Ten-year incident osteoporosis-related fractures in the population-based Canadian Multicentre Osteoporosis Study — Comparing site and age-specific risks in women and men

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Abstract

Background—Population-based incident fracture data aid fracture prevention and therapy decisions. Our purpose was to describe 10-year site-specific cumulative fracture incidence by sex, age at baseline, and degree of trauma with/without consideration of competing mortality in the Canadian Multicentre Osteoporosis Study adult cohort.

Methods—Incident fractures and mortality were identified by annual postal questionnaires to the participant or proxy respondent. Date, site and circumstance of fracture were gathered from structured interviews and medical records. Fracture analyses were stratified by sex and age at baseline and used both Kaplan–Meier and competing mortality methods.

Results—The baseline (1995–97) cohort included 6314 women and 2789 men (aged 25–84 years; mean ± SD 62 ± 12 and 59 ± 14, respectively), with 4322 (68%) women and 1732 (62%) men followed to year-10. At least one incident fracture occurred for 930 women (14%) and 247 men (9%). Competing mortality exceeded fracture risk for men aged 65+ years at baseline. Age was a strong predictor of incident fractures especially fragility fractures, with higher age gradients for women vs. men. Major osteoporotic fracture (MOF) (hip, clinical spine, forearm, humerus) accounted for 41–74% of fracture risk by sex/age strata; in women all MOF sites showed age-related increases but in men only hip was clearly age-related. The most common fractures were the forearm for women and the ribs for men. Hip fracture incidence was the highest for the 75–84 year baseline age-group with no significant difference between women 7.0% (95% CI 5.3, 8.9) and men 7.0% (95% CI 4.4, 10.3).

Interpretation—There are sex differences in the predominant sites and age-gradients of fracture. In older men, competing mortality exceeds cumulative fracture risk.

Keywords

Population-based; 10-year fracture incidence; Hip fracture; Clinical vertebral fracture; Sex; Fracture prediction

Introduction

Fractures are the primary health risk of osteoporosis [1,2]. The costs of acute and chronic care following fractures, especially those at the hip, comprise a major portion of national health-care budgets. In 2005, fractures in the USA were associated with an estimated $17 billion dollars in direct costs [3]. A portion of the post-fracture economic burden includes rehabilitation [4,5], the cost for the increased risks of long-term disability with resulting required increased support [5,6], decreased health-related quality of life [7] including the development of depression in older women [8] and increased mortality [9]. Thus considerable resources might be allocated toward fracture prevention without exceeding those incurred following a fracture [10].

The FRAX tool, developed to predict the 10-year risk of hip fracture and "major osteoporotic fracture" (MOF, defined as fractures at the hip, distal forearm, clinical vertebral, and proximal humerus) [11,12], was based on combined data from several

international cohorts [12]. Calibration of the Canadian FRAX tool used Canadian national hospital hip fracture data [13] with estimated major osteoporotic fracture rates [14].

The FRAX assessment of major osteoporotic fracture has been established as a standard outcome and measure of burden of disease. Implicit to the FRAX algorithm deriving 10-year fracture probability estimates is an adjustment for the competing risk of death. Furthermore, the FRAX tool considered risk of major osteoporotic fracture as a summary measure, but other fracture sites contributing to the overall burden of osteoporosis include the pelvis, rib and leg [15]. Rib fractures are common in both men and women, are associated with classic osteoporosis risk factors, and are a risk factor for future fracture [16–20]. The high-frequency of fractures at sites other than the hip and spine is associated with high health care utilization [21]. In short, the population health burden of osteoporotic fractures includes more skeletal sites than major osteoporotic fracture sites and is also potentially modified by competing mortality.

Our purpose was to describe the site-specific 10-year risk of fracture by sex, age at baseline, fracture site and degree of trauma with and without consideration of competing mortality risk in a national population-based cohort.

