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# Osteoporosis after adjuvant treatment for early-stage breast cancer

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## ABSTRACT

**Introduction:** Adjuvant treatment of early-stage breast cancer has been associated with bone loss in randomised trials, but evidence from unselected populations is needed. In a single-center study, we assessed the annual percentage change in bone mineral density (&;$BMD_t$) and risk of osteoporosis from two to five years after adjuvant chemotherapy in patients with oestrogen-receptor-positive and oestrogen-receptor-negative tumours.

**Methods:** Dual energy X-ray absorptiometry (DXA) was performed in 241 recurrence-free Danish breast cancer patients, among whom 157 had a prior DXA scan within two years of chemotherapy ("early"). Linear regression was used to assess &;$BMD_t$ in spine and hip according to age, different health-related variables and time since early DXA.

**Results:** Based on 157 patients, we observed annual decreases in spine BMD of 1.73% (95% confidence interval (CI): –2.01-–1.44, p < 0.001) and hip BMD of 1.30% (95% CI: –1.51-–1.09, p < 0.001). Patients aged less than 50 years at diagnosis had a significant decrease in mean spine BMD of 2.23% (95% CI: –2.78-–1.68), whereas the decline was more limited in patients aged 50-59 years and patients aged 60 years or older with a mean spine BMD of 1.70% (95% CI: –2.07-–1.34) and 0.81% (95% CI: –1.42—0.20), respectively. The results persisted in multivariable analyses. Osteoporosis was diagnosed in 9% of patients, all postmenopausal.

**Conclusions:** Adjuvant anthracycline-taxane-based chemotherapy followed by endocrine therapy caused bone loss, especially in younger compared with older patients with early-stage breast cancer, confirming the results from randomised trials.

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**Trial registration**: The study was approved by the Ethics Committee in Region of Southern Denmark (Project ID S-20140142) and the Danish Data Protection Board (ID 2008-58-0035).

Adjuvant therapy after surgery for early-stage breast cancer has contributed to an increasing survival, the five-year relative survival rates being close to 90% in the Nordic countries [1]. Today, the recommended duration of adjuvant tamoxifen for premenopausal women is ten years according to the American Society of Clinical Oncology and European Society for Medical Oncology guidelines [2, 3]. In postmenopausal women, aromatase inhibitors (AIs) can be used upfront or as extended adjuvant therapy after 2-5 years of tamoxifen [3]. The combination of a long survival and long treatment duration creates a need to be aware of long-term adverse

effects, e.g. increased risk of osteoporosis and fractures. Few human studies have addressed the effect of adjuvant chemotherapy before initiation of endocrine treatment on bone mass. Most have reported a loss in bone mass, but we [4] and others [5] have not detected such an effect.

The effect of adjuvant endocrine treatment on bone mineral density (BMD) has been studied by dual energy X-ray absorptiometry (DXA) in large randomised trials comparing tamoxifen with AIs for reducing the risk of breast cancer recurrence. These studies included 138 to 424 patients [6, 7]. Both studies demonstrated that use of tamoxifen was associated with an increase in BMD and AIs with a loss in BMD. Several adjuvant trials have reported that an increased risk of fractures is associated with AIs [8, 9]. Loss of BMD is closely related to the risk of fractures. In a cross-sectional study, 200 Chinese breast cancer survivors treated with chemotherapy followed by five years of endocrine therapy were matched with 200 healthy women, and a four-fold increased risk of vertebral fracture was detected [10].

The randomised trials had stringent inclusion and exclusion criteria, so it may be difficult to generalise the results to unselected populations seen in routine clinical practice. Our aim was to evaluate the long-term effect of adjuvant chemotherapy and endocrine therapy on BMD by DXA in a Danish cohort.

## METHODS

### Patients

Eligible were women aged 18 years or older who had surgery for a histologically verified early-stage breast cancer diagnosed between 2009 and 2012 and received adjuvant systemic treatment according to the national guidelines of the Danish Breast Cancer Cooperative Group at the Department of Oncology, Odense University Hospital, Denmark. In addition, patients had to be free of recurrence since diagnosis.

