The association between endocrine therapy use and osteoporotic fracture among post-menopausal women treated for early-stage breast cancer in Ontario, Canada

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ARTICLE INFO

ABSTRACT

Background: The use of endocrine therapy for early-stage breast cancer, particularly aromatase inhibitor therapy has been associated with an increased risk of osteoporosis and fracture in clinical trials. We sought to validate this observation in real-world practice.
Methods: We used health administrative data collected from post-menopausal women (aged ≥66 years) who were diagnosed with breast cancer and started on adjuvant endocrine therapy from 2005 to 2012. Patients were classified by use of either an aromatase inhibitor or tamoxifen and followed until 2017 for a new diagnosis of an osteoporotic fracture. A multivariable analysis using a Cox proportional hazards model was adjusting for age, medical co-morbidities, medication use and duration of endocrine therapy.
Results: We identified 12,077 patients of whom 73% were treated with an aromatase inhibitor as compared to 27% with tamoxifen. Our multivariable analysis did not demonstrate any significant difference in the rate of osteoporotic fracture between patients treated with an aromatase inhibitor when compared with tamoxifen [Hazard ratio (HR) = 1.09; 95% confidence interval (CI) = 0.96–1.23, p-value = 0.18]. The 5-year rate of osteoporotic fracture for patients treated with either an aromatase inhibitor or tamoxifen was 7.5% and 6.9%, respectively. A completed sensitivity analysis did observe a decreased risk of fracture associated with tamoxifen usage over time.
Conclusion: We could not detect a significant difference in the rate of osteoporotic fracture among patients treated with an aromatase inhibitor versus tamoxifen. Nonetheless, the risk with tamoxifen was numerically lower and significantly decreased when accounting for total duration of endocrine therapy.

1. Introduction

Endocrine therapy, a standard treatment for early-stage breast cancer, is associated with a significant reduction in disease recurrence and improvement in overall survival following a 5–10 year course of treatment [1]. Aromatase inhibitors are the preferred endocrine therapy agents among post-menopausal women diagnosed with breast cancer, supported by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis showing a decreased risk of recurrence among patients treated with aromatase inhibitors as compared to tamoxifen [2].

Endocrine therapy is associated with an increased risk of osteoporosis and osteoporotic fracture, particularly among patients receiving treatment with an aromatase inhibitor [3]. Aromatase inhibitors function as pure antiestrogens, inhibiting the function of

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the aromatase enzyme and peripheral conversion to estrogen as compared to tamoxifen which acts as a selective estrogen receptor modulator. The antiestrogen effects of aromatase inhibitors are associated with increased bone turnover and bone loss as compared to tamoxifen which has been postulated to have bone protective effects [4,5]. Researchers have observed higher rates of fracture among patients using aromatase inhibitors when compared to tamoxifen in most major clinical trials with fracture rates ranging from 5 to 11% [6–9].

The risk of fracture was not the primary outcome of most clinical trials and there is a concern that rates of osteoporotic fracture may be significantly higher in the general population [3]. The real-world incidence of fracture following adjuvant endocrine therapy is not well established. The purpose of this study is to compare the population-based rate of osteoporotic fracture among post-menopausal women treated with either aromatase inhibitor or tamoxifen for early-stage breast cancer in Ontario, Canada.

2. Materials and methods

2.1. Design

We conducted a retrospective cohort study among post-menopausal women (aged ≥66 years) with early-stage breast cancer who initiated treatment with adjuvant endocrine therapy between April 1st, 2005 and March 31st, 2012. Early-stage breast cancer patients, identified through the Ontario Cancer Registry, were required to have undergone definitive breast cancer surgery and demonstrate early-stage disease (stage I-III) where pathology was available. The study was conducted in Ontario, Canada using linked, population-based, health care administrative databases at ICES, an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data for health system evaluation and improvement [10]. ICES is a prescribed entity under section 45 of *Ontario's Personal Health Information Protection Act* (PHIPA). Section 45 is the provision that enables analysis and compilation of statistical information related to the management, evaluation and monitoring of, allocation of resources to, and planning for the health system. Section 45 authorizes health information custodians to disclose personal health information to a prescribed entity, like ICES, without consent for such purposes. Projects conducted wholly under section 45, by definition, do not require review by a Research Ethics Board.