Methods

Study population

The Canadian Multicentre Osteoporosis Study (CaMos) is an ongoing national population-based cohort study initiated in 1995. CaMos design, questionnaires and baseline data acquisition have previously been described [22]. Briefiy, recruited community dwelling participants lived within a 50-kilometer radius of one of the nine Canadian cities (St John's, Halifax, Quebec City, Toronto, Hamilton, Kingston, Saskatoon, Calgary and Vancouver) and were able to converse in English, French or Chinese (in Vancouver and Toronto only). Households were randomly selected from residential phone numbers; participants were then randomly selected within households by a sex and age-stratified protocol weighted to older adults targeting two-thirds women. Of those randomly selected, 42% agreed to full participation including clinical measurements, BMD and spine radiographs. Ethics approval was granted through McGill University and centre ethics review boards. All participants gave written informed consent and the study is conducted in accordance with the Helsinki Declaration. The population for the present study included all CaMos participants with follow-up data who were aged 25 to 84 years at baseline.

Data collection

Participants completed a standardized interviewer-administered questionnaire (CaMos questionnaire ©1995) at baseline assessing demographics, general health, nutrition, reproduction, medication use and medical history to capture detailed information about risks for fracture.

Fracture assessment

Self-reported incident fractures were identified by yearly postal questionnaire or interviewer-administered questionnaires at scheduled interviews (year 3, [baseline ages 40–60], year 5 and year 10). A structured interview confirmation of postal questionnaires determined the fracture-specific date, site, circumstances, trauma and management. Those with missing fracture questionnaires (including those who died) were identified and secondary contact information was used to complete the fracture questionnaire by proxy. Independent medical records (obtained with consent to contact the treating physician/ hospital) were obtained for 78% of all incident fractures and these could be further adjudicated (e.g. hip vs. non-hip leg). We were unable to adjudicate all fractures, therefore to avoid the underestimation of fractures due to failure to obtain relevant records we also included self-reported fractures that were confirmed in the telephone interview.

Fragility fractures were defined to be those involving a force less than or equal to a fall from a standing height. In this osteoporosis-specific description, we excluded incident fractures of the skull, face, hands, ankles, and feet. WHO major osteoporotic fractures (hip, clinical spine, forearm, and humerus) are reported for comparison purposes. Fractures designated "leg" occurred at sites excluding the proximal femur or hip.

Statistical methods

We assessed between-group differences (incident fracture vs. no incident fracture) for continuous variables using a *t*-test and for categorical variables using a chi-squared test. We performed the main analyses separately for women and men and further stratified analysis by baseline age-category (5-year bands). Person-time for this analysis included the period from study enrolment to exit (earliest date of: incident fracture, death, last complete fracture questionnaire, 10-year study anniversary). For specific skeletal sites, we considered person-time up until the fracture at that site, ignoring fractures at other sites. In the first analyses, cumulative fracture incidence or fracture risk was computed without considering competing mortality by Kaplan–Meier method treating deaths as a censored outcome. We tested age–sex interactions and age-gradients with a Cox proportional hazards model. Since the FRAX tool adjusts for competing mortality, we performed further analyses with death as a competing risk [23]. All analyses were performed with Stata (Version 12) (College Station, Texas, USA); we used the package "stcompet" for the competing risks calculations.

Results

The study sample consisted of 6314 women and 2789 men with a follow-up duration from study entry to study exit (first fracture, death, or study discontinuation) of 50,300 person-years in women and 21,800 person-years in men. The study sample excluded 186 women and 62 men who did not meet the initial age eligibility criteria (<85 years) and 39 women and 33 men who did not have at least one year of follow-up. A total of 4322 (68%) women and 1732 (62%) men were still alive and in the cohort at year 10.

Incident fracture risk and competing mortality by age, sex

A total of 930 women (14%) and 247 men (9%) had one or more incident fractures (excluding head, hands, ankles and feet) during the 10-year study period (Table 1). Those who had incident fractures were older, had lower BMD values, lower physical function (SF-36), were more likely to have entered the cohort with diagnoses of osteoporosis or prevalent fractures and were more likely to be white when compared to those without incident fracture. Fig. 1 shows the distribution of fracture sites (for the first incident fracture) by sex. The distribution of skeletal sites differed by sex; forearm fractures were most common among women and rib fractures were most common among men. For some incident fractures these occurred at multiple fracture sites in a single event; this occurred for 48 women and 11 men. Finally, among those who experienced incident fractures during the 10-year follow-up, multiple fractures (stratified as 2, 3, 4, 5+) were observed in 185 women (145, 27, 8, 5, respectively) and 43 men (35, 7, 1, 0, respectively).

For most sex and age groups, the estimates of 10-year fracture risk using Kaplan–Meier methods are very similar to the estimates of 10-year fracture risk taking into account competing mortality (Table 2), with differences exceeding 2% only among men and women aged 75–84 years.

