Introduction

Ossification of the posterior longitudinal ligament of the spine (OPLL) is the pathological ectopic ossification of this ligament at the cervical and thoracic spine. It causes myeloradiculopathy as a result of chronic pressure on the spinal cord and nerve roots [1, 2]. Epidemiologic studies have shown a relatively high prevalence of OPLL among the Japanese, a slightly lower prevalence among East Asians and a substantially lower prevalence among whites [3, 4].

In terms of its characteristics, several epidemiological studies have reported that adult-onset obesity and diabetes mellitus (DM) are independent risk factors of OPLL [5, 6]. Further, OPLL often coincides with diffuse idiopathic skeletal hyperostosis (DISH), a systemic disorder of hyperossification. McAfee et al. [7] found that seven (50 %) of 14 patients with OPLL had DISH, and in a Japanese study, DISH was present in 27 (25 %) of 109 patients with OPLL [8].

Besides the coexistence of other disorders such as DM and DISH, little detailed information is available on the profile of OPLL in the general population. These data are important in order to characterise the disease burden. In addition, limited information is available regarding factors associated with OPLL, including biochemical markers of bone turnover, bone mineral density (BMD) values, lifestyle factors, or other coexisting disorders, such as dyslipidaemia, impairment of glucose tolerance, lumbar spondylosis (LS) and knee osteoarthritis (KOA).

Thus, the aims of the present study were to clarify the prevalence of OPLL in the Japanese population and to examine the association of OPLL with biological and environmental factors as well as coexisting disorders. For this, we used a questionnaire survey and the large, population-based cohort Research on Osteoarthritis/osteoporosis Against Disability (ROAD), which included lifestyle factors and nutrition, blood and urinary examinations, BMD measurements and X-ray examinations [9, 10].

Methods

Outline of the ROAD study

We conducted the present study using the cohorts established in 2005 for the ROAD study. The ROAD study is a nationwide, prospective study of OA comprising population-based cohorts from several communities in Japan. The details of the cohort profile have been reported elsewhere [9, 10]. Briefly, in 2005–2007, we created a baseline database that included clinical and genetic information for 3,040 residents of Japan (1,061 men, 1,979 women); the mean age (deviation [SD]) of the participants was 70.3 [11.0]years (71.0 [10.7]years for men and 69.9 [11.2]years for women). The subjects were recruited from resident registration listings in three communities with different characteristics: 1,350 subjects (465 men, 885 women) were from an urban region in Itabashi, Tokyo; 864 subjects (319 men, 545 women) were from a mountainous region in Hidakagawa, Wakayama and 826 subjects (277 men, 549 women) were from a coastal region in Taiji, Wakayama.

The participants completed an interviewer-administered questionnaire of 400 items that included lifestyle information such as occupation, smoking habits and alcohol consumption; family history; medical history; physical activity; reproductive variables and health-related quality of life. A questionnaire was prepared by modifying the one used in the Osteoporotic Fractures in Men Study [11], and some new items were added to the modified questionnaire. The participants were asked whether they took prescription medication daily or nearly every day (0 = no, 1 = yes). If participants did not know the reason for the prescribed medication, they were asked to bring their medications to the medical doctor (NY).

Anthropometric measurements included height (in centimetres), body weight (in kilograms), arm span (in centimetres), bilateral grip strength (in kilograms) and body mass index (BMI; in kilograms per square metre). Experienced orthopaedic surgeons collected medical information on systematic, local and mental status, including information on back, knee and hip pain; swelling and range of motion of the joints and patellar and Achilles tendon reflexes.

In 2008–2010, we attempted to locate and follow up all 3,040 subjects. They were invited for the second survey of the ROAD study, which included a 3-year follow-up of the same examinations as the baseline.

Subjects eligible for the present study

In the present study, we enrolled all 1,690 subjects (men, 596; women, 1,094) from mountainous and coastal areas who had enrolled in the ROAD study. In the ROAD study, X-ray examination of the cervical and thoracic spine had been performed only for these subjects and not for those from the urban region. Further, for all these 1,690 participants, the BMDs for the lumbar spine and the proximal femur had been measured using dual energy X-ray absorptiometry (Hologic Discovery; Hologic, Waltham, MA, USA) during the baseline examination. Additionally, blood and urinary examinations had also been performed for these subjects.

The study participants provided written informed consent, and the study was conducted with the approval of the ethics committees of the University of Tokyo (no. 1264 and no. 1326) and the University of Wakayama Medical University (no. 373).

Radiographic assessment

Plain radiographs were obtained for the cervical, thoracic and lumbar spine in the anteroposterior and lateral views and both knees in the anteroposterior view with weight-bearing and foot-map positioning.

Cervical OPLL was diagnosed using plain radiographs of the cervical spine in the lateral view. OPLL was indicated by the presence of heterotopic ossification in the posterior longitudinal ligament on a lateral cervical radiograph. Radiographic OPLL was diagnosed by a single, experienced orthopaedic surgeon (KN) who was blinded to participants' clinical status. OPLL was classified into the following types: continuous, segmental and mixed. In the original OPLL classification by Tsuyama [3], it was categorised into four modes, namely continuous, segmental, mixed and localised. However, here, because of the small number of subjects in the localised category, these subjects were included in the continuous category. If OPLL was observed, the maximum length (continuous and localised type, upper limit to lower limit; segmental and mixed types, upper limit to lower limit of the longest serial region) and width of ossification were measured using the imaging software OsiriX (http://www.osirix-viewer.com/).

In addition, using radiographs of spine and knees, we determined the grade of OA. The severity of radiographic OA was determined according to the Kellgren–Lawrence (KL) grading [12] as follows: KL0, normal; KL1, slight osteophytes; KL2, definite osteophytes; KL3, joint or intervertebral space narrowing with large osteophytes and KL4, bone sclerosis, joint or intervertebral space narrowing and large osteophytes. Radiographs for each site, i.e. the vertebrae and knees, were examined by a single, experienced orthopaedic surgeon (SM) who was blinded to participants' clinical status. In the present study, the subject's KL grade was considered the maximum grade diagnosed for at least one intervertebral level of the lumbar spine or at least one knee joint.

We also investigated the presence of DISH using whole-spine X-ray films. The criterion for the definite diagnosis of DISH was the presence of four or more vertebral bodies with contiguous ligamentous ossification and calcification, which is known as Resnick and Niwayama's criterion [13]. DISH was diagnosed by a single, experienced orthopaedic surgeon (RK) who was blinded to participants' clinical status.

Blood and urine examinations

Samples were collected from the end of October to the middle of January from both mountainous and coastal areas. All blood and urine samples were extracted between 0900 and 1500 hours. The blood samples were centrifuged, and the sera and urine samples were immediately placed on dry ice and transferred to a deep freezer within 24 h. The samples were stored at −80 °C until assayed.

The blood samples were used to measure haemoglobin A1c (HbA1c, Japan Diabetes Society), serum levels of total cholesterol, uric acid and creatinine levels. The analyses were performed at the same laboratory within 24 h of collection (Osaka Kessei Research Laboratories, Inc., Osaka, Japan).

Serum levels of intact parathyroid hormone (iPTH) were measured using an electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany). As a marker of bone formation, serum levels of N-terminal propeptide of type I procollagen (PINP) were measured using a radioimmunoassay (Orion Diagnostics, Espoo, Finland). The urinary levels of β-isomerised C-terminal cross-linking telopeptide of type I collagen (β-CTX), a bone resorption marker, were determined using an enzyme-linked immunosorbent assay (Fujirebio, Inc., Tokyo, Japan). Urinary β-CTX values were standardised to urinary creatinine concentrations. Plasma pentosidine levels were detected using a competitive ELISA kit (FSK pentosidine ELISA kit; Fushimi Pharmaceutical, Kagawa, Japan) as previously described [14].

Three-year follow-up and definition of OPLL occurrence and progression

In 2008–2010, the 1,690 subjects were invited to enrol in the second survey of the ROAD study, a 3-year follow-up consisting of examinations identical to those conducted at baseline. Spine and knee radiographs were also obtained at follow-up. All cervical radiographs were read by the same orthopaedic surgeon who read them at the baseline (KN), and he was again blinded to participants' clinical status. He simultaneously compared the X-ray films at the baseline and 3-year follow-up and thereby diagnosed OPLL. A new OPLL case was diagnosed if heterotopic ossification in the posterior longitudinal ligament was absent on the lateral cervical radiograph obtained at baseline but present in that obtained during follow-up. OPLL progression was defined as an increase in the maximum length or width of the heterotopic ossification during follow-up compared to that at baseline.

Statistical analysis

All statistical analyses were performed using STATA statistical software (STATA Corp., College Station, TX, USA). Differences in proportions were compared using the chi-square test. Differences in continuous variables were tested for significance using analysis of variance for multiple groups or Scheffe's least significant difference test for pairs of groups. All p values and 95 % confidence intervals (CI) are two sided.

To test the association between OPLL and potential risk factors, we used logistic regression analysis with the presence or absence of OPLL (0 = absence, 1 = presence) as an objective variable and select potential explanatory variables, in addition to basic characteristics such as age (+1 year), gender (0 = men, 1 = women) and regional differences (0 = mountainous area, 1 = coastal area). The selected associated factors were those that showed a significant ($p < 0.05$) association with OPLL status in a simple linear analysis. To test the association between OPLL progression and associated factors, we used multivariate

regression analysis with the change rate (percent per year) of the maximum length or width as an objective variable and the explanatory variables used in the above-mentioned logistic regression analysis. The explanatory variables in the logistic regression analysis and multivariate regression analysis are described in the "Results" section.

Results

Prevalence of radiographic OPLL

The X-ray radiographs of 1,562 of the 1,690 subjects (92.4 %, 520 men, 1,038 women) showed all parts of the lateral cervical spine, from C1 to C7. Among these 1,562 individuals, 30 (17 men, 13 women) were diagnosed with radiographic OPLL; thus, the prevalence of OPLL was estimated at 1.9 % (men, 3.2 %; women, 1.3 %), and it was significantly higher in men than in women ($p=0.007$).

Figure 1 shows the prevalence of OPLL classified by age and gender. The prevalence of OPLL was not associated with age in either men or women.

