Vertebral fracture and cause-specific mortality: a prospective population study of 3,210 men and 3,730 women with 30 years of follow-up

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Abstract

Introduction Vertebral fractures predict mortality, but little is known about their associations with the causes of death. We studied vertebral fractures for prediction of cause-specific mortality.

Material and methods A nationally representative sample of 3,210 men and 3,730 women participated Mini-Finland health survey in 1978–1980. Vertebral fractures at the Th1–Th12 levels were identified from chest radiographs at baseline. Cox's proportional hazard model was used to estimate the strength of association between vertebral fracture and mortality.

Results The relative risk (95% confidence interval) of death from natural causes was 1.49 (0.89–2.48) in men and 0.89 (0.60–1.31) in women with vertebral fractures

(adjusted for age, body mass index, serum 25-hydroxyvitamin D, educational level, smoking, alcohol intake, physical activity and self-rated general health). Among women the adjusted relative risk of an injury death was 8.51 (3.48–20.77), whereas none of the men with vertebral fracture died due to an injury.

Conclusion The patterns of mortality predicted by fracture in the thoracic spine differ between men and women.

Keywords Vertebral fracture · Osteoporosis · Hip fracture · Cause-specific mortality

Introduction

Osteoporosis deteriorates bone tissue with a consequent increase in the fragility of bones and their susceptibility to fracture. Vertebral fractures are widely considered to be the hallmark of osteoporosis. These fractures are estimated to affect at least 20% of the elderly population [1–3]; however, only 30–40% of these come to clinical attention [4, 5]. Vertebral fractures have been associated with increased mortality in several studies [6–13], but obvious associations with specific causes of death have so far not been reported. Increased mortality has also been found to be independently associated with low bone mineral density without fractures [14–16].

Deaths from cardiovascular diseases in men and malignant neoplasms and respiratory diseases in men and women have been suggested to explain the excess mortality in subjects with vertebral fracture [9, 11, 13], whereas low bone mineral density has been linked with increased risk of stroke and also with mortality from natural causes other than cardiovascular diseases [14–16]. Vertebral fractures are known to predict the risk of subsequent hip fracture

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[17–19], but associations with deaths due to injuries have not been reported.

This limited information on the fate of men and women with vertebral fractures encouraged us to evaluate the total and cause-specific mortality in subjects who had participated in a health survey based on a nationally representative population sample (the Mini-Finland Health Survey) some 30 years ago.

Methods

Study population and baseline examination

The Mini-Finland Health Survey [20] was based on a stratified two-stage cluster sample drawn from the population register to represent Finnish adults aged 30 years or over (2,658,000 in the census of 1980). In the first stage, 40 representative areas were selected. In the second stage, a systematic sample of inhabitants was drawn from each area. The areas were stratified with regard to degree of urbanization and proportions of people employed in industry and agriculture. The sample consisted of 3,637 men and 4,363 women, of whom 3,210 men (88.3%) and 3,730 women (85.5%) participated in a comprehensive health examination in 1978–1980. All participants underwent a full-size chest (PA and lateral) radiographic examination.

Before attending a screening examination, the participants were interviewed at home and asked to fill in a basic questionnaire to elicit information on health habits and previously diagnosed diseases. The examination comprised full-size chest radiography (posterior–anterior and lateral) and other measurements and tests to identify subjects with cardiovascular, respiratory, musculoskeletal or other common diseases [20].

Measurements and definition of determinants

Information on leisure time physical activity obtained by means of the basic questionnaire was categorized into three classes: low, moderate and high activity. Self-rated general health was classified according to a three-point scale: good, moderate and poor. Self-rated health measured in this manner has proved reliable in test–retest analysis [21]. Standing height and weight were measured, and body mass index (weight/height^2 , kg/m^2) was used as a measure of relative weight. Smoking history was obtained in a standard interview and categorized as follows: never smoked; ex-smoker; current smoker of cigars, pipe or of fewer than 20 cigarettes a day, and current smoker of 20 cigarettes or more a day. The basic questionnaire also inquired about average weekly consumption of beer, wine and strong

beverages during the preceding month. The overall alcohol consumption was then calculated and expressed in grams of ethanol per week. The level of education was classified into three categories based on the years of education. Venous blood samples were taken, and the sera were kept frozen at -20°C until 2003, when the serum 25-hydroxyvitamin D concentrations were determined using the radioimmunoassay (RIA, DiaSorin, MI) [22].

