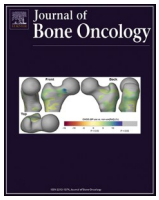
J BONE ONCOL 42 (2023) 100501

Contents lists available at ScienceDirect

Journal of Bone Oncology

journal homepage: www.elsevier.com/locate/jbo



Research Paper

DXA assessment and fracture prevention in hormone positive breast cancer patients after treatment initiation with aromatase inhibitors: A registry-based cohort study

Vanessa Rouach [a,c,*], Yona Greenman [a], Gabriel Chodick [b,c], Inbal Goldshtein [b,c]

[a] Institute of Endocrinology, Diabetes, Hypertension and Metabolism, Sourasky Medical Center, Tel Aviv, Israel
[b] Maccabitech Institute for Research and Innovation, Maccabi Healthcare Services, Tel Aviv, Israel
[c] Epidemiology Department, School of Public Health, Sackler Faculty of Medicine, Tel Aviv University, Israel

HIGHLIGHTS

- Aromatase inhibitors cause increased bone loss and increase fracture risk in postmenopausal women with breast cancer, therefore continuous evaluation of the risk of fracture is recommended.
- Despite the excess risk for fractures, bone health assessment and preventive treatment are still partial and postponed.
- In this large cohort of breast cancer patients treated with AI the incidence of fractures is substantial, despite a relatively low-risk profile.
- Strategies to increase appropriate care are needed.

ARTICLE INFO

Keywords:
Breast cancer
Aromatase inhibitors induced bone loss
Osteoporosis
Fracture prevention

ABSTRACT

Background: Several guidelines have been proposed to prevent aromatase inhibitors induced bone loss (AIBL), but there is scarce data on their endorsement in clinical practice.
Aim: To assess bone health evaluation and fracture prevention in postmenopausal women with estrogen receptor (ER)-positive breast cancer after aromatase inhibitors (AI) initiation.
Methods: An historical cohort analysis based on data from the cancer and osteoporosis Maccabi Health Services (MHS) registries from Jan 1st 2009 to Dec 31st 2020. Cases of estrogen receptor (ER)-positive breast cancer were extracted. Index date was set as the first aromatase inhibitors (AI) purchase. Variables such as age, BMI, smoking history, alcohol use, rheumatoid arthritis, diabetes, glucocorticosteroid use, previous fractures, BMD T-scores and purchases of AI and anti-resorptive agents were collected. Age under 50, previous cancer, prior major osteoporotic fractures and prior anti-resorptive treatment were exclusion criteria. Kaplan-Meier curves were generated to assess the time to outcomes. Multivariable Cox's proportional hazards survival model was performed.
Results: A total of 8617 women initiating AI were eligible. The median follow up was 6.1 years. The mean (SD) age at index was 62.8 (9.2), the mean (SD) BMI was 29.1 (5.6). The mean (SD) T-score was −1.3 (1.2) at the lumbar spine, −1.5 (0.9) at the femoral neck and −1.0 (1.0) at the total hip. Twenty percent had type 2 diabetes, 8.1 % were active smokers, 3.8% had rheumatoid arthritis and 1.2% were exposed to glucocorticoids.
A total of 37% and 53% underwent a DXA scan at 1 and 2 years from AI initiation, and 12% and 17% were prescribed an anti-resorptive agent at 1 and 2 years from index. Advanced age was associated with a higher rate of evaluation and treatment, while obesity and diabetes were associated with a lower rate. The cumulative incidence of a major osteoporotic fracture was 8.8 and 15.8 % at 5 and 10 years, respectively.
Conclusions: Despite the excess risk of fractures, bone health assessment and preventive treatment are still partial and postponed in breast cancer AI treated patients. Strategies to ensure appropriate care are needed.

* Corresponding author.
E-mail address: vanessar@tlvmc.gov.il (V. Rouach).

https://doi.org/10.1016/j.jbo.2023.100501
Received 3 May 2023; Received in revised form 24 July 2023; Accepted 22 August 2023
Available online 25 August 2023

1. Introduction

Breast cancer has important implications for bone health; of significant concern is the development of bone metastasis, but many breast cancer patients are at increased risk for developing osteoporosis, which is also associated with morbidity and mortality [1–3].

Aromatase inhibitors (AIs) are potent inhibitors of estrogen production, and have been shown to be more effective in preventing recurrence in postmenopausal women with early breast cancer compared with tamoxifen, thus representing the standard of care for adjuvant endocrine therapy. AI therapies, reducing already low endogenous postmenopausal estradiol levels, cause increased bone loss and increase fracture risk in postmenopausal women [4–10].

