

ORIGINAL ARTICLE

Fracture risk prediction: importance of age, BMD and spine fracture status

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Our purpose was to identify factors for a parsimonious fracture risk assessment model considering morphometric spine fracture status, femoral neck bone mineral density (BMD) and the World Health Organization (WHO) clinical risk factors. Using data from 2761 subjects from the Canadian Multicentre Osteoporosis Study (CaMos), a prospective, longitudinal cohort study of randomly selected community-dwelling men and women aged ≥ 50 years, we previously reported that a logistic regression model considering age, BMD and spine fracture status provided as much predictive information as a model considering these factors plus the remaining WHO clinical risk factors. The current analysis assesses morphometric vertebral fracture and/or nonvertebral fragility fracture at 5 years using data from an additional 1964 CaMos subjects who have now completed 5 years of follow-up (total N = 4725). Vertebral fractures were identified from lateral spine radiographs assessed using quantitative morphometry at baseline and end point. Nonvertebral fragility fractures were determined by questionnaire and confirmed using radiographs or medical records; fragility fracture was defined as occurring with minimal or no trauma. In this analysis, a model including age, BMD and spine fracture status provided a gradient of risk per s.d. (GR/s.d.) of 1.88 and captured most of the predictive information of a model including morphometric spine fracture status, BMD and all WHO clinical risk factors (GR/s.d. 1.92). For comparison, this model provided more information than a model considering BMD and the WHO clinical risk factors (GR/s.d. 1.74). These findings confirm the value of age, BMD and spine fracture status for predicting fracture risk.

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Introduction

Prevalent vertebral fractures increase the risk of new vertebral and nonvertebral fractures in postmenopausal women.¹⁻⁴ Other important risk factors for fracture include a femoral neck bone mineral density T-score (BMD) and a set of clinical risk factors identified by the World Health Organization (WHO), including age, cigarette smoking, systemic glucocorticoid

therapy >3 months, minimal trauma fracture after age 50, parental hip fracture, alcohol use, rheumatoid arthritis and secondary osteoporosis. We previously performed a series of logistic regression analyses to identify a parsimonious model for predicting any future vertebral or nonvertebral fragility fracture using data from the Canadian Multicentre Osteoporosis Study (CaMos), a prospective, randomly selected population-based

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community cohort.⁵ The study included BMD, lateral thoracic and lumbar spine radiographs and interviewer-administered questionnaires.⁶ According to an analysis based on 2761 CaMos subjects, the most predictive risk factors for incident fracture were age, BMD and spine fracture status (whether or not morphometric vertebral fractures were present).⁷ A model considering these risk factors provided almost all of the information provided by models that included spine fracture status, BMD and all WHO clinical risk factors.⁷ For comparison, this model captured more information than a model considering BMD and the WHO clinical risk factors.⁷

The objective of the current analysis was to validate the importance of age, BMD and spine fracture status to predict fracture risk in an independent sample using recently available data from 1964 CaMos subjects whose spine radiograph morphometric assessments were previously not complete. The risk of fracture is known to be determined by multiple independent risk factors, and consideration of multiple risk factors combined with BMD in the assessment of fracture risk increases the sensitivity of the test procedure without sacrificing specificity.⁸ We analyzed models considering a range of risk factors and compared the performance of these models for predicting fracture risk using the gradient of risk per s.d. (GR/s.d.) In this context, the GR/s.d. represents the increase in fracture risk per s.d. increase in a risk score.⁹ Models with a higher GR/s.d. more accurately identify the individuals who will fracture⁹ and enlarge the population that can be identified at any particular threshold of risk.¹⁰

Results

Subject characteristics. The original CaMos cohort initially included 7753 subjects aged 50 years and over, including 4725 with spine radiographs at both baseline and 5 years. The previous report for Cohort 1 included 2761 subjects.⁷ Analyses of vertebral deformities were subsequently completed for an additional 1964 subjects defined as Cohort 2. Baseline

characteristics of these subjects and the incidence of fractures at 5 years are shown in **Table 1**.

Comparison of models considering spine fracture status, BMD and WHO clinical risk factors versus BMD and WHO clinical risk factors. The performance of each model was assessed as the gradient of risk, that is, the increase in fracture risk per s.d. (GR/s.d.). In Cohort 1, the GR/s.d. for a model including BMD and the WHO clinical risk factors was 1.84. For a model including BMD, WHO clinical risk factors and spine fracture status (yes/no), the GR/s.d. was 2.04. Similarly, in Cohort 2, the GR/s.d. for a model including BMD and the WHO clinical risk factors was 1.74; for a model including BMD, the WHO clinical risk factors and spine fracture (yes/no), it was 1.92. Thus, in both cohorts, consideration of spine fracture status added additional prognostic information to that provided by BMD and the WHO clinical risk factors.

