JAMA Oncology | Original Investigation

Fracture Risk Prediction Using the Fracture Risk Assessment Tool in Individuals With Cancer

Carrie Ye, MD, MPH; William D. Leslie, MD, MSc; Saeed Al-Azazi, MSc; Lin Yan, PhD; Lisa M. Lix, PhD; Piotr Czaykowski, MD; Eugene V. McCloskey, MD; Helena Johansson, PhD; Nicholas C. Harvey, MD, PhD; John A. Kanis, MD; Harminder Singh, MD

IMPORTANCE The Fracture Risk Assessment Tool (FRAX) is a fracture risk prediction tool for 10-year probability of major osteoporotic fracture (MOF) and hip fracture in the general population. Whether FRAX is useful in individuals with cancer is uncertain.

OBJECTIVE To determine the performance of FRAX for predicting incident fractures in individuals with cancer.

DESIGN, SETTING, AND PARTICIPANTS This retrospective population-based cohort study included residents of Manitoba, Canada, with and without cancer diagnoses from 1987 to 2014. Diagnoses were identified through the Manitoba Cancer Registry. Incident fractures to March 31, 2021, were identified in population-based health care data. Data analysis occurred between January and March 2023.

MAIN OUTCOMES AND MEASURES FRAX scores were computed for those with bone mineral density (BMD) results that were recorded in the Manitoba BMD Registry.

RESULTS This study included 9877 individuals with cancer (mean [SD] age, 67.1 [11.2] years; 8693 [88.0%] female) and 45 877 individuals in the noncancer cohort (mean [SD] age, 66.2 [10.2] years; 41 656 [90.8%] female). Compared to individuals without cancer, those with cancer had higher rates of incident MOF (14.5 vs 12.9 per 1000 person-years; $P < .001$) and hip fracture (4.2 vs 3.5 per 1000 person-years; $P = .002$). In the cancer cohort, FRAX with BMD results were associated with incident MOF (HR per SD increase, 1.84 [95% CI, 1.74-1.95]) and hip fracture (HR per SD increase, 3.61 [95% CI, 3.13-4.15]). In the cancer cohort, calibration slopes for FRAX with BMD were 1.03 for MOFs and 0.97 for hip fractures.

CONCLUSIONS AND RELEVANCE In this retrospective cohort study, FRAX with BMD showed good stratification and calibration for predicting incident fractures in patients with cancer. These results suggest that FRAX with BMD can be a reliable tool for predicting incident fractures in individuals with cancer.

JAMA Oncol. doi:10.1001/jamaoncol.2024.4318
Published online October 3, 2024.

Supplemental content

Author Affiliations: Department of Medicine, University of Alberta, Edmonton, Alberta, Canada (Ye); Department of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada (Leslie, Al-Azazi, Yan, Lix, Czaykowski, Singh); CancerCare Manitoba, Winnipeg, Manitoba, Canada (Czaykowski, Singh); Centre for Metabolic Bone Diseases, University of Sheffield Medical School, Sheffield, United Kingdom (McCloskey, Johansson, Kanis); Mary McKillop Institute for Health Research, Australian Catholic University, Melbourne, Australia (Johansson); MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, United Kingdom (Harvey); NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom (Harvey).

Corresponding Author: Carrie Ye, MD, University of Alberta, 11350 83 Ave NW, 8-130 Clinical Sciences Building, Edmonton, AB T6G 2G3, Canada (cye@ualberta.ca).

Cancer can adversely affect the skeleton, leading to decreases in bone mineral density (BMD), osteoporosis, and nonmetastatic fractures.[1] Cancer treatments, including treatment regimens with glucocorticoids, hormone deprivation therapies, immunomodulatory therapies, surgical treatments such as gastrectomy and hysterectomy with bilateral salpingo-oophorectomy, and radiation therapy, can also increase fracture risk.[1-7]

Although cancer tends to affect an older population, bone loss in people with cancer is higher compared with the general population even after adjusting for age.[8] Additionally, individuals with cancer are at higher risk of falls than those without cancer.[9] Fractures in individuals with cancer lead to approximately 2.5-times increased risk of mortality within the first year after a major osteoporotic fracture (MOF) and 3.5 times increased risk of mortality after a hip fracture.[10] Despite being at high risk of osteoporosis and fracture, patients with cancer with fractures are rarely assessed or treated for osteoporosis with only 11% of cancer survivors receiving BMD testing and 23% receiving osteoporosis treatment within a year of an MOF.[11]

Osteoporosis treatment has shifted away from using BMD alone to determine osteoporosis treatment as most fractures occur in individuals with BMD above the threshold for osteoporosis (T score, −2.5).[12] Current guidelines, including cancer-specific guidelines, now recommend treatment thresholds based on an individual's absolute fracture risk using a fracture risk assessment tool such as the Fracture Risk Assessment Tool (FRAX).[13-16] FRAX is the most commonly used and widely validated fracture prediction tool worldwide.[17] Although FRAX includes multiple clinical risk factors, cancer and cancer treatments are not specific inputs. Although guide-

lines recommend fracture risk assessment in individuals with cancer, no fracture risk calculators have been validated in a mixed cancer population. Given the uncertainty in the applicability of FRAX to individuals with cancer and the lack of other validated tools in these individuals, we examined the performance of FRAX in a mixed cancer population as well as in specific cancer types.

