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Low Bone Mineral Density in Middle-Aged Breast Cancer Survivors: Prevalence and Associated Factors

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Keywords

Breast cancer · Menopause · Bone mass · Osteoporosis · Middle-aged women

Summary

Background: The aim of this study was to investigate the prevalence of low bone mineral density (BMD) and associated factors in middle-aged breast cancer survivors (BCS). **Patients and Methods:** A cross-sectional study was conducted with 70 BCS of 45–65 years of age undergoing complete oncology treatment. Logistic regression models were used to identify factors associated with low BMD (osteopenia and osteoporosis taken together as a single group). **Results:** The mean age of participants was 53.2 ± 5.9 years. BMD was low at the femoral neck in 28.6% of patients and at the lumbar spine in 45.7%. Body mass index ≤ 30 kg/m^2 (adjusted odds ratio (OR) 3.43; 95% confidence interval (CI) 1.0–11.3) and postmenopausal status (OR adjusted 20.42; 95% CI 2.0–201.2) were associated with low BMD at the lumbar spine. Femoral neck measurements, age > 50 years (OR 3.41; 95% CI 1.0–11.6), and time since diagnosis > 50 months (OR adjusted 3.34; 95% CI 1.0–11.3) increased the likelihood of low BMD. **Conclusion:** These findings show that low BMD is common in middle-aged BCS. Factors were identified that may affect BMD in BCS and should be considered when implementing strategies to minimize bone loss in middle-aged women with breast cancer.

Schlüsselwörter

Mammakarzinom · Menopause · Knochenmasse · Osteoporose · Frauen mittleren Alters

Zusammenfassung

Hintergrund: Ziel dieser Studie war die Bestimmung der Prävalenz niedriger Knochendichte und damit assoziierter Faktoren bei Brustkrebsüberlebenden mittleren Alters. **Patienten und Methoden:** Es wurde eine Querschnittsstudie mit 70 Brustkrebsüberlebenden im Alter von 45 bis 65 Jahren, die in kompletter onkologischer Behandlung waren, durchgeführt. Mit niedriger Knochendichte assoziierte Faktoren wurden mit logistischen Regressionsmodellen ermittelt (Osteopenie und Osteoporose wurden zu einer Gruppe zusammengefasst). **Ergebnisse:** Das mittlere Alter der Teilnehmer war 53,2 ± 5,9 Jahre. Eine niedrige Knochendichte bestand am Oberschenkelhals bei 28,6% der Patienten und im Lendenwirbelbereich bei 45,7%. Body mass index ≤ 30 kg/m^2 (adjustierte Odds-Ratio (OR) 3,43; 95% Konfidenzinterval (KI) 1,0–11,3) und postmenopausaler Status (OR adjustiert 20,42; 95% KI 2,0–201,2) waren mit einer niedrigen Knochendichte im Lendenwirbelbereich assoziiert. Umfang des Oberschenkelhalses, Alter > 50 Jahre (OR 3,41; 95% KI 1,0–11,6) sowie Zeit seit Diagnosestellung > 50 Monate (OR adjustiert 3,34; 95% KI 1,0–11,3) machten eine niedrige Knochendichte wahrscheinlicher. **Schlussfolgerung:** Diese Ergebnisse zeigen, dass niedrige Knochendichte bei Brustkrebsüberlebenden mittleren Alters häufig vorkommt. Es konnten Faktoren identifiziert werden, die die Knochendichte bei dieser Patientengruppe potentiell beeinflussen und bei der Implementierung von Strategien zur Minimierung des Knochenverlustes bei Brustkrebspatientinnen mittleren Alters berücksichtigt werden sollten.