Clinical practice guidelines recommend a careful evaluation of skeletal health in all women with breast cancer before AI therapy initiation. Pharmacological attempts to minimize AI-related bone loss have focused on using anti-resorptive agents, such as bisphosphonates and denosumab, to protect bone integrity and reduce the risk of fractures. Continuous evaluation of the risk of fracture is recommended in all premenopausal women with breast cancer and postmenopausal women during treatment with aromatase inhibitors. A pharmacological intervention is usually recommended for women with a T-score ≤ -2 or those with two or more clinical risk factors for fracture, alongside vitamin D supplementation and adequate calcium intake. There is a consensus that bisphosphonates should be used to prevent bone loss induced by cancer treatment, especially in women at intermediate or high risk of fracture. Osteoporotic treatment should be continued at least until the adjuvant breast cancer treatment program is complete or even longer in those women with the highest baseline risk of fracture [11–14].

This study aimed to assess bone health evaluation and fracture prevention strategies in postmenopausal women with estrogen receptor (ER)-positive breast cancer after AIs initiation using real-world data.

2. Subjects and Methods

2.1. Setting

The study was performed using longitudinal data from Maccabi Healthcare Services (MHS). MHS is the second largest health care provider and insurer in Israel and covers approximately 25% of the population with a countrywide distribution.

According to the 1995 national health insurance law, health medical organizations (HMOs) may not deny coverage to applicants on any grounds, including age or state of health. MHS insures and provides health services to two million members. Its central database contains patients' demographics, diagnoses, medical procedures, hospitalizations, and full capture of all prescription medication dispensations and laboratory tests since 1999.) MHS has developed several computerized registries of major chronic diseases, such as oncologic diseases, diabetes, and osteoporosis which are continuously updated.

The current study used data from the MHS osteoporosis registry. Its assembly has been previously described elsewhere, and a comprehensive approach was used to cross-validate it and ensure high specificity [15]. Briefly, the osteoporosis registry identifies patients by diagnosis, by at least two dispensations of medications for osteoporosis, by BMD in the osteoporotic range (*T*-score ≤ -2.5), or by a major osteoporotic fracture (MOF) which occurred at a typical age (50 + years for females and 60 + years for males) after excluding fractures due to motor vehicle accidents. MOF sites included the femur neck, clinical spine, forearm, and proximal humerus fractures, in accordance with fracture risk assessment definitions [16]. Cancer incidence was ascertained by the Israel National Cancer Registry (INCR). The completeness of the National Cancer Registry's database for solid tumors is about 95% [17]. BMD measurements are available in the registry from 2008 so data collection for this study started on Jan 1st 2009 and ended on Dec 31st 2020.

2.2. Participants

We included cases of estrogen receptor (ER)-positive breast cancer above the age of 50. The index date was defined as the first AI purchase. Aromatase inhibitors purchasers were treated for at least six months, and the mean medication possession ratio (MPR) was 80 %. Variables such as age, BMI, smoking history, alcohol use, previous fractures, BMD and T-scores and purchases of aromatase inhibitors and anti-resorptive agents were collected from the HMO electronic files. Subjects under 50 with previous malignancies, distant metastases, previous major osteoporotic fractures and previous anti-resorptive treatment were excluded.

2.3. Outcomes

The primary outcomes were the incidence rates of BMD assessment and anti-resorptive treatment initiation (bisphosphonates or denosumab).

The secondary outcome was the incidence rate of major osteoporotic fractures.

2.4. Additional covariates

We extracted data on age, BMI, smoking status and alcohol consumption, diagnosis of rheumatoid arthritis and diabetes mellitus, glucocorticosteroid treatment, previous major osteoporotic fractures, and bone mineral density at the lumbar spine femoral neck and hip. Vitamin D levels, anti-resorptive therapy, AI treatment, specific agent, and duration of treatment. To give an estimate of the FRAX score we grouped smoking, alcohol consumption, RA, GCS and created a variable to assess multiple risk factors.

2.5. Statistical analysis

Population demographic data were expressed as mean with corresponding standard deviations and percentages. Kaplan-Meier curves were generated to assess the time to outcomes. Analysis was conducted in R (R Core Team, 2022), and figures were produced using the package ggplot2 (Wickham, 2022).

Multivariable Cox's proportional hazards survival model was performed using SPSS (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY). The proportionality assumption was verified.

3. Results

All AI purchasers over the age of 50 were identified, and after exclusion of prior cancer diagnosis, previous MOF and previous anti-resorptive treatment 8617 patients remained for analysis (Fig. 1).

