osteoporotic fractures included 6 hip fractures (1 man, 5 women), 5 clinical vertebral fractures (1 man, 4 women), 2 wrist fractures (2 men), and 9 costal fractures (4 men, 5 women). Incidences of osteoporotic fractures in men in their 40s, 50s, 60s, and 70s were 20.8, 90.1, 44.4, and 82.6 per 10,000 person-years, respectively, and incidences in women were 20.2, 157.0, 158.2, and 170.3 per 10,000 person-years, respectively. Osteoporotic fractures tended to increase with age in women, whereas an age-related but non-significant tendency was seen in men.

Capacity of BTMs at baseline to predict rates of change of BMD and the occurrence of OP and osteoporotic fractures

Age-gender distributions of mean BTM levels at the initial survey are shown in Table 3. No significant difference was seen among age groups for BTM levels in men, while significant differences were seen for each marker between the 40s and 50–70s in women ($P < 0.05$ each).

Table 4 shows mean BTM levels in women at the initial survey classified by menstrual status, categorized into the following three groups: premenopausal group with regular period; perimenopausal group with irregular period; and postmenopausal group with no period within at least 1 year. No significant differences in BTM levels were seen between the pre- and perimenopausal groups, with the exception of serum PINP. Although a tendency toward increased levels in the perimenopausal group was seen compared to the premenopausal group, this was slight and non-significant. Conversely, all BTM levels measured in the present study were significantly higher in the postmenopausal group than in the premenopausal group ($P < 0.001$). In addition, serum total OC, PICP, PINP, beta-CTX, NTX, and urinary DPD were significantly lower in the perimenopausal group than in the postmenopausal group ($P < 0.05$). These results suggest that BTM levels were significantly accelerated after menopause.

We clarified whether values of BTMs at baseline could predict rates of change of BMD over 10 years, using multiple regression analysis with rate of change of BMD (%/year) as an objective factor, and values of BTMs (/SD) at baseline after adjusting for age, weight, and menstrual status (0 pre- and perimenopause; 1 menopause) in women at baseline. No associations were identified between any BTMs and rate of change in BMDs at L2–4 or the femoral neck over 10 years.

Table 5 shows the hazard ratios (HRs) of BTMs (/SD) for the incidence of OP at L2–4 and the femoral neck. Cox proportional hazards modeling using the occurrence of OP (yes 1; no 0) as an objective factor and BTM level (/SD) at baseline as an explanatory factor after adjusting for age and weight, and menstrual status in women, at baseline identified only the PINP level as being significantly related to the occurence of OP at L2–4 in men ($P < 0.05$). By contrast, serum PINP, beta-CTX, and NTX and urinary DPD levels were significantly related to the occurence of OP at L2–4 in women (PINP, $P < 0.05$; beta-CTX, $P < 0.001$; NTX, $P < 0.01$; DPD, $P < 0.05$). In addition to the above-mentioned analysis, we then added the baseline BMD status, i.e., osteopenia or normal range, as an adjusted factor. Using the baseline L2–4 BMD, 36 men and 71 women were categorized into the group of spinal osteopenia. After adjusting for the baseline status of L2–4 BMD (1 osteopenia; 0 normal) in addition to age, weight, and menstrual status in women, the association between PINP and the occurrence of spinal OP was diluted in men (HR 3.88, 95% confidence interval [CI] 0.92–16.4, $P = 0.066$), but the association of the BTMs, with the exception of DPD, remained significant in women (PINP, HR 1.57, 95% CI 1.02–2.43, $P < 0.05$; beta-CTX, HR 1.99, 95% CI 1.30–3.05, $P < 0.01$; NTX, HR 1.68, 95% CI 1.69–2.65, $P < 0.05$; DPD, HR 1.42, 95% CI 0.99–2.04, $P = 0.056$). However, no BTMs were identified as significant predictors of the incidence of OP at the femoral neck in either men or women.

We estimated the HRs of BTMs (/SD) for the incidence of osteoporotic fracture by Cox proportional hazards modeling, using the occurrence of osteoporotic fractures (yes 1; no 0) as an objective factor, and BTM levels (/SD) at baseline as explanatory factors after adjusting for age and weight, and menstrual status in women, at baseline. No BTMs were identified as significant predictors of the incidence of osteoporotic fractures in men or women.

Discussion

The present study first clarified rates of bone loss at the lumbar spine and femoral neck over 10 years in the general population. BMD values for men had changed slightly by the 10-year follow-up, with the exception of femoral neck BMD for men in their 70s. Although the reason of the considerable increase in femoral neck BMD among men in their 70s is uncertain, it might be partially attributable to bone proliferative degeneration, such as hip osteoarthritis. Conversely, BMD values had decreased in all age strata for women over the 10 years, at an approximate mean rate of −7%/10 years, at both L2–4 and the femoral neck. BMD values decreased most rapidly among women in their 40s, suggesting a menopausal effect, whereas rates of change did not differ significantly among age strata.

We then clarified the incidence of OP and osteoporotic fractures over the 10 years among the general population. We have previously reported the incidence of OP in individuals aged 40–79 years living in a mountain village [33].

Table 3 Mean values of biochemical markers of bone turnover for participants at baseline, classified by age and gender

Age group (years)	*n*	Sera								Urine	
		Intact OC (ng/mL)	Total OC (ng/mL)	BAP (U/L)	PICP (μg/L)	PINP (ng/mL)	ICTP (μg/L)	β-CTX (ng/mL)	NTX (nmol BCE/L)	PYR (pmol/μmol Cr)	DPD (pmol/μmol Cr)
Men											
40–49	50	3.63 (1.70)	18.8 (7.5)	26.1 (9.3)	126.8 (36.1)	41.4 (17.3)	2.85 (1.71)	0.190 (0.107)	13.3 (2.8)	18.0 (6.5)	3.02 (1.28)
50–59	50	3.80 (4.28)	19.7 (18.3)	26.7 (16.6)	115.5 (33.0)	39.4 (28.1)	2.61 (0.83)	0.197 (0.162)	14.0 (6.0)	18.9 (7.7)	3.24 (2.41)
60–69	49	3.58 (1.55)	16.4 (6.1)	26.4 (7.1)	113.1 (28.5)	34.5 (13.3)	3.00 (1.07)	0.174 (0.107)	13.6 (4.1)	19.0 (7.5)	2.81 (0.97)
70–79	50	3.41 (1.77)	18.9 (8.1)	26.9 (10.7)	121.8 (34.3)	37.4 (16.0)	3.39 (1.06)[b]	0.187 (0.099)	13.5 (3.4)	21.5 (4.9)	3.17 (0.94)
40–79	199	3.60 (2.54)	18.5 (11.1)	26.5 (10.7)	119.3 (33.3)	38.2 (19.5)	2.96 (1.24)	0.187 (0.121)	13.6 (4.2)	19.3 (6.8)	3.06 (1.53)
Women											
40–49	50	3.58 (1.72)	14.9 (5.7)	19.7 (5.2)	96.1 (25.6)	30.6 (13.3)	2.51 (0.60)	0.103 (0.066)	11.6 (2.3)	20.7 (5.9)	3.20 (1.18)
50–59	50	5.68 (2.42)[a]	28.1 (8.8)[a]	30.2 (7.5)[a]	130.2 (41.1)[a]	57.8 (20.9)[a]	3.07 (0.62)[a]	0.255 (0.121)[a]	15.4 (3.3)[a]	27.5 (5.3)[a]	5.05 (1.34)[a]
60–69	50	6.61 (3.10)[a]	32.6 (12.4)[a]	32.3 (11.2)[a]	136.2 (35.7)[a]	59.2 (20.0)[a]	3.51 (1.25)[a]	0.301 (0.136)[a]	17.8 (4.4)[a,b]	32.0 (10.8)[a]	5.79 (2.14)[a]
70–79	50	6.09 (3.51)[a]	28.3 (10.3)[a]	32.2 (10.8)[a]	143.3 (39.2)[a]	52.8(20.0)[a]	3.56 (1.22)[a]	0.275 (0.153)[a]	16.0 (3.2)[a]	29.7 (8.9)[a]	4.95 (1.84)[a]
40–79	200	5.60 (3.01)	26.0 (11.6)	28.6 (10.4)	126.4 (40.0)	50.1 (21.9)	3.16 (1.06)	0.234 (0.145)	15.2 (4.0)	27.5 (9.0)	4.76 (1.91)

Values are given as means with standard deviations in parentheses

OC osteocalcin, *BAP* bone-specific alkaline phosphatase, *PICP* C-terminal propeptide of type I procollagen, *PINP* N-terminal propeptide of type I procollagen, *ICTP* C-terminal cross-linking telopeptide of type I collagen generated by matrix metalloproteinase, *β-CTX* β-isomerized C-terminal cross-linking telopeptide of type I collagen, *NTX* N-terminal cross-linking telopeptide of type I collagen, *PYR* pyridinoline cross-links of collagen, *DPD* deoxypyridinoline cross-links of collagen, *Cr* creatinine

