models and accepted the model scale that was not rejected [6]. Failure to reject one of these specific models is not equivalent to proving that it is the appropriate scale on which to model the joint effect (note that, in our example, neither model could be rejected). Mixture models may be more appropriate than the simpler additive and multiplicative models for some complex joint mechanistic effects. Linear dose responses are preferred in much radiation risk work, particularly with cancer; the mixture model results in a non-linear dose response even if the component parts are linear, unless the mixture parameter is zero or unity. Even if the hypothesised, underlying mechanism is of the simpler linear additive or multiplicative form, a mixture model may capture more complicated aspects of causality (due, for example, to confounders or effect modifiers) that are not explicitly measured. Such effects may lead to departure in the observed data from the trends expected to result from simple causal mechanisms. Given that these uncertainties will apply to the transport of POC from an epidemiological study to an individual regardless of what model is fitted, we therefore opine that it is better to base calculation of probability of causation on the joint effect actually manifest in the observed data in the face of such lurking effects than to base it on an estimate of joint effects based on a model that, even if theoretically correct, is not estimated correctly by the data in hand.

The idea that radiation POC is related to baseline risk conditional on other risk factors is not new. The US National Academy of Sciences Subcommittee that reviewed the draft update of the radio-epidemiological tables [27] pointed out an important implication for use of POC when absolute excess risk is the same in two populations with different baseline risks: 'In the high-baseline-risk population, the POC will be lower because it is more likely that the cancer was caused by factors other than radiation' (page 22). However, the idea of specifically accounting for risk factors that partly explain the baseline risk, and possibly interact with radiation in the etiology of disease, seems to be an area of research with much potential for development.

It is apparently common procedure to decide liability, not on the estimated POC, but on an upper confidence bound for the POC [5]. It can be argued that the existence of liability should be based on the POC point estimate itself because that is the best estimate obtainable from the available data. However, if bounds on the POC are desired to allow for a margin of error in deciding causation, it might be preferable to base the bound on a posterior probability (Bayesian) interpretation of the POC rather than on the frequency properties of confidence intervals. For applications in which a prior distribution over the parameter space can be specified, a Bayesian approach—unlike more traditional approaches—would allow for simple probabilistic interpretations on the uncertainties in POC.

Finally, the term 'probability of causation' may not make sense in the case of etiologic interaction, where responsibility is shared among the contributing agents. There are varied opinions regarding how to apportion risk from interaction [10]. If the joint effect is multiplicative, the classical assigned share for radiation based on excess relative risk is independent of the other, non-radiation risk factor. However, with statistical interaction there is some proportion of cases that might not have occurred even with radiation exposure had the other risk factor not been present. We condition on the other, non-radiation risk factor when calculating POC for radiation; thus, all excess risk associated with radiation is attributed to radiation although a portion of that risk may be due to the joint effect. Exposure to non-radiation risk factors may involve personal lifestyle choices or, as in the case of genetic factors, circumstances outside the exposed person's control. Whether to assign all of the joint causation to radiation, to the other factor, or to apportion them is a decision that must be made in each individual case of application of POC. It might therefore be useful for comparison to report, in addition to the conditional POC we recommend, an alternative POC for radiation calculated by

attributing all of the joint effect to the other, non-radiation, risk factor. Attributable fractions 'attributable to interaction' [28] are also being investigated in the POC setting.

Our recommendations regarding probability of causation can be summarised as follows.

- Exposure to risk factors other than radiation can be an important determinant of the role played by radiation in leading to disease and therefore cannot be ignored when assessing probability of causation for radiation.
- Mechanistic models for the joint effect of radiation and other factors, such as the additive and multiplicative models, might not adequately fit observed epidemiological data that are subject to lurking effects of unmeasured factors.
- When based on epidemiological data without well accepted theoretical mechanistic underpinnings, we recommend calculating probability of causation using a general, empirical model, which is less likely to be biased from untestable assumptions regarding the mechanisms that generated the actual, observed data.

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Appendix. Mathematical details

A model that fits the odds of disease as a joint function of radiation dose x and factor Z (taking value z) predicts the prevalence via

$$P(D|x,z) = \frac{f[P(D|x,z)]}{1+f[P(D|x,z)]} \tag{A.1}$$

where P is the probability of being diseased and $f(P) = P/(1-P)$ is the odds of disease. The probability of causation for radiation (POC) conditional on the value of z is based on the attributable fraction:

$$\mathrm{AF}(x|z) = \frac{P(D|x,z) - P(D|0,z)}{P(D|x,z)}. \tag{A.2}$$

Equation (4) of Seiler [29], though not defined as a conditional POC, is the same as this conditional POC, because what he calls the 'attributable relative risk for radiation' in the numerator is $P(D|x,z) - P(D|0,z)$ in the case of the additive model.

With the additive excess-relative-risk model used to derive the assigned shares in follow-up studies, defining POC from the basic definition of conditional attributable fraction (equation (A.2)) produces the same estimate as that for assigned shares based on the formula for conditional excess relative risk [5]:

$$\begin{aligned}\mathrm{AF}_{\mathrm{add}}(x|z) &= \frac{P(D|x,z) - P(D|0,z)}{P(D|x,z)} = \frac{\mathrm{ERR}_x}{1+\mathrm{ERR}_z+\mathrm{ERR}_x} \\ &= \frac{\mathrm{ERR}_x/(1+\mathrm{ERR}_z)}{1+\mathrm{ERR}_x/(1+\mathrm{ERR}_z)} = \frac{\mathrm{ERR}_{x|z}}{1+\mathrm{ERR}_{x|z}} = \mathrm{AS}_{x|z},\end{aligned}$$

where, for notational simplicity, we write the excess relative risk function $\mathrm{ERR}(x)$ as ERR_x, ERR_z is similarly the excess relative risk for factor Z, $\mathrm{ERR}_{x|z}$ is the excess relative risk for exposure to x given z, and AS represents *assigned shares*. In other words, calculating POC from basic principles is equivalent to using the more familiar AS formula when the disease risk (incidence or prevalence) is directly modelled using the relative risk. Similar formulae can be derived for the multiplicative and mixture models based on the ERR:

$$\mathrm{AF}_{\mathrm{mult}}(x|z) = \frac{\mathrm{ERR}_x}{1+\mathrm{ERR}_x} = \mathrm{AS}_x$$

$$\mathrm{AF}_{\mathrm{mix}}(x|z) = 1 - \frac{1+\mathrm{ERR}_z}{[(1+\mathrm{ERR}_x)(1+\mathrm{ERR}_z)]^{\theta}[1+\mathrm{ERR}_x+\mathrm{ERR}_z]^{1-\theta}}.$$

In the case of cross-sectional studies estimating the disease prevalence via the odds, as was done in the present work, the attributable fraction is

$$\mathrm{AF}^{\mathrm{O}}(x|z) = \frac{P(D|x,z)-P(D|0,z)}{P(D|x,z)} = 1 - \frac{\left\{\frac{f[P(D|0,z)]}{1+f[P(D|0,z)]}\right\}}{\left\{\frac{f[P(D|x,z)]}{1+f[P(D|x,z)]}\right\}}$$