In the 30 subjects with radiographic OPLL, the OPLL was categorised into the continuous type in 13 subjects (six men and seven women, 43.3 %), the segmented type in eight (six men and two women, 26.7 %), the mixed type in seven (four men and three women, 23.3 %) and the localised type in two (one man and one woman, 6.7 %). The largest OPLL region was most commonly observed in C4 (ten individuals; 33.3 %; three men and seven women), followed by C5 (nine individuals; 33.0 %; eight men and one woman), C3 (seven individuals; 23.3 %; four men and three women), C6 (three individuals; 10.0 %; two men and one women) and C2 (one individual; 3.3 %; one woman). The largest OPLL region was not found in C1 or C7 in any subject.

The mean length and width (standard deviation, SD) of the largest region of ossification at the baseline were 27.6 (16.0) and 3.0 (1.5)mm, respectively. The values in men were 26.1 (14.5) and 2.9 (1.4)mm, and those in women were 29.6 (18.1) and 3.2 (1.5)mm, respectively; thus, no significant difference was observed between men and women in this regard.

Factors associated with OPLL

Table 1 shows the baseline characteristics of 1,562 participants with and without OPLL. Overall, subjects with OPLL tended to be taller and heavier than those without OPLL ($p<0.05$). Further, compared to individuals without OPLL, those with OPLL had higher plasma pentosidine levels and higher BMD values for both the lumbar spine (L2–4) and femoral neck ($p<0.05$).

Table 1 also shows the prevalence of LS, KOA and DISH on the basis of OPLL status. The prevalence of LS with ≥grade 2 KL and that of DISH was higher in the group with OPLL than in the one without OPLL ($p<0.05$), although no significant association was observed between the prevalence of KOA and the presence of OPLL.

Logistic regression analysis was performed with the OPLL status as the objective variable (0 = absence, 1 = presence). As explanatory variables, the analysis involved select associated factors that showed a significant ($p<0.05$) association with OPLL status in the simple linear analysis, namely, height (in centimetres), weight (in kilograms), values of plasma pentosidine (+1 μg/mL), BMD of the femoral neck (+1 SD), presence of LS based on KL grade (0 = KL grade 0 or 1, 1 = KL grade≥2) and DISH (0 = absent, 1 = present), after adjustments were made for age (years) and gender (0 = men, 1 = women). As seen from Table 2, plasma pentosidine levels, BMD of the femoral neck and the presence of DISH were found to be significant associated factors for the presence of OPLL (Table 2). Further, when BMD of the lumbar spine (L2–4) was used instead of that of the femoral neck, this factor was also found to be significantly associated with OPLL (+1 SD; odds ratio (OR), 1.52; 95 % CI, 1.05–2.20; $p=0.026$), but the

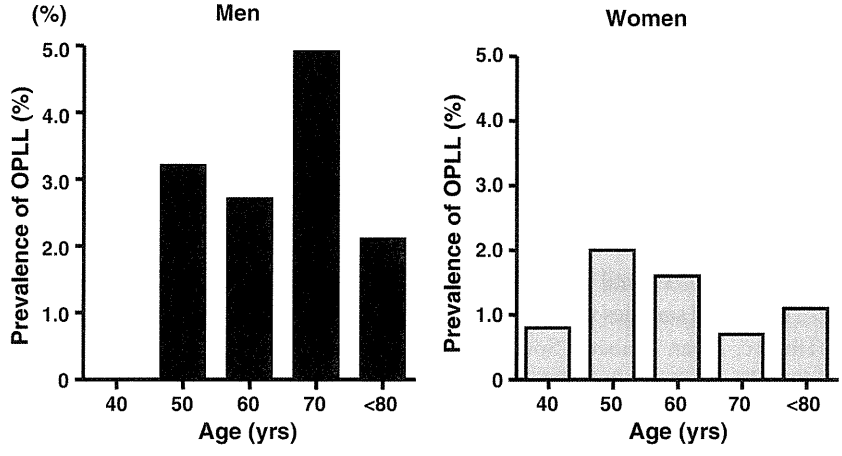

Fig. 1 Prevalence of OPLL classified by age and gender

Table 1 Baseline characteristics of participants classified by the presence or absence of OPLL

	Total (N=1,562)			Men (N=524)			Women (N=1,038)		
	OPLL (−) N=1,532	OPLL (+) N=30	p	OPLL (−) N=507	OPLL (+) N=17	p	OPLL (−) N=1,025	N=1,025 N=13	p
Age distribution (prevalence, %)									
30 years and younger	43	0 (0.0)		12	0 (0.0)		31	0 (0.0)	
40–49 years	141	1 (0.7)		39	0 (0.0)		102	1 (1.0)	
50–59 years	291	7 (2.4)	0.729	92	3 (3.2)	0.604	199	4 (2.0)	0.787
60–69 years	449	9 (2.0)		142	4 (2.7)		307	5 (1.6)	
70–79 years	468	11 (2.3)		175	9 (4.9)		293	2 (0.7)	
80 years and older	140	2 (1.4)		47	1 (2.1)		93	1 (1.1)	
Age (years), mean (SD)	62.9 (12.1)	67.0 (9.3)	0.3495	66.0 (11.7)	70.7 (8.0)	0.0990	64.4 (12.2)	62.2 (9.0)	0.5069
Height (cm), mean (SD)	154.9 (9.1)	159.1 (7.5)	0.0132*	163.3 (7.0)	163.9(5.4)	0.7414	150.8 (6.9)	152.8 (4.6)	0.2945
Weight (kg), mean (SD)	55.0 (10.3)	60.3 (10.1)	0.0053**	61.6 (10.5)	62.7 (8.2)	0.6759	51.7 (8.5)	57.1 (11.7)	0.0219*
BMI (kg/m^2), mean (SD)	22.8 (3.2)	23.8 (3.4)	0.1135	23.0 (3.1)	23.3 (2.1)	0.7434	22.7 (3.3)	24.4 (4.6)	0.0671
Residing in the coastal area (%)	49.4	53.3	0.671	46.4	58.8	0.311	50.9	46.2	0.732
Current smoking habit (regularly, ≥1/month) (%)	12.9	23.3	0.095	31.1	41.2	0.377	3.8	0.0	0.472
Current alcohol consumption (regularly, ≥1/month) (%)	39.1	43.3	0.637	66.1	64.7	0.907	25.8	15.4	0.395
Total cholesterol (mg/dL), mean (SD)	208.8 (34.5)	209.6 (36.2)	0.8954	198.6 (34.1)	204.4 (33.5)	0.4874	213.8 (33.6)	216.4 (39.8)	0.7840
Uric acid (mg/dL), mean (SD)	4.84 (1.30)	5.24 (1.21)	0.0943	5.71 (1.26)	5.71 (1.03)	0.9867	4.42 (1.09)	4.65 (1.21)	0.4528
HbA1c (Japan Diabetes Society) (%), mean (SD)	5.17 (0.70)	5.38 (0.79)	0.1124	5.20 (0.79)	5.44 (0.95)	0.2162	5.16 (0.64)	5.29 (0.56)	0.4595
Serum levels of iPTH (pg/mL), mean (SD)	41.2 (34.4)	41.2 (14.2)	0.9952	42.6 (54.4)	41.1 (13.9)	0.9083	40.5 (17.4)	41.3 (15.1)	0.8748
Serum levels of PINP (μg/L), mean (SD)	57.9 (27.0)	52.6 (29.9)	0.2915	47.5 (22.0)	42.6 (14.9)	0.3619	63.1 (27.8)	65.8 (39.2)	0.7301
Urinary levels of β-CTX (μg/mmol Cr), mean (SD)	187.2 (121.3)	150.4 (79.1)	0.0985	128.4 (78.7)	119.8 (58.3)	0.6529	216.2 (128.0)	190.5 (86.8)	0.4693
Plasma levels of pentosidine (μg/mL), mean (SD)	0.058 (0.037)	0.085 (0.140)	0.0005***	0.061 (0.048)	0.102 (0.184)	0.0042**	0.057 (0.030)	0.062 (0.037)	0.5012
BMD of the lumbar spine L2-4 (g/cm^2), mean (SD)	0.925 (0.205)	1.084 (0.205)	<0.0001***	1.038 (0.203)	1.176 (0.176)	0.0058**	0.868 (0.181)	0.965 (0.181)	0.0575
BMD of the femoral neck (g/cm^2), mean (SD)	0.667 (0.137)	0.747 (0.134)	0.0016**	0.739 (0.132)	0.797 (0.110)	0.0727	0.631 (0.124)	0.681 (0.139)	0.1558
Presence of LS (KL grade≥2) (%)	61.8	83.3	0.016*	76.1	100.0	0.022*	54.7	61.5	0.624
Presence of KOA (KL grade≥2) (%)	49.5	56.7	0.440	41.4	41.2	0.986	53.6	76.9	0.093
Presence of DISH (%)	9.4	33.3	<0.001***	0.7	52.9	0.002**	3.8	7.7	0.469

OPLL ossification of posterior longitudinal ligament, *SD* standard deviation, *BMI* body mass index, *HbA1c* haemoglobin A1c, *iPTH* intact parathyroid hormone, *PINP* N-terminal propeptide of type I procollagen, *β-CTX* β-isomerised C-terminal cross-linking telopeptide of type I collagen, *BMD* bone mineral density, *LS* lumbar spondylosis, *KOA* knee osteoarthritis, *KL grade* Kellgren–Lawrence grade, *DISH* diffuse idiopathic skeletal hyperostosis, *OPLL(−)* absence of OPLL, *OPLL(+)* presence of OPLL

*p<0.05; **p<0.01; ***p<0.001

Table 2 Odds ratios of potential factors associated with the presence of OPLL vs. the absence of OPLL

Explanatory variables	Reference	OR	95 % CI	*p*
Age (years)	+1 year	1.03	0.98–1.07	0.269
Gender	0 = men, 1 = women	1.30	0.39–4.34	0.666
Height (cm)	+1 cm	1.04	0.96–1.12	0.352
Weight (kg)	+1 kg	1.00	0.96–1.05	0.909
Pentosidine (μg/mL)	+0.01 μg/mL	1.05	1.00–1.09	0.038*
BMD (femoral neck) (g/cm2)	+1 SD	1.55	1.04–2.33	0.033*
Presence of LS (KL grade≥2)	0 = no, 1 = yes	1.94	0.67–5.61	0.219
Presence of DISH	0 = no, 1 = yes	2.78	1.11–6.92	0.029*

Logistic regression analysis was performed using the status of OPLL as the objective variable (0 = absence, 1 = presence), and the abovementioned factors were correspondingly adjusted

OPLL ossification of posterior longitudinal ligament, *BMD* bone mineral density, *LS* lumbar spondylosis, *KL grade* Kellgren–Lawrence grade, *DISH* diffuse idiopathic skeletal hyperostosis, *SD* standard deviation, *OR* odds ratios, *95 % CI* 95 % confidence interval

*$p<0.05$; **$p<0.01$; ***$p<0.001$

association of plasma pentosidine levels and DISH weakened (plasma pentosidine +0.01 μg/mL, 1.04, 0.997–1.087, $p=0.069$; presence of DISH 2.37, 0.94–6.00, $p=0.069$).