2.1.1. Data sources

Administrative health care databases capturing physician billings, hospitalizations and medications were linked using unique, encoded identifiers and analyzed at ICES. Codes from the International Classification of Diseases 10th revision, Canadian Classification of Health Interventions and Drug Identification Numbers were used to identify all diagnoses, procedures and medications. Descriptions of databases and definitions of variables and administrative codes are listed in the Data Supplement (Tables 1–5).

2.1.2. Study population

We included patients aged 66 and older with recently diagnosed breast cancer who began adjuvant endocrine therapy (tamoxifen or an aromatase inhibitor: letrozole, anastrozole or exemestane) between 2005 and 2012. The majority of Ontario residents have universal coverage for physician services and hospitalizations. Starting at age 65 years, prescription medications are also covered allowing for a 1-year look-back of previous medication usage for our cohort. Patients were excluded from the cohort if they had a previous history of dementia, lived in long-term care, did not have a

record in the Ontario Cancer Registry (OCR), did not have breast cancer surgery within the previous year, or were diagnosed with pre-malignant or metastatic breast cancer within 1-year of starting endocrine therapy. They were also excluded if they had previous endocrine therapy within 1-year or had a diagnosis of a second malignancy within the previous 10-years.

2.1.3. Patient characteristics

Patients were classified according to their first endocrine therapy prescription of either an aromatase inhibitor or tamoxifen and we collected the following patient characteristics: age, neighborhood-level income quintile, rural residence (community of <10,000 persons), type of breast surgery, previous receipt of chemotherapy and/or radiation, cancer stage (AJCC 7th edition), Charlson comorbidity index, duration of endocrine therapy (years) and any switch of prescribed endocrine therapy [11,12]. We also recorded baseline co-morbidities and healthcare history including: history of osteoporosis or osteoporotic fracture, previous use of corticosteroids, previous use of a bisphosphonate, number of hospitalizations (previous 3 years), number of hospital visits (previous 1 year), number of prescription medications (previous 1 year) and bisphosphonate or denosumab use while receiving endocrine therapy [13].

2.1.4. Outcomes

Our primary outcome was the incidence of osteoporotic fracture among patients treated with an aromatase inhibitor as compared to tamoxifen (enrollment from 2005 to 2012) with patient follow-up until March 31, 2017. We identified osteoporotic fracture using an algorithm adapted from the Canadian Chronic Disease Surveillance Osteoporosis Working Group definition that is based on previous case validations and studies investigating population-based osteoporosis prevalence and fracture incidence [13]. The algorithm identifies an osteoporotic fracture if a patient meets one of three conditions: ≥1 hospitalization associated with a fracture of the forearm, humerus, vertebrae, hip, pelvis or femur, 2) ≥1 physician visit for an vertebral or unspecified fracture or 3) ≥2 physician visits within a 3 month period for a fracture of the forearm, humerus or pelvis [13]. The date of first fracture was recorded as the date of either first hospitalization or physician visit associated with the fracture diagnosis. If greater than two physician visits were required within a 3-month period, the date of fracture was recorded as the last physician visits which fulfilled the criteria. The date of first fracture was retained for the analysis.

2.1.5. Statistical analysis

Characteristics among patients receiving an aromatase inhibitor versus tamoxifen were compared using students t-test, chi-square, and Kruskal-Wallis tests as applicable. A standardized difference of ≥0.10 were considered statistically significant.

A univariable time-to-event analysis was performed to evaluate the potential association between type of endocrine therapy and risk of developing of osteoporotic fracture up to the maximum follow-up date of March 31, 2017, allowing for a potential 5–12 year period of follow-up. Subjects were censored if they switched endocrine therapy (aromatase inhibitor to tamoxifen or vice versa), reached the end of the follow-up period or died. We also calculated a separate 5-year event rate to compare the cumulative incidence of osteoporotic fracture among patients started either on an aromatase inhibitor or tamoxifen.