(the superscript 'O' on AF stands for 'odds'). One can always compute the POC directly using equation (A.2) once a model for $P(D|x,z)$ has been fitted. Alternatively, we can derive formulae for POC analogous to those based on the ERR by substituting the appropriate model for $f(P)$ and solving algebraically in terms of the excess relative odds, ERO. Writing $f[P(D|0,0)]$ as f_0, $\mathrm{ERO}(x)$ as ERO_x and $\mathrm{ERO}(z)$ as ERO_z, the equations for attributable fractions for the odds models become

$$\mathrm{AF}^{\mathrm{O}}_{\mathrm{add}}(x|z) = 1 - \frac{\frac{1+\mathrm{ERO}_z}{1+\mathrm{ERO}_x+\mathrm{ERO}_z} + f_0(1+\mathrm{ERO}_z)}{1+f_0(1+\mathrm{ERO}_z)},$$

$$\mathrm{AF}^{\mathrm{O}}_{\mathrm{mult}}(x|z) = 1 - \frac{\frac{1}{1+\mathrm{ERO}_x} + f_0(1+\mathrm{ERO}_z)}{1+f_0(1+\mathrm{ERO}_z)},$$

and

$$\mathrm{AF}^{\mathrm{O}}_{\mathrm{mix}}(x|z) = 1 - \frac{\frac{1+\mathrm{ERO}_z}{[(1+\mathrm{ERO}_x)(1+\mathrm{ERO}_z)]^{\theta}\times[1+\mathrm{ERO}_x+\mathrm{ERO}_z]^{1-\theta}} + f_0(1+\mathrm{ERO}_z)}{1+f_0(1+\mathrm{ERO}_z)}.$$

To evaluate these three formulae, we can write them generally as

$$\mathrm{AF}(x|z) = 1 - \frac{a(x)+f_0(1+\mathrm{ERO}_z)}{1+f_0(1+\mathrm{ERO}_z)},$$

where, assuming ERO_x is an increasing function of x, $a(x) \leqslant 1$. Furthermore, $\mathrm{AF} = 0\,[a(x) = 1]$ when $x = 0$ ($\mathrm{ERO}_x = 0$) and AF increases as ERO_x increases.

Statistical interaction terms may be appended to the additive (text equation (4)) and multiplicative (text equation (5)) models to examine departure from those specific models. The additive model with interaction is

$$f[P(D|x,z)] = f[P(D|0,0)](1+\mathrm{ERO}_x+\mathrm{ERO}_z+\Delta xz), \tag{A.3}$$

and the multiplicative model with interaction is

$$f[P(D|x,z)] = f[P(D|0,0)][(1+\mathrm{ERO}_x)(1+\mathrm{ERO}_z)]\mathrm{e}^{\delta xz}, \tag{A.4}$$

where, in the presence of HCV infection, Δ is the incremental difference in the excess relative odds per unit difference in dose and e^{δ} is the relative change in the odds ratio (δ is the logarithm of the relative change) for a unit difference in dose. The attributable fractions corresponding

to these two interaction models are easily derived and equivalent to those above, except that the $a(x)$ terms include the full joint-effect risk model with interaction:

$$\mathrm{AF}^{\mathrm{O}}_{\mathrm{add,int}}(x|z) = 1 - \frac{\frac{1+\mathrm{ERO}_z}{1+\mathrm{ERO}_x+\mathrm{ERO}_z+\Delta xz} + f_0(1+\mathrm{ERO}_z)}{1+f_0(1+\mathrm{ERO}_z)},$$

and

$$\mathrm{AF}^{\mathrm{O}}_{\mathrm{mult,int}}(x|z) = 1 - \frac{\frac{1}{(1+\mathrm{ERO}_x)\times(1+\mathrm{ERO}_z)\times e^{\delta xz}} + f_0(1+\mathrm{ERO}_z)}{1+f_0(1+\mathrm{ERO}_z)}.$$

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A meta-analysis of previous fracture and subsequent fracture risk

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Abstract

Previous fracture is a well-documented 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 15259 men and 44902 women from 11 cohorts comprising EVOS/EPOS, OFELY, CaMos, Rochester, Sheffield, Rotterdam, Kuopio, DOES, Hiroshima, and two cohorts from Gothenburg. Cohorts were followed for a total of 250000 person-years. The effect of a prior history of fracture 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 by using the weighted β-coefficients.

A previous fracture history was associated with a significantly increased risk of any fracture compared with individuals without a prior fracture (RR = 1.86; 95% CI = 1.75–1.98). The risk ratio was similar for the outcome of osteoporotic fracture or for hip fracture. There was no significant difference in risk ratio between men and women. Risk ratio (RR) was marginally downward adjusted when account was taken of BMD. Low BMD explained a minority of the risk for any fracture (8%) and for hip fracture (22%). The risk ratio was stable with age except in the case of hip fracture outcome where the risk ratio decreased significantly with age.

We conclude that previous history of fracture confers an increased risk of fracture of substantial importance beyond that explained by measurement of BMD. Its validation on an international basis permits the use of this risk factor in case finding strategies.

Keywords: Prior fracture; Meta-analysis; Hip fracture; Osteoporotic fracture

Introduction

It is well established from many cohort, case-control, and cross-sectional studies that a prior osteoporotic fracture increases the risk of future fractures [1–8]. A prior forearm fracture is associated with about a twofold increase in the subsequent risk of fracture [9–13]. More recently, significant increases in risk have been described for prior fractures at other sites characteristic of osteoporosis [6,7,14–21]. The risk of another vertebral fracture is particularly high after a spine fracture [7,22–24]. Similar observations are found in the setting of randomized clinical trials. In the placebo arm, the risk of vertebral deformities is approximately fivefold

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higher in patients with a prior vertebral deformity than in those without [4,25,26]. The interrelationships between the site of prior fracture and site of subsequent fracture have been summarized by meta-analysis [27] and a large case-control study, published more recently found broadly similar relationships [8].

Increased fracture risk may be in part due to the fact that patients with fracture have low bone mineral density (BMD). Studies that have adjusted for BMD suggest that the relative risk is only modestly downward adjusted [3,20,24,28–31].

The consistent association between a prior fracture and subsequent fracture risk has led to the inclusion of prior fracture as a risk factor to be used in assessment guidelines [32–35]. For example, in Europe, it is recommended that patients be identified on the basis of risk factors for subsequent assessment by BMD [33–35]. Patients are then considered for intervention on the finding of osteoporosis (i.e., a T score of ≤ -2.5 SD). This approach is conservative since it does not recognize the independent contribution of the risk factor from BMD. This has been recognized in some guidelines where the intervention threshold is less conservative in the presence of a risk factor such as a prior fragility fracture [32,36]. The consideration of several independent risk factors permits the more accurate categorization of risk [37], and attention has focussed recently on the assessment of fracture risk using multiple risk factors, rather than the use of BMD alone, to define intervention thresholds [38,39]. This demands knowledge of the interrelationships between these risk factors.

The aim of the present study was to quantify the risk associated with a history of prior fracture for future fracture in an international setting and to explore the dependence of this risk with age, sex, and BMD.

Methods

We studied 60 161 men and women of whom 26% had a prior fracture history taken from 11 prospectively studied cohorts. Brief details of the cohorts studied are given below and summarized in Table 1.

OFELY

The OFELY cohort comprises an age-stratified cohort of 1039 women aged 31–89 years randomly selected from the regional section of a large health insurance company (Mutuelle Generale d'Education Nationale, Lyon) [40]. Eighteen percent of women contacted participated in the study. Baseline characteristics were obtained using a standardized questionnaire, including the documentation of prior wrist, humeral, vertebral, and hip fracture that occurred after the age of 45 years. Only low trauma fractures (falls from a standing height or less) were recorded. BMD was measured at the lumbar spine, at the proximal femur, distal radius, and whole body by DXA using a Hologic QDR 2000. Women were reviewed annually and fractures registered. Peripheral fractures were confirmed by radiography. Vertebral fractures were identified from sequential X-rays of the thoracic and lumbar spine by morphometry in 80% of patients, but only clinical fractures were used for this analysis.

EVOS

The European Vertebral Osteoporosis Study (EVOS) comprised age- and sex-stratified random samples from 36 centers in 19 European countries [41–43]. Equal numbers of men and women were drawn in each center within six 5-year age bands (50–54 to 75–79 years). A baseline radiograph for vertebral fracture prevalence was undertaken in 15 570 men and women (response rate, 29%). BMD was measured in 3461 men and women from 13 centers by DXA at the femoral neck using pencil beam machines that were cross-calibrated using the European spine phantom. The sample provided the framework for the European Prospective Osteoporosis study (EPOS) where repeated assessment was undertaken in 29 of the centers. Information on clinical fractures were used for this report.