Radiographic evaluation

Chest radiographs were assessed by two clinical radiologists independently of each other. Vertebral fractures at levels from Th1 to Th12 were diagnosed by the clinical method, without severity grading of vertebral compressions. All distinct vertebral fractures identified by either one of the radiologists were taken into account in this study.

To evaluate the repeatability of the diagnostic assessments, a reference reading of 1,051 chest radiographs was carried out. The material comprised radiographs of subjects who had died from an injury or had been hospitalized because of a hip fracture until 1994, and three individually matched controls for these subjects [17]. Compressions in the vertebral bodies were identified and graded according to Genant's semiquantitative classification [23] without any information on the findings of the original readings. The agreement of the two readings was as follows: 1,011 subjects with no vertebral fracture in either reading, 13 subjects with vertebral fractures identified on both readings, 17 with a fracture in the reference reading, but no fracture in the original (clinical) reading, and 10 with a fracture in the original reading but no fracture in the reference reading. The overall kappa value for agreement between the two sets of readings was 0.48 (95% confidence interval [CI] 0.31–0.65).

Follow-up

The mortality in the cohort was continuously followed up since the baseline examination until the end of 2008. Causes of death according to the International Classification of Diseases (ICD) were obtained from Statistics Finland.

Statistical methods

Cross-sectional associations between the potential determinants and the vertebral fractures were analyzed with multivariate logistic regression. The results were expressed as adjusted relative odds (OR) with 95% confidence intervals (95% CI). Cox's proportional hazards models were used to estimate the strength of association between

vertebral fracture and mortality from various causes during the follow-up. Adjusted relative risks with 95% confidence intervals were estimated. Three main models were defined: (1) an age-adjusted model, (2) a full model including age and the rest of the explanatory factors and (3) the full model in which the interaction terms of vertebral fracture and each explanatory factor were entered, one by one, to study the effect modification. Statistical significance of each interaction term was tested with the likelihood ratio test and expressed as an exact *p* value. Since significant interactions between gender and vertebral fracture emerged, the main analyses were carried out in men and women separately. Age, body mass index, education level, smoking, alcohol consumption, physical activity, serum Vitamin D concentration and self-rated health remained

potential confounding factors in the final models. All analyses were performed using the SAS System for Windows, Version 9.1 (SAS Institute, Inc., Cary, NC).

Results

The prevalence of a vertebral fracture in the thoracic spine was 0.8% (56/6,940, 19 male/37 female). Distributions of the baseline characteristics and their cross-sectional associations with the observed vertebral fractures are presented in Table 1 and its footnotes. The presence or absence of diabetes, cardiovascular disease, respiratory disease, mental disorder or self-rated general health status had no associations with vertebral fractures (data not shown).

Table 1 Baseline characteristics and their cross-sectional associations with vertebral fractures in men and women

