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 compared 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

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

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].

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

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

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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References

1. Nelson HD, Morris CD, Kraemer DF, Mahon S, Carney N, Nygren P, Helfand M (2002) Osteoporosis in postmenopausal women: diagnosis and monitoring. In: Oregon Health and Science University Evidence-Based Practice Center (eds) Evidence report/technology assessment No. 28. Agency for Healthcare Research and Quality, Rockville, MD
2. Law MR, Hackshaw AK (1997) A meta-analysis of cigarette smoking, bone mineral density and risk of hip fracture; recognition of a major effect. Br Med J 315:841–846
3. Huopio J, Kroger H, Honkanen R, Saarikoski S, Alhava E (2000) Risk factors for perimenopausal fractures: a prospective study. Osteoporos Int 11:219–227
4. Bohannon AD, Hanlon JT, Landerman R, Gold DT (1999) Association of race and other potential risk factors with non-vertebral fractures in community-dwelling elderly women. Am J Epidemiol 149:1002–1009
5. Mallmin H, Ljunghall S, Persson I, Bergstrom R (1994) Risk factors for fractures of the distal forearm: a population-based case-control study. Osteoporos Int 4:298–304
6. Kelsey JL, Browner WS, Seeley DG, Nevitt MC, Cummings SR (1992) Risk factors for fracture of the distal forearm and proximal humerus. Am J Epidemiol 135:477–489
7. Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, Cauley J, Black D, Vogt TM (1995) Risk factors for hip fracture in white women. New Engl J Med 332:767–773
8. National Osteoporosis Foundation (1998) Osteoporosis: review of the evidence for prevention, diagnosis and treatment and cost-effectiveness analysis. Osteoporos Int [Suppl 4] 8:1–88
9. National Osteoporosis Foundation (1998) Physicians guide to prevention and treatment of osteoporosis. National Osteoporosis Foundation, Washington DC, pp 1–38
10. Brown J, Josse RG for the Scientific Advisory Council of the Osteoporosis Society of Canada (2002) Clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. Canad Med Assoc J [Suppl 10] 167:S1-S34
11. Kanis JA, Delmas P, Burckhardt P, Cooper C, Torgerson D on behalf of the EFFO (1997) Guidelines for the diagnosis and management of osteoporosis. Osteoporos Int 7:390–406
12. Royal College of Physicians (1999) Osteoporosis: clinical guidelines for prevention and treatment. Royal College of Physicians, London
13. Royal College of Physicians (2000) Osteoporosis: clinical guidelines for prevention and treatment. Update on pharmacological interventions and an algorithm for management. Royal College of Physicians, London
14. Kanis JA, Black D, Cooper C, Dargent P, Dawson-Hughes B, De Laet C, Delmas P, Eisman J, Johnell O, Melton J, Oden A, Papapoulos S, Pols H, Rizzoli R, Silman A, Tenenhouse A (2002) A new approach to the development of assessment guidelines for osteoporosis. Osteoporos Int 13:527–536
15. Kanis JA (2002) Diagnosis of osteoporosis and assessment of fracture risk. Lancet 359:1929–1936
16. Kreiger N, Tenenhouse A, Joseph L et al (1999) The Canadian Multicenter Osteoporosis Study (CaMos): background, rationale, methods. Can J Aging 18:376–387
17. Jones G, Nguyen TV, Sambrook PN, Kelly PJ, Gilbert C, Eisman JA (1994) Symptomatic fracture incidence in elderly men and women. The Dubbo Osteoporosis Epidemiology Study (DOES). Osteoporos Int 4:277–282
18. Nguyen TV, Eisman JA, Kelly PJ, Sambrook PN (1996) Risk factors for osteoporotic fractures in elderly men. Am J Epidemiol 144:255–263
19. O'Neill TW, Felsenberg D, Varlow J, Cooper C, Kanis JA, Silman AJ (1996) The prevalence of vertebral deformity in European men and women: European vertebral osteoporosis study. J Bone Miner Res 11: 1010–1017
20. Felsenberg D, Silman AJ, Lunt M, Ambrecht G, Ismail AA, Finn JD, Cockerill WC, Banzer D, Benevolenskaya LI, Bhalla A, Bruges Armas J, Cannata JB, Cooper C, Dequeker J, Eastell R, Ershova O, Felsch B, Gowin W, Havelka S, Hoszowski K, Jajic I, Janot J, Johnell O, Kanis JA, Kragl G, Lopez Vaz A, Lorenc R, Lyritis G, Masaryk P, Matthis C, Miazgowski T, Parisi G, Pols HAP, Poor G, Raspe HH, Reid DM, Reisinger W, Scheidt-Nave C, Stepan J, Todd C, Weber K, Woolf AD, Reeve J, O'Neill TW (2002) Incidence of vertebral fracture in Europe: results from the European Prospective Osteoporosis Study (EPOS). J Bone Miner Res 17:716–724
21. Ismail AA, Pye SR, Cockerill WC, Lunt M, Silman AJ, Reeve J, Banzer D, Benevolenskaya LI, Bhalla A, Bruges Armas J, Cannata JB, Cooper C, Delmas PD, Dequeker J, Dilsen G, Falch JA, Felsch B, Felsenberg D, Finn JD, Gennari C, Hoszowski K, Jajic I, Janott J, Johnell O, Kanis JA, Kragl G, Lopez Vaz A, Lorenc R, Lyritis G, Marchand F, Masaryk P,