Table 1
Details of cohorts studied including individuals with information on follow-up time, prior fracture, and subsequent fracture

Cohort	Sample size	Person-years	Mean age (years)	Age range (years)	% Female	Fracture history (%)	Any fracture	Osteoporotic fracture	Hip fracture
EPOS	13366	40160	63.8	41–91	52	36	715	715	44
OFELY	426	2124	64.2	50–89	100	16	53	–	–
CaMos	9400	26653	62.1	25–103	69	44	586	316	42
Rochester	1001	6228	56.8	21–94	65	18	289	244	42
Sheffield	2147	6826	80.0	74–96	100	51	284	236	62
Rotterdam	7774	43606	70.3	55–106	61	14	992	768	284
Kuopio	11798	56602	52.3	47–57	100	17	1053	–	–
Gothenburg I	2375	16439	78.8	69–86	61	9	431	431	336
Gothenburg II	7098	29750	58.9	21–89	100	18	441	312	29
Dubbo	2163	16333	70.7	57–96	61	15	532	418	107
Hiroshima	2613	9861	65.1	47–95	70	26	187	90	32
Totals	60161	254582	62.9	21–106	75	26	5563	3530	978

CaMos

The Canadian Multicentre Osteoporosis Study (CaMos) is an ongoing prospective age-stratified cohort. The study is documenting the incidence of fractures and risk factors in a random sample of 9424 men and women aged 25 years or more selected by telephone listings. The sampling frame is from nine study centers in nine provinces [44]. Characterization of individuals was by interview. BMD was measured by DXA at the hip (Hologic QDR 1000) and lumbar spine, and an ultrasound scan taken at the heel in individuals aged 50 years or more.

Rochester

The Rochester cohort was recruited from two random population samples stratified by decade of age, one comprising women who were subsequently followed for up to 20 years [45] and another sample of women and men followed for 8 years [46]. The response rates were 49.8% in the women and 38.7% in the men. BMD of the right femoral neck was measured by dual photon absorptiometry in the first cohort (cross calibrated to DXA) and by DXA (Hologic QDR 2000) in the second group. Fractures were ascertained by periodic interview combined with review of the inpatient and outpatient medical records of all local care providers.

Sheffield

The Sheffield cohort comprised women aged 75 years or more 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 to attend for assessment of their skeletal status. Five thousand eight hundred and seventy-three women were willing to attend for the screening visit. Of these, 281 were excluded, and the remainder randomly allocated after informed consent to treatment with the bisphosphonate clodronate, or to an identical placebo. This study is still in progress, and the material used for the present paper comprised 2148 women allocated to treatment with placebo [47]. All women had baseline assessment of BMD undertaken at the femoral neck using the Hologic 4500. Outcomes were assessed by 6 monthly home visits.

Rotterdam

The Rotterdam study, begun in 1990, is a prospective cohort study that aimed to examine and follow-up all residents aged 55 years and older living in Ommoord, a district of Rotterdam [48]. By 1993, 7983 residents had been included (response rate, 78%). Bone mineral density was assessed at the femoral neck by DXA using a Lunar DPX-L [49]. Fracture follow-up was undertaken using an automated link with general practitioner computer systems and hospital admission data. Fracture data were collected and validated by two independent research physicians. For this analysis, validated fracture follow up was available for 7774 participants (3065 men) with an average follow up time of 6 years. Femoral neck BMD was measured in 5776 individuals (2432 men).

Kuopio

The Kuopio osteoporosis risk factor and prevention (OSTPRE) study in Finland comprised a postal inquiry sent to all 14220 women aged 47–56 who were residents of Kuopio province in 1989. Thirteen thousand and one hundred women responded to the inquiry, of whom 1214 were excluded for incomplete information. This left a study population of 11 886 women. A random stratified sample of 3222 women underwent bone mineral densitometry by DXA using the Lunar DPX [50].

Gothenburg I

This study comprised four birth cohorts of 2375 randomly sampled men and women aged 70 years or more followed for up to 20 years at Gothenburg [51,52] after a baseline BMD measurement. The participation rate was 73%. The participants were drawn randomly from the population register in Gothenburg by the 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 women aged 21–89 years followed up to 7.9 years (mean 4.2 years) [53]. Seventy percent of those invited (approximately 7000 women) participated in the study that examined risk factors for osteoporosis by use of a standardized questionnaire. BMD was assessed at baseline at the distal forearm using the Osteometer DTX 200.

DOES

The Dubbo Osteoporosis Epidemiology Study (DOES) is a population-based study with multiple assessments of skeletal status in men and women aged 60 years or more from Dubbo, Australia [54]. Participation in the study was 56% of the population. Baseline measurements included BMD at the femoral neck assessed using DXA (GE-Lunar, DPX). Fractures are identified through radiologists reports from the two centers servicing the region.

Hiroshima

The Adult Health Study in Hiroshima (AHS) documents the late health effects of radiation exposure among atomic

Table 2
Details of the construct of the questionnaire on fracture history in the cohorts studied

Cohort	Question
EVOS/EPOS	Have you ever suffered a fracture?
CaMos	Have you ever fractured any bones?
Rochester	Prior fracture with moderate trauma
Rotterdam	History of any fracture in the past 5 years
Gothenburg I	Evidence of any fracture (in hospital records)
OFELY	History of a fragility fracture from low trauma since age of 30 years
Sheffield	History of any fracture
Kuopio	History of any fracture from the age of 15 years
Gothenburg II	History of fracture after the age of 25 years
Dubbo	Self-reported
Hiroshima	Self-reported

bomb survivors in Hiroshima and Nagasaki. The original AHS cohort consisted of about 15000 atomic bomb survivors and 5000 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% throughout this period. BMD at the lumbar spine and proximal femur has been measured at each biennial health examination using DXA (Hologic QDR-2000) since December 1993. Trained nurses interviewed the subjects about baseline risk factors and measured height and weight at each biennial visit [55,56].

Baseline and outcome variables

The construct of the question to determine a prior fracture history differed between the cohorts studied (Table 2). Prospective fracture ascertainment was undertaken by self-report (Sheffield, Kuopio, EVOS/EPOS; Hiroshima) and/or verified from hospital central data bases (CaMos, Sheffield, EVOS/EPOS, Rochester, Rotterdam, Kuopio, Gothenburg I and II, CaMos, DOES). The EPOS and OFELY study also included sequential systematic radiography to define incident vertebral deformities, but were not used in this analysis. Information on all clinical fractures was used for this report. In addition, fractures considered to be due to osteoporosis were analyzed, and finally, hip fracture alone was considered separately. For Kuopio and OFELY, all fractures were recorded and no distinction made between fracture sites. In the case of the EPOS study and Gothenburg I, osteoporotic fractures only were recorded. In the other cohorts, an osteoporotic fracture was one considered to be due to osteoporosis either by the investigator or by the Coordinating Centre. For the EVOS study, osteoporotic fractures comprised hip, forearm, humeral, or limb 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, DOES, Hiroshima), fractures at sites considered to be characteristic for osteoporosis were [38] extracted from the data.

Statistical methods

The risk of fracture was estimated by Poisson regression applied to each cohort and each sex separately. Covariates included time since start of follow up, current age, prior history of fracture, and BMD. We additionally excluded BMD from the model. A further model included the interaction term prior fracture × time to determine whether the strength of the association of prior fracture and fracture risk waned with time. The beta value for each sex in each cohort is age-dependent, beta_{k+} beta_{k+1}·age. The estimated value of beta_{k+} beta_{k+1}·age was determined for each age from 50 to 85 years, together with the variance. Results of each cohort and the two sexes were weighted according to the variance and merged to determine the weighted means and standard deviations. The risk ratio (RR) of those with a prior fracture history versus those without a prior fracture history was equal to e^{mean}.

