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ORIGINAL ARTICLE

Hormone therapy and osteoporosis in breast cancer survivors: assessment of risk and adherence to screening recommendations

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Abstract

Summary The long-term impact of hormone therapy for breast cancer on risk of osteoporosis and the extent to which bone screening recommendations are implemented in daily practice remain unknown. We found that the aromatase inhibitor-induced risk of osteoporosis did not continue in the off-treatment follow-up. Adherence to screening recommendations was suboptimal.

Introduction A case-cohort study was undertaken to better understand the impact of hormone therapy on breast cancer patients' risk of osteoporosis, and to estimate the extent to which current bone mineral density screening recommendations are implemented in real-life daily practice.

Methods This study is based on 1692 female breast cancer survivors recruited from "Leumit" healthcare fund, who were diagnosed with primary nonmetastatic invasive breast cancer between 2002 and 2012. A 20% random subcohort was sampled at baseline, and all osteoporosis cases were identified. Adjusted hazard ratios (HR) with 95% confidence intervals (CI) were estimated by weighted Cox proportional hazards models.

Results Of 1692 breast cancer survivors, 312 developed osteoporosis during a median follow-up of 5 years. The crude cumulative incidence of osteoporosis accounting for death as a competing risk was 25.7% (95% CI, 21.9–29.5%). In multivariable analyses, osteoporosis was positively associated with the aromatase inhibitor (AI) sequential treatment after tamoxifen (HR, 3.14; 95% CI, 1.44–6.88; $P = .004$) but was more pronounced with AI use as upfront monotherapy (HR, 5.53; 95% CI, 1.46–20.88; $P = .012$). This effect did not continue in the off-treatment follow-up. In subgroup analysis by menopausal status, tamoxifen did not seem to confer a protective effect on bone health in postmenopausal patients. Adherence to screening recommendations in AI-treated postmenopausal women was suboptimal, particularly at baseline and after 48 months of continuous AI use.

Conclusions The natural, age-related reduction in bone density is exacerbated by breast cancer active AI treatment. Future research should focus on investigating screening adherence-related barriers/facilitators and effective strategies to bring practice in line with agreed standards.

Keywords Aromatase inhibitor · Bone health · Breast cancer · Osteoporosis · Survivorship · Tamoxifen

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Abbreviations

AI	Aromatase inhibitor
ARF	Attributable risk fraction
ATC	Anatomic therapeutic chemical
BC/S	Breast cancer/survivors
BMD	Bone mineral density
CI	Confidence interval
CIF	Cumulative incidence function
HR	Hazard ratio
HT	Hormone therapy
ICD-9	International classification of diseases, ninth revision
IDR	Incidence density rate
IDRR	Incidence density rate ratio
INCR	Israel National Cancer Registry
IQR	Interquartile range
LHS	Leumit Health Services
P	*P* value
PAF	Population attributable fraction
SE	Standard error
SIDR	Standardized incidence density rate ratio
$\chi 2$	Chi square

Introduction

With increased breast cancer (BC) survival, recognition of survivorship care issues, including bone health, has become more compelling than ever before [1]. Skeletal homeostasis is achieved through coupled and balanced bone resorption and formation [2, 3]. The physiologic estrogen deprivation occurring after menopause disrupts the osteoclast-osteoblast activity, promoting loss of bone mineral density (BMD), increasing thereby the risk of osteoporosis and fragility fractures [4]. This risk can be further exacerbated by estrogen-depleting treatment for hormone-responsive BC, such as aromatase inhibitors (AIs) [5, 6], which markedly suppress levels of circulating estrogen at an accelerated rate [5, 7], with a 2–4 fold increased bone loss compared to the natural, age-related ovarian failure [3].

Osteoporosis is a silent disease with few symptoms in its early stages, and often goes undiagnosed until complications, such as a fall or minimal-traumatic fracture, occur [8–10]. Osteoporotic fractures are associated with the loss of more disability-adjusted life years than any cancer other than that of the lung [11], posing enormous health burden on the individual, and taking a substantial economic toll on the society [3, 5, 10]. Prevention of treatment-induced bone loss and proactive maintenance of bone integrity with lifestyle interventions and antiresorptive therapy [12] should, therefore, be an important component of cancer supportive care [5, 12, 13]. Despite that several guidelines and consensus statements highly recommend regular assessment of osteoporosis risk during AI therapy [3, 14, 15], currently no standardized recommendations exist for bone monitoring in BC [16] with regard to screening frequency and treatment criteria [17, 18], which may be due in part to the paucity of robust scientific evidence in this area. For example, most information stems from studies that had strict inclusion and exclusion criteria, which may not reflect osteoporosis risk in the unselected population seen in routine clinical practice [3, 13]. Our understanding of how age interacts with risk to bone, for instance, is limited because the mean age in randomized clinical trials is generally below 65 years [13]. In addition, while the deleterious effect of AIs on bone has been well established, the emerging evidence suggestive of a waning off-treatment effect [18, 19], expressed in normalization of bone turnover and partial recovery of BMD [3], is less clear and needs confirmation [5, 20]. In contrast, the effect of tamoxifen is poorly understood; some studies have attributed bone-sparing effects to tamoxifen among older survivors of early-stage BC [21], whereas others did not demonstrate such protective effect [20]. It must be noted that little attention has been given to discern the effects of AIs from those of tamoxifen which leaves the question of how much of the excess risk can be ascribed to AI treatment largely unsatisfied [18]. Moreover, most studies addressing osteoporosis risk concerned patients treated in the distant past and thus may not reflect changes in hormone therapy during recent decades. Therefore, the current investigation was undertaken to better understand the association between hormone therapy and osteoporosis in a relatively large recently treated cohort of breast cancer survivors (BCS) with near-complete follow-up, as well as to estimate the extent to which current screening recommendations are implemented in real-life daily practice.

