Table 2. Baseline characteristics by sex and uric acid level. Values are mean (SD).

Uric Acid Level, mg/dl	No. of Subjects	Age, yrs	Body Mass Index, kg/m^2	Total Cholesterol, mg/dl	Hypertension, %	Diabetes, %	Current Smoking, %	Alcohol Use, g†/wk	Radiation Dose, Gy
Men									
Total	3860	49.0 (14.8)	21.1 (2.8)	181.8 (38.7)	30.4	13.0	74.1	107 (140)	0.39 (0.82)
< 5.0	1184	51.8 (14.4)	20.5 (2.6)	178.1 (36.7)	27.8	14.4	75.4	92 (126)	0.38 (0.78)
5.0–5.9	1127	48.4 (14.5)	20.8 (2.8)	180.6 (37.0)	25.9	12.6	75.3	101 (144)	0.40 (0.83)
6.0–6.9	866	46.8 (14.8)	21.3 (2.8)	183.1 (39.7)	30.4	11.1	73.7	116 (141)	0.39 (0.85)
7.0–7.9	390	46.6 (15.1)	22.1 (3.1)	187.5 (41.8)	36.9	12.8	73.3	119 (143)	0.36 (0.77)
≥ 8.0	293	49.0 (15.2)	22.5 (3.0)	189.5 (43.3)	49.5	15.0	66.9	141 (156)	0.39 (0.84)
p for trend		< 0.001	< 0.001	< 0.001	< 0.001	> 0.5	0.007	< 0.001	> 0.5
Women									
Total	6755	48.6 (13.5)	22.1 (3.4)	191.8 (41.2)	26.4	6.6	14.4	8 (41)	0.36 (0.75)
< 4.0	3015	47.2 (13.0)	21.7 (3.0)	185.1 (39.6)	19.4	5.1	12.6	5 (26)	0.35 (0.70)
4.0–4.9	2261	48.6 (13.5)	22.1 (3.4)	191.9 (39.6)	27.1	5.9	14.6	9 (42)	0.36 (0.76)
5.0–5.9	1005	50.5 (14.0)	23.1 (3.7)	202.6 (42.3)	34.5	9.4	16.2	11 (50)	0.40 (0.86)
6.0–6.9	339	52.8 (14.1)	23.9 (4.0)	209.2 (46.2)	46.0	12.7	21.2	20 (78)	0.37 (0.78)
≥ 7.0	135	56.9 (13.8)	23.9 (4.0)	212.3 (45.1)	60.0	15.6	21.5	20 (60)	0.40 (0.76)
p for trend		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.07

† Ethanol weight.

Table 3. Relation of serum uric acid level to all-cause mortality.

Uric Acid Level, mg/dl	Person-yrs	No. of Deaths	Mortality Rate*	Age Adjusted Hazard Ratio	95% CI	Fully Adjusted† Hazard Ratio	95% CI
Men							
< 5.0	25,811	754	29.2	1.0		1.0	
5.0–5.9	26,259	649	24.7	1.00	0.90, 1.11	0.99	0.89, 1.10
6.0–6.9	20,871	461	22.1	0.95	0.85, 1.07	0.94	0.83, 1.06
7.0–7.9	9243	214	23.2	1.05	0.90, 1.22	1.05	0.90, 1.23
≥ 8.0	6182	188	30.4	1.38	1.17, 1.61	1.22	1.03, 1.44
Women							
< 4.0	81,405	1130	13.9	1.0		1.0	
4.0–4.9	58,786	980	16.7	1.10	1.01, 1.20	1.07	0.98, 1.16
5.0–5.9	25,226	525	21.0	1.14	1.02, 1.26	1.08	0.97, 1.20
6.0–6.9	7458	221	29.6	1.59	1.37, 1.84	1.44	1.24, 1.67
≥ 7.0	2538	103	40.6	1.90	1.54, 2.31	1.63	1.32, 2.00

* Values are expressed per 1000 person-years. † In addition to age, adjusted for BMI, smoking status, alcohol consumption, systolic blood pressure, total cholesterol level, histories of hypertension, diabetes, coronary heart disease, kidney disease and malignant tumor, and estimated radiation dose from the atomic bombs.

significantly increased in the highest uric acid category (≥ 8.0 mg/dl) compared with subjects in the lowest uric acid category when adjustment was made only for age. However, this hazard ratio increase did not remain significant after full adjustment (Table 4). When cardiovascular disease was restricted to coronary heart disease, age-adjusted hazard ratio for mortality was significantly increased in the uric acid category ≥ 8.0 mg/dl, but it was no longer significant after full adjustment (Table 4). For stroke mortality, no significant increase in hazard ratio was observed in any of the uric acid categories in men.

In women, a significant increase in the hazard ratio for cardiovascular mortality was observed in the uric acid categories 6.0–6.9 and ≥ 7.0 mg/dl compared with the lowest uric acid category (< 4.0 mg/dl) even after full adjustment, and a higher hazard ratio was observed in the uric acid category ≥ 7.0 mg/dl compared with the 6.0–6.9 mg/dl category (Table 4). A significant increase in coronary heart disease mortality was observed for the 6.0–6.9 mg/dl category, but the increase was not significant in the ≥ 7.0 mg/dl category (Table 4). This may result from the small number of cases in this category (n = 12). For stroke mortality, a significant increase in hazard ratio was found for the ≥ 7.0 mg/dl category (Table 4).

Since menopausal status has substantial effects on both uric acid level and cardiovascular disease occurrence, the relation between uric acid level and mortality risk was examined in different age groups in women. Thus, women

Table 4. Relation of serum uric acid level to cardiovascular disease mortality.

	Uric Acid Level, mg/dl	No. of Deaths	Mortality Rate*	Age Adjusted Hazard Ratio	95% CI	Fully Adjusted† Hazard Ratio	95% CI
Cardiovascular disease mortality							
Men	< 5.0	266	10.3	1.0		1.0	
	5.0–5.9	201	7.7	0.89	0.74, 1.07	0.89	0.74, 1.07
	6.0–6.9	156	7.5	0.94	0.77, 1.14	0.83	0.67, 1.01
	7.0–7.9	65	7.0	0.94	0.71, 1.23	0.86	0.65, 1.13
	≥ 8.0	63	10.2	1.40	1.05, 1.83	1.08	0.81, 1.44
Women	< 4.0	457	5.6	1.0		1.0	
	4.0–4.9	382	6.5	1.06	0.92, 1.21	1.01	0.88, 1.15
	5.0–5.9	232	9.2	1.18	1.01, 1.38	1.08	0.91, 1.27
	6.0–6.9	111	14.9	1.91	1.54, 2.34	1.58	1.27, 1.96
	≥ 7.0	51	20.1	2.21	1.64, 2.93	1.79	1.31, 2.39
Coronary heart disease mortality							
Men	< 5.0	54	2.1	1.0		1.0	
	5.0–5.9	53	2.0	1.17	0.80, 1.71	1.14	0.78, 1.67
	6.0–6.9	33	1.6	0.99	0.63, 1.51	0.83	0.52, 1.28
	7.0–7.9	17	1.8	1.21	0.68, 2.04	1.02	0.56, 1.74
	≥ 8.0	20	3.2	2.14	1.25, 3.51	1.52	0.87, 2.58
Women	< 4.0	85	1.0	1.0		1.0	
	4.0–4.9	70	1.2	1.03	0.75, 1.42	0.96	0.69, 1.31
	5.0–5.9	49	1.9	1.33	0.93, 1.89	1.08	0.75, 1.55
	6.0–6.9	34	4.6	3.13	2.08, 4.62	2.28	1.47, 3.46
	≥ 7.0	12	4.7	2.67	1.38, 4.71	1.87	0.95, 3.38
Stroke mortality							
Men	< 5.0	139	5.4	1.0		1.0	
	5.0–5.9	96	3.7	0.83	0.64, 1.07	0.82	0.63, 1.07
	6.0–6.9	72	3.4	0.85	0.64, 1.13	0.76	0.56, 1.01
	7.0–7.9	30	3.2	0.85	0.56, 1.24	0.83	0.54, 1.22
	≥ 8.0	29	4.7	1.25	0.82, 1.84	0.95	0.61, 1.42
Women	< 4.0	216	2.7	1.0		1.0	
	4.0–4.9	175	3.0	1.01	0.83, 1.23	0.96	0.79, 1.18
	5.0–5.9	103	4.1	1.10	0.87, 1.39	1.01	0.79, 1.28
	6.0–6.9	48	6.4	1.71	1.23, 2.32	1.39	0.99, 1.91
	≥ 7.0	23	9.1	2.01	1.27, 3.03	1.67	1.05, 2.55

* Values are expressed per 1000 person-years. † In addition to age, adjusted for BMI, smoking status, alcohol consumption, systolic blood pressure, total cholesterol level, histories of hypertension, diabetes, coronary heart disease, kidney disease and malignant tumor, and estimated radiation dose from the atomic bombs.

subjects were divided into 3 groups depending on baseline age: < 45, 45–54, and ≥ 55 years. As shown in Table 5, in the age groups < 45 years (most subjects likely to be premenopausal) and ≥ 55 years (most subjects likely to be postmenopausal), a significant increase in hazard ratio for all-cause and cardiovascular mortality was observed with increasing uric acid levels. In the age group 45–54 years, which includes both menstrual and postmenopausal women, the association of uric acid level with mortality was not significant.