The component of the risk ratio explained by BMD was computed from a meta-analysis of BMD and fracture risk [57]. 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

$$\frac{[\log RR_a/\log GR] - [\log RR_b/\log GR]}{[\log RR_a/\log GR]}$$

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 60161 men and women studied, 877 men and 4686 women were identified as having a subsequent fracture of any kind, of which 680 and 2850 were characterized as osteoporotic in men and women, respectively. Two hundred and eleven men and 767 women sustained a hip fracture. The total follow-up was 61938 person years in men and 192644 in women. BMD measurements were available in 62% of individuals.

Table 3
Prevalence of a prior fracture history in men and women by age

Age (years)	Probability of fracture history (%)		
	Men	Women	Combined
30	44	15	24
40	43	18	27
50	42	23	30
60	41	29	34
70	40	35	37
80	39	41	41
90	38	48	45

Table 4
Risk ratio (RR) and 95% confidence interval (CI) of fracture associated with a history of prior fracture in men and women, without and with adjustment for BMD

Outcome fracture	Men		Women		Combined	
	RR	95% CI	RR	95% CI	RR	95% CI
A. Without BMD						
Any	2.02	1.73–2.38	1.84	1.72–1.96	1.86	1.75–1.98
Osteoporotic	1.93	1.61–2.33	1.85	1.70–2.01	1.86	1.72–2.01
Hip	2.30	1.56–3.41	1.77	1.49–2.11	1.85	1.58–2.17
B. With BMD						
Any	2.04	1.67–2.48	1.73	1.59–1.88	1.77	1.64–1.91
Osteoporotic	1.91	1.50–2.43	1.74	1.57–1.92	1.76	1.60–1.93
Hip	1.97	1.12–3.48	1.56	1.23–1.98	1.62	1.30–2.01

Probability of fracture history rose almost linearly with age (Table 3). The probability of recording a history of a prior fracture was higher in men than in women (OR = 1.19; 95% CI = 1.14–1.25).

Risk of any fracture

Previous fracture was associated with a significantly increased risk of any subsequent fracture (Table 4). There was no difference in the risk ratio between men and women. In men and women combined, the risk ratio ranged from 1.83 to 2.03 depending upon age (Table 5). The risk ratio was marginally lower by approximately 10% when account was taken of BMD. If it is assumed that the risk of any fracture increases 1.60-fold for each SD deviation decrease in hip BMD, then the difference in risk between those with and without a prior fracture is equal to an expected difference in BMD of 1.32 SD [log(1.86)/log(1.60)]. In reality, the difference in BMD at all ages in men and women combined was approximately 0.11 SD ([log(1.86)/log(1.60)] − [log(1.77)/log(1.60)]). Thus, low BMD accounts for the minority (8%; 0.11/1.32) of the difference in risk between those with or without a prior fracture.

Table 5
Risk ratio (RR) for any fracture and 95% confidence intervals (CI) comparing men and women with and without a previous fracture by age, with or without adjustment for BMI

Age (years)	RR without BMD[a]		RR with BMD[a]	
	Mean	95% CI	Mean	95% CI
50	1.92	1.63–2.20	1.91	1.59–2.29
55	1.90	1.73–2.09	1.83	1.60–2.10
60	1.98	1.80–2.18	1.94	1.73–2.17
65	2.02	1.86–2.20	1.99	1.81–2.20
70	2.03	1.87–2.21	1.98	1.79–2.18
75	1.96	1.80–2.13	1.82	1.65–2.02
80	1.88	1.72–2.06	1.72	1.54–1.91
85	1.83	1.65–2.04	1.72	1.51–1.96
All ages	1.86	1.75–1.98	1.77	1.64–1.91

[a] Prior fracture versus no fracture.

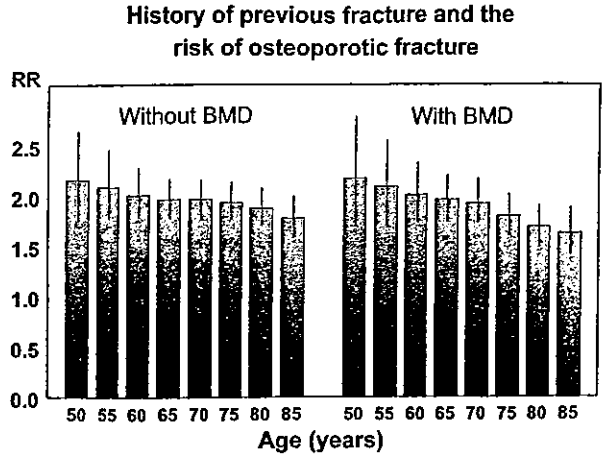

Fig. 1. Risk ratio for an osteoporotic fracture in men and women with a prior history of fracture with and without adjustment for BMD.

Risk of osteoporotic fracture

Previous fracture was also associated with a significantly increased risk of an osteoporotic fracture at all ages with and without adjustment for BMD (Table 4). The unadjusted risk ratios for an osteoporotic fracture were almost identical with the risks of a prior fracture for any fracture. For example, at the age of 80 years, the risk of any fracture was 1.88 (95% CI = 1.72–2.06) and for an osteoporotic fracture was 1.89 (95% CI = 1.72–2.09). There was no difference in risk ratio between men and women. Fracture risk decreased somewhat with age by about 10% per decade of age (Fig. 1), but the trend was short of conventional significance ($P = 0.089$).

Risk of hip fracture

A prior fracture history was a significant risk factor for hip fracture at all ages (Table 6). The risk ratio was highest at younger ages and decreased progressively with age ($P < 0.002$ for the interaction term). The risk decreased by 3%

Table 6
Risk ratio (RR) for hip fracture and 95% confidence intervals (CI) comparing men and women with and without a prior fracture by age, with and without BMD

Age (years)	RR without BMD[a]		RR with BMD[a]	
	Mean	95% CI	Mean	95% CI
50	5.04	2.66–9.56	3.88	1.79–8.43
55	4.20	2.46–7.15	3.98	2.08–7.62
60	3.40	2.21–5.24	3.16	1.88–5.32
65	2.60	1.85–3.64	2.28	1.52–3.41
70	2.31	1.76–3.02	1.90	1.37–2.65
75	2.14	1.71–2.68	1.64	1.24–2.17
80	1.90	1.58–2.28	1.41	1.12–1.78
85	1.66	1.39–1.98	1.32	1.04–1.68
All ages	1.85	1.58–2.17	1.62	1.30–2.01

[a] Prior fracture versus no fracture.

(95% CI = 1–5%) for each year of age. The RR was significantly increased at all ages, but at ages less than 60 years, the confidence estimates were wide (very few hip fractures). There was no difference in RR between men and women. Adjustment for BMD had an effect on the risk estimate for hip fracture that was quantitatively greater than for all fractures. The RR adjusted for BMD fell by approximately 30%. As in the case of all fractures, differences in BMD explained a minority of the increased risk ratio for hip fracture. In men and women combined, low BMD explained 22% of the increase in risk ratio and was constant by age (assuming a gradient of risk for hip fracture of 2.6/SD decrease in BMD).

The exclusion of data from Gothenburg (where BMD was assessed at the forearm or heel) had no material effect on these results (data not shown). There was no significant interaction of fracture history with time since baseline assessment.