Methods

Data sources

This case-cohort study, in which covariate data are examined in all cases and a representative sample of the parent cohort, 'the subcohort' [22], utilized automated data from Leumit Health Services (LHS), a nonprofit Israeli healthcare fund covering around 10% of the total population (now 8.5 million). Based on the National Health Insurance Law (1995), all Israeli citizens are insured by one of four healthcare funds, at their discretion. LHS electronic databases capture detailed information on medical encounters, pharmacy claims, diagnoses, and procedures. The pharmacy records include an exact identification of the dispensed drug in terms of substance, dosage and days' supply. All drugs are classified according to the Anatomic Therapeutic Chemical (ATC) system. Diagnoses are coded by each physician or hospital system according to the International Classification of Diseases, Ninth Revision (ICD-9), whereas outpatient procedures are coded by the LHS internal procedure code system. Linkage to the Israel National Cancer Registry (INCR) provided ascertainment of BC cases and supplementary information on cancer characterization and treatment. Patient personal characteristics that could not be assessed directly or accurately from administrative databases were attained through questionnaires in the form of telephone interviews, which are an accepted approach for quantitative data collection [23]. These data sources have been described in detail and validated in a previous report [24].

Study population

Source cohort

We assembled a patient-based cohort to estimate long-term treatment-related adverse outcomes in survivors of BC. A detailed description of the cohort is provided elsewhere [25]. Briefly, subjects were female members of LHS, BCS for at least 1 year, who were treated for early-stage or regionally advanced primary invasive BC (ICD-9: 174) between January 1, 2002, and December 31, 2012. Women with in-situ or metastatic BC, or with a previous history of any type of cancer were considered ineligible. Two thousand six hundred forty-four women matched the inclusion criteria of whom 20% were randomly sampled at baseline to comprise the subcohort.

Osteoporosis in the parent cohort

The source cohort (including the random subcohort) was further limited to BCS with no history of osteoporosis (ICD-9: 730.0) before or during the first year following BC diagnosis. The rationale for the one-year conditional osteoporosis-free survival was to assure a sufficient period for commencement of hormone therapy (HT). Other exclusion criteria included a history of any condition that may affect bone metabolism [26], including other metabolic bone disease (ICD-9: 730–733), hyperparathyroidism (ICD-9: 252), rheumatoid arthritis (ICD-9: 714), osteoarthritis (ICD-9: 715), and ankylosing spondylitis (ICD-9: 720). In total, 952 (36%) women were excluded, leaving 1692 BCS to be observed until the earliest of the following: osteoporosis occurrence (index date), death, LHS disenrollment, or the predetermined censoring date (May 31, 2016). Time at risk began 1 year after BC diagnosis.

Subcohort and cases

Data processing was restricted to the randomly selected subcohort of 323 BCS, and all those who developed osteoporosis during the study period ($n = 312$). A fraction of the osteoporosis incident cases was part of the subcohort ($n = 48$). Of the 587 eligible candidates for the administration of a constructed questionnaire, 118 women were not contacted due to death of the participant. The remaining 469 women, representatives of BCS who were alive at the time of the study ($n = 1298$), were contacted, and the survey questionnaire was satisfactorily completed by all interviewees (Appendix 1).

Data collection

LHS pharmacy claims, diagnoses and procedures billing databases were used to obtain information on HT, osteoporosis, and BMD scans, respectively. Information on potential confounders was extracted from LHS and INCR administrative databases along with the questionnaire.

Exposure to hormone therapy

HT was received by 85% of the 469 cases and the subcohort, within 7 months following BC diagnosis, and for a median duration of 5 years (interquartile range [IQR], 4–6 years). HT was started before the diagnosis of osteoporosis in all cases, with more than 90% of users receiving treatment at least 1 year before the index date. The treatment protocol was predominantly based on sequential therapy (72%) with the use of AIs after 2–3 years of tamoxifen to complete 5 years of HT. Only 5% of those exposed to HT received upfront AI monotherapy.

Outcome measures

The primary outcome was osteoporosis-free survival, which was defined as the time from study entry (1 year after BC diagnosis) to a first diagnosis of osteoporosis. Identification of incident cases was based on LHS electronic encounter code (ICD-9 = 730.0), which was shown to have high accuracy using a previously validation algorithm established on at least two of the following: BMD measurement (T-score ≤ − 2.5 derived from the dual-energy X-ray absorptiometry technique), procurement of osteoporosis specific medications (defined by a dispensed medication prescription of any of the following: bisphosphonates, strontium ranelate, or calcitonin within 1 year after osteoporosis diagnosis), or review of medical records (images, hip fracture surgery, osteoporotic fractures, clinical symptoms such as height loss, neck/low back pain, back or spine deformity, within 1 year before or after osteoporosis diagnosis). The positive and negative predictive values were 93.8% (95% confidence interval [CI], 79.9–98.3), and 100.0% (95% CI, 95.8–100.0), respectively [24]. Secondary outcomes included occurrence of a first typical osteoporotic fracture (vertebral, ICD-9: 805–806; hip, ICD-9: 820–821; arm and wrist, ICD-9: 812–814), and presence/absence of any BMD testing (measured by dual-energy X-ray absorptiometry) among postmenopausal BCS (subcohort and cases) taking AI treatment in three prespecified time periods: (1) baseline, defined as one-year interval preceding AI start [27], (2) periodic-1 (2-year repeat scan), defined as 24-month interval post AI initiation in women who remained on AI continuously for ≥ 2 years, and (3) periodic-2 (4-year repeat scan), defined as 24–48-month interval after starting AI in women who remained on AI continuously for ≥ 4 years. A definition of nonadherence to BMD screening was based on bone health guidance statements [3, 10, 12, 14, 15] which strongly endorse baseline and periodic BMD assessments for postmenopausal women taking AIs. Women who were on AI ≥ 24 months were considered nonadherent if they did not have at least 1 billed BMD test (baseline or periodic-1) [27]. Women who were on AI ≥ 48 months were considered nonadherent if they did not have at least 2 BMD tests within 12 months to AI start till 48 months post AI initiation [27]. Adherence ≥ 90% was regarded optimal [7].

Covariates

Information extracted from the INCR included: BC diagnosis date, age at diagnosis, BC stage at diagnosis, type of surgery, axillary lymph node dissection, and immigration status. Supplementary information on the region of residence, mean household income (derived from census data based on subject's residence), comorbid conditions at the time of BC diagnosis, estrogen receptor status (ER-positive and ER-negative disease were included to examine effect of hormone therapy and chemotherapy, respectively), lymph node involvement, and health services utilization were abstracted from LHS registries. The questionnaire, which was delivered in 2016–2017 only to the subcohort and to BCS diagnosed with osteoporosis, captured data on ethnicity, cohabitation status, education, reproductive history, family history of osteoporosis, work history, and lifestyles.