Key Points

Question How well does the Fracture Risk Assessment Tool (FRAX) perform at predicting incident fractures in individuals with cancer?

Findings In this retrospective population-level cohort study that included 9877 individuals with cancer, FRAX with bone mineral density results predicted incident major osteoporotic fractures and hip fractures with calibration slopes of 1.03 and 0.97, respectively.

Meaning These results suggest that FRAX with bone mineral density can predict incident fractures in individuals with cancer.

Methods

Study Design

We performed a retrospective cohort study using population-level health care administrative databases from the Canadian province of Manitoba. Manitoba is Canada's fifth most populous province with a population of 1.41 million in 2022.[18] Health services are provided to nearly all residents in Manitoba through a single public health care system.[19] All Manitoba residents are assigned a unique personal health identification number, which can be used to link their health care utilization and outcomes data within the various provincial administrative databases. Patient demographics were obtained from the provincial registration database, a list of individuals eligible for health care coverage in Manitoba. Cancer diagnosis dates were obtained from the Manitoba Cancer Registry (MCR), which maintains a record of all cancers diagnosed in the province since 1956. As a member of the North American Association of Central Cancer Registries and the Canadian Cancer Registry, the MCR is regularly audited for accurate coding of cancer data[20,21] and has been shown to have very high levels of reporting completeness and accuracy, including histologic verification.[22] The study was approved by the Health Research Ethics Board for the University of Manitoba, Manitoba's Health Information Privacy Committee, and CancerCare Manitoba Research Resource Impact Committee. Informed consent was waived because the data were deidentified.

BMD data were obtained from the Manitoba BMD Program which oversees all clinical BMD testing in the province and maintains a database of all dual-energy x-ray absorptiometry (DXA) results. This population-based database has been shown to be nearly 100% complete and accurate.[23]

Information on health care visits, procedures, and diagnosis codes were obtained from physician claims and hospital discharge databases and linked to the BMD database. Physician billing claims used the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* and hospital discharge abstracts used the *ICD-9-CM* prior to 2004 and *International Statistical Classification of Diseases, Tenth Revision, Canada (ICD-10-CA)* after 2004. Medication use was ascertained from the provincial pharmacy database, which records all medications dispensed in the outpatient setting.[24] Deaths were ascertained from the Vital Statistics registry, which records all births and deaths that take place in Manitoba.[25]

Study Population

We started by identifying all Manitoba residents aged 18 years or older with first cancer diagnoses other than nonmelanoma skin cancer between 1987 and 2014 from the MCR. The date of cancer diagnosis was defined as recorded in the MCR. Each individual with cancer was matched to up to 4 individuals without cancer by age (within 5 years), sex, and area of residence on the date of cancer diagnosis (index date) based on postal codes.[26] To compute FRAX scores and have adequate observation time for assessing fracture outcomes, we restricted the analysis to those aged 40 years and older who had DXA testing after the index date as recorded in the Manitoba BMD Program database between January 1, 1995, and March 31, 2016.

Incident Fracture Assessment

Incident fractures were ascertained from hospital discharge abstracts and physician billing claims *ICD-9-CM* and *ICD-10-CA* codes up to March 31, 2021, using previously validated fracture site-specific algorithms.[27] Site-specific fracture definitions used in this study have been adopted for national surveillance and have been radiologically validated in patients both with and without fractures from the Manitoba BMD Program database.[28,29] Hip, clinical vertebral, forearm, and humerus fracture diagnostic codes were collectively designated MOF. The fracture date was defined as the date of the first clinical encounter for the first fracture occurring after cancer diagnosis.

Fracture Probability Assessment

Ten-year probabilities of MOF and hip fracture were calculated for each individual using the country-specific (Canadian) FRAX tool (FRAX Desktop Multi-Patient Entry, version 3.8).[30] Clinical risk factors included in the FRAX tool were collected as previously described.[31] Briefly, weight and height were measured at the time of DXA. Other data required for FRAX calculation were assessed from information collected directly from individuals through the intake questionnaire at the time of each DXA scan and supplemented with population-based health care data from the linked provincial population-based health care databases.[32] The list of conditions considered secondary causes of osteoporosis was adapted from Kanis et al.[33] The designation of secondary osteoporosis is diverse and comprises many conditions associated with increased fracture risk. The secondary osteoporosis input affects FRAX calculations when BMD is not entered but not when BMD is included because the risk is assumed to be mediated through BMD. Oral glucocorticoid exposure greater than 90 days in the prior year and osteoporosis medication use for at least 180 days

in the year prior to the index DXA scan were ascertained using the provincial pharmacy system. We also assessed use of osteoporosis medications, including alendronate, risedronate, etidronate, raloxifene, calcitonin, zoledronic acid, denosumab, or teriparatide.

Statistical Analysis

Baseline characteristics were compared between individuals with and without cancer using 1-way analysis of variance (ANOVA) for continuous variables, and χ^2 and Fisher exact tests for categorical variables. Cumulative MOF and hip fracture probabilities were calculated to 10 years and observed 10-year fracture probability was estimated incorporating competing mortality risk in both groups.[34,35] Decile-stratified observed 10-year fracture probability was compared to FRAX-derived 10-year fracture probability to obtain calibration ratios.