New occurrence or progression of OPLL

During the three study years, 1,380 individuals (88.3 %; 466 men, 914 women) among the 1,562 subjects at baseline returned for follow-up, and their radiographs were available for observation. Among the 30 individuals with radiographic cervical OPLL at baseline, 25 (83.3 %; 14 men and 11 women) participated in the second survey.

The remaining 1,355 individuals who did not have cervical OPLL at baseline and who participated in the initial and second surveys were regarded as members of the population at risk for the occurrence of OPLL. Among them, only one woman was diagnosed with newly developed radiographic OPLL (incidence 2.46/10,000 per year).

At follow-up, the mean length (in millimetres, SD) and width (in millimetres, SD) of the maximum region of ossification among the 25 individuals with OPLL was 28.7 (16.1) and 3.5 (1.5)mm, respectively. Since the mean values of length and width of the maximum region of ossification of these 25 subjects were 27.0 (16.2) and 3.0 (1.5)mm at the baseline, respectively, both the length and width of the maximum region of ossification increased, although a significant difference was not observed.

To clarify the risk factors associated with this increase in the length and width of the ossification, we performed multivariate regression analysis using the rate of change in these parameters as objective variables and the explanatory variables as those used in the logistic regression analysis, namely height (in centimetres), weight (in kilograms), plasma pentosidine levels (+1 μg/mL), BMD of the femoral neck (+1 SD), presence of LS based on the KL grade (0 = KL grade 0 or 1, 1 = KL grade≥2) and DISH (0 = absence, 1 = presence). Adjustments for age (years) and gender (0 = men, 1 = women) were made. However, none of the abovementioned variables was found to be significantly associated with the rate of changes in the length or width.

Discussion

In the present population-based study, we clarified the prevalence of radiographic OPLL in the general Japanese population, and we found that it is significantly associated with high plasma pentosidine levels, high BMD and the presence of DISH. The 3-year follow-up study also showed that new cases were very rare, and the length and width of the maximum region of ossification among the subjects with OPLL tended to increase.

The prevalence of OPLL in Japan has been reported to be 1.9 to 4.3 % among individuals aged 30 years and older [1, 15–17]. In other Asian countries, such as in Korea [18, 19] and Taiwan [20], a similar prevalence was reported, but it was lower in Western countries [21], suggesting that ethnic and/or genetic factor(s) could be associated with the onset of OPLL. In the present study, the prevalence of OPLL was found to be 1.9 %. This is consistent with the value found in previous reports. However, it is difficult to clearly distinguish localised-type OPLL from osteophytic changes, and we included two individuals with localised-type OPLL in the OPLL group. Thus, we may have overestimated the presence of radiographic OPLL. If we exclude individuals with localised-type OPLL from the OPLL group, the prevalence of the OPLL in the present study is 1.8 %.

With regard to the gender difference in OPLL prevalence, the prevalence was previously reported to be three times higher in men than in women [22]. We found that men are 2.5 times more likely to have OPLL than women (men 3.2 %, women

1.3 %), which is consistent with results reported previously among Japanese subjects. In contrast, symptomatic OPLL was reported to be usually observed in the sixth decade of life [22], although we were unable to find a significant association between age and the presence of OPLL. This might be explained by the fact that previous studies on the characteristics of OPLL were performed on the subjects with symptomatic OPLL, i.e. they had been clinically diagnosed with OPLL, while our subjects had radiographic OPLL that had not been clinically diagnosed. If the OPLL in our subjects progresses in the future, the peak age at which the symptoms could be expressed may be their 60s.

With regard to the comorbidities of OPLL, several reports have indicated that obesity and DM might be associated with OPLL [5, 6]. In the present study, the values of BMI tended to be higher in the group with OPLL than in that without OPLL, although this difference was not significant. A similar pattern was found in the values of HbA1c, and this finding could be explained by previous findings that the extent of ossification was significantly associated with the fasting serum insulin level but not with the fasting glucose level or the HbA1c level [23]. However, in the ROAD study, since all subjects could not be requested to fast, we could not confirm the association between fasting serum insulin levels and OPLL.

With regard to the association between biochemical markers of bone turnover and OPLL, Matsui et al. showed that the levels of the bone markers serum procollagen type I carboxyl-terminal peptide and intact osteocalcin were higher in patients with OPLL than in normal subjects [24]. This suggested that OPLL was associated with biochemical markers of bone turnover. In the present study, to evaluate the role of bone metabolism in OPLL, we compared the serum levels of iPTH and PINP as bone formation markers and the urinary levels of β-CTX between the groups with and without OPLL. However, we could not find significant differences between the groups.

Instead, the plasma pentosidine levels of the OPLL group were found to be significantly higher than those of the group without OPLL. This tendency remained after potential associated factors were adjusted for. Pentosidine is an advanced glycation end product, products generated by the sequential nonenzymatic glycosylation of protein amino groups [25] that accumulate in various tissues including kidney and coronary arteries, resulting in the development of diabetic vascular complications [26]. The concentrations of pentosidine in cortical and trabecular bone are reported to be adversely associated with bone strength [27–29]. Yamamoto et al. [30] found that serum pentosidine levels were positively associated with the presence of vertebral fractures in postmenopausal women with type 2 diabetes. Renal insufficiency was reported to be a dominant determinant of serum pentosidine levels [31] because of which serum pentosidine levels are increased in patients with chronic renal failure [32, 33]. However, no report has shown the association between pentosidine levels and the presence of OPLL. On the basis of the abovementioned reports, we performed multivariate logistic regression analysis using the same explanatory factors we had used in the analysis shown in Table 2, along with the estimated glomerular filtration rate. We found that the plasma pentosidine levels were still significantly related to the presence of OPLL (OR, 1.05; 95 % CI, 1.00–1.09; $p=0.042$). We speculate that the levels of pentosidine might be associated with ectopic ossification, such as vascular calcification in patients with renal dysfunction, or the presence of OPLL, directly or indirectly, although the currently available information is inadequate to prove this hypothesis. One reason for the inadequacy of the information obtained in this study could be that we did not evaluate genetic factors in the present study. Further investigations are needed to clarify whether the observed relationship between pentosidine levels and OPLL remains after analysis of other possible confounders, including genetic factors.

In addition to the biochemical markers, high BMDs have been observed in patients with OPLL [24, 34, 35]. However, Morio et al. reported that the BMD was lower in patients with advanced OPLL [36], suggesting that the disuse atrophy may result during advanced-stage OPLL. Our results also showed that subjects with OPLL had higher BMDs. However, the subjects in the present study all had radiographically determined OPLL but few clinical symptoms, so their condition may not have been in the advanced stage. Therefore, based solely on the results of the present study, we were unable to discuss the association between BMD and advanced-stage OPLL.

Several reports have shown that the coexistence of OPLL and DISH is quite common [4, 7, 8]. The pathogenesis of DISH and OPLL has been speculated to be similar, although the details remain unclear. For example, Havelka et al. analysed intron 6 (−4) polymorphisms in the COL 11 A2 gene in Czech patients with DISH and Japanese patients with OPLL, but they found no agreement between the data of subjects with DISH and OPLL [37]. Additional studies with a broader spectrum of genotyping and a larger cohort of patients may clarify the presence or absence of genetic relations between DISH and OPLL.

Few studies have been reported regarding the incidence of OPLL in the general population because OPLL is relatively rare and based on ethnicity, as noted. Using data collected in a pilot study in the corporation of 360 Japanese hospitals [3], Tsuyama described the incidence of OPLL and found that 2,142 patients were treated in these hospitals and the estimated incidence of OPLL was 19 patients per million persons of the total population [3]. In the present study, only one new case of OPLL was detected, so we could not accurately estimate the incidence of OPLL and compare our results to those of previous reports. In order to confirm the incidence of OPLL, we need to follow this cohort for a longer time.

Several studies have investigated the course of OPLL. Chiba et al. use computer-assisted measurement to examine OPLL

progression, and they found that the rate of OPLL progression was 56.5 % over 2 years, and this rate was most common in younger patients with continuous- and mixed-type OPLL [38]. Murakami et al. followed the case of a 67-year-old man who had had cervical OPLL for more than 26 years, and they found that the rate of OPLL progression was 2.2, 8.8 and 2.0 mm/year from 1–4, 4–8 and 8–10 years after the first visit, respectively [39]. However, to our knowledge, no study has reported the progression of radiographically defined OPLL in the general population. In the present study, we found that both the length and width of the maximum region of ossification increased during the 3 years of the study, although it was not a significant change. A previous report [39] found no evidence of OPLL progression after 10 years. We must carefully examine whether or not radiographically defined OPLL progresses to clinical OPLL.

This study has several limitations. First, although the ROAD study includes a large number of participants, these participants may not truly be representative of the general population. To address this, we compared the anthropometric measurements and the frequencies of smoking and alcohol consumption between the study participants and the general Japanese population. No significant differences were found, with the exception that male ROAD study participants aged 70–74 years were significantly smaller in terms of body structure than men from the overall Japanese population ($p < 0.05$) [10]. This difference should be considered when evaluating potential risk factors for men aged 70–74 years; factors such as body build, particularly weight, are known to be associated with metabolic risk factors and KOA. Therefore, our results may have underestimated the prevalence of these conditions. Second, the total number of subjects with confirmed OPLL was very small, which might make the results somewhat less credible. In the present study, we used logistic regression analysis to adjust for gender differences. When the total number of the objective variable, namely OPLL cases, is small, using the multivariate model to adjust for gender differences may be more useful than using a gender-specific analysis. This is because the total number of cases in a gender-specific analysis will be even smaller, which reduces the statistical power. Although the significant associations between OPLL and the plasma levels of pentosidine and between OPLL and DISH were observed only in men in the simple comparative analysis, the pentosidine levels and DISH remained significant factors associated with the presence of OPLL even in the logistic regression analysis with adjustments for gender. We interpreted this result to mean that the female sex might dilute the strength of the association between OPLL and DISH, but the tendency in both genders remained significant.