Ethics

This study was approved by the Institutional Review Boards of LHS and the University of Haifa, and all enrolled women provided oral informed consent.

Statistical analysis

Osteoporosis excess incidence relative to the general population was quantified based on data derived from another healthcare fund, which recently established a registry of the epidemiology of this disease for the period 2003–2013 [28]. We used cumulative incidence function (CIF) to estimate the crude incidence of osteoporosis in the presence of death as a competing risk [29].

To assess the independent relation between breast cancer HT and osteoporosis risk, multiple weighted Cox regression models were applied. Impact measures of attributable risk fraction (ARF), and population attributable fraction (PAF) were assessed.

In secondary analysis, we explored the effect of AI duration on risk of osteoporosis, to address the potential of surveillance bias related to accentuated care and increased probability of outcome detection in those initiating treatment [30]. We dichotomized AI duration using the median cut-off point. Additional analysis by type of HT agent was performed.

A number of sensitivity analyses were undertaken to test out the robustness of our results, including a propensity score analysis to assess the possibility of bias resulting from confounding by indication for HT, multiple imputations of missing data to address potential introduction of survival bias, and restriction to 5-year osteoporosis-free survivors to contend with a possible misclassification bias resulting from agent switch in the sequential setting occurring after the outcome. Details of the statistical methods used are provided in Appendix 2.

Dataavailability The data that support the findings of this study are available from LHS and the authors, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of LHS.

Results

Total osteoporosis population

Incidence of osteoporosis/fractures

During a median follow-up of 5.0 years (IQR, 3.0–8.1 years), 312 of 1692 BCS developed osteoporosis (Age-standardized incidence density rate ratio, 2.7; 95% CI, 1.5–4.8; $P < .001$). Review of medical records of cases revealed that in more than 80% osteoporosis was clinically diagnosed after the development of symptoms (such as low back pain, back or spine deformity). The overall cumulative incidence of osteoporosis in the presence of death as a competing risk was 25.7% (95% CI, 21.9–29.5%) at 13 years of follow-up. Considering follow-up or attained age, osteoporosis cumulative incidence was significantly higher among women treated by HT than those who did not receive HT (Gray's test for equality of CIFs: $P < .001$) (Fig. 1). A total of 46 new fractures were recorded, of which 31 (28 fractures per 10,000 person-years) occurred in the arm/wrist, hip or vertebrae.

Subcohort and cases

Patient characteristics

Table 1 summarizes the characteristics of the 204 subcohort and 265 osteoporosis cases alive at the time of the study.

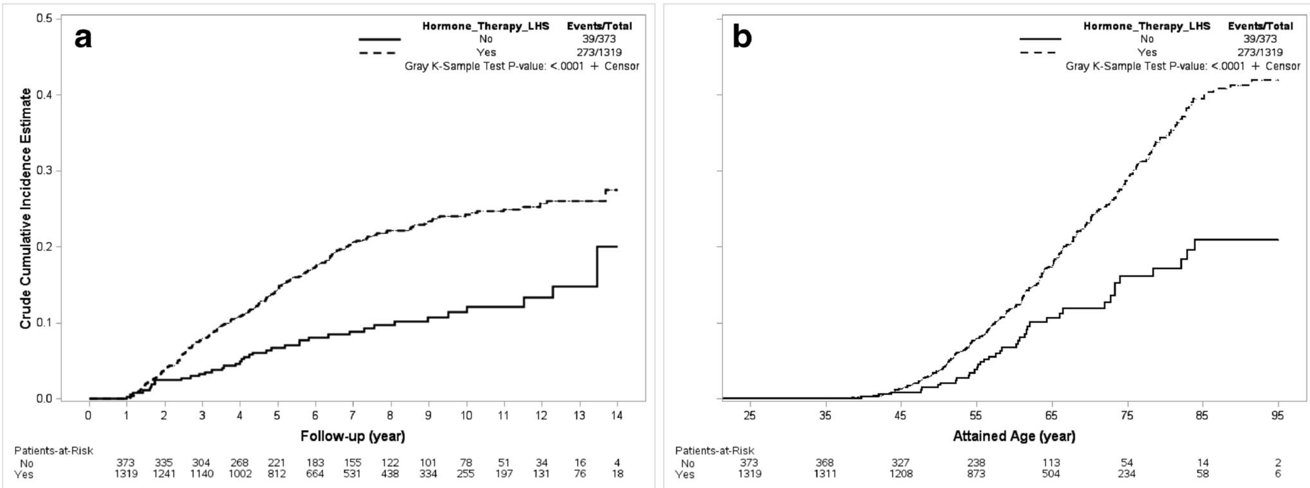

Fig. 1 Osteoporosis cumulative incidence in the presence of death as a competing risk among the entire cohort of 1692 women treated or not by hormone therapy according to the length of follow-up (**a**), and attained age (**b**)

Osteoporosis cases were more likely to be older, unmarried, and less educated than subcohort noncases. HT was more likely in cases than noncases, whereas chemotherapy was less administered to osteoporosis cases. Lifestyle components reported post-osteoporosis occurrence indicated a higher prevalence of poor nutrition and tobacco history in osteoporosis patients. Nevertheless, osteoporosis cases were more successful in controlling their weight than noncases.

Risk of osteoporosis in relation to treatment

In multivariable models, HT was significantly and positively associated with osteoporosis (hazard ratio [HR], 2.91; 95% CI, 1.36–6.22-4.79; $P = .006$). At the population level, the PAF, which is the proportion of osteoporosis incidence in the total cohort that is attributed to HT, was 58%. Modeling by HT agent to discern specific treatment effects disclosed a statistically significantly elevated osteoporosis risk related to AIs (alone or sequentially following tamoxifen) (Table 2). In contrast, tamoxifen alone did not exhibit a statistically significant protective effect, although the interval estimates were too wide for a valid interpretation of the results. When AI duration was considered, osteoporosis crude incidence density rate ratio was significantly increased during the entire AI exposure period compared to no AI use; however, in regression models, the risk of osteoporosis was significantly maintained only for AI duration beyond 2.5 years.

Confirmatory and subgroup analyses

In sensitivity analyses, no appreciable differences with primary results were observed, except for AI duration ≤ 2.5 years, which manifested a significant positive relation with osteoporosis in most models (Table 3, Models 1–4).