Since information about diuretic use was not available in our study, and since most users of diuretics are patients with hypertension, those individuals were excluded, and association of uric acid level with subsequent mortality was analyzed in women. As shown in Table 6, exclusion of hypertensive individuals (n = 1781) did not affect the association of uric acid level with all-cause and cardiovascular mortality in women. Similarly, when the subjects were restricted to those without baseline cardiovascular disease, non-diabetics, non-smokers, and those with low total cholesterol (< 200 mg/dl), association of uric acid level with mortality did not substantially change except for cardiovascular mortality for those without baseline cardiovascular disease in the uric acid category ≥ 7.0 mg/dl (Table 6).

DISCUSSION

This large prospective study found that serum uric acid concentration is independently associated with cardiovascular mortality in women and with all-cause mortality in both men and women. Association of serum uric acid level with cardiovascular disease or mortality has been described in women in several other cohort studies[2,6,7,11], whereas the results in men are more inconsistent[2-4,7-14]. Among 2 large prospective studies conducted recently in the United States,

Table 5. Relation of serum uric acid level to all-cause and cardiovascular mortality stratified by age among women (fully adjusted*).

	Baseline Age Category, yrs†					
	< 45		45–54		≥ 55	
Uric Acid Level, mg/dl	Hazard Ratio	95% CI	Hazard Ratio	95 % CI	Hazard Ratio	95% CI
All-cause mortality						
< 4.0	1.0		1.0		1.0	
4.0–4.9	1.15	0.92, 1.44	0.77	0.62, 0.95	1.13	1.02, 1.26
5.0–5.9	1.27	0.93, 1.70	0.96	0.74, 1.24	1.04	0.92, 1.19
6.0–6.9	2.11	1.32, 3.22	1.01	0.68, 1.47	1.45	1.21, 1.73
≥ 7.0	2.32	0.90, 4.86	1.28	0.67, 2.20	1.72	1.35, 2.16
Cardiovascular disease mortality						
< 4.0	1.0		1.0		1.0	
4.0–4.9	1.26	0.76, 2.07	0.78	0.54, 1.11	1.00	0.86, 1.17
5.0–5.9	1.55	0.80, 2.85	1.09	0.72, 1.63	1.00	0.82, 1.20
6.0–6.9	2.14	0.72, 5.11	1.23	0.66, 2.16	1.57	1.22, 1.99
≥ 7.0	5.88	1.36, 17.5	1.83	0.63, 4.27	1.74	1.23, 2.39

* In addition to age, adjusted for BMI, smoking status, alcohol consumption, systolic blood pressure, total cholesterol level, histories of hypertension, diabetes, coronary heart disease, kidney disease and malignant tumor, and estimated radiation dose from the atomic bombs. † The number of deaths due to all causes was 414, 509, and 2036 for the age categories < 45, 45–54, and ≥ 55 years, respectively. The number of deaths due to cardiovascular disease was 88, 193, and 952 for the same age categories, respectively.

Table 6. Relation of serum uric acid level to all-cause and cardiovascular mortality in women stratified by cardiovascular risk profiles (fully adjusted*).

		All-Cause		Cardiovascular	
	Uric Acid Level, mg/dl	Hazard Ratio†	95% CI	Hazard Ratio	95 % CI
Non-hypertensives					
	6.0–6.9	1.68	1.33, 2.09	1.88	1.25, 2.72
	≥ 7.0	1.67	1.12, 2.38	1.99	1.00, 3.55
No cardiovascular disease					
	6.0–6.9	1.42	1.21, 1.66	1.76	1.13, 2.63
	≥ 7.0	1.62	1.28, 2.02	1.95	0.86, 3.81
Non-diabetics					
	6.0–6.9	1.43	1.21, 1.67	1.52	1.19, 1.91
	≥ 7.0	1.64	1.30, 2.06	1.79	1.28, 2.45
Non-smokers	6.0–6.9	1.51	1.27, 1.78	1.71	1.32, 2.17
	≥ 7.0	1.81	1.41, 2.29	2.02	1.41, 2.82
Low total cholesterol (< 200 mg/dl)					
	6.0–6.9	1.51	1.18, 1.89	1.72	1.21, 2.40
	≥ 7.0	1.80	1.28, 2.45	1.96	1.17, 3.11

* In addition to age, adjusted for BMI, smoking status, alcohol consumption, systolic blood pressure, total cholesterol level, histories of hypertension, diabetes, coronary heart disease, stroke, kidney disease and malignant tumor, and estimated radiation dose from the atomic bombs. † Hazard ratio for only 2 categories with high uric acid levels is presented.

the Framingham Heart Study showed no significant association of uric acid level with cardiovascular or all-cause mortality in either men or women[9]. The First National Health and Nutrition Examination Survey (NHANES I), on the other hand, showed a significant and independent association of uric acid level with cardiovascular and all-cause mortality in both sexes[11]. Since both studies are population-based and their adjusted confounders are similar, the source for the difference in the results is unclear. Our study utilized the largest cohort with the longest followup period among the cohorts so far analyzed, and adds further evidence for the association of uric acid level with cardiovascular mortality in women. Our population consisted entirely of Japanese subjects, and as shown in the baseline characteristics (Table 1), they are generally slimmer and have lower cholesterol levels compared with people in Western countries. Although such baseline factors were all adjusted in the analysis, ethnic differences existing in the study population might also have

played a role in the differences in results between our study and previous studies.

The strengths of our study are its large population size, long followup period, complete coverage of mortality during the followup period, and large number of subjects reaching the endpoint. Limitations include unavailability of information regarding diuretic use. Culleton, *et al* concluded that diuretic use was the major confounding factor in the apparent association of uric acid level with cardiovascular events among women in the Framingham Heart Study population[9]. On the other hand, several other studies including the NHANES I study have shown that the association of uric acid level with cardiovascular events or mortality remained significant even after adjustment for diuretic use[5,11,15-18]. We performed an analysis excluding hypertensive individuals, the major users of diuretics, and obtained nearly identical results. Therefore, it seems unlikely that diuretic use was the source for the association of uric acid level with cardiovascular mortality in our study. Unavailability of information on serum creatinine level is one more limitation of our study. It has also been reported in other studies, however, that adjustment for serum creatinine level did not render the association of serum uric acid level with cardiovascular or total mortality insignificant[5,11,15,16]. Other limitations may include misclassification of causes of death due to inaccuracy of diagnoses coded on death certificates.

Insulin resistance may be a plausible explanation for the association of uric acid level with cardiovascular disease risk since insulin resistance has been reported to be associated with both increased risk for cardiovascular events and increased serum uric acid levels[22,23]. Several other mechanisms have also been suggested, including activation of platelets and cytokine production[24-26]. Oxygen free radicals are generated when xanthine oxidase produces uric acid, and this xanthine oxidase activity in vascular endothelial cells may be associated with impaired endothelial cell function, which may in turn lead to the development of atherosclerosis[27-29]. It has also been suggested that elevated serum uric acid level may be a compensatory mechanism to counteract oxidative damage related to atherosclerosis[30,31]. In animal models, direct association of increased uric acid level with hypertension and uric acid-induced proliferation of vascular smooth muscle cells have been suggested[32,33].

The source for the difference in association of uric acid level with cardiovascular mortality between men and women in our study is unclear. A stronger association of uric acid level with cardiovascular disease in women than in men has also been reported in previous studies[2,7]. In men, serum uric acid level is generally higher than in women, a phenomenon also observed in our study. The sex difference in serum uric acid level is largely due to the difference in renal clearance rate of uric acid: men have a lower clearance rate than women[34]. Such physiological differences controlling serum uric acid level may be functioning in men in a way that obscures the association of serum uric acid level with cardiovascular risk. It may not be the case that female hormones alone contributed to the closer association of uric acid level with mortality risk in women, because the analysis stratified by age in our study suggested that the association is significant in both premenopausal and postmenopausal women.