Matthis C, Miazgowski T, Naves-Diaz M, Pols HAP, Poor G, Rapado A, Raspe HH, Reid DM, Reisinger W, Scheidt-Nave C, Stepan J, Todd C, Weber K, Woolf AD, O'Neill TW (2002) Incidence of limb fracture across Europe: results from the European Prospective Osteoporosis Study (EPOS). Osteoporos Int 13:565–571
22. Svanborg A (1977) 70-year-old people in Gothenburg. A population study in an industrialised Swedish city II. Journal Presentation of Social and Medical Conditions. Acta Med Scand [Suppl] 611:5
23. Johansson C, Black D, Johnell O, Oden A, Mellstrom D (1998) Bone mineral density is a predictor of survival. Calcif Tissue Int 63:190–196
24. Stenstrom M, Olsson JO, Mellstrom D (2000) Thyroid hormone replacement is not related to increased risk of osteoporosis. Osteoporos Int [Suppl 2] 11:S144.
25. Fujiwara S, Kasagi F, Yamada M, Kodama K (1997) Risk factors for hip fracture in Japanese cohort. J Bone Miner Res 12:998–1004
26. Fujiwara S, Fumiyoshi K, Masunari N, Naito K, Suzuki G, Fukunage M (2003) Fracture prediction from bone mineral density in Japanese men and women. J Bone Miner Res 18:1547–1553
27. Honkanen R, Kroger H, Tuppurainen M, Alhava E, Saarikoski S (1995) Fractures and low axial bone density in perimenopausal women. J Clin Epidemiol 48:881–888
28. Melton LJ 3rd, Crowson CS, O'Fallon WM, Wahner HW, Riggs BL (2003) Relative contributions of bone density, bone turnover and clinical risk factors to long-term fracture prediction. J Bone Miner Res 18:312–318
29. Melton LJ 3rd, Atkinson EJ, O'Connor MK, O'Fallon WM, Riggs BL (1998) Bone density and fracture risk in men. J Bone Miner Res 13:1915–1923
30. Hofman A, Grobbee DE, De Jong PT, van den Ouweland FA (1991) Determinants of disease and disability in the elderly: the Rotterdam study. Eur J Epidemiol 7:403–422
31. De Laet CE, Van Hout BA, Burger H, Hofman A, Weel AE, Pols HAP (1998) Hip fracture prediction in elderly men and women: validation of the Rotterdam study. J Bone Miner Res 13:1587–1593
32. Johansson H, Oden A, Johnell O, Jonsson B, De Laet C, Oglesby A, McCloskey EV, Kayan J, Jalava T, Kanis JA (2003) Optimisation of BMD measurements to identify high-risk groups for treatment—a test analysis. J Bone Miner Res (in press)
33. Kanis JA, Oden A, Johnell O, Jonsson B, De Laet C, Dawson A (2001) The burden of osteoporotic fractures: a method for setting intervention thresholds. Osteoporos Int 12:417–427
34. Higgins JPT, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. Br Med J 327:557–560
35. Marshall D, Johnell O, Wedel H (1996) Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. Lancet 312:1254–1259
36. Cornuz J, Feskanich D, Willett WC et al (1999) Smoking, smoking cessation and risk of hip fracture in women. Am J Med 106:311–314
37. Sowers MR, Clark MK, Hollis B, Wallace RB, Jannausch M (1992) Radial bone mineral density in pre- and perimenopausal women: a prospective study of rates and risk factors for loss. J Bone Miner Res 7:647–657
38. Hannan MT, Felson DT, Dawson Hughes B, Tucker KL, Cupples LA, Wilson PWF, Keil DP (2000) Risk factors for longitudinal bone loss in elderly men and women. The Framingham Osteoporosis Study. J Bone Miner Res 15:710–720
39. Burger H, De Laet C, Van Daele P, Weel A, Witteman J, Hofman A, Pols H (1998) Risk factors of increased bone loss in an elderly population. The Rotterdam Study. Am J Epidemiol 147:871–879
40. Hermann AP, Brot C, Gram J, Kolthoff N, Mosekilde L (2000) Premenopausal smoking and bone density in 2,015 perimenopausal women. J Bone Miner Res 15:780–787
41. McKinlay SM, Bifano NL, McKinley JB (1985) Smoking and age at menopause in women. Ann Intern Med 103:350–356
42. Seeman E (1996) The effects of tobacco and alcohol use on bone. In: Marcus R, Feldman D, Kelsey J (eds) Osteoporosis 1996. Academic, San Diego, pp 577–597
43. Kiel DP, Baron JA, Anderson JJ, Hannan MT, Felson DT (1992) Smoking eliminates the potential effects of oral estrogens on the risk for hip fractures among women. Ann Intern Med 116:716–721
44. Hoidrup S, Gronbaek M, Pedersen AT, Lauritzen JB, Gottschau A, Schroll M (1999) Hormone replacement therapy and hip fracture risk: effects of modifications by tobacco smoking, alcohol intake, physical activity and body mass index. Am J Epidemiol 150:1085–1093
45. Johnell O, Gullberg B, Kanis JA, Allander E, Elffors L, Dequeker J, Dilsen G, Gennari C, Lopez Vaz A, Lyritis G, Mazzuoli G, Miravet L, Passeri M, Perez Cano R, Rapado A, Ribot C (1995) Risk factors for hip fracture in European women: the MEDOS study. J Bone Miner Res 10:1802–1815
46. Gunnes M, Mellstrom D, Johnell O (1998) How well can a previous fracture indicate a new fracture? A questionnaire study of 29,802 postmenopausal women. Acta Orthop Scand 69:508–512
47. Ensrud KE, Nevitt MC, Yunis C, Cauley JA, Seeley DG, Fox KM et al (1994) Correlates of impaired function in older women. J Am Geriatr Soc 42:481–489
48. Nelson HD, Nevitt ME, Scott JC, Stone KL, Cummings SR (1994) Smoking, alcohol and neuromuscular and physical function of older women. JAMA 272:1825–1831
49. Svendsen OL, Hassager C, Skodt T, Christiansen C (1995) Impact of soft tissue on in vivo accuracy of bone mineral measurements in the spine, hip and forearm: a human cadaveric study. J Bone Miner Res 10:868–873
50. Kanis JA, Johnell O, Oden A, De Laet C, Jonsson B (2001) Intervention thresholds for osteoporosis. Bone 31:26–31
51. Van Staa TP, Leufkens HGM, Cooper C (2002) Does a fracture at one site predict later fractures at other sites? A British cohort study. Osteoporos Int 13:624–629
52. Klotzbeucher CM, Ross PD, Landsman PB, Abbot TA, Berger M (2000) Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. J Bone Miner Res 15:721–739.
53. Guidelines Writing Group (2002) Glucocorticoid-induced osteoporosis. Guidelines for prevention and treatment. Bone and Tooth Society of Great Britain, National Osteoporosis Society and Royal College of Physicians. Royal College of Physicians, London
54. Delmas PD, Eastell R, Garnero P, Seibel MJ, Stepan J (2000) The use of biochemical markers of bone turnover in osteoporosis. Osteoporos Int [Suppl 6] 11:S2-S17

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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

Table 2 Correlation with bone mineral density of the spine and the femoral neck by univariate analysis, after adjusting for age. The results are presented as the parameter estimate ± SE

Items	Bone mineral density of the spine				Bone mineral density of the femoral neck			
	Men	*r*-square	Women	*r*-square	Men	*r*-square	Women	*r*-square
Age (10 years)	0.011 ± 0.008^{a}	0.003	-0.037 ± 0.005^{a}	0.050	-0.039 ± 0.005^{a}	0.075	-0.055 ± 0.003^{a}	0.220
Weight (10 kg)	0.070 ± 0.007^{a}	0.128	0.069 ± 0.005^{a}	0.196	0.053 ± 0.005^{a}	0.230	0.041 ± 0.003^{a}	0.329
Height (10 cm)	0.048 ± 0.012^{a}	0.031	0.044 ± 0.008^{a}	0.076	0.046 ± 0.007^{a}	0.128	0.033 ± 0.047^{a}	0.248
Smoking (vs non-smoker)	–	0.016	–	0.053	–	0.080	–	0.225
Past	0.042 ± 0.024	–	-0.001 ± 0.023	–	0.017 ± 0.016	–	-0.027 ± 0.015^{d}	–
Current	0.010 ± 0.023	–	-0.023 ± 0.017	–	-0.006 ± 0.015	–	-0.021 ± 0.011^{c}	–
No information	0.049 ± 0.023^{c}	–	0.009 ± 0.010	–	0.005 ± 0.015	–	0.050 ± 0.006	–
Tooth (4 teeth)	0.003 ± 0.003	0.005	0.002 ± 0.002	0.052	0.006 ± 0.002^{b}	0.089	0.004 ± 0.001^{b}	0.226
Estrogen use (vs no)	–	–	0.008 ± 0.023	0.051	–	–	0.005 ± 0.014	0.220
Pre-menopause (vs post)	–	–	0.061 ± 0.019^{b}	0.052	–	–	0.019 ± 0.012	0.211
Years since menopause (10 years)	–	–	-0.038 ± 0.009^{a}	0.056	–	–	-0.026 ± 0.006^{a}	0.221

$^{a}P < 0.001$, $^{b}P < 0.01$, $^{c}P < 0.05$, $^{d}0.05 < P < 0.10$

associated with age ($P < 0.001$), weight ($P < 0.001$), height ($P < 0.001$), menopausal status ($P < 0.01$), and years since menopause ($P < 0.001$), but not with number of remaining teeth ($P = 0.25$). BMD of the femoral neck was significantly associated with age ($P < 0.001$), weight ($P < 0.001$), height ($P < 0.001$), and number of remaining teeth ($P < 0.01$) in men, and with age ($P < 0.001$), weight ($P < 0.001$), height ($P < 0.001$), current smoking ($P < 0.05$), years since menopause ($P < 0.001$), and number of remaining teeth ($P < 0.01$) in women (Table 2).

