

Vertebral Fractures and Mortality in Older Women

A Prospective Study

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Background: Osteoporotic fractures, including clinically detected vertebral fractures, are associated with increased mortality. However, only one third of vertebral fractures are diagnosed. It is unknown whether vertebral fractures, whether clinically apparent or not, are associated with greater mortality.

Objectives: To test the hypothesis that women with prevalent vertebral fractures have greater mortality than those without fractures and to describe causes of death associated with vertebral fractures.

Design: Prospective cohort study with mean follow-up of 8.3 years.

Setting: Four clinical centers in the United States.

Participants: A total of 9575 women aged 65 years or older and enrolled in the Study of Osteoporotic Fractures.

Measurements: Vertebral fractures by radiographic morphometry; calcaneal bone mineral density; demographic, medical history, and lifestyle variables; blood pressure; and anthropometric measures. In a subset of 606 participants, thoracic curvature was measured dur-

ing a second clinic visit.

Main Outcome Measures: Hazard ratios for mortality and cause-specific mortality.

Results: At baseline, 1915 women (20.0%) were diagnosed as having vertebral fractures. Compared with women who did not have a vertebral fracture, women with 1 or more fractures had a 1.23-fold greater age-adjusted mortality rate (95% confidence interval, 1.10-1.37). Mortality rose with greater numbers of vertebral fractures, from 19 per 1000 woman-years in women with no fractures to 44 per 1000 woman-years in those with 5 or more fractures (*P* for trend, <.001). In particular, vertebral fractures were related to the risk of subsequent cancer (hazard ratio, 1.4; 95% confidence interval, 1.1-1.7) and pulmonary death (hazard ratio, 2.1; 95% confidence interval, 1.4-3.0). In the subset of women who underwent thoracic curvature measurements, severe kyphosis was also related to pulmonary deaths (hazard ratio, 2.6; 95% confidence interval, 1.3-5.1).

Conclusion: Women with radiographic evidence of vertebral fractures have an increased mortality rate, particularly from pulmonary disease and cancer.

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OSTEOPOROTIC fractures, especially fractures of the hip, and low bone mineral density are associated with increased mortality.¹⁻⁶ Women with clinically diagnosed vertebral fractures have a 15% higher mortality than women who do not.⁷ However, only about one third of vertebral fractures are clinically manifest, and patients with diagnosed vertebral fractures may have more severe and symptomatic fractures than those whose fractures are undiagnosed.⁸ Therefore, studies focusing on diagnosed vertebral fractures may be biased toward poorer outcomes. Also, the association between vertebral fractures and mortality may result from surveillance bias, since patients who are ill may be more

likely to have radiographs that could detect vertebral fractures than those who are healthy. Mortality among women whose vertebral fractures have been identified only by screening radiographs is not known.

The estimated prevalence of vertebral fracture increases steadily with age, reaching 40% in 80-year-old women.⁹ If vertebral fractures increase mortality, this has important implications for millions of women. To test whether vertebral fractures are associated with mortality, we prospectively studied a large cohort of older women including women who had vertebral fractures ascertained by routine radiographs, and assessed mortality rates during a mean of 8.3 years of follow-up.

SUBJECTS AND METHODS

SUBJECTS

Between September 1986 and October 1988, a total of 9704 ambulatory women aged 65 years or older without bilateral hip replacements were recruited to participate in the Study of Osteoporotic Fractures.¹⁰ They were identified from community-based listings at 4 clinical centers: Kaiser-Permanente Center for Health Research in Portland, Ore; University of Minnesota, Minneapolis; University of Maryland, Baltimore; and University of Pittsburgh, Pittsburgh, Pa. Black women and men were excluded because of their low incidence of osteoporotic fractures. The study protocol was approved by each center's institutional review board.

VERTEBRAL MORPHOMETRY MEASUREMENTS

Of the 9704 women, 9575 (98.7%) had baseline lateral radiographs of the thoracic and lumbar spine that were technically acceptable for interpretation by radiographic morphometry. Radiographs were taken in accordance with current guidelines.¹¹ The system for the diagnosis of vertebral fractures has been described elsewhere.¹²

To determine whether a specific vertebra was fractured, 3 height ratios were calculated for each vertebral level. Vertebral heights were defined as anterior (Ha), middle (Hm), and posterior (Hp), and height ratios as Ha/Hp, Hm/Hp, and Hp/Hp \pm 1 or Ha/Hp \pm 1. To determine the means of each of these height ratios for unfractured vertebrae, the most extreme 5% of values were excluded with the assumption that almost all values of fractured vertebrae exist in the tail of the distribution. By similar reasoning, the SDs were determined by trimming off the highest and lowest deciles of Q-Q plots. If any of the height ratios fell greater than 3 SDs below this study population-specific mean, the

vertebra was considered fractured.^{13,14} We also characterized a population with more severe fractures, defined as a ratio more than 4 SDs below the mean.