Our study showed that serum uric acid concentration is associated with cardiovascular mortality risk in women. Although the causal mechanism for such an association remains unknown, it can be inferred that serum uric acid level may be used in both clinical and healthcare settings as a marker reflecting cardiovascular disease risk especially for women.

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ORIGINAL ARTICLE

Smoking and fracture risk: a meta-analysis

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Abstract Smoking is widely considered a risk factor for future fracture. The aim of this study was to quantify this risk on an international basis and to explore the relationship of this risk with age, sex and bone mineral density (BMD). We studied 59,232 men and women (74% female) from ten prospective cohorts comprising EVOS/EPOS, DOES, CaMos, Rochester, Sheffield, Rotterdam, Kuopio, Hiroshima and two cohorts from Gothenburg. Cohorts were followed for a total of 250,000 person-years. The effect of current or past smoking, on the risk of any fracture, any osteoporotic fracture and hip fracture alone was examined using a Poisson model for each sex from each cohort. Covariates examined were age, sex and BMD. The results of the different studies were merged using the weighted β-coefficients. Current smoking was associated with a significantly increased risk of any fracture compared to non-smokers (RR = 1.25; 95% Confidence Interval (CI) = 1.15–1.36). Risk ratio (RR) was adjusted marginally downward when account was taken of BMD, but it remained significantly increased (RR = 1.13). For an osteoporotic fracture, the risk was marginally higher (RR = 1.29; 95% CI = 1.13–1.28). The highest risk was observed for hip fracture (RR = 1.84; 95% CI = 1.52–2.22), but this was also somewhat lower after adjustment for BMD (RR = 1.60; 95% CI = 1.27–2.02). Risk ratios were significantly higher in men than in women for all fractures and for osteoporotic fractures, but not for hip fracture. Low BMD accounted for only 23% of the smoking-related risk of hip fracture. Adjustment for body mass index had a small downward effect on risk for all fracture outcomes. For osteoporotic fracture, the risk ratio increased with age, but decreased with age for hip fracture. A smoking history was associated with a sig-

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nificantly increased risk of fracture compared with individuals with no smoking history, but the risk ratios were lower than for current smoking. We conclude that a history of smoking results in fracture risk that is substantially greater than that explained by measurement of BMD. Its validation on an international basis permits the use of this risk factor in case finding strategies.

Keywords Body mass index · Hip fracture · Meta-analysis · Osteoporotic fracture · Smoking

Introduction

It is well established that smoking is associated with a reduction in bone mineral density (BMD) in postmenopausal women and men [1]. A meta-analysis has suggested that the risk of hip fracture may also be markedly increased [2]. In current smokers, the risk of hip fracture ompared with non-smokers was similar in women up to the age of 50 years. However, it increased thereafter, to a risk ratio (RR) of 1.17 at 60 years, 1.41 at 70 years and 1.71 at 80 years. In 90-year-old women the risk ratio was 2.08 [2]. In population-based samples, the risk of other osteoporotic fractures also appears to increase [3], but this is not an invariant finding [4]. The risk of forearm fractures does not appear to increase among smokers [3, 5 ,6].

Increased fracture risk may in part be due to the fact that patients who smoke have low BMD [1]. Studies adjusted for BMD suggest that the relative risk is only modestly adjusted downward [7]. In the meta-analysis of Law and Hackshaw [2], although the difference in bone density between smokers and non-smokers was not apparent at age 50, it became noticeable with increasing age, so that at age 80 bone mineral density at the hip was 0.45 SD lower in smokers, as compared with non-smokers. From the relationship between bone mineral density in the hip and hip-fracture risk, the risk ratio in smokers was estimated at 1.56, compared with a direct estimate of 1.71 for hip fractures. This led the authors to suppose that the majority of any risk was attributable to decreased bone density.

The association between smoking and subsequent fracture risk has led to the inclusion of current smoking as a risk factor in assessment guidelines in the United States and Canada [8, 9], if not in Europe [11, 12, 13]. Since smoking is considered a risk factor, partly independent of BMD, intervention is recommended in smokers with a *T*-score for BMD of −1.5, whereas in non-smokers the intervention threshold is set at −2.0 SD. Attention has focused recently on assessing fracture probability by using multiple risk factors, rather than BMD alone, to provide intervention thresholds [8, 14, 15]. This demands knowledge of the interrelationships between these risk factors. The aim of our study was to quantify, in an international setting, the risk associated with smoking for future fractures and to explore the dependence of this risk on age, sex, body mass index (BMI) and BMD.

Materials and methods

We studied 59,232 men and women, of whom 18% had a history of current smoking, taken from ten prospectively studied cohorts. Brief details of these cohorts appear below and are summarized in Table 1.

CaMos

The Canadian Multicentre Osteoporosis Study (CaMos) is a current, prospective age-stratified cohort. The study documents the incidence of fractures and risk factors in a random sample of 9,424 men and women aged 25 years or older, selected by telephone listings. The sampling frame is from nine study centers in seven provinces [16]. Individuals were characterized by interview. BMD was measured by DXA (Dual X-ray absorptiometry) at the hip, using the Hologic QDR in seven centers and the Lunar DPX Alpha in two centers.

Table 1 Details of cohorts studied

Cohort	Sample size	% Women	Person-years	Mean age (years)	Smoking history (%)		Any kind of fracture	Osteoporotic fracture	Hip fracture
					Current	Ever			
CaMos	9,401	69	26,656	62.1	-	54	586	316	42
DOES	2,163	61	16,333	70.7	8	41	532	418	107
EVOS/EPOS	13,841	52	41,429	63.8	20	52	731	731	50
Gothenburg I	2,320	61	16,255	78.7	15	41	424	424	332
Gothenburg II	7,012	100	29,335	58.9	25	49	433	438	29
Hiroshima	1,937	69	7,563	64.8	20	34	134	64	21
Kuopio	11,798	100	56,602	52.3	11	-	1,053	-	-
Rochester	998	65	6,212	56.8	-	47	289	244	42
Rotterdam	7,590	60	42,613	70.1	23	63	967	746	271
Sheffield	2,172	100	6,900	80.0	7	46	290	241	63
Totals	59,232	74	249,898	62.8	18	52	5,444	3,495	957

DOES

The Dubbo Osteoporosis Epidemiology Study (DOES) is a population-based study with multiple assessments of skeletal status in men and women from Dubbo, Australia, and at least 60 years old [17, 18]. Study participation was 56% of the population. Baseline measurements included BMD at the femoral neck, assessed using DXA (GE-Lunar, DPX and Prodigy). Fractures are identified through radiologists' reports from the two centers servicing the region.

EVOS/EPOS

The European Vertebral Osteoporosis Study (EVOS) comprised age- and sex-stratified random samples from 36 centers in 19 European countries [19]. Equal numbers of men and women were drawn in each center within six sequential 5-year age bands (from 50 to 79 years). A baseline radiograph for vertebral-fracture prevalence was undertaken in 15,570 men and women. BMD was measured in 3,461 men and women from 13 centers, by DXA at the femoral neck using pencil-beam machines cross-calibrated with the European spine phantom. The sample provided the framework for the European Prospective Osteoporosis study (EPOS), in which repeated assessment was undertaken in 29 of the centers [20, 21].

Gothenburg I

This study comprised four birth cohorts of 2,375 randomly sampled men and women aged at least 70, followed for up to 20 years in Gothenburg, [22, 23] after a baseline BMD measurement. Participants were drawn randomly from the Gothenburg population register by date of birth, to provide cohorts aged 70, 76, 79 and 85 years at the time of investigation. Bone mineral density was measured at the right heel using dual photon absorptiometry.

Gothenburg II

The Gothenburg study comprised a randomly drawn population cohort of approximately 7,000 women aged 21–89, followed for up to 7.9 years (mean = 4.2 years) [24]. Seventy percent of those invited participated in the study, which examined risk factors for osteoporosis through a standardized questionnaire. BMD was assessed at baseline at the distal forearm, using the Osteometer DTX 200.

Hiroshima

The Adult Health Study in Hiroshima (AHS) was established to document late health effects of radiation exposure among atomic-bomb survivors in Hiroshima and Nagasaki. The original AHS cohort consisted of about 15,000 atomic-bomb survivors and 5,000 controls selected from residents in Hiroshima and Nagasaki, using the 1950 national census supplementary schedules and the Atomic Bomb Survivors Survey. AHS subjects have been followed through biennial medical examinations since 1958, with a participation rate of approximately 80%. BMD at the lumbar spine and proximal femur has been measured at each biennial health examination using DXA (Hologic QDR-2000) since December 1993. At each examination, trained nurses interviewed subjects about fractures and measured height and weight [25, 26].

