J Orthop Sci (2012) 17:526–531
DOI 10.1007/s00776-012-0253-5

ORIGINAL ARTICLE

Radiographic features and risk of curve progression of de-novo degenerative lumbar scoliosis in the elderly: a 15-year follow-up study in a community-based cohort

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Received: 19 January 2012 / Accepted: 28 May 2012 / Published online: 4 July 2012

Abstract

Background Little information is available on the prevalence, incidence, and risk factors associated with curve progression in de-novo degenerative lumbar scoliosis (DNDLS) in the general population. Development of treatment guidelines requires further knowledge about the etiology and natural history of DNDLS in the elderly.

Methods To identify the cumulative incidence and radiographic features of DNDLS in the elderly, the authors reanalyzed the results of lumbar radiographic examinations from the Miyama study, which was originally conducted in a Japanese rural community to determine the prevalence of vertebral fractures in Japanese people. DNDLS was defined as a coronal curvature greater than 10° in the Cobb angle in the second survey and progression of greater than 5° compared with curve magnitude in the initial survey. The radiological features of the new curves were documented. The DNDLS group was recruited to compare the risk of curve progression with that in a control group of participants who had no scoliosis during a 15-year follow-up. Ten radiographic features were measured for statistical analysis to determine the prognostic factors of curve progression.

Results The cumulative incidence of DNDLS was 33/194 (17.0 %) in this cohort. There was a tendency for female predominance and frequency increased with age. However, the severity of these curves was relatively low and no curves developed a Cobb angle of greater than 30°, with most in the range 10°–20°. The 2 groups differed significantly in lateral spondylolisthesis and vertebral rotation only at the L3 level.

Conclusions The radiographic features of DNDLS revealed mild scoliosis with minimal rotatory deformity. Spinal decompensation by the upper lumbar segments of the asymmetric anatomical deformity in the lower lumbar segments may induce de-novo lumbar scoliosis. Rotatory deformity and lateral spondylolisthesis of the L3 vertebra may be a prognostic factor for DNDLS in the elderly.

Introduction

Degenerative lumbar scoliosis (DLS) is one of the most prevalent disorders in the elderly population. DLS can become a leading cause of low back pain, radicular leg symptoms, and neurogenic claudication [1–3]. Increasing life expectancy and more active lifestyles among the elderly are likely to result in an increase in the number of elderly people requiring treatment for this disease, making DLS a possible major public health problem in an aging society.

Degenerative lumbar scoliosis is a multi-disease complex in the elderly involving lumbar progressive scoliosis, with or without a previous history of childhood scoliosis. Although the 2 forms of scoliosis are distinct clinical entities, determination of whether or not the curve represents a new scoliosis in an elderly person is difficult [4–7]. Hence, previous studies of DLS have been limited to curve progression in lumbar scoliosis detected in childhood after

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skeletal maturity. Lumbar curves with a Cobb angle of more than 30° have a high likelihood of progression even after skeletal maturity; surgery is usually recommended for such curves [8, 9].

In contrast, little information is available on the prevalence, incidence, and risk factors associated with curve progression in de-novo DLS (DNDLS) in the elderly. One cannot study disease prevention and treatment without knowing the disease's natural history. Therefore, the evidence available from the epidemiological database for this disease is crucial to discussions about the treatment of DNDLS in the elderly.

We conducted this study to assess results from lumbar radiographic examinations in a 15-year community-based cohort study to clarify the etiology and natural history of DNDLS in the elderly. The purpose of this study was to identify the radiographic features of DNDLS in the elderly and the risk factors for curve progression.