OTHER MEASUREMENTS

All subjects completed a baseline questionnaire that inquired about use of alcohol and cigarettes, perceived health status compared with that of women of similar age (very poor, poor, or fair vs good or excellent), diabetes, hypertension (thiazide use or blood pressure above 160/90 mm Hg), history of spine fracture, exercise frequency (total kilojoules burned per week in the past year), and current oral estrogen, corticosteroid, cholecalciferol (vitamin D), and calcium supplement use. At the clinic examination, participants had their body weight, knee height, and systolic blood pressure measured by standard techniques.¹⁵ A measure of body mass index that was not influenced by height loss was determined by dividing the weight in kilograms by the square of the knee height in meters. Bone mineral density of the calcaneus was measured by means of single photon absorptiometry (OsteoAnalyzer; Siemens-Osteon, Wahiawa, Hawaii).

We measured thoracic curvature, by means of an architect's flexicurve, in a subset of 606 participants (6.2%) who were sampled consecutively during the year 2 follow-up visit of the Study of Osteoporotic Fractures. With the use of the method¹⁶ of Milne and Lauder, the flexicurve was pressed against the subject's back while she was standing straight so that an index of thoracic curvature, the kyphosis index, could be calculated for each subject. These methods have been previously published in detail.¹⁶

ASCERTAINMENT OF DEATH

Participants were contacted by mail or telephone every 4 months: follow-up for vital statistics was 99.2% complete as

RESULTS

Of the 9575 women who had baseline radiographic morphometry, 1915 (20.0%) had 1 or more vertebral fractures; 1118 (11.7%) had 1 fracture, 407 (4.3%) had 2 fractures, 179 (1.9%) had 3 fractures, 91 (1.0%) had 4 fractures, and 120 (1.3%) had 5 or more fractures. We classified 1255 women (13.1%) as having severe fractures. Women with vertebral fractures were older and more likely to have hypertension, report poor health status, smoke, take cholecalciferol, and take calcium supplements (**Table 1**). They were less likely to exercise or drink alcohol and had a lower body mass index and calcaneal bone mineral density than women without fractures.

During a mean follow-up of 8.3 years, 1679 women (17.5%) died. Compared with women who did not have a fracture, women with 1 or more fractures had a 1.23-fold (95% CI, 1.10-1.37) greater age-adjusted mortality. The risk of death increased with the number of vertebral fractures (**Figure 1**). Women with severe fractures had a 1.34-fold (95% CI, 1.18-1.51) greater mortality.

MULTIVARIATE ANALYSIS

After adjusting for potential confounders, such as smoking, bone mineral density, and self-reported health status, women with fractures were still at a greater risk of dying (RH, 1.16; 95% CI, 1.03-1.30) (**Table 2**). Adjusting for bone mineral density in the multivariable models did not affect the association between vertebral fracture and mortality. Likewise, excluding women who had suffered hip, pelvis, or rib fractures had a negligible effect (**Table 3**).

CLINICAL AND SUBCLINICAL FRACTURES

Because it is already known that clinically detected vertebral fractures are associated with increased mortality, we sought to determine if women who were unaware of their fractures were also at increased risk of death. Of all women who had fractures, only 395 (20.6%) of 1915 reported a history of fracture, whereas 345 (28.0%) of 1230 with severe fractures reported a history of fracture. In age-adjusted models, women unaware of their fractures had a 1.16-fold increased mortality (95% CI, 1.03-1.32; $P = .02$). In models adjusting for all confounders, women with un-

of February 1997. The coordinating center obtained copies of the original death certificates of all subjects who died. A physician (W.S.B.) who was blinded to fracture status and other predictor variables determined the cause of death by reviewing death certificates, as well as hospital records, if available. Codes from the *International Classification of Diseases, Ninth Revision, Clinical Modification*, were used to classify the cause of death.¹⁷

To investigate whether vertebral fractures were associated more strongly with certain types of death, we examined cause-specific mortality as follows: (1) atherosclerosis (codes 401-404, 410-414, 430-438, 440-444, 425, 428, 429.2, and 798), which was subclassified into (a) coronary heart disease (codes 410-414) and (b) stroke (codes 430-438); (2) cancer (codes 140-239); and (3) all other causes of death (excludes all atherosclerosis and cancer-related codes). Within the "other" death category, we identified deaths caused by pulmonary diseases (codes 415-417, 480-487, 490-496, 500-508.8, and 510-519).

