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Original Article

Risk of Mortality Following Clinical Fractures

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Abstract. To examine the risk of mortality following all clinical fractures, we followed 6459 women age 55–81 years participating in the Fracture Intervention Trial for an average of 3.8 years. All fractures and deaths were confirmed by medical record or death certificate. Clinical fractures were fractures that came to medical attention. Fracture status was used as a time-dependent covariate in proportional hazards models. The 907 women who experienced a fracture were older, had lower bone mineral density and were more likely to report a positive fracture history. A total of 122 women died over the course of the study with 23 of these deaths occurring after a clinical fracture. The age-adjusted relative risk (95% confidence intervals) of dying following a clinical fracture was 2.15 (1.36, 3.42). This primarily reflected the higher mortality following a hip fracture, 6.68 (3.08, 14.52); and clinical vertebral fracture, 8.64 (4.45, 16.74). Results were similar after adjusting for treatment assignment, health status and specific common comorbidities. There was no increase in mortality following a forearm or other fracture (non-hip, non-wrist, non-vertebral fracture). In conclusion, clinical vertebral fractures and hip fractures are associated with a substantial increase in mortality among a group of relatively healthy older women.

Keywords: Fractures; Mortality; Osteoporosis; Public health impact

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Introduction

Excess mortality after a hip fracture ranges from 6% to 37%, with most excess deaths occurring within the first 6 months of the fracture [1–12]. This wide range of excess mortality reflects differences in the characteristics of the subjects: older individuals [8], those living in institutions [4], and those with more comorbidities at the time of their fracture [6] are more likely to die. Many of these studies have examined the mortality rates in hip fracture patients in excess of the *expected* mortality rates for their particular age–gender–race group. However, hip fractures tend to occur in individuals who differ from the general population with respect to their age, and general health status and comparisons with *expected* mortality may be inappropriate.

There have been few studies of mortality following other types of fractures. Most fractures occur because of low bone mass [13] and lower bone mass is associated with an increase in non-trauma mortality [14]. Therefore, it is possible that other types of osteoporotic fractures increase the risk of mortality. In the Study of Osteoporotic Fractures (SOF), hip, pelvis, humerus and rib fractures were all associated with an increase in mortality whereas wrist, foot or ankle fractures were not [9,14]. Similar results were reported from the Dubbo Osteoporosis Study [2]. An excess of mortality among women with clinical vertebral fractures [2,12] and morphometric vertebral fractures [2,15–17], which do not routinely come to medical attention, have been reported. There was no excess mortality following a wrist fracture in several studies [1,2,9,12].

In the current study, we extend previous analyses of mortality following morphometric vertebral fractures [16] and examine the risk of mortality following clinical

fractures (fractures that come to medical attention) in women enrolled in the Fracture Intervention Trial (FIT), a randomized clinical trial designed to determine the effect of alendronate on fracture risk [18]. The question of interest in this paper is to determine whether the risk of mortality is increased following specific types of clinical fractures in women age 55–81 years with low bone mineral density. A unique feature of the current analyses is the careful documentation of clinical spine fractures and their associated mortality risk.

Subjects and Methods

The study population consisted of 6459 women enrolled in the FIT. To be eligible to participate in the FIT, women had to be between the ages of 55 and 81 years at baseline, postmenopausal for at least 2 years and have a femoral neck bone mineral density (BMD) of 0.68 g/cm^2 or less using a Hologic model QDR 2000 densitometer (Hologic, Waltham, MA), which corresponds to 1.6 standard deviations below the young normal mean for US women. Women were recruited at 11 clinical centers across the United States. Details of recruitment methods and inclusion criteria have been published previously [18,19]. Women were randomized to receive either alendronate or placebo and followed for the occurrence of fracture over 3 or 4 years: women with vertebral fractures (n = 2027) at baseline were followed for an average of 2.9 years and those without baseline vertebral fractures (n = 4332) were followed for an average of 4.2 years. For these analyses, the two groups of women were combined with an average follow-up of 3.8 years.

