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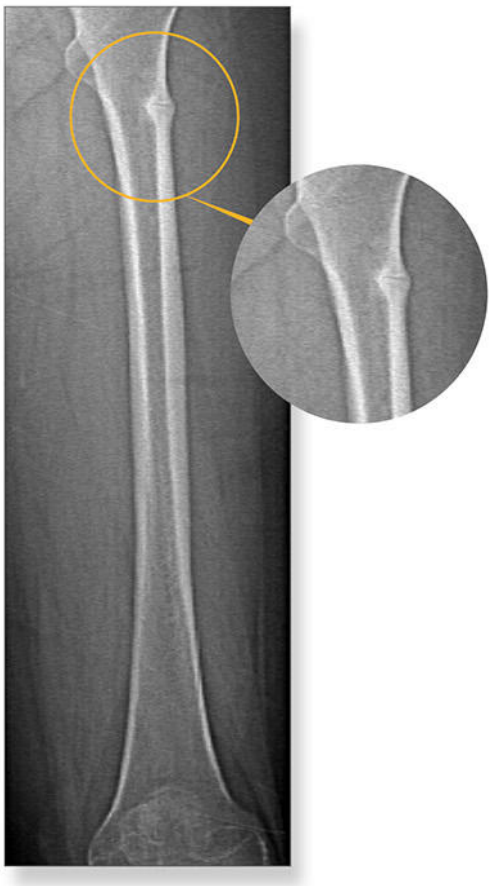

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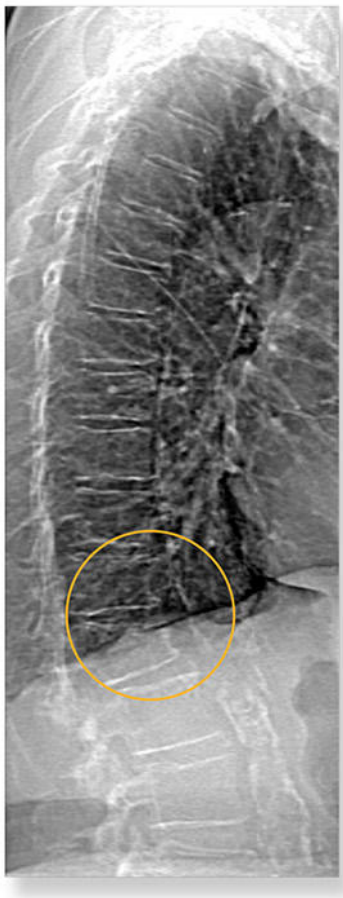

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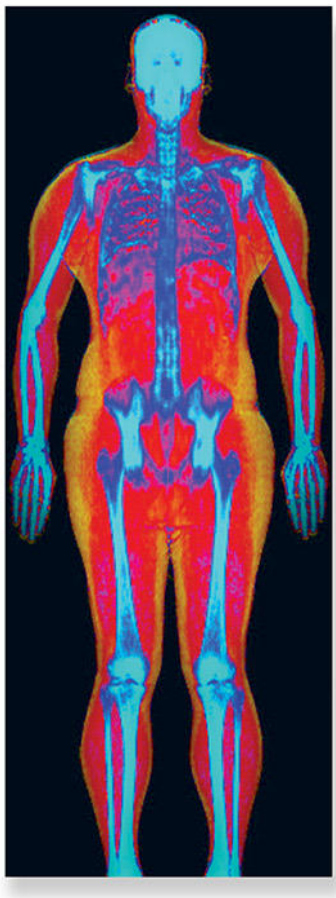

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ORIGINAL ARTICLE

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Performance of FRAX in Women with Breast Cancer Initiating Aromatase Inhibitor Therapy: A Registry-Based Cohort Study