The study population characteristics are described in Table 1. Only 13% had multiple risk factors for fractures (smoking, alcohol consumption, RA, GC exposure) with the caveat that patients with a prior MOF were excluded and that data on parental history of hip fracture was not available. We did not include type 2 DM in this risk factor category, it was evaluated separately. Vitamin D levels were available for 40% of the study population. Only 14% had 25-OH vitamin levels above 32 ng/ml but 60% had levels above 20 ng/ml. The most prevalent agent prescribed was Alendronate (34%), followed by Risedronate (23%), Zoledronic acid (21%) and Denosumab (6%). The median length of follow up was 6.1 years. (Table 1).

Thirty seven percent (37%) performed a DXA scan one year after AI initiation, and 53% underwent a DXA scan 2 years after AI initiation. Only five years after AI initiation 80% of patients had performed a DXA scan, and 88% at 10 years from index (Fig. 3.2). A total of 12% and 17%

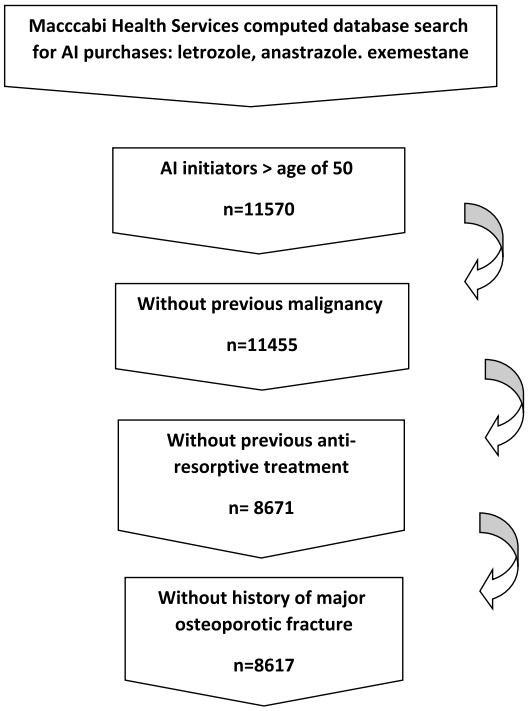


Fig. 1. Attrition table:

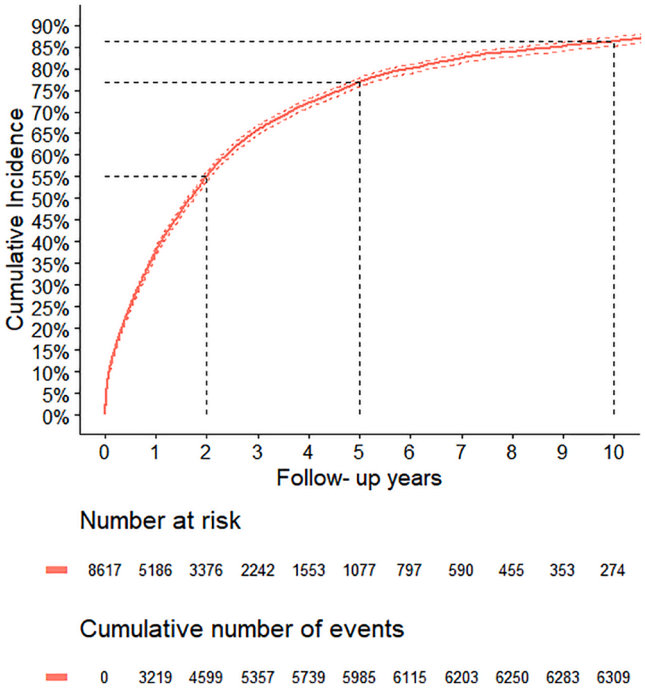


Fig. 2. Cumulative incidence of BMD assessment by DXA:

Table 1
Study population characteristics.

n		8617
Age (mean ± SD and range)		62.8 ± 9.2 (50–94)
BMI (mean ± SD and range)		29.1 ± 5.6 (15–55)
BMD T-scores (mean ± SD):	Lumbar Spine T-score	−1.3 ± 1.2
	Femoral Neck T-score	−1.5 ± 0.9
	Total Hip T-score	−1.0 ± 1.0
Type 2 Diabetes Mellitus (%)		20.3
Rheumatoid Arthritis (%)		3.8
Glucocorticoid treatment (%)		1.2
Present smoking (%)		8.1
Alcohol consumption (%)		0.3
Number of risk factors (including AI):	1 risk factor (%)	100
	2 risk factors (%)	11.8
	3 risk factors (%)	0.7
Baseline Vitamin 25-OH D levels ng/ml (mean ± SD and range)		22.1 ± 9.3 (6–84)