In subgroup analysis by age at BC diagnosis as a proxy for menopause, AIs increased the risk of osteoporosis in postmenopausal women (> 50 years), whereas tamoxifen did not seem to be inversely associated with risk of osteoporosis in this group of patients. Of note, notwithstanding AIs are contraindicated in premenopausal women as aromatase inhibition inadequately suppresses ovarian estrogen production [31], three women ≤ 50 years at BC diagnosis were treated with AI monotherapy due to intolerability with tamoxifen, all were perimenopausal at time of AI initiation, and all developed osteoporosis (Table 3, Model 5).

Off-treatment risk of osteoporosis

The association with AIs consistently attenuated over time and followed a dose-response-type gradient. By the 7th year since BC diagnosis and beyond, there was no statistically discernible difference in osteoporosis crude incidence between women taking AIs and women not treated with HT (Table 4).

Adherence to BMD screening guidelines

In the year before AI initiation, BMD scan was not completed in 74.6% of 215 postmenopausal women. Of the 157 women who remained on AI for ≥ 2 years, 59.9% had the 2-year repeat screen, whereas 29.6% did not have any BMD testing and were considered nonadherent. After 48 months of continuous AI use in 71 women, 54% had the 4-year repeat BMD screen, 24.5% had no BMD tests at all, and another 35.5% had only one BMD testing, rendering nonadherence to ≥ 2 BMD screens to 60% (Fig. 2).

Stratifying BMD screening by osteoporosis status revealed a slight trend toward an increase in adherence rates among the osteoporosis cases although the differences with noncases did not achieve statistical significance (weighted nonadherence

Table 1 Patient characteristics

Characteristic	Osteoporosis cases, weighted % (SE)	Noncases, weighted % (SE)	Weighted HR (95% CI)	
			Crude model[a]	*P*
Number	265	204		
Demographics				
Mean attained age, years (SE)	60.35 (0.52)	58.77 (0.62)	NA	
Ethnicity (Arab vs non-Arab)[b]	6.04 (1.46)	9.31 (2.04)	0.95 (0.46–1.97)	.885
Cohabitation status (unmarried vs married)[c]	35.47 (2.94)	26.47 (3.09)	1.44 (0.94–2.20)	.098
District of residence				
Northern	26.42 (2.71)	21.08 (2.86)	1.90 (1.11–3.26)	.019
Central	28.30 (2.77)	31.37 (3.25)	1.12 (0.68–1.84)	.649
Jerusalem	17.36 (2.33)	16.18 (2.58)	1.56 (0.89–2.75)	.123
Southern	27.92 (2.76)	31.37 (3.25)	1.00 (Reference)	
Immigration status (non-Israel born vs Israel born)	58.87 (3.03)	45.59 (3.49)	1.19 (0.80–1.79)	.392
Education level				
≤ 10 years	46.42 (3.07)	31.37 (3.25)	1.88 (1.14–3.10)	.013
11–12 years	23.40 (2.60)	14.71 (2.48)	2.59 (1.51–4.47)	.001
13+ years	30.19 (2.82)	53.92 (3.49)	1.00 (Reference)	
Employment before breast cancer Dx				
Full-time job	48.68 (3.07)	59.31 (3.44)	0.88 (0.56–1.38)	.574
Part-time job	8.68 (1.73)	4.41 (1.44)	1.26 (0.54–2.94)	.597
Retired	3.02 (1.05)	7.35 (1.83)	0.25 (0.10–0.61)	.003
Looking after family or home	39.62 (3.01)	28.92 (3.18)	1.00 (Reference)	
Household income, tertile (median NIS)[d]				
1 (6150)—lowest	33.58 (2.90)	33.33 (3.30)	0.99 (0.62–1.59)	.974
2 (7264)	33.96 (2.91)	38.24 (3.41)	0.62 (0.38–1.01)	.055
3 (9056)—highest	32.45 (2.88)	28.43 (3.16)	1.00 (Reference)	
Breast cancer characterization				
Breast cancer Dx year				
2002–2005	49.06 (3.07)	24.51 (3.01)	1.62 (0.97–2.71)	.064
2006–2009	35.85 (2.95)	36.27 (3.37)	1.33 (0.81–2.18)	.265
2010–2012	15.09 (2.20)	39.22 (3.42)	1.00 (Reference)	
Mean age at breast cancer Dx, years (SE)	55.87 (0.51)	51.19 (0.62)	NA	
Age distribution at breast cancer Dx, years				
≤ 39	5.28 (1.38)	18.14 (2.70)	NA	
40–49	28.68 (2.78)	25.49 (3.05)		
50–59	31.32 (2.85)	35.29 (3.35)		
≥ 60	34.72 (2.93)	21.08 (2.86)		
Regional stage (SEER)	39.62 (3.01)	44.61 (3.48)	0.87 (0.59–1.28)	.482
Lymph node involved	39.02 (3.01)	44.61 (3.48)	0.85 (0.58–1.24)	.397
Estrogen receptor (positive vs negative)	88.26 (1.98)	81.37 (2.73)	1.98 (1.17–3.36)	.011
Breast cancer treatments				
Surgery				
Breast conserving	75.47 (2.65)	75.98 (2.99)	0.87 (0.04–18.7)	.929
Mastectomy	23.77 (2.62)	22.55 (2.93)	0.93 (0.04–20.26)	.962
No surgery	0.75 (0.53)	1.47 (0.84)	1.00 (Reference)	
Axillary lymph node dissection	71.32 (2.78)	71.57 (3.16)	0.93 (0.59–1.46)	.744
Radiotherapy	76.60 (2.60)	82.84 (2.64)	0.88 (0.56–1.40)	.589
Chemotherapy	53.21 (3.07)	64.22 (3.36)	0.72 (0.47–1.08)	.109

Table 1 (continued)

