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Residual Lifetime Risk of Fractures in Women and Men

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ABSTRACT: In a sample of 1358 women and 858 men, ≥60 yr of age who have been followed-up for up to 15 yr, it was estimated that the mortality-adjusted residual lifetime risk of fracture was 44% for women and 25% for men. Among those with BMD T-scores ≤ −2.5, the risks increased to 65% in women and 42% in men.

Introduction: Risk assessment of osteoporotic fracture is shifting from relative risk to an absolute risk approach. Whereas BMD is a primary predictor of fracture risk, there has been no estimate of mortality-adjusted lifetime risk of fracture by BMD level. The aim of the study was to estimate the residual lifetime risk of fracture (RLRF) in elderly men and women.
Materials and Methods: Data from 1358 women and 858 men ≥60 yr of age as of 1989 of white background from the Dubbo Osteoporosis Epidemiology Study were analyzed. The participants have been followed for up to 15 yr. During the follow-up period, incidence of low-trauma, nonpathological fractures, confirmed by X-ray and personal interview, were recorded. Incidence of mortality was also recorded. BMD at the femoral neck was measured by DXA (GE-LUNAR) at baseline. Residual lifetime risk of fracture from the age of 60 was estimated by the survival analysis taking into account the competing risk of death.
Results: After adjusting for competing risk of death, the RLRF for women and men from age 60 was 44% (95% CI, 40–48) and 25% (95% CI, 19–31), respectively. For individuals with osteoporosis (BMD T-scores ≤ −2.5), the mortality-adjusted lifetime risk of any fracture was 65% (95% CI, 58–73) for women and 42% (95% CI, 24–71) for men. For the entire cohort, the lifetime risk of hip fracture was 8.5% (95% CI, 6–11%) for women and 4% (95% CI, 1.3–5.4%) for men; risk of symptomatic vertebral fracture was 18% (95% CI, 15–21%) for women and 11% (95% CI, 7–14%) for men.
Conclusions: These estimates provide a means to communicate the absolute risk of fracture to an individual patient and can help promote the identification and targeting of high-risk individuals for intervention.
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Key words: fracture, osteoporosis, postmenopause, short-term risk, residual lifetime risk, BMD, aging

INTRODUCTION

Among the chronic disorders that affect the elderly population, osteoporotic fracture is emerging as a major public health threat, because it causes considerable morbidity and mortality and incurs significant health care costs to the community.[1,2] One of the pressing issues in the osteoporosis field at present is therefore to develop a population-level strategy for prevention of fracture that can be applied to the large number of "at-risk" individuals. During the past two to three decades, the assessment of fracture risk has largely relied on the concept of relative risk with little attention to the background event rates. Recent shifts in the paradigm of risk estimation have focused on the absolute risk rather than the relative risk.[3,4] Lifetime risk is defined as the cumulative risk of developing a disease during an individual's remaining lifespan.[5] Because lifetime risk estimate accounts for the competing risk of death, it can provide a direct means to communicate fracture risk to an individual and a measure of the burden of disease in a population.

Among the array of risk factors for osteoporotic fracture that has been identified,[6–11] two independent factors consistently stand out: advancing age and low BMD. Each SD decrease in BMD or each 5-yr increment in age is associated with an ~2-fold increase in the risk of fracture.[10,12] However, with advancing age, despite the increase in relative risk, the reduction in potential years of exposure leads to a reduction in absolute risk. Moreover, low BMD is associated with shorter life expectancy,[13] which also reduces potential life years of exposure. Hence, the absolute residual lifetime risk of fracture for any decrement in BMD or advance in age is not known. A number of studies have

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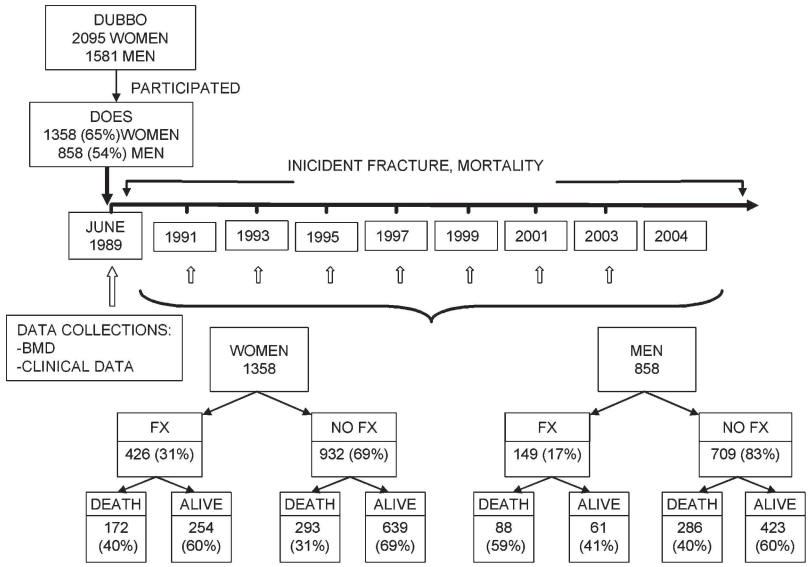