Comparing men and women, we note that the 10-year fracture risk (estimated with Kaplan–Meier methods) was relatively stable for men <65 years old at baseline, but increased with age for older men. Among women, however, the 10-year risk of fracture increased gradually over the whole age range varying from 4.3% (95% CI: 2.1–8.8) at baseline ages 25–34 years to 31.8% (95% CI: 28.3–35.6) at 75–84 years. Using a Cox model combining men and women and assuming fracture hazard increases exponentially with age, we found an age–sex interaction so that among women there was a 24% higher increase (95% CI: 10%–40%) in fracture rate (hazard) per decade compared to men.

Competing mortality risk increased exponentially with age in both sexes but was higher in men. Furthermore, there were clear sex differences in the epidemiology of fracture related to mortality. Among women, the fracture risk was higher than or similar to the risk of competing mortality; for men the mortality risk clearly exceeded the fracture risk among those aged 65+ years at baseline. The 10-year age-specific event-free survival combines fracture and mortality risk trends. In both men and women the event-free survival declined with age and dropped below 50% for those of both sexes in ages 75–84 years at baseline.

Fragility fracture risk by age and sex

For women, the 10-year risk of fragility fracture adjusted for competing mortality increases 20-fold with baseline age, from 1.2% (95% CI: 0.2%–3.8%) among women aged 25–34 years to 24.4% (95% CI: 21.4%–27.4%) among women aged 75–84 years (Fig. 2a). For men, the risk of fragility fracture increases 5.7-fold with baseline age, from 2.4% (95% CI: 0.8%–5.7%) among men aged 25–34 years to 13.7% (95% CI: 10.1%–17.8%) among men aged 75–84 years (same figure).

The proportion of all incident fractures that are fragility fractures strongly differs by baseline age (Fig. 2b). In those 25–34 years only 27–33% of overall fracture risk is accounted for by

fragility fractures, whereas in those 75–84 years, 82% of men's and 90% of women's fracture risk is accounted for by fragility fractures.

WHO major osteoporotic fracture risk by age and sex

For women, the 10-year risk of major osteoporotic fracture (MOF) fracture (clinical spine, hip, forearm, and humerus) increases 8-fold with age, from 2.5% (95% CI: 0.8%–5.8%) among women aged 25–34 years to 20.0% (95% CI: 17.3%–22.9%) among women aged 75–84 years (Fig. 3a). For men, the risk of MOF fracture increases 3.2-fold with age, from 3.6% (95% CI: 1.5%–7.3%) among men aged 25–34 years to 11.5% (95% CI: 8.2%–15.4%) among men aged 75–84 years.

The proportion of fracture risk attributable to MOF fractures is shown in Fig. 3b. The proportion of fracture risk that is attributable to fractures at the MOF sites increases slightly but not consistently with age in both sexes varying from 44% to 74% of overall fracture risk in women and from 41% to 69% of overall fracture risk in men.

Site-specific fracture risks by sex and age

Incident fractures including clinically diagnosed spine fractures show site-specific differences according to sex and age (Fig. 4). For women, the age-trends for overall MOF risk were also present separately at the hip, clinical spine, forearm and humerus. In contrast, for men, only the hip, of the MOF fracture sites, was age-related. Hip fracture incidence was the highest for the 75–84 year baseline age-group with no significant difference between women 7.0% (95% CI 5.3, 8.9) and men 7.0% (95% CI 4.4, 10.3). For women, fractures at all sites (except the leg) increased in incidence with older age. By contrast, for men age-related increases were important only for the hip and ribs.

Forearm fracture among women was the most common site with 10-year risks ranging from 1.8% (95% CI: 0.5, 4.8) among those aged 25–34 years to 6.6% (95% CI: 5.0, 8.4) among those aged 75–84 years. Forearm fracture was less common among men with a U-shaped risk by age; men 25–34 years had the highest risk, 3.6% (95% CI: 1.5, 7.3); men 55–64 years had the lowest risks, 0.7% (95% CI: 0.2,1.7); and men 75–84 years had again higher risk, 2.2% (95% CI: 1.0, 4.3). The ribs were the most common incident fractures for men as shown in Fig. 4 with risks varying from 1.8% (95% CI: 0.5, 3.8) at 25–34 years to 5.0% (95% CI: 3.0, 7.9) at 75–84 years; they increased similarly but slightly less with age in women.