Materials and methods

The study sample comprised participants from the Miyama study who had lumbar radiographic examinations performed in 1990 and 2005. That population-based epidemiological study began in 1990 and was conducted in Miyama, a village located in a mountainous area in Wakayama Prefecture, Japan. A detailed profile of the Miyama cohort is available elsewhere [10–12], and is briefly summarized here. A list of all of the inhabitants born in this village between 1910 and 1949 (40–79 years old) was compiled from the register of residents at the end of 1989. A cohort of 1543 inhabitants (716 men, 827 women) was identified, all of whom completed a self-administered questionnaire covering daily activity such as dietary habits, smoking habits, alcohol consumption, and physical exercise (125 items). From the above cohort, a sub-cohort was recruited to examine prevention of bone and joint disorders. This sub-cohort consisted of 400 participants, divided into 4 groups of 50 men and 50 women each, and stratified by decade of birth (1910–1919, 1920–1929, 1930–1939, or 1940–1949) (Table 1). The sub-cohort was confirmed not to differ from the whole cohort with regard to the distribution of lifestyle details such as smoking, alcohol consumption, sleeping hours, exercise, walking, dietary habits, and stress, as measured by the initial questionnaire. An interviewer administered a second questionnaire, covering items of past history, family history, calcium intake, dietary habits, physical exercise, occupational activity, sun exposure, and reproductive variables in women, to these 400 participants. In addition to the interviewer-administered questionnaire, medical examinations and physical measurements were also performed for these participants. Radiographic examination of the spine was performed for all participants in 1990. Standing anteroposterior and lateral images of the thoracolumbar vertebrae, Th5-L5, were used for diagnosis (initial X-ray survey).

After 15 years, the second X-ray survey of the lumbar spine of the participants was repeated as part of the Research on Osteoarthritis/osteoporosis Against Disability (ROAD) Study. The ROAD Study was a nationwide, prospective study of bone and joint diseases (with osteoarthritis and osteoporosis as the representative bone and joint diseases) in population-based cohorts established in several communities in Japan, including the Miyama cohort. A detailed profile of the ROAD Study has already been described elsewhere [13–16]. All participants provided written informed consent, and the study was conducted with the approval of the appropriate ethics committees.

In 2005, participants completed an interviewer-administered 400-item questionnaire, including lifestyle information, and also underwent anthropometric measurements and physical performance and radiographic examinations. The lumbar radiographic examinations in the second survey were also performed in a standing position. Among the participants of the ROAD Study, 81 men and 119 women who had the lumbar radiographic examinations in 1990 were identified, and their X-rays were used for evaluation in this study.

We defined DNDLS as a coronal curvature greater than 10° in the Cobb angle in the second survey and progression of greater than 5°, compared to the curve magnitude

Table 1 Number of study participants according to sex and age

Age	Male			Female		
	Inhabitants	Participants		Inhabitants	Participants	
		1st survey	2nd survey		1st survey	2nd survey
Total	716	200	81	827	200	119
40–49	130	50	25	135	50	34
50–59	252	50	30	254	50	45
60–69	224	50	23	276	50	34
70–79	110	50	3	162	50	6

measured in the initial survey. The curve magnitude, convexity of the curve, location of the apex, and rotation angle of the apex were documented by use of the images from the second survey. The DNDLS group (S-group) was recruited to compare the risk of curve progression with that for a control group (C-group) of participants who did not have scoliosis in either examination. In addition to the Cobb measurement of the main lumbar curve, the following radiographic features were measured by use of the images from the initial survey:

1 tilting angle of each vertebra (angle between the tangential line of the superior endplate of each vertebra and a horizontal line);
2 intervertebral disc angle (between the tangential lines of the inferior endplate of a vertebra and the superior endplate of the next);
3 lateral spondylolisthesis (the horizontal distance between 2 vertical lines which were drawn from the waist to the adjacent vertebra; more than 3 mm was accepted as being a significant difference);
4 axial rotation of each vertebra, based on Pedriolle [17] (more than 5° was accepted as significant);
5 lateral osteophyte differences for each intervertebral disc space using the method of Kobayashi [18];
6 coronal displacement of L1 (distance between the vertical line drawn from the center of the vertebral body of L1 and the center sacral vertical line);
7 sagittal displacement of L1, using the method of Kawakami [19] (distance between the vertical lines drawn from the center of the vertebral body of L1 and the superior-posterior corner of S1);
8 lumbar lordosis (distance from the upper endplate of L1 to the lower endplate of L5); and
9 pelvic tilt (the angle between the horizontal reference line and the intercrestal line; more than 2° was accepted as significant).

The same physician examined all radiographic features to prevent observer variability. To evaluate the intra-observer variability for this study, 100 randomly selected radiographs were measured by the same observer more than 1 month after the first reading. The intra-observer variability was evaluated by kappa analysis. As a result, the intra-observer variability was found to be sufficient for assessment (0.74).