Cox proportional hazards regression models were used to estimate hazard ratios (HRs) per SD increase in FRAX score (log-transformed due to a skewed distribution) in the cancer and noncancer groups and 95% CIs. Cox regression models adjusting for FRAX with and without BMD, individual FRAX risk factors including BMD and osteoporosis medication use were used to estimate HRs for fracture risk with cancer diagnosis. Effect modification of cancer status and cancer diagnosis site were evaluated with interaction terms FRAX × cancer status and FRAX × cancer diagnosis site, respectively. If interaction terms were significant, stratified analysis was carried out. The proportional hazards assumption was confirmed using Schoenfeld residuals. Data analysis occurred between January and March 2023 and was conducted using SAS software, version 9.4 (SAS Institute). Statistical significance was assessed at $P < .05$.

Results

A total of 117 058 individuals with cancer were matched to 460 029 individuals without cancer. Of this cohort, 9877 individuals with cancer (8.4%) had a DXA scan after their cancer diagnosis, and 45 875 individuals (10.0%) without cancer had a DXA scan after the index date, for a total study cohort of 55 752 (**Table 1**). Compared to the noncancer cohort, the cancer cohort was on average slightly older (mean [SD] age, 67.1 [11.2] years compared to 66.2 [10.2] years; $P < .001$); had a higher percentage of male individuals (1184 [12.0%] compared to 4219 [9.2%]; $P < .001$); had slightly higher mean (SD) body mass index, calculated as weight in kilograms divided by height in meters squared (27.7 [5.6] compared to 27.1 [9.2]; $P < .001$); and had a higher percentage with parental hip fracture (807 [8.2%] compared to 3202 [7.0%]; $P < .001$). They were also more likely to be current smokers (878 [8.9%] compared to 3679 [8.0%]; $P = .004$), less likely to have rheumatoid arthritis (202 [2.0%] compared to 1309 [2.9%]; $P < .001$), and more likely to have secondary causes of osteoporosis (3795 [38.4%] compared with 4572 [10.0%]; $P < .001$). This difference in secondary causes of osteoporosis may have been driven by much higher aromatase inhibitor use in the cancer cohort (n = 2917 of 9877 [29.5%]), as compared with the noncancer cohort (n = 109 of 45 875 [0.2%]). Despite the cancer cohort having a similar prior fracture history to the noncancer cohort and an overall higher FRAX MOF probability without BMD and similar FRAX MOF probability with BMD, the cancer cohort was less likely to be on an osteoporosis medication (410 [4.2%] compared with 4556 [9.9%]; $P < .001$). The top 3 cancer diagnosis sites in the cancer cohort were breast, gynecological, and colorectal, likely reflecting the female predominance of the DXA cohort (eTable 1 in Supplement 1).

The mean (SD) follow-up time of 7.6 (3.1) years in the cancer cohort was significantly shorter than in the noncancer cohort (8.5 [2.6] years; $P < .001$). A similar percentage of individuals in the cancer cohort and noncancer cohort experienced MOFs (1086 [11.0%] vs 5021 [10.9%]; $P = .89$; **Table 2**). The incidence rate of MOF per 1000 person-years was significantly higher in the cancer cohort (14.5 vs 12.9 person-years; $P < .001$), related to the higher incidence rates for hip fractures (4.2 vs 3.5 per 1000 person-years; $P = .002$) and humerus fractures (2.9 vs 2.4 person-years; $P = .02$) . A total of 2646 deaths (26.8%) occurred in the cancer cohort, which was significantly higher compared with 5670 (12.4%) in the noncancer cohort ($P < .001$).

Observed 10-year cumulative probabilities of MOFs and hip fractures were calculated incorporating the competing risk of death, stratified by risk deciles in FRAX with BMD (eTable 2 in Supplement 1). These were plotted against FRAX-predicted MOFs and hip fractures with and without BMD (**Figure**). The calibration slope for MOFs was 0.87 when BMD was not considered in FRAX and 1.03 when BMD was considered in FRAX. The slope of the calibration curve for hip fractures was 0.72 when BMD was not considered in FRAX and 0.97 when BMD was considered. Comparison of observed 10-year MOF and hip fracture probabilities with FRAX-predicted probabilities were also evaluated by risk category (eTable 3 in Supplement 1). All observed fracture probabilities fell within their respective FRAX-predicted risk categories.

FRAX showed good stratification for predicting incident fractures in all analyses. Significant effect modification by cancer status for the predictive value of FRAX for MOF without BMD was found (HR, 1.93 [95% CI, 1.88-1.99] vs 1.73 [95% CI, 1.63-1.84], respectively; P for interaction = .001). Significant effect modification was also found for MOF with BMD (HR, 2.05 [95% CI, 1.99-2.11] vs 1.84 [95% CI, 1.74-1.95], respectively; P for interaction = .001) and hip fracture without BMD (HR, 3.44 [95% CI, 3.22-3.67] vs 2.95 [95% CI, 2.59-3.37], respectively; P for interaction = .04) (**Table 3**). However, significant effect modification by cancer status was not found for hip fracture with BMD (HR per SD increase, 4.10 [95% CI, 3.82-4.41] vs 3.61 [95% CI, 3.13-4.15]; P for interaction = .11).