Discussion

The present study confirms that a history of prior fracture is a significant risk factor for future fractures. In addition, the effect is over and above that which can be explained by variations in BMD. The risk of subsequent fractures is not as great as that identified in some studies [8], but as expected, falls within the confidence estimates of most estimates [27]. Discrepancies may be related to the duration of follow-up since the risk of subsequent fracture may not be linear over time [4,5]. Other possible reasons may relate to differences in the populations studied and the questionnaire used to identify prior fractures. A particular strength of the present study is that the estimate of risk is made in an international setting from randomly selected population cohorts. Calculations were based on the primary data, decreasing the risk of publication biases. The consistency of the association between cohorts (data not shown) additionally indicates the international validity of the importance of this risk factor. The risk of any subsequent fracture was comparable to the risk of a new osteoporotic fracture or a hip fracture. The large sample size permitted the quantification of risk by age. For all fractures and for osteoporotic fractures, the risk ratios were relatively constant with age. In the case of hip fracture, risk ratios decreased with age.

The present study also quantifies the independent contributions of low BMD and prior fracture. At all ages, low BMD explained a minority of the total risk, a proportion that decreased with age. The mechanism for the BMD-independent increase in risk could not be determined from this study but is likely due, in part, to coexisting morbidity that might increase the risk of falls or impair the protective responses to injury [6,21,29,58]. In addition, changes in the microarchitecture of cancellous and cortical bone with rapid bone loss after fracture or immobilization [59–61] may weaken the resistance to mechanical force out of proportion to any effect on BMD.

Irrespective of the underlying mechanism, these data indicate that the risk of fractures is substantially greater in individuals with a prior fragility fracture than in individuals of the same age, sex, and BMD without such a fracture. This has important implications for intervention thresholds. Health economic analysis suggests that intervention is cost-effective when treatment is targeted to women without a prior fracture with a T score of −2.5 SD at the femoral neck [39]. Since a prior fracture confers a risk over and above that provided by BMD, intervention thresholds for BMD can be less stringent (say at a T score of −1.5 SD) for those with a prior fracture, and still yield the same cost effectiveness. This approach has been incorporated into health economic analyses [32,62]. However, a large number of additional independent risk factors for fracture have been identified. These include smoking, corticosteroid exposure, a family history of fracture, secondary osteoporosis [39], and possibly the biochemical indices of bone turnover [63]. The interrelationships of all these risk factors will need to be determined before they can be easily used for assessing fracture risk in the general population.

The majority of reports have provided risk ratios for fracture in those with a prior fracture history compared to those without. For practical use, it is appropriate to express risk relative to the general population since risks expressed in this way can be more readily adjusted with other risk factors, such as the risk provided by BMD measurements [64]. For this purpose, knowledge of the prevalence of the risk factor is required. The adjustment decreases the risk ratios by a factor proportional to the prevalence of the risk factor. The relative risk is computed as $RR/[p.RR + (1 - p)]$ where RR is the risk ratio and p the prevalence of the risk factor [64]. Since the prevalence of fracture history is high (26%), the quantitative effect of adjustment is substantial.

The present study has some limitations that should be mentioned. As with nearly all randomly drawn populations, nonresponse biases may have occurred, which we were unable to document for all cohorts. The effect is likely to exclude sicker members of society, and may underestimate the absolute risk of fracture. Thus, the probability of a prior fracture may be underestimated from a societal perspective (Table 3), but this is unlikely to affect risk ratios. The greatest problem is the construct of the question concerning prior fractures and the methods of documenting and characterizing subsequent fracture events. These differed substantially between cohorts. The effect of this heterogeneity is likely, however, to weaken rather than to strengthen the associations that we found, that is, the association in reality may be stronger.

We conclude that prior fracture confers a substantial risk for future fractures and that this risk is largely independent of BMD. The consistency of the association in an international setting provides the rationale for the use of this risk factor in case of finding strategies. Moreover, patients

identified can be targeted for treatment at a higher BMD than individuals of the same age without a fracture history.

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ORIGINAL ARTICLE

Case-control study of risk factors for fractures of the distal radius and proximal humerus among the Japanese population

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Abstract We conducted a case-control study to identify risk factors for fractures of the distal radius and proximal humerus. Subjects were selected from women aged 45 and over with distal radius and proximal humerus fractures, resulting from minor trauma. Two age- and gender-matched controls for each case were selected from patients who subsequently visited the same clinic for treatment of conditions other than fractures. Questionnaires including anthropometric data, past and current physical activity, and lifestyle were sent by mail to both subjects and controls. A total of 140 women with distal radius fractures (mean age 67.4 years) and 242 controls were analyzed. Falls during the previous year were a significant risk factor, while futon use (instead of bed use) before fracture was a protective factor for distal radius fractures. A total of 37 women with proximal humerus fractures (mean age 76.3 years) and 67 controls were analyzed. Weight loss was a significant risk factor, while greater frequency of going outside significantly decreased the risk of proximal humerus fracture. There was no significant correlation with eating habits, milk and alcohol consumption, or smoking to the risk of either fracture.

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Introduction

With the rapid increase in the elderly population, osteoporosis and related fractures are major health and socioeconomic issues. Osteoporosis increases the risk of vertebral fractures as well as fractures of the hip, distal radius, and proximal humerus [1]. Although recent anti-osteoporosis pharmaceuticals could reduce the risk of fragile fractures up to 50% [2], osteoporosis is not curable and the number of patients with these fractures is increasing rapidly in both Western and Asian countries.

The incidence of fractures of the hip, distal radius, and proximal humerus is lower in Asians, including Japanese, than in Caucasians in Northern Europe and North America [3]. As bone mass in Asians is known to be lower than or similar to that in Caucasians, bone mass difference does not account for the difference in the incidence of hip, distal radius, and proximal humerus fractures between these groups. Elucidation of the factors underlying the racial difference in the incidence of these fractures will suggest preventive measures that may protect against osteoporosis-related fractures.

Since osteoporosis-related fractures result from the coincidence of bone fragility and falls, falls are important in the pathogenesis of osteoporotic fracture. Aoyagi et al. found that the incidence of falls in Japanese was about half that of Caucasians, and concluded that the difference in hip fracture incidence was closely related to the incidence of falls [4]. Recent surveys found that age- and gender-specific rates of hip as well as distal radius and proximal humerus fractures are increasing among the Japanese population [3, 5]. This trend may be due to the fairly rapid change from a traditional Japanese lifestyle to a Western one. The traditional Japanese lifestyle, including squatting to toilet, use of the Japanese straw mat room, and sleeping on the floor, may

maintain muscle strength, resulting in fewer falls and lower incidence of hip, distal radius, and proximal humerus fractures.

Therefore, to understand the basis underlying reduced osteoporosis-related fracture risk, it is necessary to evaluate risk factors in Japanese subjects. Although two studies of risk factors for hip fractures among Japanese have been described [6, 7], no study has examined risk factors for fractures of the distal radius and proximal humerus. Therefore, we conducted a case-control study to identify risk factors for these fractures among the Japanese population.

Materials and methods

Cases

Subjects were selected from women aged 45 and over with distal radius and proximal humerus fractures, who were treated at six orthopedic clinics in Tottori Prefecture from January 1999 to December 2000. In Tottori Prefecture, 27 hospitals had a department of orthopedic surgery and orthopedic clinics for outpatients. The six clinics selected were among those that dealt with the most fracture patients and agreed to collect data for this study. General orthopedic disease such as osteoarthritis of the joints and spine, other forms of arthritis, traumas, and fractures, are treated at these clinics.

Patients were selected by reviewing hospital records and diagnoses were confirmed by radiograms read by doctors at each clinic. Patients were excluded if 1) they died before this study was completed, 2) the fracture was caused by a high-energy impact, such as a traffic accident or a fall from greater than standing height, 3) the fracture was caused by neoplastic disease, or 4) the patient was severely demented and unable to satisfy the requirement of informed consent. Patients were subsequently contacted by mail and asked to respond to an enclosed questionnaire.

A total of 144 women aged 46–95 years (mean 67.5 years) with distal radius fractures and a total of 38 women aged 47–90 years (mean 76.4 years) with proximal humerus fractures were registered. Thirty-eight patients with distal radius fractures and 21 patients with proximal humerus fractures were admitted, while all others were managed as outpatients.