Multiple regression analysis adjusted for all potential confounding factors that were selected by univariate 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 either men ($P = 0.67$) or women ($P = 0.37$) (Table 3). Retention of four teeth was significantly associated with 0.004 g/cm^2 ($P < 0.05$) increase of femoral neck BMD in men and 0.004 g/cm^2 ($P < 0.01$) increase of femoral neck BMD in women, although the variance of tooth loss related to femoral neck BMD was small (0.75% in men and 0.58% in women). Advancing age was significantly associated with increased BMD of the spine ($P < 0.001$) and decreased BMD of the femoral neck ($P < 0.001$) in men. Similarly, BMD tended to be higher at the spine ($P = 0.07$) and lower at the femoral neck ($P = 0.08$) with advancing age in women. However, a great number of years since menopause was significantly associated with decreased BMD of the spine ($P < 0.05$) and the femoral neck ($P < 0.001$) in postmenopausal women. Premenopausal women had significantly higher BMD of the spine than did postmenopausal women ($P < 0.01$). Higher body weight was significantly associated with increased BMD of the spine ($P < 0.001$) and the femoral neck ($P < 0.001$) in both sexes.

Discussion

BMD of the femoral neck was significantly associated with number of remaining teeth in both men and women in our study. Krall et al. found a significant association between number of remaining teeth and BMD of the femoral neck in 329 healthy Caucasian postmenopausal women aged 41–71 years [8]. May et al. observed this association in women aged 65–76 years [16], although it did not reach statistical significance. Earnshaw et al. failed to find an association, but their subjects were limited to early postmenopausal women [18]. They concluded that the lack of association in their study might have been because dental status in younger women is a

Table 3 Relationship between number of remaining teeth and bone mineral density of the spine and the femoral neck by multiple regression analysis. The results are presented as the parameter estimate ± SE

Items	Bone mineral density of spine		Bone mineral density of femoral neck	
	Men	Women	Men	Women
Age (10 years)	0.029 ± 0.001^{a}	0.002 ± 0.001^{d}	-0.020 ± 0.005^{a}	-0.012 ± 0.007^{d}
Weight (10 kg)	0.070 ± 0.007^{a}	0.068 ± 0.005^{a}	0.053 ± 0.005^{a}	0.041 ± 0.003^{a}
Tooth (4 teeth)	0.001 ± 0.003	0.002 ± 0.002	0.004 ± 0.002^{c}	0.004 ± 0.001^{b}
Pre-menopause (vs post)	–	0.051 ± 0.019^{b}	–	–
Years since menopause (10 years)	–	-0.023 ± 0.003^{c}	–	-0.023 ± 0.005^{a}
r-square	0.129	0.200	0.238	0.339

$^{a}P < 0.001$, $^{b}P < 0.01$, $^{c}P < 0.05$, $^{d}0.05 < P < 0.10$

reflection more of dietary habits and previous dental surgery than of age-related bone loss. Gur et al. also failed to find an association between the two factors in 1171 postmenopausal women aged 40–86 years recruited from multiple locations in Turkey [12], but their results were not adjusted for age, weight and smoking habit, which may have had some kind of affect on both BMD of the femoral neck and number of remaining teeth.

Only one previous study found a significant association between number of remaining teeth and BMD of the femoral neck in 608 men aged 65–76 years [16]. Our results in 605 men agreed with these results. Furthermore, the extent (0.004 g/cm^2) of BMD increase of the femoral neck associated with retention of four teeth in women was similar to that (0.004 g/cm^2) in men. This implies that a common cause, or a combination of factors, may play a role in the link between number of remaining teeth and BMD of the femoral neck in both sexes. Loss of oral bone surrounding the teeth as a consequent of accelerated skeletal bone loss may be considered one of potential causes linking number of remaining teeth and BMD of the femoral neck in women; however, it is doubtful that slow continuous phase of skeletal bone loss in men causes oral bone loss, resulting in tooth loss.

Other potential causes linking number of remaining teeth and BMD of the femoral neck may include an increased inflammation of periodontal tissue surrounding the teeth. Previous studies in Japan [10] and in Finland [15] suggested that women with higher skeletal BMD tended to have more teeth than did those with lower skeletal BMD even when both had the same degree of oral bone surrounding the teeth. Ronderos et al. demonstrated that women with osteoporosis based on femoral neck BMD were at increased risk of periodontal disease, and that this risk may be attenuated by the use of estrogen replacement therapy [31]. Similar association between increased risk of periodontal disease and low femoral BMD was also observed in men in their study. These facts indicate that increased risk of periodontal disease may be an additional cause linking number of remaining teeth and BMD of the femoral neck in both sexes. Morishita et al. recently indicated that estradiol and progesterone inhibited the production of interleukin-1 from human peripheral monocytes, although testosterone did not show any significant effect on interleukin-1 production [32]. Increased level of interleukin-1 in both men and women with low concentration of estrogen may contribute to increased inflammation of periodontal tissue surrounding the teeth.

BMD of the spine was not associated with number of remaining teeth in women in this study. We previously found a significant association between number of remaining teeth and BMD of the spine in 90 Japanese postmenopausal women without spinal fracture aged 40–68 years [10]. Krall et al. also found an association in postmenopausal women without spinal fracture [8]. Gur et al. reported an association in postmenopausal women without the fractures after 25 years of age [12], although their results were not adjusted for confounding variables related to both tooth loss and BMD of the spine. The large rate of spinal fracture incidence in medical examinations between 1998 and 2000 in our cohort suggests the possibility that spinal fracture or deformity may have influenced BMD of the spine in women in our study.

We found no association between number of remaining teeth and BMD of the spine in men, which did not agree with the finding reported by May et al. [16]. However, a significant association between advancing age and increased BMD of the spine in men strongly suggests that other factors related to advancing age such as spinal fracture, spinal deformity, aortic calcification and/or osteophyte formation may have influenced BMD of the spine in our study.

This study has limitations. Self-reported tooth count might be inaccurate in comparison with the number of remaining teeth that dentists or trained professionals can determine clinically or radiographically. However, Douglass et al. demonstrated that self-reported number of remaining teeth was highly correlated with the actual number of teeth found in clinical examinations in a general population ($r = 0.97$) [33]. Pitiphat et al. also reported that the self-reported numbers of remaining teeth, fillings, root canal therapy, and prosthesis were strongly correlated with clinical records ($r = 0.74$–1.0), although self-reporting was less accurate for measuring periodontal disease ($r = 0.56$) [34]. Self-reported number of remaining teeth is used to investigate the association between tooth loss and systemic diseases such as stroke [35] or peripheral arterial disease [36] in large population studies. Although there have been no previous studies demonstrating the validity of self-reported tooth count in Japan, it is likely that the self-reported number of remaining teeth may accurately reflect the actual number of remaining teeth in our subjects, because all subjects expressed a strong interest in their general health, including oral health.

In conclusion, self-reported number of remaining teeth was significantly associated with BMD of the femoral neck in both men and women, but not with BMD of the spine. Our results suggest that there may be common causes relating to tooth loss accompanied by low BMD of the femoral neck in both men and women, although it is unknown whether these causes include the effect of estrogen.