Fracture Documentation

Participants were contacted every 3 months and specifically questioned about the occurrence of a fracture. Participants were also instructed to notify the clinic if they sustained a fracture. All fractures were confirmed by a written report of a radiological procedure (radiograph, bone scan). Information was collected about the circumstances surrounding each fracture, including the degree of trauma. As predefined, we excluded pathologic fractures (e.g., those due to malignant disease), those due to excessive trauma (e.g., motor vehicle accident) and those involving the face and skull, because of the lack of association with osteoporosis [13].

Clinical vertebral fractures were defined as those that came to medical attention and were reported to the clinical centers by the participants. A copy of the radiograph obtained by the participant's physician was sent to the study radiologist for a semiquantitative reading, comparing it with the baseline radiograph [18]. Clinical fractures were grouped into six categories: all symptomatic fractures, non-spine symptomatic fractures, hip fractures, wrist fractures, spine fractures, and other fractures (other than a spine, wrist or hip fracture). Women were classified according to whether they had any fracture within each category. Since women could have more than one fracture, and because categories overlapped , women could be included in more than one category.

Ascertainment of Deaths

Participants were contacted every 3 months. All deaths were confirmed by death certificate. Follow-up was 100% complete.

Other Information

Information on reproductive history, use of cigarettes, medical and fracture history, physical activity and self-reported health status was collected by a questionnaire which was reviewed with participants by a trained interviewer. Weight was measured without shoes or heavy outer clothing using a balance-beam scale. Hip and lumbar spine BMD was measured at baseline and annually thereafter using dual-energy X-ray absorptiometry (DXA) [18].

Statistical Analysis

All follow-up time for each woman enrolled in the trial was included in the analysis. Each woman contributed time at risk from the date of randomization to the earliest of (a) the date of death or (b) the date of last follow-up. Person-years at risk for the fracture-free period were computed from women without a clinical fracture and from women with a clinical fracture in the period prior to a clinical fracture. Person-years at risk for the post-fracture period was computed from women with a fracture.

Crude mortality rates were calculated by dividing the number of deaths by the total number of person-years in the fracture-free and post-fracture period. Relative risks estimates (95% confidence intervals) were obtained from the time-dependent proportional hazards model and compare the mortality rate in the post-fracture period with the mortality rate in the pre-fracture period. Clinical fracture status was the time-dependent covariate. Models were run separately for each type of fracture. The number of deaths and the total number of person-years varies across each fracture site since the time to fracture differs for each specific fracture. This results in some small variability in the pre-fracture mortality rates. All analyses were done using the PHREG procedure in SAS. We controlled for attained age, treatment assignment and baseline vertebral fracture status (yes vs no) in all analyses. We also adjusted for other factors which are known to influence mortality including self-reported health status, smoking status, total hip BMD, physical activity, and history of diabetes, hypertension or coronary heart disease. However, because of the small number of deaths after a fracture, these variables were added one at a time to determine their effect on our results. Finally, we

examined the relative risk of dying after a fracture separately in women who had a prevalent vertebral fracture at entry into the study and women who did not.

Results

A total of 907 women experienced at least one symptomatic fracture over the course of the study. Women who fractured tended to be older, had lower BMD, and were more likely to report a positive history of fracture than women who did not experience a fracture (Table 1). There was no difference in body weight, smoking, prior estrogen use or health status between women who fractured and women who did not fracture.

A total of 122 women died over the course of the study including 99 deaths in the fracture-free period and 23 deaths after the fracture. The overall rate of mortality in the FIT study was 4.95 per 1000 person-years (PY). The primary causes of death among 23 the women who died after the fracture were cardiovascular diseases ($n = 11$), cancer ($n = 6$), pulmonary disease ($n = 3$) and other ($n = 3$).

The crude mortality rate in the fracture-free period was 4.3 per 1000 PY and 12.8 per 1000 PY after the fracture (Table 2). Mortality after a hip and spine fracture was elevated. The mortality rate following a hip fracture was 50 per 1000 PY after the fracture, compared with 4.7 per 1000 PY in the fracture-free period. Similarly, the mortality following a spine fracture was 67.5 per 1000 PY, compared with 4.5 per 1000 PY in the fracture-free period. The rate of dying after other types of fractures was slightly higher than the pre-fracture mortality rate but the magnitude of the difference in mortality rates before and after the fracture was much smaller.