Controls

For each eligible patient registered, two age- (±3 years) and gender-matched controls were chosen from patients who subsequently (within 3 days) visited the same orthopedic clinic for the first time for treatment of a condition other than fractures. Most controls visited because of joint pain, low back pain, and neck pain. Patients who were demented or needed assistance to walk were excluded.

Data collection

A questionnaire consisting of four parts with 43 items was mailed. The first part concerned sociodemographic data, anthropometric data, and daily physical activity such as abiding place; marital status; occupation; body height; body weight; dominant hand; distance able to walk without rest; frequency of going outdoors; vision; and ability to dress, eat, perform household tasks, stand up from a chair, ascend stairs, walk outdoors, and bath. Part two evaluated likes and dislikes and consumption of coffee, tea, Japanese tea, milk, yogurt, cheese, meat, fish, alcohol, and cigarettes. Part three concerned past history of medications and diseases. Part four dealt with previous or recent lifestyle data including sports participation in youth, room style (western or tatami), type of bed (bed or futon) prior to fracture, toilet style (western or Japanese), and frequency of falls. Missing observations were completed by telephone, when necessary and possible, for both cases and controls.

Statistical analysis

Comparisons of background characteristics such as age, body height, body weight, and body mass index (BMI) between the two groups were performed with *t*-tests, while comparison of number of children was performed with a Mann-Whitney test.

Odds ratios for the risk variables were calculated using a conditional logistic regression model. Multivariate analysis was performed for the variables selected by univariate analysis. First, variables were screened by univariate analysis with a significance level of $P=0.10$. Next, multivariate adjusted odds ratios were calculated for variables selected in the first step, where all *P*-values were calculated using the chi-square likelihood ratio test with appropriate degrees of freedom. When considering the effect of a variable with more than two levels, we constructed several indicator variables that represent each level of the original variable. The trend test was performed when the variable had more than two levels. Multivariate analysis made it possible to estimate the odds ratio of a variable after adjusting for the effects of other variables. The Epicure software package for conditional logistic regression, specifically the PECAN program, (Hirosoft International Corporation, Seattle, USA) was used for analysis.

Results

Distal radius fractures

Among 144 patients with distal radius fractures, both controls replied in 102 cases, one control replied in 38 cases, and no controls replied in four cases. Therefore, 140 cases with at least one control and 242 controls in total were selected and analyzed. There was no significant difference in age, body height, body weight, BMI, or number of children between patients with fractures and controls (Table 1).

Table 1 Selected characteristics of cases with distal radius fracture and controls. A significance level of $P<0.05$ was using for this analysis

Characteristics	Case ($n=140$)	Control ($n=242$)	*P*
Age group			
<49	4	6	–
50–59	27	58	–
60–69	51	80	–
70–79	43	79	–
80–89	12	18	–
90+	3	1	–
Mean age ± SD (years)	67.4 ± 9.6	66.8 ± 9.2	NS
Body height (cm)	153.7 ± 34.3	151.6 ± 28.2	NS
Body weight (kg)	51.5 ± 8.6	52.2 ± 8.4	NS
BMI (kg/m^2)	22.3 ± 4.4	22.9 ± 4.3	NS
Number of children (mean)	0–6 (2.1)	0–6 (2.3)	NS
Dominant hand			
Right	131	223	–
Left	4	15	–
Unknown	5	4	–

Table 2 Selected risk factors for distal radius fracture by univariate analysis. Factors with significance level $P < 0.10$ are shown

	Odds ratio	95% CI	P	P trend
Ascend and descend stairs				
Easy	1.00	Reference	–	0.017
Difficult	0.43	(0.21–0.89)	0.017	–
Unable	0.45	(0.13–1.56)	0.19	–
Walk outside				
Easy	1.00	Reference	–	0.050
Difficult	0.31	(0.14–0.67)	0.0012	–
Unable	1.24	(0.34–4.48)	0.75	–
Walkable distance without rest				
< 100 m	1.00	Reference	–	0.26
100 m to 1 km	2.28	(1.10–4.73)	0.023	–
> 1 km	1.94	(0.97–3.89)	0.054	–
Frequency of going outside				
Rarely or not at all	1.00	Reference	–	0.045
Once in 2 or 3 days	0.69	(0.22–2.15)	0.52	–
Once a day	1.37	(0.55–3.41)	0.49	–
> Once a day	1.94	(0.78–4.78)	0.14	–
Bed or futon use when sleeping				
Bed use	1.00	Reference	–	–
Futon use	0.62	(0.37–1.03)	0.064	–
Falls during the previous year				
Never	1.00	Reference	–	–
> Once a year	2.26	(1.45–3.54)	0.0002	–
Number of children				
Each one	0.86	(0.71–1.03)	0.090	–

In the first step by univariate analysis, ability to ascend and descend stairs, ability to walk outside, distance capable of walking without rest, frequency of going outside, bed or futon use before the fracture, falls during previous years, and number of children were selected ($P < 0.1$) (Table 2). Physical activity such as greater ability to ascend and descend stairs, increased walkable distance without rest, and greater frequency of going outside increased the risk of distal radius fracture. However, other variables of daily physical activity such as ability to dress, walking inside, household tasks, and bathing showed no association with fracture risk. Recent futon use (as opposed to bed use) before the fracture and increased number of children both decreased the risk of fracture. No variables related to dietary habits (coffee, tea, Japanese tea, milk, cheese, fish), past alcohol use, and medication (antihypertensive drugs and diuretics) showed any association with the risk of distal radius fracture.

In the second step by multivariate analysis, falls during the previous year was a significant risk factor, while futon use (instead of bed use) before fracture was a protective factor (Table 3).

Table 3 Selected risk factors for distal radius fracture by multivariate analysis. Factors with significance level $P < 0.10$ by univariate analysis are presented

	Odds ratio	95% CI	P	P trend
Ascend and descend stairs				
Easy	1.00	Reference	–	0.23
Difficult	0.74	(0.23–2.26)	0.59	–
Unable	0.06	(0.0014–1.25)	0.072	–
Walk outside				
Easy	1.00	Reference	–	0.84
Difficult	0.42	(0.12–1.43)	0.17	–
Unable	28.0	(1.22–641.9)	0.031	–
Walkable distance without rest				
> 100 m	1.00	Reference	–	0.97
100 m to 1 km	2.07	(0.79–5.70)	0.14	–
> 1 km	1.53	(0.58–4.28)	0.40	–
Frequency of going outside				
Rarely or not at all	1.00	Reference	–	0.051
Once in 2 or 3 days	1.69	(0.41–7.13)	0.47	–
Once a day	2.33	(0.73–8.53)	0.16	–
> Once a day	3.20	(1.00–11.9)	0.049	–
Bed or futon use when sleeping				
Bed use	1.00	Reference	–	–
Futon use	0.55	(0.31–0.97)	0.039	–
Falls during the previous year				
Never	1.00	Reference	–	–
> Once a year	2.52	(1.54–4.24)	0.0002	–
Number of children				
Each one	0.84	(0.68–1.04)	0.10	–

Proximal humerus fractures

For proximal humerus fractures, both controls replied in 30 cases, one control replied in seven cases, and no controls replied in one of 38 cases. Therefore, 37 cases with at least one control and 67 controls in total were selected and analyzed. There were no significant differences in age, body height, body weight, BMI, or number of children, between patients with fractures and controls (Table 4).