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ABSTRACT

FRAX was developed to predict 10-year probability of major osteoporotic fracture (MOF) and hip fracture in the general population. Aromatase inhibitors (AI) used in breast cancer induce loss in bone mineral density (BMD) and are reported to increase fracture risk. AI exposure is not a direct input to FRAX but is captured under "secondary osteoporosis". To inform use of FRAX in women treated with AI, we used a population-based registry for the Province of Manitoba, Canada, to identify women aged ≥40 years initiating AI for breast cancer with at least 12 months' AI exposure ($n = 1775$), women with breast cancer not receiving AI ($n = 1016$), and women from the general population ($n = 34{,}205$). Among AI users, fracture probability estimated without BMD (AI use coded as secondary osteoporosis) significantly overestimated risk (10-year observed/predicted ratio 0.56, 95% confidence interval [CI] 0.45–0.68; 10-year hip fracture observed/predicted ratio 0.33, 95% CI 0.18–0.49). However, when BMD was included in the fracture probability, there was no significant difference between observed and predicted fracture risk. In Cox proportional hazards models, FRAX stratified risk of MOF, hip, and any fracture equally well in all subgroups (p-interaction >0.1). When adjusted for FRAX score without BMD, with AI use coded as secondary osteoporosis, AI users were at significantly lower risk for MOF (hazard ratio [HR] = 0.78, 95% CI 0.64–0.95), hip fracture (HR = 0.46, 95% CI 0.29–0.73) and any fracture (HR = 0.75, 95% CI 0.63–0.89). AI use was no longer significantly associated with fractures when AI use was not entered as secondary osteoporosis in FRAX without BMD or when BMD was included in the FRAX calculation. In conclusion, FRAX scores stratify fracture risk equally well in women receiving AI therapy as in non-users, but including secondary osteoporosis as a risk factor for AI users overestimates fracture risk. Our results call this practice into question. © 2019 American Society for Bone and Mineral Research.

KEY WORDS: OSTEOPOROSIS; BREAST CANCER; AROMATASE INHIBITORS; BONE DENSITOMETRY; FRACTURE RISK; FRAX

Introduction

The fracture risk assessment tool (FRAX) was developed to predict an individual's 10-year probability of major osteoporotic fracture (MOF; a composite of hip, humerus, forearm, and clinical vertebral fractures) and hip fracture from readily assessed clinical risk factors (age, sex, body mass index [BMI], and dichotomized risk factors comprising prior fragility fracture, parental history of hip fracture, current tobacco smoking, ever use of long-term oral glucocorticoid use, rheumatoid arthritis, high alcohol intake, causes of "secondary osteoporosis") and optionally femoral neck bone mineral density (BMD).[1] The designation secondary osteoporosis is diverse and comprises conditions associated with increased fracture risk, including aromatase inhibitor (AI) exposure.[2] The secondary osteoporosis input affects FRAX calculations when BMD is not entered but not when BMD is included, since the risk is assumed to be mediated through BMD. The FRAX framework also considers competing mortality to avoid overestimates in older individuals and those with risk factors for death.[3] More than 100 clinical practice guidelines include FRAX in their

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recommendations, making it the most widely used fracture prediction tool worldwide.[4]

Although initially developed for use in the general population, there is increasing interest in the application of FRAX to individuals with special conditions. Breast cancer is the most common cancer of women globally.[5] AI therapy is recommended to reduce the risk of cancer recurrence in postmenopausal women with hormone receptor–positive breast cancer[6] but has been reported to increase bone turnover, bone loss, and fracture risk.[7] Concomitant bisphosphonate therapy and more recently denosumab are therapeutic options to prevent bone loss in AI users.[8–10] Although one position paper has offered guidance on prevention of bone loss and fractures in postmenopausal women treated with AI for breast cancer that incorporates FRAX in the algorithm, the authors highlight concerns that FRAX was not designed to assess fracture risk in this setting and its accuracy is unknown.[10]

Given uncertainty regarding the application of FRAX in AI users, we examined performance of FRAX in routine clinical practice using a large clinical registry of BMD results for the province of Manitoba, Canada. This registry allowed us to identify and compare women initiating AI therapy for breast cancer, women with breast cancer not receiving AI therapy, and women from the general population without breast cancer.

Materials and Methods

Study population and setting

We performed a registry-based cohort study to examine fracture outcomes among women aged 40 years or older who had undergone baseline BMD of the hip between 2005 and 2016 with retrospectively calculated FRAX scores and had at least 1 year of follow-up after BMD testing (index date). In the Canadian province of Manitoba, health services are provided to nearly all residents through a single public health care system.[11] For each health system contact, information is recorded to document the patient's demographics, date and type of service, and diagnosis code(s). Hospital discharge abstracts (diagnoses and procedures) are coded using the International Classification of Diseases (ICD), 9th revision, Clinical Modification (ICD-9-CM) before 2004 and the 10th revision of ICD, Canadian version (ICD-10-CA) thereafter. Physician billing claims are coded using ICD-9-CM as previously described.[12,13] Medication use is obtained from the provincial pharmacy system.[14] BMD testing through the Manitoba Density Program has been managed as an integrated program since 1997.[15] The Manitoba Density Program maintains a database of all results that can be linked with the other provincial population-based databases through an anonymous personal identifier. The associated database exceeds 99% in terms of completeness and accuracy.[16] The study was approved by the Research Ethics Board of the University of Manitoba and the Health Information Privacy Committee of Manitoba Health.

