scores were all low in breast cancer patients, whereas the proportion of bone loss and osteoporosis were high [6].

As a consequence of this, according to current National Comprehensive Cancer Network guidelines, women receiving aromatase inhibitor (AI) treatment for breast cancer should have their BMD monitored with a baseline scan and then on a regular basis after that [7].

No research has been done to compare the efficacy of osteoporosis treatment in individuals with a history of breast cancer with those who have not. The focus of this study was to look into how BMD levels were affected by radiotherapy, chemotherapy, and breast cancer history both before and one year after osteoporosis treatment.

Materials and methods

Study design

This study was conducted after obtaining approval (Protocol No. P202300018 dated 31.03.2023) in the format required by the clinical research ethics committee of the local institute and under the principles set forth in the declaration of Helsinki. The study procedure was clarified to those who participated, and their written informed consent was collected in the manner mandated by the local institute's ethical committee.

This is a retrospective case-control study included 32 patients with breast cancer and a control group of 33 age-matched patients with osteoporosis, totaling 65 female cases. The records of 65 female patients who were followed up in the physical medicine and rehabilitation outpatient clinic were diagnosed with postmenopausal OP for the first time by lumbar and/or femoral neck BMD scanning were evaluated.

Stable breast cancer and OP patients who have a history of chemotherapy and/or radiotherapy but have not received chemotherapy and/or radiotherapy in the last 5 years, group 1 (n=32, patient group), those with OP diagnosis compatible with age and body mass index, group 2 (n=33, control group) were included in the study. Patients under 50 years of age, who had an additional disease other than a cancer history or were diagnosed with an additional disease during follow-up, were using irregular medication and were excluded from the study.

Demographics and Disease Characteristics

Demographic characteristics, total lumbar and femoral neck BMD levels, and biochemical parameters of all patients were recorded. Patients were questioned whether they had suffered a fracture or not.

The cancer stage of the patients with a history of cancer is presented in Table 1 with TNM (tumor, lymph node, metastasis) staging [8]. Oestrogen positivity, chemotherapy, and radiotherapy histories were questioned.

BMD measurements were conducted by a dual-energy x-ray absorptiometry (DEXA) instrument. Lumbar spine (L1-L4) total score and hip region (femoral neck), T-scores, and serum biochemical parameters measured according to standard protocols were recorded (T0). In all patient groups, 1200 mg calcium carbonate and vitamin D3 were administered along with alendronate (70 mg/wk) to correct the existing hypocalcemia and prevent hypocalcemia during treatment. Patients who attended regular check-ups and continued their medication were included. The (T1) values of the patients at the end of the first year were recorded.

Table 1 TNM staging of breast cancer

Stage	Notes
Stage 0	This N0 M0
Stage 1	
1a	Tmic N0 M0/T1 N0 M0
1b	T0 Nmic M0/Tmic Nmic M0/T1 Nmic M0
Stage 2	
2a	T0 N1 M0/T1 N1 M0/T2 N0 M0
2b	T2 N1 M0/T3 N0 M0
Stage 3	
3a	T0 N2 M0/T1 N2 M0/T2 N2 M0/T3 N1 M0/T3 N2 M0
3b	T4 N0 M0/T4 N1 M0/T4 N2 M0
3c	T1-4 N3 M0
Stage 4	Any T, Any N, M1

T: tumor, N: regional lymph nodes, M: metastasis, is: in situ, mic: micro invasion

Statistical analysis

It was found that 28 patients would be enough for each group to produce a power of 80% with a significance of 0.05, provided an effect size of 0.4 (Cohen's d) for the sample size. With a 10% standard deviation, the effect size was computed to find a 10% variation in the DEXA screening recommendation.

The Statistical Package for Social Sciences (SPSS) 22.0 for Windows was used to analyze the data. In descriptive statistics, data were expressed as median (25%-75% quartile range) for continuous variables, frequency, and percentage (%) for nominal variables. Normality was evaluated with the Kolmogorov-Smirnov test. None of the continuous variables were normally distributed. The Wilcoxon Signed Rank test was utilized to assess statistically significant variations in the group's repeated measurements. Statistically, the difference between the groups was evaluated with the Mann-Whitney-U test. $p<0.05$ scores were considered significant.

Results

The median age of the patient group was 58.2 years, whereas that of the control group was 57.6 years (p=0.182). The patient group's body mass index (BMI) was 29.5 kg/m2, while that of the control group was 29.7 kg/m2 (p=0.895). The patient and control groups shared similar demographic features. No fractures occurred in either patient group.