Table 4 Selected characteristics of cases with proximal humerus fracture and controls. Significance level of $P < 0.05$ was using for this analysis

Characteristics *Age group*	Case ($n = 37$)	Control ($n = 67$)	P
–49	1	1	–
50–59	3	6	–
60–69	7	15	–
70–79	10	17	–
80–89	15	24	–
90+	1	4	–
Mean age ± SD (years)	76.3 ± 11.1	74.9 ± 11.2	NS
Body height (cm)	148.7 ± 9.9	150.7 ± 6.7	NS
Body weight (kg)	46.5 ± 10.4	49.0 ± 7.4	NS
BMI(kg/m^2)	21.0 ± 4.2	21.8 ± 2.8	NS
Number of children (mean)	0–6 (2.0)	0–6 (2.4)	NS
Dominant hand			
Right	37	66	–
Left	0	1	–
Unknown	0	0	–

In the univariate analysis, abiding place, body weight, weight loss, frequency of going outside, alcohol consumption, and falls during the past year were selected ($P < 0.1$) (Table 5). Increased physical activity, such as greater frequency of going outside, decreased the risk of proximal humerus fracture. No variables related to dietary habits (coffee, tea, Japanese tea, milk, cheese, fish), and medication (antihypertensive drugs and diuretics) showed any association with the risk of proximal humerus fracture.

Table 5 Selected risk factors for proximal humerus fracture by univariate analysis. Factors with significance level $P<0.10$ are presenting

	Odds ratio	95% CI	P
Residence			
Home	1.00	Reference	–
Nursing home	5.88	(1.20–28.8)	0.015
Body weight			
Each 10 kg	0.57	(0.30–1.10)	0.087
Weight loss			
No	1.00	Reference	–
Yes	2.15	(0.90–5.10)	0.077
Frequency of going outside			
Rarely or not at all	1.00	Reference	–
More than once every 2 or 3 days	0.22	(0.07–0.68)	0.004
Alcohol consumption			
Non-drinker	1.00	Reference	–
Drinker	0.19	(0.055–0.68)	0.003
Falls during the previous year			
Never	1.00	Reference	–
> Once a year	2.87	(1.03–8.00)	0.038

Table 6 Selected risk factors for proximal humerus fracture by multivariate analysis. Factors with significance level $P<0.10$ by univariate analysis are presenting

	Odds ratio	95% CI	P
Residence			
Home	1.00	Reference	–
Nursing home	1.76	(0.071–111.2)	0.75
Body weight			
each 10 kg	0.58	(0.23–1.31)	0.19
Weight loss			
No	1.00	Reference	–
Yes	5.00	(1.37–24.9)	0.013
Frequency of going outside			
Rarely or not at all	1.00	Reference	–
More than once every 2 or 3 days	0.14	(0.015–0.88)	0.035
Alcohol drinking			
Non-drinker	1.00	Reference	–
Drinker	0.29	(0.052–1.16)	0.083
Falls during the previous year			
Never	1.00	Reference	–
> Once a year	2.60	(0.55–14.9)	0.23

Multivariate analysis showed that weight loss was a significant risk factor, while greater frequency of going outside significantly decreased the risk of proximal humerus fracture (Table 6).

Discussion

The incidence of distal radius fractures increases with age, from the late 50s. However, the increase correlated with aging is not observed in subjects older than 60 years [3]. In contrast, the incidence of proximal humerus fractures, similar to that for hip fractures, increases markedly in subjects older than 80 years [3, 8]. Therefore, risk factors for distal radius fractures are different from those for proximal humerus fractures. Mean ages of the subjects in the present study were 67.4 years for distal radius fractures and 76.3 years for proximal humerus fractures, ages in which fractures are caused by bone fragility.

Epidemiological studies have indicated that risk factors for distal forearm fracture are low bone mass, estrogen deficiency [9], falls [10], drinking alcohol [11, 12], and consumption of animal protein [13]. Poor visual acuity [14, 15], frequent walking [14, 16], and walking at a brisk pace [17] are also risk factors for distal forearm fractures. A recent cohort study showed a 60% reduction in the risk of wrist fractures in women with no vigorous exercise in the past 2 weeks [15]. The authors suggested that strategies to increase exercise level among older people might have the adverse effect of increasing the number of wrist fractures.

This study demonstrated that increased physical activity, in particular increased walking ability, is a risk factor for distal radius fractures. This is in agreement with factors identified in previous studies, which concluded that increased physical activity, increased walking ability, and frequent outdoor walking all increase the risk of falls. Since nearly all distal radius fractures are caused by falls [18], these fractures are most likely to occur in highly active patients with low bone mass. This study also confirmed that tendency to fall is the most significant risk factor for distal radius fractures after adjusting for other factors by multivariate analysis.

Risk factors for proximal humerus fractures include low level of physical activity [19] and infrequent walking [14]. This contrasts with risk factors for distal radius fractures, indicating that distal radius fractures are most likely in patients with fragile bones and increased physical activity, while proximal humerus fractures are most likely in patients with fragile bones and decreased physical activity. Our results agree with those obtained in past cohort and case-control studies. Patients with reduced physical activity tend to fall before supporting themselves with their hands, which could result in injury of the proximal humerus. Greater weight loss was also a significant risk factor for proximal humerus fractures. Low body weight is a significant risk factor for bone loss [20], and therefore, becoming thinner increases the risk of fracture.

The finding that greater physical activity increases the risk of distal radius fractures and decreases the risk of proximal humerus fractures corresponds with changes in the incidence of fractures with aging. Distal radius fractures are most likely in 50- to 79-year-old patients with normal or high physical activity, while proximal humerus and hip fractures are most likely in those older than 80 years with decreased physical activity.

Although risk factors for hip fractures have been well defined in Caucasian subjects, only two epidemiological studies have examined the risk factors for hip fractures in Japanese subjects [6, 7]. Suzuki et al. performed a case-control study on hip fractures and found that sleeping on a bed (as opposed to a futon) was a significant risk factor (OR = 1.95), as were known risk factors

such as reduced physical activity [6]. They also reported that Japanese lifestyle, such as drinking Japanese tea, was effective in preventing fractures.

One significant preventive factor for distal radius fractures among Japanese was the use of a futon. This was also a preventive factor for hip fractures, as reported by Suzuki et al. [6]. Therefore, futon use (as opposed to bed use) may be important in reducing the risk of falls. One reason may be that spreading futons and putting them away in a closet everyday contributes to the maintenance of muscular strength in the lower limbs, and thereby reduces the risk of falls.

This study had several limitations. Since controls were selected from outpatients at orthopedic clinic, bias from other orthopedic disease cannot be dismissed. All control subjects were outpatients, and all patients with reduced activity of daily living, such as inability to walk outdoors without assistance, were excluded. However, control subjects may have lower walking ability than healthy subjects, which might result in the finding of an apparent risk of physical activity among subjects. It should be noted that tendency to fall was a significant risk factor for distal radius fractures, independent of the ability to walk outside. Second, this study was a cross-sectional study and information was obtained after the fracture event, which could bias the findings. It is necessary to perform case-control studies with a larger number of subjects, including population-based controls, as well as cohort studies in Asian countries where the incidence of osteoporosis related fractures is lower than in Caucasians.

In conclusion, risk factors for fractures of the upper limbs were elucidated here for the first time in Asian subjects. Falling is a significant risk factor for both fractures and futon use (instead of bed use) is a protective factor for distal radius fractures. Efforts to maintain physical activity, while being cautious to avoid falls, should be considered to reduce fracture risk among the elderly.