Kuopio

The Kuopio Osteoporosis Risk Factor and Prevention (OSTPRE) study in Finland was based on a postal enquiry sent to all of the 14,220 women aged 47–56 residing in Kuopio province in 1989. Of these, 13,100 responded, 1,214 of whom were excluded due to incomplete information. This left a study population of 11,886 women. A random stratified sample of 3,222 underwent bone mineral densitometry at the femoral neck, with DXA using the Lunar DPX [27].

Rochester

The Rochester cohort was recruited from two random population samples stratified by decade of age. One sample included women who were followed for up to 20 years [28], and the other was composed of women and men followed for 8 years [29]. BMD of the right femoral neck was measured—by dual photon absorptiometry for the first cohort (cross-calibrated to DXA), and by DXA (Hologic QDR 2000) for the second group. Fractures were ascertained by periodic interview combined with review of the inpatient and outpatient medical records of all local care providers.

Rotterdam

The Rotterdam study, begun in 1990, was a prospective cohort study that aimed to examine and follow up on all residents aged 55 years and older living in Ommoord, a district of Rotterdam [30]. By 1993, 7,983 residents had been included (response rate 78%). Bone mineral density was assessed at the femoral neck by DXA, using a Lunar DPX-L. Fracture follow-up was done using an automated link with general practitioner computer systems and hospital admission data [31]. Fracture data were collected and validated by two independent research physicians. For this analysis, validated fracture follow-up was available for 7,590 participants (3,012 men), with an average follow-up time of 6 years.

Sheffield

The Sheffield cohort comprised women aged 75 years or older, selected randomly from the population of Sheffield, UK, and surrounding districts, between 1993 and 1999. Approximately 35,000 women, identified from general practitioner listings, were contacted by letter and invited for assessment of their skeletal status. Of the 5,873 women agreeing to attend the screening visit, 281 were excluded. The remainder were randomly allocated after they gave informed consent to treatment with the bisphosphonate clodronate, or to an identical placebo. This study is still in progress. The material used for the present paper included 2,148 women allocated to treatment with placebo [32]. All women had baseline assessment of BMD at the femoral neck, using the Hologic 4500. Outcomes were assessed by home visits at 6-month intervals.

Baseline and outcome variables

A history of current or past smoking was obtained by self-report. For the EVOS/EPOS, Hiroshima and Gothenburg I cohorts, this was recorded as past or current use of tobacco. For the Gothenburg II cohort, the same data were collected, but use for 6 months qualified as past or current use. For Rotterdam, Sheffield and DOES, tobacco use was recorded as previous, current or never. Data on current smoking was not available for two cohorts (CaMos and Rochester). Height and weight were measured using standard techniques in all cohorts. BMI was calculated as weight in kg divided by height squared in m. Bone mineral density was assessed by multiple techniques as described above. For the purposes of this analysis, we utilized BMD assessed at the femoral neck by DXA, with the exception of the Gothenburg cohorts, for which BMD was assessed by DPA at the heel and DXA at the distal forearm.

Fractures were ascertained from self-reports (Sheffield, Kuopio, EVOS/EPOS, Hiroshima) and/or verified from hospital or central databases (Gothenburg, CaMos, DOES, Sheffield, EVOS/EPOS, Rochester, Rotterdam). The EPOS study also included sequential systematic radiography to define incident vertebral deformities, but the data were not used in this analysis. Our analysis used information on any kind of clinical fracture and on clinical fractures considered to be osteoporotic. In addition, hip fracture was considered separately. An osteoporotic fracture was one that the investigator considered to be due to osteoporosis, except as indicated below. For the EVOS/EPOS study, osteoporotic fractures comprised hip, forearm, humeral or spine fractures. For the CaMos study, they comprised fractures of the spine, pelvis, ribs, distal forearm, forearm and hip. In the other cohorts (Sheffield, Rotterdam, Rochester, Gothenburg I and II, Hiroshima) fractures at sites considered characteristic for osteoporosis were extracted [33]. Details about the number of participants, gender and fractures are provided in Table 1.

Statistical methods

The risk of fracture was estimated by Poisson regression, applied separately to each cohort and sex [32]. Covariates included time since start of follow-up, current age, history of smoking, and BMD. We also excluded BMD from the model. The beta coefficient for each sex in each cohort is age-dependent, $\text{beta}_k + \text{beta}_{k+1} \times \text{age}$. The estimated value of the βcoefficients and their variance was determined for each age within the range of 50 to 85 years. Results of each cohort and both sexes were weighted according to the variance and merged to determine the weighted mean and standard deviations. The risk ratio of those who currently smoked or ever smoked versus those without a smoking history was equal to weighted e^{mean}. In further models, we examined the effects including BMI with and without BMD. There was little heterogeneity between cohorts in the relationship between hip-fracture risk and smoking ($I^2 = 12\%$; 95% CI (confidence interval) = 0–53%), and a fixed-effect model was used [34].

The component of the risk ratio explained by BMD was computed from a meta-analysis of BMD and fracture risk [35]. The risk of any fracture was assumed to increase 1.6-fold for each SD decrease in BMD. For hip fracture, the gradient of risk was assumed to be 2.6 per SD. The proportion of risk attributed to a low BMD was computed as

$$\frac{[\log\ RRa/\log\ GR] - [\log\ RRb/\log\ GR]}{[\log\ RRa/\log\ GR]}$$

Where RR_a is the unadjusted risk ratio, RR_b is the risk ratio adjusted for BMD, and GR is the gradient of risk.

Results

Of 59,232 men and women studied, 867 men and 4,577 women were identified as having a subsequent fracture

Table 2 Prevalence of smoking history in men and women by age

Age (years)	Probability of smoking (%)		
	Men	Women	Combined
50	41.3	26.8	32.9
55	37.2	22.3	28.4
60	33.3	18.3	24.3
65	29.6	15.0	20.6
70	26.1	12.1	17.4
75	22.9	9.7	14.6
80	20.0	7.8	12.1
85	17.4	6.2	10.0

(any kind), of which 677 men and 2,817 women were characterized as osteoporotic. Of these, 207 men and 750 women sustained a hip fracture. The total follow-up in person years was 61,563 in men and 188,334 in women. BMD measurements were available in 36,550 individuals (64%) and BMI in 96%. The prevalence of smoking among the cohorts decreased almost linearly with age in men and women ($p < 0.001$; Table 2). At all ages, current smoking was higher in men than in women.

Current smoking

Current smoking was associated with a significantly increased risk of any kind of fracture, including osteoporotic or hip fractures taken alone, in both men and women (Table 3). For any kind of fracture and for osteoporotic fractures taken alone, the risk in smokers was significantly higher in men ($p = 0.015$) than in women ($p = 0.03$). For hip fractures taken alone, there was no difference in the risk ratio between men and women. For men and women combined, risk with current smoking was highest for hip fracture (RR = 1.84), lowest for fractures taken overall (RR = 1.25) and intermediate for osteoporotic fracture (RR = 1.29).

Risk ratio was adjusted downward somewhat when taking BMD into account (see Table 3). In women, for any fracture overall or osteoporotic fracture specifically, the associations between smoking and fracture were no longer significant. In men, the effect was less marked or not apparent. In men and women together, low BMD accounted for the minority of the risk associated with current smoking. For fractures overall, 45% of the risk was explained by BMD, whereas for osteoporotic fracture alone it was 40% and for hip fracture, only 23%.

BMI

The risk ratios for smokers were also adjusted downward when account was taken for BMI, though all ratios remained significantly increased (Table 4). The downward adjustment was less than the adjustment for BMD alone. When smoking, BMI and BMD were entered into the model, a further decrease in risk ratio was observed, although the risk ratios remained above unity, significantly so for the risk of (any) fractures overall and for hip fracture.