To clarify the effect of sex differences in the interaction among OPLL, pentosidine levels and DISH, the logistic regression analysis was performed in men and women separately (Supplementary Table 1). In this logistic regression analysis, the presence of OPLL was significantly associated with the pentosidine levels and femoral neck BMD in men, but the association of OPLL with the presence of DISH was diluted to a marginal association ($p=0.080$). Further, since all male patients with DISH had radiographic LS, we could not evaluate the association between OPLL and LS. In women, the associations among OPLL, pentosidine levels and DISH were not significant. Although these results may indicate that the significant associated factors were observed only in men, they may even be skewed by the small number of female cases. Under these circumstances, it is difficult to distinguish which model should be used, i.e. logistic regression analysis or the multivariate model. It may be necessary to first include an adequate number of OPLL cases before this can be decided. To compensate for these limitations, we decided to include the urban cohort of the ROAD study in the OPLL survey. Thus, more participants will be included in the third ROAD survey planned from 2012 to 2013, and further detailed investigation regarding the risk factors for the presence, occurrence or exacerbation of OPLL may be possible.

In summary, the present study clarified that the prevalence of radiographic cervical OPLL in 1,562 individuals was 1.9 %, which was significantly higher in men than in women ($p=0.007$), but no association with age was observed. In logistic regression analysis, OPLL showed a significant association with the femoral neck BMD, presence of DISH and plasma pentosidine levels. Only one new case of radiographic OPLL was detected, but OPLL progressed in all affected subjects.

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Conflicts of interest None.

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ORIGINAL ARTICLE

Prevalence, incidence and progression of lumbar spondylosis by gender and age strata

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Abstract

Objectives. To identify the prevalence, incidence and progression of radiographic lumbar spondylosis (LS).
Methods. From the Adult Health Study conducted by the Radiation Effects Research Foundation, 1,204 participants aged 44–85 years who had lumbar spine radiographs in 1990–1992 were reexamined in 1998–2000 (mean 7.9-year interval). The radiographic severity of LS was determined by Kellgren/Lawrence (KL) grading.
Results. In the overall population, the prevalence of radiographic KL ≥ 2 and ≥ 3 LS was 52.9% and 23.6%, respectively. KL ≥ 2 LS was more prevalent in men, whereas KL ≥ 3 LS was more prevalent in women. During the 8-year follow-up, the incidence of KL ≥ 2 LS in men and women was 65.5% and 46.6%, that of KL ≥ 3 LS was 27.3% and 29.5%, that of progressive LS was 31.3% and 34.0%, and multilevel LS was 44.9% and 33.4%, respectively. Body–mass index was a risk factor for both KL ≥ 2 and KL ≥ 3 LS, after adjusting for age and sex.
Conclusions. The present longitudinal study revealed the prevalence, incidence and progression of radiographic LS. Prevalence and incidence of KL ≥ 2 LS was higher in men than women, while, those of KL ≥ 3 were similar between men and women.

Keywords

Incidence, Lumbar spine, Prevalence, Progression, Spondylosis

History

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Introduction

Lumbar spondylosis (LS), characterized by disc degeneration and osteophytosis [1,2], is a major public health issue in most countries and causes chronic disability among the elderly [1,3–8]. Despite the urgent need for strategies to prevent and treat this condition, epidemiologic data on LS are sparse. Past studies reported wide ranged prevalence of radiographic LS from 40% to 85% based on the limited number of study subjects in a clinical setting [9–17]. This variability may be due to the differences in age, communities, sample sizes, imaging modality and ethnic variations, yet the disorder burden remains unclear. Further, there are few studies regarding the incidence or progression of LS [7,12,15,18,19].

Plain radiography is considered the gold standard as a method that is non-invasive, inexpensive, convenient, simple and fast to use in assessing osteoarthritis (OA) severity. The most popular grading system for radiographic severity of OA is the Kellgren/Lawrence (KL) system, which is classified into five grade (0–4) scales; KL ≥ 2 is the conventional standard for diagnosis [20]. For LS, KL Grade 2 is defined as osteophyte formation and KL Grade 3 is defined as osteophyte formation along with disc-space narrowing. Hence, to assess osteophyte formation alone and disc-space narrowing with or without osteophyte formation, the prevalence and incidence of KL ≥ 2 LS as well as that of KL ≥ 3 LS is needed.

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In the present study, we analyzed the prevalence, incidence and progression of LS according to gender and age strata in Japan.

Materials and methods

Subjects

The Adult Health Study (AHS) was established by the Radiation Effects Research Foundation in 1958 to document the late health effects of radiation exposure among atomic-bomb survivors in Hiroshima and Nagasaki, and study subjects have been followed through biennial medical examinations. The participation rate has been over 70% throughout this period. More detail concerning recruitment and examination of participants was reported elsewhere [21].

Among AHS subjects, 1,297 subjects (363 men and 934 women) aged 44–85 years underwent radiographic examinations of the lumbar spine in Hiroshima between 1990 and 1992 (baseline). Of those 1,297 subjects, 1,204 (92.8%) subjects participated in the follow-up study between 1998 and 2000. All participants provided written informed consent, and the study was conducted with the approval of ethical committees of the Radiation Effects Research Foundation. Anthropometric measurements included height, weight and body–mass index (BMI; weight [kg]/height [m^2]) was calculated. We used individual radiation dose estimates from the Radiation Effects Research Foundation's Dosimetry System 2002 (DS02) [22].

Radiographic assessments

Plain radiographs of the lumbar spine were taken in the lateral position to assess radiographic LS. The severity of LS was

Table 1. Characteristics of participants.

	Men					Women				
	Overall	<50	50–59	60–69	≥70	Overall	<50	50–59	60–69	≥70
No. of subjects	363	56	83	158	66	934	129	217	414	174
Age, years	61.2 ± 9.4	46.4 ± 1.3	55.8 ± 3.3	63.2 ± 2.6	75.5 ± 4.1	61.6 ± 8.9	46.5 ± 1.3	55.6 ± 3.0	64.2 ± 2.8	74.2 ± 3.2
Height, cm	163.2 ± 5.8	166.6 ± 6.3	163.9 ± 5.6	163.0 ± 5.3	159.9 ± 5.2	150.7 ± 5.6*	153.4 ± 5.0*	151.9 ± 5.5*	150.7 ± 5.3*	147.3 ± 5.1*
Weight, kg	59.9 ± 8.6	61.6 ± 7.7	61.9 ± 9.1	60.1 ± 8.4	55.6 ± 7.6	52.4 ± 8.7*	54.2 ± 8.5*	54.5 ± 9.0*	52.1 ± 8.3*	49.3 ± 8.6*
BMI, kg/m^2	22.5 ± 2.8	22.2 ± 2.7	23.0 ± 2.9	22.6 ± 2.7	21.7 ± 2.8	23.1 ± 3.5*	23.1 ± 3.6	23.6 ± 3.5	22.9 ± 3.4	22.7 ± 3.6*

Data are mean ± standard deviation.
BMI, body–mass index.
*$p < 0.05$ vs. men in the corresponding group by non-paired Student's t test.

determined according to the KL grading [20] at each intervertebral level from L1/2 to L5/S1 by a well-experienced orthopedists (S.M.), who was masked to the patients' backgrounds. The KL scale defines radiographic OA in five categories: KL Grade 0, no radiographic features of OA; KL Grade 1, minimal osteophytosis only; KL Grade 2, definite osteophytosis with some sclerosis of the anterior part of the vertebral plate; KL Grade 3, marked osteophytosis and sclerosis of the vertebral plates with slight narrowing of the disc space and KL Grade 4, large osteophytes, marked sclerosis of the vertebral plates and marked narrowing of the disc space. To evaluate the intra-observer variability of the KL grading, 100 randomly selected radiographs of the lumbar spine were scored by the same observer more than a month after the first reading. A further 100 radiographs were scored by two experienced orthopedic surgeons. They used the same radiographic atlas for inter-observer variability. The intra- and inter-observer variabilities were evaluated by kappa analysis. These variabilities in the KL grading on lumbar radiographs have been shown to be sufficient for assessment (0.84 and 0.76, respectively).

For the purposes of this study, we defined four LS outcomes. First, a subject could have incident KL ≥ 2 radiographic LS if all vertebral interspaces had < Grade 2 disease at baseline, and if at least one vertebral interspace had ≥ Grade 2 disease at follow-up. Second, a subject could have incident KL ≥ 3 radiographic LS if all vertebral interspaces had < Grade 3 disease at baseline, and if at least one vertebral interspace had Grade ≥ 3 at follow-up. Third, progressive LS was defined as KL ≥ 2 LS at baseline and an increase by at least one grade in the affected vertebral interspace at follow-up. Fourth, multilevel LS was defined as KL ≥ 2 grade at two or more interspaces. A subject could have incident multilevel LS if the subject had less than two interspaces with KL ≥ 2 LS at baseline, and if he or she had two or more interspaces with KL ≥ 2 at follow-up.

Statistical analysis

We used the chi-square test to compare the prevalence and incidence with radiographic LS between men and women. Incidence was calculated as follows: the number of subjects with LS at follow-up among those without LS at baseline divided by the number of subjects without LS at baseline. The association of variables such as age, BMI and gender with the prevalence and incidence of radiographic LS was evaluated by multiple logistic regression analysis. Data analyses were performed using SAS version 9.0 (SAS Institute Inc., Cary, NC).

Results

Characteristics of the 1,297 participants at baseline are shown in Table 1. The mean age of those participating in the follow-up study was 69.1 ± 9.0 years. The interval between baseline examination and follow-up was 7.9 ± 1.1 years.

The prevalence of KL ≥ 2 LS in the overall population and subgroups classified by gender and age strata at baseline is shown in Table 2. The prevalence was significantly higher at all interspaces and at the most severe space in men compared with women in the overall population. The prevalence of multilevel LS was also significantly higher in men than in women. Logistic regression analysis showed that the prevalence of KL ≥ 2 LS at all interspaces as well as at the most severe level, and multilevel spondylosis was significantly associated with age in men and women. In men, the prevalence was highest at L3/4 at almost all age strata, whereas in women, the prevalence was highest at L4/5.

In contrast to KL ≥ 2 LS, the prevalence of KL ≥ 3 LS was significantly higher at all interspaces and at the most severe space in women than men in the overall population (Table 3). The prevalence of multilevel LS was also higher in women than in men. Logistic regression analysis showed that the prevalence of KL ≥ 3 LS at all interspaces as well as at the most severe level, and

Table 2. Number (percentage) of participants with KL ≥ 2 LS at each vertebral interspace as well as the most severe space, and multilevel KL ≥ 2 LS according to gender and age strata at baseline.