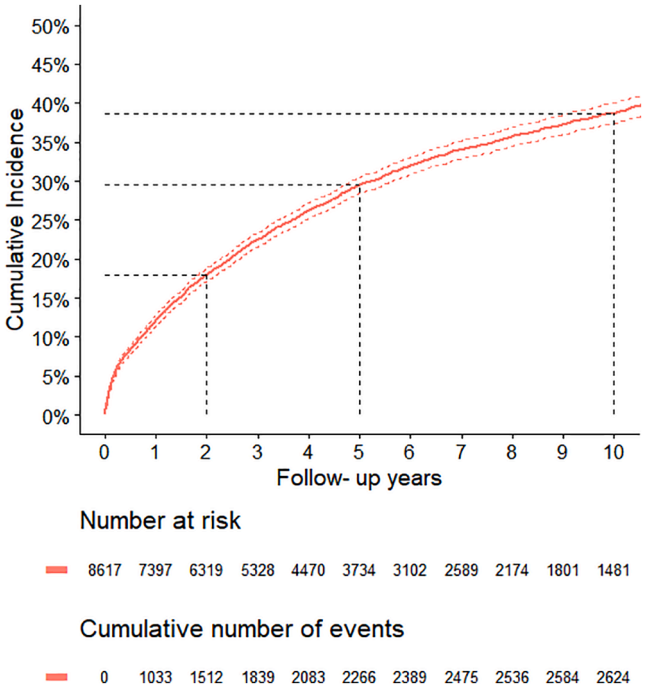


Fig. 3. Cumulative incidence of anti-resorptive treatment initiation:

were prescribed an anti-resorptive agent 1 and 2 years from index respectively, with a cumulative incidence of 29% at 5 years and nearly 40% at 10 years from index (Fig. 3.3).

A total of 970 fractures were recorded during the follow-up: approximately 20% were distal radius fractures, 17% humerus fractures, 16% vertebral fractures, 14% hip fractures. Another 12% ankle fractures, 12% ribs fractures and 6% pelvic fractures suspected as fragility fractures were recorded too.

The mean age at the time of the fracture diagnosis was 76.4 ± 10 years, and the mean time from AI purchase was 6.4 ± 4.5 years. The cumulative incidence of a major osteoporotic fracture was 8.8% and 15.8 % at 5 and 10 years respectively (Fig. 3.4).

According to the joint position statement of the IOF, CABS, ECTS, IEG, ESCEO IMS, and SIOG [12] women with a T-score < 2 should receive preventive treatment as well as patients with two risk factors: a T-score < -1.5, age > 65, smoking, BMI < 20, GC exposure, prior MOF, family history of hip fracture [16]. A total of 457 and 427 subjects answered the criteria of a T-score < 2 and a T-score < -1.5 with age above 65 respectively. Among patients with a T-score < -2, 33% were prescribed an anti-resorptive agent 2 years after AI initiation, and among those above 65 years with a T-score < -1.5 26% were (Figs. 5 and 6).

Advanced age was associated with a higher rate of evaluation (HR 1.220, 1.090–1.637) and treatment (HR 1.3.43, 1.163–1.551) (Tables 2 and 3). A higher BMI was associated with a lower rate of evaluation (HR 0.828, CI 0.739–0.928) and treatment (HR 0.718; CI 0.626–0.824). The

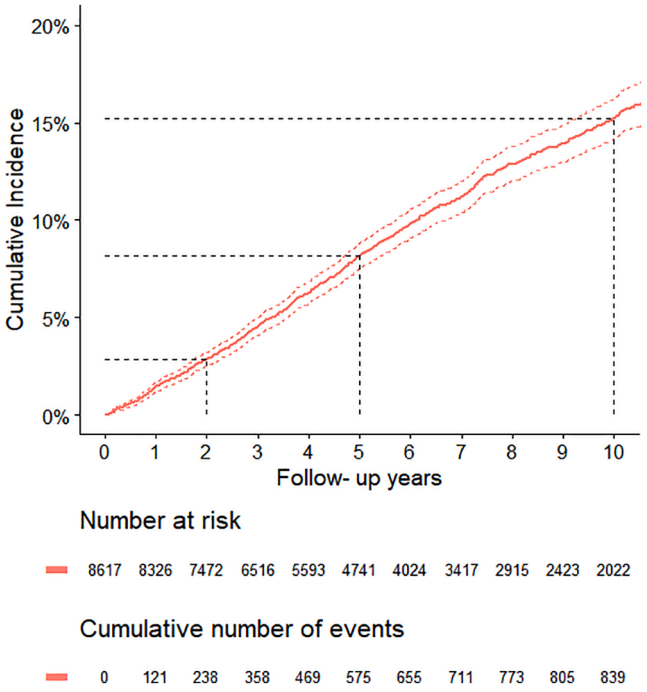


Fig. 4. Cumulative incidence of major osteoporotic fractures:

