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# Performance of FRAX in Men With Prostate Cancer: A Registry-Based Cohort Study

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## ABSTRACT

The Fracture Risk Assessment Tool (FRAX<sup>®</sup>) was created to predict major osteoporotic fractures (MOF) and hip fractures in the general population. Whether FRAX accurately predicts fractures in men with prostate cancer is unknown. Our objective was to assess the performance of FRAX for predicting incident fractures in men with prostate cancer. Men from the Manitoba Bone Mineral Density (BMD) Registry (1996–2018) with prostate cancer diagnoses in the 3 years prior to dual-energy X-ray absorptiometry (DXA) were identified. FRAX scores with and without BMD were calculated. From population-based healthcare data we identified incident MOF, hip fracture, any osteoporotic fracture and death from the date of BMD testing to March 31, 2018. Cox regression was performed to estimate hazard ratios (HRs) with 95% confidence intervals (95% CIs) per standard deviation increase in FRAX score. Observed 10-year probability (estimated with competing risk of mortality) was compared with 10-year FRAX-predicted fracture probability to assess calibration. The study population included 684 men with prostate cancer (mean age 74.6 years) and 8608 men without prostate cancer (mean age 65.5 years). FRAX stratified risk for MOF (HR 1.91, 95% CI 1.48–2.45 with BMD; HR 1.96, 95% CI 1.43–2.69 without BMD) and hip fracture (HR 3.37, 95% CI 1.90–6.01 with BMD; HR 4.58, 95% CI 2.17–9.67 without BMD) in men with prostate cancer. There was no effect modification observed with prostate cancer status or current androgen deprivation therapy. Observed 10-year fracture probability in men with prostate cancer showed good agreement with FRAX with and without BMD included in the calculation (observed/predicted calibration ratios MOF 0.97, hip 1.00 with BMD; MOF 0.92, hip 0.93 with BMD). In conclusion, FRAX reliably predicts incident fractures in men with prostate cancer. © 2023 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

**KEY WORDS:** FRACTURE RISK ASSESSMENT; GENERAL POPULATION STUDIES; DXA; CANCER; OSTEOPOROSIS

## Introduction

Prostate cancer is one of the most prevalent cancers in men, with approximately 1.4 million incident cases worldwide each year.<sup>(1)</sup> A cornerstone of prostate cancer treatment is androgen deprivation, via surgical castration or the use of androgen deprivation therapies (ADT). ADT is started in about

one-half of men with prostate cancer.<sup>(2)</sup> Although the prevalence of osteoporosis in men tends to lag women by 10 years, prostate cancer tends to occur in older men and the additional risk conferred by androgen deprivation makes fracture risk a major concern in this population. Fracture risk is increased by almost 40% in ADT users and this appears to be dose-dependent.<sup>(3)</sup>

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Fracture Risk Assessment Tool (FRAX<sup>®</sup>), the most commonly used fracture risk prediction tool worldwide (<http://www.sheffield.ac.uk/FRAX/>), is freely available in over 70 countries and has been extensively validated.<sup>(4,5)</sup> FRAX considers multiple clinical risk factors including age, sex, body mass index (BMI), smoking and alcohol history, personal and family history of fracture, glucocorticoid use, rheumatoid arthritis, secondary osteoporosis and, when available, femoral neck bone mineral density (BMD), to estimate long-term (10-year) fracture probability. However, FRAX was developed for and thus calibrated to the general population and considers competing mortality in the general population when estimating the 10-year probability of fracture. Thus, FRAX may not perform as well in individuals with higher risk of death, such as those with cancer.<sup>(6)</sup>

Although ADT use can be entered into FRAX as a cause of secondary osteoporosis, secondary osteoporosis only modifies FRAX output in the absence of BMD. It is unknown if the increased fracture risk seen in individuals with prostate cancer on ADT is fully accounted for through the FRAX clinical risk factors and femoral neck *T*-score. Although current guidelines recommend using FRAX to estimate individual fracture risk in men with prostate cancer, no studies to date have assessed the performance of FRAX or any other fracture risk assessment tools in men with prostate cancer.<sup>(7,8)</sup>

Osteoporosis treatment is recommended in men with prostate cancer who are at high risk for fracture.<sup>(8-12)</sup> Given the uncertainty of the applicability of FRAX in men with prostate cancer and the lack of other validated tools in these individuals, we examined the performance of FRAX in men with prostate cancer and contrasted these results to the performance of FRAX in men without prostate cancer, using the BMD results of the Manitoba BMD Program.<sup>(13)</sup>