FIG. 1. The Dubbo Osteoporosis Epidemiology Study. DOES, the Dubbo Osteoporosis Epidemiology Study; FX, fracture.

attempted to estimate the lifetime risk of fracture in the past[14–18]; however, these studies did not follow individuals for a long time, did not measure BMD, or did not directly record the mortality data. Therefore, the adjustment for the competing risk of death in these studies was based on statistical modeling.[16–18]

This study was designed to address the above gaps in knowledge by estimating the remaining lifetime risk of fracture by age and BMD level for elderly men and women of white background. The ultimate aim was to provide estimates of absolute risk of fracture susceptibility that could be conveyed to, and more easily understood, by an individual patient.

MATERIALS AND METHODS

Setting and subjects

This study is part of an on-going longitudinal Dubbo Osteoporosis Epidemiology Study (DOES), for which details of protocol and study design have been previously described.[10,19–21] Briefly, in 1989, all men and women ≥60 yr of age (as of 1989) living in Dubbo, a city of ~32,000 people 400 km northwest of Sydney (Australia), were invited to participate in an epidemiological study. At that time, the population was made up of 1581 men and 2095 women ≥60 yr, of whom 98.6% were white and 1.4% were indigenous Aboriginal. These individuals were invited to participate in DOES. This study was approved by the St Vincent's Campus Research Ethics Committee, and informed written consent was obtained from each participant.

Dubbo had been selected for the study because the age and sex distribution of the population closely resembled the Australian population, and it is relatively isolated in terms of medical care; virtually complete ascertainment of all fractures in the target population is possible. A schematic summary of study design and follow-up is shown in Fig. 1. During the follow-up period, ~5% of women were on anti-osteoporosis treatment, with the majority (4.5%) being calcium and vitamin D.

Fracture ascertainment

Nontraumatic and nonpathological fractures were considered the primary outcome of this study. Fractures occurring during the study period were identified for residents of the Dubbo local government area through radiologists' reports from the two centers providing X-ray services as previously described.[10,19] Fractures were only included if the report of fracture was definite and, on interview, had occurred with minimal trauma (e.g., fall from standing height or less). Fractures clearly caused by major trauma (such as motor vehicle accidents), those caused by underlying diseases (such as cancer or bone-related diseases) or those of digit, skull, or cervical spine were excluded from the analysis.

Fractures were classified into six groups according to site as follows: any fracture; hip fracture; symptomatic vertebral fracture; forearm fracture, including Colles' Smith's, and meta-carpal fractures; shoulder fracture, including humerus, scapular, and clavicle; rib fracture(s); and "other fractures", including remaining osteoporotic fractures such as distal femur, proximal tibia, patella, pelvis, and sternum. Not all individuals who sustained a fracture had or agreed to have BMD measurements. The total number of individuals with fracture reported in this study accounted for 92% of all fractured subjects in the entire DOES population.

BMD measurements

BMD (g/cm^2) was measured at the lumbar spine or femoral neck (FN) by DXA initially using a LUNAR DPX densitometer and subsequently a GE LUNAR Prodigy (GE-LUNAR, Madison, WI, USA). The radiation dose with this method is <0.1 μGy. The coefficient of reliability of BMD in our institution in normal subjects is 0.96 and 0.98 at the proximal femur and lumbar spine, respectively.[22] Based on the actual values of FN BMD obtained, each subject was classified as "osteoporotic," with a BMD being 2.5 SD or more below the young normal level,; "osteopenic," with a BMD between 2.5 and 1.0 SD below the young normal

level, or "normal," being 1.0 SD below or above. The "young normal" BMD was obtained from the referent database for Australian women.[23] The young normal BMD was obtained from a sample of Australian men and women between 20 and 32 yr of age. These values are identical to those of LUNAR white databases.[24]

Statistical analysis

Statistically, residual lifetime risk is the cumulative absolute risk of fracture during an individual's remaining lifetime. The remaining lifetime can be based on the survivorship experienced by the participants in the study or the life expectancy of the general population. However, the life expectancy is dependent on a subject's sex and baseline age. For example, the life expectancy for 60-yr-old Australian women and men is 25 and 21 yr, respectively.[25] The risk can also be affected by the competing risk of mortality, which in turn reduces the actual cumulative risk of fracture. Therefore, in this analysis, both unadjusted and mortality-adjusted lifetime risk from the age of 60 were estimated.

