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ORIGINAL RESEARCH

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Evaluation of bone health in breast cancer patients with germline pathogenic variants

Aysun Isiklar[1,*], Gul Basaran[2]

[1]Department of Internal Medicine, Acibadem Altunizade Hospital, 34000 Istanbul, Turkey
[2]Department of Internal Medicine and Medical Oncology, Acibadem Mehmet Ali Aydinlar University, School of Medicine, 34000 Istanbul, Turkey

***Correspondence**
aysun.isiklar@acibadem.com
(Aysun Isiklar)

Abstract

Patients with breast cancer (BC) have an increased risk of bone loss due to both the cancer itself and the side effects of antineoplastic therapies. This study evaluated the bone health of survivors of BC with germline pathogenic variants (PVs). This is a retrospective cross-sectional study. We identified 165 BC patients in whom PVs in BC susceptibility genes were diagnosed between February 2017 and December 2022 at our breast health center in Acibadem Altunizade Hospital. Only 80 patients underwent dual-energy X-ray absorptiometry (DXA) at the time of diagnosis. The median patient age was 44 years. Of 80 patients, 47% had (n = 38) had *BRCA1* and *BRCA2*, while the remaining 53% (n = 42) had other PVs, which we refer to as *non-BRCA*. Risk-reducing bilateral salpingo-oophorectomy (RRBSO) was performed in 21 patients with BRCA and 6 patients with *non-BRCA* PVs patients ($p < 0.001$). At the 68-months follow up period, a total of 53% had osteopenia, and 11% had osteoporosis. According to the mutation type, among patients with *BRCA1* and *BRCA2*, 47% exhibited osteopenia and 11% had osteoporosis. In *non-BRCA*, 57% had osteopenia and 12% had osteoporosis ($p > 0.05$). In this study, we showed that patients with *BRCA* and *non-BRCA* mutations have similar rates of osteopenia and osteoporosis. This is particularly important for *non-BRCA* mutation carriers, because there is insufficient data on this subject.

Keywords

Hereditary breast cancer; Germline pathogenic variants; Osteopenia; Osteoporosis; Bone health

1. Introduction

Osteopenia is defined as decrease in bone mineral density below normal reference values, while osteoporosis is defined as further loss of bone density with deformation of bone tissue architecture [1, 2].

Aging is the most common cause of osteopenia and osteoporosis [3, 4]. The rate of osteopenia is reported to be 53.4%, and the rate of osteoporosis is 15.4% in women aged $\geq$50 years in the USA [5]. In Turkish women, the rate of osteopenia and osteoporosis are reported to be 50% and 25%, respectively [6].

Patients with breast cancer (BC) are at a higher risk of osteopenia and osteoporosis due to antineoplastic therapies, which include chemotherapy, hormone therapy and radiotherapy. Antineoplastic treatments can either induce early menopause or directly impact bone tissue, which is critical for maintaining bone health [7–9]. The prevalence of bone density loss in survivors of postmenopausal BC is reported to be as high as 80% [10, 11]. Previous studies reported that patients with BC carrying *BRCA1* and *BRCA2* germline pathogenic variants (PVs) experience a higher degree of bone density loss and structural deterioration, mainly associated with risk-reducing bilateral salpingo-oophorectomy (RRBSO), If RRBSO is performed before age of 45, the risk of fracture is shown to increase by 3.63 times [12]. Information regarding bone loss in patients with BC susceptibility genes other than BRCA is lacking. Of note, to date, presence of some of the non-BRCA germline mutations linked with hereditary BC do not confer an increased in ovarian cancer risk, thus are not indication for RRBSO.

This study aimed to elucidate bone health status of patients BC carrying PVs in BC susceptibility genes.

2. Methods

Patients with BC who had documented germline PVs in BC susceptibility genes and who underwent a dual-energy X-ray absorptiometry (DXA) scan to assess bone status at the time of diagnosis were included in our study. All the patients had early-stage BC.

We reviewed the medical records of 165 breast cancer patients followed up by our breast health center and who had been referred to a multigene panel testing based on NCCN (National Comprehensive Cancer Network) criteria and had a PVs in one of the BC susceptibilities genes. All patients underwent multigene panel testing after referral for genetic counseling. Our 26-gene inherited cancer panel includes *ATM*, *ABRAXAS1*, *BARD1*, *BLM*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CHEK2*, *EP-*

CAM, *MEN1*, *MLH1*, *MRE11*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *PALB2*, *PMS2*, *PTEN*, *RAD50*, *RAD51C*, *RAD51D*, *STK11*, *TP53* and *XRCC2*. Data on age, menopausal status, tumor subtype, histology, bone mineral density scores, and type of germline mutation were extracted from medical records. We used the World Health Organization definition of bone health: normal bone if the T-score was above −1.0, osteopenia, if a T-score between −2.5 and −1.0 and osteoporosis if the T-score was equal or below −2.5 [6]. We analyzed the clinical and pathologic characteristics of patients and assess their correlation with bone density.