Table 5 Risk ratio (*RR*) and 95% confidence intervals (CI) for osteoporotic and hip fractures in current smokers for men and women combined

Age (years)	Without BMD		Adjusted for BMD	
	RR	95% CI	*RR*	95% CI
(a) Osteoporotic fracture				
50	1.05	0.80–1.37	0.82	0.57–1.18
55	1.06	0.86–1.30	0.85	0.65–1.12
60	1.08	0.92–1.26	0.88	0.72–1.08
65	1.14	1.00–1.30	0.91	0.76–1.09
70	1.27	1.12–1.45	1.01	0.85–1.20
75	1.45	1.28–1.65	1.20	1.01–1.43
80	1.54	1.34–1.77	1.30	1.08–1.57
85	1.52	1.28–1.80	1.28	1.00–1.63
(b) Hip fracture				
50	2.52	1.24–5.10	2.28	0.94–5.51
55	2.35	1.32–4.19	2.09	1.03–4.24
60	2.17	1.38–3.44	1.87	1.07–3.25
65	1.98	1.38–2.86	1.68	1.07–2.65
70	1.92	1.42–2.60	1.69	1.15–2.48
75	1.94	1.52–2.49	1.76	1.30–2.37
80	1.91	1.55–2.35	1.69	1.31–2.19
85	1.80	1.43–2.26	1.57	1.16–2.13

Table 3 Risk ratio of fracture (*RR*) and 95% confidence interval (CI) associated with current smoking by fracture outcome in men and women

Outcome	Sex	*RR*	95%CI	RR[a]	95%CI
Any kind of fracture	M	1.50	1.26–1.77	1.49	1.20–1.84
	F	1.18	1.07–1.30	1.02	0.90–1.16
	M+F	1.25	1.15–1.36	1.13	1.01–1.25
Osteoporotic Fracture	M	1.53	1.27–1.83	1.54	1.21–1.95
	F	1.20	1.06–1.35	1.01	0.87–1.17
	M+F	1.29	1.17–1.43	1.13	1.00–1.28
Hip fracture	M	1.82	1.34–2.49	1.69	1.16–2.48
	F	1.85	1.46–2.34	1.55	1.16–2.07
	M+F	1.84	1.52–2.22	1.60	1.27–2.02

[a]Risk ratio adjusted for BMD

Table 4 Risk ratio (*RR*) for fracture in current smokers (men and women combined) adjusted for age, BMD, BMI and both BMD and BMI. *CI* confidence interval

	Outcome fracture					
	Any		Osteoporotic		Hip	
Adjustment	*RR*	95% CI	*RR*	95% CI	RR	95% CI
Age	1.25	1.15–1.36	1.29	1.17–1.43	1.84	1.52–2.22
Age BMD	1.13	1.01–1.25	1.13	1.00–1.28	1.60	1.27–2.02
Age BMI	1.19	1.09–1.30	1.21	1.08–1.34	1.65	1.34–2.03
Age, BMI, BMD	1.12	1.01–1.25	1.11	0.98–1.26	1.55	1.23–1.96

Age

Risk ratios increased with age for any fracture and for osteoporotic fractures specifically, but they were significantly higher than unity at all ages (Table 5). With adjustment for BMD, current smoking was a significant risk only from the age of 70 years. In contrast, for hip fracture risk, the risk ratio decreased with age but was significantly higher than unity at all ages with or without adjustment for BMD.

Ever-smokers

A history of smoking (ever smoked) was also associated with a significant risk increase for any fracture, and, specifically, for an osteoporotic or hip fracture (Table 6). The risk ratios were lower than for current smoking (see Table 3), but, just as in that case, were highest for hip fracture. There was no significant difference in risk ratio between men and women, no difference when adjusted for BMD, and no significant effect of age on the risk ratio (data not shown). The exclusion of data from the Gothenburg cohorts (where BMD was assessed at the heel or forearm) had no material effect on these results (data not shown).

Discussion

The present study confirms that a history of smoking carries a modest but significant risk for future fractures. In addition, the effect of smoking is over and above that which can be explained by variations in BMD. The risk of subsequent fractures was greater in the case of hip fracture than for all fractures, and intermediate for osteoporotic fractures. For hip-fracture risk in women, the increase in risk ratio (1.85) was comparable to that described in the meta-analysis from Law and Hackshaw [2]. In their findings, risk ratios increased with age; however, in the present study risk ratios for hip fracture tended to decrease with age. In contrast, risk ratios for osteoporotic fractures (which included hip fractures) increased with age. The strength of the association we found was lower than for ever-smokers, consistent with the view that the effect of smoking appears to wane slowly after a person stops smoking [36].

A particular strength of the present study is that the estimate of risk is from an international setting, from randomly or quasi-randomly selected population cohorts, and the calculations were based on the primary data. This decreases the risk of publication and selection biases, which may have large effects. For example, in the large, prospective study from Kuopio, the risk of fracture for current smokers was 1.47 (95% CI = 1.05–2.06) when the sample included individuals selected on the basis of risk factors. From the random population sample used in the present study, the relative risk for fractures overall was 1.18 (95% CI = 0.70–2.00) [3]. Furthermore, the consistency of the association within cohorts indicates the generalizability of this risk factor's importance.

The large sample size studied permitted us to examine risk by age. For all fractures and for osteoporotic fractures specifically, the risk ratios were relatively constant with age. If anything, they tended to increase with age. In the case of hip fracture, risk ratios decreased with age, but this was not significant. Much larger samples would be needed to verify such an effect. A limitation of this study was that we were unable to examine the dose dependency of the association, due to differences in the way that smoking histories were obtained. In this regard, men tend to smoke more than women. This may account for the slightly higher risk ratios observed in men.

The present study also quantifies the independent contributions of low BMD or BMI to the risks associated with smoking. Low BMD explained a minority of the total risk, contradicting the findings of Law and Hackshaw [2] but agreeing with others [7]. With regard to BMD, there are several mechanisms whereby smoking might adversely affect fracture risk. Female smokers may have increased rates of bone loss after menopause [37], but this is not consistently found [38, 39]. Smoking women also have earlier menopause [37, 40, 41]. It has been suggested that smoking may enhance estrogen catabolism [42]. The effects of hormone replacement therapy (HRT) have in some, but not all, studies been attenuated among smokers [43, 44]. Smokers are also thinner and, hence, have lower body mass index [40, 45]. Consequently, the protective effect of adipose tissue and peripheral estrogen metabolism is impaired. Bone loss is reported to be higher in male smokers than in female smokers [38], perhaps due to men's higher exposure to cigarette smoking. We observed higher risk ratios for men than for women for any fracture and for osteoporotic fracture specifically. Such effects may explain the component of fracture risk that is attributable to low BMD or BMI. However, as shown in the present study, this represents a minority of the risk.

The mechanism for the BMD-independent increase in risk could not be determined from this study. Possibly, it results, in part, from lower levels of physical activity or

Table 6 Risk ratio (*RR*) associated with a smoking history by subsequent fracture outcome in men and in women. *RR* is not adjusted for BMD

Outcome	Sex	*RR*	95% confidence interval
Any fracture	M	1.27	1.07–1.51
	F	1.18	1.10–1.26
	M + F	1.19	1.12–1.27
Osteoporotic fracture	M	1.34	1.10–1.63
	F	1.15	1.07–1.25
	M + F	1.18	1.09–1.27
Hip fracture	M	1.11	0.67–1.83
	F	1.42	1.18–1.72
	M + F	1.38	1.15–1.65

to co-existing morbidity, which might in turn increase the risk of falls or impair protective responses to injury [46, 47, 48]. It is also possible that smoking-induced changes in the microarchitecture of cancellous bone would weaken the resistance to mechanical force out of proportion to any effect on BMD. Finally, errors in measurement of BMD [49] will result in the underestimation of bone's contribution to fracture risk.

Whatever the mechanism involved, these data indicate that the risk of fractures is greater for smokers and those with a history of smoking than it is for individuals of the same age, sex and BMD who do not or did not smoke. This has implications for intervention thresholds. Health economic analyses suggest that intervention is cost-effective when treatment is targeted to women with a *T*-score of −2.5 SD at the femoral neck [15]. Since smoking carries a risk over and above that provided by BMD alone, intervention thresholds for BMD can be less stringent in smokers and still yield the same cost-effectiveness. This approach has been incorporated into health economic analyses [8, 50]. However, a large number of additional and stronger independent risk factors for fracture have been identified. These include a history of fracture, corticosteroid exposure, a family history of fracture, secondary osteoporosis, and possibly the biochemical indices of bone turnover [15, 51, 52, 53, 54]. Before these risk factors can be readily used for assessing fracture risk in the general population, their interrelationships will need to be determined.

We conclude that a history of smoking results in a substantial risk for future fractures and that this risk is largely independent of BMD. The fact that this association holds up on an international scale provides a rationale for using this risk factor in case-finding strategies. Moreover, identified patients can be targeted for treatment at lower BMD thresholds than are non-smoking individuals of the same age who have osteoporosis .