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Introduction

Breast cancer is the most common malignancy in women worldwide [1]. Women aged 45–64 years account for 47% of new breast cancer cases in the United States [2]. A large proportion of women will be diagnosed with breast cancer during the menopausal transition or in the postmenopause, stages characterized by changes in reproductive hormones [3]. In breast cancer survivors (BCS), ovarian failure resulting from chemotherapy or the reproductive aging process [3] is associated with decreased bone density [4]. Breast cancer patients > 40 years of age are more likely to develop amenorrhea after chemotherapy than younger women [4, 5], with rapid bone loss [4, 6]. Bone loss starts to accelerate 2 years before the last menstruation, with a significant loss in the 2 years after menopause [7]. Current guidelines recommend that hormone therapy should be considered in women with established bone loss to prevent further reduction in bone mineral density (BMD) and decrease osteoporotic fractures [8]. Despite its effects on bone, hormone therapy increases the risk of recurrence in BCS [9]. BMD has previously been investigated in BCS [4–6, 10–13]. Some authors have reported an association between chemotherapy-induced ovarian failure and bone loss [4, 6]. Others have suggested that a decrease in BMD may occur in BCS undergoing chemotherapy irrespective of the effect of chemotherapy on ovarian function [5]. Osteoclastic activity may increase from the breast cancer itself, enhancing bone resorption [14]. Other factors that may damage bone health include the use of aromatase inhibitors [15] and secondary causes such as vitamin D deficiency and hyperparathyroidism [16]. A combination of factors may contribute to bone loss, leading to a greater fracture risk in BCS [17]. The frequency of abnormal BMD may vary according to the skeletal site [5, 10, 11, 18]. In a follow-up study of postmenopausal women, a greater reduction in BMD was observed at the lumbar spine than at the femoral neck [18]. As in healthy women [19, 20], BMD in BCS may be affected by menopausal status [6], body mass index (BMI) and weight [6, 10–13]. Most studies investigating BMD in BCS were conducted in developed countries [4–6, 10–13]. The aim of the present study was to investigate the prevalence of low BMD in middle-aged women with breast cancer and its associated factors.

Patients and Methods

Patients

A complete description of the participant selection process has been published previously [21]. Briefly, the current sample originated from a study conducted to investigate the prevalence of menopausal symptoms, quality of life, and BMD in middle-aged BCS [21]. A cross-sectional study was conducted at the Women's Hospital, University of Campinas, Brazil. Women of 45–65 years of age, who had not used hormone therapy or tamoxifen in the previous 6 months and had no history of other malignant tumors, were included in the study. None of the participants was taking aromatase inhibitors. 100 BCS were consecutively invited to participate in the study. 3 patients refused due to lack of time. 22 patients were undergoing oncology treatment, and 5 had no BMD measurements. 70 BCS comprised the present study sample. Participants provided information on their sociodemographic characteristics. Clinical characteristics included BMI (kg/m^2), time since breast cancer diagnosis, tumor stage, chemotherapy, radiotherapy, diabetes mellitus, and hypertension. Study approval was obtained from the institution's internal review board, and all women signed an informed consent form.

Bone Mineral Density Measurement

BMD (g/cm^2) was measured at the femoral neck and lumbar spine (L2–L4) using a Lunar DPX device (DXA, Madison, WI, USA). BMD was also expressed as T-scores, using the World Health Organization criteria [22]: normal: T-score ≥ –1 standard deviation (SD); osteopenia: T-score between –1 and –2.5 SD; and osteoporosis: T-score ≤ –2.5 SD. A BMD T-score < –1 SD was considered low.

Statistical Analysis

The relationship between the characteristics of the breast cancer patients and BMD, classified as low or normal, was assessed using logistic regression models [23], calculating the crude and adjusted (for age and BMI) odds ratio (OR) as measures of association, with the respective 95% confidence intervals (95% CI). SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) was used to perform all statistical analysis.

Results

The mean age of the participants was 53.2 ± 5.9 years. Mean time since breast cancer diagnosis was 65.2 ± 55.1 months. Approximately 74% of participants were white, 82.9% were postmenopausal, and 11.4% were smokers. The prevalence of diabetes mellitus and hypertension was 10 and 25.7%, respectively. Distribution according to tumor stage was: 0 (11.4%), I (17.1%), II (52.9%), and III (18.6%). Approximately 73% had undergone chemotherapy, while 70% had been submitted to radiotherapy. Mean BMD (g/cm^2) was 0.930 ± 0.139 at the femoral neck and 1.090 ± 0.147 at the lumbar spine (L2–L4). The prevalence of low BMD was 28.6% at the femoral neck and 45.7% at the lumbar spine (L2–L4) (table 1). BMI ≤ 30 kg/m^2 (OR adjusted 3.43; 95% CI 1.0–11.3) and postmenopausal status (OR adjusted 20.42; 95% CI 2.0–201.2) increased the risk of low BMD at the lumbar spine (L2–L4) (table 2). Age > 50 years (OR 3.41; 95% CI 1.0–11.6) and time since diagnosis > 50 months (OR adjusted 3.34; 95% CI 1.0–11.3) were factors associated with low BMD at the femoral neck (table 3).

Discussion

Low BMD was associated with a 1.80–4.0-fold increase in fracture rate [19]. Our findings suggest that middle-aged BCS are at an increased risk of fracture. Similarly, in the Women's Health Initiative Observational Study, fracture risk was found to be 15% higher in BCS compared to cancer-free women [17]. In the present study, mean BMD (g/cm^2) was 0.930

Table 1. Prevalence of low bone mineral density in breast cancer survivors according to T-score (n = 70)

Site	Patients, n (%)			
	normal BMD	low BMD[a]	osteopenia	osteoporosis
Femoral neck	50 (71.4)	20 (28.6)	18 (25.7)	2 (2.8)
Lumbar spine (L2–L4)	38 (54.3)	32 (45.7)	23 (32.8)	9 (12.8)

[a]T-score < – 1SD (osteopenia + osteoporosis).
BMD = Bone mineral density.