## Subjects and Methods

### Data sources

Health services are provided to nearly all residents in the Canadian province of Manitoba (population 1.36 million in 2018) through a single public healthcare system.<sup>(14,15)</sup> All permanent residents of the province have been assigned a unique personal health identification number, which can be used to link their data in the various population-based administrative healthcare databases, including hospital discharge and physician claims databases which records patient's demographics, date and type of service and diagnosis codes. Hospital discharge abstracts use the International Classification of Diseases (ICD), Ninth Revision, Clinical Modification (ICD-9-CM) prior to 2004 and ICD, Tenth Revision, Canadian Enhancements (ICD-10-CA) thereafter. Physician billing claims use ICD-9-CM codes. Medication use was obtained from the provincial pharmacy system.<sup>(16)</sup> The Vital Statistics registry records all births and deaths that take place in Manitoba (<https://vitalstats.gov.mb.ca/>).

The Manitoba BMD Program runs all BMD testing in Manitoba and maintains a database of all results that can be linked with the other provincial administrative healthcare databases.<sup>(13)</sup> The study was approved by the Health Research Ethics Board for the University of Manitoba and approval for data access was provided by the Health Information Privacy Committee.

### Study population

We identified all adult men aged 40 years or older who had undergone baseline dual-energy X-ray absorptiometry (DXA)

(index date) between 1996 and 2018. We excluded those not registered for health care in Manitoba and without coverage after DXA.

### Prostate cancer and ADT assessment

We categorized men into two groups according to prostate cancer status prior to baseline DXA. Prostate cancer diagnosis was ascertained in the 3 years prior to baseline DXA based upon any hospitalization code or at least two physician codes for prostate cancer (ICD-9 code 185 and ICD-10 code C61). This definition of prostate cancer has a very high agreement with cancer registry data (kappa of 0.95, 95% confidence interval [CI] 0.95–0.96).<sup>(17)</sup>

ADT use in both groups was assessed using the provincial pharmacy system (Anatomical Therapeutic Chemical code stem L02BB). Any ADT use was defined as any ADT prescriptions filled prior to or within the year following baseline DXA. Current ADT use was defined as at least 6 months of ADT use within the year prior to or the year following DXA testing.

### Incident fracture assessment

Linked provincial population-based databases were assessed between the date of DXA testing and March 31, 2018 for fracture diagnostic codes for fractures at any site other than head/neck, hands/feet and ankle using previously published and validated algorithms.<sup>(18)</sup> We subcategorized incident fractures into any fracture, major osteoporotic fracture (MOF, aggregate of hip, clinical vertebral, forearm and humerus fractures) and hip fractures.

### BMD and fracture probability assessment

All BMD measurements were assessed using a small number of DXA devices, all of which showed stable performance (long-term phantom coefficient of variation <0.5%). Scanners were cross-calibrated using human volunteers according to International Society for Clinical Densitometry (ISCD) standards<sup>(19)</sup> and in vivo *T*-score differences were less than 0.1. Femoral neck BMD *T*-scores were calculated using the Third National Health and Nutrition Examination Survey (NHANES III) white female reference values in accordance with ISCD and WHO recommendations and FRAX requirements.<sup>(19-21)</sup>

Using the Canadian FRAX tool (FRAX Desktop Multi-Patient Entry version 3.8), 10-year probability of a MOF or hip fracture was calculated for each individual. The Canadian FRAX tool was calibrated using Canadian hip fracture and mortality data.<sup>(22)</sup> The Canadian FRAX tool has been independently validated in the general population, which we recognize may have different mortality risk compared to those with prostate cancer.<sup>(23,24)</sup> Clinical risk factors included in the FRAX tool were collected as recently described.<sup>(25)</sup> Briefly, weight and height were measured at the time of DXA and BMI was calculated from these measurements. Other data required for FRAX calculation were assessed from information collected directly from subjects through the intake questionnaire at the time of each DXA scan. Questionnaire information was supplemented with population-based healthcare data from the above-described under Data sources, linked provincial population-based healthcare databases as recently described, thereby ensuring complete information for all subjects. Hypogonadism, assessed as a cause of secondary osteoporosis, was defined as prior orchiectomy (since 1984) or current ADT use as described under Prostate cancer and ADT

assessment. Oral glucocorticoid exposure greater than 3 months in the prior year and osteoporosis medication use (including alendronate, risedronate, etidronate, zoledronic acid, denosumab, calcitonin and teriparatide) for at least 6 months in the year prior to the index DXA scan were ascertained using the provincial pharmacy system.