Aromatase inhibitor use and breast cancer diagnosis

We categorized the women into one of three mutually exclusive subgroups: breast cancer with AI use, breast cancer without AI use, and general population without a breast cancer diagnosis or AI use (referent). Breast cancer diagnosis within the prior 3 years was based upon physician and hospitalization codes for malignant neoplasm of breast (ICD-9-CM 174-175, ICD-10-CA C50), an approach that agrees closely with cancer registry data (kappa 0.97).[17] AI use (ATC code L02BG) was obtained from the provincial pharmacy system for up to 5 years before the index date (full 5 years available in 95%) and 5 years after the index date (full 5 years available in 61%) and was tabulated as yearly total number of medication days, regardless of agent used.[14] AI use has been the standard of care for management of estrogen receptor (ER)-positive breast cancer in postmenopausal women since approximately 2005. We defined AI use as at least 365 days of medication exposure after the index date, with at least 180 days in the first year. The intensity of exposure was quantified as the medication possession ratio (MPR; medication days dispensed divided by the total number of days). We excluded long-term AI users (more than 180 days' use before the index date) to reflect the typical clinical scenario of a woman initiating AI therapy when BMD changes are expected to be greatest. Women from the general population without a breast cancer diagnosis or AI use (controls) and breast cancer cases without AI use had no exposure to these medications.

Assessment of incident fractures

Longitudinal health service records (ie, hospital discharge abstract and physician billing claims) were assessed between April 1, 1987, and March 31, 2017, for the presence of MOF, hip fracture, and any fracture (excluding head/neck, hands/feet, and ankle) not associated with codes indicative of severe trauma (ie, external injury) using published definitions.[12] Hip and forearm fractures were required to have a site-specific fracture reduction, fixation, or casting code. To minimize misclassification of prevalent and incident fractures at the same skeletal site, we required that there be no hospitalization or physician visit(s) with the same fracture type in the 12 months preceding an incident fracture. There was no time restriction on prior and incident fractures involving different skeletal sites.

Bone densitometry and fracture probability

All dual-energy X-ray absorptiometry (DXA) scans were performed with a commercial fan-beam device (Prodigy or iDXA, GE Healthcare, Madison, WI, USA) and analyzed in accordance with manufacturer recommendations. Femoral neck BMD *T*-scores were calculated using the NHANES III white female reference values.[18] The DXA instruments were cross-calibrated using anthropomorphic phantoms and no clinically significant differences were identified (*T*-score differences < 0.1). Short-term reproducibility (coefficient of variation [CV]) for femoral neck BMD from the multiple technologists was 2.3% (more than 400 repeat hip DXA scans performed within 28 days).

Ten-year probability of a MOF and hip fracture was calculated for each subject using the Canadian FRAX tool (FRAX Desktop Multi-Patient Entry, version 3.8). The Canadian FRAX tool was calibrated using nationwide hip fracture and mortality data[19] and independently validated in the general population.[18,19] We used the same FRAX tool that would be available in clinical practice to compute fracture probability in all subgroups, including those with breast cancer, but recognize that mortality assumptions may differ from the general population. The Manitoba BMD Registry was not used

in the creation or calibration of the FRAX tool. For the primary analysis, AI use was entered in the FRAX calculation without BMD as secondary osteoporosis as per Kanis and colleagues.[2] For non-AI users, the following conditions were ascertained from health service diagnoses and included under secondary osteoporosis: hyperthyroidism, ankylosing spondylitis, celiac disease, chronic liver disease, inflammatory bowel disease, cerebrovascular disease, multiple sclerosis, muscular dystrophy, pancreatitis, Parkinson's disease, or organ transplantation (kidney, heart, lung, bone marrow). Weight and height were measured at the time of DXA, and BMI was calculated as weight (in kilograms) divided by height (in meters) squared. Prior fracture and other FRAX input variables were assessed using linkage to the population-based research registry that includes hospital discharge abstracts and physician billing claims as previously described.[20] We defined prior fragility fracture as any non-traumatic MOF that occurred before the baseline DXA test examining medical records back to 1987. Parental hip fracture and current smoking was self-reported. High alcohol use was by self-report from 2012 onward and from a proxy variable in earlier years (alcohol substance abuse diagnosis codes). Rheumatoid arthritis diagnosis was from health service diagnoses. Prolonged oral corticosteroid use (>90 days dispensed in the 1 year before DXA) was obtained from the provincial pharmacy system.[14] We ascertained drug use in the year before and after the index date as >180 days' dispensation of an osteoporosis medication (oral or parenteral bisphosphonate [~90% of all osteoporosis medication use], raloxifene, denosumab, calcitonin, teriparatide), systemic estrogen product, or tamoxifen.