The chi-squared test was used to examine differences between the prevalence of lateral spondylolisthesis, rotation deformities, and pelvic tilt abnormalities in the S and C-groups. To compare the differences in the other radiographic features between the 2 groups, non-paired *t* tests were used for statistical analysis. The level of significance was set at $p < 0.05$. The results are presented as mean ± standard error.

Results

Twelve participants had scoliosis of greater than 10° in the Cobb angle at the time of the initial survey in 1990. The prevalence of DLS in this cohort was 12/400 (3.0 %) at the beginning of the follow-up. Analysis of difference by sex indicated that prevalence was 1.0 in men and 5 % in women. All of the scoliosis curvatures identified were low-grade with the Cobb angle ranging between 10° and 12°, with minimal rotatory deformity. Six of the 12 participants with scoliosis participated in the second survey. Three curves were unchanged; the others had retrograded. When estimating the cumulative incidence of DNDLS, these 6 subjects were excluded from the study, leaving the X-ray films of 194 subjects (81 men, 113 women, with an average age of 69.8 years at the time of the initial survey) for radiographic evaluation. To avoid the effects of drop-out, cumulative incidence in this study was calculated by using the number who completed both of the radiographic examinations as the denominator. Thirty-three of the 194 subjects who had no scoliosis (Cobb angle <10°) in 1990 had DNDLS in 2005. The overall cumulative incidence of DNDLS in this cohort was, therefore, 33/194 (17.0 %).

Ten of the 81 men (12.3 %) and 23 of the 113 women (20.4 %) developed DNDLS. The male-to-female cumulative incidence ratio was approximately 1:2. The occurrence of DNDLS tended to increase with age. The cumulative incidence in each age stratum was: 4/57 (7.0 %) in the 40–49 year-group, 9/74 (12.2 %) in the 50–59 year-group, 15/55 (27.3 %) in the 60–69 year-group, and 5/8 (62.5 %) in the 70–79 year-group (Table 2).

The radiographic features of DNDLS in the study participants are summarized in Table 3. None of the scoliotic curvatures exceeded 30° in the Cobb angle, which ranged from 10° to 26°; the mean Cobb angle of DNDLS was 13.5 ± 4.4°. The convexity of scoliosis was to the left in 24 patients and to the right in 9 patients. The apexes were usually located at L3 or L4. None of the rotation angles exceeded 15° when measured by use of the Perdriolle method; the rotation angles ranged from 0–15°, and the mean rotation angle of DNDLS was 5.2° ± 3.3°.

The tilting angle was significantly larger in the S-group than in the C-group, at all levels. The intervertebral disc angles and lateral osteophyte differences were significantly larger in the S-group than in the C-group in the upper lumbar segments only, and these features did not differ between groups in the L4–5 and L5–S1 segments. The 2 groups differed significantly in lateral spondylolisthesis and vertebral rotation only at the L3 level. Pelvic tilt, lumbar scoliotic Cobb angle, coronal and sagittal spinal balance, and lumbar lordosis did not differ significantly between the S and C-groups (Table 4).

Table 2 Incidence of de-novo degenerative lumbar scoliosis in participants, grouped by sex and age

Age at 1st survey	Male	Female	Total
40–49	3/25 (12.0)	1/32 (3.1)	4/57 (7.0)
50–59	2/30 (6.7)	7/43 (16.3)	9/73 (12.3)
60–69	4/23 (17.4)	11/33 (33.3)	15/56 (26.8)
70–79	1/3 (33.3)	4/5 (80.0)	5/8 (62.5)
Total	10/81 (12.3)	23/113 (20.4)	33/194 (17.0)