Discussion

This study describes the 10-year cumulative incidence of osteoporosis-related fracture by sex, age, trauma and site in a North American country-wide, population-based community dwelling cohort. Hip fracture risks were similar in the oldest community-dwelling men and women. Fragility fractures show a stronger age gradient than do fractures of all traumas in both men and women. We documented that the predominant site of fracture in women is the forearm, while in men the predominant site is the ribs. Fractures of the hip, clinical spine and arm (forearm and humerus) constitute a majority of the fracture burden in both men and

women; the age-gradients and predominant sites of MOF, however, are very different in men and women.

Competing mortality

These data show that fracture risk with competing mortality adjustment is similar to the Kaplan–Meier estimates for those of both sexes who are younger than 65 years, but that Kaplan–Meier estimates are higher than the competing mortality estimates for those >65 years, with clinically important differences among those >75 years. Our comparison of the Kaplan–Meier vs. competing risk analysis is concordant with a previous Manitoba study [24] that used both parametric and non-parametric methods to adjust for competing mortality. Finally, we note that the 10-year fracture risk is lower than the 10-year competing mortality risk for men aged >65 years. This observation is consistent with data from other studies, e.g. the Dubbo study that assessed residual lifetime fracture risk showing that more men died without fracture than the number of fracture cases, implying a higher risk of competing mortality vs. fracture risk among men in their cohort [25].

Hip fractures

A surprising finding of this study was that the 10-year hip fracture risk is similar in community-dwelling men and women aged 75–84 years. Canadian hospitalization data on hip fracture show that women account for 72% of hip fractures [13]. Women survive to an older age than men and thus make up a higher proportion of long-term care residents, an increased risk that might have been underestimated in the present study. A decreasing hip fracture incidence over time potentially shows a narrowing of the gap between hip fracture rates in men and women [26]. Hip fracture risk changes over time show the influence of a combination of trends; birth cohort trends are dominant in men and period trends are dominant in women [27]. The period trends in women are likely due to environmental exposures (such as uptake of prevention strategies and being prescribed effective treatments) proximal to the fracture outcome, an effect that might be exaggerated in CaMos as participants became more aware of osteoporosis risk factors. Finally, although the observed sex-related hip fracture risks were similar by sex in the very oldest cohort, the low numbers of events does not preclude clinically important differences between men and women were a larger sample available.

Site-specific fractures differ by sex

Skeletal sites of fractures differ markedly in men and women. In women, major osteoporotic fracture risks [12] increase with age and show a clear association with overall fracture risk. By contrast, in men increasing age is not associated with an increased risk of forearm fracture; age-related risks of humerus and clinical spine fractures in men increase only minimally with age. In short, in men, hip is the only MOF site that clearly increases with age. It is not clear whether in the case of spine fracture, there is greater sex-specific under-diagnosis of spine fracture among men who present with back pain.

Our observed sex- and site-specific age-related fracture risk trends in men are similar to those in Olmstead County, especially the U-shaped age-related forearm fracture incidence [17]. Distal forearm strength shows sex-based age trajectory differences; adolescent men

have thicker trabeculae than teen women and better age-related strength preservation [28]. In women, factors related to forearm strength change differently with age; cortical porosity increases more and periosteal expansion is less with aging than in men [29].

Our observation that rib fractures are prominent in men and increase with age is similar to results from the Study of Osteoporotic Fractures in Men (MrOS-USA) although in that 65 year-old cohort the age-effect was not significant [16]. The MrOS study also showed that prevalent rib fractures were associated with increased risks for incident rib, forearm or hip fractures [16]. Others have also noted men's higher incidence of rib fracture and its relationship with future fracture [17–20]. This suggests that, especially in men, rib fractures merit further attention as an osteoporosis-related fracture.

Strengths and limitations

Strengths of this study include random selection from a known sample frame with potential to assess selection bias into the study, inclusion of men as well as women and younger as well as older participants, a trans-continental geographic catchment, interviewer-administered questionnaires and long-term prospective follow-up with good cohort retention. We computed fracture risk with competing mortality with a comparison to the more customary Kaplan–Meier estimates enabling better comparison across studies.