Statistical analyses

Statistical analyses were performed with Statistica (version 13.0, StatSoft Inc, Tulsa, OK, USA). Descriptive statistics for demographic and baseline characteristics are presented as mean ± SD for continuous variables or number (%) for categorical variables. Student *t* tests (continuous measures) and chi-square tests (categorical measures) were used to test for between-subgroup differences. We computed cumulative fracture incidence to 10 years and calibration ratios (observed versus predicted fracture probability with 95% confidence interval [CI]) for each patient subgroup (breast cancer with AI use, breast cancer without AI use, and general population). Observed 5-year and 10-year fracture probability was derived from the cumulative incidence function (CIF) for MOF and hip fracture incorporating competing mortality risk.[3,21] Predicted 5-year fracture probability was assumed to be one-half of the 10-year fracture probability based upon previous work.[22] Cox proportional hazards models were used to estimate risk gradients for incident fracture from the fracture probability measurements within each patient subgroup as hazard ratio (HR) per SD decrease with 95% CI. Two-way interaction terms were included in models to test for between-group differences. FRAX scores were log-transformed because of a skewed distribution. Cox proportional hazards models were also used

Table 1. Baseline Characteristics of the Study Population Stratified by Breast Cancer Status and Aromatase Inhibitor (AI) Use

	General population	Breast cancer, AI user	Breast cancer, non-AI user
	n = 34,205	*n* = 1775	*n* = 1016
Age (years)	65.0±11.0	64.7±9.9	65.1±11.6
BMI (kg/m^2)	27.6±6.3	28.8±5.9[a]	27.3 ± 5.4[c]
Prior fracture	5608 (16.4)	140 (7.9)[a]	138 (13.6)[c]
Parental hip fracture	4017 (11.7)	160 (9.0)[a]	109 (10.7)
Smoking	4658 (13.6)	160 (9.0)[a]	112 (11.0)
Glucocorticoid use	1190 (3.5)	22 (1.2)[a]	15 (1.5)[b]
Rheumatoid arthritis	823 (2.4)	25 (1.4)	11 (1.1)
High alcohol use	161 (0.5)	5 (0.3)	3 (0.3)
Secondary osteoporosis	3187 (9.3)	1775 (100)[a]	59 (5.8)[b,c]
Femoral neck *T*-score	−1.4±1.0	−1.1 ± 1.0[a]	−1.4 ± 1.0[c]
Femoral neck *T*-score osteoporotic	4035 (11.8)	103 (5.8)[a]	110 (10.8)[c]
FRAX MOF percent (without BMD) + AI secondary	11.6±8.8	13.0±9.3[a]	11.4 ± 9.0[c]
FRAX hip percent (without BMD) + AI secondary	3.5±5.5	4.1±6.3[a]	3.5 ± 5.6
FRAX MOF percent (without BMD) − AI secondary	11.6±8.8	9.9±7.3[a]	11.4 ± 9.0[c]
FRAX hip percent (without BMD) − AI secondary	3.5±5.5	2.6±4.3[a]	3.5 ± 5.6[c]
FRAX MOF percent (with BMD)	10.5±7.5	8.7±5.7[a]	10.2 ± 7.5[c]
FRAX hip percent (with BMD)	2.5±4.3	1.6±3.0[a]	2.5 ± 4.5[c]
Observation time (years)	7.0±3.1	6.2±2.8[a]	7.3 ± 3.2[b,c]
Incident MOF	2616 (7.6)	104 (5.9)	75 (7.4)
Incident hip fracture	825 (2.4)	19 (1.1)[a]	20 (2.0)
Incident any fracture	3502 (10.2)	133 (7.5)[a]	100 (9.8)
Death	3450 (10.1)	210 (11.8)	148 (14.6)[b]

BMI = body mass index; MOF = major osteoporotic fracture; S = small cell size suppressed; + (with) and − (without) AI use entered as secondary osteoporosis in FRAX.

Data are mean ± SD or *n* (%).

[a]$p < 0.05$ for general population versus AI user.

[b]$p < 0.05$ for general population versus non-AI user.