The method of estimation was based on the modified technique of multiple decrement life table analysis.[5,26] In this method, the duration of follow-up was determined for each subject, from which a modified Kaplan-Meier curve was constructed using age as the time scale. Thus, the residual lifetime risk of fracture for a 60-yr-old woman is simply the cumulative incidence of fracture (denoted by I_{60}) over T years (i.e., $I_{60} = \sum_{t=60}^{T} h_t S_{t-1}$), where h_t is the conditional probability of sustaining a fracture at age t years given survival beyond age $t - 1$ years, S_{t-1} is the probability of survival beyond age $t - 1$ years free of fracture, and $h_t S_{t-1}$ is the unconditional probability of fracture at age t years. Two values of T (maximum life expectancy) were considered. Because the maximal survival age in the sample was 101, T was assigned to be 40; however, using the Australian population life expectancy, T was assigned to be 25.[25]

In the unadjusted analysis, participants who died without sustaining a fracture were treated as "censored observation." In the mortality-adjusted analysis, the residual lifetime risk was adjusted for competing risk of death using double decrement life table analyses.[26] In these analyses, nonfracture participants who died were treated as "escapees" (i.e., they could not sustain a fracture and do not contribute to the estimation of fracture incidence). All database management and statistical analyses were performed using the SAS Statistical Analysis System.[27]

RESULTS

In total, data from 1358 women and 858 men who had been followed from 1989 to the end of August 2004 were available for analysis. The response rate (relative to the target population) was 65% for women and 54% for men. The relative age and sex distributions of participants in this sample were not significantly different from that in the target population (data not shown).[20] The median duration of follow-up was 13 yr (interquartile range: 7–14 yr), yielding a total follow-up of 14,443 person-yr for women and 8695 person-yr for men. The average age at baseline was 71 ± 8 (SD) yr for women and 70 ± 6 yr for men. Basic clinical and anthropometric characteristics of study subjects are shown in Table 1. Approximately 13% of men and 27% of women were classified as having osteoporosis (FN BMD T-score ≤ –2.5) at baseline.

Table 1. Baseline Characteristics of Subjects as of 1989

Variable	*Women (n = 1358)*	*Men (n = 858)*
Age (years)	71 (8)	70 (6)
Age group (*n*; %)		
60–69	659 (51.0)	438 (48.5)
70–79	492 (36.2)	332 (38.7)
80+	207 (15.2)	88 (10.3)
Weight (kg)	65 (13)	78 (13)
BMI (kg/m^2)	26 (4)	26 (5)
BMI category (*n*; %)		
Normal	598 (46.0)	291 (34.5)
Overweight	490 (37.7)	413 (49.2)
Obese	211 (16.2)	135 (16.1)
Femoral neck BMD (g/cm^2)	0.78 (0.13)	0.90 (0.15)
BMD category (*n*; %)		
Osteoporosis	368 (28.6)	103 (12.6)
Osteopenia	630 (49.0)	332 (40.4)
Normal	289 (22.5)	386 (47.0)
Prior fracture* (*n*;%)	158 (11.6)	75 (8.7)
Ever smokers (*n*; %)	395 (29.1)	530 (61.7)

Values are mean (SD), unless otherwise specified.
*Prior fracture, any fracture within 5 yr before entry to study.

Incidence of fracture and mortality

During the follow-up period, 426 women and 149 men sustained at least one fracture, making the overall incidence of 35 per 1000 person-yr in women and 18 per 1000 person-yr in men. In both sexes, the most common sites of fracture were symptomatic vertebral (28% in women and 34% in men), hip (17% for both sexes), forearm (2% in women and 4% in men), and rib (5% in women and 23% in men; Table 2).

In the entire sample, among fractured cases, 43.3%, 46.5%, and 10.2% of women were classified as osteoporotic, osteopenic, and normal BMD, respectively. The corresponding proportions in men were 12.6%, 40.4%, and 47.0%.

