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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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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, intraocular 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 $j = 1, ..., R$ and Y is an $(R + 1)$-ordered polytomous outcome that takes a value in $\{0, 1, ..., R\}$, 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.

Dose (Sv)	Age (years) *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

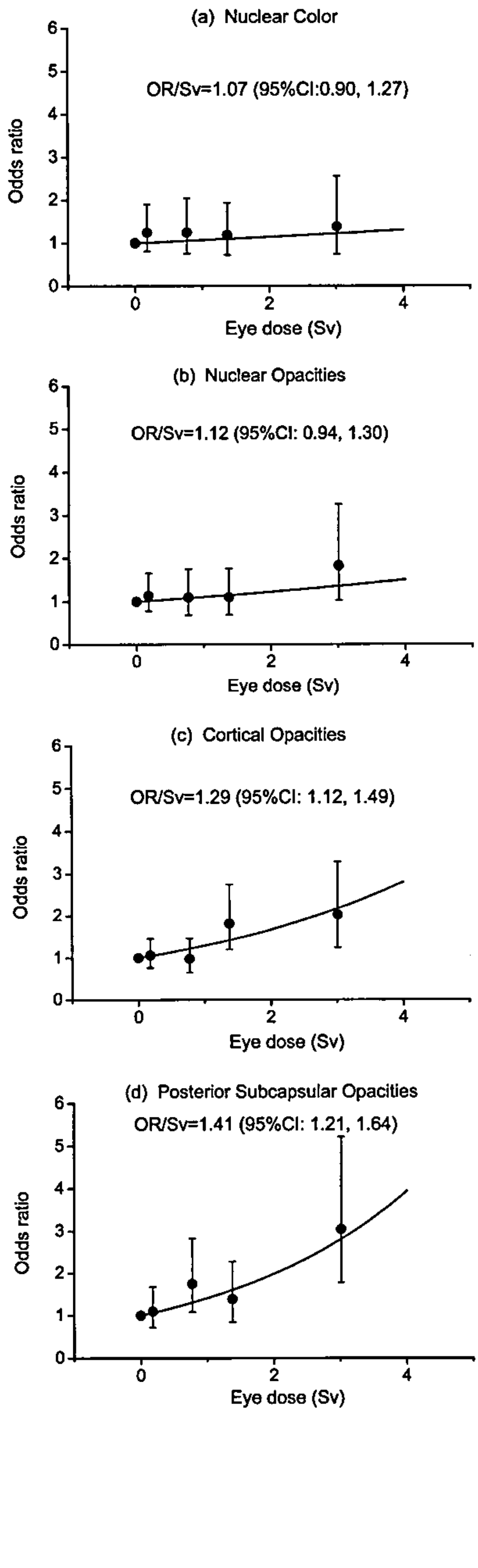
Table 4. Odds ratios of ophthalmological findings at 1 Sv adjusting for city, sex, age at the time of the bombings and smoking.

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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ORIGINAL ARTICLE

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

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

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Introduction

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

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

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

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

Materials and methods

Cases

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

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

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

Controls

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

Data collection

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

Statistical analysis

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

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

Results

Distal radius fractures

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

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

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

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

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

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

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

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

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

Proximal humerus fractures

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

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

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

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

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

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

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

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

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

Discussion

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

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

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

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

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

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

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

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

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

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超音波骨量測定値による骨折予知

－骨密度による予知との比較－

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ー骨密度による予知との比較ー

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要　旨

縦断調査から，QUS 測定値および骨密度の骨折リスクの予測能力を比較した。超音波骨量測定（A-1000 plus）および DXA（QDR-4500）による骨密度検査を受けた 2,434 人（男 750 人，女 1,684 人，平均年齢 69.0 歳，52〜97 歳）を約２年間追跡した。追跡期間中の自己申告による脊椎骨折発生は 19 人，脊椎以外の骨折は 40 人であった。BUA, stiffness は，脊椎以外の骨折を，SOS, BUA, stiffness，腰椎骨密度は，脊椎骨折を予知した。脊椎以外の骨折については，骨密度より BUA, stiffness が，脊椎骨折については QUS 測定値より骨密度がよりよく予測した。

はじめに

わが国において，超音波骨量測定は，骨粗鬆症検診に広く使われている。しかし，縦断的調査から，超音波骨量測定値と骨折発生との関係を調べた調査は少ない。そこで，長期コホート研究を続けている集団を対象に，ベースラインの超音波骨量測定値および DXA による骨密度と骨折リスクとの関連を検討したので報告する。

表１　ベースラインの対象者の特性

	男　性	女　性
対象者数	750	1684
年齢（歳）	66.4±9.4 (52-95)	70.2±9.2 (52-97)
閉経後女性割合（%）	−	96.7
閉経年齢（歳）	−	48.5
BMD　腰椎（L2-4）（g/cm^2）	0.993±0.177	0.808±0.156
大腿骨頸部（g/cm^2）	0.730±0.123	0.592±0.110
QUS　SOS（m/sec）	1531.8±28.3	1510.1±22.8
BUA（dB/MHz）	110.6±10.7	98.2±9.3
Stiffness index	82.6±14.0	68.3±11.4
身長（cm）	163.0±6.3	149.4±6.0
体重（kg）	60.6±9.3	51.5±8.9

Prediction of Self-Reported Fracture by Quantitative Bone Ultrasound Measures in a Cohort Study

Saeko Fujiwara: Department of Clinical Studies, Radiation Effects Research Foundation, et al.

Key Words: Quantitative bone ultrasound, Osteoporosis, Nonvertebral fracture, Cohort, Bone mineral density

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