Characteristic	Osteoporosis cases, weighted % (SE)	Noncases, weighted % (SE)	Weighted HR (95% CI)	
			Crude model[a]	*P*
Hormone therapy				
Anti-estrogens	13.58 (2.11)	27.45 (3.13)	1.28 (0.64–2.53)	.483
Aromatase inhibitors	6.04 (1.46)	1.96 (0.97)	3.24 (1.09–9.63)	.035
Sequential	68.30 (2.86)	51.96 (3.50)	2.03 (1.19–3.46)	.009
No hormone use	12.08 (2.00)	18.63 (2.73)	1.00 (Reference)	
Reproductive and medical history				
Parity (at least one child birth vs nulliparous)	92.08 (1.66)	91.67 (1.94)	1.01 (0.47–2.19)	.979
Mean age at first birth[e], years (SE)	23.65 (0.17)	22.76 (0.17)	1.04 (0.97–1.12)	.299
Menopausal status at breast cancer Dx (postmenopausal vs premenopausal)	66.04 (2.91)	54.90 (3.49)	0.73 (0.40–1.33)	.300
Mean age at menopause[f], years (SE)	49.40 (0.20)	49.07 (0.30)	0.96 (0.89–1.05)	.366
Family history of osteoporosis	0.75 (0.53)	0.49 (0.49)	2.47 (0.22–28.47)	.468
Oophorectomy during follow-up	2.26 (0.91)	4.41 (1.44)	0.61 (0.23–1.58)	.306
Total hip replacement during follow-up	0.75 (0.53)	0.49 (0.49)	3.82 (0.35–42.21)	.274
Comorbidity at time of breast cancer Dx				
Hypertension	32.08 (2.87)	24.02 (2.99)	1.19 (0.72–1.95)	.503
Hyperlipidemia	32.08 (2.87)	28.92 (3.18)	1.11 (0.72–1.71)	.638
Renal failure	1.13 (0.65)	0.49 (0.49)	0.97 (0.19–4.96)	.966
Cardiovascular disease	9.06 (1.76)	10.78 (2.17)	1.27 (0.62–2.59)	.515
Diabetes	9.43 (1.80)	8.82 (1.99)	0.90 (0.44–1.84)	.776
Depression	1.89 (0.84)	4.41 (1.44)	0.63 (0.19–2.13)	.460
Health services utilization				
Mean outpatient specialist visits per year, quartile (median)[g]				
1 (7.1)—lowest	18.87 (2.41)	24.02 (2.99)	0.50 (0.29–0.85)	.011
2 (12.4)	23.40 (2.60)	25.00 (3.03)	0.48 (0.28–0.83)	.009
3 (16.8)	24.91 (2.66)	25.00 (3.03)	0.64 (0.38–1.09)	.101
4 (25.6)—highest	32.83 (2.89)	25.98 (3.07)	1.00 (Reference)	
Consumption of medications[h]				
Vitamin D	11.32 (1.95)	15.20 (2.52)	0.51 (0.30–0.87)	.014
Calcium	3.02 (1.05)	2.94 (1.18)	0.68 (0.21–2.16)	.508
Corticosteroids	10.19 (1.86)	10.78 (2.17)	0.75 (0.42–1.33)	.322
GnRH	12.22 (3.46)	19.57 (4.15)	1.01 (0.44–2.32)	.975
Lifestyle at time of survey (post osteoporosis diagnosis)				
Mean BMI, Kg/m^2 (SE)	27.29 (0.25)	27.94 (0.29)	0.95 (0.91–0.99)	.019
Weight change since breast cancer Dx				
Weight increased	32.83 (2.89)	49.02 (3.50)	0.60 (0.37–0.99)	.045
Weight decreased	42.64 (3.04)	32.35 (3.28)	0.92 (0.55–1.54)	.740
Same weight	24.53 (2.65)	18.63 (2.73)	1.00 (Reference)	
Tobacco use				
Ever	6.79 (1.55)	13.24 (2.38)	0.61 (0.33–1.16)	.130
Former	9.81 (1.83)	7.84 (1.88)	2.12 (1.07–4.17)	.031
Never	83.40 (2.29)	78.92 (2.86)	1.00 (Reference)	
Physical activity				
≥ 3 per week	21.89 (2.54)	28.43 (3.16)	0.71 (0.44–1.15)	.160
1–2 per week	13.58 (2.11)	20.59 (2.83)	0.64 (0.38–1.09)	.103
1–2 per month	19.25 (2.42)	9.31 (2.04)	1.66 (0.90–3.04)	.105
≤ 1 per month	45.28 (3.06)	41.67 (3.46)	1.00 (Reference)	

Table 1 (continued)

Characteristic	Osteoporosis cases, weighted % (SE)	Noncases, weighted % (SE)	Weighted HR (95% CI)	
			Crude model[a]	*P*
Healthy diet (No. of fruits and vegetable servings per day)				
0	18.11 (2.37)	1.96 (0.97)	23.78 (8.96–63.08)	<.001
1–2	72.45 (2.75)	63.24 (3.38)	4.00 (2.42–6.61)	<.001
≥ 3	9.43 (1.80)	34.80 (3.34)	1.00 (Reference)	
Oral contraceptive use (ever vs never)	6.42 (1.51)	22.06 (2.91)	0.36 (0.19–0.65)	.001
Hormonal infertility treatments (ever vs never)	4.15 (1.23)	1.47 (0.84)	3.17 (1.47–6.85)	.003
Hormone replacement therapy for menopause (ever vs never)	14.72 (2.18)	16.18 (2.58)	0.83 (0.48–1.43)	.508

SE, standard error; *NIS*, new Israeli shekel; *Dx*, diagnosis; *SEER*, Surveillance, Epidemiology, and End Results; *GnRH*, gonadotropin-releasing hormone; *BMI*, body mass index; *NA*, not applicable

Weights: cases = 1; noncases = 1/sampling fraction of noncases, where sampling fraction of noncases = subcohort/full cohort without cases = 204/(1298–265). Percentages may not sum to 100, due to rounding

[a] Unadjusted model; sampling weight: 1298/246 = 5.276

[b] Arab females were contrasted to non-Arab females (Jews and others)

[c] Unmarried category comprised all women not married or living with a spouse, i.e., divorced, separated, widowed, or single

[d] Income was measured using the proxy variable of mean income of family unit, derived from census data based on subject's residence, and divided into tertiles, with tertiles 1 and 3 having the lowest and highest median incomes, respectively

[e] Only for parous women (cases: *n* = 244, noncases: *n* = 187); all parous women had children before osteoporosis diagnosis

[f] Only for postmenopausal women at time of breast cancer diagnosis (cases: *n* = 175, noncases: *n* = 112)

[g] Outpatient visits included visits to internists, family doctors, endocrinologists, rheumatologists, physiatrists, orthopedists, and geriatricians.; measured as average visits per year from date of breast cancer diagnosis till end of follow-up

[h] At least three dispensed prescriptions of drugs within an interval of 6 months during follow-up. GnRH use restricted to premenopausal women at time of breast cancer diagnosis (cases: 90, noncases: *n* = 92)

rates between osteoporosis cases and noncases were at baseline 67.9 vs. 75.9% [*P* = .214], periodic-1, 23.1 vs. 32.1% [*P* = .088], periodic-2, 56.4 vs. 62.5% [*P* = .478], respectively).