Percentage incidence are given in parenthesis

Table 3 Radiographic features of de-novo degenerative lumbar scoliosis

Case	Age at the 2nd survey	Gender	Cobb angle at the 2nd survey	Convexity of the curve	Location of the apex	Rotation angle of the apex
1	61	M	26	L	L3	5
2	77	F	12	L	L3	5
3	72	F	10	L	L3	5
4	71	F	12	L	L2	5
5	57	F	12	R	L3	15
6	85	F	10	L	L3	0
7	79	F	10	L	L3	5
8	83	F	17	L	L3	5
9	82	F	24	L	L3	5
10	67	M	10	L	L3	0
11	76	M	21	L	L2	10
12	76	F	10	R	L4	5
13	57	M	10	R	L3	0
14	75	M	18	L	L3	5
15	67	F	15	L	L3	10
16	86	F	19	R	L4	0
17	71	F	10	L	L3	5
18	85	M	10	R	L3	5
19	81	F	14	L	L3	5
20	70	F	11	R	L3	5
21	79	F	12	L	L3	5
22	77	M	11	L	L4	0
23	81	F	13	R	L3	15
24	90	F	13	L	L3	5
25	78	F	12	L	L3	5
26	73	F	11	L	L2	15
27	82	F	12	R	L3	5
28	89	F	18	L	L3	5
29	72	M	10	L	L3	5
30	76	M	18	L	L3	5
31	71	F	10	L	L3	5
32	69	F	13	R	L3	5
33	63	M	12	L	L3	5

Table 4 Results from measurement of radiographic features comparing the S-group (subjects who developed de-novo degenerative lumbar scoliosis during the follow-up period) and the C-group (the subjects who did not develop scoliosis)

	S-group ($n = 33$)	C-group ($n = 161$)	P value
Tilting angle			
L1	3.06 ± 2.12	1.19 ± 1.45	<0.01
L2	2.42 ± 2.03	1.13 ± 1.43	<0.01
L3	2.00 ± 1.82	1.23 ± 1.46	<0.01
L4	3.15 ± 3.38	1.20 ± 1.38	<0.01
L5	2.33 ± 1.81	0.98 ± 1.29	<0.01
Intervertebral disc angle			
L1/2	1.03 ± 1.56	0.3 ± 0.67	<0.01
L2/3	1.56 ± 1.88	0.48 ± 0.83	<0.01
L3/4	1.34 ± 1.33	0.71 ± 1.13	<0.01
L4/5	0.78 ± 1.16	0.69 ± 1.17	0.69
L5/S	0.13 ± 0.49	0.30 ± 0.85	0.87
Lateral spondylolisthesis (case)			
L1	0	0	–
L2	0	0	–
L3	5	1	<0.01
L4	0	2	0.52
L5	0	0	–
Axial rotation (case)			
L1	2	5	0.39
L2	5	11	0.12
L3	12	8	<0.01
L4	1	1	0.23
L5	0	2	0.52
Lateral osteophyte difference			
L1/2	1.03 ± 1.56	0.3 ± 0.67	<0.01
L2/3	1.56 ± 1.88	0.48 ± 0.83	<0.01
L3/4	1.34 ± 1.33	0.71 ± 1.13	<0.01
L4/5	0.78 ± 1.16	0.69 ± 1.17	0.69
L5/S	0.13 ± 0.49	0.30 ± 0.85	0.87
Cobb angle	3.66 ± 2.53	1.79 ± 2.03	<0.01
Pelvic tilt (case)	12	33	0.07
Coronal spinal balance	4.03 ± 3.54	3.42 ± 3.50	0.36
Sagittal spinal balance	9.0 ± 16.4	10.1 ± 15.4	0.71
Lumbar lordosis	26.7 ± 14.0	27.1 ± 10.6	0.85

Discussion

A 15-year follow-up study of lumbar radiographic examinations was conducted in a community-based cohort of 194 adults, 40 years of age or older, at the beginning of the study. The cumulative incidence of DNDLS over the 15-year study period was 33/194 (17.0 %) in this cohort. Compared with childhood scoliosis, which affects approximately 2 % of the population, DNDLS seems to be more common in the elderly population. There was a tendency for female predominance, and the frequency of the disorder increased with age. However, the severity of these curves was relatively low, and none of the curves developed a Cobb angle of greater than 30°, with most in the range 10°–20°.