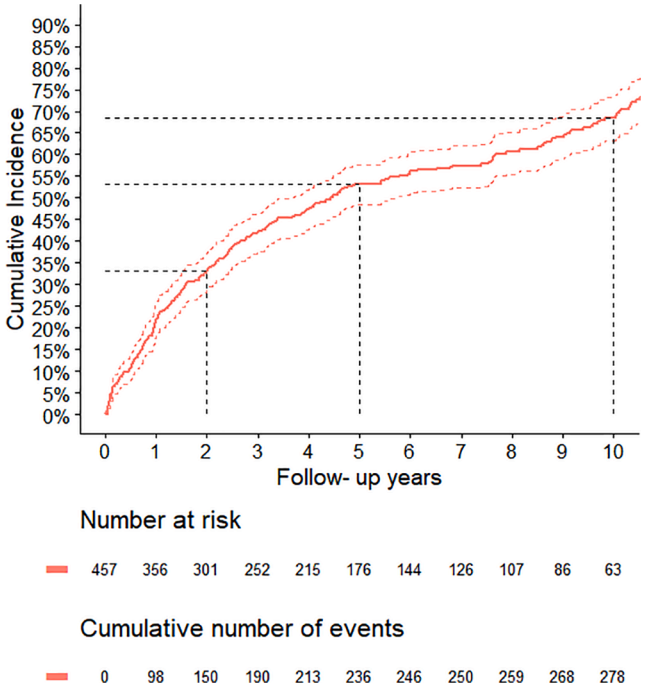


Fig. 5. Cumulative incidence of anti-resorptive treatment initiation among women with femoral neck T-score < -2.

prevalence of type 2 DM was associated with a lower rate of assessment (HR 0.897, CI 0.807–0.996) but this association did not remained significant for treatment prescription (HR 0.976, CI 0.851–1.120), there was a significant interaction between BMI and Type 2 DM. Additional risk factors (smoking, alcohol consumption. GCs, RA) were not associated with the incidence of evaluation or treatment (Table 3).

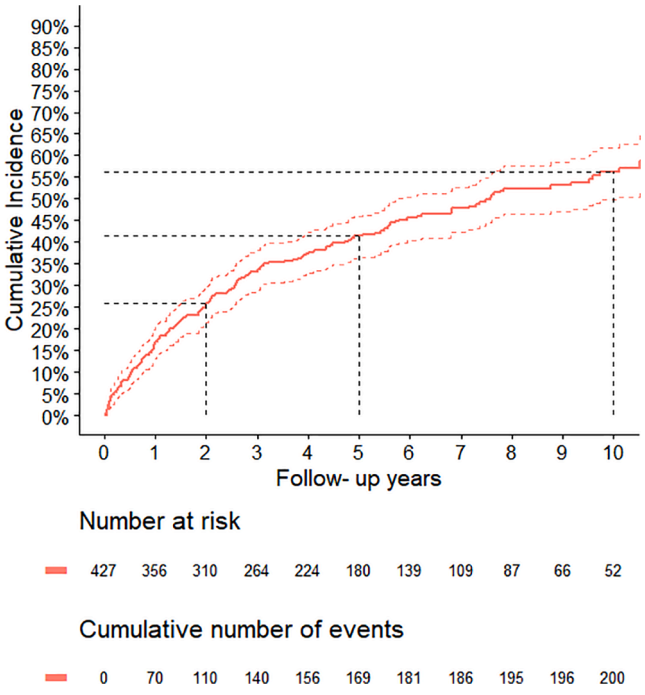


Fig. 6. Cumulative incidence of anti-resorptive treatment initiation among women with femoral neck T-score < -1.5 and age above 65 years old.

Table 2
Multivariate analysis: Cox regression model for BMD assessment by DXA.

	HR	95% CI	P value
Age 50–59 (reference)			
60–69	1.119	1.021–1.226	0.016
70–79	1.220	1.090–1.637	<0.01
>80	1.458	1.161–1.831	0.001
BMI 20–25 (reference)			
26–30	0.860	0.781–0.948	0.02
31–35	0.828	0.739–0.928	0.01
>35	0.775	0.672–0.893	<0.01
Type 2 Diabetes Mellitus	0.897	0.807–0.996	0.042
Additional Risk Factors	1.034	0.930–1.131	0.549

Table 3
Multivariate analysis: Cox regression model for anti-resorptive treatment prescription.