Age at baseline	L1/2	L2/3	L3/4	L4/5	L5/S	Severest	Multilevel
Overall	231 (17.8)	370 (28.5)	381 (29.4)	413 (31.8)	180 (13.9)	697 (53.8)	430 (33.2)
Men	102 (28.1)	138 (38.0)	157 (43.2)	140 (38.6)	52 (14.3)	246 (67.8)	167 (46.0)
<50	5 (8.9)	12 (21.4)	15 (26.8)	9 (16.1)	4 (7.1)	22 (39.3)	11 (19.6)
50–59	18 (21.7)	17 (20.5)	25 (30.1)	27 (32.5)	6 (7.2)	48 (57.8)	29 (34.9)
60–69	50 (31.6)	71 (44.9)	76 (48.1)	64 (40.5)	25 (15.8)	118 (74.7)	80 (50.6)
≥70	29 (43.9)	38 (57.6)	41 (62.1)	40 (60.6)	17 (25.8)	58 (87.9)	47 (71.2)
Women	129 (13.8)*	232 (24.8)*	224 (24.0)*	273 (29.2)*	128 (13.7)*	451 (48.3)*	263 (28.2)*
<50	3 (2.3)	9 (7.0)	7 (5.4)	15 (11.6)	6 (4.7)	29 (22.5)	9 (7.0)
50–59	16 (7.4)	32 (14.7)	39 (18.0)	47 (21.7)	26 (12.0)	88 (40.6)	35 (16.1)
60–69	59 (14.3)	121 (29.2)	111 (26.8)	129 (31.2)	61 (14.8)	215 (51.9)	136 (32.9)
≥70	51 (29.3)	70 (40.2)	67 (38.5)	82 (47.1)	35 (20.1)	119 (68.4)	83 (47.7)

Multilevel LS was defined as KL grade ≥ 2 at two or more interspaces.
*$p < 0.05$ vs. men by chi-square test in the overall population.

Table 3. Number (percentage) of participants with KL ≥ 3 LS at each vertebral interspace as well as the most severe space, and multilevel KL ≥ 3 LS according to gender and age strata at baseline.

Age at baseline	L1/2	L2/3	L3/4	L4/5	L5/S	Severest	Multilevel
Overall	30 (2.3)	75 (5.8)	105 (8.1)	236 (18.2)	110 (8.5)	320 (24.7)	141 (10.9)
Men	6 (1.7)	12 (3.3)	19 (5.2)	41 (11.3)	14 (3.9)	58 (16.0)	22 (6.1)
<50	0 (0.0)	0 (0.0)	2 (3.6)	3 (5.4)	1 (1.8)	4 (7.1)	1 (1.8)
50–59	1 (1.2)	1 (1.2)	1 (1.2)	4 (4.8)	1 (1.2)	6 (7.2)	2 (2.4)
60–69	1 (6.3)	6 (3.8)	8 (5.1)	18 (11.4)	6 (3.8)	27 (17.1)	10 (6.3)
≥70	4 (6.1)	5 (7.6)	8 (12.1)	16 (24.2)	6 (9.1)	21 (31.8)	9 (13.6)
Women	24 (2.6)	63 (6.7)*	86 (9.2)*	195 (20.9)*	96 (10.3)*	262 (28.1)*	119 (12.8)*
<50	0 (0.0)	2 (1.6)	2 (1.6)	10 (7.8)	5 (3.9)	16 (12.4)	3 (2.3)
50–59	1 (0.5)	7 (3.2)	12 (5.5)	30 (13.8)	19 (8.8)	47 (21.7)	14 (6.5)
60–69	10 (2.4)	23 (5.6)	38 (9.2)	88 (21.3)	43 (10.4)	116 (28.0)	55 (13.3)
≥70	13 (7.5)	30 (17.3)	34 (19.7)	66 (38.2)	29 (16.8)	82 (47.4)	46 (26.6)

Multilevel LS was defined as KL grade ≥ 3 at two or more interspaces.
*$p < 0.05$ (chi-square test) vs. men in the overall population.

multilevel spondylosis was significantly associated with age in men and women. The prevalence was low at L1/2 and the highest at L4/5 among all interspaces in men and women.

Table 4 shows the incidence of KL ≥ 2 and ≥ 3 LS in the overall population and subgroups classified by gender and age strata. The incidence of KL ≥ 2 LS was significantly higher in men than in women. Logistic regression analysis showed that the incidence of KL ≥ 2 LS was significantly associated with age in men and women. The incidence of KL ≥ 3 LS was significantly higher in women. When the incidence was compared among generations, the incidence of KL ≥ 3 radiographic LS tended to increase with age after the 50s in men and women, whereas that of KL ≥ 2 radiographic LS was not much different between the 40s and 50s.

We also examined progressive and multilevel LS (Table 4). Among subjects with KL = 2 LS at baseline, 31% subjects had KL = 3 LS and 9% subjects had KL = 4 LS at follow-up. Among subjects with KL = 3 LS at baseline, 31% subjects had KL = 4 LS at follow-up. The progression of LS was not associated with gender or age strata. The incidence of multilevel LS was higher in men than in women, and tended to increase with age in men and women.

We next analyzed the independent association of age, gender and BMI with the prevalence of LS by multiple logistic regression analysis (Table 5). Age and BMI were associated with an increased prevalence of KL ≥ 2 LS as well as KL ≥ 3 at the most severe space and multilevel LS. Female gender was associated with decreased prevalence for KL ≥ 2 LS at the most severe space and that of multilevel LS; it was also associated with increased prevalence for KL ≥ 3 LS.

We also analyzed the independent association of age, gender and BMI with the incidence of LS by multiple logistic regression analysis (Table 6). Age and BMI were associated with increased risk for the incidence of KL ≥ 2, KL ≥ 3 and multilevel LS, but not for progressive LS. Female gender was associated with decreased incidence for KL ≥ 2 and multilevel LS, whereas there was no significant association of gender with KL ≥ 3 and progressive LS.

No significant relationship was found between atomic-bomb radiation and prevalence and incidence of KL ≥ 2, KL ≥ 3 and multilevel LS.

Discussion

The present study revealed the prevalence of radiographic KL ≥ 2 and KL ≥ 3 LS in men and women. Although prevalence of KL ≥ 2 LS was more frequent in men than in women, KL ≥ 3 LS was more prevalent in women. Given an 8-year follow-up, we also revealed the incidence of KL ≥ 2 and KL ≥ 3 LS as well as progressive LS and multilevel LS in men and women.

Most previous epidemiologic studies on LS focused on middle-aged or younger populations, reporting the prevalence to be 40–85% [9,11–13,15,16]. This variability may be due to the differences in age, communities, sample sizes and ethnic variations. In terms of ethnic variations, we reported a different prevalence of LS in Japan and the United Kingdom in a small-scale comparative study [14], whereas our previous study of an elderly Japanese population showed a prevalence of 84.1% and 70.7% in men and women, respectively [23], which is similar to the prevalence seen in this study among subjects in their 70s.

Table 4. Incidence of KL ≥ 2 and ≥ 3 LS according to gender and age strata.

	KL ≥ 2		KL ≥ 3		Progressive LS		Multilevel LS	
Age at baseline	No. at risk	Cumulative incidence	No. at risk	Cumulative incidence	No. at risk	Cumulative incidence	No. at risk	Cumulative incidence
Overall	567	285 (50.3)	920	265 (28.8)	696	230 (33.0)	866	312 (36.0)
Men	110	72 (65.5)	286	78 (27.3)	246	77 (31.3)	196	88 (44.9)
<50	33	18 (54.6)	49	8 (16.3)	22	8 (36.4)	45	14 (31.1)
50–59	33	20 (60.6)	74	15 (20.3)	48	11 (22.9)	54	24 (44.4)
60–69	37	28 (75.7)	125	43 (34.4)†	118	40 (33.9)	78	42 (53.8)
≥70	7	6 (85.7)	45	12 (26.7)	58	18 (31.0)	19	8 (42.1)
Women	457	213 (46.6)*	634	187 (29.5)	450	153 (34.0)	670	224 (33.4)
<50	94	35 (37.2)	105	19 (18.1)	29	6 (20.7)	120	22 (18.3)
50–59	122	43 (35.3)	162	35 (21.6)	88	32 (36.4)	182	51 (28.0)
60–69	193	106 (54.9)†	288	93 (32.3)	215	79 (36.7)	277	110 (39.7)†
≥70	48	29 (60.4)†	91	40 (44.0)	118	36 (30.5)	91	41 (45.1)†

*$p < 0.05$ (chi-square test) vs. men in the overall population.
†$p < 0.05$ vs. the corresponding gender at <50 years by logistic regression analysis.

Table 5. Association of age, BMI and gender with prevalence of radiographic lumbar spondylosis at baseline examination.

	Radiographic LS				Multilevel radiographic LS			
	KL≥2		KL≥3		KL≥2		KL≥3	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age, years	1.08	1.07–1.10	1.08	1.06–1.09	1.08	1.07–1.10	1.1	1.07–1.12
BMI, kg/m^2	1.08	1.05–1.12	1.08	1.04–1.12	1.08	1.05–1.12	1.05	1.00–1.11
Women (vs. men)	0.36	0.27–0.47	1.99	1.44–2.78	0.36	0.28–0.48	2.27	1.42–3.79

BMI, body–mass index; LS, lumbar spondylosis; OR, odds ratio; CI, confidence interval.
Radiographic spondylosis was determined at the severest level among L1/2-L5/S1.
The odds ratios were calculated by logistic regression analysis.

Interestingly, KL≥2 LS was more prevalent in men than in women, whereas KL≥3 LS was more prevalent in women. We and others have reported that osteophytosis of the lumbar spine was more common in men than in women [12,14,23], while disc-space narrowing was more prevalent in women [14]. Based on the definition of KL grading [20], the discrepancy may be due to distinct etiologic mechanisms between osteophyte formation and disc-space narrowing. A cross-sectional study that investigated the extent, prevalence and distribution of spinal LS in women also showed that osteophytosis and disc-space narrowing were significantly correlated, but each predicted only 19% of the variation in the other [16]. Further clinical and basic research will disclose the distinct backgrounds of these two representative OA features.

We also investigated the age-specific prevalence of LS. Although KL≥2 LS tended to increase with age in men and women, significant differences were not detected in the prevalence of KL≥3 between the 40s and the 50s in men. In fact, the incident of KL≥3 was quite low in the 40s, indicating that the incidence of disc space narrowing was low during middle age.