Table 2 Disease characteristics of patients with breast cancer:

	Patient Group (n=32) n (%), Median (%25-%75 quartile range)
Number of patients receiving chemotherapy	32 (100)
Number of patients receiving radiotherapy	13 (40.6)
Number of patients who underwent surgery	32 (100)
Affected breast	
Right	19 (59.4)
Left	13 (40.6)
Bilateral	0
Stage	
1a	7 (21.9)
2a	8 (25.0)
2b	9 (28.1)
3a	8 (25.0)
Untreated time (years)	7.28 (5.12-8.25)

Table 3 Comparison of pretreatment (T0) BMD and biochemical parameters of the groups

Parameter	Patient Group(n=32) Median (%25-%75 quartile range)	Control Group (n=33) Median (%25-%75 quartile range)	p
L1-4 total T score	-2.90 (-3.50_-1.95)	-2.80 (-3.12_-2.01)	0.171
Femur neck T score	-2.85 (-3.45_-2.10)	-2.15 (-2.92_-1.90)	**0.038**
Serum Ca (mg/dl)	7.10 (6.70-9.12)	9.80 (8.80-.11.15)	**0.007**
Serum P (mg/dl)	3.45 (2.85-4.40)	3.20 (2.91-3.98)	0.092
Serum ALP (U/l)	47.30 (31.15-94.22)	46.50 (34.15-97.24)	0.134
Serum PTH (ng/L)	28.12 (17.60-56.22)	26.20 (19.25-57.18)	0.592
Serum calcidiol (ng/mL)	21.18 (17.20-26.30)	23.45 (18.35-32.64)	0.357
Serum osteocalcin(µg/L)	9.60 (6.58-12.65)	8.85 (7.78-11.72)	0.172

BMD: Bone mineral density, Ca: calcium, P: phosphorus ALP: alkaline phosphatase, PTH: parathormone

Table 4 Comparison of BMD and biochemical parameters of the groups at the 1st year of treatment (T1)

Parameters	Patient Group(n=32) Median (%25-%75 quartile range)	Control Group (n=33) Median (%25-%75 quartile range)	p
Total lumbar (L1-4) T score	-2.60 (-3.32_-1.12)	-2.50 (-3.00_-1.92)	0.532
Total femoral neck T score	-2.05 (-3.01_-1.54)	-2.08 (-2.97_-2.06)	0.427
Serum Ca (mg/dl)	9.80 (8.62-11.38)	9.90 (8.70-11.15)	0.918
Serum P (mg/dl)	3.60 (2.92-4.32)	3.50 (3.04-4.25)	0.134
Serum ALP (U/l)	46.50 (21.12-98.24)	47.10 (27.18-96.44)	0.262
Serum PTH (ng/L)	28.21 (18.72-60.15)	26.95 (21.35-58.32)	0.098
Serum Calcidiol (ng/mL)	22.48(18.61-32.78)	22.50 (19.61-35.44)	0.699
Serum Osteocalcin (µg/L)	9.62 (7.76-11.28)	9.15 (7.92-11.05)	0.128

BMD: Bone mineral density, Ca: calcium, P: phosphorus ALP: alkaline phosphatase, PTH: parathormone

Table 5 Comparison of treatment changes in patient and control groups

Parameters	Patient Group(n=32) Median (%25-%75 quartile range)	Control Group (n=33) Median (%25-%75 quartile range)	p
Total lumbar (L1-4) T score	0.30 (0.18-0.80)	0.21 (0.16-0.69)	0.589
Total femoral neck T score	0.68 (0.37-0.80)	0.10 (-0.21-0.52)	**0.027**
Serum Ca (mg/dl)	2.26 (1.77_2.85)	0.0 (-0.10_0.10)	**0.001**
Serum P (mg/dl)	0.17 (-0.08-0.25)	0.25 (0.13-0.32)	0.253
Serum ALP (U/l)	-0.80 (-6.97-0.60)	-0.80 (-10.03-4.02)	0.940
Serum PTH (ng/L)	1.12 (0.09-3.93)	1.14 (0.75-2.10)	0.637
Serum Calcidiol (ng/mL)	1.41 (1.30-6.48)	1.29 (-0.95-2.80)	0.076
Serum Osteocalcin (µg/L)	0.02 (-1.37-1.18)	0.14 (-0.67-0.30)	0.154

Ca: calcium, P: phosphate, ALP: alkaline phosphatase, PTH: parathormone

All of the patients had received chemotherapy after surgery and were estrogen receptor-positive (n=32, 100%). The characteristics of the disease are presented in Table 2.