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References

1. Melton LJ 3rd (2003) Adverse outcomes of osteoporotic fractures in the general population. J Bone Miner Res 18:1139–1141

2. Shimazaki Y, Soh I, Saito T, Yamashita Y, Koga T, Miyazaki H et al. (2001) Influence of dentition status on physical disability, mental impairment, and mortality in institutionalized elderly people. J Dent Res 80:340–345
3. Ritchie CS, Joshipura K, Hung HC, Douglass CW (2002) Nutrition as a mediator in the relation between oral and systemic disease: associations between specific measures of adult oral health and nutrition outcomes. Crit Rev Oral Biol Med 13:291–300
4. Morita M, Kimura T, Kanegae M, Ishikawa A, Watanabe T (1994) Reasons for extraction of permanent teeth in Japan. Commun Dent Oral Epidemiol 22:303–306
5. Dental Health Division of Health Policy Bureau Ministry of Health, Labour and Welfare Japan (1999) Report on the survey of dental disease. Oral Health Association, Tokyo
6. Daniell HW (1982) Postmenopausal tooth loss. Contributions to edentulism by osteoporosis and cigarette smoking. Arch Int Med 143:1678–1682
7. Kribbs PJ (1990) Comparison of mandibular bone in normal and osteoporotic women. J Prosthet Dent 63:218–222
8. Krall EA, Dawson-Hughes B, Papas A, Garcia RI (1994) Tooth loss and skeletal bone density in healthy postmenopausal women. Osteoporos Int 4:104–109
9. Krall EA, Garcia RI, Dawson-Hughes B (1996) Increased risk of tooth loss is related to bone loss at the whole body, hip, and spine. Calcif Tissue Int 59:433–437
10. Taguchi A, Suei Y, Ohtsuka M, Otani K, Tanimoto K, Hollender LG (1999) Relationship between bone mineral density and tooth loss in elderly Japanese women. Dentomaxillofac Radiol 28:219–223
11. Inagaki K, Kurosu Y, Kamiya T et al. (2001) Low metacarpal bone density, tooth loss, and periodontal disease in Japanese women. J Dent Res 80:1818–1822
12. Gur A, Nas K, Kayhan O, Atay MB, Akyuz G, Sindal D, et al (2003) The relation between tooth loss and bone mass in postmenopausal osteoporotic women in Turkey: a multicenter study. J Bone Miner Metab 21:43–47
13. Mohammad AR, Hooper DA, Vermilyea SG, Mariotti A, Preshaw PM (2003) An investigation of the relationship between systemic bone density and clinical periodontal status in post-menopausal Asian-American women. Int Dent J 53:121–125
14. Elders PJ, Habets LL, Netelenbos JC, van der Linden LW, van der Stelt PF (1992) The relation between periodontitis and systemic bone mass in women between 46 and 55 years of age. J Clin Periodontol 19:492–496
15. Klemetti E, Collin HL, Forss H, Markkanen H, Lassila V (1994) Mineral status of skeleton and advanced periodontal disease. J Clin Periodontol 21:184–188
16. May H, Reader R, Murphy S, Khaw KT (1995) Self-reported tooth loss and bone mineral density in older men and women. Age Ageing 24:217–221
17. Mohammad AR, Bauer RL, Yeh CK (1997) Spinal bone density and tooth loss in a cohort of postmenopausal women. Int J Prosthodont 10:381–385
18. Earnshaw SA, Keating N, Hosking DJ, Chilvers CE, Ravn P, McClung M et al. (1998) Tooth counts do not predict bone mineral density in early postmenopausal Caucasian women. EPIC study group. Int J Epidemiol 27:479–483
19. Paganini-Hill A (1995) The benefits of estrogen replacement therapy on oral health. The Leisure World cohort. Arch Int Med 155:2325–2329
20. Grodstein F, Colditz GA, Stampfer MJ (1996) Post-menopausal hormone use and tooth loss: a prospective study. J Am Dent Assoc 127:370–377
21. Krall EA, Dawson-Hughes B, Hannan MT, Wilson PW, Kiel DP (1997) Postmenopausal estrogen replacement and tooth retention. Am J Med 102:536–542
22. Smith EP, Boyd J, Frank GR, Takahashi H, Cohen RM, Specker B et al. (1994) Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. N Engl J Med 331:1056–1061
23. Morishima A, Grumbach MM, Simpson ER, Fisher C, Qin K (1995) Aromatase deficiency in male and female siblings caused by a novel mutation and the physiological role of estrogens. J Clin Endocrinol Metab 80:3689–3698
24. Bilezikian JP, Morishima A, Bell J, Grumbach MM (1998) Increased bone mass as a result of estrogen therapy in a man with aromatase deficiency. N Engl J Med 339:599–603
25. Slemenda CW, Longcope C, Zhou L, Hui SL, Peacock M, Johnston CC (1997) Sex steroids and bone mass in older men. Positive associations with serum estrogens and negative associations with androgens. J Clin Invest 100:1755–1759
26. Falahati-Nini A, Riggs BL, Atkinson EJ, O'Fallon WM, Eastell R, Khosla S (2000) Relative contributions of testosterone and estrogen in regulating bone resorption and formation in normal elderly men. J Clin Invest 106:1553–1560
27. Riggs BL, Khosla S, Melton LJ 3rd (1998) A unitary model for involutional osteoporosis: estrogen deficiency causes both type I and type II osteoporosis in postmenopausal women and contributes to bone loss in aging men. J Bone Miner Res 13:763–773
28. Fujiwara S, Kasagi F, Masunari N, Naito K, Suzuki G, Fukunaga M (2003) Fracture prediction from bone mineral density in Japanese men and women. J Bone Miner Res 18:1547–1553
29. Genant HK, Wu CY, van Kuijk C, Nevitt MC (1993) Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res 8:1137–1148
30. National Osteoporosis Foundation Working Group on Vertebral Fractures (1995) Report: assessing vertebral fractures. J Bone Miner Res 10:518–523
31. Ronderos M, Jacobs DR, Himes JH, Pihlstrom BL (2000) Associations of periodontal disease with femoral bone mineral density and estrogen replacement therapy: cross-sectional evaluation of US adults from NHANES III. J Clin Periodontol 2000 27:778–786
32. Morishita M, Miyagi M, Iwamoto Y (1999) Effects of sex hormones on production of interleukin-1 by human peripheral monocytes. J Periodontol 70:757–760
33. Douglass CW, Berlin J, Tennstedt S (1991) The validity of self-reported oral health status in the elderly. J Public Health Dent 51:220–222
34. Pitiphat W, Garcia RI, Douglass CW, Joshipura KJ (2002) Validation of self-reported oral health measures. J Public Health Dent 62:122–128
35. Joshipura KJ, Hung HC, Rimm EB, Willett WC, Ascherio A (2003) Periodontal disease, tooth loss, and incidence of ischemic stroke. Stroke 34:47–52
36. Hung HC, Willett W, Merchant A, Rosner BA, Ascherio A, Joshipura KJ (2003) Oral health and peripheral arterial disease. Circulation 107:1152–1157

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Cataract in atomic bomb survivors

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Abstract.
Purpose: Ophthalmologic examinations were conducted on atomic bomb (A-bomb) survivors 55 years after exposure.
Materials and methods: A-bomb survivors who had been exposed before 13 years of age at the time of the bombings in 1945 or who had been examined in a previous study between 1978 and 1980. The examinations, conducted between June 2000 and September 2002, included slit-lamp examination, digital photography and a cataract grading system for three parts of the lens (nucleus, cortex and posterior subcapsule) as an outcome variable. Proportional odds logistic regression analysis was conducted using the lowest grading class as a reference and included explanatory variables such as age, sex, city, dose and various cataract-related risk factors. When the grades in an individual differed, the worst grade was used.
Results: Results indicate that odds ratios (ORs) at 1 Sv were 1.07 (95% confidence intervals [CI] 0.90, 1.27) in nuclear colour, 1.12 (95% CI 0.94, 1.30) in nuclear cataract, 1.29 (95% CI 1.12, 1.49) in cortical cataract and 1.41 (95% CI 1.21, 1.64) in posterior subcapsular cataract. The same was true after excluding 13 people whose posterior subcapsular cataracts had been previously detected.
Conclusion: Significant radiation effects were observed in two types of cataracts in A-bomb survivors.