[a] Significantly different ($P < 0.05$) from values of participants in their 40s

[b] Significantly different ($P < 0.05$) from values of participants in their 50s

Table 4 Mean values of biochemical markers of bone turnover at baseline classified by menstrual status in women

Menstrual status	*n*	Age (years)	Sera								Urine	
			Intact OC (ng/mL)	Total OC (ng/mL)	BAP (U/L)	PICP (μg/L)	PINP (ng/mL)	ICTP (μg/L)	β-CTX (ng/mL)	NTX (nmol BCE/L)	PYR (pmol/μmol Cr)	DPD (pmol/μmol Cr)
Premenopause	41	44.2 (3.0)	3.35 (1.28)	14.5 (4.4)	19.0 (5.1)	96.5 (26.6)	29.5 (11.1)	2.49 (0.56)	0.099 (0.060)	11.3 (2.0)	20.7 (4.9)	3.12 (0.89)
Perimenopause	14	47.4 (4.9)	4.83 (2.75)	20.4 (10.2)	25.7 (7.0)	94.4 (24.8)	45.2 (25.9)[a]	2.88 (0.82)	0.165 (0.120)	13.0 (2.8)	24.1 (7.8)	4.09 (1.84)
Menopause	145	65.3 (8.1)[a,b]	6.20 (3.07)[a]	29.8 (10.8)[a,b]	31.6 (10.1)[a]	138.0 (38.3)[a,b]	56.4 (20.2)[a,b]	3.38 (1.10)[a]	0.278 (0.138)[a,b]	16.5 (3.7)[a,b]	29.7 (9.0)[a]	5.28 (1.86)[a,b]
Total	200	59.7 (11.6)	5.60 (3.01)	26.0 (11.6)	28.6 (10.4)	126.4 (40.0)	50.1 (21.9)	3.16 (1.06)	0.234 (0.145)	15.2 (4.0)	27.5 (9.0)	4.76 (1.91)

Values are given as means with standard deviations in parentheses

n number of subjects, *OC* osteocalcin, *BAP* bone-specific alkaline phosphatase, *PICP* C-terminal propeptide of type I procollagen, *PINP* N-terminal propeptide of type I procollagen, *ICTP* C-terminal cross-linking telopeptide of type I collagen generated by matrix metalloproteinase, *β-CTX* β-isomerized C-terminal cross-linking telopeptide of type I collagen, *NTX* N-terminal cross-linking telopeptide of type I collagen, *PYR* pyridinoline cross-links of collagen, *DPD* deoxypyridinoline cross-links of collagen, *Cr* creatinine

[a] Significantly different ($P < 0.05$) from values of participants in the premenopausal group

[b] Significantly different ($P < 0.05$) from values of participants in the perimenopausal group

Estimated incidences of lumbar spine OP in men and women in that village over 10 years were 55.6 and 231.7 per 10,000 person-years, respectively. The incidences of spinal OP in the present study were approximately half of those found in the mountain village, indicating regional differences in the incidence of OP among Japanese populations. We have already reported on regional differences between cohorts in mountainous and seaside (the present cohort) areas [34–36]. Residents of the mountainous area tended to show lower BMDs [34], and proportions of fast bone losers were higher [35] than those in residents of the seaside area. In addition, we found that levels of BTMs, including serum intact OC and urinary PYR and DPD, in the residents of the mountainous area were significantly higher than those in residents of the seaside area [36]. These differences in the incidence of OP between regions support the concept of regional differences in bone metabolism in Japan, and might be due to environmental differences. From meteorological data in 1990, when the cohort from the mountainous area was started, the total annual duration of sunlight exposure was 1340.9 h in the mountainous area, lower than the 2224.4 h in the seaside area. In addition, based on the results of a nutrition survey of Wakayama Prefecture in 1993, total calcium intake for inhabitants of the mountainous area was 542 mg/day, compared to 563 mg/day for the seaside area [37]. However, this finding was only a result of an ecological study, not a direct survey of participants from our two cohorts. In addition, cohorts in both studies comprised only 400 individuals each, so these differences need to be confirmed in larger population-based cohorts. We have therefore established larger-scale cohorts based on the cohort in the present study, entitled the ROAD study [3, 38], in which BMD and X-ray examinations were performed in all 1,690 participants, and serum and urinary samples were collected. This enlarged population-based cohort study may confirm regional differences in bone metabolism and in OP and osteoporotic fractures.

The present study found no significant differences in baseline levels of the various BTMs among men in any age groups, with the exception of serum ICTP. By contrast, each marker showed significant differences between women in their 40s and those in their 50–70s ($P < 0.05$). In addition, the values of the BTMs in women started to increase in the perimenopausal period, with rapidly accelerating elevations after menopause, according to estrogen deficiency. We had already measured levels of endogenous estrogen and sex hormone-binding globulin in the present cohort, and reported serum estradiol (E2) and BMD levels among postmenopausal women at the 3-year follow-up [39], but cannot confirm any association between BTMs and endogenous sex steroids yet. Further studies to clarify levels of E2 and BTMs in women are warranted. In

Table 5 Hazard ratios of biochemical markers of bone turnover for the occurence of osteoporosis over the 10-year study period

	BTMs		Occurence of osteoporosis (L2–4)			Occurence of osteoporosis (femoral neck)		
	At baseline	Reference	HR	95% CI	Significance	HR	95% CI	Significance
Men								
Serum	Intact OC	+1SD	1.23	0.35–4.27		1.50	0.61–3.71	
	Total OC	+1SD	1.86	0.73–4.75		1.06	0.28–4.07	
	BAP	+1SD	0.95	0.23–3.93		1.61	0.73–3.59	
	PICP	+1SD	0.95	0.33–2.70		0.85	0.24–3.03	
	PINP	+1SD	2.80	1.18–6.63	*	1.09	0.32–3.69	
	ICTP	+1SD	0.74	0.17–3.25		1.10	0.26–4.58	
	β-CTX	+1SD	2.02	0.76–5.34		1.12	0.31–4.02	
	NTX	+1SD	0.95	0.29–3.08		0.64	0.09–4.54	
Urine	PYR	+1SD	1.79	0.79–4.06		2.11	0.98–4.53	+
	DPD	+1SD	2.86	0.78–10.50		1.53	0.63–3.73	
Women								
Serum	Intact OC	+1SD	0.78	0.47–1.29		0.99	0.64–1.53	
	Total OC	+1SD	1.52	0.92–2.52		1.32	0.90–1.93	
	BAP	+1SD	1.46	0.94–2.25	+	1.03	0.65–1.63	
	PICP	+1SD	1.13	0.69–1.84		1.00	0.62–1.64	
	PINP	+1SD	1.65	1.11–2.47	*	1.26	0.73–2.18	
	ICTP	+1SD	1.44	0.90–2.30		1.01	0.66–1.55	
	β-CTX	+1SD	1.80	1.27–2.56	***	1.21	0.76–1.91	
	NTX	+1SD	1.96	1.23–3.13	**	1.13	0.73–1.75	
Urine	PYR	+1SD	1.28	0.97–1.69	+	1.06	0.772–1.56	
	DPD	+1SD	1.40	1.06–1.84	*	1.23	0.84–1.80	

The hazard ratio was estimated using Cox proportional hazards modeling after adjustment for age and weight, and menstrual status of women, at the baseline

BTMs biochemical markers of bone turnover, *HR* hazard ratio, *CI* confidence interval, *OC* osteocalcin, *BAP* bone-specific alkaline phosphatase, *PICP* C-terminal propeptide of type I procollagen, *PINP* N-terminal propeptide of type I procollagen, *ICTP* C-terminal cross-linking telopeptide of type I collagen generated by matrix metalloproteinase, *β-CTX* β-isomerized C-terminal cross-linking telopeptide of type I collagen, *NTX* N-terminal cross-linking telopeptide of type I collagen, *PYR* pyridinoline cross-links of collagen, *DPD* deoxypyridinoline cross-links of collagen

$^{+}$ $P < 0.1$; * $P < 0.05$; ** $P < 0.01$, *** $P < 0.001$

addition, we had already measured serum free testosterone (FT) levels in male subjects from the present cohort, and found that the serum FT level could offer a useful predictor of bone loss within 3 years [40]. The use of these data might clarify relationships among endogenous sex steroids and BTMs in men and women, and provide some clues to the distinct gender differences in BTM levels.