STATISTICAL ANALYSIS

To test for significant differences in baseline characteristics between the reference and fracture groups, *t* test and χ^2 tests were used as appropriate. We used Cox proportional hazards analyses to determine the age-adjusted relationship (as relative hazards [RH] and 95% confidence intervals [CI]) between vertebral fractures at baseline and subsequent mortality, confirming that the hazard rates were proportional throughout follow-up. We defined women as having vertebral fractures by 1 of several criteria: (1) at least 1 fracture by the 3-SD rule; (2) at least 1 fracture by the 4-SD rule (considered severe fractures); and (3) stratified by 1, 2, 3, 4, or 5 or more fractures by the 3-SD rule. The reference group for each analysis was the group of women whose data fell below the chosen SD cutoff point.

Potential confounders of the association between vertebral fractures and mortality were considered in separate age-adjusted analyses. Factors that had strong biological relevance (such as estrogen use) or were significantly related to both vertebral fractures and mortality ($P < .05$) were included in multivariable models. To determine whether the mortality risk differed in women who were unaware of their fractures vs those who self-reported a history of spine fracture, we created dummy variables to represent those with only a self-reported history of fracture, those with only a morphometrically defined fracture, and those who had both a self-reported and a morphometric fracture. Survival curves were estimated by means of the life table method, comparing mortality in women who had 1 or more vertebral fractures with mortality in those who did not.

Morphometry does not distinguish between different fracture causes. To determine if vertebral fractures caused by metastatic disease might be the explanation for our findings, we (1) compared the survival curves of those with and without fractures who died of cancer; (2) repeated the analyses excluding all deaths within the first 2 years; and (3) had the study radiologist (H.K.G.) review a randomly mixed sample of films ($n = 185$) that included all those who had fractures and died of cancer ($n = 135$) to ensure that the deformities were caused by osteoporosis rather than obvious pathologic fractures.

To determine whether pulmonary mortality could be in part explained by severe kyphosis caused by vertebral fractures, we used proportional hazards analysis to determine whether there was a significant relationship between kyphosis and pulmonary mortality. We also compared pulmonary mortality in women in the upper quintile of kyphosis severity with those in the lower 4 quintiles by means of the Fisher exact test. SAS software (SAS Institute, Cary, NC) was used for all analyses.

diagnosed severe fractures had increased mortality (RH, 1.17; 95% CI, 1.00-1.36; $P = .05$), but not women unaware of any vertebral fractures (RH, 1.10; 95% CI, 0.96-1.25; $P = .16$). Women with a self-reported history of spine fracture that was not confirmed by morphometry also had increased mortality after adjusting for all measured confounders (RH, 1.37; 95% CI, 1.01-1.86; $P = .04$).

VERTEBRAL FRACTURES AND CANCER MORTALITY

Women with mild to severe vertebral fractures had an age-adjusted 35% to 40% increased risk of cancer death. After adjusting for smoking, bone mineral density, and self-reported health, the relative hazards still remained significant (**Table 4**). Censoring data from women who died of other causes, the cancer mortality rates for women with and without vertebral fractures did not diverge until about 2 years into the study (**Figure 2**). Furthermore, the age-adjusted association between vertebral fracture and cancer mortality remained significant even after excluding cancer deaths within the first 2 years (RH, 1.20; 95% CI, 1.06-1.35). In addition, the study radiologist classified only 5

women (2.7%) as having possible pathologic (4 of whom died of cancer), rather than osteoporotic, fractures.

Women with vertebral fractures were more likely to die of lung cancer than women without vertebral fractures, even after adjusting for current and past cigarette smoking (RH, 2.0; 95% CI, 1.3-2.9). Otherwise, there were no substantial differences in mortality from specific types of cancer between those with fracture and those without (data not shown).