A cause-specific multivariable Cox proportional hazards model was estimated to evaluate the possible association between type of endocrine therapy (aromatase inhibitor versus tamoxifen) and the risk of developing an osteoporotic fracture. We chose a Cox proportional hazards model due to the presence of incomplete follow-

up time. The multivariable model adjusted for other important confounding factors including age, Charlson comorbidity index, previous medical co-morbidities (osteoporosis of history of osteoporotic fracture) previous medication history (use of corticosteroids or a bisphosphonate), previous use of chemotherapy and duration of endocrine therapy. The cancer stage variable was not included in the multivariable model due to large amounts of missing data. Patients with missing neighborhood income quintile were also excluded. The analysis was an intention to treat analysis and the duration of endocrine therapy variable was recorded as a time-dependent covariate measured on an annual basis up to a maximum of 5 years. The proportional hazards assumption was assessed by plotting Schoenfeld residuals against rank-transformed time.

A univariable and multivariable sensitivity analysis was also conducted using a more specific definition of osteoporotic fracture which excluded any fracture associated with radiation therapy within 60 days, as these fractures may have represented pathologic fractures associated with the patients underlying breast cancer diagnosis. We also measured the rate of osteoporotic fracture in a select group of high-risk patients for osteoporotic fracture defined as patients ≥75 years of age who had a history of osteoporosis or osteoporotic fracture or had a previous history of bisphosphonate at initiation of endocrine therapy. An additional sensitivity analysis was also conducted modelling the effect of duration of endocrine therapy for both an aromatase inhibitor and tamoxifen using two separate time-dependent covariates and controlling for bisphosphonate or denosumab use while receiving endocrine therapy. A Fine and Gray competing risk model was also performed using death as a competing risk for developing an osteoporotic fracture.

All tests were two sided and a p-value of 0.05 or less was considered statistically significant. No statistical corrections for multiple testing were conducted. Statistical analyses were performed using the SAS software program version 9.4 (SAS Institute, Cary, NC).

3. Results

A total of 12,077 patients were identified as receiving endocrine therapy from 2005 to 2012 after applying exclusions (Fig. 1). The median age of the cohort was 73 years (IQR 69–78). Seventy-three percent of patients started therapy with an aromatase inhibitor as compared to 27% originally treated with tamoxifen. Sixty-one percent of patients completed ≥5 years of therapy and 21% of patients switched therapy during their course of treatment. In the observed cohort, 64% percent of patients had a lumpectomy, 19% and 27% percent were treated with adjuvant chemotherapy and radiation respectively. Staging information was missing in 34% percent of patients. Among those with recorded staging information, 46% were Stage I, 42% Stage II and 12% Stage III disease at presentation.

Table 1 demonstrates the baseline characteristics among patients receiving an initial prescription for either an aromatase inhibitor or tamoxifen. There were significant differences noted between the two groups regarding age, stage, adjuvant chemotherapy, baseline history of osteoporosis and/or osteoporotic fracture and previous use of corticosteroids and bisphosphonate therapy based on a standardized difference of ≥0.10.

In a univariable analysis, the cumulative incidence of osteoporotic fracture was 12.0% (n = 1049) among patients treated with an aromatase inhibitor and 11.0% (n = 364) among patients treated with tamoxifen (Table 2). The unadjusted risk of osteoporotic fracture was not significantly different among patients treated with an aromatase inhibitor as compared to tamoxifen [Hazard Ratio

(HR) = 0.89, 95% confidence internal (CI) 0.79–1.00, p-value = 0.06]. The 5-year fracture rate was 7.5% and 6.9% among patients treated with aromatase inhibitors and tamoxifen respectively. The 5-year rate of fracture at age of study entry is also presented in Fig. 2 and the cumulative incidence fracture curve in the Data Supplement (Fig. 1). Fracture sites included forearm (45%), hip (27%), vertebrae (16%), pelvis (10%), and unspecified (2%).