Regarding the capacity of BTMs to predict bone loss, Garnero et al. [9] reported that BTMs could be useful for forecasting BMD changes in the forearm over 4 years. Others have found that BTMs can only poorly predict bone loss at the spine and hip [10, 11]. Iki et al. [12] found an association between CTX and bone loss at the hip during the first 3 years of follow-up in a female population-based cohort followed for 6 years. In a previous report, we clarified that urinary PYR in men and serum intact OC in women were significantly related to BMD changes at the spine over 3 years [17]. Nevertheless, the present study could not identify any significant associations between BTMs and rates of change in BMDs over 10 years. The influence of BTMs measured at one specific point during BMD change thus appears to be limited to within a relatively short period, such as up to 4 years.

As few reports have examined associations between BTMs and the incidence of OP, evaluating the usefulness of BTMs as predictors of future OP is difficult. However, the present study found that high PINP levels in both men and women and high levels of serum beta-CTX, serum NTX, and urinary DPD in women were significant predictors of future OP at the lumbar spine. This association with PINP, beta-CTX, and NTX in women remained significant after adding baseline BMD status as an adjustment factor. This means that these BTMs could predict the future occurrence of spinal OP in women independent of baseline BMD status showing either osteopenia or normal range BMD. This shows that high bone turnover becomes an important determinant of the occurrence of spinal OP, particularly in women.

We could not establish any BTMs as useful predictors of OP at the femoral neck. Although the reasons for site differences in the predictive capacity of BTMs are obscure, we have previously reported that the characteristics of the lumbar spine and femoral neck differ among individuals who rapidly lose bone [41]. These results suggest that the predictive capacity of BTMs might differ according to the site involved. Different strategies are therefore required to prevent OP of the lumbar spine and that of the femoral neck.

Several reports have found that the risk of osteoporotic fractures could be predicted by BTM levels independently of BMD. Prospective studies of postmenopausal French women have clarified that higher levels of bone resorption markers are associated with an increased risk of osteoporotic fractures [13–15]. In contrast, the present study could not identify any associations between osteoporotic fractures and BTMs. The sample size and characteristics of the present cohort might explain this difference. Our cohort comprised 400 participants aged 40–79 years, and the mean age was approximately 60 years, which might be too young to collect a sufficient number of individuals with new osteoporotic fractures. In fact, only 32 fractures (10 in men, 22 in women) were accumulated during 10 years in the present cohort. Further observation in larger cohorts, such as that in the above-mentioned ROAD study, might be required to confirm the absence of an association between BTMs and osteoporotic fractures.

Besides the small sample size, the present study shows several limitations. First, samples were not all taken at a fixed time. Circadian variability is known to affect BTM levels, with levels of most BTMs increasing at night and peaking between 02:00 and 08:00, then rapidly decreasing to a nadir between 13:00 and 23:00 [42]. Because we collected samples at the point when BTM levels would have been decreasing towards the nadir, our results might represent underestimations. Second, long-term storage might have influenced the BTM levels. In this study, serum and urine samples were immediately frozen in dry ice and then stored in a deep freezer at −80°C within 24 h. However, serum total OC, BAP, PINP, beta-CTX, and NTX were measured in baseline samples after 7 years, as technical methods for identifying these BTMs were unavailable in 1993. Storage for 7 years at −80°C might thus have influenced BTM values, although Seibel et al. [43] stated that BTMs should remain stable in serum and urine samples if stored at −70°C or below and at −20°C or below, respectively.

On the other hand, one advantage of the present survey was that various BTMs were measured in men and women who were randomly selected from the general population and followed for a decade, with a high degree of compliance. Another advantage was that the effects of various BTMs on changes in BMD, the presence of individuals who rapidly lose bone, and the occurrence of OP and osteoporotic fractures could be estimated directly.

In conclusion, we clarified that various BTMs, including markers of both bone resorption and bone formation, such as PINP, beta-CTX, NTX, and DPD in women, and PINP in men, could predict the occurrence of spinal OP. Among these, PINP, beta-CTX, and NTX in women could predict the occurrence of spinal OP, independent of baseline BMD status. We therefore speculate that BTM levels could help to predict OP at the lumbar spine, especially in women, but not OP at the femoral neck, the rate of change in BMD, or osteoporotic fractures.

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Conflict of interest None.

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ORIGINAL ARTICLE

Prevalence of Falls and the Association With Knee Osteoarthritis and Lumbar Spondylosis As Well As Knee and Lower Back Pain in Japanese Men and Women

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Objective. There is little information on falls by sex and age strata in Japan, and few factors associated with falls have been established. However, the association between bone and joint diseases and falls remains unclear. We examined prevalence of falls by sex and age strata, determined its association with radiographic osteoarthritis (OA) of the knee and lumbar spine, and determined knee and lower back pain after single and multiple falls.

Methods. A questionnaire assessed the number of falls during 12 months preceding baseline. Knee and lumbar spine radiographs were read by Kellgren/Lawrence (K/L) grade; radiographic knee OA and lumbar spondylosis were defined as a K/L grade of 3 or 4. Knee and lower back pain were estimated by an interview.

Results. A total of 587 men and 1,088 women (mean ± SD age 65.3 ± 12.0 years) were analyzed. During 1 year, 79 (13.5%) men and 207 (19.0%) women reported at least 1 fall. With increasing age, the prevalence of multiple falls was higher in women, but lower in elderly men age >60 years. In men, few factors were significantly associated with falls. In women, radiographic knee OA and lumbar spondylosis, as well as knee and lower back pain, were significantly associated with multiple falls without adjustment. Lower back pain and knee pain were independently associated with multiple falls in women after adjustment.

Conclusion. Lower back pain and knee pain were significantly associated with multiple falls in women.

INTRODUCTION

Falls are one of the main causes of injury, disability, and death among the elderly (1,2). In Japan, according to the recent National Livelihood Survey of the Ministry of Health, Labour and Welfare, fall and fracture are ranked fifth among diseases that cause disabilities and subsequently require support with activities of daily living (3). However, there have been few population-based studies for prevalence of fall based on sex and age strata. Further, in terms of factors associated with falls, muscle strength, balance, vision, and functional capacities, there are traits that diminish with aging, and these factors have been suggested as predictive risk factors for falls and fractures (4). Cognitive impairment has also been established as a risk factor for falls (5), but the association of bone and joint diseases, especially osteoarthritis (OA), with falls remains unclear.

The representative sites of OA are the knee and lumbar spine. Knee OA and lumbar spondylosis (LS) are major public health issues since they cause chronic pain and disability (6–11). The prevalence of radiographic knee OA and LS is high in Japan (12,13), with 25,300,000 and 37,900,000 subjects ages ≥40 years estimated to experience radiographic knee OA and LS, respectively (14). The National Livelihood Survey ranked OA fourth among diseases that cause disabilities and subsequently require sup-

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Significance & Innovations

- During 1 year, 13.5% of men and 19.0% of women reported at least 1 fall.
- With increasing age, prevalence of multiple falls was higher in women, but lower in elderly men age >60 years.
- Lower back pain and knee pain were independently associated with multiple falls in women.

port with activities of daily living (3), but there have been few studies of the association between falls and OA (15,16). In previous studies, knee OA was assessed only by interview and not by radiography. The principal clinical symptom of knee OA is pain (17), but its correlation with the radiographic severity of knee OA is not as strong as expected (12,18–20). In fact, in a study in Japan, ~20% of the subjects without knee OA had knee pain, and 30% of the subjects with severe knee OA had no knee pain (12). Therefore, knee OA diagnosed by interview could be limited by variable accuracy. In addition, men and women were not examined separately in these previous studies, although sex differences have been found in the prevalence of knee OA (12). Furthermore, knee OA is conventionally defined according to Kellgren/Lawrence (K/L) grade (21), and our previous study showed that the association of a K/L grade of 2 (knee OA with pain) was weak, but that a K/L grade of 3 or 4 (knee OA with pain) was strong (12); therefore, the association of knee OA with falls may be different between a K/L grade of 2 for knee OA and a K/L grade of 3 or 4 for knee OA. However, there are no population-based studies on the association of severity of knee OA with falls. With regard to LS, to the best of our knowledge, there have been no population-based studies regarding its association with falls.

Previous studies have shown that associations between individual risk factors and a single fall are few in number and weak compared to risk factors for multiple falls (16), indicating that single and multiple falls may have different backgrounds. Therefore, to determine factors associated with falls, single and multiple falls should be analyzed separately.

The objectives of this study were to clarify prevalence of single and multiple falls by sex and age strata in Japan using a large-scale, population-based cohort study known as Research on Osteoarthritis/osteoporosis Against Disability (ROAD). Further, we examined the associations of radiographic knee OA and LS, as well as knee and lower back pain, with single and multiple falls in Japanese men and women.