	HR	95% CI	P value
Age 50–59 (reference)			
60–69	1.195	1.057–1.351	0.004
70–79	1.343	1.163–1.551	<0.001
>80	1.379	1.045–1.820	0.023
BMI 20–25 (reference)			
26–30	0.801	0.704–0.912	<0.001
31–35	0.718	0.626–0.824	<0.001
>35	0.629	0.523–0.756	<0.001
Type 2 Diabetes Mellitus	0.976	0.851–1.120	0.728
Additional Risk Factors	0.956	0.795–1.147	0.623

4. Discussion

Aromatase inhibitors are the first-line therapy for hormonal-positive early breast cancer, and the recommended duration of treatment varies from 5 to 10 years. It has been well established that women initiating AI should have their bone health evaluated and, if at risk for osteoporosis,

prescribed preventive treatment.

In this large cohort of breast cancer patients treated with AI, we reported that 37% and 53% had their bone mineral density evaluated after 1 and 2 years of treatment, and a total of 12 % and 17% were prescribed an anti-resorptive agent after 1 and 2 years of AI treatment, reaching approximately 30% after five years. Advanced age and low BMD were associated with a higher rate of assessment and treatment, obesity and diabetes were associated with a lower rate. The number of additional risk factors (smoking, RA. GCs, and alcohol consumption) was not associated with a better assessment or treatment initiation rate. Contrarily to BMD assessment, which is recommended for all patients treated with AI, preventive treatment is not always mandatory and should be prescribed to patients at risk [11–15]. In the sub-group of patients who should have received a preventive treatment according to the guidelines issued from the joint position statement by Hadji et al. [12], only 33% received an anti-resorptive agent if they had a T-score < -2 and 26% if they had a T-score < -1.5 and were older than 60 two years after AI initiation. A minority of patients had additive risk factors, which did not affect the treatment rate. However, prior MOF was an exclusion criterion, and we had no hip fracture parental history.

The cumulative incidence of MOF in our cohort was 8.8% and 15.8% at 5 and 10 years, respectively. The real-world fracture risk has been investigated in several case-control studies, prescription-based analyses [18], and one RCT [19]. In the latter, the fracture incidence in women with breast cancer on an AI was reported to be around 18–20% after five years of follow-up, indicating that in clinical practice, about one in five women will sustain an AI-related fracture. The incidence of fracture in our cohort was lower than previously reported. It may result from differences in the age and the general risk profile of the patients in the different studies and from the preventive treatment prescribed to some patients at a higher risk in our study. Moreover, it may be due to improved awareness and a better evaluation before AI initiation, so patients with a high risk for fracture are often prescribed Tamoxifen instead of AI.

The limitations of our study were mainly related to the completeness of the data. The lack of data on the parental history of hip fracture and other possible causes of secondary osteoporosis did not allow us a more accurate fracture risk assessment. We could not evaluate calcium and vitamin D supplements exposure because those are mainly purchased over the counter. Women starting AI are often recommended supplements, which might have affected the fracture incidence. However, vitamin D levels were sufficient for most of the study population. We defined index time as AI purchase and did not collect data on patients who underwent DXA scans before starting AI but focused on the care of those already receiving AI therapy. The design of our study did not allow us to separate patients who were maybe recommended or even prescribed treatment but did not purchase it. Finally, MHS covers approximately 25% of the population and our data do not address the whole Israeli population.

The strengths of this study are our large cohort of patients, which is representative of the Israeli population as MHS is the second largest healthcare provider and insurer in Israel covering approximately three million people with a countrywide distribution and a good quality real-world data, which, we believe, reflect the everyday clinical practice in our country.

AI-treated breast cancer patients are at risk of fractures, but bone health assessment and preventive treatment do not meet the recommendations. We can hypothesize that the awareness of the need for prevention measures is not high enough for both patients and physicians. Patients may have a better screening before starting AI so that they may be perceived as low-risk patients, which may explain a low rate of BMD assessment at 1 and 2 years from starting AI. The reluctance of patients to take drugs and the fear of side effects might constitute a barrier to treatment initiation. The increase in treatment rate with time may be due to a decrease in BMD and the incidence of fractures while on AI therapy.

Although the FRAX tool is not designed to assess fracture risk in women with breast cancer, some recommend using it with the mention of RA to estimate the influence of AI, as it is recommended for DM2 [20]. The FRAX calculation tool might need better integration into the risk assessment process by oncologists and primary care physicians. Computerized alerts for primary care physicians, who met treatment guidelines based on patient's electronic medical records, may be an efficient method to raise awareness [21]. Patient education about the importance of preventing osteoporosis and reassurance about side effects are needed as well.

5. Conclusions

In this relatively low-risk population of patients initiating AI, the incidence of fractures was still substantial. Despite the well-established deleterious effect of AI on bone health, assessment and preventive treatments were still partial and postponed, especially among obese and diabetic women. Strategies to ensure optimal care are still needed.