In our adjusted analysis presented in Table 3, the risk of developing an osteoporotic fracture was also not significantly higher in patients treated with an aromatase inhibitor as compared to tamoxifen (HR = 1.09, 95% CI: 0.96–1.23, p-value = 0.18). In the multivariable model, there were 1413 (11.7%) fracture events, 2261 (18.7%) deaths, 2487 (20.6%) patients censored for switching endocrine therapy and 5916 (49.0%) patients who reached the end of follow-up. There were 1709 (19.5%) deaths among patients treated with aromatase inhibitors as compared to 552 (16.7%) deaths among patients treated with tamoxifen. The median follow-up time was 5.9 years. The following variables were also significant in the adjusted model: age (HR = 1.07, 95% CI: 1.06–1.08, p-value=<0.001), Charlson comorbidity index ≥2 (HR = 1.18, 95%CI: 1.06–1.31, p-value = 0.002), history of osteoporosis or osteoporotic fracture (HR = 1.42, 95% CI: 1.24–1.62, p-value<0.001), history of corticosteroid use (HR = 1.30, 95%CI: 1.06–1.60, p-value = 0.012), history of bisphosphonate use (HR = 1.19; 95%CI: 1.05–1.35, p-value = 0.006). Previous use of chemotherapy, type of endocrine therapy and duration of endocrine therapy measured as a time-dependent covariate were not significant.

A sensitivity analysis was also performed excluding fractures treated with radiation within 60 days. This only excluded 28 (<1%) fracture events and the results of the multivariable analysis comparing the risk of developing an osteoporotic fracture in patients treated with an aromatase inhibitor as compared to tamoxifen did not significantly change [Data Supplement Table 6: (HR = 1.09, 95% CI: 0.96–1.23, p-value = 0.19)]. The cumulative incidence of osteoporotic fracture was also calculated among patients at high risk of osteoporotic fracture (defined as age ≥75 year of age and previous baseline history of osteoporosis or osteoporotic fracture or previous use of a bisphosphonate). The high-risk fracture rate was 20.5% (n = 240) among patient treated with an aromatase inhibitor and 16.6% (n = 123) among patients treated with tamoxifen (Table 2). The unadjusted risk of osteoporotic fracture was not significantly different among high-risk patients treated with an aromatase inhibitor as compared to tamoxifen [HR = 1.13, 95% CI: 0.91–1.40, p-value = 0.27]. The 5-year fracture rate was 13.5% and 12.2% for patients receiving aromatase inhibitors and tamoxifen, respectively.