PATIENTS AND METHODS

Patients. The ROAD study is a nationwide prospective study designed to establish epidemiologic indexes for evaluation of clinical evidence for the development of a disease-modifying treatment for bone and joint diseases (OA and osteoporosis are the representative bone and joint diseases, respectively). It consists of population-based cohorts in 3 communities in Japan. A detailed profile of the ROAD study has been described elsewhere (12–14,22); a brief summary is provided here. To date, we have completed the creation of a baseline database that includes clinical and genetic information for 3,040 subjects (1,061 men and 1,979 women) with a mean age of 70.6 years (range 23–95 years), who were recruited from resident registration listings in 3 communities: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a coastal region in Taiji, Wakayama.

Residents of these regions were recruited from the resident registration list of the relevant region. The participants in the urban region were recruited from a randomly selected cohort from the Itabashi-ward residents' registration database (22). The participation rate was 75.6%. The participants in mountainous and coastal regions were also recruited from the resident-registration lists, and the participation rates in these 2 areas were 56.7% and 31.7%, respectively. The inclusion criteria, apart from residence in the communities mentioned above, were the ability to 1) walk to the survey site, 2) report data, and 3) understand and sign an informed consent form. The baseline survey of the ROAD study was completed in 2006. All participants provided their written informed consent, and the study was conducted with the approval of the ethics committees of the University of Tokyo and the Tokyo Metropolitan Institute of Gerontology.

Falls assessment. All subjects were interviewed with regard to falls and fractures by experienced interviewers and were asked the following questions: "Have you experienced falls during the 12 months preceding baseline, and if yes, how many falls did you experience?" and "Have you experienced any fractures when you fell?" According to a previous study on falls (23), a fall is defined as a sudden, unintentional change in position causing an individual to land at a lower level on an object, the floor, or the ground, other than as a consequence of a sudden onset of paralysis, epileptic seizure, or overwhelming external force.

Pain assessment. All subjects were also interviewed by experienced orthopedists (SM and HO) with regard to knee pain and lower back pain and were asked the following questions: "Have you experienced knee pain on most days in the past year, in addition to now?" and "Have you experienced lower back pain on most days in the past year, in addition to now?" Those who answered yes were defined as having pain.

Radiographic assessment. All participants underwent radiographic examination of both knees using anteroposterior and lateral views with weight-bearing and foot map positioning; radiographic examination of the anteroposterior and lateral views of the lumbar spine, including intervertebral levels L1/2 to L5/S, was also performed. Knee and lumbar spine radiographs were read without the knowledge of participant clinical status by a single, experienced orthopedist (SM) using the K/L radiographic atlas

(21) to determine the severity of K/L grading. Radiographs were scored as grade 0 through 4, with higher grades being associated with more severe OA. We defined knee OA and LS as a K/L grade of ≥3 in at least 1 knee and 1 intervertebral level, respectively. To evaluate the intraobserver variability of K/L grading, 100 randomly selected radiographs of the knee and the lumbar spine were scored by the same observer more than 1 month after the first reading. One hundred other radiographs were also scored by 2 experienced orthopedic surgeons (SM and HO) using the same atlas for interobserver variability. The intra- and interobserver variabilities evaluated were confirmed by kappa analysis to be sufficient for assessment (0.86 and 0.80 for knee OA, and 0.84 and 0.76 for LS, respectively).

Covariates. Anthropometric measurements included height, weight, and body mass index (BMI; kg/m^2). Grip strength was measured on bilateral sides using a TOEI LIGHT handgrip dynamometer, and the best measurement was used to characterize maximum muscle strength. To measure physical performance, the time taken to walk 6 meters at normal walking speed in a hallway was recorded. Subjects were told to walk from a marked starting line to a 6-meter mark as if they were walking down their hallway at home. Time was measured in seconds with a stopwatch and rounded to the nearest hundredth of a second. The average of 2 trials was recorded. These gait-speed trial measurements are considered highly reliable in community-dwelling elderly subjects (24–27).

The time taken for 5 consecutive chair rises without the use of hands was also recorded. Hands were folded in front of the chest with feet flat on the floor, following the protocol described by Guralnik et al (28) and used by other researchers (25,29,30). Time was measured in seconds with a stopwatch and rounded to the nearest hundredth of a second. Timing began with the command "go" and ended when the buttocks contacted the chair on the fifth landing. The reliability of this protocol is adequate (25,28,29). Cognition was also evaluated for all subjects using a Mini-Mental State Examination, and a cutoff score of <24 was used to select participants with cognitive impairment (31).

Statistical analyses. The differences in age, anthropometric measurements, and physical performance measurements between men and women were examined by Student's unpaired *t*-test, and among groups of nonfallers, single fallers, and multiple fallers using one-way analysis of variance (ANOVA). The prevalence of cognitive impairment, radiographic knee OA and LS, and knee and lower back pain was compared between men and women, and among nonfallers, single fallers, and multiple fallers by using the chi-square test. The prevalence of single and multiple falls was also compared between men and women, among subjects with no knee OA (K/L grade 0 or 1), with K/L grade 2 for knee OA and K/L grade 3 or 4 for knee OA, and among subjects with no LS (K/L grade 0 or 1), with K/L grade 2 for LS, and K/L grade 3 or 4 for LS by using the chi-square test. The association of knee pain and lower back pain with physical performance was determined by logistic regression analysis. Multinomial logistic regression analysis was also used to determine the association of anthropometric measurements, physical performance, cognitive impairment, radiographic knee OA and LS defined as K/L grade 3 or 4, and knee and lower back pain, with single and multiple falls compared with nonfalls. Further, to determine the independent association of radiographic knee OA and LS, and knee and lower back pain with single and multiple falls compared with nonfalls, we first used multinomial logistic regression analysis with age, BMI, cognitive impairment, radiographic knee OA and LS, and knee and lower back pain as independent variables. In addition to the above independent variables, we additionally adjusted for grip strength, 6-meter walking time, and chair stand time. Data analyses were performed using SAS software, version 9.0.

RESULTS

Of the 1,690 subjects in the mountainous and seaside cohorts at baseline, 15 subjects provided incomplete fall questionnaires, leaving a total of 1,675 subjects (587 men, 1,088 women). Table 1 shows the age, anthropometric measurements, and physical performance of the participants in the present study. Regarding physical performance, grip strength, 6-meter walking time, and chair stand time were significantly better in men than in women. The prevalence of cognitive impairment was not significantly different between men and women. The prevalence of radiographic knee OA and knee pain was significantly higher in women than in men, while that of LS and lower back pain was not different between men and women.

During the 12 months preceding the baseline examination, 79 men (13.5%, 95% confidence interval [95% CI] 10.9–16.5%) and 207 women (19.0%, 95% CI 16.8–21.5%) reported at least 1 fall, and 48 men (8.2%, 95% CI 6.2–10.7%) and 80 women (7.4%, 95% CI 5.9–9.1%) reported multiple falls. Chi-square test showed that the prevalence of single and multiple falls were significantly different between men and women ($P < 0.0001$). Among 286 subjects with at least 1 fall, 6 subjects (2.1%) had a wrist fracture, 2 (0.7%) had a proximal humerus fracture, 1 (0.3%) had a vertebral fracture, and 12 (4.2%) had fractures at other sites. With increasing age, the prevalence of falls was lower in elderly men age >60 years; however, the prevalence of falls was higher in women with increasing age (Table 2). Moreover, with increasing age, the prevalence of multiple falls was also lower in elderly men age >60 years, but it was higher in women with increasing age (Table 2). The prevalence (95% CI) of a single fall (%) was similar among age strata in men and women (for men: 5.3% [1.8–14.4%], 6.8% [3.3–13.4%], 3.2% [1.4–7.3%], 5.5% [3.2–9.4%], and 7.4% [1.0–12.5%] in the age subgroups of <50 years, 50–59 years, 60–69 years, 70–79 years, and ≥80 years, respectively; for women: 11.9% [7.5–18.5%], 11.1% [7.5–16.1%], 12.0% [8.9–16.0%], 11.6% [8.6–15.6%], and 11.4% [6.7–18.9%] in the age subgroups of <50 years, 50–59 years, 60–69 years, 70–79 years, and ≥80 years, respectively).