Table 2. Factors associated with low bone mineral density at the lumbar spine of breast cancer survivors according to T-score (n = 70)

Characteristics	Bone mineral density, n (%)		Crude		Adjusted	
	low	normal	OR	95% CI	OR	95% CI
Age, years						
≤ 50	12 (38)	15 (39)	ref.			
> 50	20 (63)	23 (61)	1.09	0.4–2.9	–	–
Race[a]						
White	26 (81)	26 (68)	ref.		ref.	
Non-white	6 (19)	12 (32)	0.50	0.1–1.5	0.55	0.1–1.8
Age at menarche[a], years						
> 12	21 (66)	19 (50)	ref.		ref.	
≤ 12	11 (34)	19 (50)	0.52	0.1–1.4	0.51	0.1–1.4
Body mass index[b], kg/m^2						
> 30	5 (16)	14 (37)	ref.		ref.	
≤ 30	27 (84)	24 (63)	3.15	1.0–10.0	3.43	1.0–11.3
Menopausal status[a]						
Premenopausal	1 (3)	11 (29)	ref.		ref.	
Postmenopausal	31 (97)	27 (71)	12.63	1.5–104.3	20.42	2.0–201.2
Parity[a]						
0	4 (13)	7 (18)	ref.		ref.	
≥ 1	28 (88)	31 (82)	1.58	0.4–6.0	1.59	0.4–6.3
Smoking[a]						
No	27 (84)	35 (92)	ref.		ref.	
Yes	5 (16)	3 (8)	2.16	0.4–9.9	1.84	0.3–8.7
Time since diagnosis, months[a]						
≤ 50	13 (41)	22 (58)	ref.		ref.	
> 50	19 (59)	16 (42)	2.01	0.7–5.2	1.71	0.6–4.7
Hypertension[a]						
No	27 (84)	25 (66)	ref.		ref.	
Yes	5 (16)	13 (34)	0.36	0.1–1.1	0.50	0.1–1.8
Diabetes[a]						
No	29 (91)	34 (89)	ref.		ref.	
Yes	3 (9)	4 (11)	0.88	0.1–4.2	1.60	0.2–9.5
Chemotherapy[a]						
No	12 (38)	7 (18)	ref.		ref.	
Yes	20 (63)	31 (82)	0.38	0.1–1.1	0.41	0.1–1.3
Radiotherapy[a]						
No	9 (28)	12 (32)	ref.		ref.	
Yes	23 (72)	26 (68)	1.18	0.4–3.3	1.04	0.3–3.1

[a]OR adjusted for age and body mass index.
[b]OR ajusted for age.
OR = Odds ratio; 95% CI = 95% confidence interval; ref. = reference

± 0.139 at the femoral neck and 1.090 ± 0.147 at the lumbar spine. An investigation of healthy Brazilian women (mean age 53.9 years) showed a mean BMD (g/cm^2) of 0.912 ± 0.151 at the femoral neck and 1.069 ± 0.177 at the lumbar spine [24], values very close to those found in this cohort of BCS. In this study, the prevalence of osteopenia and osteoporosis was 25.7 and 2.8%, respectively, at the femoral neck. According to lumbar spine measurements, 32.8% of the participants had osteopenia and 12.8% had osteoporosis. In a study of postmenopausal BCS, Twiss et al. [11] reported that 16.5% had osteopenia and 2.4% had osteoporosis according to total hip measurement. The same authors also found that 27.3% had osteopenia and 10.8% had osteoporosis at the lumbar spine [11]. Those results are consistent with the present data regarding a higher prevalence of changes at the lumbar spine. Low BMD may be more prevalent at the lumbar spine because the trabecular bone which forms a major part of the vertebral body is highly responsive to hormonal alterations [17] common in the age group evaluated in the present study.