The main limitation of this study is that it initially included only those who were community-dwelling at cohort entry (excluding those in institutions) and that it under-represents (in part because of population race distribution) those of non-European descent. Further limitations include possible "study effect", whereby participants have increased knowledge of osteoporosis (e.g. BMD status) potentially impacting behavior despite the lack of formal intervention, and the bias introduced when frail elders (who are at higher fracture risk) decline further follow-up, each of which may result in an underestimation of fracture risk. We also note that the importance of competing mortality could be underestimated if subjects with poor health status and high mortality decline further followup. We realize that a healthy cohort effect might differentially affect men and women if women were more often lost to follow-up due to transfer into long-term care.

In summary, this population-based, largely Caucasian Canadian initially community dwelling cohort study of 10-year incident osteoporosis-related fractures shows that hip fracture risks in the oldest men and women are similar. Forearm fractures are known to be associated with osteoporosis for women but rib fractures appear to show a similar predominance as osteoporotic fractures in men. These data in randomly sampled men and women show that skeletal-site specific and age-specific fracture risks are substantially different in men and women thus any osteoporosis fracture descriptions need to include these specificities. Finally, the importance of considering competing mortality in those at high risk for death is underscored by our observation that among older men the 10-year cumulative mortality exceeds cumulative fracture incidence.

Acknowledgments

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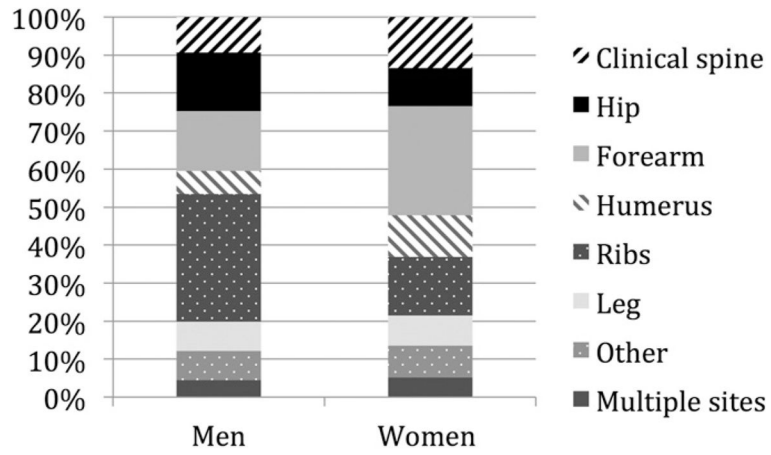
Fig. 1.
The distribution of 10-year first incident fractures by sex and skeletal site in the Canadian Multicentre Osteoporosis Study cohort. "Other" includes cervical, pelvis, clavicle, scapula and coccyx.