VERTEBRAL FRACTURES AND PULMONARY MORTALITY

Women with the most severe vertebral fractures had an age-adjusted 1.5-fold increased risk of dying of "other" causes (95% CI, 1.2-1.8); this increased risk was caused by pulmonary conditions such as chronic obstructive pulmonary disease and pneumonia. The age-adjusted relative risk for pulmonary mortality (not including lung cancer) was 2.0 (95% CI, 1.4-2.9); in women with severe fractures, the risk was 2.7 (95% CI, 1.9-4.0). Adjusting for dose and duration of corticosteroid use, current, past, or pack-years of cigarette smoking, body mass index,

Table 1. Baseline Characteristics of Subjects, Classified by Vertebral Fracture, by Means of 3-SD Rule*

	No Fracture (n = 7660)	≥1 Fracture (n = 1915)	Odds Ratio or Mean Difference† (95% CI)
Age, mean ± SD, y	71.2 ± 5.1	73.3 ± 5.8	2.1 (1.8 to 2.4)
Education >12 y	2869 (37)	732 (38)	1.0 (0.9 to 1.1)
History of diabetes	560 (7)	117 (6)	0.8 (0.7 to 1.0)
History of hypertension	2906 (38)	782 (41)	1.1 (1.0 to 1.3)
Currently taking oral estrogen	1069 (14)	248 (13)	0.9 (0.8 to 1.1)
Currently taking calcium	3107 (41)	959 (50)	1.5 (1.3 to 1.6)
Currently taking cholecalciferol	3312 (44)	896 (47)	1.1 (1.0 to 1.3)
Self-reported health status (fair/poor/very poor vs good/excellent)	1229 (16)	371 (19)	1.3 (1.1 to 1.4)
Current smoker	743 (10)	217 (11)	1.2 (1.0 to 1.4)
Alcohol use in past year	5446 (71)	1259 (66)	0.8 (0.7 to 0.9)
Physical activity, mean ± SD, kJ/wk	1631 ± 1682	1498 ± 1629	-133 (-217 to -48)
Modified body mass index, mean ± SD, kg/m ² ‡	277 ± 50	268 ± 49	-9.7 (-12.1 to -7.2)
Calcaneal bone mass, mean ± SD, g/cm ²	0.41 ± 0.09	0.36 ± 0.09	-0.05 (-0.055 to -0.045)

*All data are given as number (percentage) unless otherwise specified.

†Odds ratios are listed for categorical variables, while mean differences are listed for continuous variables. The comparison group in each case is the "No Fracture" group. CI indicates confidence interval.

‡Calculated as body weight in kilograms divided by square of the knee height.

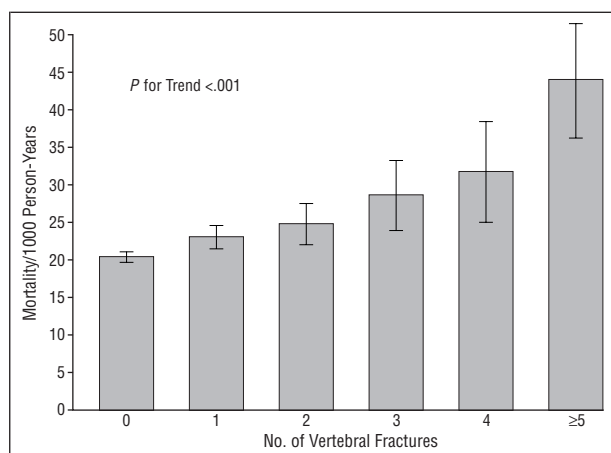


Figure 1. Age-standardized mortality by number of vertebral fractures.

physical activity, and self-reported health made no significant difference (Table 4).

KYPHOSIS AND MORTALITY

Of the 606 women with flexicurve measurements, 8 died of a pulmonary cause. Degree of kyphosis was significantly related to risk of subsequent pulmonary death in the age-adjusted analysis (RH, 2.6 per SD increase in kyphosis index; 95% CI, 1.3-5.1; $P = .005$). Six of the 8 deaths caused by pulmonary disease were in women in the top fifth of kyphosis index severity (**Figure 3**). Women in the upper quintile of kyphosis index severity compared with those in the lower 4 quintiles were more likely to die of a pulmonary cause ($P = .04$). However, only 3 of the 8 kyphotic women who died a pulmonary death had vertebral fractures.