There are few epidemiological data on DNDLS in the elderly. To our knowledge, only 2 longitudinal studies have been published describing community-based cohorts. Robin et al. reported that 55 of 554 subjects (10 %) developed a spinal deformity during the 7–13-year follow-up. None of the reported curves exceeded 20° for the Cobb angle and most were in the 1°–9° range [20]. Kobayashi et al. reported that 22 of 60 subjects without any scoliosis (36.6 %) developed de-novo scoliosis curves of 10° or more during the follow-up period, with a mean of 12.0 years. None of the scoliosis curvatures exceeded 20° in the Cobb angle, which ranged from 10° to 18°, and the mean Cobb angle for de-novo scoliosis was 13.0° [18]. These data indicate that incidence varies substantially, from 10 to 36.6 %, depending on the study sample. The radiographic features of DNDLS reported in these studies are similar to those reported in our study. Taken together, these studies show that DNDLS is a common condition that is characterized by low-grade curve magnitude and slow progression in the elderly and that the prognosis of the clinical course of DNDLS seems to be benign.

Berner and Ehni [2] reported that asymmetric degeneration of the intervertebral space was the key risk factor for curve progression. Kobayashi et al. also suggested that asymmetric intervertebral disc degeneration leads to the development of scoliosis [18]. By contrast, in our study the presence of an intervertebral disc angle, which indicates asymmetric intervertebral disc degeneration, occurred often in the lower lumbar segments in the S-group, but the disc angle at L4–5 and L5–S1 did not differ significantly between the S and C-groups. This study did not identify asymmetric intervertebral disc degeneration in the lower lumbar segments as a key risk factor for curve progression.

Some authors have proposed that rotatory subluxation is the initial event in the induction of de-novo scoliosis [6, 21]. Our results strongly support this hypothesis, because rotatory deformity and lateral spondylolisthesis of L3 were observed significantly more often in the S-group than in the C-group. Although rotatory subluxation could not be judged from the combination of anteroposterior and lateral radiographs alone, these findings suggest the existence of rotatory subluxation.

We offer the following hypothesis to explain the pathological mechanism responsible for induction of DNDLS in the elderly. Asymmetric anatomical changes in the lower lumbar segments are generally compensated by the relatively undegenerated upper lumbar segments, so maintaining normal spinal balance in the early stage of spinal degeneration. However, this compensatory mechanism cannot compensate when disc degeneration advances to the upper lumbar segments. As a result, the mechanical stress concentrates at the L3–4 intervertebral disc level, located at the junction between the fixed, unbalanced, lower lumbar segments and the mobile, upper lumbar segments. DNDLS progresses when rotatory subluxation occurs at L3–4, because of decompensation during the advanced stages of spinal degeneration.

The rotatory deformation and translation of the L3 vertebra observed in the standing, anteroposterior lumbar X-rays may indicate the initiation of DNDLS, and rotatory subluxation at L3–4 may be a predisposing factor for curve progression in the elderly. In this study, the inclination angles of all segments of the lumbar spine were significantly larger in the S-group. These findings may also indicate the beginning of decompensation and its effects on spinal balance in the aging spine, although total spinal balance was maintained fairly well at this point.

Much has been written about lumbar scoliosis detected during childhood, and the risk factors for pain and curve progression have been clearly demonstrated by radiographic follow-up studies. A Cobb angle greater than 30°, loss of lumbar lordosis, apical rotation greater than Nash–Moe grade II, lateral listhesis greater than 5 mm, and an intercrestal line through or below the L4–5 disc space are regarded as potential risk factors for curve progression [1, 20, 22–25]. Although none of the participants in our study met these criteria after the 15-year follow-up period, we cannot conclude that DNDLS does not carry a potential risk of progression to a high-grade deformity, on the basis of the results from this longitudinal study. It is possible that some of the participants with DNDLS in this study may progress to a high-grade deformity in the future. It would be interesting to follow these subjects over a longer period to determine the percentage of individuals who develop high-grade curve magnitudes with disabling pain and a collapsing spine.

This study has several limitations. First, the study sample is not large, so the cumulative incidence determined in this study may not be generalized to the Japanese population. Second, follow-up of this cohort was relatively low. Although the main reason for drop-out is presumed to be death, the authors were unable to identify all of the reasons for study drop-out. Therefore, the real cumulative incidence may be different from that reported in this study. Nonetheless, the long-term observations of the progression of new lumbar curves in the elderly are noteworthy. The results obtained in this study are helpful for understanding the etiology and natural history of DNDLS in the elderly, and further follow-up on this cohort will provide additional useful information.