### Statistical analyses

Baseline characteristics were compared between men with and without prostate cancer using one-way analysis of variance (ANOVA) for continuous variables, and chi-square tests of independence for categorical variables. Cumulative MOF and hip fracture incidence were calculated to 10 years and observed 10-year fracture probability was estimated incorporating competing mortality risk in both groups.<sup>(6)</sup> Observed 10-year fracture probability was compared to FRAX-derived 10-year fracture probability to obtain calibration ratios (calibration-in-the-large). Calibration within MOF risk tertiles was assessed for the prostate cancer and control cohorts according to FRAX-predicted MOF probabilities. Cox regression was performed to estimate hazard ratios (HRs) per standard deviation (SD) increase in the log-transformed FRAX score with 95% CIs. Cox regression models used time to first fracture event (MOF, hip and any fracture). Analyses for any fracture were derived from the 10-year FRAX risk for MOF. The proportional hazards assumption was confirmed. Effect modification for incident fracture outcome was tested using two-way interaction terms for (i) prostate cancer and FRAX-derived 10-year MOF probability and (ii) current ADT use and FRAX-derived 10-year MOF probability. Area under the curve (AUC) estimates for receiver operating characteristic curves with 95% CI were calculated for FRAX and femoral neck *T*-score, stratified by prostate cancer status. Statistical analyses were performed with Statistica (Version 13.0; StatSoft Inc., Tulsa, OK, USA).

### Results

The study population included 684 men with prostate cancer with mean age  $74.6 \pm 8.4$  years and 8606 men without prostate cancer with mean age  $65.5 \pm 12.1$  years (Table 1). Over 19% (19.4%) of men with prostate cancer had a fracture prior to baseline DXA as compared to 26.3% of men without prostate cancer ( $p < 0.001$ ). Men with prostate cancer were less likely to be smokers (9.4% versus 14.3%, respectively,  $p < 0.001$ ) and less likely to have prolonged glucocorticoid exposure (9.6% versus 18.1%,  $p < 0.001$ ). 10.1% of men with prostate cancer were current ADT users (66.2% with any ADT use), as compared with 0.1% and 1.7% of men without prostate cancer, respectively ( $p < 0.001$ ).

Although men with and without prostate cancer had the same mean femoral neck *T*-scores ( $-1.1 \pm 1.1$ ), men with prostate cancer had higher FRAX MOF and hip scores estimated both with and without BMD ( $p < 0.001$ ). Over a mean follow-up of  $5.5 \pm 4.2$  years, 310 (45.3%) men with prostate cancer died and 70 (10.2%) suffered any fracture including 52 (7.6%) with MOF and 20 (2.9%) with hip fracture. Over a mean follow-up of  $6.9 \pm 4.9$  years, 2526 (29.3%) men without prostate cancer died and 940 (10.9%) suffered any fracture including 685 (8.0%) with MOF and 207 (2.4%) with hip fracture. The follow-up period for men with prostate cancer was significantly shorter than for men without prostate cancer ( $p < 0.001$ ) but the mortality rate was significantly higher (82.2 per 1000 person-years versus 42.7 per 1000 person-years, respectively,  $p < 0.001$ ). Current osteoporosis treatment rates were similar between the two groups (15.8% of men with prostate cancer versus 15.5% of men without prostate cancer,  $p = 0.820$ ).

In men with prostate cancer, FRAX stratified risk for incident MOF (HR 1.91 per SD increase in FRAX with BMD, 95% CI 1.48–2.45; HR 1.96 per SD increase in FRAX without BMD, 95% CI 1.43–2.69), hip fracture (HR 3.37 per SD increase in FRAX with BMD, 95% CI 1.90–6.01; HR 4.58 per SD increase in FRAX without BMD, 95% CI 2.17–9.67), and any fracture (HR 2.05 per SD