In the cancer cohort, FRAX with BMD predicted incident MOF and hip fracture, both slightly lower than in those without cancer. HRs were consistently higher when BMD was included in the FRAX score for both cancer and noncancer cohorts. There was no effect modification by cancer diagnosis site (interaction term: FRAX × cancer diagnosis site).

In models adjusted for FRAX without BMD and individual FRAX risk factors excluding BMD but including osteoporosis medication use, cancer diagnosis was a nonsignificant modifier of MOF risk compared to the noncancer cohort

Table 1. Baseline Characteristics Stratified by Cancer Status

Characteristic	Cohort, No. (%)		*P* value
	General (n = 45 875)	Cancer (n = 9877)	
Age at index BMD, mean (SD), y	66.2 (10.1)	67.1 (11.2)	<.001
Sex			
Female	41 656 (90.8)	8693 (88.0)	<.001
Male	4219 (9.2)	1184 (12.0)	
BMI, mean (SD)	27.1 (9.2)	27.7 (5.6)	<.001
Prior MOF	7287 (15.9)	1498 (15.2)	.08
Parental hip fracture	3202 (7.0)	807 (8.2)	<.001
Current smoker	3679 (8.0)	878 (8.9)	.004
Prolonged glucocorticoid use	2402 (5.2)	538 (5.4)	.40
Rheumatoid arthritis	1309 (2.9)	202 (2.0)	<.001
Secondary osteoporosis	4572 (10.0)	3795 (38.4)	<.001
High alcohol intake	224 (0.5)	47 (0.5)	.87
Femoral neck T score, mean (SD)	−1.34 (1.08)	−1.29 (1.05)	<.001
MOF			
FRAX without BMD, mean (SD), %	11.6 (8.3)	13.1 (9.6)	<.001
FRAX with BMD, mean (SD), %	10.7 (7.2)	10.6 (7.4)	.10
Hip fracture			
FRAX without BMD, mean (SD), %	3.6 (5.1)	4.5 (6.4)	<.001
FRAX with BMD, mean (SD), %	2.6 (4.1)	2.7 (4.5)	.05
Osteoporosis medication use	4556 (9.9)	410 (4.2)	<.001

Abbreviations: BMD, bone mineral density; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); FRAX, Fracture Risk Assessment Tool; MOF, major osteoporotic fracture.

Table 2. Incident Fracture Outcomes After Index Dual-Energy X-Ray Absorptiometry by Cancer Status

Outcome	Cohort		*P* value
	General (n = 45 875)	Cancer (n = 9877)	
Follow-up time, mean (SD), y	8.5 (2.6)	7.6 (3.1)	<.001
MOF, No. (%)	5021 (10.9)	1086 (11.0)	.91
Hip	1368 (3.0)	320 (3.2)	.18
Vertebral	1143 (2.3)	230 (2.3)	.34
Humerus	944 (2.1)	218 (2.2)	.35
Forearm	1566 (3.4)	317 (3.2)	.31
MOF incidence rate, per 1000 person-years	12.9	14.5	<.001
Hip	3.5	4.2	.002
Vertebral	2.9	3.1	.54
Humerus	2.4	2.9	.02
Forearm	4.0	4.2	.42
Death, No. (%)	5670 (12.4)	2646 (26.8)	<.001

Abbreviation: MOF, major osteoporotic fracture.

(**Table 4**). Similar results were seen for hip fracture after adjusting for FRAX without BMD or FRAX risk factors including osteoporosis medication use without BMD. However, when adjusted for FRAX with BMD and when adjusted for individual FRAX risk factors with BMD and osteoporosis medication use, cancer diagnosis increased the hazard of both MOF and hip fracture.