During the same period, there were 839 deaths (465 women and 374 men), among whom 579 (293 women and 286 men) died without having sustained any fracture. Women and men with fracture had significantly higher risk of death than those without a fracture, and the effect was more pronounced in men than in women (hazard ratio [HR]: 1.4; 95% CI: 1.1–1.7 for women and HR: 1.8; 95% CI: 1.4–2.3 for men; Fig. 2).

Residual lifetime risk of fractures

The maximal survival age among the study's participants was 101 yr. Using this survival age, the unadjusted residual lifetime risk of fracture for individuals 60 yr of age was estimated as 84.8% (95% CI: 74.5–95.1) for women and

TABLE 2. INCIDENCE OF FRACTURES AND MORTALITY AMONG PARTICIPANTS DURING THE FOLLOW-UP PERIOD

Variable	*Women (n = 1358)*	*Men (n = 858)*
Any fracture	426	149
Total number of fractures	572	180
Hip	96 (16.8)	31 (17.2)
Clinical vertebral	159 (27.8)	61 (33.9)
Forearm	112 (19.7)	8 (4.4)
Shoulder	60 (10.5)	15 (8.3)
Rib	27 (4.7)	41 (22.8)
Others	118 (20.6)	24 (13.3)
Number of deaths	465	374
After a fracture	172 (37.0)	88 (23.5)
Without a fracture	293 (63.0)	286 (76.5)

Values are number and percentage per category by sex.

Any fracture included any first low-traumatic fractures excluded skull and digits; forearm fractures included Colles', Smiths', and meta-carpal; shoulder fractures included humerus, scapula, and clavicle; other fractures included remaining osteoporotic fractures such as distal femur, patella, pelvis, sternum.

The total number of fractures at different sites for each sex do not add up to total subjects sustained fracture (any fracture) because of multiple fractures.

50.4% (95% CI, 42.1–58.8) for men. After adjusting for competing risk of death, the lifetime risk reduced to 57.6% (95% CI: 47.3–61.8) and 32.5% (95% CI: 24.1–38.4) for women and men, respectively (Fig. 3).

However, according to the current estimate, the life expectancy for individuals 60 yr of age is 21 for men and 25 for women.[25] Therefore, if the life expectancy of both sexes is taken as 85 yr, the mortality-adjusted RLRF for men and women is 25% (95% CI: 19–31) and 44% (95% CI: 40–48), respectively (Table 3). The mortality-adjusted lifetime risk of hip fracture for women was 9% (95% CI: 6–11), which was higher than that in men of 4% (95% CI: 1.3–5). Similarly, lifetime risk of clinical vertebral fractures was also higher in women (18%; 95% CI, 15–21) than in men (11.0%; 95% CI, 7–14). The sex difference in the lifetime risk of wrist/forearm fractures was much more pronounced: 15% (95% CI: 11–18) in women and 1.7% (95% CI: 0.2–3) in men.

Analysis by age: Analysis of residual lifetime risk of fracture by duration, age and fracture site is shown in Table 4 and Fig. 4. In both sexes, the cumulative risk of fracture seemed to increase with advancing age, even in the very old age groups. For example, the 5-yr risk of fracture for an 80-yr-old woman was 17%, which was higher than the 5-yr risk for a 70-yr-old woman (~11%). For 70-yr-old men and women, the mortality-adjusted RLRF in the next 15 yr (which is approximately equivalent to the life expectancy for 70-yr-old Australian men and women) was estimated to be 18% and 35%, respectively. Given that an 80-yr-old man or woman is expected to live for 10 yr (which is approximately the average life expectancy in Australians), the risk of fracture for the man and woman during that period was ~20% and 32%, respectively.

Although the residual lifetime risk of fracture in women was higher than in men, for a given age, the short-term (5-yr) risk in men was not much different from that in women. For example, Fig. 4 shows that the mortality-adjusted cumulative 5-yr risk of fracture in 60-yr-old men was 6.4%, which was virtually equivalent to the risk in women with the same age (7.1%).