Table 3 shows the age, anthropometric measurements,

Table 1. Characteristics of participants*

	Overall	Men	Women
Subjects, no.	1,675	587	1,088
Age, years	65.3 ± 12.0	66.3 ± 11.7	64.7 ± 12.1†
Height, cm	155.1 ± 9.3	163.4 ± 7.2	150.6 ± 6.9†
Weight, kg	55.6 ± 10.8	62.3 ± 10.9	52.0 ± 8.9†
BMI, kg/m^2	23.0 ± 3.4	23.3 ± 3.2	22.9 ± 3.5†
Grip strength, kg	27.4 ± 9.8	35.7 ± 9.3	22.9 ± 6.8†
6-meter walking time, seconds	5.5 ± 2.5	5.3 ± 2.2	5.6 ± 2.6†
Chair stand time, seconds	10.1 ± 4.4	9.7 ± 3.6	10.4 ± 4.8†
Cognitive impairment, %	4.5	5.2	4.2
Radiographic knee OA, %	20.3	15.0	23.0‡
Radiographic lumbar spondylosis, %	37.1	37.7	36.9
Knee pain, %	24.4	18.9	27.4‡
Lower back pain, %	20.1	21.7	21.2

* Values are the mean ± SD unless indicated otherwise. BMI = body mass index; OA = osteoarthritis.
† $P < 0.05$ vs. men by Student's unpaired *t*-test.
‡ $P < 0.05$ vs. men by chi-square test.

physical performance, and prevalence of cognitive impairment among nonfallers, single fallers, and multiple fallers. One-way ANOVA showed that there were no significant associations of age, anthropometric measurements, physical performance, and prevalence of cognitive impairment with falls in men, while age and BMI were higher in multiple fallers than in nonfallers in women. With regard to physical performance, grip strength was lower and 6-meter walking time and chair stand time were longer in multiple fallers than in nonfallers and single fallers in women. Further, prevalence of cognitive impairment was also different among nonfallers, single fallers, and multiple fallers in women. Further, to determine the association of anthropometric measurements, physical performance, and cognitive impairment with single and multiple falls, we also used multinomial logistic regression analysis and found that age (odds ratio [OR] 1.04, 95% CI 1.02–1.06), BMI (OR 1.10, 95% CI 1.03–1.17), grip strength (OR 0.92, 95% CI 0.89–0.96), 6-meter walking time (OR 1.10, 95% CI 1.02–1.17), chair stand time (OR 1.06, 95% CI 1.02–1.10), and cognitive impairment (OR 3.86, 95% CI 1.67–3.83) were significantly associated with multiple falls in women.

To determine the association of the severity of knee OA with falls, we classified subjects as those with no knee OA (K/L grade 0 or 1), with K/L grade 2 for knee OA, and with K/L grade 3 or 4 for knee OA. The prevalence of falls in subjects with no knee OA, K/L grade 2 for knee OA, and K/L grade 3 or 4 for knee OA was 11.8%, 17.1%, and 12.5%, and 17.7%, 17.6%, and 25.6% in men and women, respectively. There were no significant associations between falls and the severity of knee OA in men (chi-square test; $P = 0.27$), while prevalence of falls was higher in women with K/L grade 3 or 4 for knee OA than those with no knee OA and K/L grade 2 for knee OA ($P = 0.01$). Similar to knee OA, we classified subjects as those with no LS (K/L grade 0 or 1), those with K/L grade 2 for LS, and those with K/L grade 3 or 4 for LS. The prevalence of falls in subjects with no LS, K/L grade 2 for LS, and K/L grade 3 or 4 for LS was 16.3%, 11.3%, and 14.0%, and 17.0%, 20.5%, and 20.7% in men and women, respectively. There were no significant associations between falls and the severity of LS in men and women (chi-square test, $P = 0.38$ and 0.32, respectively). We next used the chi-square test to determine the association of single and multiple falls with knee OA and LS defined as K/L grade 3 or 4 (Table 4). A chi-square test showed that no significant factors were associated with falls in men, but radiographic knee OA, knee pain, and lower back pain were significantly associated with falls in women.

Multinomial logistic regression analysis also showed that radiographic knee OA, LS, and knee and lower back pain were significantly associated with multiple falls in women (Table 5). Because knee pain and lower back pain were also significantly associated with grip strength, 6-meter walking time, and chair stand time in men and women

Table 2. Prevalence of falls by age strata in men and women*

	Single fall		Multiple falls	
Age, years	Men	Women	Men	Women
<50	15.8 (8.5–27.4)	13.4 (8.7–20.2)	10.5 (4.9–21.1)	1.5 (0.4–5.3)
50–59	10.7 (6.1–18.1)	17.4 (12.8–23.1)	3.9 (1.5–9.6)	6.3 (3.7–10.4)
60–69	16.7 (11.6–23.3)	18.8 (14.9–23.4)	13.5 (9.0–19.7)	6.8 (4.5–10.1)
70–79	12.4 (8.7–17.5)	21.1 (16.9–25.9)	6.9 (4.2–11.1)	9.4 (6.7–13.1)
≥80	11.1 (5.2–22.2)	23.8 (16.7–32.8)	3.7 (1.0–12.5)	12.4 (7.4–20.0)

* Values are the percentage (95% confidence interval).

Table 3. Comparison of characteristics among nonfallers, single fallers, and multiple fallers in men and women*

	Men				Women			
	Nonfallers	Single fallers	Multiple fallers	*P*	Nonfallers	Single fallers	Multiple fallers	*P*
Subjects, no.	508	31	48		881	127	80	
Age, years	66.4 ± 11.7	67.6 ± 11.9	64.6 ± 11.3	0.50	64.4 ± 12.1	64.3 ± 12.2	69.1 ± 10.4	0.004
Height, cm	163.5 ± 7.4	162.3 ± 6.3	162.9 ± 5.9	0.56	150.9 ± 6.8	150.7 ± 7.7	148.5 ± 7.0	0.01
Weight, kg	62.6 ± 11.1	60.7 ± 10.4	60.3 ± 9.0	0.27	51.8 ± 8.8	53.3 ± 9.2	52.8 ± 8.9	0.15
BMI, kg/m^2	23.3 ± 3.2	23.0 ± 3.1	22.7 ± 2.8	0.27	22.7 ± 3.4	23.4 ± 3.6	23.9 ± 3.7	0.002
Grip strength, kg	35.8 ± 9.3	34.0 ± 9.6	35.5 ± 9.1	0.57	23.3 ± 6.8	22.6 ± 6.5	19.9 ± 5.3	< 0.001
6-meter walking time, seconds	5.2 ± 2.2	5.8 ± 2.5	5.6 ± 2.3	0.21	5.5 ± 2.6	5.7 ± 2.6	6.3 ± 2.7	0.03
Chair stand time, seconds	9.6 ± 3.6	10.3 ± 3.8	10.2 ± 3.3	0.30	10.2 ± 4.8	10.5 ± 4.6	11.9 ± 5.1	0.01
Cognitive impairment, %	4.6	6.5	10.6	0.26	3.3	5.6	11.7	0.008

* Values are the mean ± SD unless indicated otherwise. One-way analysis of variance was used to determine the differences in age, height, weight, body mass index (BMI), grip strength, 6-meter walking time, normal step length, and chair stand time among nonfallers, single fallers, and multiple fallers. Chi-square test was used to determine the differences in prevalence of cognitive impairment among nonfallers, single fallers, and multiple fallers.

(logistic regression analysis; $P < 0.05$); to examine the independent association between radiographic knee OA, knee pain, radiographic LS, and lower back pain in women, we first used multinomial logistic regression analysis with age, BMI, cognitive impairment, radiographic knee OA, knee pain, radiographic LS, and lower back pain as independent variables (Table 5). In this analysis, only lower back pain was independently associated with multiple falls in women. In addition to the above independent variables, we also adjusted for grip strength, 6-meter walking time, and chair stand time, and found that the significant association of lower back pain with multiple falls disappeared, while knee pain was independently associated with multiple falls in women (Table 5).

DISCUSSION

The present study is the first large-scale population-based cohort study of the prevalence of single and multiple falls and their association with radiographic knee OA and LS, as well as pain in Japanese men and women. We found that lower back pain and knee pain were independently associated with multiple falls in women.

There were distinct associations between age strata and single and multiple falls. We found that several factors were associated with multiple falls in women, but no factors were associated with a single fall in women. Previous studies have shown that associations between individual risk factors and a single fall are few in number and weak compared with risk factors for multiple falls (16). A single fall in a year could be accidental and occur due to individual as well as environmental factors, which may partly explain why there were no factors significantly associated with a single fall in our study. In contrast, several factors were associated with multiple falls in the present study, indicating that multiple falls may occur primarily due to individual factors.