Patients were excluded if they had been diagnosed with other malignancies or conditions that required chemotherapy within five years prior to their breast cancer, pre-existing osteoporosis, or treatment with bisphosphonates or methotrexate. Patients who had completed five years of follow-up without recurrence of cancer and had no active contact with the department were not included. All patients provided written informed consent to have a DXA and to use results of prior DXAs.

### Adjuvant treatments

All patients received adjuvant chemotherapy with epirubicin (90 mg/m$^2$) and cyclophosphamide (600 mg/m$^2$) followed by docetaxel (100 mg/m$^2$). Premenopausal patients with oestrogen receptor (ER) positive tumours received tamoxifen (20 mg daily), whereas postmenopausal patients received an aromatase inhibitor (2.5 mg daily). The hospital provided endocrine treatment free of charge.

### Data sources

Baseline data on patients and disease characteristics were abstracted from patient records and pathology reports. Data were derived directly from the DXA scanner at the Osteoporosis Clinic, Department of Endocrinology, Odense University Hospital, and included dates of DXAs, height, weight, T- and Z-scores, area (g), bone mineral content (cm$^2$) and BMD (g/cm$^2$) in the spine, hip, and forearm. Information on health-related questions was collected by use of a questionnaire. Data collection was initiated on 1 November 2014.

### Bone densitometry

A total of 157 patients had a DXA within two years since receiving their first cycle of chemotherapy. BMD was measured at the first to the fourth vertebrae of the lumbar spine (L1-L4) and the left hip (total hip) using one of four Hologic Discovery QDR scanners. These DXAs were included in the analyses and referred to as the early

measure of BMD. At the follow-up DXA, each patient was scanned with the same Hologic Discovery QDR scanner that was used for the early DXA, and BMD was measured at the vertebrae of the lumbar spine (L1-L4), the left hip (total hip) and the mid third of the left forearm. The scanners were not cross calibrated; but for each individual scanner, quality standards were tested daily with the Hologic spine phantom. The coefficient of variation of the BMD measurements was 1.0% for the lumbar spine and forearm and 0.9% for the hip. Osteoporosis was defined by the World Health Organization (WHO) as a T-score for BMD ≤ 2.5 standard deviations (SDs) below the mean value expected for a young healthy female adult in the spine and/or the hip. The Z-score describes the number of SDs by which the BMD in an individual differs from the mean value expected for age and sex [11]. All scans were performed by specially trained personnel.

### Statistical analyses

Patients with an early DXA were compared with patients without an early DXA by Fisher's exact test. Based on the T-score in spine and/or hip, all patients were categorised as normal BMD, osteopenic or osteoporotic. For patients who had an early DXA and a follow-up DXA, the annual percentage change (&;$BMD_t$) in the spine and hip was calculated as: ((BMD in follow-up DXA – BMD in early DXA)/BMD in early DXA)/ (time difference in years between follow-up DXA and early DXA) × 100. The mean &;$BMD_t$ in the spine and hip was presented with 95% confidence intervals (95% CI) for all patients and for subgroups. Simple and multivariable linear regression models were used, and model assumptions were checked graphically and with tests. Multivariable analysis included age, calcium/vitamin D supplement, endocrine therapy, smoking, alcohol, exercise, weight change and time from early DXA. The level of statistical significance was set to 5%. Statistical analyses were performed.

*Trial registration:* The study was approved by the Ethics Committee in Region of Southern Denmark (Project ID S-20140142) and the Danish Data Protection Board (ID 2008-58-0035).

## RESULTS

In 2009 through 2012, a total of 496 breast cancer patients received adjuvant chemotherapy for early-stage breast cancer, among whom 125 did not meet the inclusion criteria. Invitations were sent to 371 patients of whom 100 declined participation. Among the 271 patients who accepted a DXA, 30 patients with a mean age of 55 years (range: 43-68 years) were excluded; 25 patients because they had been diagnosed with osteoporosis before breast cancer and five patients due to prior or current treatment with alendronate or methotrexate. In total, 241 patients with a mean age of 52 years (range: 28-77 years) were included in the final analyses. Among these, 157 patients (65%) had an early DXA performed about five months after initiation of chemotherapy (mean 0.40 years, 95% CI: 0.33-0.48). Patients without an early DXA (n = 84) were similar in tumour characteristics to patients with an early DXA, but significant differences in menopausal status (p = 0.04), endocrine therapy (p < 0.001) and smoking (p = 0.03) were seen (**Table 1**).