The relative risk of dying following a clinical fracture

Table 1. Baseline characteristics of women with and without clinical fractures during the follow-up period

Baseline variable	New clinical fracture status during the study		
	No new fractures ($n = 5552$)	New fractures ($n = 907$)	p value
Age (years)	68.6 (6.1)[a]	69.5 (6.3)	<0.001
Years since menopause	22.1 (8.5)	23.5 (8.4)	<0.001
Weight (kg)	64.5 (11.0)	64.8 (10.8)	0.480
Spine BMD (g/cm^2)	0.83 (0.14)	0.80 (0.12)	<0.001
Hip BMD (g/cm^2)	0.70 (0.09)	0.67 (0.09)	<0.001
Alcohol (drinks/past month)	4.2 (1.9)	4.1 (2.0)	<0.001
Current smokers (%)	10.6%	11.6%	0.38
Fair/poor health status (%)	5.2%	5.4%	0.75
History of prior fracture (%)	40.6%	51.7%	<0.001
Any cardiovascular disorder (%)	41.3%	43.7%	0.181
Diabetes (%)	1.9%	2.2%	0.576
Past estrogen use (%)	2.3%	1.8%	0.352
Regular exercise program (%)	46.8%	47.2%	0.825
Alendronate treatment (%)	50.9%	45.5%	0.003
Prevalent vertebral fracture (%)	30.7%	35.6%	0.003

Mean (SD).

Table 2. Crude mortality rates during the fracture free and post fracture periods

Fracture site (no. of fractures)	Fracture-free period			Post-facture period		
	No. of Deaths	PY	Crude rate[a]	No. of deaths	PY	Crude rate[a]
Symptomatic (907)	99	22 866	4.33	23	1796	12.81
Non-spine (825)	106	22 984	4.61	16	1677	9.54
Hip (76)	115	24 522	4.69	7	139	50.26
Spine (119)	111	24 498	4.53	11	163	67.53
Forearm (216)	119	24 210	4.92	3	451	6.65
Other[b] (608)	113	23 460	4.82	9	1201	7.50

PY, person years.
[a] Crude rate per 1000 person-years (PY).
[b] Other than hip, spine, forearm.

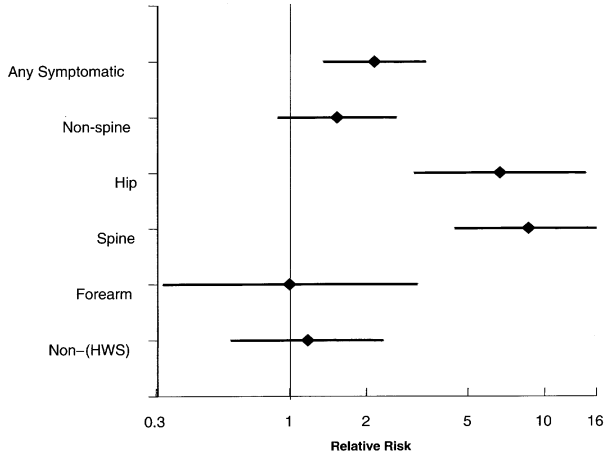

Fig. 1. Age-adjusted relative risk (95% confidence interval) of mortality following any clinical fracture and following specific types of clinical fractures. (HWS), hip, wrist or spine.

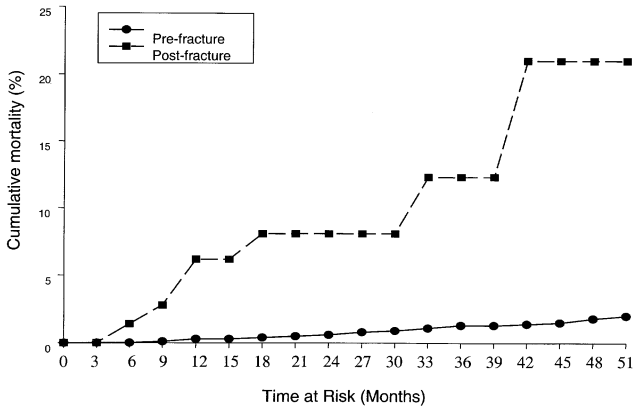

Fig. 2. Cumulative mortality in the pre-fracture and post-fracture period.