In women, the prevalence of multiple falls was higher with increasing age, but in men, the prevalence of multiple falls was lower in subjects ages >60 years, although this could be a random error because of small prevalence, particularly in men. This may be partly explained by the

Table 4. Comparison of radiographic knee OA and LS, as well as knee and lower back pain, among nonfallers, single fallers, and multiple fallers in men and women*

	Men				Women			
	Nonfallers	Single fallers	Multiple fallers	*P*	Nonfallers	Single fallers	Multiple fallers	*P*
Subjects, no.	508	31	48		881	127	80	
Radiographic knee OA†	77/507 (15.2)	4/31 (12.9)	7/47 (14.9)	0.9417	186/875 (21.3)	31/127 (24.4)	33/79 (41.8)	0.0002
Knee pain‡	97/508 (19.1)	3/31 (9.7)	11/48 (22.9)	0.3268	224/880 (25.5)	37/127 (29.1)	37/80 (46.3)	0.0003
Radiographic LS	190/508 (37.4)	12/31 (38.7)	19/48 (39.6)	0.9490	318/881 (36.1)	45/127 (35.4)	38/80 (47.5)	0.1210
Lower back pain§	99/508 (19.5)	10/31 (32.3)	9/48 (18.8)	0.2203	177/880 (20.1)	31/127 (24.4)	28/80 (35.0)	0.0062

* Values are the number/total number (percentage) unless otherwise indicated. The chi-square test was used to determine the differences in radiographic findings and pain among nonfallers, single fallers, and multiple fallers. Radiographic knee OA and LS were defined as Kellgren/Lawrence grade 3 or 4. OA = osteoarthritis; LS = lumbar spondylosis.
† Nine subjects with total knee arthroplasty were excluded.
‡ One subject with incomplete information regarding knee pain was excluded.
§ One subject with incomplete information regarding lower back pain was excluded.

Table 5. Association of radiographic knee OA and LS, as well as knee and lower back pain, with single and multiple falls in women*

	Crude OR (95% CI)		Adjusted OR_1 (95% CI)†		Adjusted OR_2 (95% CI)‡	
	Single falls	Multiple falls	Single falls	Multiple falls	Single falls	Multiple falls
Radiographic knee OA	1.20 (0.76–1.83)	2.66 (1.64–4.26)	1.07 (0.63–1.82)	1.43 (0.78–2.61)	1.04 (0.60–1.77)	1.31 (0.70–2.43)
Knee pain	1.20 (0.79–1.81)	2.52 (1.58–4.02)	1.00 (0.62–1.61)	1.61 (0.92–2.79)	0.99 (0.60–1.61)	1.87 (1.06–3.28)
Radiographic LS	0.97 (0.65–1.43)	1.60 (1.01–2.54)	0.87 (0.57–1.32)	1.12 (0.68–1.85)	0.88 (0.57–1.33)	1.04 (0.61–1.74)
Lower back pain	1.28 (0.82–1.96)	2.14 (1.30–3.46)	1.34 (0.84–2.08)	1.72 (1.01–2.88)	1.33 (0.84–2.08)	1.58 (0.91–2.70)

* Radiographic knee osteoarthritis (OA) and lumbar spondylosis (LS) were defined as Kellgren/Lawrence grade 3 or 4. Multinomial logistic regression analysis was used to calculate the odds ratio (OR) and 95% confidence interval (95% CI) compared with nonfallers. Eight subjects with total knee arthroplasty or incomplete information regarding pain were excluded.
† Adjusted OR_1 was calculated using multinomial logistic regression analysis with age, body mass index, cognitive impairment, radiographic knee OA, knee pain, radiographic LS, and lower back pain as independent variables.
‡ Adjusted OR_2 was calculated using multinomial logistic regression analysis with grip strength, 6-meter walking time, and chair stand time in addition to the above independent variables.

fact that elderly men generally retire from their occupations at approximately ages 60–70 years; therefore, their environment may change and men may become more sedentary as they age, leading to lower risks of falls. Women, however, must often continue to do household chores even after age 60 years, and their environment may therefore change to a smaller extent than that of men, but their health or muscle strength continues to decline (32), leading to the higher risk of falls.

Our study is the first population-based study to examine the association between knee OA and LS diagnosed by radiography and falls in Japanese men and women. Radiographic knee OA and LS were significantly associated with multiple falls in women, but not in men, although no significant association of radiographic knee OA or LS with falls may be due to the small number of falls in men. The sex differences identified in the association between radiographic knee OA and falls may be partly explained by the weaker quadriceps muscles and increased postural sway associated with knee OA (33,34), both of which are known to be independent risk factors for falls (16,35). In men, muscle strength was higher than that in women in all decades (32), which may obscure the association between radiographic knee OA and falls. LS was also significantly associated with falls in this study, but the OR was lower than that for knee OA. Therefore, falls may be more strongly associated with problems of the lower extremities rather than the trunk.

After adjustment for age, BMI, and cognitive impairment, lower back pain was independently associated with multiple falls, and after adjustment for age, BMI, grip strength, cognitive impairment, 6-meter walking time, and chair stand time, knee pain was independently associated with multiple falls. Given that the significant association of radiographic knee OA and LS with multiple falls disappeared after adjustment, multiple falls may occur due to symptoms such as pain caused by radiographic knee OA or LS rather than radiographic changes in the knee or lumbar spine itself. A previous study also suggested that subjects with knee pain had an increased risk of falls (15). In other words, falls may be preventable when pain is relieved by medical care, even if subjects have radiographic knee OA or LS.

The present study has several limitations. First, this is a large-scale population-based study with a cross-sectional analysis of baseline data. Therefore, causal relationships could not be determined. The ROAD study is a longitudinal survey; therefore, further progress may help elucidate any causal relationships. Second, our subjects lived in the community, and therefore our findings may not apply to elderly persons residing in institutions. Third, we did not include other weight-bearing OA diseases, such as hip OA, in the analysis, although this disorder also affects falls (36). However, the prevalence of K/L grade 3 or 4 for hip OA is 1.4% and 3.5% in Japanese men and women (37), respectively, which is smaller than that of K/L grade 3 or 4 for knee OA in the present study. Therefore, it is possible that hip OA would not strongly affect the results of the present study. Fourth, the prevalence of fall was comparably small, particularly in men. Therefore, our results regarding the prevalence may include random error, but the present study is the first large-scale, population-based cohort study of the prevalence of falls in Japanese men and women.

In conclusion, the present cross-sectional analysis using a large-scale population from the ROAD study revealed the prevalence and factors associated with falls in men and women. In women, lower back pain and knee pain were significantly associated with multiple falls. Further studies, along with continued longitudinal surveys in the ROAD study, will help elucidate the background of knee OA and LS, and their relationship with falls.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Muraki had full access to all of the data in the study and takes

responsibility for the integrity of the data and the accuracy of the data analysis.

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Independent Association of Joint Space Narrowing and Osteophyte Formation at the Knee With Health-Related Quality of Life in Japan

A Cross-Sectional Study

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Objective. **To clarify the individual associations of joint space narrowing (JSN) and osteophytosis at the knee with quality of life (QOL) in Japanese men and women using a large-scale population-based cohort from the Research on Osteoarthritis Against Disability (ROAD) study.**

Methods. **The associations of minimum joint space width (JSW) and osteophyte area in the medial compartment of the knee with QOL parameters, such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), were examined. Minimum JSW and osteophyte area in the medial compartment of the knee were measured using a computer-aided system for the diagnosis of knee osteoarthritis.**

Results. **Of the 3,040 participants in the ROAD study, the present study included 2,039 participants age 40 years or older who completed the questionnaires (741 men and 1,298 women with a mean ± SD age of 68.6 ± 10.9 years). Multiple regression analysis after adjustment for age and body mass index showed that minimum JSW was significantly associated with scores on the pain domains of the WOMAC in men and women, while osteophyte area was significantly associated with scores on the physical function domains of the WOMAC in men and women.**

Conclusion. **The findings of this cross-sectional study using a large-scale population from the ROAD study indicate that JSN and osteophytosis are independently associated with QOL.**

Knee osteoarthritis (OA) is a major public health issue that causes chronic pain and disability (1–3). The prevalence of radiographic knee OA is high in Japan (4), with 25,300,000 persons age 40 years and older estimated to have radiographic knee OA (5). According to the recent National Livelihood Survey of the Ministry of Health, Labor, and Welfare of Japan, OA is ranked fourth among diseases that cause disabilities that subsequently require support with activities of daily living (6).

Knee OA is characterized by the pathologic features of joint space narrowing (JSN) and osteophytosis, but there is some controversy regarding whether osteophytosis affects knee symptoms or quality of life

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Patents for the Knee Osteoarthritis Computer-Aided Diagnosis (KOACAD) system are held by the University of Tokyo.

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(QOL). Nevertheless, researchers examining the hand and hip have argued that the separate radiographic features should be recorded and may be more meaningful than overall composite scores such as the Kellgren/Lawrence (K/L) scale (7). Furthermore, a previous study showed that osteophytes were well correlated with knee symptoms and performed better as a primary diagnostic feature than JSN in cross-sectional epidemiologic studies of knee OA (8). However, most conventional systems for grading radiographic severity have consisted of categorical grades, such as the K/L scale (9), which is unable to individually assess JSN and osteophytosis. Several studies have shown that knee OA had a strong effect on QOL (10–13), but in those studies, knee OA was defined by categorical grades such as the K/L grade or the American College of Rheumatology grade (14), total knee arthroplasty, and self-questionnaire.