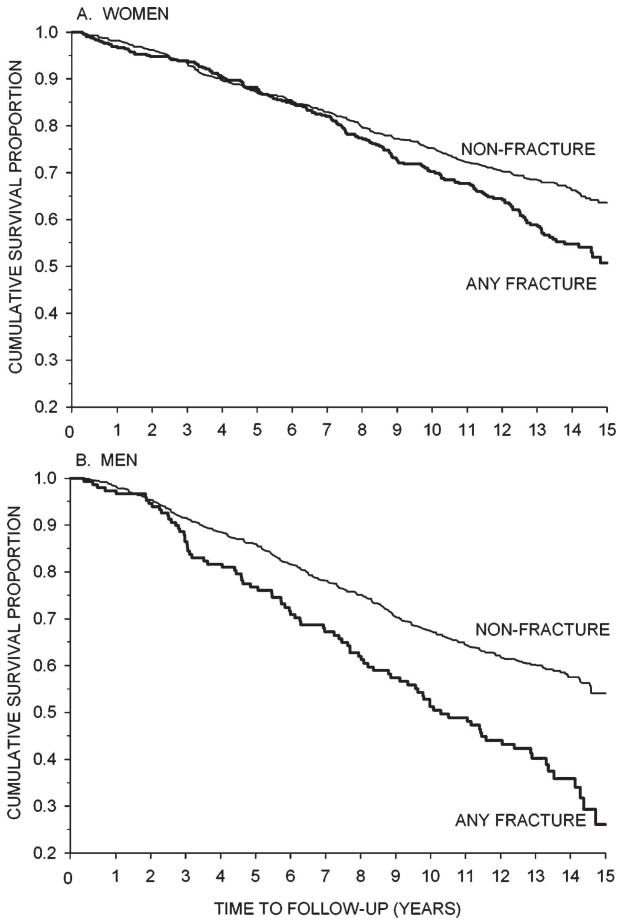

FIG. 2. Survival curve of alive proportion during the follow-up period.

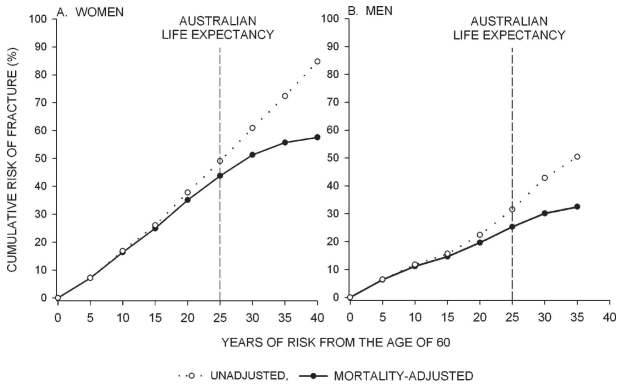

FIG. 3. Unadjusted (broken line) and mortality-adjusted (solid line) residual lifetime risk of fracture from the age of 60 for women (left) and men (right). Using maximal survival age of 101, the mortality-adjusted cumulative risk of fracture was 58% for women and 33% for men. However, using the general population life expectancy (85 yr, represented by the vertical line), the risk was 44% for women and 25% for men.

TABLE 3. UNADJUSTED AND MORTALITY-ADJUSTED RESIDUAL LIFETIME RISK OF FRACTURES FROM THE AGE OF 60 CLASSIFIED BY FRACTURE TYPE AND SEX

	Women		*Men*	
Fracture type	*Unadjusted RLRF*	*Mortality-adjusted RLRF*	*Unadjusted RLRF*	*Mortality-adjusted RLRF*
Any fracture	49.0 (45.0, 53.1)	43.8 (39.7, 47.8)	31.6 (25.7, 37.4)	25.3 (19.4, 30.9)
Hip	10.3 (7.8, 12.9)	8.5 (6.0, 10.6)	5.4 (3.0, 7.9)	3.7 (1.3, 5.4)
Clinical vertebrae	23.5 (19.8, 27.1)	18.4 (14.8, 21.3)	15.4 (11.3, 19.4)	10.9 (6.8, 13.9)
Wrist/forearm	16.4 (12.8, 20.1)	14.5 (10.8, 18.1)	2.0 (0.5, 3.4)	1.7 (0.2, 2.9)
Shoulder	8.6 (5.6, 11.7)	7.5 (4.4, 10.4)	5.3 (0.3, 10.4)	4.5 (0, 9.5)
Rib(s)	3.3 (1.8, 4.8)	2.6 (1.2, 3.8)	12.6 (8.3, 16.8)	9.1 (4.8, 12.3)
Other fractures	18.7 (15.4, 22.1)	15.8 (12.4, 18.7)	6.5 (3.6, 9.5)	4.9 (2.0, 7.3)

Values are percent (95% CI). These estimates were cumulative risk of fracture based on the life expectancy of both sexes as 85 yr.[25]

Any fracture included any first minimal traumatic fractures excluded skull and digits; forearm fractures included Colles', Smiths', and meta-carpal; shoulder fractures included humerus, scapula, and clavicle; other fractures included remaining osteoporotic fractures such as distal femur, patella, pelvis, sternum.