**Table 1.** Baseline Characteristics

Characteristic	Men with prostate cancer ( <i>n</i> = 684)	Men without prostate cancer ( <i>n</i> = 8608)	<i>p</i>
Age (years)	74.6 ± 8.4	65.5 ± 12.1	<0.001
BMI (kg/m <sup>2</sup> )	27.9 ± 4.4	27.7 ± 18.0	0.761
Prior fracture	133 (19.4)	2268 (26.3)	<0.001
Parental hip fracture	51 (7.5)	713 (8.3)	0.449
Current smoker	64 (9.4)	1229 (14.3)	<0.001
Prolonged glucocorticoid use	66 (9.6)	1559 (18.1)	<0.001
Rheumatoid arthritis	28 (4.1)	427 (5.0)	0.312
Secondary causes of osteoporosis	144 (21.1)	1910 (22.2)	0.491
High alcohol intake	7 (1.0)	184 (2.1)	0.048
Femoral neck <i>T</i> -score	−1.1 ± 1.1	−1.1 ± 1.1	0.186
FRAX percent, median (IQR)			
MOF (without BMD)	7.7 (5.4–10.9)	7.0 (4.7–10.3)	<0.001
Hip (without BMD)	2.2 (1.0–4.0)	1.4 (0.5–3.2)	<0.001
MOF (with BMD)	7.3 (5.3–10.4)	6.7 (4.5–9.9)	<0.001
Hip (with BMD)	2.0 (1.0–3.8)	1.3 (0.4–3.0)	<0.001
ADT			
Any use	453 (66.2)	146 (1.7)	<0.001
Current use	69 (10.1)	6 (0.1)	<0.001
Current osteoporosis medication use	108 (15.5)	1331 (15.5)	0.820

Note: Data are mean ± SD or *n* (%). FRAX scores are median (interquartile range).

Abbreviations: BMI = body mass index; MOF = major osteoporotic fracture; BMD = bone mineral density; ADT = androgen deprivation therapy.

**Table 2.** HRs with 95% CIs for Outcome of Incident Fracture According to Fracture Site Stratified by Prostate Cancer Status

Parameter	MOF	Hip fracture	Any fracture
Men with prostate cancer			
FRAX without BMD, per SD increase	1.96 (1.43–2.69)	4.58 (2.17–9.67)	2.05 (1.57–2.68)
FRAX with BMD, per SD increase	1.91 (1.48–2.45)	3.37 (1.90–6.01)	2.14 (1.71–2.66)
Femur neck <i>T</i> -score, per unit decrease	1.85 (1.42–2.41)	2.41 (1.56–3.71)	2.04 (1.61–2.58)
Men without prostate cancer			
FRAX without BMD, per SD increase	1.72 (1.59–1.86)	3.14 (2.64–3.74)	1.55 (1.45–1.66)
FRAX with BMD, per SD increase	1.84 (1.71–1.99)	4.09 (3.38–4.95)	1.69 (1.59–1.81)
Femur neck <i>T</i> -score, per unit decrease	1.75 (1.62–1.89)	2.73 (2.35–3.17)	1.65 (1.54–1.76)

Note: Data are HR (95% CI). FRAX scores are log-transformed due to a skewed distribution.

Abbreviations: BMD = bone mineral density; CI = confidence interval; HR = hazard ratio; MOF = major osteoporotic fracture; SD = standard deviation.

increase in FRAX with BMD, 95% CI 1.57–2.66; HR 2.68 per SD increase in FRAX without BMD, 95% CI 1.51–2.46). FRAX with BMD gave slightly higher HRs than femoral neck *T*-score alone for MOF, hip fracture and any fracture (Table 2). Similar HRs were seen in men with and without prostate cancer. Prostate cancer status did not modify the effect of FRAX MOF on incident MOF ( $p = 0.82$  for the interaction term between FRAX MOF and prostate cancer status). Similarly, current ADT use did not modify the effect of FRAX MOF on incident MOF ( $p = 0.93$  for the interaction term between FRAX MOF and current ADT use). AUC estimates with 95% CI for FRAX, with and without BMD, and femoral neck *T*-score are included as Table S1. These results are stratified by prostate cancer status although the AUCs are not strictly comparable given the age difference in those with and without prostate cancer.