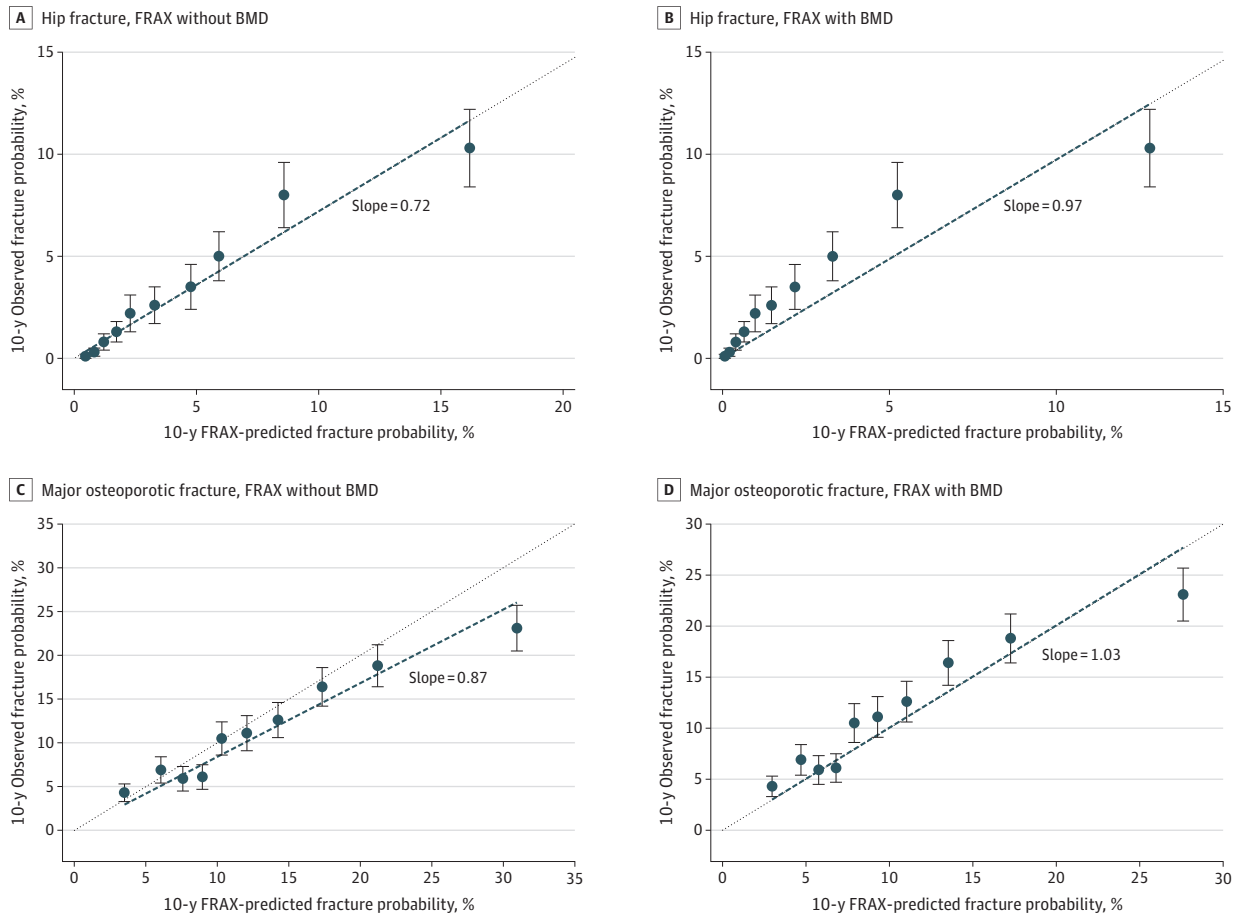
Discussion

This retrospective cohort study showed that FRAX with BMD results were associated with MOFs and hip fractures in patients diagnosed with cancer. FRAX without BMD slightly overestimated MOF and hip fracture risk in these patients, underscoring the importance of BMD testing in this at-risk population.

In the general population, FRAX is the most widely used and validated fracture risk prediction tool.[17] Importantly for cancer survivors, FRAX considers competing risk of mortality when estimating the 10-year probability of fracture, which can significantly impact risk assessment in those at high risk of death.[35] However, population-specific tools were modeled on fracture epidemiology of the general population, not a cancer population, which has its own unique fracture and mortality risk. The new FRAX Plus tool, which includes several modifying factors that improve the performance of FRAX, does not include any cancer-specific risk factors.[36]

FRAX includes secondary causes of osteoporosis, which in our study was 3 times more prevalent in the cancer popu-

Figure. Calibration Curves of Observed vs Fracture Risk Assessment Tool (FRAX)–Predicted 10-Year Fracture Probability for Individuals With Cancer



These graphs represent the calibration curves for observed vs FRAX-predicted 10-year fracture probability for individuals with cancer. Error bars represent 95% CIs. BMD indicates bone mineral density. The gray dotted line is 1.0 calibration line, and the blue dashed line is the line for which the slope is specified (the line of best fit).

Table 3. Interaction Between Fracture Risk Assessment Tool (FRAX) Score and Cancer Status

	HR per SD (95% CI)			
	MOF		Hip fracture	
	FRAX without BMD	FRAX with BMD	FRAX without BMD	FRAX with BMD
Noncancer cohort	1.93 (1.88-1.99)	2.05 (1.99-2.11)	3.44 (3.22-3.67)	4.10 (3.82-4.41)
Cancer cohort	1.73 (1.63-1.84)	1.84 (1.74-1.95)	2.95 (2.59-3.37)	3.61 (3.13-4.15)
FRAX × cancer status, *P* for interaction	.001	.001	.04	.11

Abbreviations: BMD, bone mineral density; HR, hazard ratio; MOF, major osteoporotic fracture.

lation than the general population. This variable will only modify fracture risk in the absence of BMD results. This may explain why FRAX without BMD overestimates MOF and hip fracture risk in patients with cancer. Similar findings were seen in a previous study, which found that including secondary osteoporosis as a risk factor for aromatase inhibitors users overestimates FRAX-predicted fracture risk.[32]

A recent study found that cancer survivors had double the risk of fracture as compared with those without a history of cancer.[37] However, these results were not adjusted for BMD or FRAX. In our study, we showed that there was no difference in risk of fracture between individuals with and without a history of cancer when adjusted for FRAX without BMD, even when osteoporosis medication use was considered. However, once adjusted for FRAX with BMD, with or without controlling for osteoporosis medication use, individuals with cancer history had a significantly higher risk of fracture than those without a history of cancer, with an approximately 10% to 30% increased risk of fracture, likely explained by unique cancer-specific risk factors for MOF that are not captured by FRAX.