Univariate analyses for 5-year risk of new fractures. In both cohorts, age, femoral neck T-score and spine fracture status (yes/no) provided the highest GR/s.d. Previous clinical fracture had the next highest GR/s.d. and other risk factors provided lower GR/SDs (**Figure 1**).

Multivariate analyses for 5-year risk of new fractures. These analyses provided results that were similar in men and women (data not shown); therefore, multivariate analyses were performed combining the data for both sexes. The performance characteristics of models with sequential addition of the most important risk factors are shown in **Figure 2**. In both cohorts, compared with a model including age alone, the GR/s.d. increased with models including age, femoral neck BMD T-score and spine fracture status. However, the GR/s.d. did not increase for models including these risk factors plus additional WHO clinical risk factors.

Table 1 Baseline characteristics and 5-year incidence of fracture in CaMos participants aged 50 and older who had complete assessments at baseline and 5 years

| | Cohort 1 | | Cohort 2 | |
|---|-------------------|------------------|-------------------|------------------|
| | Women n = 1985 | Men n = 776 | Women n = 1447 | Men n = 517 |
| Age (years), mean \pm s.e. | 64.4 \pm 0.2 | 64.3 \pm 0.3 | 65.5 \pm 0.2 | 64.8 \pm 0.4 |
| Height (cm), mean | 159.6 | 173.2 | 160.0 | 173.9 |
| Weight (kg), mean | 68.3 | 81.6 | 69.9 | 83.8 |
| BMI (kg m ⁻²), mean | 26.8 | 27.1 | 27.3 | 27.7 |
| Lumbar spine T-score \leq -2.5, n (%) | 284 (14.31) | 16 (2.06) | 249 (17.21) | 25 (4.84) |
| Femoral neck T-score \leq -2.5, n (%) | 178 (8.97) | 31 (3.99) | 187 (12.92) | 34 (6.58) |
| Vertebral fracture, % | 20.9 | 19.8 | 22.7 | 22.2 |
| Femoral neck T-score, mean \pm s.e. | -1.24 \pm 0.02 | -0.91 \pm 0.03 | -1.41 \pm 0.02 | -1.01 \pm 0.04 |
| Prior clinical fracture, % | 15.5 | 6.7 | 20.5 | 11.8 |
| Parental history of hip fracture, % | 11.4 | 9.4 | 12.3 | 10.3 |
| Prior glucocorticoid use, % | 1.2 | 1.5 | 1.7 | 0.8 |
| Current smoking, % | 12.5 | 13.9 | 12.3 | 17.6 |
| Consume >2 units of alcohol per day, % | 1.4 | 7.1 | 0.8 | 8.3 |
| Rheumatoid arthritis, % | 6.2 | 4.6 | 7.9 | 4.4 |
| Incidence of fracture, n (%) | | | | |
| Vertebral fracture | 239 (12.0) | 105 (13.5) | 216 (14.9) | 68 (13.2) |
| Nonvertebral fracture | 148 (7.5) | 23 (3.0) | 115 (7.9) | 29 (5.6) |
| Any ^a | 352 (17.7) | 122 (15.7) | 303 (20.9) | 88 (17.0) |

^aMorphometric vertebral fracture and/or nonvertebral fragility fracture.

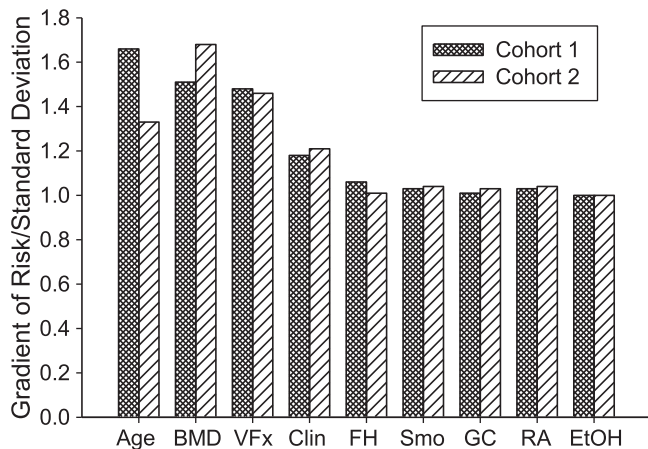


Figure 1 Univariate analyses of GR/s.d. for predicting 5-year fracture risk. BMD, femoral neck T-score; VFx, spine fracture status (yes/no); Clin, previous clinical fracture; FH, parental history of hip fracture; Smo, current smoking; GC, systemic glucocorticoids > 3 months; RA, rheumatoid arthritis; EtOH, > 2 alcoholic drinks/day.