CRediT authorship contribution statement

Vanessa Rouach: Conceptualization, Methodology, Data curation, Writing – original draft. **Yona Greenman:** Supervision. **Gabriel Chodick:** Supervision. **Inbal Goldshtein:** Methodology, Data curation, Visualization, Software.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] J.D. Adachi, G. Ioannidis, L. Pickard, C. Berger, J.C. Prior, L. Joseph, D.A. Hanley, W.P. Olszynski, T.M. Murray, T. Anastassiades, W. Hopman, J.P. Brown, S. Kirkland, C. Joyce, A. Papaioannou, S. Poliquin, A. Tenenhouse, E. A. Papadimitropoulos, The association between osteoporotic fractures and health-related quality of life as measured by the Health Utilities Index in the Canadian Multicentre Osteoporosis Study (CaMos), Osteoporos Int. 14 (11) (2003 Nov) 895–904, https://doi.org/10.1007/s00198-003-1483-3. Epub 2003 Aug 12 PMID: 12920507.

[2] S.R. Cummings, L.J. Melton, Epidemiology and outcomes of osteoporotic fractures, Lancet 359 (9319) (2002 May 18) 1761–1767, https://doi.org/10.1016/S0140-6736(02)08657-9. PMID: 12049882.

[3] R. Hasserius, M.K. Karlsson, B.E. Nilsson, I. Redlund-Johnell, O. Johnell, European Vertebral Osteoporosis Study. Prevalent vertebral deformities predict increased mortality and increased fracture rate in both men and women: a 10-year population-based study of 598 individuals from the Swedish cohort in the European Vertebral Osteoporosis Study, Osteoporos. Int. (London) 14 (1) (2003 Jan) 61–68, https://doi.org/10.1007/s00198-002-1316-9. PMID: 12577186.

[4] G. Schiavon, I.E. Smith, Status of adjuvant endocrine therapy for breast cancer, Breast Cancer Res. 16 (2) (2014) 206, https://doi.org/10.1186/bcr3636. PMID: 25032258; PMCID: PMC4053079.

[5] B.L. Riggs, S. Khosla, L.J. Melton 3rd., A unitary model for involutional osteoporosis: estrogen deficiency causes both type I and type II osteoporosis in postmenopausal women and contributes to bone loss in aging men, J. Bone Miner. Res. 13 (5) (1998 May) 763–773, https://doi.org/10.1359/jbmr.1998.13.5.763. PMID: 9610739.

[6] S.R. Cummings, W.S. Browner, D. Bauer, K. Stone, K. Ensrud, S. Jamal, B. Ettinger, Endogenous hormones and the risk of hip and vertebral fractures among older women. Study of Osteoporotic Fractures Research Group, N. Engl. J. Med. 339 (11) (1998 Sep 10) 733–738, https://doi.org/10.1056/NEJM199809103391104. PMID: 9731089.

[7] Baum M, Budzar AU, Cuzick J, Forbes J, Houghton JH, Klijn JG, Sahmoud T; ATAC Trialists' Group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. Lancet. 2002 Jun 22;359 (9324):2131-9. doi: 10.1016/s0140-6736(02)09088-8. Erratum in: Lancet 2002 Nov 9;360(9344):1520. PMID: 12090977.

[8] Baum M, Buzdar A, Cuzick J, Forbes J, Houghton J, Howell A, Sahmoud T; ATAC (Arimidex, Tamoxifen Alone or in Combination) Trialists' Group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety

update analyses. Cancer. 2003 Nov 1;98(9):1802-10. doi: 10.1002/cncr.11745. PMID: 14584060.

[9] M. Dowsett, J. Cuzick, J. Ingle, A. Coates, J. Forbes, J. Bliss, M. Buyse, M. Baum, A. Buzdar, M. Colleoni, C. Coombes, C. Snowdon, M. Gnant, R. Jakesz, M. Kaufmann, F. Boccardo, J. Godwin, C. Davies, R. Peto, Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen, J. Clin. Oncol. 28 (3) (2010 Jan 20) 509–518, https://doi.org/10.1200/JCO.2009.23.1274. Epub 2009 Nov 30 PMID: 19949017.

[10] Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet. 2015 Oct 3;386(10001):1341-1352. doi: 10.1016/S0140-6736(15)61074-1. Epub 2015 Jul 23. PMID: 26211827.Gaudio A, Xourafa A, Rapisarda R, Castellino P. Therapeutic Options in the Management of Aromatase Inhibitor-Associated Bone Loss. Endocr Metab Immune Disord Drug Targets. 2021 Aug 9. doi: 10.2174/1871530321666210809153152. Epub ahead of print. PMID: 34370654.).