Discussion

The current study, in line with other reports [32–36], has demonstrated a marked increase in the risk of osteoporosis by virtue of AI use, reflecting the almost complete estrogen depletion and subsequent disruption in bone homeostasis achieved by these agents [37]. The strength of this effect was not weakened across multiple sensitivity analyses, suggesting that selection bias or information bias were unlikely the main explanation for the observed association. The manifestation of a dose-response effect after classification of AI use into treatment for ≤ 2.5 years and > 2.5 years argues against a likelihood of precipitated osteoporosis diagnosis around the time of AI initiation. However, consistent with the 7-year findings from the ATAC trial [19], the risk of osteoporosis during the active AI treatment period did not continue in the off-treatment follow-up. Nevertheless, as noted in the ATAC trial [19], caution is urged against generalizing results due to the small number of patients entering the extended follow-up periods. Further research with a larger sample is, therefore, warranted to understand the long-term effects of AI on bone turnover.

Interestingly, over 13 years of observation, tamoxifen use seems not to confer a protective effect on bone health in postmenopausal BCS. The lack of modification by menopausal status merits discussion. While this finding lends support to previous research showing tamoxifen not to influence BMD scores [38] or reduce fracture risk in older women [20], it is discordant with other data showing a favorable bone-sparing effect of tamoxifen on BMD in postmenopausal women [21, 39], probably related to its partial agonist activity leading to reduction in bone resorption [40]. However, even if tamoxifen exerts a protective effect, its ability to preserve BMD is unlikely to last beyond the treatment period [20]. Given the extended follow-up in our study, it is plausible that tamoxifen was long terminated by the time a diagnosis of osteoporosis was made. A recent report demonstrated a significantly reduced osteoporotic fracture risk associated with current use of tamoxifen, but not with either recent or remote past tamoxifen use [41], and concluded that a protective effect might not persist after cessation of the drug, further corroborating our finding.

Unlike tamoxifen, the detrimental effect of AIs on skeletal health appears to apply equally to women of all ages exposed to this treatment. To the extent that AIs were the mainstay of BC

Table 2 Hazard ratios and 95% confidence intervals for incident osteoporosis, by hormone therapy exposure

						Weighted HR (95% CI)						
	No. of osteoporosis cases	Pearson-years*	IDR	IDRR	*P*	Crude model	*P*	Adjusted model**	*P*	ARF (%)	CF	PAF (%)
Hormone therapy												
Yes	233	6392	36.45	1.78 (1.24–2.61)	.001	1.92 (1.14–3.24)	.015	2.91 (1.36–6.22)	.006	65.64	0.88	57.76
No	32	1560	20.51	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]				
Hormone therapy type												
Tamoxifen	36	2055	17.52	0.85 (0.53–1.38)	.517	1.28 (0.64–2.53)	.483	1.95 (0.82–4.67)	.132			
AIs	16	204	78.43	3.82 (2.05–6.92)	< .001	3.24 (1.09–9.63)	.035	5.53 (1.46–20.88)	.012	81.92	0.06	4.92
Sequential	181	4133	43.79	2.14 (1.48–3.15)	< .001	2.03 (1.19–3.46)	.009	3.14 (1.44–6.88)	.004	68.15	0.68	46.34
No hormone use	32	1560	20.51	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]				
AI duration												
≤ 2.5 years	72	1976	36.44	1.94 (1.39–2.70)	< .001	1.60 (0.98–2.59)	.059	1.75 (0.90–3.38)	.098			
> 2.5 years	125	2361	52.94	2.82 (2.10–3.80)	< .001	2.11 (1.31–3.38)	.002	2.99 (1.58–5.65)	.001	66.56	0.47	31.28
No AI use	68	3615	18.81	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]				

AI, aromatase inhibitor; *HR*, hazard ratio; *CI*, confidence interval; *ARF*: attributable risk fraction; *IDR*, incidence density rate per 1000 person-years; *IDRR*, incidence density rate ratio; *CF*, case fraction (number of exposed cases divided by overall number of cases); *PAF*, population attributable fraction (CF x ARF)

* Person years lived in the total cohort alive at time of study, extrapolated from the random subcohort data. Sampling weight: 1298/246 = 5.276

** Adjusted for ethnicity, cohabitation status, residence, education, employment before treatment, income, menopausal status at breast cancer diagnosis, chemotherapy, outpatient specialist visits, use of Vitamin D, and year of breast cancer. Education, income, outpatient specialist visits and year of breast cancer were modeled in all analyses as continuous variables to avoid losing information. Estrogen receptor status was not included in all models to avoid collinearity with hormone therapy

Table 3 Sensitivity and subgroup analyses for the association between hormone therapy and incidence of osteoporosis

	Model 1[a]		Model 2[b]		Model 3[c]		Model 4[d]		Model 5[e]			
									≤ 50 years		> 50 years	
	Weighted adjusted HR (95% CI)	*P*	Weighted adjusted HR (95% CI)	*P*	Weighted adjusted HR (95% CI)	*P*	Weighted adjusted HR (95% CI)	*P*	Weighted adjusted HR (95% CI)	*P*	Weighted adjusted HR (95% CI)	*P*
Hormone therapy												
Yes	2.59 (1.33–5.04)	.005	2.36 (1.27–4.37)	.006	3.18 (1.15–8.76)	.026	3.49 (1.25–9.73)	.017	1.53 (0.52–4.53)	.440	4.00 (1.30–12.35)	.016
No	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]		1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
Hormone therapy type												
Tamoxifen	1.39 (0.66–2.95)	.389	1.13 (0.54–2.37)	.759	1.30 (0.31–5.49)	.723	1.64 (0.52–5.15)	.401	1.25 (0.37–4.26)	.720	2.86 (0.77–10.57)	.116
AIs	4.70 (1.51–14.7)	.008	2.75 (0.77–9.84)	.120	6.44 (0.74–55.96)*	.091	11.48 (1.15–114.66)*	.038	4.22 (0.25–72.7)*	.322	12.84 (2.07–79.76)*	.006
Sequential	2.32 (1.30–4.15)	.004	2.95 (1.54–5.66)	.001	3.91 (1.34–11.42)	.013	4.99 (1.52–16.39)	.008	1.71 (0.50–5.80)	.392	7.08 (1.72–29.12)	.007
No hormone use	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]		1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
AI duration												
≤ 2.5 years	1.86 (1.07–3.22)	.028	2.09 (1.19–3.68)	.010	1.99 (0.64–6.18)	.233	2.99 (1.10–8.12)	.032	0.79 (0.25–2.50)	.686	2.95 (0.95–9.14)	.061
> 2.5 years	2.76 (1.59–4.80)	<.001	3.56 (2.02–6.28)	<.001	5.32 (1.89–14.96)	.002	6.59 (2.08–20.91)	.001	4.47 (1.33–15.03)	.016	2.96 (1.13–7.77)	.027
No AI use	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]		1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	