	Men				Women			
	<i>n</i>	<i>N</i>	OR	95% CI	<i>n</i>	<i>N</i>	OR	95% CI
Age per one standard deviation	3,210		1.77	1.15–2.72	3,730		3.36	2.28–4.96
Serum vitamin D per one standard deviation	3,210		0.77	0.46–1.29	3,730		0.99	0.70–1.39
Body mass index per one standard deviation	3,210		1.13	0.74–1.74	3,730		0.76	0.53–1.08
Educational level								
<8 years	2,170	14	1.00		2,557	28	1.00	
8–12 years	670	4	1.25	0.40–3.90	781	6	1.49	0.60–3.69
>12 years	370	1	0.59	0.08–4.56	392	3	2.35	0.67–8.20
Smoking status								
Never smoked	956	4	1.00		2,892	30	1.00	
Ex-smoker	1,092	7	1.32	0.38–4.54	356	5	3.01	1.11–8.17
Pipe, cigars or < 20 cigarettes/day	651	5	1.87	0.50–7.00	371	2	1.24	0.29–5.41
≥20 cigarettes/day	511	3	1.77	0.39–8.09	111	0		
Alcohol intake (grams of ethanol per week)								
0	868	3	1.00		2,272	30	1.00	
1–49	1,623	14	3.64	1.01–13.1	1,361	6	0.81	0.32–2.01
50–249	227	0			47	1	6.85	0.83–56.25
≥249	492	2	2.12	0.34–13.39	50	0		
Physical activity at leisure								
Low	1,034	7	1.00		1,481	23	1.00	
Moderate	1,603	10	1.09	0.41–2.91	1,765	12	0.72	0.35–1.48
High	573	2	0.71	0.14–3.54	484	2	0.62	0.14–2.73
Self-rated general health								
Good	1,516	7	1.00		1,750	9	1.00	
Moderate	1,146	5	0.68	0.21–2.23	1,431	17	1.23	0.54–2.81
Poor	548	7	1.70	0.56–5.21	550	11	1.60	0.64–3.99

Age-adjusted relative odds (ORs) with 95% confidence intervals (CIs). Ranges and mean values $\pm$ standard deviations were the following. Age in men: 30–91, 49.8 ± 13.6 ; in women: 30–90, 52.3 ± 14.3 years. Serum vitamin D in men: 5–180, 45.1 ± 20.3 ; in women: 4–151; 41.9 ± 18.6 nmol/l. Body mass index in men: 16.4–42.8, 25.8 ± 3.5 ; in women: 16.0–47.8, 26.0 ± 4.5 kg/m²

n number of subjects examined, *N* number of subjects with vertebral fracture

Table 2 Mortality from various causes according to the presence of vertebral fracture in the thoracic spine

Cause of death (ICD 8 codes)	<i>n</i> 3,191	<i>N</i> 19	Men				<i>n</i> 3,693	<i>N</i> 37	Women			
			Adjusted for age		Adjusted for all used determinants*				Adjusted for age		Adjusted for all used determinants*	
			RR	95% CI	RR	95% CI			RR	95% CI	RR	95% CI
All deaths	1,673	15	1.84	1.10–3.06	1.40	0.84–2.34	1,683	32	1.15	0.81–1.64	1.07	0.75–1.52
Non-injury death	1,561	15	1.96	1.18–3.27	1.49	0.89–2.48	1,622	26	0.96	0.65–1.42	0.89	0.60–1.31
Cardiovascular death	860	7	1.53	0.73–3.23	1.23	0.58–2.60	821	15	0.95	0.57–1.59	0.85	0.51–1.42
Respiratory death	132	4	6.16	2.24–16.96	3.50	1.24–9.86	126	1	0.37	0.05–2.69	0.35	0.05–2.53
Cancer death	387	3	1.76	0.57–5.50	1.29	0.41–4.04	368	4	0.95	0.35–2.55	0.97	0.36–2.62
Injury death	112	0					61	6	8.03	3.37–19.11	8.51	3.48–20.77

Adjusted relative risks (RRs) with 95% confidence intervals (CIs). The number of subjects examined was 6,940. ICD 8 codes of the cause-specific deaths were: all (000–999), non-injury death (000–796), cardiovascular (390–458), respiratory (460–519), cancer (140–209) and injury (800–999)

n number of death among subjects without vertebral fracture, *N* number of deaths among subjects with vertebral fracture

* Age, body mass index, education level, smoking, alcohol consumption, physical activity, serum vitamin D and self-rated general health