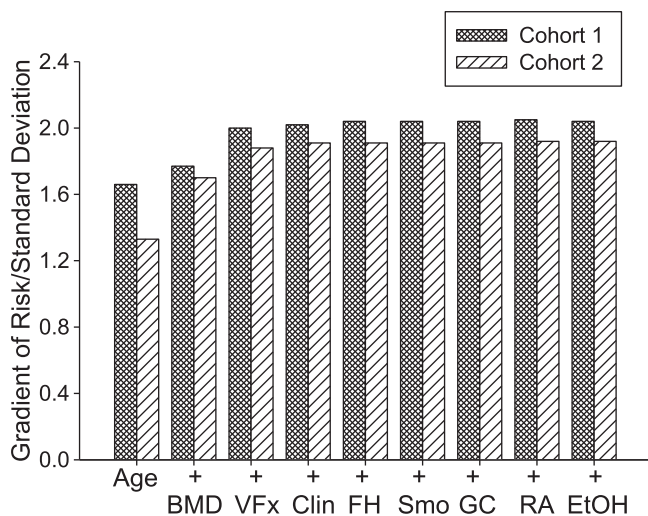


Figure 2 GR/s.d. for models including baseline age, age + femoral neck T-score, age + femoral neck T-score + spine fracture status (yes/no), etc. BMD, femoral neck T-score; VFx, spine fracture status; Clin, previous clinical fracture; FH, parental history of hip fracture; Smo, current smoking; GC, systemic glucocorticoids > 3 months; RA, rheumatoid arthritis; EtOH, > 2 alcoholic drinks/day.

Absolute risk of fracture based on age, femoral neck BMD T-score and spine fracture status. The 5-year absolute risk of incident fragility fracture for data from pooling of CaMos Cohorts 1 and 2 based on age, BMD and presence or absence of spine fracture is shown for women (**Figure 3, Table 2**) and men (**Table 3**). Fracture risk increased in both men and women with increasing age, lower BMD and presence of spine fracture. **Figure 3** shows that, at any age, the risk conferred by presence of vertebral fracture was approximately equal to a femoral neck T-score reduction of 2.5.

Predicting 5-year morphometric vertebral fracture risk. Additional multivariate analyses including all CaMos subjects were undertaken to identify the most important risk factors for predicting morphometric vertebral fracture. The results showed that the predictive performance for a model including age only

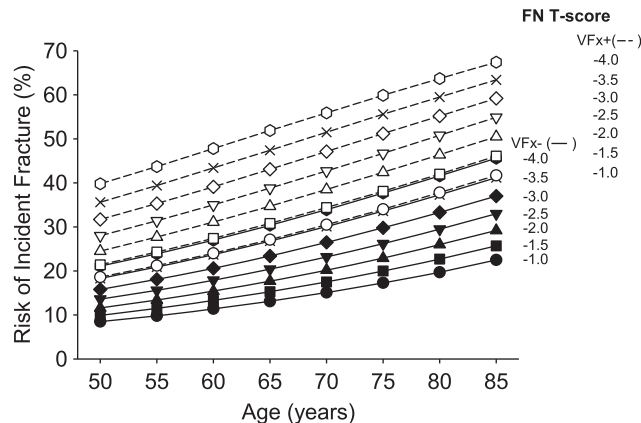


Figure 3 Predicted 5-year risk of incident fragility fracture in CaMos women based on the logistic regression model with predictors including baseline age, femoral neck T-score and spine fracture status (Yes/No). Shaded symbols with solid lines represent FN T-scores for patients with no prevalent vertebral fractures; open symbols with dashed lines represent FN T-scores for patients with prevalent vertebral fractures. FN, femoral neck; VFx +, prevalent spine fracture; VFx -, no prevalent spine fracture.

(GR/s.d. 1.55) increased in a model including age plus BMD (GR/s.d. 1.66) and further increased in a model including age, BMD and spine fracture status (GR/s.d. 1.95). However, no additional increment in predictive performance was achieved in models considering these risk factors plus additional WHO clinical risk factors (GR/s.d. 1.96).