A radiographic atlas of individual features published by the OA Research Society International in 1995 (15) and revised in 2007 (16) allows JSN and osteophyte formation to be evaluated separately. However, the grading is still limited in reproducibility and sensitivity due to the subjective judgment of individual observers and the categorical classification into 4 grades (0–3). To overcome this problem, joint space width (JSW) and osteophyte area should be evaluated using a fully automatic system. To the best of our knowledge, no population-based studies have been conducted to separately measure JSW or osteophyte area in order to clarify the associations of JSN with QOL and of osteophytosis with QOL, despite the fact that the associations between these major features of knee OA and QOL are likely to be different.

Differences between the sexes have also been observed in knee OA. The prevalence of knee OA is higher in women than in men (4), and the association of knee pain with knee OA also differs by sex (4). Thus, the impact of JSN on QOL and of osteophytosis on QOL may also differ between the sexes. However, to the best of our knowledge, no population-based studies have been conducted to assess the associations of JSN and osteophytosis with QOL in men and women separately.

The objective of this study was therefore to separately clarify the association between JSN and QOL and the association between osteophytosis and QOL in Japanese men and women in a large-scale, population-based cohort from the Research on Osteoarthritis Against Disability (ROAD) study. A fully automatic system was used to measure JSW and osteophyte area. QOL was measured using disease-specific scales for knee OA, such as the Western Ontario and McMaster Universities OA Index (WOMAC).

SUBJECTS AND METHODS

Participants. The ROAD study is a nationwide prospective study designed to establish epidemiologic indexes for the evaluation of clinical evidence for the development of a disease-modifying treatment for bone and joint diseases (with OA and osteoporosis as the representative bone and joint diseases). It consists of population-based cohorts in several communities in Japan. The ROAD study has been described in detail previously (4,5,17). To date, we have completed the creation of a baseline database including clinical and genetic information for 3,040 participants (1,061 men and 1,979 women) ranging in age from 23 to 95 years (mean 70.6 years), who were recruited from resident registration listings in 3 communities: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a seacoast region in Taiji, Wakayama. All participants provided written informed consent, and the study was conducted with the approval of the ethics committees of the University of Tokyo and the Tokyo Metropolitan Institute of Gerontology. Height, weight, and body mass index (BMI) (weight [kg]/height [m^2]) were measured. Among the 2,995 participants in the ROAD study who were age 40 years or older, 2,222 (74.2%) completed the WOMAC. The 2,222 participants who completed the WOMAC were younger than those who did not (mean age 68.9 years for those who completed the WOMAC versus 75.9 years for those who did not; $P < 0.0001$). These 2,222 participants were also less likely to be women (63.8% of those who completed the WOMAC versus 68.3% of those who did not; $P < 0.05$), and were less likely to have knee OA than the subjects who did not complete the WOMAC (54.1% versus 60.4%; $P < 0.01$). Of the 2,222 subjects, 183 subjects with lateral knee OA or total knee arthroplasty were excluded. Therefore, a total of 2,039 participants (741 men and 1,298 women) age 40 years or older (mean ± SD 68.6 ± 10.9 years) who had completed the WOMAC were included in the present study.

Radiographic assessment. Radiographic examinations of both knees of all participants, using an anteroposterior view with weight-bearing and foot map positioning, were performed by experienced radiologic technicians. The beam was positioned parallel to the floor with no angle and aimed at the joint space. To visualize the joint space properly and to center the patella over the lower end of the femur, we used fluoroscopic guidance with an anteroposterior x-ray beam, and the images were downloaded into Digital Imaging and Communication in Medicine (DICOM) format files. Knee radiographs were read by a single experienced orthopedist (SM), who was blinded with regard to participant clinical status, using the K/L radiographic atlas for overall knee radiographic grades (9), and knee OA was defined as a K/L grade of 2 or severe. Minimum JSW in the medial compartment and osteophyte area at the medial tibia were measured by the Knee Osteoarthritis Computer-Aided Diagnosis (KOACAD) system, and for each subject the knee with the lower minimum JSW was defined as the designated knee. The KOACAD system is a fully automatic system that can quantify the major features of knee OA

on standard radiographs and allows for objective, accurate, and simple assessment of the structural severity of knee OA in general clinical practice. This system was programmed to measure minimum JSW in the medial and lateral compartments and osteophyte area at the medial tibia using digitized knee radiographs. The KOACAD system has been described in detail previously (18). The KOACAD system was applied to the DICOM data by the experienced orthopedist who developed this system (HO), and the reliability of measurement is good (18). Lateral knee OA was defined as a K/L grade of ≥2 with lower lateral minimum JSW than medial minimum JSW.

QOL instrument. To carry out the QOL assessment, we used the WOMAC. The WOMAC, a 24-item OA-specific index, consists of 3 domains: pain, stiffness, and physical function. Each of these 24 items is graded on either a 5-point Likert scale (scores of 0–4) or a 100-mm visual analog scale (19,20). In the present study, we used the Likert scale (version LK 3.0). The domain score ranges from 0 to 20 for pain, 0 to 8 for stiffness, and 0 to 68 for physical function. Japanese versions of the WOMAC have been validated (21).

Statistical analysis. Differences in age, height, weight, BMI, minimum JSW, osteophyte area, and QOL measurements between men and women were examined using Student's unpaired *t*-test. Associations of minimum JSW and osteophyte area with scores on the pain and physical function domains of the WOMAC were determined using multiple regression analysis without adjustment. To assess independent associations of minimum JSW and osteophyte area with QOL, multiple regression analysis was used with age, BMI, minimum JSW, and osteophyte area as independent variables. Data analysis was performed using SAS, version 9.0.

RESULTS

The characteristics of the 2,039 participants in the present study are shown in Table 1. The minimum JSW was significantly lower and osteophyte area was significantly higher in women than in men. Scores on all domains of the WOMAC were significantly lower (indicating better status) in men than in women. Osteophyte area was only moderately associated with minimum JSW on linear regression analysis ($R^2 = 0.173$, $P < 0.05$).

Linear regression analysis without adjustment showed that minimum JSW and osteophyte area were significantly associated with scores on the pain and physical function domains of the WOMAC in the overall population as well as in men and women analyzed separately (Table 2). To determine the independent associations of minimum JSW and osteophyte area with scores on the pain and physical function domains of the WOMAC, we used multiple regression analysis with age, sex, BMI, minimum JSW, and osteophyte area as independent variables in the overall population (Table 2). Minimum JSW and osteophyte area were independently associated with scores on the pain and physical function domains of the WOMAC (β coefficients −0.16 and 0.11 for the association of pain domain score with minimum JSW and osteophyte area, respectively, and β coefficients −0.13 and 0.16 for the association of physical function domain score with minimum JSW and osteophyte area, respectively).

When men and women were analyzed separately (Table 2), in men, minimum JSW was independently associated with the pain domain scores (β coefficient −0.13), but not with the physical function domain scores (β coefficient 0.07) of the WOMAC, while osteophyte area was independently associated with the physical function domain scores (β coefficient 0.14), but not with the pain domain scores (β coefficient −0.07) of the WOMAC. In women, both minimum JSW and osteophyte area were independently associated with scores on the pain and physical function domains of the WOMAC, and the absolute values of the beta values for minimum JSW for scores on the pain domains of the WOMAC

Table 1. Characteristics of the subjects*

	Overall population (n = 2,039)	Men (n = 741)	Women (n = 1,298)
Age, years	68.6 ± 10.9	69.7 ± 10.5	67.9 ± 11.2†
Height, cm	154.7 ± 8.9	162.8 ± 6.5	150.1 ± 6.5†
Weight, kg	55.1 ± 10.4	61.4 ± 10.2	51.5 ± 8.6†
BMI, kg/m^2	22.9 ± 3.3	23.1 ± 3.1	22.8 ± 3.4†
Minimum JSW, mm	2.61 ± 0.98	2.97 ± 0.92	2.40 ± 0.96†
Osteophyte area, mm^2	2.99 ± 8.68	1.28 ± 4.46	3.98 ± 10.25†
Radiographic knee OA, %	50.2	39.0	56.8
WOMAC			
Pain	1.35 ± 2.42	1.10 ± 2.12	1.50 ± 2.57†
Stiffness	0.72 ± 1.25	0.63 ± 1.10	0.77 ± 1.33†
Function	3.99 ± 7.84	3.24 ± 6.69	4.42 ± 8.41†

* Except where indicated otherwise, values are the mean ± SD. BMI = body mass index; JSW = joint space width; OA = osteoarthritis; WOMAC = Western Ontario and McMaster Universities OA Index.
† $P < 0.05$ versus men, by Student's unpaired *t*-test.