Significant differences were found between men and women in the associations of vertebral fractures and cause-specific mortality (Table 2). The presence of a vertebral fracture in the thoracic spine predicted mortality from natural causes, respiratory diseases in particular, in men (fully adjusted RR 3.50, 95% CI 1.24–9.86), but not in women. *P* values for the interaction terms of gender and vertebral fracture were 0.03 and 0.004, respectively. In contrast, a strong association was observed between vertebral fracture and mortality from injuries among women (fully adjusted RR 8.51, 95% CI 3.48–20.77), whereas none of the men with vertebral fracture died due to an injury. *P* value for the interaction term of gender and vertebral fracture was 0.01. In five of the six fatal injuries among women with vertebral fracture, a subsequent fracture was stated as the main cause of death. Four of these fatal fractures were hip fractures and the fifth was a pelvic fracture. The sixth injury death had resulted from a non-specific contusion of the lower limb.

Among either men or women, none of the interaction terms between vertebral fracture and the baseline factors given in Table 2 showed any significant association with mortality.

Discussion

A vertebral fracture in the thoracic spine showed significant prediction for respiratory mortality in men and injury mortality in women. Most of the injury deaths in women had occurred in conjunction with a hip fracture.

Validity of the study

The strengths of this study lie in the fairly large study population, high participation rate and the long follow-up period extending up to 30 years. Altogether, 3,403 out of 6,940 subjects died during the 30 years of follow-up, which provides a sound basis for mortality evaluation. The study was population based, and therefore presumably devoid of any appreciable selection bias. Furthermore, self-reported general health status showed no association with vertebral fracture, suggesting that these fractures were asymptomatic. Vertebral fractures at baseline were closely associated with known risk factors for osteoporosis (high age, low BMI and smoking) suggesting that these fractures were true osteoporotic fractures. Traumatic vertebral fractures could not, however, be excluded from this study population. Other weaknesses of this study include the fact that our analysis for practical reasons could be concentrated only on the thoracic spine, and corresponding information concerning the lumbar and cervical spine was missed. However, the thoracic spine and the thoracolumbar junction are considered the principal sites of osteoporotic vertebral fractures [24, 25]. The severity of vertebral fracture was not assessed. The kappa value for agreement between the original and the reference readings was only moderate. The distributions of vertebral fractures differ between those identified by means of the semiquantitative method (SQ) and those diagnosed clinically. Compared with the clinical diagnosis, the SQ method may be more sensitive for identifying vertebral compressions. On the other hand, this method may more easily misdiagnose low-height vertebrae without endplate depression (degenerative changes or normal variations) as vertebral fractures.

Comparison with previous data

Vertebral fractures have been associated with increased mortality [6–13], and cancer, pulmonary and cardiovascular deaths are suggested to explain the excess mortality. In our study, a strong association was found between vertebral fractures and respiratory deaths in men. Impaired pulmonary function resulting from pronounced thoracic kyphosis due to vertebral fracture may explain this association. However, vertebral fractures showed no association with respiratory diseases at baseline. In women, the association between vertebral fracture and subsequent mortality caused by injury was significant. Such association has, to the best of our knowledge, not been observed earlier. Vertebral fractures notoriously increase the risk of subsequent hip fracture [17–19], and most of the fatal injuries in the present study were fractures of the hip. Vertebral fractures in the thoracic spine may be related to poor general health status and frailty. Under such conditions, an acute trauma is likely to increase the risk of a fatal outcome. However, the presence or absence of such conditions as diabetes, cardiovascular disease, respiratory disease, mental disorder or self-rated general health status showed no associations with vertebral deformities in this study. Cancer mortality was not increased among subjects with vertebral deformity. Our earlier study from a similar, but larger material showed an association between vertebral fracture and cancer mortality [13]. The absence of such association in the present study may be due to a smaller study population.

Conclusion

The patterns of mortality predicted by vertebral fracture in the thoracic spine clearly differ between men and women. Further research is needed to explore whether such divergent mortality patterns between the genders should be taken into account in the provision of preventive measures against osteoporosis and accidental injuries.

Ethical aspects This study precedes current legislation on medical research. The participants were fully informed about the study, they attended it on a voluntary basis and the use of the information for medical research was explained to them.

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Conflict of interest There is no conflict of interest.

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