Statistical analysis was performed using SPSS (version 22.0, IBM Corp., Armonk, NY, USA). Descriptive statistical analysis, including frequency, percentage, mean and standard deviation was used to evaluate the data and explore relationships between variables. Univariate analysis was performed for significant association, and each statistical test chosen was based on the type of variables and distribution of populations. A p-value < 0.05 was considered as statistically significant result.

3. Results

Among 165 BC patients with PVs in BC susceptibility genes, we identified 80 patients who had bone mineral density (BMD) assessments at the time of diagnosis, and that from now on are referred as our sample. The median age of the patients was 44 years, and all patients were female. More than half of the patients (n = 58, 73%) were between 22–50 years-old. The median follow-up duration was 68 (24–288) months. The median body mass index (BMI) was 26.3 kg/m^2. Among 80 patients with BC, 27 had undergone RRBSO, 21 had PVs in *BRCA* genes, and 6 had PVs in *non-BRCA* genes ($p <$ 0.001). Among patients who had undergone RRBSO, 22 were ≤50 years of age (all of them were using tamoxifen), and 5 were >50 years of age. Of 80 patients, 42 (53%) patients had osteopenia, 9 (11%) had osteoporosis, and 29 (36%) had a normal BMD scores (Table 1). A total of 65% of patients had stage I BC, while 35% (n = 28) had stage II–III BC. As expected, the majority of patients had hormone receptor positive BC (n = 58), 10 had Her-2 positive BC, and 12 had triple- negative BC (Table 2). The distribution of tumor subtypes according to germline PVs is shown in **Supplementary Table 1**.

PVs were identified in *BRCA1, BRCA2, CHEK2, ATM, PALB2, MUTHY, RAD50D, BARD1, TP53, BLM, BRIP, MRE11, PMS2, MSH6* and *RAD51C* genes in our study group. At the time of diagnosis, 53% of 80 patients had osteopenia and 11% had osteoporosis. They were not using bisphosphonates and had only daily routine exercise. The frequency of osteopenia in relation to the type of PVs is shown in Table 3. Osteopenia was more commonly observed in patients with BRCA (57%), BRCA1 (37%), MUTHY (71%), ATM (63%) and CHEK2 (45%) PVs. Osteoporosis was observed less commonly and was present in patients with BRCA 1 and 2 PVs, as well as in patients with ATM, PALB2, MUTHY, TP53 and BRIP PVs (Table 3). A slightly higher percentage of osteopenia was present in patients with PVs in non-BRCA gens (57%) in comparison to BC patients with PVs in BRCA 1 and 2 (47%). Similar rate of osteoporosis (10 *vs.* 11%) was observed in patients with PVs in the BRCA and non-BRCA genes, respectively. BMI, age, histological type, molecular subtype, stage, treatment and PVs type (BRCA *vs.* non-BRCA) were not associated with an increased risk of bone loss in univariate analysis.

4. Discussion

Survivors of BC are at an elevated risk of developing osteopenia and osteoporosis. Previous studies have shown that patients with *BRCA1* and *BRCA2* PVs have an increased risk of osteopenia and osteoporosis [12]. However, there are no data regarding patients with PVs in *non-BRCA* genes. In our study patients with *non-BRCA* PVs represent half of the study group, 46% (n = 38) had *BRCA1* and *BRCA2* mutations, while 53% (n = 42) had *non-BRCA* PVs.

In a prospective cohort study in young breast cancer survivors (n = 211) compared to cancer free women (n = 567), with a mean follow up of nearly 72 months; 66% of the BC group and 53% of the control group underwent BMD examination during the follow-up period. In the BC survivor group, the mean age was 48 years. Among the participants, 19% were carriers of *BRCA1* and *BRCA2*, 51% were postmenopausal, 34% had undergone RRBSO before the age of 45, and the mean BMI was 25.9. The tumor histology showed that 75% were hormone receptor positive, 14% were Her-2 positive, and 19% were triple-negative. During an average follow-up of 5.8 years, 66% survivors of BC and 53% of women without cancer reported having undergone a DXA, and there were 112 cases of osteopenia and/or osteoporosis (75% osteopenia only) [13]. This risk was higher in patients BC under the age of 50 years, those with hormone receptor (HR)-positive tumors, and patients treated with aromatase inhibitors, chemotherapy or other endocrine therapies [13].

Do Valle *et al.* [14] conducted a retrospective population-based study between 1996 and 2017 with 359 patients with *BRCA1* and *BRCA2* mutations who underwent RRBSO before the age of 50 without a cancer diagnosis. They concluded that while osteoporosis risk was higher in carriers of BRCA mutations, the risk of fracture was not.

Another study evaluated bone loss in 238 women with *BRCA1* and *BRCA2* mutations carriers, 218 undergone RRBSO with a median age of 57, whilst 20, with a median age of 54, did not. Prevalence of bone loss was 55% in the latter group, and 72.5% in RRBSO group [15].