Predicting 5-year nonvertebral fracture risk. Additional multivariate analyses including all CaMos subjects were undertaken to identify the most important risk factors for predicting nonvertebral fragility fracture. The results showed that the predictive performance for a model including age only (GR/s.d. 1.35) increased in a model including age plus BMD (GR/s.d. 1.82) and further increased in a model including age, BMD and spine fracture status (GR/s.d. 1.90). However, for this end point, the gradient of risk further increased in a model considering these risk factors plus previous clinical fracture (GR/s.d. 1.98), but not in models considering these plus all remaining WHO clinical risk factors (GR/s.d. 2.00). A model including age, BMD and previous clinical fracture provided a GR/s.d. of 1.92, which was inferior to a model considering these risk factors plus spine fracture status (GR/s.d. 1.98).

Importance of spine imaging for identifying vertebral fracture and for identifying people at high risk for fracture. After pooling Cohorts 1 and 2, Venn diagrams were constructed to further explore the importance of spine imaging. **Figure 4a** shows the prevalence of vertebral fracture using radiograph versus by questionnaire. Among 947 subjects with morphometric vertebral fracture, 66 reported a history of vertebral fracture by questionnaire and 881 did not. Thus, 93% of subjects with a morphometric vertebral fracture were unaware of the fracture. Additionally, among a total of 84 subjects with a history of clinical vertebral fracture by questionnaire, 66 (79%) were found to have a vertebral fracture by morphometric analysis of radiographs, whereas 18 (21%) were found not to have a vertebral fracture.

Figures 4b and c show subjects with at least a 30% 5-year fracture risk as assessed using various logistic regression models. In **Figure 4b**, subjects with this level of risk are shown

Table 2 A 5-year risk of incident fragility fracture in CaMos women based on age, femoral neck T-score and spine fracture (yes/no)

| Femoral neck T-score | Spine fracture | Age (years) | | | | | | | |
|----------------------|----------------|-------------|------|------|------|------|------|------|------|
| | | 50 | 55 | 60 | 65 | 70 | 75 | 80 | 85 |
| -1.0 | No | 8.5 | 9.8 | 11.4 | 13.1 | 15.1 | 17.3 | 19.7 | 22.5 |
| | Yes | 18.6 | 21.2 | 24.0 | 27.1 | 30.5 | 34.0 | 37.8 | 41.7 |
| -1.5 | No | 9.9 | 11.5 | 13.3 | 15.3 | 17.5 | 20.0 | 22.7 | 25.7 |
| | Yes | 21.4 | 24.3 | 27.4 | 30.8 | 34.4 | 38.1 | 42.0 | 46.1 |
| -2.0 | No | 11.6 | 13.4 | 15.4 | 17.7 | 20.2 | 22.9 | 26.0 | 29.2 |
| | Yes | 24.5 | 27.7 | 31.1 | 34.7 | 38.5 | 42.4 | 46.4 | 50.5 |
| -2.5 | No | 13.6 | 15.6 | 17.9 | 20.4 | 23.2 | 26.2 | 29.5 | 33.0 |
| | Yes | 28.0 | 31.4 | 35.0 | 38.8 | 42.7 | 46.7 | 50.8 | 54.9 |
| -3.0 | No | 15.8 | 18.1 | 20.6 | 23.4 | 26.5 | 29.8 | 33.3 | 37.0 |
| | Yes | 31.7 | 35.3 | 39.1 | 43.1 | 47.1 | 51.2 | 55.2 | 59.2 |
| -3.5 | No | 18.3 | 20.9 | 23.7 | 26.8 | 30.1 | 33.6 | 37.3 | 41.2 |
| | Yes | 35.6 | 39.4 | 43.4 | 47.4 | 51.5 | 55.6 | 59.5 | 63.4 |
| -4.0 | No | 21.1 | 23.9 | 27.0 | 30.4 | 33.9 | 37.7 | 41.6 | 45.6 |
| | Yes | 39.8 | 43.7 | 47.8 | 51.9 | 55.9 | 59.9 | 63.7 | 67.4 |