[c]$p < 0.05$ for AI user versus non-AI user.

to test for differences in time to first fracture controlled for baseline FRAX probability, with patient subgroup (breast cancer with AI use, breast cancer without AI use, and general population [referent]) as the covariate of interest. For model 1, AI use was entered in the FRAX calculation without BMD as secondary osteoporosis. For model 2, we performed the FRAX calculation without BMD where AI use was not included under secondary osteoporosis. Finally, for model 3, FRAX calculations were repeated with BMD, which is unaffected by the secondary osteoporosis input as noted earlier. In sensitivity analyses, we also looked at women with a minimum of 5 years of observation, at women without osteoporotic BMD at baseline, and for an interaction according to age (<65 years versus age 65 years and older). We also tested models that adjusted for drug use (osteoporosis medication, systemic estrogen product, tamoxifen) in the year before or after BMD testing.

Results

The study population included 36,996 women, among whom 1775 (4.8%) had breast cancer treated with an AI (median exposure 4.2 years), 1016 (2.7%) had breast cancer without AI use, and 34,205 (92.5%) were women from the general population without breast cancer of AI use (Supplemental Fig. S1). In breast cancer women initiating AI therapy, there was a consistently high level of use: median MPR during the first year was 0.99 (interquartile range 0.90–1.00), and median MPR throughout the period of AI was 0.95 (interquartile range 0.81–0.99).

The groups were similar in terms of age at baseline, but there were significant between-group differences in other characteristics (Table 1). Specifically, AI users had significantly higher BMI than women from the general population and breast cancer women without AI use ($p < 0.001$). Femoral neck BMD was also greater in AI users but similar among women from the general population and women with breast cancer not receiving an AI ($p < 0.001$). There was a similar lower proportion of AI users with BMD *T*-scores in the osteoporotic range or with prior fracture ($p < 0.001$). Fracture probability from FRAX calculated without BMD but including AI use as a cause of secondary osteoporosis was significantly greater in AI users ($p < 0.001$) but was lower when calculated without secondary osteoporosis ($p < 0.001$) or when FRAX was calculated with BMD ($p < 0.001$). Osteoporosis medication use was similar for all groups before BMD testing but was less frequent among AI users after BMD testing (Supplemental Table S1). Estrogen use was less frequent in women with breast cancer compared with women from the general population ($p < 0.001$), while tamoxifen use was greater ($p < 0.001$), both before and after BMD testing.

Mean follow-up ranged from 6.2 years in AI users to 7.3 years for women with breast cancer who were not AI users. During the observation period, incident MOF were experienced by 2795 women, incident hip fractures by 864 women, any clinical fracture by 3736 women, and death by 3808 women. The crude (unadjusted) cumulative incidence for fracture to 10 years is shown in Fig. 1. No significant between-group differences were found for incident MOF, but there was a significant difference for incident hip fracture and any fracture, which was lower among AI users than in the general population. Compared with the general population, women with breast cancer were at higher risk of death (AI users HR = 1.35, 95% CI 1.17–1.55; non-users 1.37, 95% CI 1.16–1.61).