In terms of pre-treatment parameters between the groups, the patient group had lower serum Ca levels and a lower femoral neck T-score than the control group (p=0.038, p=0.007, respectively). In the first year, the two groups' results did not differ from one another (p>0.05), but when the change within the group was examined, the increase in the femoral neck T-score and serum Ca levels was significant in the patient group (p=0.027, p=0.001, respectively), while the change in the control group was not significant (p>0.05) (Tables 3-5).

The pre- and post-treatment evaluation results of the patients who had radiotherapy (n=13) and those who did not receive radiotherapy (n=19) are presented in Table 6.

The femoral neck BMD levels in the patients who underwent radiotherapy were lower at the beginning and after the treatment than the patients who did not receive radiotherapy (p=0.021, p=0.024, respectively), and the post-treatment recovery was not different (p>0.05) (Table 6).

Discussion

In our study, the effect of breast cancer history and bone mineral density (BMD) on postmenopausal osteoporosis (OP) treatment was investigated.

Table 6 Pretreatment (T0) and 1st year (T1) results of patients who received and did not receive radiotherapy (RT).

Parameters	Administered RT (n=13) Median (%25-%75 quartile range)		No RT (n=19) Median (%25-%75 quartile range)		P		
	T0	T1	T0	T1	P*	P#	P&
Total lumbar (L1-4) T score	-3.05 (-3.50_-2.31)	-2.75 (-3.32_-2.15)	-2.82 (-3.21_-1.95)	-2.57 (-2.80_-1.12)	0.246	0.392	0.308
Total femoral neck T score	-3.05 (-3.45_-2.32)	-2.38 (-3.01_-1.91)	-2.75 (-2.98_-2.10)	-1.81 (-2.56_-1.54)	**0.024**	**0.021**	0.127
Serum Ca (mg/dl)	7.05 (6.70-8.50)	9.72 (8.62-10.30)	7.24 (6.90-9.12)	9.95 (9.17-11.38)	0.542	0.724	0.361
Serum P (mg/dl)	3.30 (2.85-3.47)	3.45 (2.92-4.01)	3.55 (3.27-4.40)	3.75 (3.18-4.32)	0.458	0.337	0.872
Serum ALP (U/l)	46.65 (31.15-84.50)	45.58 (21.12-86.77)	48.27 (40.26-94.22)	47.63 (42.60-98.24)	0.265	0.185	0.644
Serum PTH (ng/L)	26.57 (17.60-48.67)	27.14 (18.72-58.21)	29.21 (20.15-56.22)	29.34 (24.21-60.15)	0.282	0.894	0.102
Serum Calcidiol (ng/mL)	19.11 (17.20-20.12)	21.33 (18.61-25.52)	22.25 (19.18-26.30)	24.15 (20.05-32.78)	0.169	0.203	0.836
Serum Osteocalcin (µg/L)	9.58 (6.58-10.05)	9.55 (7.76-10.28)	9.74 (7.21-12.65)	9.71 (8.85-11.28)	0.326	0.181	0.753

Ca: calcium, P: phosphate, ALP: alkaline phosphatase, PTH: parathormone
**: p value between groups before treatment*

#: p value between groups at the 1st year of treatment

&: p value between groups for change with treatment

Before treatment, femoral neck T-score and serum Ca levels were lower in the patient group than in the control group. There was no difference between groups for the first year, but when the change within a group was examined, only the patient group showed a significant increase in femoral neck T-score and serum Ca levels. Patients who received radiotherapy had lower femoral neck BMD levels before and after treatment than those who did not receive radiotherapy, and the post-treatment recovery was not different.

OP and breast cancer are prevalent diseases that affect people of similar ages in the postmenopausal period. This means that the primary risk factor for OP is estrogen deficiency while excess estrogen after menopause is considered to be the key risk factor for breast cancer [9].

Bisphosphonate therapy improves BMD in postmenopausal women using AI and premenopausal women with breast cancer who become amenorrheic throughout treatment, according to randomized, placebo-controlled clinical trials [10].

Bisphosphonates are the current gold standard for oral therapeutics in osteoporosis [11].

In our study, similar results were obtained at the end of the treatment between the patients diagnosed with osteoporosis and regardless of their history of breast cancer, and the patients who received and did not receive RT as a subgroup analysis.