The follow-up DXA revealed that 42% had a normal BMD, 49% had osteopenia and 9% (n = 22) had osteoporosis; 21 patients had a T-score ≤ –2.5, and one patient a vertebral fracture (**Table 2**). The prevalence of osteoporosis was higher in the spine (20 out of 21 patients) than in the hip (one out of 21 patients).

**TABLE 1 /** Disease and clinical characteristics of 241 Danish patients with early-stage breast cancer who received chemotherapy during 2009-2012. The values are n (%).

| | DXA within 2 yrs since chemotherapy | | | |
|---|---|---|---|---|
| | no ($N_n$ = 84) | yes ($N_y$ = 157) | patients in total ($N_{tot}$ = 241) | p-value[a] |
| *Age at diagnosis* | | | | 0.38 |
| < 50 yrs | 35 (42) | 52 (33) | 87 (36) | |
| 50-59 yrs | 35 (42) | 78 (50) | 113 (47) | |
| ≥ 60 yrs | 14 (16) | 27 (17) | 41 (17) | |
| *Menopausal status at diagnosis* | | | | 0.04 |
| Premenopausal | 50 (60) | 71 (45) | 121 (50) | |
| Postmenopausal | 34 (40) | 86 (55) | 120 (50) | |
| *Type of surgery* | | | | 0.66 |
| Lumpectomy | 56 (67) | 110 (70) | 166 (69) | |
| Mastectomy | 28 (33) | 47 (30) | 75 (31) | |
| *Type of carcinoma* | | | | 0.78 |
| Ductal | 74 (88) | 140 (89) | 214 (89) | |
| Lobular | 6 (7) | 10 (7) | 16 (7) | |
| Others | 4 (5) | 5 (3) | 9 (3) | |
| DCIS | 0 | 2 (1) | 2 (1) | |
| *Tumour size* | | | | 0.23 |
| 0-9 mm | 11 (13) | 21 (13) | 32 (13) | |
| 10-19 mm | 30 (36) | 73 (47) | 103 (43) | |
| ≥ 20 mm | 43 (51) | 63 (40) | 106 (44) | |
| *Histological grade* | | | | 0.68 |
| Low: I | 9 (11) | 23 (14) | 32 (13) | |
| Moderate: II | 40 (47) | 64 (41) | 104 (43) | |
| High: III | 31 (37) | 64 (41) | 95 (40) | |
| Not graded | 4 (5) | 6 (4) | 10 (4) | |
| *Nodal status* | | | | 0.79 |
| Negative | 37 (44) | 73 (46) | 110 (46) | |
| Positive | 47 (56) | 84 (54) | 131 (54) | |
| *Endocrine therapy* | | | | < 0.001 |
| ER negative | 33 (39) | 30 (19) | 63 (26) | |
| Tamoxifen | 25 (30) | 47 (30) | 72 (30) | |
| Letrozole | 9 (11) | 57 (36) | 66 (27) | |
| Sequential[b] | 17 (20) | 23 (15) | 40 (17) | |
| *HER2 status* | | | | 0.45 |
| Negative | 59 (70) | 118 (75) | 177 (73) | |
| Positive | 25 (30) | 39 (25) | 64 (27) | |
| *Smoking status at diagnosis* | | | | 0.03 |
| Never/former | 61 (73) | 133 (85) | 194 (80) | |
| Current | 23 (27) | 24 (15) | 47 (20) | |
| *BMI at follow-up DXA* | | | | 0.36 |
| Normal: < 25 kg/m$^2$ | 29 (35) | 64 (41) | 93 (39) | |
| Overweight: 25-30 kg/m$^2$ | 27 (32) | 54 (34) | 81 (33) | |
| Obese: > 30 kg/m$^2$ | 28 (33) | 39 (25) | 67 (28) | |

DCIS = ductal carcinoma in situ; DXA = dual energy X-ray absorptiometry; HER2 = human epidermal growth factor receptor 2; ER = oestrogen receptor.

a) Fisher's exact test.

b) Switch of endocrine therapy between tamoxifen and letrozole, or switch between letrozole and arimidex or exemestane.