1. Introduction

The eye lens is in the anterior part of the eye in a capsule consisting of non-nucleated lens fibre cells forming the lens nucleus and cortex (outer layer), and one layer of nucleated epithelial cells covering the surface of the lens (Masuda 1993). It is one of the most radiosensitive organs in both humans and animals because epithelial cells at the equator (located in the rim portion of the lens) proliferate and continue moving towards the centre of the lens for the entire life of the organism. While moving toward the centre of the lens, the epithelial cells are stretched, squeezed and lose nuclei, resulting in fibre cells. The fibre cells contain specific proteins called crystallins that keep the lens transparent by chaperon activity. Cataract pathogenesis, induced by a variety of insults such as ultraviolet light, is impairment of epithelial cell proliferation and/or oxidative degeneration of lens fibre proteins. Impaired epithelial cells let water and minerals into the lens; healthy cells keep them out by active transport. Pathogenic changes of the lens are clinically observed as opacities (opaque change). Visual acuity is usually not impaired by the opacities if they have not advanced to the central part (visual axis) of the lens.

Previous ophthalmological studies conducted among atomic (A) bomb survivors provide important evidence of the stochastic effect of radiation (Miller *et al.* 1969, Choshi *et al.* 1983). Radiation-induced cataract develops relatively early (6 months to 2 years) among the late effects of radiation (Miller *et al.* 1969, Choshi *et al.* 1983). Infants who receive radiotherapy (1–8 Gy) for haemangioma, however, develop posterior subcapsular or cortical opacities in the untreated eyes 30–45 years later, and defective lens fibre formation can continue, probably because of a clone of damaged germinal epithelial cells (Wilde and Sjöstrand 1997). Children exposed to a lenticular dose of 1 Gy have a 50% increased risk (OR 1.50; 95% confidence interval [CI] 1.10–2.05) of developing a posterior subcapsular opacity and a 35% increased risk of developing a cortical opacity (OR 1.35; 95% CI 1.07–1.69) (Hall *et al.* 1999), indicating early onset cortical opacities.

The relationship between these types of lens changes and radiation dose in A-bomb survivors exposed in their youth was studied in the present paper. To assess precise radiation effects, two systems were used. First, to grade different degrees of opacities (opaqueness) in nuclear (central part of the lens), cortical (outer layer of the lens) and posterior subcapsular cataracts (rear portion of the lens and underneath the lens capsule), the Lens Opacity

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Classification System (LOCS) II was used, in which standard pictures of nuclear (opalescence and colour), cortical (five standards) and subcapsular cataracts (four standards) were employed. The system shows good inter- and intra-observer reproducibility (Chylack *et al.* 1989). LOCS II enabled assessment of quantitative lens changes not previously studied in A-bomb survivors. Second, to assess the effect of various cataract risk factors on radiation-induced cataract, 17 ophthalmological findings, 23 host and environmental factors, 15 laboratory tests for potentially relevant conditions, i.e. diabetes mellitus, cardiovascular disease, obesity (Klein *et al.* 1998, Hutnik *et al.* 1999, Leske *et al.* 1999), steroid medications (Cumming and Mitchell 1998), ultraviolet light exposure (Katoh *et al.* 1997, Cruickshanks 1998, Hayashi *et al.* 1998), inflammation (Schaumberg *et al.* 1999), calcium level (Srivastava and Srivastava 1989), and smoking (Hiller *et al.* 1997) were tested. We then searched for 'intermediate risk factors', to which radiation causes some alterations that in turn cause lens opacities.

2. Materials and methods

2.1. *Subjects*

Subjects were part of the Adult Health Study (AHS) conducted in Hiroshima and Nagasaki who have undergone biennial examinations since 1958. Two groups, those undergoing ophthalmological examinations in the previous study (1978–80) and who satisfied the study requirements, as well as those who were less than 13 years old at the time of the bombings were eligible for study. Among the 2042 people who underwent ophthalmological examination in the previous studies, 1284 were alive at September 1999. Among those who were 13 years old or less at the time of the bombings, 2774 were alive at September 1999. Of those, 913 agreed to participate in the study initially and again at the time of their visits. All were given a full explanation of the procedures and the possible adverse effects of the mydriatics (0.5% tropicamide and 0.5% phenylephrine hydrochloride) that would be administered. The Human Investigation Committee at the Radiation Effects Research Institute (RERF) approved the study protocol.

2.2. *Study methods*

2.2.1. *Ophthalmologic examinations.* Ophthalmological examinations were conducted one or two mornings a week at the RERF during the study period by ophthalmologists from Hiroshima or Nagasaki universities. Comprehensive examinations for the function and structure of the eye, including visual acuity, intra-ocular pressure, refraction, and pictures of various parts of the eye with ophthalmological apparatuses, were conducted. For those with signs of serious disease, careful medical procedures were taken.

Specifically, the following nine ophthalmological examinations were conducted: (1) questionnaire; (2) objective refractory examination with an autorefractometer (RM-8000, Tokyo, Japan); (3) corrected visual acuity test with a 5-metre acuity chart; (4) intra-ocular pressure measurement with an applanation tonometer; (5) anterior chamber examination with a slit-lamp biomicroscope (chamber angle with gonioscopy, if necessary); (6) lens examination with a slit-lamp biomicroscope; (7) lens photographs; (8) posterior retina examination with an indirect ophthalmoscope and a slit-lamp biomicroscope; and (9) retro-illumination examination of the lens with a fundus camera and a slit-lamp biomicroscope. Examinations 1–5 were conducted on all participants. When a narrow anterior chamber angle was detected, a further examination under mydriasis was not performed. When a normal anterior chamber angle was detected, mydriatics were instilled, we waited for 30 min and then conducted examinations 6–9. After examination, a miotic (1% pilocarpine hydrochloride) was instilled. Digital images of the lens were stored in a computer (ImageNet®, Topcon).

2.2.2. *LOCS II classification.* Ophthalmologists made diagnoses using lens photographs and coded them according to LOCS II, in which standard pictures of nuclear (opalescence and colour), cortical (five standards) and subcapsular cataracts (four standards) were used. The classification system provides good inter- and intra-observer reproducibility (Chylack *et al.* 1989). Diagnostic standardization was conducted every 6 months, and agreement among the ophthalmologists in Hiroshima and Nagasaki was consistently over 80%.

2.2.3. *Medical questionnaire and clinical laboratory tests.* Information about ocular diseases, eye surgery, past and present systemic diseases that might have induced lens opacities, duration of exposure to ultraviolet light during outdoor work and leisure activities, and radio- and/or chemotherapy history were obtained by interview. Clinical laboratory tests related to cataract development among the AHS examinations, such as white blood cell count, erythrocyte sedimentation rate, alpha 1 globulin, alpha 2 globulin, calcium, phosphorus, glucose, and haemoglobin A1C (HbA1C) were incorporated into the analysis.