was elevated more than 2-fold (Fig. 1). This primarily reflected the higher mortality following a hip and spine fracture. The relative risk of dying following a hip fracture was almost 6-fold greater, and almost 9-fold greater following a spine fracture. There was no significant increase in mortality following any non-spine fracture, forearm fracture or other fractures, i.e., non-hip, wrist or spine fractures. Adjustment for other factors including hypertension, smoking, physical activity, health status, coronary heart disease and history of diabetes, and total-hip BMD had little effect on our estimates of the relative risk for mortality following hip and spine fractures (Table 3). The risk of mortality following a hip fracture was greater among women who had a prevalent vertebral fracture at entry into the study, compared with those who did not have a vertebral fracture (Table 4). In contrast, the risk of dying following a clinical spine fracture was greatest among women without a prevalent vertebral fracture at study entry, although the confidence intervals were wide.

The cumulative mortality among women who experienced any clinical fracture is shown in Fig. 2. A total of

Table 3. Relative risks of mortality following a fracture when adjusted for age, treatment assignment and study group and several individual risk factors

Adjusted for age, study group, treatment assignment	Relative risk (95% confidence interval)		
	Any clinical	Hip	Spine
	2.15 (1.35, 3.42)	6.68 (3.08, 14.52)	8.64 (4.45, 16.74)
In addition, adjusted individually for each of the factors below:			
Hypertension	2.16 (1.36, 3.43)	6.68 (3.08, 14.52)	8.62 (4.44, 16.72)
Smoking	2.11 (1.33, 3.36)	6.15 (2.83, 13.36)	7.79 (4.02, 15.08)
Physical activity	2.17 (1.36, 3.44)	6.66 (3.07, 14.46)	8.52 (4.39, 16.52)
Health status	2.17 (1.36, 3.45)	6.37 (2.93, 13.87)	8.21 (4.23, 15.93)
Cardiovascular disease	2.14 (1.35, 3.40)	6.56 (3.02, 14.24)	8.45 (4.36, 16.39)
Diabetes	2.14 (1.35, 3.41)	6.76 (3.11, 14.69)	8.60 (4.44, 16.66)
Hip BMD	2.08 (1.31, 3.32)	6.10 (2.78, 13.41)	8.16 (4.19, 15.88)

Table 4. Relative risks of mortality following a fracture when adjusted for age, treatment assignment and prevalent vertebral fracture status at baseline

Adjusted for age and treatment assignment	Relative risk (95% confidence interval)		
	Any clinical	Hip	Spine
With prevalent vertebral fracture	3.94 (2.09, 7.41)	11.37 (4.45, 29.03)	7.15 (3.07, 16.63)
Without prevalent vertebral fracture	1.26 (0.60, 2.64)	4.64 (1.14, 18.94)	11.88 (4.25, 33.21)

12 of the 23 deaths following any clinical fracture occurred within 1 year of the fracture. The remaining deaths were scattered over the remainder of the follow-up period. Four of the 7 hip fracture deaths occurred within 1 year of the fracture and all 11 deaths following a clinical vertebral fracture occurred within 1 year of the fracture event.

Discussion

Women who experienced a clinical vertebral fracture or a hip fracture had a substantial increased risk of mortality: specifically a 6- to 9-fold increased risk was observed. Our study was unique in its focus on mortality among a group of relatively healthy older women. Most previous studies of mortality after a hip fracture have included a majority of women over the age of 80 years. A finding of importance is the increase in mortality after a hip and spine fracture even among women $\leqslant$ age 80 years at entry to the study. There was no excess mortality following a forearm or other, non-hip, non-spine, non-wrist fracture, consistent with previous reports [1,2]. In the Study of Osteoporotic Fractures, women who experienced a rib or humerus fracture experienced an increased mortality but we had too few of these fractures to analyze separately.