**TABLE 2 /** Prevalence of osteoporosis 2-5 years after adjuvant chemotherapy in 241 Danish early-stage breast cancer patients. The values are n (%).

| | Time since chemotherapy | | | | |
|---|---|---|---|---|---|
| | 2-3 yrs (mean age: 52 yrs) | 3-4 yrs (mean age: 55 yrs) | 4-5 yrs (mean age: 52 yrs) | ≥ 5 yrs (mean age: 49 yrs) | All (mean age: 52 yrs) |
| *Normal BMD* | 25 (36) | 24 (39) | 31 (47) | 22 (50) | 102 (42) |
| Osteopenia | 38 (55) | 33 (53) | 27 (41) | 19 (43) | 117 (49) |
| Osteoporosis | 6 (9) | 5 (8) | 8 (12) | 3 (7) | 22 (9) |
| All patients | 69 | 62 | 66 | 44 | 241 |

BMD = bone mineral density.

At diagnosis, 63 patients (27%) received a daily supplement of calcium and/or vitamin D. This number increased to 121 (51%) patients during chemotherapy, and further to 176 (74%) among patients after cessation of chemotherapy. The patients received an average of 732 mg of calcium and 25 µg of vitamin D daily.

**Changes in bone mineral density measurements**

**Table 3** shows the annual percentage change in BMD in 157 early-stage breast cancer patients with a decrease in spine BMD of 1.73% (95% CI: –2.01-–1.44, p < 0.001), and hip BMD of 1.30% (95% CI: –1.51-–1.09, p < 0.001). The median time between early and follow-up DXA was 2.9 years (range: 1.3-5.2 years). In the spine, patients aged less than 50 years at diagnosis had significant decreases with a mean annual percentage change (&;$BMD_t$) of 2.23% (95% CI: –2.78-–1.68), whereas patients aged 50-59 years and patients aged 60 years or older had mean &;$BMD_t$ decreases of 1.70% (95% CI: –2.07-–1.34) and 0.81% (95% CI: –1.42-–0.20), respectively. After adjusting the changes for all variables, the relative mean annual decreases at the spine were 0.75% (95% CI:–1.57- 0.08) among patients aged 50-59 years, and 1.59% (95% CI: –2.56-–0.62) in patients aged less than 50 years at diagnosis compared with patients aged 60 years or older (p = 0.005). Thus, the absolute losses were significantly lower among the older age groups. Similar observations were made for hip BMD.

**TABLE 3 /** Annual percentage change and annual percent change in bone mineral density for each category in relation to the reference group in univariable ($B_1$) and multivariable ($B_2$) linear regression analyses in lumbar spine and hip in 157 Danish patients with early-stage breast cancer.