TABLE 4. MORTALITY-ADJUSTED RESIDUAL LIFETIME RISK ACCORDING TO AGE FREE OF FRACTURE

		Baseline age (yr) for women			*Baseline age (yr) for men*		
Fracture type	*Time (yr)*	*60+*	*70+*	*80+*	*60+*	*70+*	*80+*
Any fracture	5	7.1	10.9	17.1	6.4	4.3	10.6
	10	16.4	23.9	32.0	11.2	10.7	19.8
	15	24.9	34.9	NA	14.6	17.9	NA
	20	35.2	NA	NA	19.7	NA	NA
	25	43.8	NA	NA	25.3	NA	NA
Hip fracture	5	0.4	1.2	5.0	0.0	0.5	2.7
	10	1.5	3.5	0.7	0.8	1.4	4.8
	15	2.7	7.5	NA	1.3	3.3	NA
	20	4.8	NA	NA	2.0	NA	NA
	25	8.5	NA	NA	3.7	NA	NA
Clinical vertebral	5	1.0	3.2	6.1	1.2	2.1	5.1
	10	3.7	8.3	15.0	3.0	5.6	7.6
	15	7.7	13.0	NA	5.0	9.2	NA
	20	12.3	NA	NA	8.8	NA	NA
	25	18.4	NA	NA	10.9	NA	NA
Wrist and forearm	5	4.6	2.5	4.0	0.5	0.6	0.3
	10	6.6	6.1	9.2	0.7	0.9	0.3
	15	9.4	9.0	NA	1.2	1.1	NA
	20	12.2	NA	NA	1.7	NA	NA
	25	14.5	NA	NA	1.7	NA	NA

Values are percents.

Any fracture included any first minimal traumatic fractures excluded skull and digits; forearm fractures included Colles', Smiths', and meta-carpal.

NA, not applicable.

Analysis according to BMD category: BMD was classified into three groups, osteoporosis, osteopenia, and normal, according to the World Health Organization criteria.[28] For a given age and sex, the mortality-adjusted lifetime risk of fracture was, as expected, highest among those with osteoporosis, followed by osteopenic and normal BMD (Table 5). The mortality-adjusted RLRF for those with osteoporosis was 41.9% (95% CI: 23.6–71.2) in men and 64.6% (95% CI: 57.6–73.3) in women, which represented an increase of 70% and 48% compared with the average lifetime risk for men and women, respectively. It is, however, interesting to observe that the 10-yr risk of fracture for those 60 yr of age was almost identical between men and women (~1 of 3). The lifetime risk of fracture among those with osteopenia was almost comparable with the average lifetime risk for the entire sample. Based on the mortality-adjusted lifetime risk given in Table 5 and number of subjects in each BMD category, the predicted number of fractures was estimated and shown in Table 6.

DISCUSSION

Fracture caused by osteoporosis is increasingly becoming a global public health problem.[28] In the United States alone, each year, there are 1.5 million fractures, including 300,000 hip fractures and 300,000 clinical vertebral fractures, which cost approximately $14 billion in 1997.[29,30] To contain and manage the increase of osteoporotic fractures and their associated health care costs, the community at large and individual patients have to make decisions about intervention. To make informed chooses, decision-makers must know something about the fracture risk and relevant outcomes. This study, to our knowledge, is the first to provide comprehensive absolute lifetime risks of fracture by index age and BMD level. It is estimated that the death-adjusted lifetime risk of any fracture at age 60 was 44% for women and 25% for men.