Most previous studies regarding LS have been cross-sectional, so incidence has not been clarified. The present study was a longitudinal study that assessed incidence and natural history of LS. In this study, KL≥2 LS occurred at rates of 65.5% and 46.6% after 8-year follow-up, respectively. The only longitudinal study using KL grade reported that 45% of women deteriorated after 8.7 years follow-up [7], but deterioration was defined as an increase in KL grade at any level, which was a different definition from our study, so strict comparisons are limited. Considering the definition of KL grade, the incidence of KL≥2 LS may represent osteophytosis. We also found that the incidence of LS was higher in men than in women at all ages and increased with age after the 50s, but was not much different between the 40s and 50s in men and women. In this study, among subjects with incident KL≥2 LS, the percentage of those with KL≥3 LS was extremely high in the 70s compared with other generations. This finding may indicate that at middle age, LS progresses slowly in subjects without LS at baseline, but it progresses faster in the elderly.

This study also clarified that the incidence of KL≥3 LS was similar between men and women. Considering the definition of KL grade, the incidence of KL≥3 LS may represent the occurrence of disc space narrowing. A longitudinal study regarding disc space narrowing of the lumbar spine has been performed [15], but it focused only the progression of disease and not on its incidence. Unlike KL≥2 LS, the incidence of KL≥3 was similar in the 40s, 50s and 60s, and was higher in women than in men at age 70 years or older. When compared among generations, the incidence was similar in the 40s and 50s and increased in the 60s in men and women. In the 70s, the incidence further increased in women, but in men, was similar to the incidence in the 60s. Elderly men generally retire from their occupations around 60–70 years of age, whereas women continue to do household chores even after the age of 70, which may partly explain the increase of incidence after age 70 in women.

We also analyzed the progression of LS. The rate of progressive LS was similar in men and women (4.5% and 4.6% per year, respectively), and was not associated with age, despite the fact that the incidence of KL≥3 LS tended to increase with age. This finding may be due to the fact that the percentage of subjects with KL≥3 LS was extremely high in the 70s compared with other generations among those with incident KL≥2 LS, as mentioned above, which could indicate that in subjects without LS, the incidence of disc space narrowing was associated with age, but not in subjects with osteophytosis, especially in men.

There are several limitations to the present study. First, the study subjects may be biased as persons who received radiographs in both 1990–1992 and 1998–2000. In addition, this study investigated participants who lived independently, and not those who lived in institutional settings. Therefore, the calculated prevalence or incidence may be underestimated. Second, because the KL system emphasizes osteophytosis, it is unclear how to handle LS with disc-space narrowing but no osteophytosis. We are developing a computer-aided diagnostic program that enables measurement of major features of LS, including disc-space narrowing and osteophytosis, on plain radiographs. Furthermore, participants were atomic bomb survivors and thus not representative of the general Japanese population, although we adjusted for radiation, and there are no indications from earlier studies of this cohort that radiation affected BMD and fracture.

In summary, the present longitudinal study revealed the prevalence of radiographic KL≥2 and≥3 LS was 52.9% and 23.6%, respectively. KL≥2 LS was more prevalent in men, whereas KL≥3 LS was more prevalent in women. During the 8-year follow-up, the incidence of KL≥2 LS in men and women was

Table 6. Association of age, BMI and gender with incidence of radiographic lumbar spondylosis.

	KL≥2		KL≥3		Progressive LS		Multilevel LS	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age, years	1.05	1.03–1.07	1.05	1.04–1.07	1	0.98–1.02	1.06	1.04–1.08
BMI, kg/m^2	1.07	1.02–1.07	1.06	1.01–1.11	1	0.95–1.05	1.02	0.98–1.07
Women (vs. men)	0.37	0.23–0.58	1.09	0.80–1.51	1.08	0.76–1.52	0.5	0.35–0.71

BMI, body–mass index; LS, lumbar spondylosis; OR, odds ratio; CI, confidence interval.
Radiographic spondylosis was determined at the severest level among L1/2-L5/S1.
The odds ratios were calculated by logistic regression analysis.

65.5% and 46.6%, that of KL ≥ 3 LS was 27.3% and 29.5%, respectively. The incidence of KL ≥ 2 was higher in men than women, while, that of KL ≥ 3 was similar between men and women, indicating that different mechanisms might influence osteophytosis and disc space narrowing.

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Conflict of Interest

None.

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Associations between radiographic lumbar spinal stenosis and clinical symptoms in the general population: the Wakayama Spine Study

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SUMMARY

Objective: Many asymptomatic individuals have radiographic lumbar spinal stenosis (LSS), but the prevalence of symptoms among individuals with radiographic LSS has not yet been established. The purpose of this study was to clarify the association between radiographic LSS and clinical symptoms in the general population.

Methods: In this cross-sectional study, data from 938 participants (308 men, 630 women; mean age, 66.3 years; range, 40–93 years) were analyzed. The severity of radiographic LSS, including central stenosis, lateral stenosis, and foraminal stenosis, was assessed by mobile magnetic resonance imaging and rated qualitatively. Assessment of clinical symptoms was based on the definition of symptomatic LSS in the North American Spine Society guideline.

Results: We found that 77.9% of participants had more than moderate central stenosis and 30.4% had severe central stenosis. Logistic regression analysis after adjustment for age, sex, body mass index, and severity of radiographic LSS showed that severe central stenosis was related to clinical symptoms. However, only 17.5% of the participants with severe central stenosis were symptomatic.

Conclusion: Although radiographic LSS was common in our cohort, which resembled the general Japanese population, symptomatic persons were relatively uncommon.

Introduction

Radiographic lumbar spinal stenosis (LSS) is defined as a narrowing of the lumbar canal with encroachment of neural structures by surrounding bone and soft tissue[1]. Symptomatic LSS, which requires both the presence of clinical symptoms and radiographic LSS[2], is usually associated with impaired walking and other disabilities in the elderly[1,3] and is the most frequent indication for spinal surgery in patients older than 65 years[4]. Because of the high number of elderly persons in Japan, there is an urgent need for evidence-based data regarding radiographic LSS occurring as a result of degenerative changes. However, little information is available regarding the epidemiology of radiographic LSS. This is because previous studies on radiographic LSS have not included subjects who were part of the general population[5–7]. Furthermore, for radiographic LSS to be diagnosed, the detection of minute changes of the intervertebral discs and ligaments using a tool like magnetic resonance imaging (MRI) is essential[8,9], but to the best of our knowledge, no studies of radiographic LSS among the general population have been performed using MRI.

LSS symptoms include a range of possible clinical presentations resulting from dilatation of the intrinsic vessels of the nerve roots[10]. However, inconsistent with this observation, severe radiographic LSS is often present in asymptomatic patients[7], and little is known of the prevalence of symptoms among individuals with radiographic LSS. Previous studies have reported on the relationship between radiographic LSS and quality of life, function, and pain due to symptoms in symptomatic patients[11–14]. To the best of our knowledge, there has been no study on the association between radiographic LSS and clinical symptoms among the general population, which includes both symptomatic and asymptomatic individuals.

In this study, we aimed to determine the prevalence of radiographic LSS assessed by MRI and its association with clinical symptoms using mobile MRI in a population-based cohort.

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Methods

Participants

The present study, entitled The Wakayama Spine Study, assessed a subcohort drawn from Research on Osteoarthritis/Osteoporosis Against Disability (ROAD), which is a large-scale, prospective study of bone and joint diseases among population-based cohorts established in several communities throughout Japan. As the detailed profile of the ROAD study is described elsewhere, only a brief summary is provided here[15–18]. A database including baseline clinical and genetic information relating to 3,040 inhabitants (1,061 men, 1,979 women) with a mean age of 70.6 years (range, 23–95 years) has been created. We recruited individuals listed in resident registrations in three communities: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a coastal 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. Participants completed an interviewer-administered questionnaire that included 400 items covering lifestyle information, and they underwent anthropometric measurements and assessments of physical performance. Blood and urine samples were collected for biochemical and genetic examinations.

The ROAD study team made a second visit to the mountainous region of Hidakagawa and the coastal region of Taiji between 2008 and 2010. Of the inhabitants who participated in this second visit, 1,063 volunteers were recruited for MRI. Fifty-two of these declined to attend the examination, and the remaining 1,011 were registered in the Wakayama Spine Study. All participants provided their written, informed consent for the MRI examination. Participants who had sensitive implanted devices (such as a pacemaker) or other disqualifiers were excluded. In total, 977 participants underwent lumbar spine MRI. Ten participants who had undergone a previous lumbar operation for LSS were excluded, and 29 participants who were younger than 40 years were excluded because LSS is a degenerative disease. Thus, MRI results were available for 938 participants (308 men and 630 women) with an age range of 40–93 years (mean, 68.3 years for men and 66.9 years for women).

Similar to the baseline study, the second ROAD study included an interviewer-administered questionnaire that included 400 items that covered lifestyle information such as smoking habits, alcohol consumption, family history, past history, physical activity, reproductive variables, and health-related quality of life. Anthropometric measurements included height, weight, bilateral grip strength, and body mass index (BMI) (kg/m^2). Co-morbidities were defined according to blood data (diabetes: HbA1c $> 6.5\%$[19], hyperuricemia: uric acid > 7.0 mg/dL[20], hyperlipidemia: high-density lipoprotein cholesterol < 40 mg/dL[21]). The ankle-brachial index (ABI) of all participants was measured using PWV/ABI (OMRON Co., Kyoto, Japan).

MRI

All participants underwent total spinal MRI with a mobile MRI unit (Excelart 1.5 T; Toshiba, Tokyo, Japan) on the same day as the examination. MRI exclusion criteria included the presence of a cardiac pacemaker, claustrophobia, or other reasons. The participants were supine during the MRI, and those with rounded backs used triangular pillows under their head and knees. The imaging protocol included sagittal T2-weighted fast spin echo (FSE) (repetition time [TR]: 4,000 ms/echo, echo time [TE]: 120 ms, field of view [FOV]: 300 mm × 320 mm) and axial T2-weighted FSE (TR: 4,000 ms/echo, TE: 120 ms, FOV: 180 mm × 180 mm). Sagittal images were taken of the entire spine, but axial images were taken at each lumbar intervertebral level (L1/2–L5/S1) parallel to the vertebral endplates.