Conclusion

The radiographic features of DNDLS in this cohort of elderly subjects revealed mild scoliosis with minimal rotatory deformity. Spinal decompensation by the upper lumbar segments to the asymmetric anatomical deformity in the lower lumbar segments may induce de-novo lumbar scoliosis. The rotatory deformity and lateral spondylolisthesis of the L3 vertebra may be a prognostic factor for de-novo lumbar curve progression in the elderly.

Conflict of interest The authors declare that they have no conflict of interest.

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ARTHRITIS & RHEUMATISM
Vol. 64, No. 5, May 2012, pp 1447–1456
DOI 10.1002/art.33508

Incidence and Risk Factors for Radiographic Knee Osteoarthritis and Knee Pain in Japanese Men and Women

A Longitudinal Population-Based Cohort Study

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Objective. **To examine the incidence and progression of radiographic knee osteoarthritis (OA) and the incidence of knee pain, and their risk factors in Japan, using the large-scale population of the nationwide cohort study ROAD (Research on Osteoarthritis/osteoporosis Against Disability).**

Methods. **Subjects from the ROAD study who had been recruited in 2005–2007 were followed up with knee radiography 3 years later. A total of 2,262 paired radiographs (74.4% of the original sample) were scored using the Kellgren/Lawrence (K/L) grading system, and the incidence and progression rate of knee OA was examined. The incidence rate of knee pain was also examined. In addition, risk factors were tested for their association with incident and progressive radiographic knee OA and incident knee pain.**

Results. **Given the ~3.3-year followup, the rate of incident K/L grade ≥2 radiographic knee OA was 6.9% and 11.9% in men and women, respectively, while that of K/L grade ≥3 knee OA was 8.4% and 13.9% in men and women, respectively. The rate of progressive knee OA was 17.8% and 22.3% in men and women, respectively. The incident rate of knee pain was 21.2% and 27.3% in men and women, respectively. Female sex was a risk factor for incident K/L grade ≥2 knee OA, but was not associated with incident K/L grade ≥3 knee OA or progressive knee OA. Knee pain was a risk factor for incident and progressive knee OA. Previous knee injury was a risk factor for knee pain but not for radiographic knee OA.**

Conclusion. **The present longitudinal study revealed a high incidence of radiographic knee OA in Japan.**

Knee osteoarthritis (OA), characterized by pathologic features including joint space narrowing and osteophytosis, is a major public health issue causing chronic pain and disability in the elderly in most developed countries (1). The prevalence of radiographic knee OA is high in Japan (2), with 25,300,000 subjects ages ≥40 years estimated to experience radiographic knee OA (3). According to the recent National Livelihood Survey of the Ministry of Health, Labor, and Welfare in Japan, OA is ranked fourth among diseases that cause

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Supported by grants-in-aid for Scientific Research (S19109007, B20390182, C20591737, C20591774), for Young Scientists (A18689031), and for Exploratory Research (19659305) from the Japanese Ministry of Education, Culture, Sports, Science, and Technology; grants H17-Men-eki-009, H18-Choujyu-037, H20-Choujyu-009, and H21-Chouju-Wakate-011 from the Ministry of Health, Labor, and Welfare; research funding from the Japanese Orthopaedic Association (JOA-Subsidized Science Project Research 2006-1 and 2010-2); and grant 166 from the Japan Orthopaedics and Traumatology Foundation.

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Submitted for publication February 8, 2011; accepted in revised form November 22, 2011.

disabilities that subsequently require support with activities of daily living (4). Despite the urgent need of strategies for the prevention and treatment of this condition, there have only been a few studies of rates of incidence and progression of knee OA (5–9). Furthermore, to the best of our knowledge, there has been no study of the incidence or progression of knee OA in Asians, although large differences in prevalence of knee OA exist among the different races (2,10,11).

Previous studies that investigated risk factors for knee OA (12–23) showed that obesity, previous knee injury, female sex, muscle strength, occupational activities, and older age were risk factors for knee OA mainly in Caucasians. However, in addition to the differences in prevalence among different ethnic groups, anthropometric measurements and environmental situations varied substantially in different countries. Thus, findings in Caucasians cannot be applied to different ethnic groups. Few population-based cohort studies have examined risk factors for knee OA in Asians.