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ORIGINAL ARTICLE

Self-reported number of remaining teeth is associated with bone mineral density of the femoral neck, but not of the spine, in Japanese men and women

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Abstract Recent studies suggest that a small number of remaining teeth may be associated with low skeletal bone mineral density (BMD) in postmenopausal women. Estrogen deficiency after menopause is considered potential cause relating to tooth loss accompanied by low skeletal BMD in women. Since estrogen plays a dominant role in regulating the male skeleton, it is likely that a small number of remaining teeth also may be associated with low skeletal BMD in men. However, it remains uncertain whether tooth loss is associated with low skeletal BMD in both men and women. We investigated the association between self-reported number of remaining teeth and BMD of the spine and the femoral neck in a cohort of 1914 Japanese subjects aged 48–95 years who were recruited from the Adult Health Study conducted by the Radiation Effects Research Foundation (RERF). BMD of the spine and the femoral neck was measured by dual energy X-ray absorptiometry (DXA). Tooth count was self-reported in response to a simple question to subjects about the number of remaining teeth they had at the time of the survey. Multiple regression analysis adjusted for age, weight, height, smoking, estrogen use, and years since menopause revealed a significant association between number of remaining teeth and BMD of the femoral neck in both men and women; however, no association was found between number of remaining teeth and BMD of the spine in both sexes. Retention of four teeth was significantly associated with a 0.004 g/cm^2 increase in femoral neck BMD in men ($P < 0.05$), which was similar to that observed in women ($P < 0.01$). Our results suggest the presence of common causes, except age and body weight, relating to tooth loss accompanied by low BMD of the femoral neck in both men and women.

Keywords Bone mineral density · Femoral neck · Osteoporosis · Self-reported · Tooth loss

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Introduction

Osteoporotic fractures are associated with substantial morbidity, increased medical costs and high mortality risk in the elderly [1]. Tooth loss is also associated with deterioration in the systemic health of the elderly through alteration of dietary intake [2,3]. Causes of tooth loss include dental caries, periodontal disease, eruption problems, trauma, and orthodontics, among others [4]. It is generally known that women lose significant amounts of bone after menopause; however, women also lose more teeth after 50 years of age, which is mean menopausal age, than do men of the same age, in spite of a higher frequency of tooth brushing and a smaller number of untreated teeth [5].

Since Daniell [6] first reported a significant association between postmenopausal tooth loss and metacarpal bone mass, some investigators have linked tooth loss with low general skeletal bone mineral density (BMD) and high bone loss rates in postmenopausal women [7,8,9,10,11,12,13]. However, others failed to find an association between tooth loss and skeletal BMD in postmenopausal women [14,15,16,17,18]. It is likely that variance in the size and the age range of study populations may have contributed to this controversy.

Three epidemiological studies in the United States suggested the protective effect of estrogen use on tooth retention in postmenopausal women [19,20,21]. Men lose significant amounts of bone with age, although they do not have the equivalent of menopause. Recent reports suggested that estrogen plays a dominant role in

regulating the skeleton in both sexes [22,23,24,25,26]. Riggs et al. proposed a new unitary model for the pathophysiology of involutional osteoporosis that identifies estrogen deficiency as the cause of both the early, accelerated and the late, slow phases of bone loss in postmenopausal women and as a contributing cause of the continuous phase of bone loss in aging men [27].

The potential role of estrogen deficiency linking tooth loss and low skeletal BMD in postmenopausal women suggests that tooth loss also may be associated with low skeletal BMD in men. Only one study reported that a small self-reported number of remaining teeth was associated with low BMD of the spine and the hip in Caucasian men [16]. However, since the age range of the subjects in this study was limited to only 10 years (65–76 years of age), it remains uncertain whether tooth loss is associated with low BMD in both men and women.

The purpose of this study was therefore to investigate whether self-reported number of remaining teeth is associated with BMD of the spine and the femoral neck in a large population, including both men and women, with a wide age range.

Materials and methods

Subjects

The Adult Health Study (AHS) was established by the Radiation Effects Research Foundation (RERF) in 1958 to document the 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 about 5000 controls selected from residents in Hiroshima and Nagasaki using Japan's 1950 national census supplementary schedules and the Atomic Bomb Survivors Survey. AHS subjects have been followed through biennial medical examinations since 1 July 1958. The participation rate has been around 80% throughout this period. Details concerning recruitment and examination of participants have been reported [28].

Of AHS subjects who underwent physical examinations in Hiroshima between 2000 and 2002, 1914 subjects (616 men and 1298 women) aged 48–95 years were recruited for this study. Exclusion criteria were: impaired bone metabolism (such as hyperparathyroidism, renal osteodystrophy, and bilateral oophorectomy), and use of medications that affect bone metabolism (such as corticosteroids, calcitonin, vitamin D, bisphosphonate, and vitamin K) except estrogen.

BMD measurement and self-reported tooth count

BMD of the spine (L2–L4) and the femoral neck was measured using dual X-ray absorptiometry (DXA, QDR-2000, Hologic Inc., Waltham, Mass., USA). An anthropomorphic spine phantom was scanned daily to calibrate the instrument. There was no drift in machine performance during the study period. The instrument's precision was also carefully monitored over the study period using the anthropomorphic phantom, and was found to be less than 1%. No subjects had undergone spinal X-ray radiographs prior to DXA assessment between 2000 and 2002, because of concerns about exposure to high radiation doses. In medical examinations between 1998 and 2000 in this cohort, 3.7% of men and 10.2% of women had spinal fractures determined by X-ray radiographs. Vertebral fracture was diagnosed by lateral and posterior-anterior chest and spine X-ray examination. The vertebral fracture was assessed using semi-quantitative assessment [29,30]. All subjects gave written informed consent for BMD measurements and all other health examinations. Tooth count was self-reported in response to a simple question that asked subjects about the number of remaining teeth they had at the time of the survey.

Statistical analysis

The linear regression model was used to analyze the relationship between potential risk factors and BMD of the spine and the femoral neck. Since we previously demonstrated no association between exposure to atomic bomb radiation and skeletal BMD in this AHS cohort [28], exposure to atomic bomb radiation was not included in potential risk factors. Multivariate analysis was performed in addition to univariate analysis. First, variables were selected by univariate analysis adjusting only for age, using the level of $P=0.05$ as an indicator of significance. Next, a search for the best model was conducted in stages. Initially, all factors selected in the univariate analysis were included in the model. Non-significant variables were successively eliminated until all remaining variables except age and number of teeth were significant, with $P<0.05$. All computations were carried out using the Statistical Analysis System (SAS) package of programs. There were numerous unknown responses to each item on the questionnaire, as is common in mail surveys. For example, information about smoking was missing in 28% of the responses. In the linear regression analysis, the missing values were grouped together as one category, without excluding them from the study sample, to avoid a decrease in statistical power.

Results

Characteristics of the study population are shown in Table 1. BMD of the spine in men was significantly associated with age ($P<0.001$). In univariate analysis after adjusting for age, BMD of the spine in men was significantly related to weight ($P<0.001$), and height ($P<0.001$), but not to the number of remaining teeth ($P=0.30$). In women, BMD of the spine was significantly

Table 1 Characteristics of the study population (mean ± SD or %)

	Men	Women
No. of subjects	616	1298
Age (years)	66.9 ± 9.0	70.8 ± 9.0
Height (cm)[a]	162.9 ± 6.4	149.4 ± 6.1
Weight (kg)[a]	60.6 ± 9.2	51.3 ± 9.0
Age at menopause (years)[b]	–	48.4 ± 4.9
Bone mineral density (g/cm²)		
Lumbar spine[c]	1.00 ± 0.18	0.80 ± 0.16
Femoral neck[d]	0.74 ± 0.12	0.59 ± 0.11
No. of remaining teeth	15.7 ± 10.6	13.4 ± 10.2
Smoking habit[e]		
No. (%) who never smoked	88 (20.3%)	811 (86.2%)
No. (%) who used to smoke	155 (35.8%)	43 (4.6%)
No. (%) who smoke currently	190 (43.9%)	87 (9.2%)
No. (%) who use estrogen	–	48 (3.7%)

[a]Four women had no data on height and weight
[b]Nine hundred and fifty-one women were postmenopausal, 839 of whom had information about age at menopause
[c]Two men and one woman had no BMD data of the spine
[d]One man and six women had no BMD data of the femoral neck
[e]One hundred and eighty-three men and 357 women had no information