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INVITED PAPER

Saeko Fujiwara

Epidemiology of osteoporosis in Japan

Key words Epidemiology · Osteoporosis · Prevalence · Incidence · Spine fracture

Introduction

Osteoporosis is a common disease among postmenopausal women and the elderly, leading to an increased susceptibility to bone fracture. Spine fracture or hip fracture cause profound physical impairment and a reduction in quality of life in the elderly. In Japan, the average life expectancy is 84 years for women and 77 years for men, one of the longest in the world. More than 90% of women live to be 65, and about 70% are alive at the age of 80. With the lengthening of the life span, fractures related to osteoporosis become a major health problem and an enormous economic burden in Japan and Asian countries as well as in other developed countries. Spine fractures are the most common form of osteoporotic fractures, but few epidemiological studies of spine fracture are available in Japan or in other Asian countries. Results from such studies are discussed here.

Spine fracture prevalence

The prevalence of spine fracture varies according to the population studied and the diagnostic criteria used. Some reports exist on the prevalence of spine fracture in Japan. Because different diagnostic criteria were used in each cohort, however, we cannot strictly compare the prevalence among the three cohorts. The three prevalence studies [1–3] demonstrated that the prevalence of spine fracture ranged from 8% to 13% and from 30% to 40% in women in their sixties and seventies, respectively (Fig. 1).

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In Asian countries, the prevalence among Japanese in Hiroshima was compared with that among Japanese-Americans in Hawaii and Caucasian Americans in Minnesota (United States) using the same diagnostic criteria [1]. In the criteria used, fractures were defined as vertebral height more than 3 standard deviations (SD) below the vertebra-specific mean. Compared to Japanese-Americans in Hawaii, the prevalence of spine fracture is greatest among Japanese in Hiroshima; odds ratios were 1.8 for Japanese women and 1.5 for American Caucasians (Fig. 2). A study in Hong Kong showed that the prevalence of spine fracture was 30% [4] in Chinese women aged 70–79, compared with 26% in American Caucasians, when a cutoff of 3 SD below the mean for vertebral height ratio was used. In Chinese people in Taiwan, the overall adjusted prevalence rate of spine fracture for women older than 65 was 20% and that for men 12.5% [5]. From these three studies, we may summarize that the prevalence of spine fracture in Asians is higher than that in Caucasians. However, a study in Beijing [6] demonstrated that the age-standardized prevalence of spine fracture was 5.5% lower among Chinese than that found using similar methods among women in Rochester, MN (USA). Further study is needed to determine if regional differences exist in the prevalence of spine fracture among Asian countries, or between Asians and Caucasians in the United States and Europe, using standardized diagnostic criteria.

Incidence of spine fracture

To our knowledge, there are only two reports determining the incidence of spine fracture among Japanese, but no reports about other Asian countries. Both reports in Japan are based on data obtained from the Adult Health Study (AHS) [7,8]. The AHS was established in 1950 to observe the late effects of radiation exposure among atomic bomb survivors in Hiroshima and Nagasaki. The original AHS cohort consisted of about 20000 atomic bomb survivors selected from residents in Hiroshima and Nagasaki using

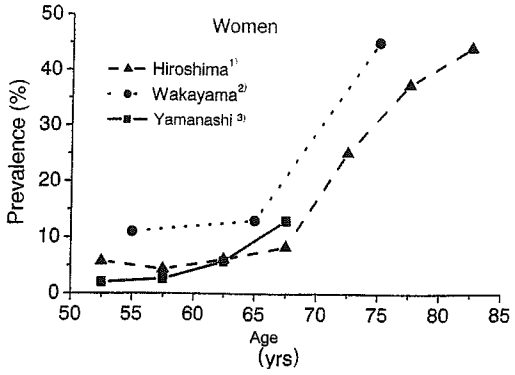

Fig. 1. Comparison of prevalence of spine fracture among three regions in Japan

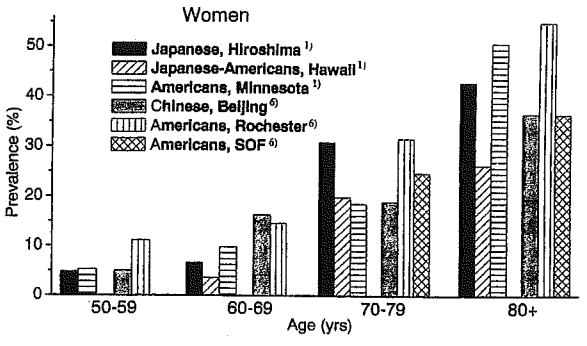

Fig. 2. International comparison of prevalence of spine fracture in women. *SOF*, Study of Osteoporotic Fractures

the 1950 national census. Since 1958, the AHS subjects have been followed through biennial health examinations including physical examination, measurements of height and weight, chest X-rays, and others. In a recent report [8], incidence of spine fracture was determined among about 2300 participants in the AHS during 1994 and 1996. Spine fracture was assessed using semiquantitative methods in which a new radiographic spine fracture was defined as a decrease of at least 20% in height of any vertebral body from initial reading to the end of the study.

The incidence of spine fracture increased exponentially with age among men and women. The age-specific incidence was twice as high in women as in men (Fig. 3). The incidence of spine fracture in the AHS cohort was compared with Caucasians in two European cohorts [9,10] (Fig. 3). Although we cannot compare these results strictly because of the use of different criteria for defining spine fractures, it seems that the incidence was about twofold higher in Hiroshima than in the Rotterdam and the European Prospective Osteoporosis Study (EPOS) cohorts.

Predictors for future fractures

Compared with Caucasians in the United States and Europe, bone mineral density (BMD) among Japanese is

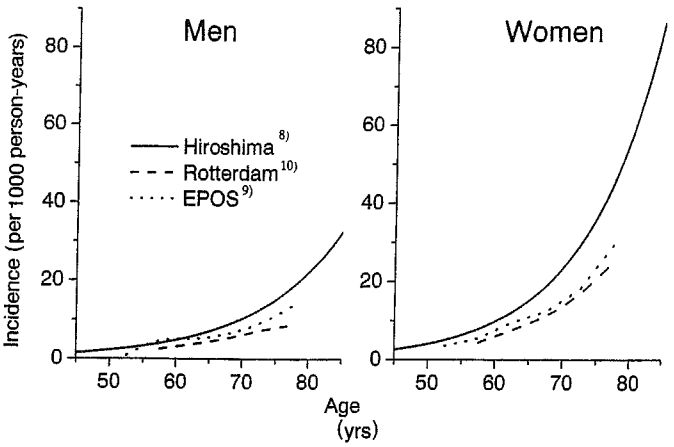

Fig. 3. Comparison of incidence of spine fracture among Hiroshima cohort and cohorts in Europe. *EPOS*, European Prospective Osteoporosis Study

lower, the prevalence of spine fracture is higher, and the incidence of hip fracture is lower. It is well recognized that BMD could predict future fracture. In the United States and Europe, a number of prospective studies have assessed the value of BMD as a predictor of future fracture. However, there is one report [8] based on a longitudinal study on BMD and subsequent fracture risk in Japan and in other Asian countries.

The relationship between baseline BMD and future fracture risk was determined among about 2400 men and women who participated in the AHS from 1994 to 1995. The mean ages in the 1994–1995 examination of the subjects ±1 SD were 62.9 ± 9.8 years for men and 65.4 ± 9.8 years for women. BMD at the spine (L2–L4) and proximal femur was measured at each biennial health examination using dual X-ray absorptiometry (DXA; QDR-2000; Hologic, Waltham, MA, USA). During the follow-up period, 27 men and 149 women developed a new spine fracture and 21 women but no men developed a new hip fracture. Follow-up averaged 4 years after baseline measurements of BMD.

Multivariate analyses showed that age, baseline BMD at the spine and hip, and prior spine fracture independently predicted future spine fracture in both men and women and hip fracture in women. However, weight, height, body mass index (BMI), and age at menopause did not predict spine fracture after adjusting for age, BMD, and prior spine fracture.