Table 3 A 5-year risk of incident fragility fracture in CaMos men based on age, femoral neck T-score and spine fracture (yes/no)

| Femoral neck T-score | Spine fracture | Age (years) | | | | | | | |
|----------------------|----------------|-------------|------|------|------|------|------|------|------|
| | | 50 | 55 | 60 | 65 | 70 | 75 | 80 | 85 |
| -1.0 | No | 9.9 | 10.8 | 11.9 | 13.0 | 14.2 | 15.6 | 17.0 | 18.5 |
| | Yes | 21.3 | 23.1 | 25.0 | 27.0 | 29.1 | 31.3 | 33.6 | 36.0 |
| -1.5 | No | 11.3 | 12.4 | 13.5 | 14.8 | 16.2 | 17.6 | 19.2 | 20.9 |
| | Yes | 23.9 | 25.8 | 27.9 | 30.0 | 32.3 | 34.6 | 37.0 | 39.5 |
| -2.0 | No | 12.9 | 14.1 | 15.4 | 16.8 | 18.3 | 19.9 | 21.6 | 23.5 |
| | Yes | 26.7 | 28.8 | 31.0 | 33.3 | 35.6 | 38.1 | 40.6 | 43.1 |
| -2.5 | No | 14.6 | 16.0 | 17.4 | 19.0 | 20.7 | 22.4 | 24.3 | 26.3 |
| | Yes | 29.8 | 32.0 | 34.3 | 36.7 | 39.2 | 41.7 | 44.2 | 46.8 |
| -3.0 | No | 16.6 | 18.1 | 19.7 | 21.4 | 23.2 | 25.1 | 27.2 | 29.3 |
| | Yes | 33.0 | 35.3 | 37.8 | 40.2 | 42.8 | 45.4 | 48.0 | 50.6 |
| -3.5 | No | 18.8 | 20.4 | 22.2 | 24.1 | 26.0 | 28.1 | 30.2 | 32.5 |
| | Yes | 36.4 | 38.8 | 41.3 | 43.9 | 46.5 | 49.1 | 51.7 | 54.3 |
| -4.0 | No | 21.2 | 23.0 | 24.9 | 26.9 | 29.0 | 31.2 | 33.5 | 35.9 |
| | Yes | 39.9 | 42.5 | 45.0 | 47.6 | 50.2 | 52.8 | 55.4 | 58.0 |

based on models including risk factors: (1) age, (2) age plus BMD and (3) age plus BMD plus spine fracture status. This analysis revealed that consideration of the three factors identified not only more but also different subjects having a 30% 5-year risk for fracture.

In **Figure 4c**, subjects with at least a 30% 5-year fracture risk are shown as identified using logistic regression models including risk factors: (1) age plus BMD plus spine fracture status versus and (2) these factors plus the remaining WHO clinical risk factors. This analysis revealed that these approaches largely identified the same subjects. In 97% of the population, the two models agreed in defining subjects as having less than versus at least a 30% 5-year risk of fracture.

Discussion

Data from this analysis of Cohort 2 ($n = 1964$) in CaMos confirm our previous report in Cohort 1 ($n = 2761$)⁷ and demonstrate the value of morphometric spine fracture status for predicting the

risk of new vertebral and nonvertebral fragility fractures. In univariate analyses, we found that morphometric spine fracture status was one of the most important predictors of 5-year fracture risk. In addition, we assessed models for predicting future fracture risk by sequentially adding the most important clinical risk factors and found that a model including age, femoral neck BMD and spine fracture status provided information similar to a model considering BMD, the WHO clinical risk factors and spine fracture status. For comparison, this model provided more prognostic information than a model considering BMD and the WHO clinical risk factors.

A femoral neck BMD T-score is a strong risk factor for predicting fracture risk and is a key factor in diagnosing osteoporosis in many countries. However, it is clear that relying on a T-score of < -2.5 precludes diagnosing and treating many older persons at high risk for fracture based on non-BMD clinical risk factors.^{11,12} For instance, age contributes additional prognostic information regarding fracture risk regardless of other clinical risk factors.¹³ This is consistent with the findings of a bone histomorphometry study, which showed that several parameters of bone strength deteriorate with increasing age,¹⁴ as well as with previous data using high-resolution peripheral quantitative computed tomography in the CaMos cohort, which demonstrated age-related changes in the bone.¹⁵ Additionally, at any particular level of BMD, spine fracture status provides additional prognostic information.¹ Increasing spine fracture burden is associated with deterioration of bone microarchitecture.¹⁶ Thus, age and spine fracture status appear to provide information regarding bone quality that is supplemental to the information provided by the femoral neck BMD T-score. Although other WHO clinical risk factors were prognostic in univariate analyses, including them in multivariate analyses contributed little additional information beyond that provided by age, BMD and spine fracture status. Thus, it appears that the information obtained from these other risk factors was captured by morphometric spine fracture status. Importantly, in the absence of knowledge about spine fracture status, assessments based on BMD and the WHO clinical risk factors alone may under- or overestimate the true risk of an individual experiencing an incident fracture.¹