2.3. *Statistical methods*

Findings from the worse eye were used to produce a univariate outcome from bivariate outcomes of the right and left eyes. In the current study, outcomes were binary or ordered polytomous. To estimate outcome prevalences, we applied a logistic regression model to the binary outcome the proportional odds regression model to ordered polytomous data which is a standard model for ordered polytomous data like ophthalmological changes. The fitted model was as follows:

$$\log\left[\frac{\gamma_j}{1-\gamma_j}\right]=\theta_j+\beta_C C+\beta_S S+\beta_B(\text{ageATB}-5)/10+\beta_D D,$$

where $\gamma_j=\Pr(Y\geqslant j)$ for $j=1, \ldots, R$ and Y is an $(R+1)$-ordered polytomous outcome that takes a value in $\{0, 1, \ldots, R\}$, θ_j's are cut points, C is the city indicator (0 = Hiroshima, 1 = Nagasaki), S is a sex indicator (0 = male, 1 = female) and D is DS86 eye dose (Sv) for those older than 0 years at the time of the bombings and DS 86 mother's uterus dose for those in gestation, with relative biological effects (RBE) for a neutron being 10. Age ATB is age at the time of bombings. Gamma and neutron eye doses were truncated at 4 Gy in a total Kerma dose. The meaning of β_D in the proportional odds model above is the log OR per Sv in the logistic model for new binary outcomes produced from the ordered polytomous data in the way that the new binary response is 1 for $Y\geqslant j$ and 0 for $Y<j$ using cut-off category level j. When slopes are defined in this way, the slope parameter β_D is generally dependent on the cut-off category level. However, the proportional odds model assumes the β's to be common, and the common parameter is estimated by an iterative multivariate least-squares method (McCullagh and Nelder 1989).

Inflammation-related variables (white blood cell count, alpha 1 globulins, alpha 2 globulins, and erythrocyte sedimentation rate) were summarized by principal component analysis. The first principal component score (size factor) that was adjusted to the variance equal to 1 was used for an explanatory variable in the regression analysis for posterior subcapsular opacity in the Results. All computations were done with a STATA 8.0 statistical package.

3. Results

The study was conducted between June 2000 and September 2002. Total examinees numbered 913 (table 1). A slit-lamp examination was not conduct on 30 people because of contraindication or refusal. Among the 883 people examined, six had undergone surgery in both lenses and four had received unknown radiation doses. Therefore, 873 people were included in the analysis. Among them, a lens was present in only the right eye in 15 people, in only the left in 21, and in both in 827. Among those with lenses in both eyes, the worse finding was used for analysis. The distribution of examinees by A-bomb radiation dose and age at exposure is shown in table 2. Of the 873 subjects, 533 were in Hiroshima at the time of the bombings and 340 were in Nagasaki. Age at the time of the bombings ranged from −0.8 to 37.9 years (mean 8.8 years). Age at the time of the examination ranged from 54.3 to 94.4 years (mean 64.8 years). The subjects comprised 344 men and 529 women. The participation rate stratified by radiation dose groups did not vary with radiation dose.

Table 3 shows the distribution of cases by LOCS II classification. Regression analysis with the proportional odds model which used the lowest group as a reference revealed that ORs at 1 Sv were 1.07 (95% CI 0.90, 1.27) in nuclear colour, 1.12 (95% CI 0.94, 1.30) in nuclear opacities, 1.29 (95% CI 1.12, 1.49) in cortical opacities, and 1.41 (95% CI 1.21, 1.64) in posterior subcapsular opacities (table 4 and figure 1). The same was true after removing 13 people who had

Table 1. Profile of examinees in the ophthalmological study of A-bomb survivors during 2000–02.

All examinees	913
No slit-lamp examination	30
Instillation refusal	6
Contraindication	24
Slit-lamp examination	883
Postoperative state	6
Dose unknown	4
Single eye, right	15
Single eye, left	21
Both eyes	837

Values are numbers (*n*).

Table 2. Age of subjects at the time of the bombings, and radiation dose.

	Age (years)			
Dose (Sv)	*In utero*	0–13	>13	Total
<0.005	87	233	131	451
0.005 to <0.5	50	129	11	190
0.5 to <1.0	4	59	28	91
1.0 to <2.0	1	48	40	89
2.0	1	32	19	52
Total	143	501	229	873

Participation rate stratified by radiation dose groups did not vary with radiation dose.

Table 3. Distribution of cases by Lens Opacity Classification System (LOCS) II grade ($n=873$).

	LOCS II grade						
	0	1	2	3	4	5	6
Nuclear colour	528	297	48				
Nuclear opacity	322	441	85	21	4		
Cortical opacity	111	289	153	164	110	43	3
Posterior subcapsular opacity	631	178	49	10	5		

The LOCS II grades different degrees of opacities (opaqueness) in nuclear (central part of the lens), cortical (outer layer of the lens) and posterior subcapsular cataracts (rear portion of the lens and underneath the lens capsule) by using standard pictures.

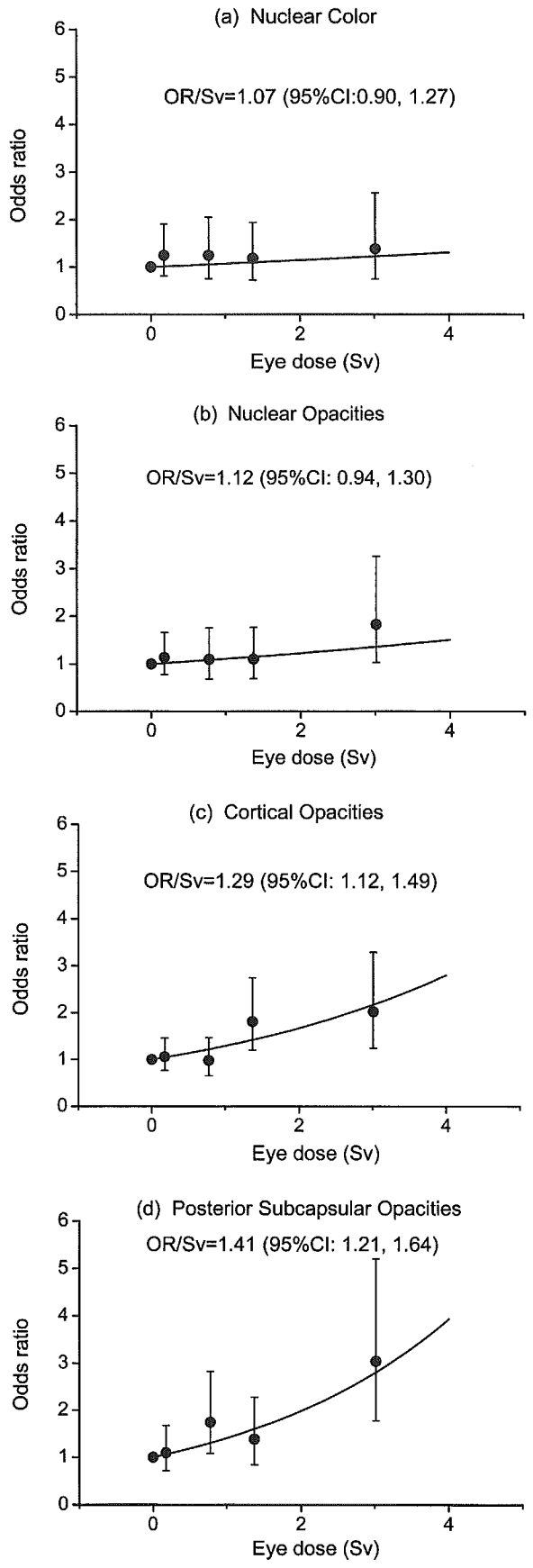
posterior subcapsular opacities during the previous study. After adjusting for city, sex, age at the time of the bombings and smoking, significant dose–effects were found for diabetic retinopathy, retinal arteriolosclerosis and retinal degeneration, ORs being 1.71 (95% CI 1.25, 3.33), 1.58 (95% CI 1.26, 1.97), and 1.42 (95% CI 1.07, 1.86), respectively (table 4). The prevalence of cortical opacities was significantly higher in women, the elderly and Nagasaki residents than in men, the young and Hiroshima residents. Posterior subcapsular opacities were significantly more prevalent in the elderly than in the young but were not associated with city or sex (table 5). Cortical and posterior subcapsular opacities were significantly correlated each other ($r=0.333$, $p<0.001$).