HR; hazard ratio; *CI*; confidence interval; *AI*, aromatase inhibitor

[a] Model 1: Propensity score model; sampling weight 1298/246 = 5.276. Adjusted for propensity score that embeds pretreatment predictive variables (ethnicity, cohabitation status, residence, education, employment before treatment, income, menopausal status at breast cancer diagnosis, chemotherapy, year of breast cancer), outpatient specialist visits, and use of vitamin D. Regarding hormone therapy, a binomial logistic regression model was applied, whereas for hormone therapy type or AI duration, multinomial logistic regression models were used

[b] Model 2: Multiple imputations; sampling weight: 1692/323 = 5.238. Adjusted for all variables listed in Table 2

[c] Model 3: Restriction to 5-year osteoporosis-free survivors; sampling weight 886/172 = 5.151. Adjusted for all variables listed in Table 2

[d] Model 4: Restriction to women who had no BMD screen claim at baseline or during follow-up (censored at one year before end of follow-up); sampling weight 664/118 = 5.627. Adjusted for all variables listed in Table 2

[e] Model 5: Stratification by age at breast cancer diagnosis; sampling weight for < = 50 years and > 50 years: 567/108 = 5.250, and 731/138 = 5.279, respectively. Adjusted for all variables listed in Table 2, except for menopausal status

* Unstable estimates associated with wide CI due to small number of patients exposed to aromatase inhibitors

Table 4 Incidence of osteoporosis, by treatment and osteoporosis-free survival

Osteoporosis-free survival (year)*	Treatment							
	Aromatase inhibitors (alone or sequential)			No hormone therapy				
	No. of osteoporosis cases	Pearson-years**	IDR	No. of osteoporosis cases	Pearson-years**	IDR	IDRR (95% CI)	*P*
5+	77	1864	41.31	13	775	16.77	2.46 (1.40–4.61)	.001
6+	52	1446	35.96	11	628	17.52	2.05 (1.10–4.12)	.022
7+	24	1069	22.45	9	482	18.67	1.20 (0.57–2.73)	.656
8+	15	802	18.70	7	357	19.61	0.95 (0.39–2.50)	.898

CI, confidence interval; *IDR*, incidence density rate per 1000 person-years; *IDRR*; incidence density rate ratio

* Data are reported up to the 8th year of follow-up, as the sample size became too small to reliably infer meaningful associations in this year and thereafter. Multiple regression models were not performed due to small sample sizes

** Person years lived in the total cohort (alive and dead at time of study), extrapolated from the random subcohort data. Sampling weights for the survival times 5+, 6+, 7+, 8+: 886/172 = 5.151, 739/135 = 5.474, 604/107 = 5.645, and 506/85 = 5.953, respectively

adjuvant treatment for approximately 60% of BCS, either as upfront monotherapy or sequential treatment after tamoxifen, it was critically important to assess adherence to BMD screening guidelines in a growing population of BCS at risk of AI-induced osteoporosis. We found that adherence to BMD screening recommendations was alarmingly below satisfactory levels, particularly at baseline and after 48 months of continuous AI use. Although osteoporosis cases received slightly more screening scans than noncases, apparently due to development of symptoms, adherence to screening recommendations was suboptimal in both groups. Underutilization of BMD screening may allude to a lack of proactive monitoring for a preventable and treatable condition [16] to minimize the risk of clinical fractures. Factors that may pose hurdles in achieving optimal adherence could be related to the system, the care provider, the patients [16, 27], but also to the nonuniform guideline recommendations for osteoporosis screening in women with BC with respect to screening eligibility criteria, timing, frequency and delivery strategy, which may in turn impede their dissemination into clinical practice [17, 42]. Given the high incidence of osteoporosis above national standards, the dramatic impact of BMD non-screening on osteoporosis (Table 3, Model 4), and the recognition of AI treatment as a risk factor accounting for more than 45% of osteoporosis incidence at the BCS population level, BMD screening adherence rates will need to be improved if treatment-induced risk is to be abrogated.