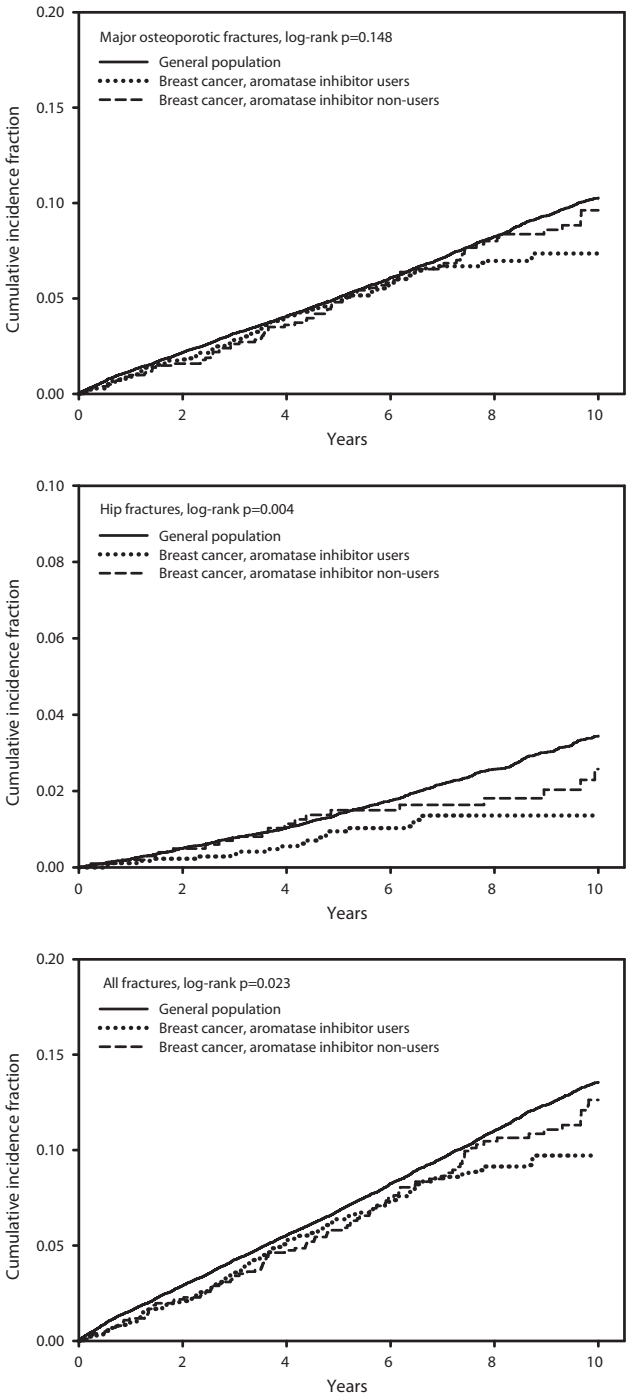

Fig. 1. Crude (unadjusted) cumulative incidence of fracture to 10 years, including competing mortality risk. Major osteoporotic fractures (*A*), hip fractures (*B*), and all fractures (*C*).

Figure 2 shows observed versus predicted fracture probability at 10 years for the three subgroups with competing mortality incorporated in the calculation. Among AI users, fracture probability estimated without BMD (AI use coded as secondary osteoporosis) significantly overestimated risk (10-year predicted MOF 13.0% versus observed 7.2%, observed/predicted ratio 0.56, 95% CI 0.45–0.68; 10-year hip fracture predicted 4.1% versus observed 1.3%, observed/predicted ratio 0.33, 95% CI 0.18–0.49).

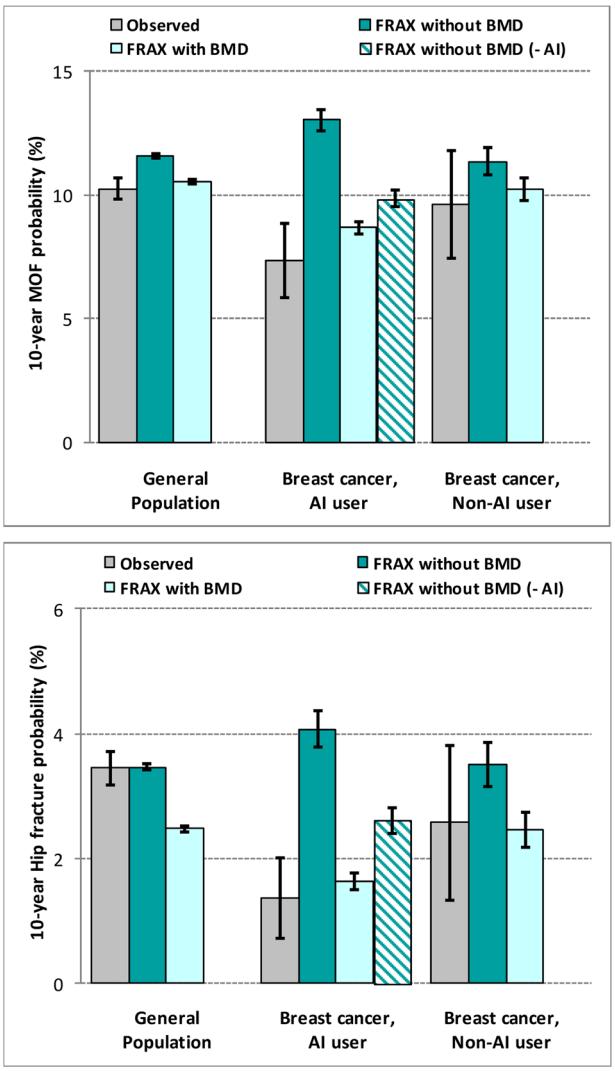

Fig. 2. Observed versus predicted 10-year major osteoporotic fracture (MOF) and hip fracture probability stratified by breast cancer status and aromatase inhibitor (AI) use, including competing mortality risk. AI use entered as secondary osteoporosis in FRAX (solid bar) and without secondary osteoporosis (-AI, hatched bar).