Table 2. Associations of minimum JSW and osteophyte area with WOMAC domain scores*

	Pain				Physical function			
	Crude regression coefficient (95% CI)	*P*	Adjusted regression coefficient (95% CI)†	*P*	Crude regression coefficient (95% CI)	*P*	Adjusted regression coefficient (95% CI)†	*P*
Overall population								
Minimum JSW	−0.71 (−0.81, −0.60)	<0.0001	−0.37 (−0.48, −0.25)	<0.0001	−2.33 (−2.66, −1.99)	<0.0001	−0.97 (−1.34, −0.59)	<0.0001
Osteophyte area	0.07 (0.05, 0.08)	<0.0001	0.03 (0.02, 0.04)	<0.0001	0.25 (0.21, 0.29)	<0.0001	0.14 (0.10, 0.18)	<0.0001
Men								
Minimum JSW	−0.47 (−0.64, −0.31)	<0.0001	−0.29 (−0.47, −0.11)	0.002	−1.34 (−1.86, −0.82)	<0.0001	−0.48 (−1.04, 0.08)	0.10
Osteophyte area	0.07 (0.04, 0.11)	<0.0001	0.03 (−0.005, 0.07)	0.09	0.30 (0.19, 0.41)	<0.0001	0.20 (0.09, 0.32)	0.0005
Women								
Minimum JSW	−0.83 (−0.97, −0.69)	<0.0001	−0.41 (−0.57, −0.25)	<0.0001	−2.89 (−3.35, −2.43)	<0.0001	−1.22 (−1.72, −0.72)	<0.0001
Osteophyte area	0.06 (0.05, 0.08)	<0.0001	0.03 (0.01, 0.04)	0.0001	0.24 (0.20, 0.29)	<0.0001	0.12 (0.08, 0.17)	<0.0001

* WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; 95% CI = 95% confidence interval.
† Calculated by multiple regression analysis with age, sex, body mass index, minimum joint space width (JSW), and osteophyte area as the independent variables in the overall population and with age, body mass index, minimum JSW, and osteophyte area as the independent variables in the groups of men and women only.

were larger than those for osteophyte area (−0.15 and 0.11, respectively), while the absolute values of the beta values for minimum JSW for scores on the physical function domains of the WOMAC were smaller than those for osteophyte area (−0.14 and 0.15, respectively).

When the analysis was restricted to the partici-

Table 3. Associations of minimum JSW and osteophyte area with WOMAC domain scores in the subjects with knee OA*

	Pain				Physical function			
	Crude regression coefficient (95% CI)	*P*	Adjusted regression coefficient (95% CI)†	*P*	Crude regression coefficient (95% CI)	*P*	Adjusted regression coefficient (95% CI)†	*P*
Overall population								
Minimum JSW	−0.81 (−0.97, −0.65)	<0.0001	−0.51 (−0.69, −0.33)	<0.0001	−2.77 (−3.32, −2.22)	<0.0001	−1.46 (−2.05, −0.87)	<0.0001
Osteophyte area	0.06 (0.04, 0.07)	<0.0001	0.03 (0.01, 0.04)	0.0007	0.22 (0.18, 0.27)	<0.0001	0.12 (0.07, 0.17)	<0.0001
Men								
Minimum JSW	−0.59 (−0.86, −0.31)	<0.0001	−0.42 (−0.72, −0.11)	0.009	−1.95 (−2.81, −1.08)	<0.0001	−0.97 (−1.97, −0.01)	0.05
Osteophyte area	0.07 (0.02, 0.11)	0.003	0.02 (−0.02, 0.07)	0.40	0.34 (0.21, 0.48)	<0.0001	0.24 (0.10, 0.39)	0.001
Women								
Minimum JSW	−0.89 (−1.09, −0.68)	<0.0001	−0.56 (−0.78, −0.34)	<0.0001	−3.00 (−3.71, −2.29)	<0.0001	−1.61 (−2.35, −0.88)	<0.0001
Osteophyte area	0.05 (0.04, 0.07)	<0.0001	0.03 (0.01, 0.04)	0.002	0.20 (0.15, 0.26)	<0.0001	0.11 (0.05, 0.16)	0.0001

* Knee osteoarthritis (OA) was defined as a Kellgren/Lawrence grade of ≥2. WOMAC = Western Ontario and McMaster Universities OA Index; 95% CI = 95% confidence interval.
† Calculated by multiple regression analysis with age, sex, body mass index, minimum joint space width (JSW), and osteophyte area as the independent variables in the overall population and with age, body mass index, minimum JSW, and osteophyte area as the independent variables in the groups of men and women only.

pants with knee OA, the results were almost the same (Table 3). In men with knee OA, minimum JSW was independently associated with pain domain scores (β coefficient -0.17), but not with physical function domain scores (β coefficient 0.05). In women with knee OA, both minimum JSW and osteophyte area were independently associated with physical function domain scores, but the beta value for minimum JSW for physical function domain scores was smaller than that for osteophyte area (-0.12 and 0.20, respectively).

DISCUSSION

This is the first study to separately examine the associations of JSN and osteophytosis with QOL, measured by a disease-specific scale such as WOMAC, using a large-scale population-based Japanese cohort. In addition, JSN and osteophytosis were estimated not by categorical grade but by continuous values such as minimum JSW and osteophyte area at the knee. In the present study, JSN as well as osteophytosis was independently associated with QOL.

The present study showed that both JSN and osteophytosis reduce QOL. Osteophytosis appears to begin with the activation of periosteal layers, with initial generation of chondrophytes and subsequent calcification to real osteophytes. The process is probably an adaptive reaction of the joint in order to cope with joint instability, and thus osteophyte area may indicate the severity of joint instability (22), which might lead to loss of QOL. When men and women were analyzed separately, minimum JSW was significantly associated with scores on the WOMAC pain domain but not the WOMAC physical function domain in men, while osteophyte area was associated with scores on the physical function domain but not the pain domain. According to the methodology of the WOMAC, pain domains estimate the severity of pain, indicating that JSN may be strongly associated with pain. In contrast, physical function domains assess difficulties in activities of daily living, indicating that osteophytosis may be mainly associated with activities of daily living, particularly in men.

Our findings also indicated differences between the sexes in the associations of JSN and osteophytosis with QOL. Minimum JSW was significantly associated with scores on the physical function domains of the WOMAC in women, but not in men. Similarly, osteophyte area was associated with scores on the pain domains of the WOMAC in women, but not in men. These differences may indicate that JSN and osteophytosis were more strongly associated with loss of QOL in women than in men. Our previous study also showed that the odds ratio of knee pain for K/L grade 3 or 4 knee OA was approximately twice as high in women as in men (4). This may be partly explained by the lower muscle mass in women than in men. Previous reports have shown that muscle mass is also associated with QOL (23,24). In men, muscular strength may obscure the associations of JSN and osteophytosis with QOL loss; thus, these were not associated with some QOL parameters in men.

The present study has several limitations. First, this is a large-scale, population-based study, with a cross-sectional study of baseline data. Thus, causal relationships could not be determined. The ROAD study is a longitudinal survey, so further progress may help elucidate any causal relationships. Second, we did not include other weight-bearing forms of OA, such as hip OA, in the analysis, although this disorder may also affect QOL. However, the prevalence of K/L grade 3 or 4 hip OA is 1.4% and 3.5% in Japanese men and women (25), respectively, which is lower than the prevalence of K/L grade 3 or 4 knee OA (13.5% and 24.6% in Japanese men and women, respectively) (4). Thus, it is possible that including hip OA would not strongly affect the results of the present study. Third, the QOL questionnaire was completed by 74.2% of all participants age 40 years or older in the ROAD study. Participants who completed the questionnaire were younger and more likely to have knee OA than the participants who did not complete the questionnaire, and thus the participants included in this study may have had better QOL than those who did not complete the questionnaire, and our results may have overestimated QOL. Fourth, although osteophytes may be even more pronounced in the contralateral tibiofemoral compartment (26), at present the KOACAD system can only measure medial osteophytes at the tibia. We are now developing the KOACAD system to measure osteophytes at other sites; thus, we may be able to clarify the association between osteophytes at other sites and QOL in the near future.

In conclusion, the present cross-sectional study using a large-scale population from the ROAD study revealed that JSN and osteophytosis are independently associated with QOL. Further studies, along with continued longitudinal surveys in the ROAD study, will help clarify the mechanisms of JSN and osteophytosis at the knee, and their relationship with QOL.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Muraki had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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