An advantage of including a small number of variables in the assessment of future fracture risk is that 5-year absolute fracture risk for people who are similar to those in CaMos can be reported in simple tables.⁷ However, whether the current results are generalizable to other populations is an important consideration. In this regard, an analysis of the Hiroshima study of Japanese using a similar statistical approach showed comparable findings.¹⁷ However, in that analysis, a statistical model including age, femoral neck BMD T-score, spine fracture status (yes/no) and prior clinical fracture performed better than a model not including prior clinical fracture.¹⁷

Additional analyses of all CaMos subjects were undertaken to assess the most important risk factors for the specific outcome, vertebral fracture. These analyses also confirmed the primary importance of age, BMD and spine fracture status. However, analyses of all CaMos subjects to assess the most important risk factors for nonvertebral fragility fracture showed that a model considering these risk factors plus previous clinical fracture performed better.

At the top of the National Osteoporosis Foundation list of who should be treated for osteoporosis are those with hip or spine fractures, including morphometric or clinical vertebral

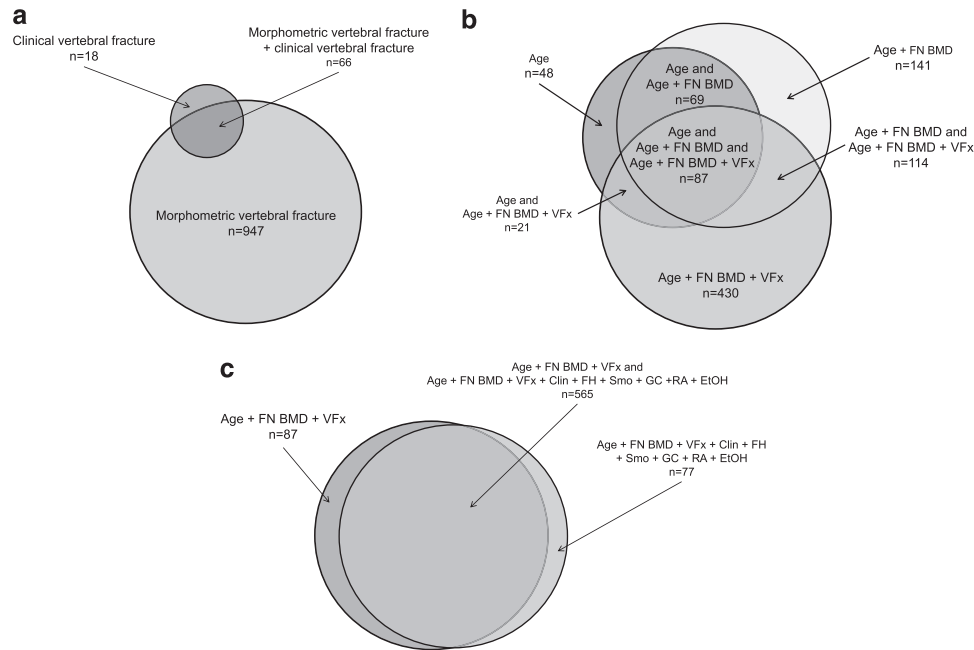


Figure 4 Venn diagram showing (a) subjects with prevalent vertebral fractures as assessed by questionnaire versus lateral spine imaging, (b) subjects having >30% 5-year fracture risk as assessed by models considering age, age plus femoral neck BMD (FN BMD) and age plus FN BMD plus spine fracture status (VFX) (yes/no) and (c) subjects having >30% 5-year fracture risk as assessed by models considering age plus FN BMD plus VFX, and age plus FN BMD plus VFX plus previous clinical fracture (Clin) plus the remaining WHO clinical risk factors: parental history of hip fracture (FH) plus current smoking (Smo) plus systemic glucocorticoids >3 months (GC) plus rheumatoid arthritis (RA) plus >2 alcoholic drinks/day (EtOH).

fractures.¹⁸ To identify people with vertebral fractures versus those without vertebral fractures, several lines of evidence suggest that routine screening with spine imaging may be necessary. In the current study, over 20% of men and women at baseline in CaMos had a morphometric vertebral fracture.⁶ Among these, 93% were not aware of that fracture. In a recent study conducted in Spain, 98.5% of those in the population who had a vertebral fracture were not aware of the fracture.¹⁹ A study from the United Kingdom showed that routine screening of women over the age of 65 by vertebral fracture assessment revealed moderate or severe vertebral fractures in 20% of women, with targeted screening based on reported height loss (>2.5 cm, 1 inch), Dowager's hump, suspected fracture on anterior-posterior spine dual energy X-ray absorptiometry (DXA), and known vertebral fracture missing 90% of the fractures;²⁰ this study supports the conduct of routine rather than targeted screening for vertebral fractures in women over the age of 65.