This discrepancy was attenuated but not eliminated when secondary osteoporosis was not included in the FRAX estimates (10-year observed/predicted ratio 0.75, 95% CI 0.60–0.90; 10-year hip fracture observed/predicted ratio 0.52, 95% CI 0.27–0.77). Finally, when BMD was included in the fracture probability, there was no significant difference between observed and predicted fracture risk (MOF observed/predicted ratio 0.85, 95% CI 0.68–1.02; hip fracture observed/predicted ratio 0.83, 95% CI 0.44–1.22). Similar results were found for assessment of 5-year fracture outcomes (Supplemental Fig. S2). For the other patient subgroups there was agreement between observed and predicted fracture probability with one exception (general population observed 10-year hip fracture probability exceeded predicted probability when BMD was included in the risk calculation but not when BMD was omitted or when based on 5-year hip probability).

The performance of FRAX as a tool for stratification of fracture probability was assessed in models stratified by breast cancer status and AI use (Table 2). FRAX without BMD was significantly associated with incident MOF, hip fractures, and any fractures in each of the subgroups. HRs were greater when BMD was included in the fracture probability score. Results were essentially unchanged when analysis was limited to the 1090 (61%) of women with at least 5 years of observation and AI therapy (median MPR for AI use over the 5 years 0.93, interquartile range 0.74–0.98) (Supplemental Table S2). There was no evidence that AI use affected fracture risk differently in women below versus above age 65 years (all age-interaction $p > 0.2$).

When BMD was not included in baseline fracture probability, AI users (with secondary osteoporosis, model 1) appeared to be at significantly lower risk for MOF (HR = 0.78, 95% CI 0.64–0.95), hip fracture (HR = 0.46, 95% CI 0.29–0.73), and any fracture (HR = 0.75, 95% CI 0.63–0.89) (Table 3). When secondary osteoporosis was excluded (model 2) or BMD was included (model 3) in the estimation of baseline fracture risk, AI use was no longer significantly associated with fracture. Breast cancer without AI use was not associated with a significant increase in any fracture outcomes. Similar results were found in models that adjusted for drug use (osteoporosis medication, systemic estrogen product, tamoxifen) in the year before or after BMD testing (Supplemental Tables S3 and S4, respectively).

Discussion

This analysis of fracture risk among women with breast cancer initiating AI therapy found unexpected results. Contrary to our hypothesis that these women would be at increased fracture risk compared with the general population and that FRAX would underestimate that risk, we found that fracture risk was actually lower than predicted when secondary osteoporosis was included in the estimation of baseline fracture risk without BMD. Conversely, baseline BMD in these women was higher than for the general population and for breast cancer women not receiving AI and resulted in a lower fracture probability when BMD was included in the calculation. This is explained by the fact that secondary osteoporosis in FRAX does not affect fracture probability when BMD is included in the calculation. Our data may help to inform clinical guidelines regarding the role of BMD testing and FRAX in fracture risk assessment for AI recipients and support the incorporation of FRAX with BMD in management algorithms of women treated with AI for breast cancer.[10]

Although one report suggested a threefold increased fracture incidence,[23] a large nationwide population-based cohort study using US Medicare data identified minimal excess risk from AI use compared with tamoxifen (11% higher for nonvertebral fractures, not significantly increased for hip fractures).[24] Our findings are therefore in agreement with the latter study. Our observation that fracture risk was relatively low in women initiating AI therapy may indicate that higher baseline BMI, BMD, and lower prevalence of prior fracture may offset the adverse effects of AI exposure. Indeed, higher BMI is a known risk factor for estrogen receptor–positive breast cancer and is also correlated with higher BMD and lower fracture risk.[25,26] Estrogen receptor–positive breast cancer has also been associated with higher baseline BMD, with several studies

Table 2. Hazard Ratios (HR) With 95% Confidence Intervals (CI) for Outcomes of Incident Fracture According to Fracture Probability Stratified by Breast Cancer Status and Aromatase Inhibitor (AI) Use

	FRAX without BMD HR per SD	FRAX with BMD HR per SD
Outcome: MOF		
General population	**2.03 (1.94–2.11)**	**2.12 (2.03–2.21)**
Breast cancer, AI user	**1.63 (1.34–1.98)**	**1.66 (1.37–2.01)**
Breast cancer, non-AI user	**1.95 (1.52–2.51)**	**2.11 (1.64–2.71)**
p-interaction	0.414	0.447
Outcome: hip fracture		
General population	**3.76 (3.45–4.09)**	**4.33 (3.95–4.73)**
Breast cancer, AI user	**4.50 (2.59–7.82)**	**4.38 (2.49–7.73)**
Breast cancer, non-AI user	**5.45 (2.89–10.3)**	**7.27 (3.78–14.0)**
p-interaction	0.345	0.256
Outcome: any fracture		
General population	**1.81 (1.75–1.88)**	**1.91 (1.85–1.98)**
Breast cancer, AI user	**1.72 (1.44–2.05)**	**1.75 (1.48–2.08)**
Breast cancer, non-AI user	**1.82 (1.47–2.26)**	**1.93 (1.55–2.39)**
p-interaction	0.928	0.969

MOF = major osteoporotic fracture.