10-year absolute risk of fragility fracture

Fragility fracture as percentage of total fracture risk
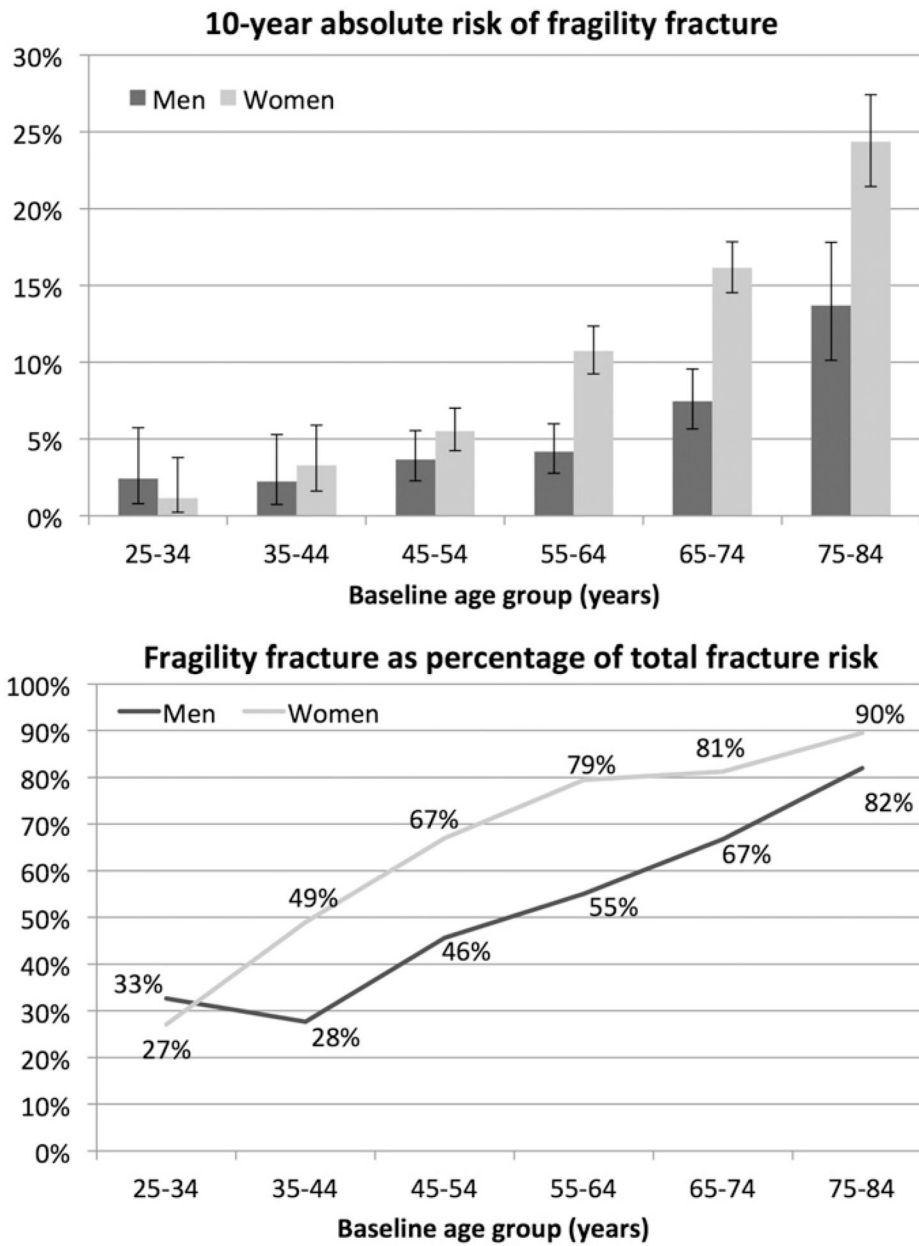

Fig. 2.
(a) Estimated 10-year risk of fragility fracture (low-trauma, equivalent to fall from standing height or less; all sites except the head, hands, ankles and feet) adjusted for competing mortality by sex and baseline age group along with estimated (b) percent of all fracture risk (of any trauma) from the Canadian Multicentre Osteoporosis Study. Error bars indicate 95% CI.