In a study monitoring breast cancer patients scheduled for cytotoxic chemotherapy were assessed by measuring BMD in the 6th month before the start of chemotherapy, the percentage decreases in BMD in the lumbar spine, femoral neck and total hip were found to be $-2{,}36 \pm 2{,}90$, $-2{,}63 \pm 3{,}79$ and $-2{,}08 \pm 2{,}80$, respectively [12].

In our study, the patient group had lower femoral neck T-scores and serum Ca levels before treatment. This implies that BMD measures are impacted by breast cancer therapy. In the literature, which supports our hypothesis, BMD was assessed before starting AI treatment and at the 6th month of treatment in 45 patients included in a study by Erbag et al. [13] Femoral T-scores and BMD levels significantly decreased in the analysis of the patients with two measurement findings. In the analysis of the patients with two measurement results, a significant decrease was found in the femoral T-score and BMD values. When the lumbar vertebra T-scores of the patients were compared, it was found that the second measured vertebra T-score, Z-score, and BMD values were significantly lower. Based on these findings, it has been shown that AI treatment significantly affects BMD even in the first 6 months [13].

Following treatment, our study found no differences between the two groups. There was a significant increase in femoral neck T-score and serum calcium levels in the patient group after 1 year of treatment, but the control group did not experience any notable changes. Similarly in the literature, in a 2-year randomized double-blind placebo-controlled study by Greenspan et al. [14,15] weekly oral risedronate therapy was found to be beneficial for spine and hip BMD in postmenopausal breast cancer women with or without AI therapy.

In breast cancer, RT can be applied to the breast after breast-conserving surgery, to the chest wall, and regional lymph nodes after mastectomy. RT is used as palliative treatment in metastatic breast cancer [16]. Radiation-related bone complications include malignancy, fractures, growth arrest, and osteopenia. Certain complications, including osteopenia, can be reversed, and the

degree of these complications varies with dosage. After radiation therapy, insufficiency fractures are common complications that typically affect bones with the highest trabecular/cortical bone ratio and the highest physiological stress [17]. It has been reported that besides causing bone atrophy, radiotherapy can have a direct effect on the bone in the irradiated area and affect bone vascularity by changing it [18].

In our study, patients who received RT at baseline and afterward had lower femoral neck than those who did not receive RT. Recovery with treatment was also not different from the control group. That is, in our study, we see the negative effect of RT on bone, but the fact that treatment and recovery were not different between the two groups emerged as a pleasing result.

The fact that the BMD values before the cancer history were not known can be considered a limitation.

Conclusion

This study demonstrated the success of osteoporosis treatment in patients with a previous diagnosis of breast cancer. Patients with breast cancer must be screened for osteoporosis and treated accordingly.

Author Contributions: Conceptualization, Y.T., E.K.U.; drafting or revising critically, Y.T., E.K.U., E.U.A., E.G.; data collection or processing, E.K.U., F.N.U., M.K.S.; analysis or interpretation, Y.T., E.K.U., F.N.U., O.Z.K.; literature search, Y.T., E.K.U.; writing, Y.T., O.Z.K., E.U.A., E.G.; supervision: Y.T., E.K.U. All authors have read and agreed to the final version of the manuscript.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: None.

Funding: None.

Ethics approval: The study protocol received institutional review board approval (dated 31.03.2023; Protocol No. P202300018) and all participants provided informed consent in the format required by the clinical research ethics committee of Kirklareli University, Kirklareli, Turkey.

Informed consent: All participants provided written informed consent in the format required by the clinical research ethics committee of the local institute.

Availability of data and material: The authors confirm that the data supporting the findings of this study are available within the article. The data associated with the paper are not publicly available but are available from the corresponding author on reasonable request.