Although the lifetime risk of any fracture estimated in this study was somewhat higher than previous indirect estimates (47% in women and 22% in men), this study's estimated risk of hip and Colles' fractures is comparable with

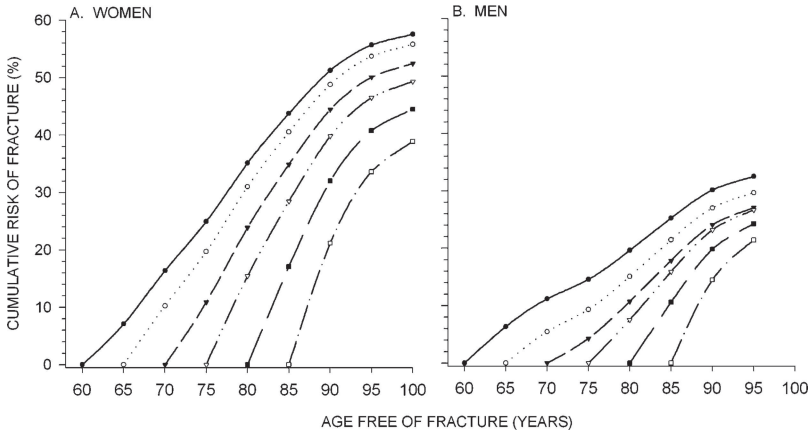

FIG. 4. Mortality-adjusted residual lifetime risk of fracture by baseline age for women (left) and men (right). Individual curves are shown for baseline age 60–85 by 5-yr interval. In each age group, cumulative risks of up to 100 yr old are shown.

TABLE 5. MORTALITY-ADJUSTED RESIDUAL LIFETIME RISK OF ANY FRACTURE ACCORDING TO BASELINE BMD AND AGE FREE OF FRACTURE

BMD category	Time (yr)	Baseline age (yr) for women			Baseline age (yr) for men		
		60+	70+	80+	60+	70+	80+
Osteoporosis	5	11.9	24.3	26.2	12.5	15.5	7.6
	10	33.9	40.1	42.3	30.0	28.9	24.2
	15	48.2	51.9	NA	35.7	32.2	NA
	20	57.6	NA	NA	40.7	NA	NA
	25	64.6	NA	NA	41.9	NA	NA
Osteopenia	5	13.1	8.7	14.0	5.4	3.8	15.2
	10	20.4	20.3	25.6	9.3	9.7	21.9
	15	27.9	30.2	NA	12.2	20.0	NA
	20	36.7	NA	NA	19.2	NA	NA
	25	44.2	NA	NA	26.4	NA	NA
Normal	5	1.0	5.9	2.4	8.5	2.5	5.7
	10	3.6	13.2	13.0	9.7	7.6	15.1
	15	10.0	14.9	NA	12.3	11.7	NA
	20	15.6	NA	NA	16.9	NA	NA
	25	19.0	NA	NA	19.5	NA	NA

Values are percents.

Any fracture included any first minimal traumatic fractures excluded skull and digits.

Osteoporosis, BMD T-scores ≤ –2.5; osteopenia, –1.0 < BMD T-scores < –2.5; and normal, BMD T-scores ≥ –1.0.

NA, not applicable.

TABLE 6. PREDICTED NUMBER OF FRACTURES (MORTALITY-ADJUSTED) ACCORDING TO BASELINE BMD AND AGE FREE OF FRACTURE

BMD category	Time (yr)	Baseline age (yr) for women			Baseline age (yr) for men		
		60+	70+	80+	60+	70+	80+
Osteoporosis		(368)	(271)	(113)	(103)	(67)	(19)
	5	44	66	30	13	10	1
	10	125	109	48	31	19	5
	15	177	141	NA	37		NA
	20	212	NA	NA	42	NA	NA
	25	238	NA	NA	43	NA	NA
Osteopenia		(630)	(282)	(53)	(332)	(172)	(31)
	5	83	25	7	18	7	5
	10	129	57	14	31	17	7
	15	176	85	NA	41	34	NA
	20	231	NA	NA	64	NA	NA
	25	278	NA	NA	88	NA	NA
Normal		(289)	(82)	(10)	(386)	(152)	(23)
	5	3	5	0	33	4	1
	10	10	11	1	37	12	3
	15	29	12	NA	47	18	NA
	20	45	NA	NA	65	NA	NA
	25	55	NA	NA	75	NA	NA

Any fracture included any first minimal traumatic fractures excluded skull and digits.

Values in parentheses are number of subjects in each BMD category.

Osteoporosis, BMD T-scores ≤ –2.5; osteopenia, –1.0 < BMD T-scores < –2.5; and normal, BMD T-scores ≥ –1.0.