In the current study, in 18 of 84 (21%) women with a history of clinical vertebral fracture, no vertebral fracture was found to be present by lateral spine imaging. Similarly, among 425 women with self-report of a fracture in the Kuopio Osteoporosis Risk Factor and Prevention Study (OSTPRE),²¹ 70 (16%) were found not to have a fracture by review of medical records. Also, among 453 women known to have a fracture by review of the medical records, 98 women (22%) did not self-report the fracture in OSTPRE. These data suggest that patient reporting of fracture is sometimes erroneous.

Models with a higher GR/s.d. identify more patients having any particular threshold of risk. For example, in CaMos, consideration of age, femoral neck BMD T-score and spine fracture status identified not only more but also different participants with at least a 30% 5-year risk of fracture than would be identified by

consideration of age only or of age plus femoral neck BMD T-score. Finally, consideration of age, femoral neck BMD T-score and spine fracture status versus consideration of these variables plus the remaining WHO clinical risk factors identified a similar group of subjects with at least 5-year risk of fracture. These findings highlight the value of knowledge of the spine fracture status in individuals who may have vertebral fractures.

The current analysis has some limitations. The methodology for assessing the radiographs was quantitative morphometry. Other methodologies including semiquantitative assessment or a mixture of quantitative morphometry plus semiquantitative assessment have been used in various other studies.²² However, we are reassured by the marked prognostic importance of spine fracture status in this analysis, in that the CaMos methodology for reading the radiographs indeed generated clinically important information. Our current analysis only considered presence versus absence of vertebral fracture, as in our previous analysis, additional detail—including number, maximum severity and spine deformity index—did not appreciably increase the GR/s.d.⁷ Of course, subjects with higher spine fracture burden are likely to have relatively higher risk, just as greater burden of any of the particular risk factors is likely to confer greater risk. Use of glucocorticoids was present only in a small number of subjects, so it is possible that this analysis may have underestimated the importance of this risk factor.

In conclusion, the current analysis confirms and extends the findings of the preliminary analysis from the population-based CaMos cohort and reinforces the value of using prevalent spine fracture status combined with age and BMD to predict future fracture risk. Simple tables show 5-year absolute fracture risk based on these factors. This work, therefore, demonstrates the potential to provide high predictive performance parsimoniously by considering these risk factors.

Materials and Methods

Study participants and population. Details of the objectives, purpose and methodology of CaMos, a prospective cohort study following a randomly selected population-based community cohort of 9423 community-dwelling men and women aged 25 and over living within 50 km of one of nine regional centers in Canada have been reported.⁵ Recruitment of the cohort began in September 1995 and ended in September 1997. The study was approved by all regional institutional ethics review boards. Subjects provided written informed consent in accordance with the Helsinki Declaration. The previously reported findings were limited to the 2761 subjects aged 50 and older for whom spine radiographs at baseline and year 5 had been completed.⁷ The data from these subjects were re-analyzed for purposes of comparison and are denoted as Cohort 1. An additional 1964 subjects who now have completed readings of spine radiographs at baseline and year 5 are now analyzed and denoted as Cohort 2; both cohorts comprise the CaMos adult population for whom spinal radiographs were available.

Bone mineral density. Lumbar spine (L1–L4) and hip BMD were assessed by DXA with Hologic QDR 1000, 2000 or 4500 densitometers at seven centers and Lunar DPX densitometers at two centers. BMD results were converted to a Hologic standard.²³ A semi-anthropomorphic spine phantom (Siemens, Munich, Germany) was measured annually at each center for cross-calibration purposes.²⁴ Femoral neck T-scores used in this analysis were derived from CaMos reference data.^{25,26}

Clinical risk factor measurement. An extensive interviewer-administered questionnaire was used to assess osteoporosis and fracture-related risk factors at baseline. A second intensive interview conducted 5 years after enrollment was used to re-assess these risk factors. Clinical risk factors were derived from the baseline interview except for parental history of hip fracture, which was obtained from the year 5 questionnaires. Subject responses were coded to identify current cigarette smokers, use of systemic glucocorticoid therapy for more than 3 months (without regard to dose), minimal trauma fracture after 50 years of age,²⁷ hip fracture in either or both parents, consumption of greater than two units of alcohol per day and rheumatoid arthritis by subject self-reporting a physician diagnosis of rheumatoid arthritis.