Clinically, these results demonstrate that individuals with a diagnosis of cancer are at higher risk of fracture, even after adjusting for FRAX with BMD, but that excess risk appears to be balanced with excess mortality in this population, preserv-

Table 4. Incident Fracture Outcomes for FRAX Score–Adjusted Models in the Cancer Cohort

Adjusted model[a]	Cancer cohort, HR (95% CI)[b]	
	MOF	Hip fracture
FRAX without BMD	1.04 (0.97-1.11)	1.07 (0.95-1.21)
FRAX with BMD	1.17 (1.09-1.25)	1.30 (1.15-1.47)
Individual FRAX risk factors and OP drug (without BMD)	1.06 (0.99-1.13)	1.05 (0.92-1.19)
Individual FRAX risk factors and OP drug (with BMD)	1.12 (1.04-1.20)	1.15 (1.01-1.30)

Abbreviations: BMD, bone mineral density; FRAX, Fracture Risk Assessment Tool; HR, hazard ratio; MOF, major osteoporotic fracture; OP, osteoporosis.

[a] The models were adjusted for each of the variables in the first column.

[b] The cancer cohort is being compared to the noncancer cohort to calculate the HRs and 95% CIs in each model.

ing the accuracy of FRAX with BMD to predict MOF and hip fractures in cancer survivors. Further, the lack of effect modification by cancer diagnosis sites on the predictive value of FRAX supports the generalizability of these results across cancer sites, albeit certain cancer sites were less well represented in this predominantly female cohort. Reassuringly, FRAX, particularly with BMD, has previously been shown to perform well in those with prostate cancer and breast cancer.[31,32] The increased sample size of this study allowed for the evaluation of greater quantiles resulting in more precise calibration curves. The matched control group also allowed us to compare fracture risk among individuals with and without cancer.

The major strength of this study is that this is the largest cohort of patients with a history of cancer diagnosis with associated BMD and FRAX data, along with long-term outcome data, allowing sufficient sample size to perform the first validation of a fracture prediction tool with and without BMD across fracture risk categories and cancer types. Additionally, fracture definitions used in this study have previously been validated against radiograph review.[38]

Limitations

One limitation of this study is that the study cohort is a selected group of cancer survivors who have been referred for DXA and may not be representative of a general cancer cohort. However, as a result, it is representative of a clinically meaningful referral population that is being assessed for fracture risk. Our female-predominant cohort makes the results of our study less robust and generalizable to males with cancer. Further, the cancer population is extremely heterogeneous, and we cannot conclude that our results can be applied equally to all cancer subgroups. We do not have information on the cancer stage or presence of bone metastases at the time of fracture risk assessment and thus could not examine effect modification by cancer stage or presence of bone metastases. Finally, the current validation results are reflective of the current mortality risk seen in the cancer population. Improved survival of patients with cancer will need to be assessed in the context of emerging evidence that the newest class of cancer systemic therapy, immune checkpoint inhibitors, may increase the risk of fractures.[7,39,40]

There is an important care gap in patients with cancer and osteoporosis.[11] Even in the cohort of cancer survivors who have been referred for DXA, only 4.2% were on osteoporotic medications, despite 15.2% having experienced a prior MOF, a significantly smaller percentage than that of the general population, in which a similar percentage had a prior MOF, but more than double were on osteoporosis treatment. We recognize that DXAs are not always accessible. Although our study shows that FRAX with BMD is more accurate at predicting fracture risk, FRAX without BMD can still accurately stratify individuals with cancer into clinically important fracture risk categories.

Conclusions

This retrospective cohort study demonstrates that individuals with cancer are at higher risk of fracture than individuals without cancer and that FRAX, particularly with BMD, may accurately predict fracture risk in this population. These results, along with the known mortality risk of osteoporotic fractures among cancer survivors,[10] further emphasize the clinical importance of closing the current osteoporosis care gap among cancer survivors. Having a validated fracture risk prediction tool in patients with cancer is an important step in this direction; however, further research is necessary to examine ways to increase the assessment of fracture risk and DXA screening in patients with cancer.

ARTICLE INFORMATION

Accepted for Publication: June 27, 2024.

Published Online: October 3, 2024. doi:10.1001/jamaoncol.2024.4318

Author Contributions: Dr Leslie and Mr Al-Azazi had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Leslie, Yan, Lix, Czaykowski, Kanis, Singh.
Acquisition, analysis, or interpretation of data: Ye, Leslie, Al-Azazi, Yan, Lix, Czaykowski, McCloskey, Johansson, Harvey, Singh.
Drafting of the manuscript: Ye.
Critical review of the manuscript for important intellectual content: Leslie, Al-Azazi, Yan, Lix, Czaykowski, McCloskey, Johansson, Harvey, Kanis, Singh.
Statistical analysis: Ye, Leslie, Al-Azazi, Yan, Lix, McCloskey.
Obtained funding: Czaykowski, Singh.
Administrative, technical, or material support: Leslie, McCloskey, Harvey, Singh.
Supervision: Singh.