Data are from Cox proportional hazards models. Significant results are in boldface.

showing that BMD measurements are associated with increased risk of overall and ER-positive breast cancer independent of the Gail score.[27–29] The FRAX algorithm incorporates competing mortality based upon the general population mortality hazard function, and fracture probability would be slightly overestimated in women with breast cancer with long-term follow-up due to excess mortality.

Limitations to this study are acknowledged. We do not have information on tumor markers or staging. Some of the fractures could have been pathologic (related to breast cancer metastases), but this would bias results toward higher fracture rates rather than lower fracture rates. Although fractures were ascertained from administrative data, the definitions used have been directly validated against X-ray confirmed fractures and adopted for national osteoporosis surveillance.[12,13,30] FRAX does not estimate probability for vertebral fracture alone, though clinical vertebral fractures are included among the MOF outcomes. If rapid trabecular bone loss in women using AIs preferentially affects vertebral fracture risk, then this might be difficult to detect, though we saw no difference in the numbers of clinical vertebral fractures between the groups (data not shown). We did not adjust for osteoporosis medication use in

Table 3. Hazard Ratios (HR) With 95% Confidence Intervals (CI) for Outcomes of Incident Fracture According to Breast Cancer Status and Aromatase Inhibitor (AI) Use, Adjusted for Baseline Risk

	Model 1: adjusted for FRAX without BMD (+ AI secondary) HR (95% CI)	Model 2: adjusted for FRAX without BMD (– AI secondary) HR (95% CI)	Model 3: adjusted for FRAX with BMD HR (95% CI)
Outcome: MOF			
General population	1 (REF)	1 (REF)	1 (REF)
Breast cancer, AI user	**0.78 (0.64–0.95)**	1.02 (0.84–1.24)	1.09 (0.89–1.33)
Breast cancer, non-AI user	0.90 (0.72–1.14)	0.90 (0.72–1.14)	0.91 (0.73–1.15)
p-value	**0.034**	0.671	0.512
Outcome: hip fracture	HR (95% CI)	HR (95% CI)	HR (95% CI)
General population	1 (REF)	1 (REF)	1 (REF)
Breast cancer, AI user	**0.46 (0.29–0.73)**	0.71 (0.45–1.12)	0.81 (0.52–1.28)
Breast cancer, non-AI user	0.73 (0.47–1.13)	0.73 (0.47–1.13)	0.75 (0.48–1.17)
p-value	**0.002**	0.132	0.315
Outcome: any fracture	HR (95% CI)	HR (95% CI)	HR (95% CI)
General population	1 (REF)	1 (REF)	1 (REF)
Breast cancer, AI user	**0.75 (0.63–0.89)**	0.94 (0.79–1.12)	1.00 (0.84–1.19)
Breast cancer, non-AI user	0.90 (0.74–1.10)	0.90 (0.74–1.10)	0.91 (0.75–1.11)
p-value	**0.003**	0.482	0.646

MOF = major osteoporotic fracture. + (with) and – (without) AI use entered as secondary osteoporosis in FRAX.

Data from Cox proportional hazards models. Significant results are in boldface.

the primary analysis because FRAX is robust to these effects[31]; this would not account for observed differences as rates of use were similar or lower in women receiving AI therapy. The median use of AI therapy was 4.2 years rather than the currently recommended 5 years. However, subgroup analysis showed comparable results in women receiving 5 years of AI therapy. Finally, there is the importance of confirming that our findings generalize to other populations and, if so, determining how this should be incorporated into routine clinical practice. The present findings should not be misinterpreted to infer that patients taking AI are not at future risk of fracture. It is important to identify those women receiving AI therapy who experience accelerated BMD loss and develop a level of fracture risk where intervention is warranted.

In summary, our findings challenge the view that the average woman with breast cancer is at high fracture risk at the time of initiation of AI therapy. In fact, at baseline these women appear to be at relatively lower fracture risk than the general population and women with breast cancer not initiating AI therapy because of higher BMI, BMD *T*-score, and lower prevalence of prior fracture. Fracture probability scores from FRAX stratify fracture risk equally well in women receiving AI therapy as in non-users, but including secondary osteoporosis as a risk factor for AI users in the calculation leads to overestimation in predicted fracture risk. Our results call this practice into question.

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