Qualitative ratings

The severity of radiographic LSS was qualitatively assessed after all examinations were completed. An experienced orthopedic surgeon (YI) without knowledge of the participants' symptom status examined the images, which were provided on films. The features assessed included the severity of central, lateral recess, and foraminal stenosis, rated on a four-grade scale. We used Fardon and Millette's[22] definition of lateral recess: a recess extending from the medial edge of the facet to the edge of the neuroforamen. We also applied the classification included in a general guideline[2] in which mild stenosis was defined as narrowing of one-third of the normal area or less, moderate stenosis as narrowing of between one- and two-thirds, and severe stenosis as narrowing of more than two-thirds of the area. Central stenosis and lateral recess stenosis were rated on the axial images and foraminal stenosis on the sagittal images. For lateral and foraminal stenosis, the rating for the side with the worst score was used. To evaluate the intraobserver variability of the severity rating, 50 randomly selected lumbar MRI films were scored by the same observer more than 1 month after the first reading. Fifty other lumbar MRI films were also scored by two experienced orthopedic surgeons (YI & KN) to determine the interobserver variability. The intraobserver variabilities in severity rating were confirmed by kappa analysis to be sufficient for the assessment of central, lateral, and foraminal stenosis (0.82, 0.71, and 0.66, respectively); interobserver variability was also sufficient (0.77, 0.66, and 0.66, respectively).

Assessment of clinical symptoms

An experienced orthopedic surgeon (YI) took the medical history and performed the physical examination of all the participants. The history included information about the presence of lower back pain, buttock pain, and leg pain; areas of pain or other discomfort; the presence of intermittent claudication (IC) and its distance; and items on a modified Zurich Claudication Questionnaire[23] (except six items about satisfaction and a history of lumbar surgery for symptomatic LSS). Physical examination included assessments to determine whether any symptoms could be induced by lumbar extension or were improved or induced by lumbar flexion, floor finger distance (cm), and peripheral circulation (good or poor); a straight-leg raising test; manual muscle testing of both the upper and lower extremities; tendon reflex testing for both the upper and lower extremities; and Babinski reflex testing. In addition, an MRI study of the entire spine was performed for all participants on the same day as the physical examination.

Assessment of clinical symptoms in the present study was based on the LSS definition in the North American Spine Society (NASS) guideline[24] and required one or more of the following symptoms: pain, numbness and neurological deficits in the lower extremities and buttocks, and bladder/bowel dysfunction. In addition, the above symptoms were required to be induced or exacerbated by walking or prolonged standing and relieved by lumbar flexion, sitting, and recumbency.

Statistical analysis

All statistical analyses were performed using JMP, version 8 (SAS Institute Japan; Tokyo, Japan). Differences between men and women in age, height, weight, and BMI were examined using non-paired Student's *t* test., co-morbidities, and clinical symptoms were compared between men and women with the chi-square test. The chi-square test was also used to determine the association between radiographic LSS and age stratum. Logistic regression analysis was performed stratified for sex to determine the effect of age and BMI

on severe stenosis of all locations or the severest stenosis in each area, with the latter as an objective variable and age and BMI as explanatory factors. A further logistic regression analysis was performed stratified for sex to determine the effect of age, BMI, and each level of severity of central stenosis with clinical symptoms, using radiographic LSS as an objective variable and age, BMI, and each severity level as explanatory factors. We constructed a set of two dummy variables defining the three different central stenosis groups (none/mild, moderate, and severe).

Results

Table I summarizes characteristics of the 938 participants (308 men and 630 women; mean age 67.3 years, range 40–93 years), including age and anthropometric measurements. Two-thirds of them were women. Mean age was not significantly different between men and women. BMI was significantly lower in women than in men.

For all locations except central L1/2 and L2/3, several MRIs were found to be inadequate for interpretation; in particular, the sample for qualitative analysis of foraminal L1/2 was reduced to 907 (Table II). Regarding both central and lateral canal stenosis, the prevalence of severe stenosis was highest at L4/5, followed by L3/4. One-third of the participants had severe canal stenosis of at least one level. On the other hand, the distribution of the prevalence of severe foraminal stenosis was entirely different from that of central and lateral severe stenosis. The level with the highest prevalence of severe foraminal stenosis was L5/S1, followed by L4/5. There were few participants with more than moderate stenosis at the upper levels of the foramen. Concerning severe stenosis in all locations, multiple logistic regression analysis after adjustment for age and BMI revealed that more men had severe stenosis at lateral L2/3, L3/4, and L4/5 than women (odds ratios [ORs] and 95% confidence intervals [CIs] for lateral stenosis were 2.05, 1.13–3.73 at L2/3; 1.95, 1.34–2.86 at L3/4; and 1.52, 1.11–2.08 at L4/5). To identify factors related to the severest stenosis at each location, we performed a further multiple logistic regression analysis with age, BMI, and sex as explanatory variables. Age was significantly associated with severe stenosis at all locations for both sexes (ORs and 95% CIs were 1.06, 1.04–1.07 for central stenosis; 1.09, 1.07–1.10 for lateral stenosis; and 1.11, 1.08–1.15 for foraminal stenosis). BMI was also significantly associated with severe central stenosis in the overall cohort and in men, but not in women (overall: 1.06, 1.02–1.10; men: 1.08, 1.00–1.17; women: 1.05, 0.99–1.10). There was no significant difference in the prevalence of central stenosis of more than moderate severity between agricultural/forestry/fishery workers or not ($P = 0.60$). There was also no significant difference in radiographic LSS between persons with diabetes, hyperuricemia, and hyperlipidemia or not, each (Diabetes: $P = 0.21$, hyperuricemia: $P = 0.65$, hyperlipidemia: $P = 0.71$).

Table I
Characteristics of participants

	Total	Men	Women
No. of participants	**938**	**308**	**630**
Age group (years)			
<49	96	26	70
50–59	175	59	116
60–69	222	65	157
70–79	258	87	171
≧80	187	71	116
Demographic characteristics			
Age, years	67.3 ± 12.4	68.3 ± 12.5	66.9 ± 12.3
Height, cm	155.7 ± 9.3	164.4 ± 6.9**	151.4 ± 7.1
Weight, kg	56.7 ± 11.4	64.3 ± 11.3**	53.0 ± 9.4
BMI, kg/m^2	23.3 ± 3.6	23.7 ± 3.3*	23.1 ± 3.6
Job titles, no.			
Clerical workers/technical experts	197	79	118
Agricultural/forestry/fishery workers	105	62	43
Factory/construction workers	48	23	25
Others	588	144	444
Co-morbidities, no.			
Diabetes	48	23*	25
Hyperuricaemia	71	54**	17
Hyperlipidemia	41	30**	11

A non-paired t-test was used to determine differences in demographic characteristics and measurements of physical performance between men and women. Values are the means ± standard deviation. *$P < 0.05$, **$P < 0.01$.

Fig. 1 shows the prevalence of moderate and severe radiographic LSS for the severest stenosis identified in each area and classified by age and sex. Both central and lateral stenosis of more than moderate severity were quite common among the elderly, but foraminal stenosis of more than moderate severity was less common. The prevalence of severe stenosis at each location was significantly higher with increasing age stratum in both sexes (central, men: $P = 0.008$; central, women: $P < 0.0001$; lateral, both: $P < 0.0001$; foraminal, both: $P < 0.0001$ [all by chi-square test]).

There were 105 individuals with clinical symptoms (men: 35, women: 70). There was no significant difference between sexes in the prevalence of clinical symptoms ($P = 0.91$). Fifty-four of the 105 participants identified as having clinical symptoms had IC. Five of these 54 participants presented with an ABI <0.9. However, these five participants also had symptomatic LSS, and their leg symptoms were dependent on position. These five cases were unspecified IC, caused by both neurogenic and vascular claudication. We used cases of central stenosis to clarify the association between radiographic LSS and clinical symptoms. The prevalence of clinical symptoms significantly increased with increasing severity of central stenosis, for both sexes, according to chi-square test (men: $P = 0.009$; women: $P = 0.004$). Furthermore, to clarify the relationship between individuals with clinical symptoms and each grade of severity, we performed a logistic regression analysis to estimate the OR and 95% CI after adjustment for age, BMI, sex, and severity of radiographic LSS, and we constructed a set of two dummy variables defining the three central stenosis groups (none/mild, moderate, and severe). Severe central stenosis was confirmed to be related to symptomatic individuals, but moderate stenosis was not (men, severe vs none/mild: 4.42, 1.44–17.0; men, moderate vs none/mild: 1.53, 0.49–5.86; women, severe vs none/mild: 2.50, 1.44–17.0; women, moderate vs none/mild: 1.83, 0.82–4.66). Among symptomatic persons ($n = 105$), there were 16 taking painkillers, seven taking trigger injections, and 13 in rehabilitation. We added these treatment statuses to the multivariate model and logistic regression analysis for the association between radiographic LSS and clinical symptoms, but the result was unchanged (Table III).

Discussion

In this study, we evaluated the prevalence of radiographic LSS assessed by MRI and its association with clinical symptoms in the general population. The intervertebral level with the highest prevalence of both severe central stenosis and severe lateral stenosis was L4/5; the prevalence of severe foraminal stenosis was greatest at L5/S. The prevalence of moderate or severe central stenosis was 64.0% in patients in their 50s and 93.1% in those in their 80s. There was a significant association between the severity of central stenosis and the presence of clinical symptoms. Of those with severe central stenosis, 17.5% had clinical symptoms. In addition, logistic regression after adjustment for age, BMI, sex, and severity of radiographic LSS revealed that severe central stenosis was related to clinical symptoms.