| | | | Univariable analyses | | Multivariable analyses | |
|---|---|---|---|---|---|---|
| | n | Mean $\Delta BMD_t$ (95% CI), % | $B_1$ (95% CI), % | p-value | $B_2$ (95% CI), % | p-value |
| *Lumbar spine* | 51 (18.1) | 5 (1.9) | 1 (0.4) | 57 (20.4) | | |
| All patients | 157 | −1.73 (−2.01–−1.44) | - | | - | |
| Age at diagnosis: | | | | 0.003 | | 0.005 |
| ≥ 60 yrs | 27 | −0.81(−1.42–−0.20) | 0 (ref.) | | 0 (ref.) | |
| 50-59 yrs | 78 | −1.70 (−2.07–−1.34) | −0.89 (−1.82-0.03) | | −0.75 (−1.57-0.08) | |
| < 50 yrs | 52 | −2.23 (−2.78–−1.68) | −1.42 (−2.40–−0.44) | | −1.59 (−2.56–−0.62) | |
| Calcium/vitamin D: | | | | 0.72 | | 0.93 |
| No | 26 | −1.61 (−2.27–−0.95) | 0 (ref.) | | 0 (ref.) | |
| Yes | 130 | −1.75 (−2.07–−1.43) | −0.14 (−0.91-0.63) | | 0.03 (−0.73-0.80) | |
| Endocrine therapy: | | | | 0.08 | | 0.09 |
| ER-negative[a] | 30 | −0.96 (−1.56–−0.37) | 0 (ref.) | | 0 (ref.) | |
| Tamoxifen | 47 | −1.92 (−2.36–−1.49) | −0.96 (−2.04-0.12) | | −0.05 (−1.00-0.90) | |
| Letrozole | 57 | −1.92 (−2.37–−1.47) | −0.96 (−2.00-0.08) | | −0.92 (−1.77–−0.07) | |
| Sequential[b] | 23 | −1.83 (−2.95–−0.70) | −0.87 (−2.14-0.41) | | −0.69 (−1.69-0.32) | |
| Smoking at diagnosis: | | | | 0.43 | | 0.48 |
| Never/former | 133 | −1.77 (−2.09–−1.46) | 0 (ref.) | | 0 (ref.) | |
| Current | 24 | −1.45 (−2.15–−0.76) | 0.32 (−0.47-1.11) | | 0.28 (−0.50-1.05) | |
| Alcohol consumption: | | | | 0.13 | | 0.31 |
| 0 U/wk | 20 | −1.29 (−2.29–−0.30) | 0 (ref.) | | 0 (ref.) | |
| 1-7 U/wk | 112 | −1.91 (−2.25–−1.57) | −0.62 (−1.65-0.41) | | −0.36 (−1.22-0.51) | |
| ≥ 8 U/wk | 24 | −1.23 (−1.77–−0.69) | 0.06 (−1.22-1.35) | | 0.21(−0.85-1.28) | |
| Exercise after chemotherapy: | | | | 0.64 | | 0.78 |
| 0-1 day/wk | 13 | −1.72 (−2.62–−0.81) | 0 (ref.) | | 0 (ref.) | |
| 2-4 days/wk | 85 | −1.85 (−2.26–−1.44) | −0.13 (−1.40-1.14) | | −0.04 (−1.06-0.99) | |
| 5-7 days/wk | 58 | −1.56 (−2.02–−1.09) | 0.16 (−1.15-1.48) | | 0.17 (−0.88-1.23) | |
| Weight change[c]: | | | | 0.32 | | 0.25 |
| Loss: < 0 kg | 67 | −1.56 (−1.97–−1.15) | 0 (ref.) | | 0 (ref.) | |
| Gain: ≥ 0 kg | 90 | −1.85 (−2.24–−1.45) | −0.29 (−0.86-0.29) | | −0.33 (−0.89-0.23) | |
| Time from early DXA: | | | | 0.04 | | 0.03 |
| > 2.9 yrs | 78 | −1.43 (−1.76–−1.09) | 0 (ref.) | | 0 (ref.) | |
| ≤ 2.9 yrs | 79 | −2.02 (−2.47–−1.56) | −0.59 (−1.15–−0.03) | | −0.62 (−1.18–−0.05) | |
| *Hip* | | | | | | |
| All patients | 157 | −1.30 (−1.51–−1.09) | - | | - | |
| Age at diagnosis: | | | | 0.25 | | 0.055 |
| ≥ 60 yrs | 27 | −0.93 (−1.42–−0.45) | 0 (ref.) | | 0 (ref.) | |
| 50-59 yrs | 78 | −1.33 (−1.59–−1.06) | −0.39 (−1.09-0.30) | | −0.22 (−0.81-0.37) | |
| < 50 yrs | 52 | −1.45 (−1.88–−1.02) | −0.52 (−1.26-0.22) | | −0.79 (−1.49–−0.09) | |
| Calcium/vitamin D: | | | | 0.55 | | 0.93 |
| No | 26 | −1.17 (−1.62–−0.71) | 0 (ref.) | | 0 (ref.) | |
| Yes | 130 | −1.34 (−1.57–−1.10) | −0.17 (−0.73-0.39) | | 0.02 (−0.53-0.58) | |
| Endocrine therapy: | | | | 0.01 | | 0.001 |
| ER-negative | 30 | −0.65 (−1.09–−0.22) | 0 (ref.) | | 0 (ref.) | |
| Tamoxifen | 47 | −1.19 (−1.52–−0.88) | −0.54 (−1.32-0.23) | | 0.04 (−0.65-0.73) | |
| Letrozole | 57 | −1.62 (−1.95–−1.30) | −0.97 (−1.71–−0.21) | | −0.98 (−1.59–−0.36) | |
| Sequential[b] | 23 | −1.57 (−2.36–−0.78) | −0.92 (−1.84-0.01) | | −0.81 (−1.53–−0.09) | |
| Smoking at diagnosis: | | | | 0.80 | | 0.85 |
| Never/former | 133 | −1.31 (−1.54–−1.09) | 0 (ref.) | | 0 (ref.) | |
| Current | 24 | −1.24 (−1.84–−0.64) | 0.07 (−0.51-0.65) | | 0.05 (−0.51-0.62) | |
| Alcohol consumption: | | | | 0.08 | | 0.15 |
| 0 U/wk | 20 | −1.23 (−2.01–−0.45) | 0 (ref.) | | 0 (ref.) | |
| 1-7 U/wk | 112 | −1.44 (−1.68–−1.19) | −0.21 (−0.96-0.55) | | −0.01 (−0.63-0.62) | |
| ≥ 8 U/wk | 24 | −0.77 (−1.15–−0.38) | 0.46 (−0.48-1.40) | | 0.56 (−0.21-1.33) | |
| Exercise after chemotherapy: | | | | 0.64 | | 0.64 |
| 0-1 day/wk | 13 | −1.51 (−2.54–−0.49) | 0 (ref.) | | | |
| 2-4 days/wk | 85 | −1.35 (−1.61–−1.10) | 0.16 (−0.78-1.10) | | | |
| 5-7 days/wk | 58 | −1.18 (−1.57–−0.80) | 0.33 (−0.64-1.29) | | 0.31 (−0.46-1.07) | |
| Weight change[c]: | | | | 0.19 | | 0.19 |
| Loss: < 0 kg | 67 | −1.46 (−1.77–−1.15) | 0 (ref.) | | 0 (ref.) | |
| Gain: ≥ 0 kg | 90 | −1.18 (−1.47–−0.90) | 0.28 (−0.14-0.70) | | 0.27 (−0.13-0.68) | |
| Time from early DXA: | | | | 0.02 | | 0.005 |
| > 2.9 yrs | 78 | −1.06 (−1.30–−0.83) | 0 (ref.) | | 0 (ref.) | |
| ≤ 2.9 yrs | 79 | −1.54 (−1.88–−1.20) | −0.48 (−0.89–−0.07) | | −0.59 (−1.00–−0.18) | |