Conflict of Interest Disclosures: Prof Lix reported grants from the Canadian Institutes of Health Research and the Canada Research Chairs Program (CRC-2017-00186) during the conduct of the study. Dr McCloskey reported membership on the FRAX development team with no financial interest. Dr Singh reported personal fees from Pendopharm, Amgen Canada, AbbVie Canada, Sandoz Canada, Takeda Canada, Innomar Strategies, Eli Lily Canada, and Guardant Health, Inc; investigator-initiated grants from Pfizer Canada; and stock holdings in VasCon outside the submitted work. No other disclosures were reported.

Funding/Support: This study received funding from the CancerCare Manitoba Foundation (grant No. 763045126). The Manitoba Centre for Health Policy allowed for the use of data contained in the Manitoba Population Research Data Repository.

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The results and conclusions are those of the authors and no official endorsement by the Manitoba Centre for Health Policy, Manitoba Health

and Seniors Care (MHASC), or other data providers is intended or should be inferred.

Data Sharing Statement: See Supplement 2.

REFERENCES

1. Ye C, Leslie WD. Fracture risk and assessment in adults with cancer. *Osteoporos Int*. 2023;34(3):449-466. Published online December 13, 2022. doi:10.1007/s00198-022-06631-4

2. Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. *Clin Cancer Res*. 2006;12(20 Pt 2):6243s-6249s. doi:10.1158/1078-0432.CCR-06-0931

3. Seo GH, Kang HY, Choe EK. Osteoporosis and fracture after gastrectomy for stomach cancer: a nationwide claims study. *Medicine (Baltimore)*. 2018;97(17):e0532. doi:10.1097/MD.0000000000010532

4. Faubion SS, Kuhle CL, Shuster LT, Rocca WA. Long-term health consequences of premature or early menopause and considerations for management. *Climacteric*. 2015;18(4):483-491. doi:10.3109/13697137.2015.1020484

5. Bazire L, Xu H, Foy JP, et al. Pelvic insufficiency fracture (PIF) incidence in patients treated with intensity-modulated radiation therapy (IMRT) for gynaecological or anal cancer: single-institution experience and review of the literature. *Br J Radiol*. 2017;90(1073):20160885. doi:10.1259/bjr.20160885

6. Balasubramanian A, Wade SW, Adler RA, Saag K, Pannacciulli N, Curtis JR. Glucocorticoid exposure and fracture risk in a cohort of US patients with selected conditions. *J Bone Miner Res*. 2018;33(10):1881-1888. doi:10.1002/jbmr.3523

7. Ye C, Lee K, Leslie WD, Lin M, Walker J, Kolinsky M. Fracture rate increases after immune checkpoint inhibitor treatment: a potential new immune related adverse event. *Osteoporos Int*. 2023;34(4):735-740. Published online February 2, 2023. doi:10.1007/s00198-023-06690-1

8. Reuss-Borst M, Hartmann U, Scheede C, Weiß J. Prevalence of osteoporosis among cancer patients in Germany: prospective data from an oncological rehabilitation clinic. *Osteoporos Int*. 2012;23(4):1437-1444. doi:10.1007/s00198-011-1724-9

9. Sattar S, Haase K, Kuster S, et al. Falls in older adults with cancer: an updated systematic review of prevalence, injurious falls, and impact on cancer treatment. *Support Care Cancer*. 2021;29(1):21-33. doi:10.1007/s00520-020-05619-2

10. Ye C, Leslie WD, Al-Azazi S, et al. Fractures and long-term mortality in cancer patients: a population-based cohort study. *Osteoporos Int*. 2022;33(12):2629-2635. Published online August 29, 2022. doi:10.1007/s00198-022-06542-4

11. Leslie WD, Edwards B, Al-Azazi S, et al. Cancer patients with fractures are rarely assessed or treated for osteoporosis: a population-based study. *Osteoporos Int*. 2021;32(2):333-341. doi:10.1007/s00198-020-05596-6

12. Ghannam NN. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis assessment of fracture risk and its application to screening for postmenopausal osteoporosis. *Ann Saudi Med*. 1994;14(6):527. doi:10.5144/0256-4947.1994.527

13. Gralow JR, Biermann JS, Farooki A, et al. NCCN Task Force report: bone health in cancer care. *J Natl Compr Canc Netw*. 2013;11(suppl 3):S1-S50. doi:10.6004/jnccn.2013.0215

14. Rizzoli R, Body JJ, Brandi ML, et al; International Osteoporosis Foundation Committee of Scientific Advisors Working Group on Cancer-Induced Bone Disease. Cancer-associated bone disease. *Osteoporos Int*. 2013;24(12):2929-2953. doi:10.1007/s00198-013-2530-3

15. Shapiro CL, Van Poznak C, Lacchetti C, et al. Management of osteoporosis in survivors of adult cancers with nonmetastatic disease: ASCO Clinical Practice Guideline. *J Clin Oncol*. 2019;37(31):2916-2946. doi:10.1200/JCO.19.01696

16. Body JJ, Terpos E, Tombal B, et al. Bone health in the elderly cancer patient: a SIOG position paper. *Cancer Treat Rev*. 2016;51:46-53. doi:10.1016/j.ctrv.2016.10.004

17. Kanis JA, Johansson H, Harvey NC, McCloskey EV. A brief history of FRAX. *Arch Osteoporos*. 2018;13(1):118. doi:10.1007/s11657-018-0510-0

18. Manitoba Bureau of Statistics. Province of Manitoba. Manitoba Bureau of Statistics. Accessed November 7, 2022. https://www.gov.mb.ca/mbs/

19. Roos NP, Shapiro E. Revisiting the Manitoba Centre for Health Policy and Evaluation and its population-based health information system. *Med Care*. 1999;37(6)(suppl):JS10-JS14.