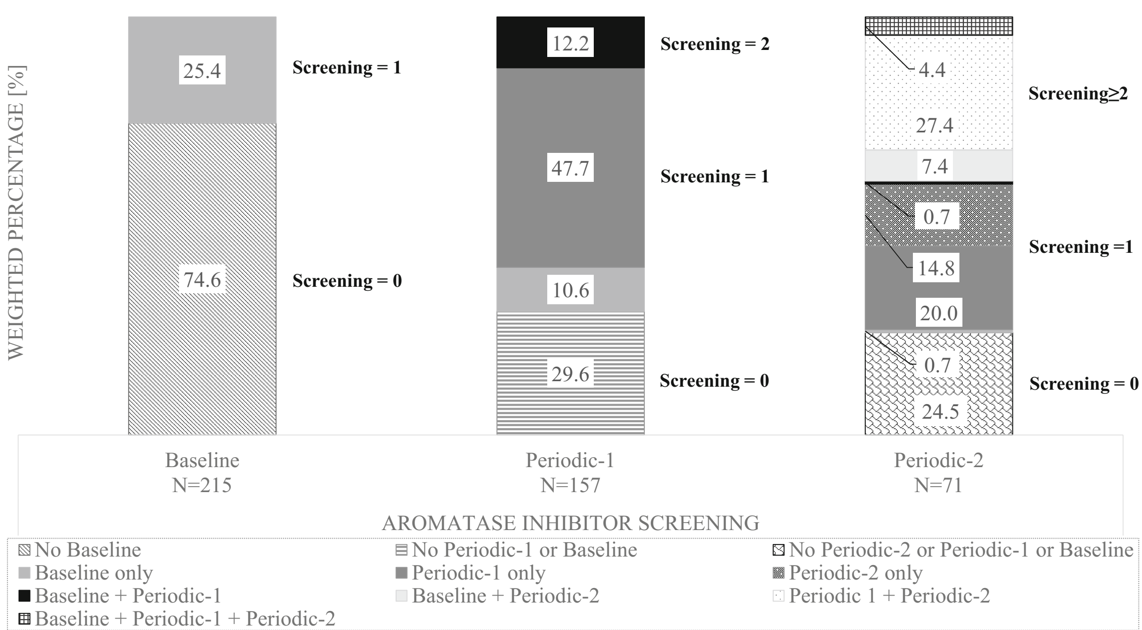

Fig. 2 Bone mineral density screening among postmenopausal breast cancer patients receiving aromatase inhibitors during selected time periods: baseline (within 12 months before the start of an AI), periodic-1 (within 2 years of continuous AI), and periodic-2 (within 24–48 months after AI initiation)

Consolidation of guidelines and implementation of a multidisciplinary follow-up care plan that gets the primary care provider, the oncologist and other bone specialists to coordinate and work out streamlined transitions in bone care [43], are essential steps toward realizing this goal.

Certain limitations of this work must be acknowledged. First, all BCS were selected from one healthcare fund, so their experiences may not reflect those in the general population. However, by law, all Israeli citizens can register with and move between any of the four healthcare funds at their discretion, abating the likelihood for selection bias. Second, the sample size was limited by stringent inclusion criteria to obtain a relatively homogenous sample of women for whom screening could alter the natural history of osteoporosis. More than half of the excluded women had osteoporosis at baseline and therefore were no longer at risk of the disease or eligible for osteoporosis screening. The remaining women had a history of other conditions that not only may contribute to osteoporosis [10] and in turn mask an effect of cancer therapy but also, they may artefactually alter values of BMD [44]. Nonetheless, the robustness of our findings in sensitivity analyses may reflect an adequate power obtained with our cohort to detect an effect when that existed. It should be noted though, that unlike osteoporosis, the small number of fracture events did hinder us from examining clinically relevant questions, such as the impact of HT on fractures. Third, we sometimes did not have BMD screen results which could have affected BMD testing frequency, although based on current recommendations, even women with BMD results in the normal range should have a repeat scan within 1–2 years [12, 14, 15]. Fourth, we could not differentiate between BMD tests intended for screening or monitoring of already diagnosed osteoporosis [27]. To mitigate this misclassification bias, we limited BMD screens to 1 year before the end of follow-up. Fifth, considering the substantial proportion of women who did not undergo BMD testing at baseline or during AI therapy, osteoporosis could have gone undiagnosed and untreated if BMD criteria were used alone. Given that most osteoporosis cases in the present study were not screen-detected but rather clinically detected, following the development of symptoms, independently of the exposure status, this misclassification bias is unlikely to affect our conclusions. If anything, it could have resulted in diluting the true risk, but more importantly, it particularly argues against a likelihood of surveillance bias associated with AI therapy. Detection by symptoms, such as back pain, per se could have introduced misclassification bias because these symptoms could be indicative of arthralgia commonly seen in patients treated with an aromatase inhibitor. However, given that the validation algorithm was established on at least two criteria (BMD scan, procurement of osteoporosis medications, and review of medical records for clinical symptoms), the likelihood of this misclassification bias is abated. Moreover, detection by symptoms in the advanced stages of the disease may allude that osteoporosis in early stages, which typically do not provoke noticeable signs of bone loss, could have gone undetected. Notwithstanding the negative predictive value of osteoporosis diagnosis was large, our validation algorithm was limited by available reported data. Therefore, a cautious interpretation of findings is warranted. Sixth, the data are lacking several variables used to compute FRAX 10-year probability of a major osteoporotic fracture (parental history of fracture, the quantity of daily alcohol consumption, and sometimes bone mineral density). When FRAX variables are not available, any calculated fracture risk will be inaccurate based on the FRAX limitations [45]. However, the FRAX score, which has been shown to be a reliable tool to assess the risk of fracture in healthy women, does not include anti-cancer treatment as a specific risk factor and thus its value in determining the risk of fracture in women with BC has not been evaluated. Seventh, it should be noted that vertebral fractures are often undiagnosed. Asymptomatic vertebral fractures are very prevalent in elderly women and may represent around two-thirds of all vertebral fractures [18]. It is likely, therefore, that we underestimated the risk of these fractures. Finally, residual confounding, which we tried to address by adjusting for several potential covariates, should be recognized. Uncontrolled confounders, such as smoking and physical inactivity that are known to affect bone density [12], could potentially bias the results. While these lifestyle factors were available from the questionnaires' data, however, to avoid potential reverse causality, they were not accounted for in risk analyses. Despite these potential drawbacks, this report is unique in utilizing data from an ethnically and geographically diverse cohort, with well-ascertained outcomes, and a relatively extended period of follow-up. Additional strengths include the use of different but complementary data sources to obtain valid information on important determinants of bone density, including medications and clinical history.

To recapitulate, in the context of bone health, the natural, age-related reduction in bone density is aggravated by BC active AI treatment. The wide gap between expert screening recommendations and real-life clinical practice constitutes an impediment to a timely diagnosis and earlier treatment with osteoporosis-modifying therapy. Future research should focus on investigating BMD adherence-related barriers/facilitators and effective strategies to bring practice in line with agreed standards. Meanwhile, clinicians caring for women with BC shall be cognizant of the potential for BC therapy to alter bone health, else, they would be sailing straight into an iceberg, underestimating the hidden, non-self-dissolving bulk lurking beneath surface, which will sooner than later affect BCS outcome.

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Compliance with ethical standards

Ethics approval The study protocol was duly approved by the Institutional Review Boards of LHS and the University of Haifa.

All procedures performed in studies 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 later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Conflicts of interest None.

Disclaimer The results, conclusions, view and opinions contained herein are those of the authors and not to be construed as the official policy of Israel's Ministry of Health, or of Leumit Health Organization.

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