The sensitivity analysis using two time-dependent covariates modelling duration of aromatase inhibitor and tamoxifen treatment observe a decreased risk of fracture associated with tamoxifen use over time [Data Supplement: Table 7: (HR = 0.90; 95%CI: 0.83–0.97; p-value = 0.007)]. Conversely, fracture risk was unchanged when investigating duration of aromatase inhibitor therapy over time. No significant difference in fracture risk according to first prescription of an aromatase inhibitor or tamoxifen was observed even when controlling for bisphosphonate or denosumab use while on endocrine therapy [HR = 0.87; 95% CI: 0.64–1.17; p-value = 0.35]. The Fine and Gray competing risk model did not demonstrate any significant difference in osteoporotic fracture risk among patients treated with an aromatase inhibitor as compared to tamoxifen when adjusting for death as a competing risk to developing a fracture event [Data Supplement: Table 8: HR = 1.07, 95% CI: 0.94–1.21, p-value = 0.30]
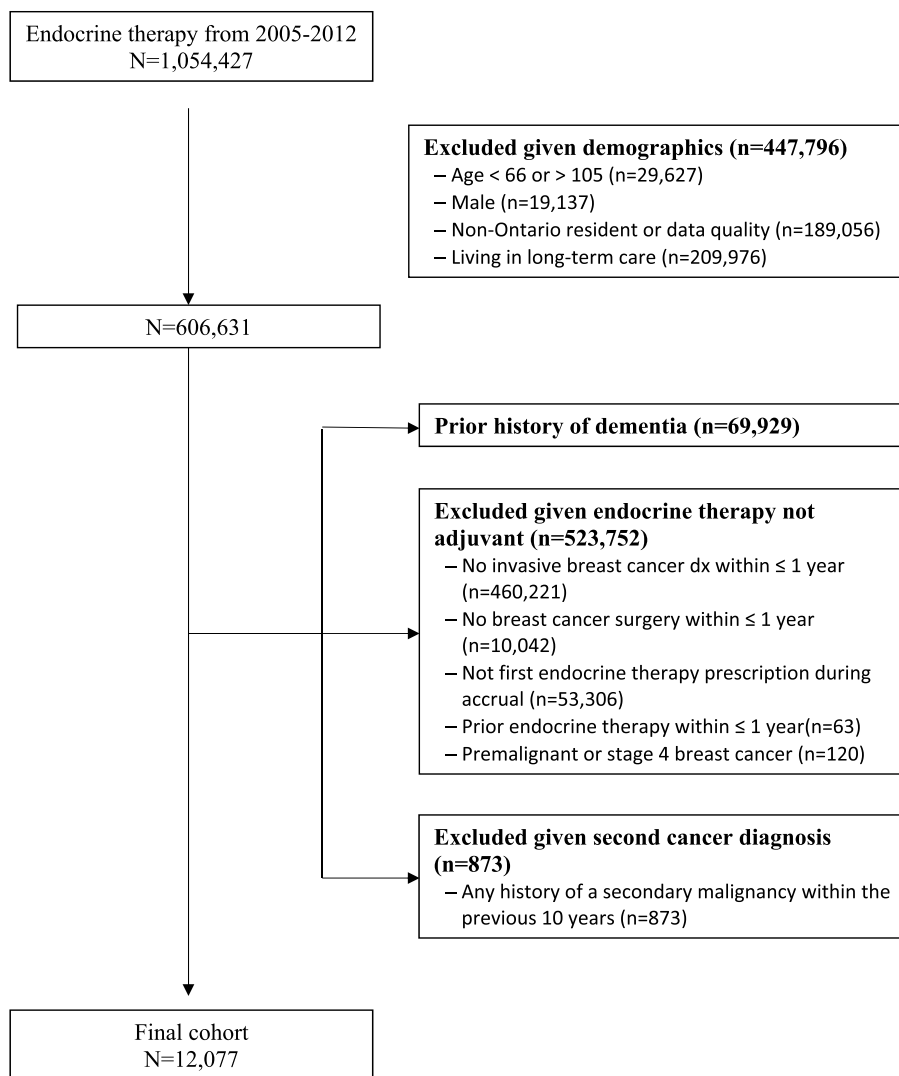
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┌─────────────────────────────┐
│  Endocrine therapy from      │
│  2005-2012                   │
│  N=1,054,427                 │
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Excluded given demographics (n=447,796)
 — Age < 66 or > 105 (n=29,627)
 — Male (n=19,137)
 — Non-Ontario resident or data quality (n=189,056)
 — Living in long-term care (n=209,976)

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┌─────────────────────────────┐
│  N=606,631                   │
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Prior history of dementia (n=69,929)

Excluded given endocrine therapy not adjuvant (n=523,752)
 — No invasive breast cancer dx within ≤ 1 year (n=460,221)
 — No breast cancer surgery within ≤ 1 year (n=10,042)
 — Not first endocrine therapy prescription during accrual (n=53,306)
 — Prior endocrine therapy within ≤ 1 year(n=63)
 — Premalignant or stage 4 breast cancer (n=120)

Excluded given second cancer diagnosis (n=873)
 — Any history of a secondary malignancy within the previous 10 years (n=873)

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┌─────────────────────────────┐
│  Final cohort                │
│  N=12,077                    │
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Fig. 1. Consort diagram.