Bone health studies in patients with hereditary BC have primarily concentrated on *BRCA1* and *BRCA2* mutations. This emphasis is due to the early onset of menopause in this patients, which is a result of the recommendation of RRBSO [12].

Chen *et al.* [16] performed an epidemiologic study that evaluated osteoporosis and bone loss in almost 3 thousand women of which 209 postmenopausal breast cancer survivors. All participants were up to 50 years and postmenopausal, and the follow up period was 6.7 years. Breast cancer survivors had increased risk for bone loss and osteoporosis as expected.

In patients with BC, in addition to the side effects of the disease itself and the treatments they receive, the patient's age, family history, and previous bone structure are also important

TABLE 1. Baseline characteristics of patients.

	All patients n = 80 (100%)	BRCA1/2 n = 38 (47%)	Non-BRCA n = 42 (53%)	*p* Value
Median age (range)	44 (22–74)	42 (26–77)	46 (22–74)	-
	n (%)	n (%)	n (%)	
Age group				
22–50	58 (73)	30 (79)	28 (67)	0.316
51–77	22 (28)	8 (21)	14 (33)	0.316
Menopausal status				
Premenopausal	59 (74)	31 (82)	28 (67)	0.203
Postmenopausal	21 (26)	7 (18)	14 (33)	0.203
RRBSO	27 (34)	21(55)	6 (14)	<0.001
BMD				
Osteopenia	42 (53)	18 (47)	24 (57)	0.502
Osteoporosis	9 (11)	4 (11)	5 (12)	1.000
BMI kg/m^2 median (range)	26.4 (17–44)	26.7 (19–34)	24.6 (17–44)	-
<25	39 (49)	17 (45)	22 (52)	0.512
25–30	17 (21)	8 (21)	9 (21)	1.000
>30	24 (30)	13 (34)	11 (26)	0.635

RRBSO: risk-reducing bilateral salpingo-oophorectomy; BMD: bone mineral density; BMI: body mass index.

TABLE 2. Pathologic and clinical characteristics of patients (n: 80).

	All patients n = 80	BRCA1/2 n = 38 (47)	Non-BRCA n = 42 (53)	*p* Value
Stage at diagnosis				
I	52 (65)	26 (68)	26 (62)	0.641
II–III	28 (35)	12 (32)	16 (38)	
Tumor subtype (IHC)				
HR positive	58 (73)	23 (61)	35 (83)	0.141
Her-2 positive	10 (12)	6 (16)	4 (10)	
TN	12 (15)	9 (24)	3 (7)	
Histology				
IDC	67 (84)	34 (89)	33 (79)	0.112
ILC	6 (7)	1 (3)	5 (12)	
Other	7 (9)	3 (8)	4 (10)	
Treatment				
Chemotherapy	65 (81)	32 (84)	33 (79)	0.577
Hormone therapy by type				
Tamoxifen	47 (74)	22 (58)	25 (60))	0.009
Aromatase inhibitor	18 (26)	5 (13)	13 (31)	

HR: hormone receptor; TN: triple negative; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; IHC: immunohistochemistry.

TABLE 3. Distribution of osteoporosis and osteopenia by pathogenic mutations.

Germline pathogenic variants	Number of patients	Osteopenia n (%)	Osteoporosis n (%)
BRCA1	16	6 (37)	2 (13)
BRCA2	21	12 (57)	1 (5)
BRAC1 + 2	1		1
CHEK2	10	4 (40)	
CHEK2 + TP53	1	1	
ATM	7	4 (57)	1
ATM + BARD1	1	1	
PALB2	7	3 (43)	1
MUTHY	7	5 (71)	1
TP53	2	1	1
RAD50	2		
BLM	1	1	
BRIP	1		1
MRE11	1	1	
MSH6	1	1	
PMS2	1	1	
RAD51C	1	1	
Total	80	42 (53)	9 (11)

factors, as shown in earlier studies [17]. Due to the side effects of treatments such as bisphosphonate and denosumab used in the treatment of osteoporosis in patients with BC, the benefit-loss relationship must be taken into consideration. Additionally, precautions such as vitamin D intake, calcium intake, smoking and alcohol cessation should be taken [18, 19].

5. Conclusions

In conclusion, bone loss and osteoporosis rates were similar in survivors of BC who were *BRCA* PVs and *non-BRCA* PVs. Knowing these is important for us to take precautions in patients with BC who carry pathogenic mutations, especially since this information is lacking in carriers of *non-BRCA* PVs.

AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

AI—Performed material preparation, data collection and analysis; AI and GB—Written the first draft of the manuscript. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval of this retrospective study was granted in 2023 by Mehmet Ali Aydinlar University Ethics Committee (2023-13/462). All participants signed a written informed consent form.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.ejgo.net/files/article/1713796672807419904/attachment/Supplementary%20material.docx.

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