Among the 23 questionnaire items and 15 laboratory findings that are reportedly risk factors for lens opacities, significant association with radiation dose was found for smoking, white blood cell count, alpha 1 globulin, alpha 2 globulin, erythrocyte sedimentation rate, calcium, glucose and HbA1C. Among the above radiation-associated factors, factors in turn associated with lens opacities or intermediate risk factors were further tested and significant association with posterior subcapsular opacities was found in white blood cell counts, serum calcium levels and HbA1C, and suggestive association with cortical opacities was found in retinal arteriolosclerosis and alpha 1 globulin. Only smoking was a potential confounding factor, but it was not significant risk factor. Regression analysis with the proportional odds model that included those intermediate risk factors

Table 4. Odds ratios of ophthalmological findings at 1 Sv adjusting for city, sex, age at the time of the bombings and smoking.

Item	Odds ratio	95% Confidence interval
Lens Opacity Classification System II:		
Nuclear colour	1.07	0.90, 1.27
Nuclear opacity	1.12	0.94, 1.30
Cortical opacity	1.29	1.12, 1.49
Posterior subcapsular opacity	1.41	1.21, 1.64
Other ophthalmological findings:		
Visual acuity (log MAR)	0.005*	−0.006, 0.017
Intra-ocular pressure (mmHg)	0.088*	−0.127, 0.303
Abnormality in eyelid ($n=38$)	1.01	0.66, 1.53
Conjunctiva ($n=26$)	0.91	0.53, 1.59
Refraction (diopter) (axis)	−1.417*	−4.602, 1.767
Abnormality in cornea ($n=93$)	1.24	0.99, 1.55
Abnormality in anterior chamber ($n=41$)	1.24	0.92, 1.68
Abnormality in iris ($n=24$)	1.09	0.72, 1.64
Abnormality in pupil ($n=28$)	1.11	0.75, 1.65
Abnormality in light reflex direct ($n=12$)	0.29	0.05, 1.70
Abnormality in light reflex indirect ($n=10$)	0.89	0.40, 2.01
Abnormality in macula ($n=92$)	1.06	0.83, 1.35
Papilla atrophy ($n=51$)	1.18	0.89, 1.58
Diabetic retinopathy ($n=20$)	1.71	1.26, 2.33
Retinal arteriolosclerosis ($n=84$)	1.58	1.26, 1.97
($n=69$)**	1.49	1.15, 1.94
Retinal degeneration ($n=55$)	1.42	1.07, 1.88
($n=41$)***	1.42	1.00, 2.02
Retinal atrophy ($n=27$)	1.26	0.90, 1.77
($n=22$)***	1.49	1.04, 2.14

*Coefficient for continuous variables.
**Diabetic retinopathy excluded.
***Diabetic retinopathy and arteriolosclerosis excluded.



and smoking, and used the lowest group as a reference revealed that ORs at 1 Sv in cortical and posterior subcapsular opacities were 1.34 (95% CI 1.16–1.52) and 1.36 (95% CI 1.17–1.58), respectively. The differences of ORs at 1 Sv with and without adjustment of the intermediate risk factors were 17 % in cortical opacities and 12 % in posterior subcapsular opacities.

4. Discussion

The study revealed that 57 years after radiation exposure, the prevalence of cortical and posterior subcapsular opacities among A-bomb survivors showed a statistically significant correlation with radiation dose after adjusting for city, sex, age at the time of the bombings and smoking. The same was true after excluding the 13 subjects with posterior subcapsular opacities at the previous study (1978–80). The results were consistent with previous reports (Wilde and Sjöstrand 1997) of cortical opacities and demonstrated late onset posterior subcapsular opacities in A-bomb survivors. The ORs of 1.29 in cortical opacity and 1.41 in posterior subcapsular opacity were similar to the 1.35 and 1.50, respectively, reported by Hall (1999). In addition, by introducing the LOCS II system into the present study, interobserver variation in posterior subcapsular opacities was overcome, but not in cortical opacities, as shown by city difference (table 5). The dose–response in cortical opacities, however, was not affected by interobserver variation. The study suggests that the two opacities of cortical and posterior subcapsular regions were significantly associated with each other ($r=0.333$, $p<0.001$), indicating common biological interactions for the two opacities.

The participation rate was low because only a limited number of ophthalmological examinations were offered each week. However, since the examinations were conducted blindly and showed no variation in participation rate with radiation dose, the low sampling rate was unlikely to have caused a bias in the dose–effect besides the low power for detection of radiation effects.

As for significant correlations with radiation dose in diabetic retinopathy, retinal arteriolosclerosis and retinal degeneration, the findings agree with evidence

Figure 1. Odds ratios (OR) of the prevalence for nuclear colour (a), nuclear opacities (b), cortical opacities (c) and posterior subcapsular opacities (d) at 1 Sv (DS86) in 873 A-bomb survivors during 2000–02 using a proportional odds regression model with 'no opacity' as the reference of the LOCS II and adjusting for city, sex and age at the time of the bombings.

Table 5. Odds ratios of city, sex, age the at time of bombings and radiation dose in the prevalence of cortical and posterior subcapsular opacities.

Variable	Odds ratio	95% Confidence interval
Cortical opacity:		
City (Nagasaki/Hiroshima)	3.31	2.56, 4.28
Sex (females/males)	1.62	1.26, 2.08
Age at the time of bombings (/10 years)	3.70	3.09, 4.44
Radiation dose (Sv)	1.29	1.12, 1.49
Posterior subcapsular opacity:		
City (Nagasaki/Hiroshima)	0.92	0.67, 1.26
Sex (females/males)	1.17	0.86, 1.61
Age at the time of bombings (/10 years)	2.10	1.71, 2.58
Radiation dose (Sv)	1.41	1.21, 1.64

previously observed in A-bomb survivors, such as increases of prevalence of diabetes mellitus (Hayashi *et al.* 2003) and findings of fundus photos (unpublished data), although the mechanism(s) is not clear. As a possible mechanism, since inflammation has been persistently observed in A-bomb survivors (Neriishi *et al.* 2001) and since inflammation has been proposed as a risk factor of diabetes mellitus (Pradhan *et al.* 2001) and/or arteriosclerosis (Ross 1999), the present paper is analysing the effect of inflammation on the above findings.

We searched for 'intermediate risk factors' to which radiation causes some alterations, that in turn cause lens opacities and it was found that they comprised retinal arteriolosclerosis and alpha 1 globulin for cortical opacities, and white blood cell count, calcium, and haemoglobin A1C values for posterior subcapsular opacities. Inclusion of the significant intermediate risk factors into the analysis changed the ORs of cortical and posterior subcapsular opacities to 1.34 (17% change) and 1.36 (12% change), respectively. However, it did not affect the statistical significances of the dose–response relationship in either cortical or posterior subcapsular opacities. When inflammatory tests were combined as a primary component and adjusted for, the dose coefficient change was as large as 20% (data not shown). Since elevated levels of inflammation and serum calcium have been significantly associated with A-bomb radiation (Fujiwara *et al.* 1992, Neriishi *et al.* 2001), elevated levels of inflammation and calcium could have played important roles as micro-environmental factors in the development of radiation cataracts. One cannot yet draw conclusions, however, because the study did not show impairment of the blood aqueous barrier, which blocks the influx of blood components into the anterior chamber. To demonstrate that would require further studies, including animal experiments.