[11] P. Hadji, M.S. Aapro, J.J. Body, M. Gnant, M.L. Brandi, J.Y. Reginster, M. C. Zillikens, C.C. Glüer, T. de Villiers, R. Baber, G.D. Roodman, C. Cooper, B. Langdahl, S. Palacios, J. Kanis, N. Al-Daghri, X. Nogues, E.F. Eriksen, A. Kurth, R. Rizzoli, R.E. Coleman, Management of Aromatase Inhibitor-Associated Bone Loss (AIBL) in postmenopausal women with hormone sensitive breast cancer: Joint position statement of the IOF, CABS, ECTS, IEG, ESCEO IMS, and SIOG, J Bone Oncol. 23 (7) (2017 Mar) 1–12, https://doi.org/10.1016/j.jbo.2017.03.001. PMID: 28413771; PMCID: PMC5384888.

[12] K. Waqas, J. Lima Ferreira, E. Tsourdi, J.J. Body, P. Hadji, M.C. Zillikens, Updated guidance on the management of cancer treatment-induced bone loss (CTIBL) in pre- and postmenopausal women with early-stage breast cancer, J Bone Oncol. 18 (28) (2021 Mar), 100355, https://doi.org/10.1016/j.jbo.2021.100355. PMID: 33948427; PMCID: PMC8080519.

[13] C.L. Shapiro, C. Van Poznak, C. Lacchetti, J. Kirshner, R. Eastell, R. Gagel, S. Smith, B.J. Edwards, E. Frank, G.H. Lyman, M.R. Smith, R. Mhaskar, T. Henderson, J. Neuner, Management of Osteoporosis in Survivors of Adult Cancers With Nonmetastatic Disease: ASCO Clinical Practice Guideline, J. Clin. Oncol. 37 (31) (2019 Nov 1) 2916–2946, https://doi.org/10.1200/JCO.19.01696. Epub 2019 Sep 18 PMID: 31532726.

[14] F.A. Trémollieres, I. Ceausu, H. Depypere, I. Lambrinoudaki, A. Mueck, F.R. Pérez-López, Y.T. van der Schouw, L.M. Senturk, T. Simoncini, J.C. Stevenson, P. Stute, M. Rees, Osteoporosis management in patients with breast cancer: EMAS position statement, Maturitas 95 (2017 Jan) 65–71, https://doi.org/10.1016/j.maturitas.2016.10.007. Epub 2016 Oct 6 PMID: 27802892.

[15] I. Goldshtein, J. Chandler, V. Shalev, S. Ish-Shalom, A.M. Nguyen, V. Rouach, G. Chhodick, Osteoporosis in the community: findings from a novel computerized registry in a large health organization in Israel, J. Aging Res. Clin. Pract. (2005).

[16] J.A. Kanis, O. Johnell, A. Oden, H. Johansson, E. McCloskey, FRAX™ and the assessment of fracture probability in men and women from the UK, Osteoporos Int. 19 (4) (2008) 385–397.

[17] E. Moore, B.G. Silverman, Y. Fishler, E. Ben-Adiva, O. Davidov, R. Dichtiar, H. Edri, M. Zatlawi, L. Keinan-Boker, An Assessment of the Completeness and Timeliness of the Israel National Cancer Registry, Isr. Med. Assoc. J. 23 (1) (2021 Jan) 23–27. PMID: 33443338.

[18] B.A. Mincey, M.S. Duh, S.K. Thomas, E. Moyneur, M. Marynchencko, S.P. Boyce, D. Mallett, E.A. Perez, Risk of cancer treatment-associated bone loss and fractures among women with breast cancer receiving aromatase inhibitors, Clin. Breast Cancer 7 (2) (2006 Jun) 127–132, https://doi.org/10.3816/CBC.2006.n.021. PMID: 16800971.

[19] N. Schimdt, L. Jacob, R. Coleman, K. Kostev, P. Hadji, The impact of treatment compliance on fracture risk in women with breast cancer treated with aromatase inhibitors in the United Kingdom, Breast Cancer Res. Treat. 155 (1) (2016) 151–157.

[20] W.D. Leslie, S.N. Morin, L.M. Lix, S.R. Majumdar, Does diabetes modify the effect of FRAX risk factors for predicting major osteoporotic and hip fracture? Osteoporos Int. 25 (12) (2014 Dec) 2817–2824, https://doi.org/10.1007/s00198-014-2822-2. Epub 2014 Aug 5 PMID: 25092059.

[21] I. Goldshtein, O. Shamai-Lubovitz, M. Guindy, V. Shalev, G. Chodick, U. Lerner, V. Rouach, Development and efficacy of a computerized decision support system for osteoporosis management in the community, Arch. Osteoporos. 15 (1) (2020 Feb 26) 27, https://doi.org/10.1007/s11657-020-00718-3. PMID: 32103347.