The most frequent intervertebral level of severe stenosis was consistent with the intervertebral location of severe stenosis that is most frequently seen in clinical settings. However, to the best of our

Table II
Prevalence of central, lateral, and foraminal stenosis

	L1/2	L2/3	L3/4	L4/5	L5/S1	Severest
Central stenosis						
No. of total†	938	938	937	937	936	938
None	112 (11.9)	57 (6.1)	36 (3.8)	31 (3.3)	163 (17.4)	13 (1.4)
Mild	606 (64.6)	435 (46.4)	305 (32.6)	276 (29.5)	580 (62.0)	194 (20.7)
Moderate	205 (21.9)	389 (41.5)	445 (47.5)	406 (43.3)	161 (17.2)	446 (47.5)
Severe	15 (1.6)	57 (6.1)	151 (16.1)	224 (23.9)	32 (3.4)	285 (30.4)
Lateral stenosis*						
No. of total†	933	933	929	931	925	938
None	439 (47.1)	199 (21.3)	80 (8.6)	29 (3.1)	333 (36.0)	11 (1.2)
Mild	393 (42.1)	454 (48.7)	347 (37.4)	251 (27.0)	414 (44.8)	205 (21.9)
Moderate	90 (9.6)	231 (24.8)	359 (38.6)	368 (39.5)	126 (13.6)	380 (40.5)
Severe	11 (1.2)	49 (5.0)	143 (15.4)	283 (30.4)	52 (5.6)	342 (36.5)
Foraminal stenosis*						
No. of total†	907	915	930	930	926	937
None	676 (74.5)	535 (58.5)	316 (34.0)	154 (16.6)	265 (28.6)	84 (9.0)
Mild	210 (23.2)	335 (36.6)	513 (55.2)	524 (56.3)	421 (45.5)	474 (50.6)
Moderate	18 (2.0)	42 (4.6)	90 (9.7)	220 (23.7)	202 (21.8)	313 (33.4)
Severe	3 (0.3)	3 (0.3)	11 (1.2)	32 (3.4)	38 (4.1)	66 (7.0)

Number (%). Percentage shows the prevalence at the same location.
* The rating of the most severely affected side was used.
† Participants were omitted if interpretation of their MRI was difficult because of poor image quality at each level.

knowledge, there has been no study on the prevalence of radiographic LSS assessed by MRI among the general population. We found a differential distribution in the prevalence of canal stenosis (including central and lateral stenosis) and foraminal stenosis, which may be partly explained by the difference in anatomy between these two locations. Canal stenosis consists of a bulging disk, thickening of the ligamentum flavum, and hypertrophy of the facet joints, whereas loss of disk height, disk protrusion, and facet joint osteoarthritis (OA) lead to foraminal stenosis[1]. The difference in anatomy between canal stenosis and foraminal stenosis (in terms of compression of the nerve root) may be related to the differential distribution of prevalence.

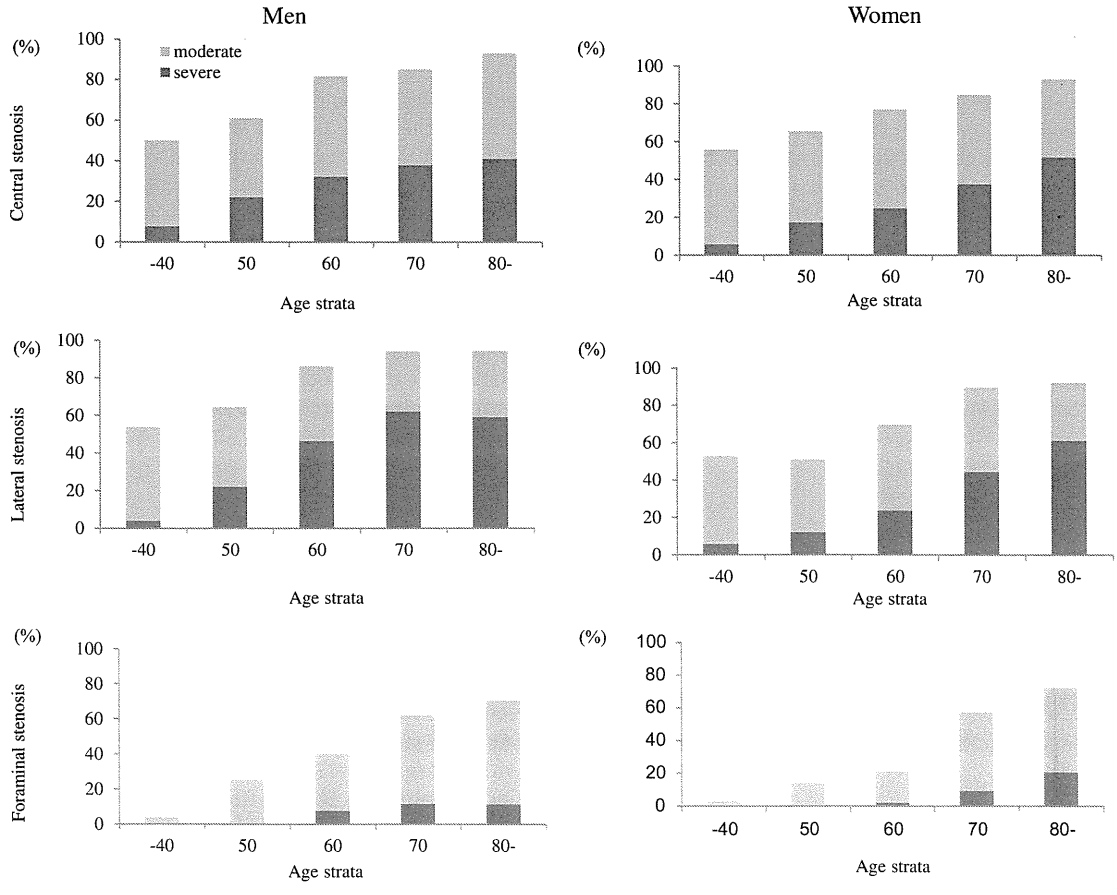

Fig. 1. Prevalence of severe central stenosis, severe lateral stenosis, and compressing foraminal stenosis classified by age and sex for 938 participants from a community cohort in Japan.

Table III
The association of radiographic LSS with clinical symptoms

	None/Mild	Moderate	Severe	Total
Men				
Radiographic LSS*	66	144	98	308
Clinical symptoms	4 (6.1)	12 (8.3)	19 (19.4)	35 (11.4)
Women				
Radiographic LSS*	141	302	187	630
Clinical symptoms	7 (5.0)	32 (10.6)	31 (16.6)	70 (11.1)
Total				
Radiographic LSS*	207	446	285	938
Clinical symptoms	11 (5.3)	44 (9.9)	50 (17.5)	105 (11.2)

Number (%).
* Radiographic LSS means central stenosis.

Many participants had radiographic LSS, although most were asymptomatic: 77.9% had more than moderate central stenosis and about 30.4% had severe central stenosis. Boden *et al.*[7] reported that 21% of 14 asymptomatic volunteers who were over 60 years of age had spinal stenosis, but their criteria for spinal stenosis (loss of epidural fat with compression of neural tissue within the canal) were different from ours. To our best knowledge, there is no report on the prevalence of radiographic LSS using MRI in a large population-based cohort. These findings indicate that radiographic LSS is quite common among the elderly.

We found that severe central stenosis was significantly associated with clinical symptoms, but only 17.5% of participants with severe central stenosis were symptomatic. Previous studies of the relationship between disabilities and radiographic LSS have yielded varied results[11–14]. One study with a 12-year follow-up[11] period showed a clear association between Oswestry Disability Index (ODI) and degree of stenosis. The subjects were assessed by myelography, but only 56.0% (75/134) were followed up and the ODI was determined by telephone interview. Ogikubo *et al.*[12] reported an association between the cross-sectional area of the lumbar spine and walking distance and pain among patients who subsequently underwent surgery. On the other hand, Amundsen *et al.*[13] found no relationship between the degree of stenosis measured by myelography and computed tomography (CT) and clinical symptoms in 100 symptomatic patients. Lohman *et al.*[14] also found no relationship between cross-sectional areas of the canal measured by CT and clinical symptoms in 117 patients who were referred from a primary health service because of chronic lower back pain and clinical suspicion of spinal stenosis. Jenson *et al.*[25] noted that abnormal MRI findings in individuals with lower back pain may frequently be coincidental. Thus, although one would expect that associations between radiographic LSS and symptoms or other disabilities due to LSS would be related to the degree of stenosis, previous studies have yielded varied results. In this study, severe central stenosis was related to clinical symptoms, but less than 20% of those with severe central stenosis were symptomatic. It thus seems to be impossible to clarify the cause of clinical symptoms by imaging alone; an expert clinician's opinion of both clinical assessment and imaging studies is essential for interventions such as surgery in symptomatic individuals.

There were several limitations to the present study. First, our participants may not represent the general population, as they were recruited from only two areas. However, anthropometric measurements were compared between the participants and the general Japanese population, and no significant differences in BMI were found (men: 23.71 [3.41] vs 23.95 [2.64], women: 23.06 [3.42] vs 23.50 [3.69])[26]. In addition, the proportions of current smokers and current drinkers (those who regularly smoked or drank more than one drink per month) in the general Japanese population were compared with those in the study population. The proportions of current smokers and drinkers (men) and current drinkers (women) were significantly higher in the general Japanese population than in the study population (smokers, men: 32.6% of the Japanese population vs 25.2% of the study participants; smokers, women: 4.9% of the Japanese population vs 4.1% of the study participants; drinkers, men: 73.9% of the Japanese population vs 56.8% of the study participants; drinkers, women: 28.1% of the Japanese population vs 18.8% of the study participants). This suggests the study participants (both men and women) likely had healthier lifestyles than the general Japanese population. Second, this was a cross-sectional study, so it does not provide conclusive evidence of any causal relationship between radiographic LSS and clinical symptoms. Third, this study only represented the Japanese population, and the prevalence in other countries may be quite different. Fourth, this study investigated elderly participants who lived independently rather than those who lived in institutional settings, so the calculated prevalence may be an underestimate. Fifth, we excluded 10 subjects who had already had surgery for LSS, and this could have influenced the results. However, LSS surgery is a major intervention that interferes with radiographic assessment of LSS, because it involves decompression and instrumentation that could produce artifacts. Finally, concerning facet OA and disc degeneration, which are important factors for radiographic LSS, we reported the prevalence of radiographic lumbar spondylosis assessed by Kellgren/Lawrence grading elsewhere[15,17]. We did not assess facet OA in this MRI study. We have been assessing disc degeneration in this cohort and will have results to report about this important investigation in the near future.

Nevertheless, this is the first trial to evaluate the prevalence of radiographic LSS and its association with clinical symptoms in the general population using MRI. In addition, the Wakayama Spine Study is a longitudinal survey, so future results will help to elucidate any causal relationships.

In conclusion, the present study evaluated the prevalence of radiographic LSS and clarified its association with clinical symptoms in a population-based cohort. Many participants had radiographic LSS, but few had clinical symptoms. The prevalence of clinical symptoms increased with increasing severity of radiographic LSS.

Contributors

All authors worked collectively to develop the protocols and methods described in this paper. YI, SM, KN, NO, HO, TA, and NY were the principal investigators responsible for the fieldwork in the Wakayama Spine Study. YI and SM performed the statistical analysis. YI, HY, SM, KN, HH, HO, TA, MY, and NY contributed to the analysis and interpretation of results. YI wrote the report. All authors read and approved the final report.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Role of the funding source

The study sponsors played no role in the study design, the collection, analysis, and interpretation of data, writing of the report, or the decision to submit the paper for publication. The corresponding author had full access to all the data and had the final decision to submit for publication.

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