Fracture diagnosis. The methods were the same as previously reported.⁷ The risk of any fracture was defined as the risk of an incident morphometric vertebral fracture and/or a non-vertebral fragility fracture. Additional analyses were also performed to assess risk factors for predicting vertebral fracture and for predicting nonvertebral fragility fractures.

Lateral thoracic and lumbar spine radiographs obtained on subjects 50 years and older at baseline and after 5 years were assessed at central sites in Edmonton (Alberta) and Quebec City (Quebec) with quality control to confirm agreement between the sites. Spine fracture status (yes/no) was determined by quantitative morphometric analysis.⁶ Vertebrae were graded as without fracture if the height ratio was ≤ 3 s.d. below the mean of respective uninvolved vertebrae by sex (vertebral reference), whereas they were graded fractured if the height ratio was > 3 s.d. below the vertebral reference. Nonvertebral fragility fractures were self-reported by annual questionnaire

and defined as a fracture with minimal trauma, and confirmed using radiograph or medical records.

Statistical analyses. The previously published analyses were repeated for both Cohort 1 and Cohort 2. Logistic regression analyses were performed to determine the importance of baseline morphometric spine fracture status, BMD and the WHO clinical risk factors²⁸ (age, prior fragility fracture, current smoking, alcohol use, parental history of hip fracture, glucocorticoid use, rheumatoid arthritis) for predicting the 5-year risk of any future vertebral or nonvertebral fragility fracture. To test the hypothesis that inclusion of spine fracture status with clinical risk factors would improve the prediction of future fracture risk, a logistic regression model was built including clinical risk factors compared with models including these plus spine fracture status (yes/no). The performance of each model was assessed using the GR/s.d., that is, the risk ratio per 1 s.d. change in risk score.^{9,29}

Further analyses were conducted to determine the predictive ability of sequential addition of the most predictive clinical risk factors and spine fracture status. For this purpose, univariate logistic regression analysis was used to investigate the associations of future fracture risk among age, femoral neck T-score, prior fragility fracture, spine fracture (yes/no), current smoking, alcohol use, parental history of hip fracture, glucocorticoid use and rheumatoid arthritis. The gradient of fracture risk was examined in multivariate models, with sequential addition of the most important risk factors determined from the univariate analyses.

For each sex, 5-year absolute fracture risk was estimated using the logistic regression model, including these factors: age, femoral neck T-score and spine fracture status. The prevalence of morphometric vertebral fracture to the prevalence of clinical vertebral fractures was compared using a Venn diagram. Subjects identified to have at least 30% 5-year fracture risk as assessed by different logistic regression models were compared using additional Venn diagrams.

All analyses used SAS drug development software (SAS Institute, Cary, NC, USA).

Conflict of Interest

John H. Krege is a full-time employee of Eli Lilly and Company, and Xiaohai Wan was a full-time employee of Eli Lilly and Company at the time the study was conducted. Jonathan D. Adachi has served as consultant/speaker for Amgen, Astra Zeneca, Eli Lilly, GlaxoSmithKline, Merck, Novartis, Pfizer, Procter & Gamble, Roche, Sanofi-Aventis and Servier. Jacques P. Brown has received a research grant from or has served as a consultant/speaker for Abbott, Amgen, Eli Lilly, Genizon, GlaxoSmithKline, Merck, Novartis, Pfizer, Procter & Gamble, Roche, Sanofi-Aventis, Servier, Wyeth and Zelos. Wojciech P. Olszynski has served as a consultant for Abbott Laboratories, Merck Frosst, Amgen, Novartis, Aventis, Pfizer, Boehringer Ingelheim, Procter & Gamble, Eli Lilly, Sanofi-Synthelabo, Genzyme, Schering Canada, GlaxoSmithKline, Solvay Pharma, Hoffmann-LaRoche, Wyeth and Janssen-Ortho Inc./Ortho-Biotech. Robert G. Josse has served on advisory boards and received honoraria and research grants from Eli Lilly, Procter & Gamble, Sanofi-Aventis, Merck, Novartis, Servier, Glaxo-SmithKline and Amgen. David Goltzman has received honoraria from and served on the advisory boards of Eli Lilly, Procter &

Gamble, Merck Frosst and Novartis. The remaining authors declare no conflict of interest.

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