$\Delta BMD_t$ = annual percentage change in BMD = ((BMD at follow-up DXA − BMD at early DXA)/BMD at early DXA)/(time difference in yrs between follow-up and early DXA) × 100.

$B_1$ = change in $\Delta BMD_t$ in relation to the reference group; $B_2$ = change in $\Delta BMD_t$ in relation to the reference group, adjusted for all variables listed; BMD = bone mineral density; CI = confidence interval; DXA = dual energy X-ray absorptiometry; ER = oestrogen receptor; ref. = reference.

a) Patients with ER-negative tumours who did not receive endocrine therapy.

b) Endocrine therapy switched between letrozole and tamoxifen, anastrozole or exemestane.

c) Change in weight between "early" DXA and follow-up DXA.

In the spine, patients with ER-negative tumours had a &;$BMD_t$ decrease of 0.96% (95% CI:–1.56–−0.37), whereas patients who received endocrine therapy with tamoxifen, letrozole or sequential treatment, had a &;$BMD_t$ decrease of 1.92% (95% CI: –2.36–−1.49), 1.92% (95% CI: –2.37–−1.47), and 1.83% (95% CI: –2.95–−0.70), respectively. The differences in annual bone loss between the four treatment groups were not significant (p = 0.09). Furthermore, a longer time interval between DXAs was significantly related to a more limited bone loss (Table 3, p = 0.03). Similar results were observed for hip BMD (Table 3).