Although based on a relatively small number of deaths, the results of our study are consistent with previously published studies of excess mortality following a hip fracture [1–12]. About half the deaths following a hip fracture occurred within 1 year of the fracture. It is of note, however, that the excess risk of mortality persisted for several years after the hip fracture, consistent with the findings of other studies which had longer follow-up periods [1–3,12]. There may be two groups of hip fracture patients. One group consists of subjects who have a number of comorbid conditions and older age and die within the first year of the fracture. In a second group of healthier subjects, the hip fracture may either signal or actually induce a progressive decline in health, possibly leading to excess mortality that persists for several years after the fracture [20]. This progressive decline in health could result from a lack of mobility, loss in strength and lean mass leading to an increase in disability and its associated health consequences.

The observed excess mortality among women who experience a clinical vertebral fracture widens the public health impact of these fractures. Three other studies have reported an increase in mortality among individuals with prevalent morphometric vertebral fractures. In the Study of Osteoporotic Fractures, women who had at least one prevalent vertebral fracture had a 23% greater age-adjusted mortality rate compared with age-matched controls [15]. Similarly, among FIT women [16] and women in the European Prospective Osteoporosis Study [17], the relative risk of dying was about 60% higher among those with a prevalent vertebral fracture versus those without. However, these previous studies all relied on a morphometric definition of vertebral fracture and only one-third of vertebral fractures come to medical attention. Many of these vertebral fractures may have occurred many years prior to study entry and, hence, have a lower impact on mortality. Clinical vertebral fractures may represent the more serious fractures and, hence, poorer outcomes. Nevertheless, the elevated risk of death following clinical vertebral fractures in our study may also reflect an ascertainment bias, whereby women who have more medical conditions and poor health are more likely to get a diagnosis of a clinical vertebral fracture.

To our knowledge, two other studies have reported the risk of mortality after a clinical vertebral fracture: women from Rochester, Minnesota who had a radiologic vertebral fracture experienced about a 20% decreased survival over the 5 years of the study relative to controls [12]. There was a 60% increased risk of mortality among women in the Dubbo cohort who experienced an incident clinical vertebral fracture [2]. We found a much higher risk of dying after a clinical vertebral fracture, which may reflect our healthy comparison group. Both previous studies were population-based cohort studies. The Dubbo cohort was not systematically screened for vertebral fractures at entry to the study. Misclassification of prevalent fractures as incident fractures could have biased their results towards a weaker effect [2]. Finally, incomplete ascertainment of clinical vertebral fractures could have led to an underestimate of their impact on mortality.

There are a number of limitations to our study. Our study was limited to a group of primarily healthy Caucasian women participating in a clinical trial. Women were excluded from the FIT for a number of specific medical conditions relating to the study, e.g., severe malabsorption syndrome, but we also excluded women who had any major health problem that would have precluded their participation in the study for 3 years. The large relative risks may in part reflect the healthy nature of our comparison group. We cannot comment on other groups of women or on men. Indeed, mortality after a hip fracture has previously been shown to be higher among African-American women [3], men [3] and institutionalized subjects [4]. Nevertheless, we used internal comparisons of mortality experiences among women who fractured and those who did not. Previous studies which relied on comparisons of mortality rates among women who fracture with those of the general population may be biased and have limited ability to adjust for other factors that may have contributed to the death.

The number of deaths was small. We were unable to examine specific causes of death in detail. This may be important because specific fractures may be associated with specific causes of death. For example, deaths due to pulmonary diseases were particularly elevated among women with morphometric vertebral fractures [15].

Finally, we were unable to estimate whether the mortality after a fracture was due to the fracture itself or to an underlying medical condition. Most investigators

believe that the increase in mortality reflects poor underlying health status and comorbidity in addition to the fracture itself [9]. Women in poorer health may be more likely to be diagnosed with a clinical spine fracture in the year prior to their death since they would be under greater medical surveillance Clinical spine fractures may be a marker for increased mortality and not independently linked to an increased risk of death. Although we adjusted for self-reported health status, and several medical conditions, we had limited data on other comorbidities and clinical conditions which may explain the relationships we observed.

In summary, hip and clinical vertebral fractures were associated with a substantial increase in mortality even among a relatively healthy group of women. These data imply that the public health impact of osteoporosis on mortality may be greater than previously believed.

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