4. Discussion

Our study did not detect a significant difference in osteoporotic fracture risk among post-menopausal women treated either with an aromatase inhibitor or tamoxifen for early breast cancer in Ontario, Canada. The osteoporotic fracture risk was 7.5% among patients treated with an aromatase inhibitor as compared to 6.9% in patients treated with tamoxifen with 5-years follow-up. After adjustment in the multivariable analysis, the risk of fracture was not significantly different (HR = 1.09, 95% CI: 0.96–1.23; p-value = 0.18).

Large clinical trials have demonstrated an increased risk of fracture among patients receiving an aromatase inhibitor as compared to tamoxifen. The EBCTCG meta-analysis noted a higher 5-year fracture risk of 8.2% versus 5.5% among patients treated with aromatase inhibitor as compared to tamoxifen [14]. While we expected to observe a higher rate of fracture among patients treated with an aromatase inhibitor, we did not observe any significant difference in comparison with patients treated with tamoxifen. This may reflect unmeasured confounding as oncologists may have preferentially offered tamoxifen to patients viewed at higher risk of osteoporotic fracture. A large study by Schimdt et al. from the United Kingdom using health administrative data was able to demonstrate a significant increased risk of fracture among patients treated with aromatase inhibitors [15]. We were not able to control for height, weight, smoking status, alcohol consumption and baseline bone mineral density which are important elements of the Fracture Risk Assessment Tool (FRAX), commonly used in clinical practice to estimate a patient's future risk of fracture, as this information was not available in our health administrative databases [16]. Our study also reflects an older post-menopausal population where fracture risk may be more influenced by age, medical co-morbidities and pre-existing osteoporosis rather than medication associated effects.

Two of our study's greatest strengths are the use of comprehensive real-world population of breast cancer patients from Ontario, Canada and use of a strict clinical fracture definition adapted from the Canadian Chronic Disease Surveillance Osteoporosis Working Group [13]. Our results are consistent with a previous Canadian study using health administrative data, which also did not demonstrate a higher risk of fracture among patients treated with aromatase inhibitors as compared to non-aromatase inhibitor users or the general population [17]. Additionally, our sensitivity analysis did demonstrate an association between longer durations of tamoxifen therapy and a decreased risk of osteoporotic fracture, consistent with previously published reports demonstrating

Table 1
Baseline characteristics of post-menopausal breast cancer patients according to type of endocrine therapy treated in Ontario, Canada from 2005 to 2012 (n = 12,077).

Baseline Characteristics	Endocrine therapy		Standardized Differences
	Aromatase Inhibitor n = 8770	Tamoxifen n = 3307	
Age (years)			
Median (IQR)	72 (69–78)	74 (69–80)	0.23
Income quintile, n (%)			
1 (low)	1688 (19%)	627 (19%)	0.01
2	1827 (21%)	669 (20%)	0.01
3	1708 (19%)	656 (20%)	0.01
4	1707 (19%)	646 (20%)	0
5 (high)	1818 (21%)	697 (21%)	0.01
Missing	22 (<1%)	12 (<1%)	0.02
Rural (<10,000 residents)	1169 (13%)	531 (16%)	0.08
Type of surgery, n (%)			
Mastectomy	3128 (36%)	1142 (35%)	0.02
Lumpectomy	5589 (64%)	2149 (65%)	0.03
Missing	53 (<1%)	16 (<1%)	0.02
Radiation therapy, n (%)	2277 (26%)	948 (29%)	0.06
Chemotherapy, n (%)	1949 (22%)	378 (11%)	0.29
Cancer stage, n (%)			
I	2672 (31%)	1054 (32%)	0.03
II	2605 (30%)	739 (22%)	0.17
III	802 (9%)	132 (4%)	0.21
Missing	2691 (31%)	1382 (42%)	0.23
Charlson comorbidity index, n (%)			
≤1 (low)	678 (8%)	280 (9%)	0.03
2	2285 (26%)	999 (30%)	0.09
≥3 (high)	1915 (22%)	596 (18%)	0.1
No hospitalization	3892 (44%)	1432 (43%)	0.02
Medical co-morbidities, n (%)			
Osteoporosis and/or history of fracture	1471 (17%)	834 (25%)	0.21
Previous medications, n (%)			
Corticosteroids	1788 (20%)	390 (12%)	0.24
Bisphosphonates	1983 (23%)	1188 (36%)	0.30
No. of hospitalizations (previous 3-years)			
Median (IQR)	0 (0–0)	0 (0–0)	0.02
No. of hospital visits (previous year)			
Median (IQR)	8 (5–13)	8 (5–13)	0.03
No. of prescriptions (previous year)			
Median (IQR)	7 (4-11)	7 (4-11)	0.03
Duration of endocrine therapy, n (%)			
1 year	876 (10%)	498 (15%)	0.15
2 years	837 (10%)	446 (14%)	0.12
3 years	641 (7%)	479 (15%)	0.23
4 years	575 (7%)	347 (11%)	0.14
≥5 years	5841 (67%)	1537 (47%)	0.41
Switch of endocrine therapy, n (%)	1355 (16%)	1214 (37%)	0.5
Medication use during endocrine therapy, n (%)			
Bisphosphonates	4230 (48%)	1546 (47%)	0.03
Bisphosphonates or denosumab	4307 (49%)	1579 (48%)	0.03