## DISCUSSION

In this cohort of 157 Danish early-stage breast cancer patients diagnosed between 2009 and 2012 who received adjuvant chemotherapy and endocrine therapy depending on tumour characteristics, we observed annual decreases in spine and hip BMD of 1.73% and 1.30%, respectively. Higher rates of bone loss were observed in younger (< 50 years) than in older (≥ 60 years) women in the hip and especially in the spine. These results agree well with those from a randomised trial reporting decreases in spine, hip and femoral neck BMD of 1.8%, 1.2% and 1.08% [12], respectively, illustrating that our data from an unselected real-world population are in line with the results of a randomised trial.

In another study of postmenopausal early-stage breast cancer patients on AI treatment, those < 55 years had an estimated annual bone loss in the spine of 2.4%, whereas women ≥ 75 years had estimated bone loss in the spine of 0.9%. In hip BMD, the < 55 year group had decreases of 1.4% versus 0.9% for the ≥ 75 year group [13]. Tamoxifen, a selective oestrogen receptor modulator, has shown different effects depending on the target tissue and on menstrual status. In postmenopausal women, tamoxifen has an oestrogen-agonistic effect on bone with preservation of bone, whereas tamoxifen decreases BMD in premenopausal women [14]. These annual bone losses are consistent with the results of our study.

The higher rate of bone loss observed in younger women than in older women may be explained by the effect of chemotherapy on ovarian function, which may lead to chemotherapy-induced ovarian failure (CIOF) and menopause. A rapid decrease in oestrogen levels is seen at menopause which is accompanied by a shift in bone turnover from a low to a high state. At menopause, bone loss occurs in an initial accelerated phase that lasts for 4-8 years and a subsequent slow phase that lasts indefinitely [15]. During the rapid phase, up to 7% of BMD may be lost per year in premenopausal women with CIOF [16]. In postmenopausal women, a natural annual loss of 1% in spine BMD is observed [17]. A bone loss of 10% corresponds to a reduction of one standard deviation, which may increase the risk of fractures by a factor two to three depending on the scanning site, e.g., lumbar spine or hip [18]. Based on our results, breast cancer patients treated with letrozole or tamoxifen could potentially loose approximately 10% of spine BMD during a five-year treatment period. Since 2015, postmenopausal breast cancer patients have received adjuvant treatments with zoledronic acid twice a year for four years to prevent bone metastases and maintain bone mass [19], whereas premenopausal women have not. Therefore, we recommend monitoring bone status by DXA, especially in breast cancer patients with CIOF, and counselling to reduce risk factors for osteoporosis.

In our study population, 9% (n = 22) of the 241 included patients were diagnosed with osteoporosis at the follow-up DXA. These results are similar to those of a cross-sectional Danish population-based study [20] and to our own results from breast cancer patients receiving adjuvant chemotherapy [4]. Others have reported osteoporosis in 10.7% of breast cancer patients [13]. Thus, our findings are consistent with previous findings.

The main strength of our study is that patients with an early DXA were scanned on the same scanner when they had the follow-up DXA. This made it possible to compare measurements. It is also a strength that the questionnaire was pilot tested before use, which may have contributed to the high response rate of the questionnaire. It is a limitation that the study design included a historical cohort and that not all participants had two measurements of BMD. In patients who had two DXAs, these were not necessarily obtained at the same intervals relative to treatment. This may have resulted in under- or overestimation of bone loss in relation to treatment. We had no blood samples of bone turnover markers, vitamin D status or menopausal status, which is a weakness.

## CONCLUSIONS

In this real-world unselected cohort of Danish early-stage breast cancer patients who received adjuvant chemotherapy and endocrine therapy depending on tumour characteristics, we found annual bone losses that followed the pattern of normal physiology of bone metabolism in relation to CIOF and endocrine therapy. The bone losses were consistent with previous results from randomised trials. To act in time, we recommend that breast cancer patients, especially with CIOF, are monitored with DXA and advised to reduce risk factors for osteoporosis.

Ethical approval: All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its subsequent amendments and comparable ethical standards.

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