After adjusting for prior spine fracture, both baseline spine and femoral neck BMD predicted spine and hip fracture risk, and the relative risk declined with age. This finding suggests that the contribution of fracture risk factors such as falls and neuromuscular impairment other than BMD may be greater to develop hip or spine fracture among the eldest population. The meta-analysis [11] showed that most measurement sites had virtually the same predictive ability for a decrease of 1 SD in BMD, and each standard deviation reduction in BMD at the spine or hip increased the age-adjusted risk of fracture by a factor of about 2. However, femoral neck BMD was better for

Table 1. Relative risk for fracture per 1 SD decrease in bone mineral density (BMD): Japanese vs. Caucasian women

Population	Site of BMD	Fracture site	
		Spine	Hip
Japanese [8]	Spine	1.5 (1.3–1.9)	1.4 (1.0–2.5)
Meta-analysis [11]		1.9 (1.8–2.0)	1.5 (1.3–1.7)
Japanese [8]	Femoral neck	1.8 (1.4–2.3)	2.9 (1.3–4.4)
Meta-analysis [11]		1.9 (1.8–2.1)	2.4 (2.2–2.6)

predicting hip fracture, with relative risk of 2.6. Comparing the relative risks between Japanese and Caucasian populations, the relative risk for spine or hip fracture per decrease in BMD is similar in Japanese to that in other populations including Caucasians in the United States and Europe (Table 1), even if BMD at the same age differed between these populations.

After adjusting for age and baseline spine BMD, prior spine fracture was associated with about a fourfold increase in future spine fracture risk among men and a threefold increase among women. Numerous studies and meta-analysis [12,13] using mainly Caucasian populations have reported that prior fracture is an independent risk factor for future fracture among men and women, with a relative risk of about 2. Prior fracture is an important predictor for future fracture among Japanese as well as among Caucasian populations.

In summary, age, BMD, and prior spine fracture are important predictors of future fracture among Japanese. Predictive abilities of BMD and prior fracture for future fracture are similar in men and women, and similar in Japanese and Caucasians.

Conclusions

Epidemiological studies in Japan and in other Asian countries have demonstrated that prevalence or incidence of spine fracture differed among regions and countries, and most of the results showed that the prevalence of spine fracture was higher among Asians compared with Caucasians in the United States and Europe. The prospective study in Japan demonstrated that BMD and prior fracture could predict future fracture in Japanese as well as BMD did in the other cohorts in the United States and Europe, with similar predictive ability.

In Asian countries, several cross-sectional epidemiological studies have been conducted, but few prospective studies. More prospective studies are needed in Asian countries to clarify the incidence and relationship between risk factors, including BMD and future fracture risk.

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SPECIAL REPORT

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The Subcommittee to Study Diagnostic Criteria for
Glucocorticoid-Induced Osteoporosis**

Guidelines on the management and treatment of glucocorticoid-induced osteoporosis of the Japanese Society for Bone and Mineral Research (2004)

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Key words Steroid (glucocorticoid) · Osteoporosis · Guideline

Introduction

Osteoporosis is the most frequent adverse effect of glucocorticoids. Management guidelines were developed [1] in the United States in 1996 when the seriousness of glucocorticoid-induced osteoporosis as a complication of glucocorticoid therapy was recognized, and they have since been revised [2–6]. In Japan, the Japanese Society for Bone and Mineral Research established a study group on osteoporosis diagnostic criteria in 1999 and then the Subcommittee to Study Diagnostic Criteria for Glucocorticoid-Induced Osteoporosis in 2001 to examine diagnostic criteria for glucocorticoid-induced osteoporosis, and the present guidelines were developed for clinical practice (Fig. 1).

Guidelines on the management and treatment of glucocorticoid-induced osteoporosis

Drafting policy

The Subcommittee to Study Diagnostic Criteria for Glucocorticoid-Induced Osteoporosis was initially organized to determine diagnostic criteria. However, guidelines on glucocorticoid-induced osteoporosis in various countries

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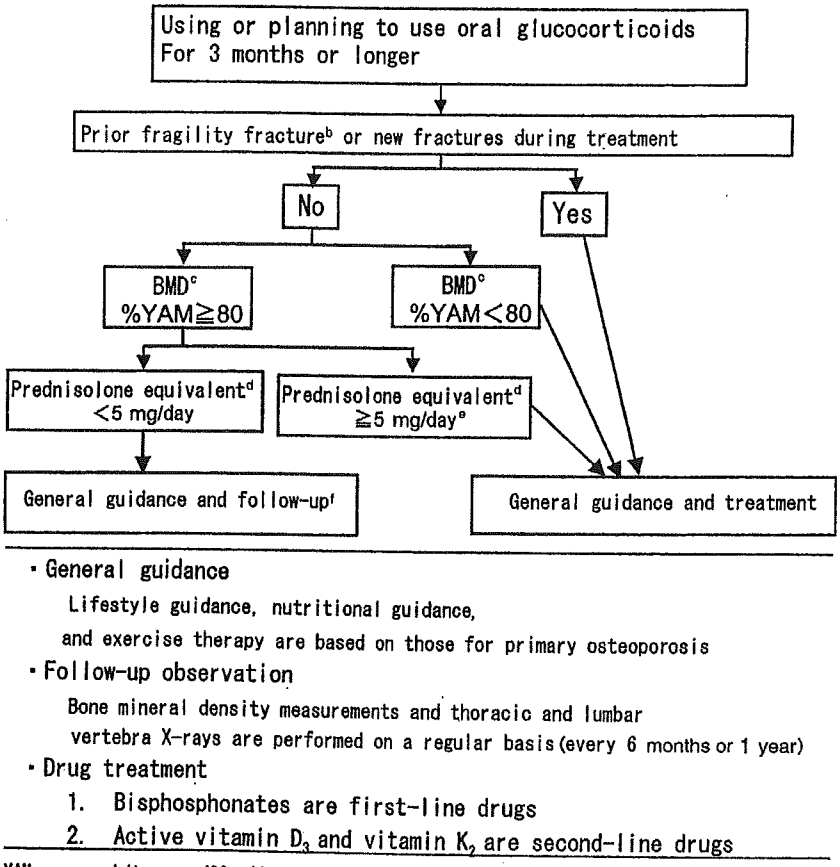
Fig. 1. Guidelines on the management and treatment of corticosteroid-induced osteoporosis (2004 edition)[a]



YAM. young adult mean (20–44 years old); BMD, bone mineral density
[a]These Guidelines cover patients 18 years of age and older
[b]Definition of fragility fractures is the same as that for primary osteoporosis
[c]Bone mineral density (BMD) measurements are based on those for primary osteoporosis (2000 revised edition)
[d]Mean daily dose
[e]Patients administered 10 mg or more per day are at risk of fractures even when bone mineral density is high (cut-off value, %YAM90)
[f]Risk of fractures is higher in the elderly

are guidelines for primary and secondary prevention and do not specify diagnostic criteria. The subcommittee discussed this point, and a draft of management and therapeutic guidelines in Japan based on evidence available at present was prepared.

Patients studied by the Subcommittee to Study Diagnostic Criteria for Glucocorticoid-Induced Osteoporosis

The survey items were sex, age, height, body weight, underlying disease, bone mineral density (type of instrument used, region, measured value), glucocorticoid treatment history (dose, mean dose for 6 months until measurement of bone mineral density, maximum dose throughout administration period, total administration period, total dose, pulse therapy within 1 year, use of glucocorticoids for inhalation), osteoporosis treatment history, and fracture history. The facilities connected with the Subcommittee, that is, Osaka City University, Kawasaki Medicine University, Kyushu University, Kyushu University Hospital at Beppu, Kinki University, Sapporo Yamanoue Hospital, Research Institute and Practice for Involutional Diseases, Tokyo Metropolitan Tama Geriatric Hospital, Tokyo Metropolitan Geriatric Medical Center, Hamamatsu University School of Medicine, Fujita Health University, and Radiation Effects Research Foundation, were requested to conduct the survey. As a result, a total of 692 patients were recruited up to 2002 in addition to the 299 patients recruited in 1999 and 2000, including 627 women and 65 men. The most common underlying disease was rheumatoid arthritis (RA) in 319 patients, and 373 patients had diseases other than RA; these included 162 cases of systemic lupus erythematosus (SLE), 27 of progressive systemic sclerosis (PSS), 26 with mixed connective tissue disease (MCTD), 20 with polymyositis/dermatomyositis (PM/DM), 16 with polymyalgia rheumatica (PMR), 12 with nephrosis, 10 with asthma, 10 with idiopathic thrombocytopenic purpura

(ITP), and 90 with other diseases. The results of an analysis of a 2-year follow-up survey on 220 patients administered glucocorticoids by Tanaka and Oshima [7] were added to these analytical results, and work on establishment of the guidelines proceeded.