NA, not applicable.

earlier indirect estimates.[31] For hip fracture, this study estimates the residual lifetime risk at 9% in women and 4% in men, which are in the lower range of previous estimates (between 13% and 23% in women and 5% and 11% in men).[17,32] The discrepancy in estimates is likely caused by different methods of computation and study design. All previous studies have been based on indirect estimation by combining data from cross-sectional studies and population-based census.[18,33–35] The problem with this approach is that it could not directly incorporate the mortality into the model of estimation. This study minimized this technical problem because it is based on long-term follow-up with complete data on fracture and mortality, which allows the estimation of unadjusted and death-adjusted lifetime risks more reliable and accurate. Lifetime risk is generally overestimated if the prevalence of disease in the population is >10%, and competing risks of death are high.[5,26,36]

One way to appreciate the magnitude of fracture risk in the general population is to consider these estimates within the context of other chronic diseases. In men, the ~1 in 3 lifetime risk of sustaining an osteoporotic fracture was lower than the 1 in 2 lifetime risk of getting CHD[37] or 45% chance of being diagnosed with some type of cancer[38] but comparable with lifetime risk of developing diabetes mellitus.[39] However, in women, the 3 in 5 risk of sustaining a fracture was higher than the 1 in 3 risk of getting CHD[37] or 39% chance of being diagnosed with

some type of cancer.[38] In women, this study also suggests that the lifetime risk of hip fracture at the age of 60 (1 in 7, or 15%) is higher than the lifetime risk of breast cancer, which has recently been estimated at 9.3%.[40] In men, the lifetime risk of hip and vertebral fractures (15%) is comparable with the lifetime risk of being diagnosed with prostate cancer.[38] These comparisons re-emphasize that osteoporotic fracture is a public health burden and that, with the aging of the population, the societal burden is likely going to increase further unless the lifetime risk is affected by public health interventions.

Screening for osteoporosis is currently not recommended, and in this situation, appropriate selection of patients for primary intervention or prevention is considered an optimal strategy in clinical and public health practice. At present, effective antiresorptive therapies (e.g., bisphosphonates) are available for the prevention and treatment of osteoporosis. The efficacy of these therapies have been shown in women with low BMD (T-scores ≤ -2.5), but their effectiveness in the general population has not been evaluated. These results can serve as a metric for translating the impact of such therapy in the general population. For example, these data indicate that more than one half of the remaining lifetime risk of fracture for ≥60-yr-old individuals is experienced over the initial 10 yr of follow-up. Thus, among 60-yr-old women with low BMD, the 10-yr risk of fracture was ~30%; if a treatment approximately halves the risk as has been shown in most clinical trials,[41] the risk would be reduced to 15%. In other words, treating 100 such women for 10 yr will cut the number of fracture events from 30 to 15, suggesting an number needed to treat (NNT) of 6.5 over 10 yr.

Communication of risk in the osteoporosis field has traditionally relied on the concept of relative risk. However, relative risk can be misleading to patients and clinicians,[42] because the interpretation of a relative risk or its change is highly dependent on the baseline risk. For instance, doubling a minor risk is still minor, but doubling a common risk is alarming. It is therefore desirable that individuals who have BMD measurements be informed about their fracture probability risk category instead of their relative scores.[4] The lifetime risk estimates from this study provide such a means for communication of risk to an individual patient.

The data presented here raise the issue of threshold for intervention. It seems clear that the threshold for intervention should be based on absolute risk including the impact of age. Thus, if a 10-yr risk of 20% or above is considered to be cost-effective for treatment, 60- or 70-yr-old women with BMD T-scores < -2 would qualify as candidates for treatment. Any "blanket" criterion for screening is questionable, and these results open a window of opportunity to enroll patients based on their 10-yr or lifetime risk, rather than on BMD T-scores alone, into clinical trials.

There are some potential limitations of this study. First, the study population is of white background; therefore, extrapolation to other populations is not possible. Second, despite the large sample size and long-term follow-up, the number of fracture events in those with high BMD was relatively small, making the estimates of lifetime risk in this subgroup unstable, which is shown by the wide CIs. Third, selection bias was also present in this study, in that participants were healthier than nonparticipants.[1] Finally, cause of death was not available for all individuals, who may have died soon after a fracture, which could have lead to the lifetime risk being underestimated. These estimates of lifetime risk by BMD level assumed that BMD did not change with time, which is of course not true; therefore, the observed estimates could be underestimates. At present, there is no statistical method to handle such a problem.[26]

In the time of evidence-based medicine, patients are encouraged to participate in the clinical decision. This approach requires that physicians be facile in communicating the risks and benefits to patients. In either case, patients and physicians need reliable data on risks and benefits to reach an informed decision. This study provides some supporting data for physicians and patients to foster such efforts. The lifetime risks presented could be used to promote identification of high-risk individuals and target for intervention in the population.

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