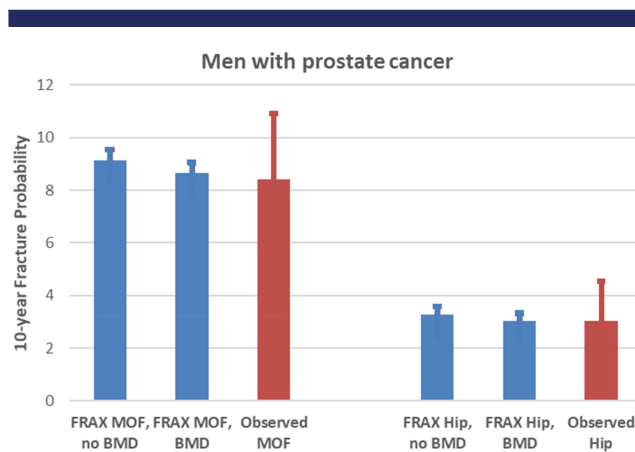
Observed 10-year MOF probability (8.40%, 95% CI 5.89–10.90) in men with prostate cancer, which considered the effect of competing mortality, showed good agreement with FRAX predicted 10-year MOF probability without BMD (9.12%, 95% CI 8.71–9.53) and with BMD (8.66%, 95% CI 8.28–9.04) included in the calculation (calibration-in-the-large, Fig. 1). Observed/predicted calibration ratio for FRAX MOF without BMD was 0.92 (95% CI 0.65–1.20) and for FRAX MOF with BMD was 0.97 (95% CI 0.68–1.26). Similarly, the observed 10-year hip fracture probability (3.04%, 95% CI 1.54–4.53) showed good agreement with FRAX predicted 10-year hip fracture probability without BMD (3.27%, 95% CI 2.98–3.57) and with BMD (3.04%, 95% CI 2.77–3.32) included in the calculation. Observed/predicted calibration ratios for FRAX hip fracture without BMD was 0.93 (95% CI 0.47–1.39) and for FRAX hip fracture with BMD was 1.00 (95% CI 0.51–1.49).

Calibration within MOF risk tertiles was assessed for the prostate cancer and control cohorts according to FRAX-predicted MOF probabilities, without and with BMD (there were insufficient hip fractures for tertile-based analyses). Within each prostate cancer risk category, observed/predicted calibration 95% CIs included the line of identity; only minor deviations from the line of identity were seen in controls (Fig. 2A,B).

## Discussion

This is the first study to validate the use of FRAX in men with prostate cancer. FRAX demonstrated good calibration and stratification in predicting MOF and hip fracture risk in men with and without prostate cancer. Further, no effect modification was seen with ADT use.

These results are important because men with prostate cancer are at increased risk of bone loss and fracture. Most guidelines



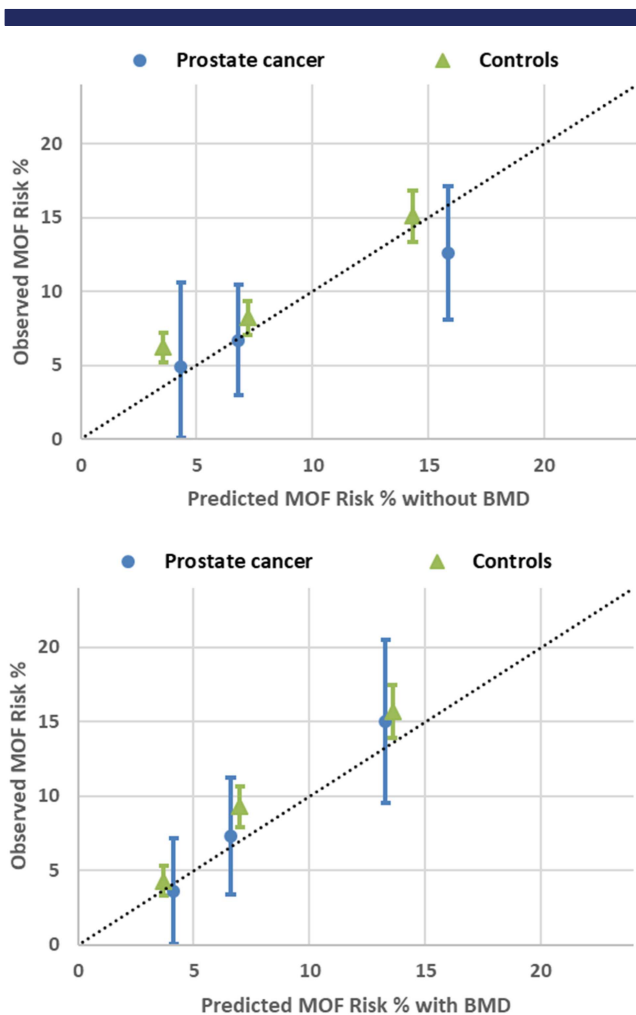
**Fig. 1.** Comparison of FRAX-predicted and observed fracture probability (with 95% CI bars) for MOF and hip fracture in men with prostate cancer. CI = confidence interval; MOF = major osteoporotic fracture.

recommend treatment based on fracture risk assessment.<sup>(8–12)</sup> Until now, there were no validated fracture risk assessment tools in this unique population. Two smaller studies of men with prostate cancer found that BMD and age are independent predictors of fracture.<sup>(26,27)</sup> Our study shows that BMD alone does not predict fractures as well as FRAX with BMD.