Table 2
Univariable incidence of developing an osteoporotic fracture according to endocrine therapy among post-menopausal women diagnosed with early-stage breast cancer treated in Ontario, Canada from 2005 to 2012 (N = 12,077) and among patients classified as high-risk for fracture (n = 1913).

Characteristics	Endocrine Therapy	Event rate n (%)	HR	95% CI	P-value
Osteoporotic fracture	Aromatase Inhibitor	1049 (12.0%)	0.89	0.79–1.00	0.06
	Tamoxifen	364 (11.0%)		Reference	
Osteoporotic facture (among high-risk patients[a])	Aromatase Inhibitor	240 (20.5%)	1.13	0.91–1.40	0.27
	Tamoxifen	123 (16.6%)		Reference	

HR: hazard ratio, CI: confidence interval.
Patients censored at death, end of follow-up (March 2017) and upon a switch of endocrine therapy (aromatase inhibitor to tamoxifen or vice versa).
[a] High-risk patients were defined as age ≥75 years and history of osteoporosis or osteoporotic fracture or previous use of a bisphosphonate.
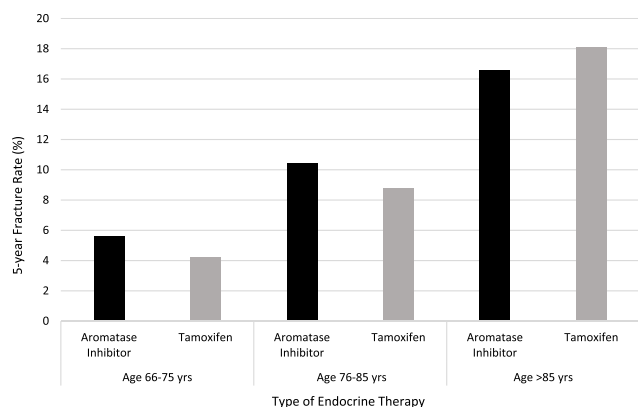
Fig. 2. 5-year osteoporotic fracture rate by patients age and type of endocrine therapy among post menopausal women treated for early-stage breast cancer in Ontario, Canada from 2005 to 2012 (n = 12,077).

use of adjuvant bisphosphonate therapy in breast cancer which may also potentially reduce risk of osteoporotic fracture among post-menopausal women [20]. Further studies among patients treated with adjuvant bisphosphonates are warranted.

Our study is one of a few population-based studies of fracture in early-stage breast cancer patients among the general population. While our study did not observe a significant difference in fracture among postmenopausal breast cancer patients using either aromatase inhibitors or tamoxifen, the study does give reasonable estimates for fracture in a real-world population-based setting in a country with publicly funded health care. Of note, the fracture risk among high-risk patients (age ≥75 years and previous baseline history of osteoporosis or osteoporotic fracture or previous use of a bisphosphonate) was 20.5% after starting an aromatase inhibitor. Patients and clinicians need to be aware of a significant fracture risk with endocrine therapy and appropriate surveillance and optimized treatment of osteoporosis is required irrespective of choice of endocrine therapy.