There might be other, as yet unknown, mechanisms of lens changes caused by A-bomb exposure, such as a radiation-induced decrease in lens epithelial stem cells. It is also plausible, since inflammation in A-bomb survivors is significantly and negatively associated with CD4 T-cell levels (Neriishi and Nakashima 1999, Hayashi *et al.* 2003) that radiation has an indirect effect via immune impairment (Kusunoki *et al.* 2002). Taking into account the presence of auto-antibodies in those with cataract (Patel *et al.* 1990, Nayak *et al.* 2002), it would be intriguing to investigate lens auto-antibodies in A-bomb survivors.

In conclusion, the present study showed a significant correlation between A-bomb radiation dose and cortical and posterior subcapsular opacities. It also suggested indirect effects of elevated levels of inflammation and serum calcium in the dose–response of posterior subcapsular opacities.

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References

Choshi, K., Takaku, I., Mishima, H., Takase, T., Neriishi, S., Finch, S. C. and Otake, M., 1983, Ophthalmologic changes related to radiation exposure and age in the Adult Health Study sample, Hiroshima and Nagasaki. *Radiation Research*, **96,** 560–579.

Chylack, L. T., Leske, C., Mccarthy, D., Khu, P., Kashiwagi, T. and Sperduto, R., 1989, Lens Opacity Classification System II (LOCS II). *Archives of Ophthalmology*, **107,** 991–997.

CRUICKSHANKS, K. J., 1998, Sunlight exposure and risk of lens opacities in a population-based study. *Archives of Ophthalmology*, **116,** 1666.

CUMMING, R. G. and MITCHELL, P., 1998, Medications and cataract. The Blue Mountains Eye Study. *Ophthalmology*, **105,** 1751–1758.

FUJIWARA, S., SPOSTO, R., EZAKI, H., AKIBA, S., NERIISHI, K., KODAMA, K., HOSODA, Y. and SHIMAOKA, K., 1992, Hyperparathyroidism among atomic bomb survivors in Hiroshima. *Radiation Research*, **130,** 372–378.

HALL, P., GRANATH, F., LUNDELL, M., OLSSON, K. and HOLM, L. E., 1999, Lenticular opacities in individuals exposed to ionizing radiation in infancy. *Radiation Research*, **152,** 190–195.

HAYASHI, L. C., TAMIYA, N. and YANO, E., 1998, Correlation between UVB irradiation and the proportion of cataract—an epidemiological study based on a nationwide patient survey in Japan. *Industrial Health*, **36,** 354–360.

HAYASHI, T., FUJIWARA, S., MORISHITA, Y., KUSUNOKI, Y., NAKASHIMA, E., NAKANISHI, S., SUZUKI, G., NAKACHI, K. and KYOIZUMI, S., 2003, HLA haplotype is associated with diabetes among atomic bomb survivors. *Human Immunology*, **64,** 910–916.

HAYASHI, T., KUSUNOKI, Y., HAKODA, M., MORISHITA, Y., KUDO, Y., MAKI, M., KASAGI, F., KODAMA, K., MACPHEE, D. G. and KYOIZUMI, S., 2003, Radiation dose-dependent increases in inflammatory response markers in A-bomb survivors. *International Journal of Radiation Biology*, **79,** 129–136.

HILLER, R., SPERDUTO, R. D., PODGOR, M. J., WILSON, P. W., FERRIS III, F. L., COLTON, T., D'AGOSTINO, R. B., ROSEMAN, M. J., STOCKMAN, M. E. and MILTON, R. C., 1997, Cigarette smoking and the risk of development of lens opacities. The Framingham studies. *Archives of Ophthalmology*, **115,** 1113–1118.

HUTNIK, C. M. and NICHOLS, B. D., 1999, Cataracts in systemic diseases and syndromes. *Current Opinion in Ophthalmology*, **10,** 22–28.

KATOH, N., ONO, M., FUJISAWA, K., KOJIMA, M., SAKAMOTO, Y. and SASAKI, K., 1997, Relationship between pure cortical cataract appearance and the wearing of glasses. A preliminary report of a case-control study performed on the subjects in the Noto area, Japan. *Developments in Ophthalmology*, **27,** 56–62.

KLEIN, B. E., KLEIN, R. and LEE, K. E., 1998, Diabetes, cardiovascular disease, selected cardiovascular disease risk factors, and the 5-year incidence of age-related cataract and progression of lens opacities: the Beaver Dam Eye Study. *American Journal of Ophthalmology*, **126,** 782–790.

KUSUNOKI, Y., YAMAOKA, M., KASAGI, F., HAYASHI, T., KOYAMA, K., KODAMA, K., MACPHEE, D. G. and KYOIZUMI, S., 2002, T cells of atomic bomb survivors respond poorly to stimulation by *Staphylococcus aureus* toxins *in vitro*: does this stem from their peripheral lymphocyte populations having a diminished naive CD4 T-cell content? *Radiation Research*, **158,** 715–724.

LESKE, M. C., WU, S. Y., HENNIS, A., CONNELL, A. M., HYMAN, L. and SCHACHAT, A., 1999, Diabetes, hypertension, and central obesity as cataract risk factors in a black population. The Barbados Eye Study. *Ophthalmology*, **106,** 35–41.

MASUDA, K., 1993, *Current Encyclopedia of Ophthalmology* (Tokyo: Nakayama Shoten).

MCCULLAGH, P. and NELDER, J. A., 1989, *Generalized Linear Models* (London: Chapman & Hall).

MILLER, R. J., FUJINO, T. and NEFZGER, M. D., 1969, Lens findings in atomic bomb survivors, Hiroshima and Nagasaki 1963–64. *American Journal of Epidemiology*, **89,** 129–138.

NAYAK, S., SASHIDHAR, R. B. and BHAT, K. S., 2002, Development of an immunoanalytical method for the detection of beta- and gamma-crystallins and anti-crystallin antibodies. A molecular biomarker for cataract. *Indian Journal of Ophthalmology*, **50,** 41–48.

NERIISHI, K. and NAKASHIMA, E., 1999, Persistent inflammation in survivors. *RERF Update*, **10,** 10–11.

NERIISHI, K., NAKASHIMA, E. and DELONGCHAMP, R. R., 2001, Persistent subclinical inflammation among atomic-bomb survivors. *International Journal of Radiation Biology*, **77,** 475–482.

PATEL, M., SHINE, B. and MURRAY, P. I., 1990, Antilens antibodies in cataract and inflammatory eye disease: an evaluation of a new technique. *International Ophthalmology*, **14,** 97–100.

PRADHAN, A. D., MANSON, J. E., RIFAI, N., BURING, J. E. and RDKER, P. M., 2001, C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *Journal of the American Medical Association*, **286,** 327–334.

ROSS, R., 1999, Atherosclerosis—an inflammatory disease. *New England Journal of Medicine*, **340,** 115–126.

SCHAUMBERG, D. A., RIDKER, P. M., GLYNN, R. J., CHRISTEN, W. G., DANA, M. R. and HENNEKENS, C. H., 1999, High levels of plasma C-reactive protein and future risk of age-related cataract. *Annals of Epidemiology*, **9,** 166–171.

SRIVASTAVA, V. K. and SRIVASTAVA, S. K., 1989, Vitamin D3 and calcitonin-induced regulation of calcium and phosphate in rat lens—its significance in cataract formation. *Annals of Ophthalmology*, **21,** 149–152.

WILDE, G. and SJÖSTRAND, J., 1997, A clinical study of radiation cataract formation in adult life following gamma irradiation of the lens in early childhood. *British Journal of Ophthalmology*, **81,** 261–266.

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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