Fig. 3.
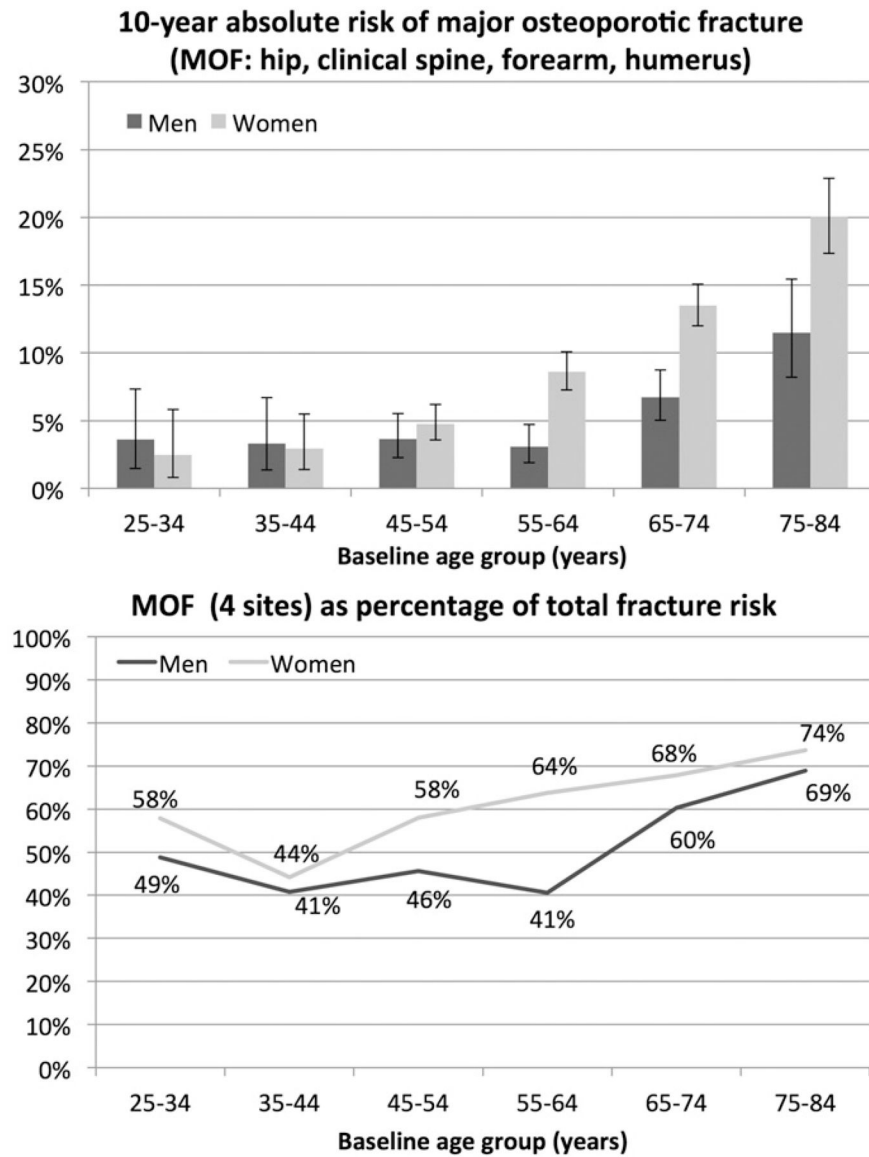(a) Estimated 10-year risk of major osteoporotic fracture (MOF 4 sites: hip, clinical spine, forearm, humerus; including all degrees of trauma) adjusted for competing mortality by sex and baseline age group along with estimated (b) percent of fracture risk (at all skeletal sites except the head, hands, ankles and feet) from the Canadian Multicentre Osteoporosis Study. Error bars indicate 95% CI.
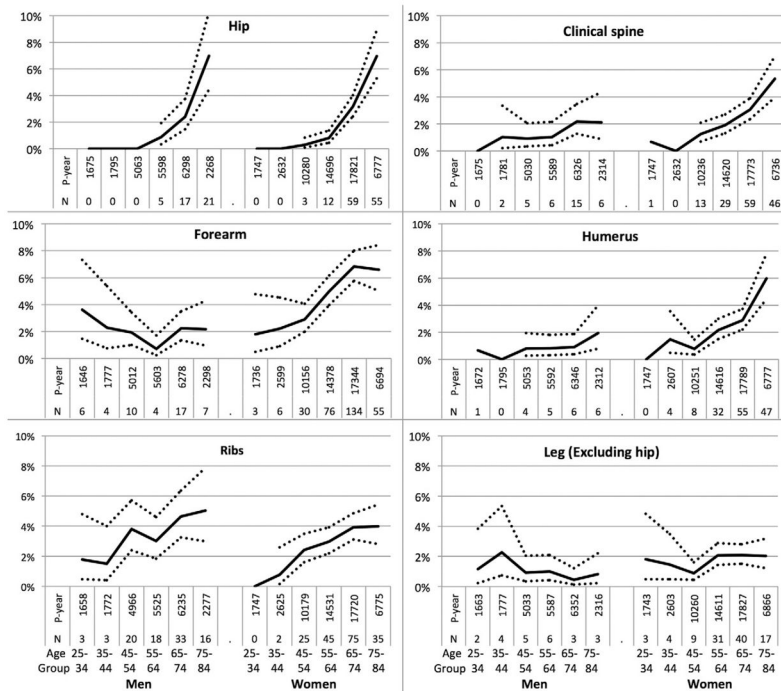
Fig. 4.
Estimated 10-year risk of fracture (including all degrees of trauma) adjusted for competing mortality by fracture site (clinical spine, hip, forearm, humerus, ribs and leg), sex and baseline age group from the Canadian Multicentre Osteoporosis Study. Estimates are shown by the solid lines, dotted lines indicate the 95% CI.

Table 1

Baseline demographic and bone mineral density (BMD) data stratified by sex and 10-year incident fracture (FX) outcome status (excluding head, hands, ankles and feet) among those aged 25–84 years in the Canadian Multicentre Osteoporosis Study. Data are mean ± SD or N (%). Bold font indicates statistically significant differences between those with and without an incident fracture within each sex group.