Table 3
Multivariable Cox proportional hazards model for factors influencing the risk of osteoporotic fracture among post-menopausal women treated for breast cancer in Ontario, Canada from 2005 to 2012 (N = 12,077).

Characteristics	Units	HR	95% CI	P-value
Endocrine therapy	AI vs. Tamoxifen	1.09	0.96–1.23	0.18
Age	Per Year	1.07	1.06–1.08	<.0001
Charlson comorbidity index	High vs. Low	1.18	1.06–1.31	0.002
History of osteoporosis or osteoporotic fracture	Yes vs. No	1.42	1.24–1.62	<0.001
Previous use of steroids	Yes vs. No	1.30	1.06–1.60	0.012
Previous use of bisphosphonate	Yes vs. No	1.19	1.05–1.35	0.006
Previous use of chemotherapy	Yes vs. No	0.89	0.72–1.10	0.27
Duration of endocrine therapy[a]	Per Year	0.97	0.91–1.02	0.20

AI: Aromatase inhibitor, HR: hazard ratio, CI: confidence interval.
Charlson comorbidity index: High (≥2) vs. Low (0–1 or no hospitalization).
Patients censored at death, end of follow-up (March 2017) and upon a switch of endocrine therapy (aromatase inhibitor to tamoxifen or vice versa).
[a] Time-dependent co-variate.

tamoxifen's more favorable effect on bone re-modelling, formation and density [5].

Nonetheless, our analysis does provide valuable estimates of osteoporotic fracture risk among early-stage breast cancer patients treated with endocrine therapy. The incidence of osteoporotic fracture observed in our study is consistent with the EBCTCG meta-analysis and large-scale clinical trials [2]. Other clinical trials have suggested higher rates of osteoporotic fracture including the ABCSG-18 clinical trial investigating adjuvant denosumab [18]. In this study the fracture rate was 26.2% at 7-years, significantly higher than the rates observed in our current study. We acknowledge the possibility that our study using health administrative data may underestimate osteoporotic fracture incidence, especially in regard to vertebral or milder fracture events. Our fracture definition cannot truly differentiate the cause of fracture (osteoporotic, traumatic, or pathologic), however, our sensitivity analysis results did not significantly change after restricting potential cases of pathologic fracture who received radiation treatment within 60 days of their fracture event. Additionally, our real-world data did not show a reduction in osteoporotic fracture with the concomitant use of a bisphosphonate. Denosumab does significantly lower the risk of osteoporotic fracture as demonstrated in the ABCSG-18 and D-CARE clinical trials, however, we were not able to confirm this observation as denosumab utilization was relatively uncommon during our study time period [18,19].

Our analysis is also focused on older post-menopausal women and the finding should not represent fracture risk in pre- or peri-menopausal breast cancer patients. Our study also pre-dates the

Declaration of competing interest

KIP has received honoraria from Pfizer, Roche, Amgen, Novartis, Eisai, Genomic Health, and Myriad Genetics Laboratories. She has also consulted for Pfizer and Gilead Sciences and received royalties from UpToDate. TV has consulted for Novartis and Roche. RF has consulted for Novartis, Janssen, Pfizer and Bayer. JR has received honoraria from Roche and consulted for Lilly, Merck and Novartis. DND has received honoraria from Amgen and consulted for Novartis. All other authors report no conflicts.

Acknowledgements

Author contributions

PSB, ML, BL, LR, SZS, KIP, JR, TV, RF, DND, KKWC and CCE created the study design and conception. Data analysis and interpretation was performed by PSB, ML, BL and AO. PSB, ML, BL, LR, SZS, KIP, JR, TV, RF, DND, KKWC and CCE were responsible for writing the original drafted manuscript and all authors approved the final manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2021.09.010.

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