Various authors have identified a positive relationship between higher BMI and bone mass both in BCS [6, 10–13] and cancer-free women [18–20]. Waltman et al. [12] reported BMD findings in 249 BCS. These authors identified an association between higher BMI and greater BMD at the spine. These results confirm the findings of the present study and are consistent with results from other studies conducted with

Table 3. Factors associated with low bone mineral density at the femoral neck of breast cancer survivors according to T-score (n = 70)

Characteristics	Bone mineral density, n (%)		Crude		Adjusted	
	low	normal	OR	95%CI	OR	95%CI
Age, years						
≤ 50	4 (20)	23 (46)	ref.			
> 50	16 (80)	27 (54)	3.41	1.0–11.6	–	–
Race[a]						
White	15 (75)	37 (74)	ref.		ref.	
Non-white	5 (25)	13 (26)	0.95	0.2–3.1	1.01	0.28–3.7
Age at menarche[a], years						
> 12	10 (50)	30 (60)	ref.		ref.	
≤ 12	10 (50)	20 (40)	1.50	0.5–4.3	1.79	0.5–5.5
Body mass index[b], kg/m^2						
> 30	3 (15)	16 (32)	ref.		ref.	
≤ 30	17 (85)	34 (68)	2.67	0.6–10.4	3.87	0.9–16.1
Menopausal status[a]						
Premenopausal	1 (5)	11 (22)	ref.		ref.	
Postmenopausal	19 (95)	39 (78)	5.36	0.6–44.6	2.73	0.2–27.0
Parity[a]						
0	2 (10)	9 (18)	ref.		ref.	
≥ 1	18 (90)	41 (82)	1.98	0.3–10.1	1.94	0.3–10.8
Smoking[a]						
No	18 (90)	44 (88)	ref.		ref.	
Yes	2 (10)	6 (12)	0.81	0.1–4.4	0.64	0.1–3.8
Time since diagnosis, months[a]						
≤ 50	5 (25)	30 (60)	ref.		ref.	
> 50	15 (75)	20 (40)	4.50	1.4–14.4	3.34	1.0–11.3
Hypertension[a]						
No	16 (80)	36 (72)	ref.		ref.	
Yes	4 (20)	14 (28)	0.64	0.1–2.3	0.84	0.2–3.5
Diabetes[a]						
No	19 (95)	44 (88)	ref.		ref.	
Yes	1 (5)	6 (12)	0.39	0.04–3.4	0.49	0.04–5.1
Chemotherapy[a]						
No	6 (30)	13 (26)	ref.		ref.	
Yes	14 (70)	37 (74)	0.82	0.2–2.6	1.12	0.3–3.8
Radiotherapy[a]						
No	4 (20)	17 (34)	ref.		ref.	
Yes	16 (80)	33 (66)	2.06	0.5–7.1	1.74	0.4–6.4

[a]OR adjusted for age and body mass index.

[b]OR adjusted for age.

OR = Odds ratio; 95% CI = 95% confidence interval; ref. = reference

BCS [6, 10, 11, 13]. The osteo-protective effect of BMI is unclear. However, osteo-protection is probably based on a complex combination of mechanical and hormonal factors, including the role of adiponectin in bone mass regulation [25].

Several studies have shown that postmenopausal status constitutes a risk factor for bone loss [6, 20]. Estrogen exerts a protective effect on bones and plays an important role in maintaining bone health [26]. A decrease in bone mass due to an imbalance between bone resorption and bone formation is typical of osteoporosis in women with estrogen depletion [26]. As found in cancer-free women [6, 20], the results of the present study show that menopause increases the risk of low BMD in BCS.

In the present cohort, age > 50 years was associated with low BMD. However, other studies found no relationship between age and BMD [10, 12]. Age-related bone loss has been reported by other authors [18–20], confirming our findings. In a population-based study with a 15-year follow-up that included 955 postmenopausal women, BMD was shown to decrease significantly at the femoral neck and lumbar spine [18]. The decline in BMD was greater at the lumbar spine (–3.12% per year), than at the femoral neck (–1.67% per year), suggesting that estrogen deficiency may act differently at different bone sites [18].

This case study showed an association between a longer time since diagnosis and low BMD. Another study evaluated BMD in 30 postmenopausal BCS with a mean of 61.7 ± 42.1 months since diagnosis; however, no association was found between time since diagnosis and BMD [10]. A longer time since diagnosis may imply older age. However, in the current study, analysis of the factors associated with low BMD was adjusted for age, minimizing the effect of the variable age.

The present study had some limitations due to its cross-sectional design and lack of a healthy control group. Physical activity, medication, and calcium intake were not investigated. However, in a systematic review [27], evidence of an association between current physical activity or calcium intake and BMD was inconsistent. Factors associated with low BMD described in non-BCS (age, BMI, menopause) were identified, and also negatively affected BMD in BCS. Breast cancer

treatment, ovarian failure, and contraindication to hormone therapy may intensify bone loss in midlife. The findings of this study may prove useful when establishing and implementing strategies to minimize bone loss in middle-aged BCS.

Disclosure Statement

The authors declare no conflict of interest.

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