There is concern that FRAX may underestimate fracture risk in men with prostate cancer as ADT use is not a variable that is directly considered in FRAX. However, hypogonadism is included in the secondary osteoporosis variable in FRAX.<sup>(4)</sup> A large proportion of the men in the prostate cancer group were diagnosed with secondary osteoporosis, reflecting prior orchiectomy and/or current ADT use. The secondary osteoporosis input, which would only increase FRAX 10-year probability of fracture when BMD is absent, along with other FRAX clinical risk factors was able to predict 10-year MOF and hip fracture risk accurately in the absence of BMD.

Further, FRAX considers competing mortality when estimating the 10-year probability of fracture, which, if not considered, can result in overestimation of fracture risk by up to 50% in individuals at high mortality risk.<sup>(6)</sup> It appears in our study that the additional osteoporosis risk unique to men with prostate cancer that is not accounted for in FRAX is offset by decreased survival and thus decreased year-at-risk for fracture, resulting in excellent calibration when BMD is considered.

Interestingly, although the men with prostate cancer were on average almost 10 years older than the men without



**Fig. 2.** Observed 10-year MOF risk versus FRAX-predicted risk (A) without BMD and (B) with bone mineral density stratified by risk tertile. Error bars are 95% CIs. Dotted line is the line of identity. BMD = bone mineral density; CI = confidence interval; MOF = major osteoporotic fracture.

prostate cancer, the mean femoral neck *T*-scores were the same in these two groups. Although some have postulated that men who develop prostate cancer might have higher baseline BMD due to their association with endogenous sex hormones, the Osteoporotic Fractures in Men (MrOS) Study found an inverse association between BMD and prostate cancer risk.<sup>(28)</sup> Thus, our finding of equal BMD and equal proportion of current osteoporosis medication users, despite increased age in the prostate cancer group, reflects a selection of men without prostate cancer who have other fracture risk factors that led to them undergoing DXA scans. Thus, one limitation of our study is that our comparison group of men without prostate cancer is likely not representative of the general male population, but instead, a selected group of men with risk factors for fracture. Perhaps compared to a more representative general population of men, there might be an interaction between prostate cancer and FRAX.

Although the choice of control group would not affect our assessment of the calibration of FRAX in men with prostate cancer, it is important to note that our cohort of men with prostate cancer may not necessarily be generalizable to all men with

prostate cancer as it is a selected subgroup that underwent DXA and may represent men with prostate cancer at higher risk of fracture. Another limitation of this study is that the number of hip fractures in the prostate cancer group was not sufficiently large to assess calibration of FRAX for hip fracture across different quantiles of risk. There were also insufficient MOF events to assess calibration over more than three risk categories in order to generate reliable calibration slope-intercept estimates. Further, while we did not find a significant interaction between current ADT use and FRAX-derived 10-year MOF probability, this may reflect limited power due to the small number of current ADT users.

In conclusion, FRAX can be used to accurately predict fracture risk in men with prostate cancer. Osteoporotic fractures in men with prostate cancer are associated with increased mortality risk.<sup>(29,30)</sup> Given there are effective treatments to prevent bone loss and fracture in men with prostate cancer,<sup>(31)</sup> it is imperative that men at high risk of fracture are identified and treated.

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## Author Contributions

**Carrie Ye:** Conceptualization, Formal Analysis, Methodology, Writing – Original Draft Preparation, Writing – review & editing. **Suzanne N. Morin:** Writing – review & editing. **Lisa M. Lix:** Writing – review & editing. **Eugene V. McCloskey:** Writing – review & editing. **Helena Johansson:** Writing – review & editing. **Nicholas C. Harvey:** Writing – review & editing. **John A. Kanis:** Writing – review & editing. **William D. Leslie:** Conceptualization, Data Curation, Formal Analysis, Methodology, Writing – review & editing.

## Peer Review

The peer review history for this article is available at <https://publons.com/publon/10.1002/jbmr.4793>.

## Data Availability Statement

The data that support the findings of this study are available from Manitoba Population Health Research Data Repository. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the author(s) with the permission of Manitoba Population Health Research Data Repository.

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