	Men		Women	
	Incident FX N = 247	**No FX N = 2542**	**Incident FX N = 930**	**No FX N = 5384**
Age	**62.8 ± 14.0**	**60.0 ± 14.0**	**67.1 ± 10.2**	**61.5 ± 12.3**
Body mass index	26.6 ± 3.9	27.1 ± 4.1	26.8 ± 4.9	27.0 ± 5.2
Femoral neck BMD	**0.749 ± 0.132**	**0.817 ± 0.126**	**0.652 ± 0.118**	**0.719 ± 0.124**
Lumbar spine BMD	**0.983 ± 0.162**	**1.054 ± 0.167**	**0.861 ± 0.168**	**0.951 ± 0.169**
SF-36 physical component	**45.8 ± 10.9**	**49.4 ± 9.4**	**43.6 ± 11.3**	**47.3 ± 10.2**
SF-36 mental component	54.8 ± 8.4	45.8 ± 10.9	53.4 ± 9.0	52.9 ± 9.0
Caucasian	**239 (96.8)**	**2358 (92.8)**	**907 (97.5)**	**5136 (95.4)**
High school diploma	166 (67.2)	1730 (68.1)	561 (60.3)	3318 (61.6)
Current smoker	50 (20.2)	465 (18.3)	122 (13.1)	798 (14.8)
Alcohol use (2+/day)	38 (15.4)	383 (15.1)	**54 (5.8)**	**215 (4.0)**
Sedentary time (16+ h/day)	84 (34.0)	847 (33.2)	**193 (20.8)**	**1319 (24.5)**
Prevalent fracture	**155 (62.8)**	**1243 (48.9)**	544 (58.5)	2051 (38.1)
Osteoporosis diagnosis[a]	**7 (2.9)**	**26 (1.0)**	**176 (19.4)**	**466 (8.8)**

[a] Self-reported physician-diagnosed osteoporosis (affirmative response).

Table 2

Estimated 10-year fracture risk[a] (excluding head, hands, ankles and feet) calculated using the Kaplan–Meier method (without competing mortality) and using competing mortality methods, competing mortality[a], and 10-year event-free survival[a] in the Canadian Multicentre Osteoporosis Study.

Sex	Baseline age group (years)	Fracture risk (Kaplan–Meier)	Fracture risk (with competing mortality)	Competing mortality	Event-free survival
Men	25–34	7.4 (4.2–12.8)	–	None	92.6 (87.2–95.8)
	35–44	8.1 (5.0–13.1)	8.1 (4.7–12.6)	0.5 (0.0–2.6)	91.4 (86.3–94.7)
	45–54	8.2 (6.1–11.0)	8.0 (5.9–10.6)	3.9 (2.5–5.9)	88.0 (84.9–90.5)
	55–64	7.8 (5.9–10.4)	7.6 (5.6–9.9)	9.3 (7.1–11.9)	83.1 (79.8–85.9)
	65–74	12.6 (10.2–15.5)	11.1 (9.0–13.6)	21.0 (18.0–24.1)	67.9 (64.3–71.2)
	75–84	23.1 (17.8–29.6)	16.7 (12.8–21.1)	43.4 (37.8–48.9)	39.9 (34.3–45.5)
Women	25–34	4.3 (2.1–8.8)	–	None	95.7 (91.2–97.9)
	35–44	6.7 (4.3–10.4)	6.7 (4.1–10.1)	0.8 (0.2–2.6)	92.6 (88.7–95.1)
	45–54	8.3 (6.8–10.2)	8.2 (6.6–10.0)	1.8 (1.8–2.8)	89.9 (87.9–91.6)
	55–64	13.9 (12.2–15.7)	13.5 (11.8–15.3)	4.8 (3.8–5.9)	81.7 (79.7–83.6)
	65–74	21.3 (19.5–23.3)	19.9 (18.1–21.7)	11.7 (10.3–13.2)	68.4 (66.3–70.5)
	75–84	31.8 (28.3–35.6)	27.2 (24.2–30.3)	25.9 (22.8–29.0)	46.9 (43.3–50.4)

[a]
10-year risks and event-free survival are expressed as percentage (95% CI).