Evidence for drafting the guidelines

Subjects

These guidelines cover men and women 18 years of age or older. Growth disorders caused by glucocorticoids are a serious problem in children, but at present no evidence that can be used has been reported in Japan or overseas, and children were excluded. Because of the same lack of evidence concerning glucocorticoids injected intravenously, only patients using oral glucocorticoids for which evidence is available in Japan and overseas were subjects. There is no evidence concerning the administration period in Japan. The most recent guidelines of the United States, UK, and Canada cover treatment with administration for 3 months or longer [3–6]. In a meta-analysis of the risk of bone fractures after starting treatment with oral glucocorticoids overseas, it was reported that the incidence of new vertebral bone fractures reaches a maximum at 3–6 months after administration and forms a plateau thereafter [8], suggesting that treatment simultaneously with or in the very early stage of glucocorticoid administration is important. Therefore, the subjects were patients with planned administration for 3 months or longer (see Fig. 1).

Prior fragility fractures

The results of an analysis in a 2-year longitudinal study by Tanaka and Oshima showed that the risk of new bone fractures in patients with prior fragility fractures showed the highest value compared with other fractures at an odds ratio of 7.92 [7]. Among the patients collected by the Subcommittee to Study Diagnostic Criteria, the 154 cases (103 cases of RA, 51 cases of collagen disease) that could be analyzed longitudinally for 2 years had a high odds ratio of 5.22. Therefore, the first evaluation criterion for starting treatment was patients with prior fragility fractures and patients with new bone factures during treatment. The definition of a fragility fracture is the same as that for primary osteoporosis [9].

Bone mineral density

Table 1 shows the cut-off values of bone mineral density (BMD), which can efficiently separate fracture and nonfracture cases, estimated from the receiver-operating characteristic (ROC) curve based on an analysis of cases collected by the Subcommittee to Study Diagnostic Criteria. The cut-off value for all patients was 0.776 g/cm^2. When the patients were divided into those with RA, the most common underlying disease, and those with diseases other than RA, the cut-off values were 0.744 g/cm^2 and 0.820 g/cm^2, respectively. In cases with SLE, the most common underlying disease other than RA, the cut-off value was 0.841 g/cm^2. Judging from these results, it appeared necessary to set different cut-off values for RA and for other underlying diseases. Table 2 shows the results of an investigation of this point with respect to age. In Table 2, all patients were grouped by age from those less than 40 to those 70 years of age and older. The cut-off values of bone mineral density in fracture and nonfracture cases were obtained by age and expressed as percent (%) young adult mean (YAM). When the level of differences in cut-off values (%YAM) was examined for age differences of 10 years, the values were 6.5% for patients in their forties and in their fifties and 7.1% for patients in their fifties and in their sixties. The mean age of RA patients was 60.4 years and that for diseases other than RA 48.8 years, an age difference of 11.6 years. The cut-off values were 73.6% for RA and 81.1% for diseases other than RA, a difference of 7.5%; i.e., this difference was almost the same as that for age, and the difference in cut-off values of RA and diseases other than RA is not considered as a difference caused by differences in disease but a difference due to age.

Table 1. Cut-off values of bone mineral density (BMD) to efficiently separate fracture and nonfracture cases

		BMD (g/cm^2)	T score	% YAM
Primary osteoporosis		0.708	−2.60	70%
Osteopenia		0.809	−1.70	80%
Glucocorticoid-treated patients	All patients	0.776	−1.97	76.8%
	RA	0.744	−2.24	73.6%
	Non-RA	0.820	−1.60	81.1%
	SLE	0.841	−1.43	83.2%

YAM, young adult mean; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus

Table 2. Cut-off values of bone mineral density by age and underlying disease of patients administered glucocorticoid

Age (all patients)	%YAM		Mean age (years)	Underlying disease
Less than 40 years old	86.9			
Forties	85.9			
	6.5	81.1	48.8	Non-RA
Fifties	79.4			
	7.1	7.5	11.6	
Sixties	72.3			
		73.6	60.4	RA
Seventies and older	69.3			

Table 3. Cut-off values of bone mineral density by dose of glucocorticoids

	Daily dose (prednisolone equivalent) (mg)	%YAM (T score)
All patients	≧5	77.7 (−1.90)
	≧7.5	80.3 (−1.67)
	≧10	82.1 (−1.52)
RA	≧7.5	75.1 (−2.12)
Non-RA	≧5	81.8 (−1.55)
	≧7.5	82.6 (−1.48)

Table 3 shows the relationship between glucocorticoid dose and the cut-off values. In all patients, the cut-off value (%YAM) in the group with a prednisolone equivalent dose of 5 mg/day or higher was 77.7%, that in the group with a dose of 7.5 mg/day or higher was 80.3%, and that in the group with a dose of 10 mg/day or higher was 82.1%. These results showed that as the daily dose increased, factures occurred at higher bone mineral densities. For RA, the cut-off value was 75.1% in the group with a prednisolone equivalent dose of 7.5 mg/day or higher, and for diseases other than RA, it was 81.8% in the group with a dose of 5 mg/day or higher and 82.6% in the group with a dose of 7.5 mg/day or higher. The results of a cross-sectional analysis of all patients collected by the Subcommittee to Study Diagnostic Criteria showed a cut-off value of %YAM 77%, and the cut-off value in the group with a prednisolone equivalent dose of 5 mg/day or higher, at which it was reported based on a meta-analysis that the bone mineral density rapidly decreased and bone fractures increased, was 78%. It was clear that it is not necessary to consider differences in cut-off values due to differences in underlying diseases. In the longitudinal analysis by Tanaka and Oshima, the cut-off value in the group with a prednisolone equivalent dose of 5 mg/day or higher was %YAM 80% [7]. Based on these results, bone mineral density of less than %YAM 80% was taken as the second evaluation criterion for starting treatment.

Dose of glucocorticoids

The number of patients collected by the Subcommittee was not enough to clarify the relationship between the fracture risk and the total glucocorticoid dose, and the analysis could not be performed. Almost no difference was found in the relationship between the fracture risk and the administration period, but this was because of insufficient data on individual patients, and the relationship will have to be clarified in the future. Sufficient evidence on the relationship between the glucocorticoid dose and fracture risk rate or its cut-off value of bone mineral density has still not been obtained in Japan, and overseas reports had to be used for reference. The results of an overseas meta-analysis showed a reverse correlation between the bone mineral density of the lumbar vertebra and the total dose of glucocorticoid (daily dose × period), and the risk of a spinal fracture even at a daily dose of less than 2.5 mg of prednisolone equivalent was more than 1.0, i.e., 1.55. The fracture rate increased dose dependently and was 5.18 at 7.5 mg or higher doses [8]. It has been reported that a dose of 5 mg or higher is the threshold value for increased fracture risk. Therefore, the third evaluation criterion for the start of treatment was proposed as a dose of 5 mg/day or higher (mean daily dose) as prednisolone equivalent (see Fig. 1). However, in a longitudinal study, the cut-off value of bone mineral density was %YAM 90% in the group administered a 10 mg/day or higher dose of prednisolone equivalent, and even at a %YAM close to 100%, the risk rate of fractures was clearly higher in the patients given glucocorticoid than in patients not administered glucocorticoids [7].

Old age

In the study by Tanaka and Oshima [7], the incidence of bone fractures increased significantly with increase in age, and age was identified as a risk factor of new spinal fractures in patients administered glucocorticoids; however, a cut-off value of age to clearly separate fracture and nonfracture cases could not be determined.

Treatment of glucocorticoid-induced osteoporosis

General guidance. In the same way as with primary osteoporosis, it is necessary to provide guidance on improvements in lifestyle and on nutrition, as well as exercise therapy. This guidance is based on that given for primary osteoporosis [10].

Follow-up observation. The risk of bone fractures is higher in patients administered glucocorticoid than in those who were not treated with glucocorticoid. Therefore, in patients evaluated as the follow-up observation group based on the present guidelines, it is essential to conduct follow-up observation by measuring bone mineral density and taking X-rays of the thoracic and lumbar vertebra on a regular basis.

Drug treatment. In prospective randomized control trials (RCT) overseas [11–15] and in Japan [16,17], evidence that the bisphosphonate products etidronate, alendronate, and risedronate significantly prevent bone fractures caused by glucocorticoid-induced osteoporosis has been reported. Therefore, these drugs have been recommended as first-line drugs at present. Active vitamin D_3 has been reported to have fracture-preventing effects, although these are inferior to those of the bisphosphonates [18], and vitamin K_2 has also been found to have fracture-preventing effects from a longitudinal study in Japan [7]. These two vitamins have been recommended as second-line drugs. Although the parameter was bone mineral density, it was reported based on a meta-analysis that vitamin D and bisphosphonates administered concomitantly are more effective than bisphosphonates alone in the treatment of glucocorticoid-induced osteoporosis [19]. Concomitant administration of active vitamin D_3 and bisphosphonates should be considered in patients with serious or high-risk osteoporosis. When bisphosphonates are difficult to administer to postmeno-