COMMENT

Older women with vertebral fractures, if clinically manifest, multiple, or severe, have a significantly increased mor-

Table 2. Multivariable Model of the Association Between Vertebral Fractures and Mortality

Predictor (Units)*	Relative Hazard (95% Confidence Interval)	P
Vertebral fracture	1.16 (1.03-1.30)	.02
Age, per 5 y	1.57 (1.50-1.64)	<.001
Education >12 y	0.96 (0.87-1.07)	.51
Diabetes	1.82 (1.56-2.12)	<.001
Hypertension	1.37 (1.24-1.52)	<.001
Self-reported health status	1.64 (1.45-1.85)	<.001
Current smoker	2.02 (1.75-2.34)	<.001
Alcohol use, past year	0.89 (0.80-1.00)	.04
Physical activity, per SD increase	0.87 (0.81-0.92)	<.001
Current estrogen use	0.87 (0.73-1.03)	.12
Current calcium use	0.89 (0.79-1.00)	.06
Current cholecalciferol use	0.94 (0.84-1.07)	.33
Body mass index, per SD increase	0.92 (0.86-0.98)	.006
Calcaneal bone mass, per SD increase	0.93 (0.88-0.99)	.02

*When not specified, predictors are dichotomous.

tality. Women with multiple vertebral fractures and those with more severe fractures had the greatest increase in risk regardless of whether they were aware of their fractures. Most vertebral fractures go clinically undetected, and many of them are severe.

Vertebral fractures appear to affect mortality in a way not explained by increased age, health behaviors, chronic medical conditions, low bone density, and self-reported health. It is plausible that underlying inflammatory disease may lead to bone remodeling and subsequent fracture. Alternatively, vertebral fractures may be a marker of physiological aging by mechanisms that include (1) oxidative damage and (2) cellular senescence. Future research on aging that can link cellular mechanisms to clinically meaningful outcomes may ultimately provide new avenues for treatment and prevention.

Table 3. Multivariable Models of Association Between Vertebral Fractures and Mortality*

Fracture Definition	Relative Hazard (95% Confidence Interval)			
	Age-Adjusted (n = 9575)	Full† (n = 9126)	Full + Bone Mass (n = 9089)	Excluding Selected Fractures‡ (n = 8665)
3 SDs	1.23 (1.10-1.37)	1.18 (1.05-1.33)	1.16 (1.03-1.30)	1.15 (1.01-1.30)
4 SDs	1.34 (1.18-1.51)	1.27 (1.11-1.45)	1.25 (1.10-1.43)	1.25 (1.08-1.44)

*With and without adjustment for calcaneal bone mass, or excluding women with other types of osteoporotic fractures.

†Full model adjusted for age, clinic, education, diabetes, hypertension, alcohol consumption, smoking, health status, physical activity, body mass index, estrogen, calcium, and cholecalciferol use.

‡Women with hip, pelvis, or rib fractures were excluded from this analysis; fully adjusted, including bone mass.

Table 4. Multivariate Associations Between Vertebral Fractures (by Severity) and Cause-Specific Mortality*

Cause of Death (No. of Deaths)	Fracture (≥3 SDs)		Severe Fracture (≥4 SDs)	
	Relative Hazard (95% CI)	P	Relative Hazard (95% CI)	P
Cancer (526)†	1.3 (1.0-1.6)	.02	1.3 (1.0-1.6)	.04
Atherosclerosis (635)‡	1.1 (0.9-1.4)	.18	1.2 (1.0-1.5)	.11
Coronary heart disease (280)‡	1.0 (0.8-1.4)	.76	1.0 (0.8-1.4)	.83
Stroke (174)‡	1.0 (0.7-1.4)	.92	1.2 (0.8-1.8)	.36
Other (518)§	1.2 (1.0-1.5)	.03	1.5 (1.2-1.8)	<.001
Pulmonary disease (134)	1.7 (1.2-2.5)	.003	2.2 (1.5-3.2)	<.001

*CI indicates confidence interval.

†Adjusted for age, self-reported health, smoking, and calcaneal bone density.

‡Adjusted for age, self-reported health, smoking, diabetes, hypertension, estrogen use, alcohol use, and physical activity.

§Adjusted for age.

||Adjusted for age, self-reported health, smoking, corticosteroid use, body mass index, and physical activity.

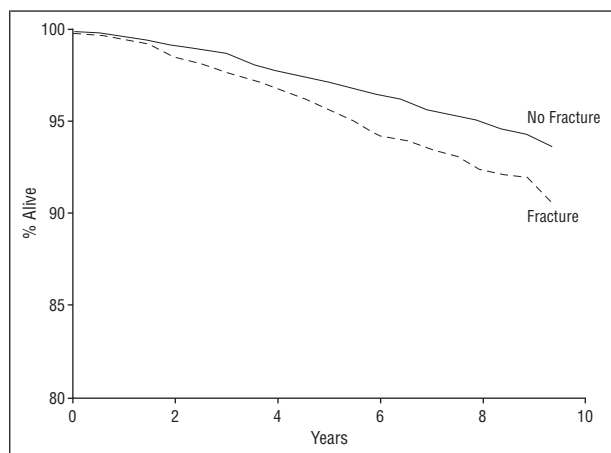


Figure 2. Percentage free of cancer death by baseline vertebral fracture.