References

1. Duque G, Troen BR. Understanding the mechanisms of senile osteoporosis: new facts for a major geriatric syndrome. *J Am Geriatr Soc*. 2008; 56(5): 935–941. https://doi.org/10.1111/j.1532-5415.2008.01764.x.
2. Manolagas SC, O'Brien CA, Almeida M. The role of estrogen and androgen receptors in bone health and disease. *Nat Rev Endocrinol.* 2013; 9(12): 699–712. https://doi.org/10.1038/nrendo.2013.179.
3. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S et al. Clinician's Guide to Prevention and Treatment of Osteoporosis [published correction appears in Osteoporos Int. 2015; 26: 2045-47]. *Osteoporos Int.* 2014; 25(10): 2359–2381. https://doi.org/10.1007/s00198-014-2794-2.
4. Mahon SM. Osteoporosis: A concern for cancer survivors. Oncol Nurs Forum. 1998; 25: 843–851.
5. Bruning PF, Pit MJ, de Jong-Bakker M, van den Ende A, Hart A, van Enk A. Bone mineral density after adjuvant chemotherapy for premenopausal breast cancer. *Br J Cancer* 1990; 61(2): 308–310. https://doi.org/10.1038/bjc.1990.58.
6. Zhao F, Li C, Wang W, Zhang Y, Yao P, Wei X, Jia Y, Dang Sh, Zhang Sh. Machine learning predicts the risk of osteoporosis in patients with breast cancer and healthy women. *J Cancer Res Clin Oncol*. 2024; 150(2): 102. https://doi.org/10.1007/s00432-024-05622-8.
7. Gradishar WJ, Anderson BO, Blair SL, Burstein HJ, Cyr A, Elias AD, Farrar WB, Forero A, Giordano SH, Goldstein LJ, Hayes DF, Hudis CA, Isakoff SJ, Ljung BM, Marcom PK, Mayer IA, McCormick B, Miller RS, Pegram M, Pierce LJ, Reed EC, Salerno KE, Schwartzberg LS, Smith ML, Soliman H, Somlo G, Ward JH, Wolff AC, Zellars R, Shead DA, Kumar R; National Comprehensive Cancer Network Breast Cancer Panel. Breast cancer version 3.2014. *J Natl Compr Canc Netw* 2014; 12: 542–590.
8. Edge SB, Byrd DR, Compton CC, editors. The American Joint Committee on Cancer: the 7th edition of AJCC cancer staging manual. Springer-Verlag, New York: Springer-Verlag; 2010. 347 p.
9. Fontanges E, Fontana A, Delmas PD. Osteoporosis and breast cancer. *J Bone Spine* 2004; 71(2): 102–110. https://doi.org/10.1016/j.jbspin.2003.02.001.
10. VanderWalde A, Hurria A. Aging and osteoporosis in breast and prostate cancer. *CA Cancer J Clin.* 2011; 61(3): 139–156. https://doi.org/10.3322/caac.20103.
11. Shoback D, Rosen CJ, Black DM, Cheung AM, Murad MH, Eastell R. Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society Guideline Update. *J Clin Endocrinol Metab.* 2020; 105(3): dgaa048. https://doi.org/10.1210/clinem/dgaa048.
12. Nisha Y, Dubashi B, Bobby Z, Sahoo JP, Kayal S, Ananthakrishnan R, Ganesan P. Cytotoxic chemotherapy is associated with decreased bone mineral density in postmenopausal women with early and locally advanced breast cancer. *Arch Osteoporos.* 2023; 18(1): 41. https://doi.org/10.1007/s11657-023-01231-z.
13. Erbag G. The risk of developing osteoporosis of the early-stage breast cancer patients using aromatase inhibitor. [DoctoralThesis]. Kocaeli University School of Medicine; 2011, Available from: https://acikbilim.yok.gov.tr/handle/20.500.12812/409288.
14. Greenspan SL, Vujevich KT, Brufsky A, Lembersky BC, van Londen GJ, Jankowitz RC, Puhalla SL, Rastogi P, Perera S. Prevention of Bone Loss with Risedronate in Breast Cancer Survivors: A Randomized, Controlled Clinical Trial. *Osteoporos Int.* 2015; 26(6): 1857–1864. https://doi.org/10.1007/s00198-015-3100-7.
15. Greenspan SL, Brufsky A, Lembersky BC, Bhattacharya R, Vujevich KT, Perera S, et al. Risedronate prevents bone loss in breast cancer survivors: a 2-year, randomized, double-blind, placebo-controlled clinical trial. *J Clin Oncol.* 2008; 26(16): 2644-52. https://doi.org/10.1200/JCO.2007.15.2967.

16. Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. *N Engl J Med.* 2002; 347(8): 567–575. https://doi.org/10.1056/NEJMoa020128.
17. Pacheco R, Stock H. Effects of radiation on bone. *Curr Osteoporos Rep.* 2013; 11(4): 299–304. https://doi.org/10.1007/s11914-013-0174-z.
18. Shapiro CL, Van Poznak C, Lacchetti C, Kirshner J, Eastell R, Gagel R, Smith S, Edwards BJ, Frank E, Lyman GH, Smith MR, Mhaskar R, Henderson T, Neuner J. Management of Osteoporosis in Survivors of Adult Cancers With Nonmetastatic Disease: ASCO Clinical Practice Guideline. *J Clin Oncol.* 2019; 37(31): 2916–2946. https://doi.org/10.1200/JCO.19.01696.