20. North American Association of Central Cancer Registries. NAACCR certified registries. Published November 1, 2016. Accessed November 7, 2022. https://www.naaccr.org/certified-registries/

21. Canadian Cancer Registry. Canadian Research Data Centre Network. Published September 16, 2021. Accessed November 7, 2022. https://crdcn.ca/data/canadian-cancer-registry/

22. Cancer in North America: 1999-2003. Incidence North American Association of Central Cancer Registeries Inc. https://www.naaccr.org/cina-data-products-overview/

23. Leslie WD, Caetano PA, Macwilliam LR, Finlayson GS. Construction and validation of a population-based bone densitometry database. *J Clin Densitom*. 2005;8(1):25-30. doi:10.1385/JCD:8:1:025

24. Kozyrskyj AL, Mustard CA. Validation of an electronic, population-based prescription database. *Ann Pharmacother*. 1998;32(11):1152-1157. doi:10.1345/aph.18117

25. Manitoba Vital Statistics Branch. Province of Manitoba. Accessed March 21, 2023. https://vitalstats.gov.mb.ca/

26. Concept: Regional Health Authority (RHA) Districts and Zones in Manitoba. Accessed November 4, 2022. http://mchp-appserv.cpe.umanitoba.ca/viewConcept.php?printer=Y&conceptID=1219

27. Lix LM, Azimaee M, Osman BA, et al. Osteoporosis-related fracture case definitions for population-based administrative data. *BMC Public Health*. 2012;12:301. doi:10.1186/1471-2458-12-301

28. O'Donnell S; Canadian Chronic Disease Surveillance System (CCDSS) Osteoporosis Working Group. Use of administrative data for national surveillance of osteoporosis and related fractures in Canada: results from a feasibility study. *Arch Osteoporos*. 2013;8:143. doi:10.1007/s11657-013-0143-2

29. Leslie WD, Epp R, Morin SN, Lix LM. Assessment of site-specific X-ray procedure codes for fracture ascertainment: a registry-based cohort study. *Arch Osteoporos*. 2021;16(1):107. doi:10.1007/s11657-021-00980-z

30. Leslie WD, Lix LM, Langsetmo L, et al. Construction of a FRAX model for the assessment of fracture probability in Canada and implications for treatment. *Osteoporos Int*. 2011;22(3):817-827. doi:10.1007/s00198-010-1464-2

31. Ye C, Morin SN, Lix LM, et al. Performance of FRAX in men with prostate cancer: a registry-based cohort study. *J Bone Miner Res*. 2023;38(5):659-664. Published online February 20, 2023. doi:10.1002/jbmr.4793

32. Leslie WD, Morin SN, Lix LM, et al. Performance of FRAX in women with breast cancer initiating aromatase inhibitor therapy: a registry-based cohort study. *J Bone Miner Res*. 2019;34(8):1428-1435. doi:10.1002/jbmr.3726

33. Kanis JA, McCloskey EV, Johansson H, Strom O, Borgstrom F, Oden A. How to decide who to treat. *Best Pract Res Clin Rheumatol*. 2009;23(6):711-726. doi:10.1016/j.berh.2009.09.002

34. Nolan EK, Chen HY. A comparison of the Cox model to the Fine-Gray model for survival analyses of re-fracture rates. *Arch Osteoporos*. 2020;15(1):86. doi:10.1007/s11657-020-00748-x

35. Leslie WD, Lix LM, Wu X; Manitoba Bone Density Program. Competing mortality and fracture risk assessment. *Osteoporos Int*. 2013;24(2):681-688. doi:10.1007/s00198-012-2051-5

36. Schini M, Johansson H, Harvey NC, Lorentzon M, Kanis JA, McCloskey EV. An overview of the use of the fracture risk assessment tool (FRAX) in osteoporosis. *J Endocrinol Invest*. 2024;47(3):501-511. doi:10.1007/s40618-023-02219-9

37. Rees-Punia E, Newton CC, Parsons HM, et al. Fracture risk among older cancer survivors compared with older adults without a history of cancer. *JAMA Oncol*. 2023;9(1):79-87. doi:10.1001/jamaoncol.2022.5153

38. Epp R, Alhrbi M, Ward L, Leslie W. Radiological validation of fracture definitions from administrative data: the Manitoba bone mineral density database. *J Bone Miner Res*. 2018;33:275.

39. Pantano F, Tramontana F, Iuliani M, et al. Changes in bone turnover markers in patients without bone metastases receiving immune checkpoint inhibitors: an exploratory analysis. *J Bone Oncol*. 2022;37:100459. doi:10.1016/j.jbo.2022.100459

40. Filippini DM, Gatti M, Di Martino V, et al. Bone fracture as a novel immune-related adverse event with immune checkpoint inhibitors: case series and large-scale pharmacovigilance analysis. *Int J Cancer*. 2021;149(3):675-683. doi:10.1002/ijc.33592