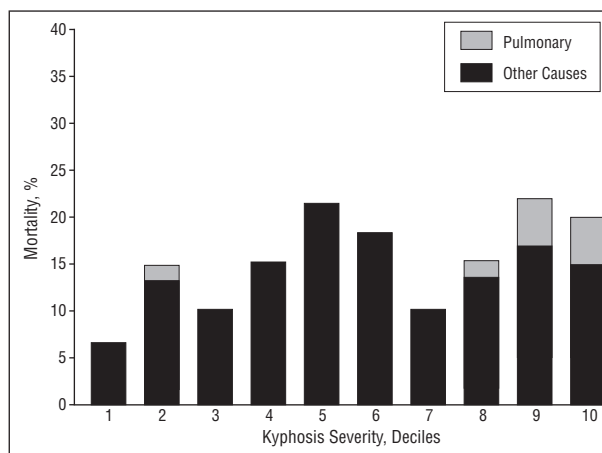


Figure 3. Distribution of pulmonary and other deaths by deciles of increasing severity of kyphosis.

Women with vertebral fractures were 2 to 3 times more likely to die of pulmonary causes than those without fractures. This finding could not be explained by long-term corticosteroid or tobacco use. Severe kyphosis was strongly predictive of pulmonary deaths, perhaps because those with underlying lung disease and decreased respiratory reserves may not tolerate restrictive changes in thoracic anatomy resulting from vertebral fractures. It has been previously shown that there is a 9% decrease in predicted forced vital capacity per vertebral fracture.¹⁸

We also found that vertebral fractures were associated with increased cancer mortality. On the basis of the radi-

ologist's blinded review of the films, the comparison of the cancer-free survival curves in those with and without fractures, and the assumption that women with cancer advanced enough to cause pathologic fractures would not likely survive longer than 2 years, it seems unlikely that metastatic disease to the spine is the explanation for our findings. These study results are also in agreement with those of Cooper et al,⁷ who reported that compared with expected mortality rates, there was increased cancer mortality in women with clinically diagnosed vertebral fractures.

There are several other potential explanations for the association between vertebral fractures and cancer

deaths. Biological modulators, such as cytokines (interleukin 1, interleukin 6, tumor necrosis factors), nitric oxide, and parathyroid hormone-related protein, are produced by malignant neoplasms and may affect skeletal metabolism.¹⁹⁻²³ For example, cytokines may be mediators of bone loss in solid tumors or myeloma.^{24,25}

There is also indirect evidence that the underlying pathogenesis of vertebral fractures and that of cancer spread may share common factors. Not only has it been shown that bisphosphates reduce the incidence of vertebral fractures,²⁶ but bisphosphonate use in patients with breast cancer seems to reduce the rate of bone and organ metastases as well as cancer mortality.²⁷

Our study has several limitations. First, radiographic morphometry, although valuable for large epidemiological studies because of its reproducibility and reliability, does not distinguish among different causes of fracture. However, an expert radiologist confirmed that very few fractures were caused by metastatic cancer. Second, there is not complete agreement between morphometric and subjective readings of spine x-ray films; therefore, morphometric abnormalities are usually referred to as "deformities" rather than "fractures." However, for moderate and severe fractures, the agreement between subjective radiological readings and morphometry is strong.¹² Third, we were unable to assess whether women with vertebral fractures were more likely to have cancer at baseline than women without vertebral fractures, so that it is unclear which may have preceded the other. Fourth, because our subjects were elderly white women, our results may not be generalizable to other populations. Fifth, causes of death in patients who were not hospitalized were ascertained from death certificates that were often missing important details. However, our study also has some strengths. First, it is a large prospective cohort study with a mean follow-up time of 8 years and greater than 99% ascertainment of vital status. Second, baseline radiographs were taken in all participants, enabling us to ascertain mortality risk in a population of women regardless of whether they had a clinically diagnosed vertebral fracture.

We conclude that women with clinically diagnosed and clinically silent severe or multiple vertebral fractures have an increased mortality, particularly from cancer and pulmonary deaths. This study raises the possibilities that early and aggressive treatment of pulmonary disease in women with vertebral fractures and prevention of further vertebral fractures among those with kyphosis might reduce mortality rates.

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