The principal clinical symptom of knee OA is knee pain (24). Ours and other previous studies have demonstrated that the impact of knee pain on quality of life is disproportionate to the radiographic changes themselves in the knee (25,26). Several cross-sectional studies have investigated the factors associated with knee pain (25,27), but in most of those studies, radiographic findings were not included in the analysis, although radiographic severity of knee OA is an important factor for knee pain (2). Furthermore, there have been few longitudinal studies of the incidence of knee pain that include radiographic findings in the analysis.

The objective of the present study was to clarify the incidence and progression rate of radiographic knee OA as well as the incidence of knee pain in Japanese men and women using the large-scale, population-based cohort study known as the Research on Osteoarthritis/osteoporosis Against Disability (ROAD). In addition, we examined the risk factors for the incidence and progression of knee OA as well as for the incidence of knee pain.

SUBJECTS AND METHODS

Subjects. The ROAD study was a nationwide prospective study of bone and joint diseases (with osteoarthritis and osteoporosis as the representative bone and joint diseases) constituting population-based cohorts established in several communities in Japan. As a detailed profile of the ROAD study has already been described elsewhere (2,3,28), a brief summary is provided here. In 2005–2007, we created a baseline database that included the clinical and genetic information for 3,040 inhabitants (1,061 men, 1,979 women) in the age range of 23–95 years (mean 70.6 years), recruited from listings of resident registrations in 3 communities: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a coastal region in Taiji, Wakayama. Participants in the urban region were recruited from a randomly selected cohort from the Itabashi-ward residents' registration database (29). The participation rate was 75.6%. 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 walk to the survey site, report data, and understand and sign an informed consent form. 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 Geriatric Medical Center.

Participants completed an interviewer-administered questionnaire of 400 items that included lifestyle information such as smoking habit, alcohol consumption, family history, medical history, and previous knee injury history. Anthropometric measurements included height and weight, from which the body mass index (BMI) (weight [kg]/height [m^2]) was calculated. Grip strength was measured on bilateral sides using a TOEI LIGHT handgrip dynamometer, and the better measurement was used to represent maximum muscle strength. Furthermore, all participants were interviewed by well-experienced orthopedists regarding pain in both knees, who asked "Have you experienced right knee pain on most days in the past month, in addition to now?" and "Have you experienced left knee pain on most days in the past month, in addition to now?" Subjects who answered "yes" were defined as having knee pain.

In 2008–2010, we attempted to trace and review all 3,040 subjects; they were invited to attend a followup interview and undergo repeat radiography. The interviews, which included questions about current knee pain, were conducted by the same trained orthopedists who undertook the baseline study in 2005–2007. Anthropometric measurements also included height, weight, and grip strength at followup.

Radiographic assessment. All participants underwent radiographic examination of both knees using an anteroposterior view with weight-bearing and foot map positioning. Fluoroscopic guidance with a horizontal anteroposterior x-ray beam was used to properly visualize the joint space. Knee radiographs at baseline and followup were read in pairs without knowledge of the participant's clinical status by a single well-experienced orthopedist (SM), and the Kellgren/Lawrence (K/L) grade was defined using the K/L radiographic atlas for overall knee radiographic grades (30). In the K/L grading system, radiographs are scored from grade 0 to grade 4, with the higher grades being associated with more severe OA. To evaluate the intraobserver variability of the K/L grading, 100 randomly selected radiographs of the knee were scored by the same observer >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 intervariabilities evaluated for K/L grade (0–4) were confirmed by kappa

Table 1. Baseline characteristics of the participants*

	Overall (n = 2,262)	Men (n = 763)	Women (n = 1,499)
Age, years	68.7 ± 11.3	69.6 ± 11.1	68.2 ± 11.4†
Height, cm	154.6 ± 8.8	163.1 ± 6.6	150.3 ± 6.4†
Weight, kg	55.4 ± 10.2	62.2 ± 9.9	51.9 ± 8.4†
BMI, kg/m^2	23.1 ± 3.3	23.3 ± 3.0	23.0 ± 3.4†
Grip strength, kg	26.2 ± 9.2	34.3 ± 8.8	22.1 ± 6.2†
OA prevalence, no. (%)			
K/L grade ≥1	1,898 (83.9)	586 (76.8)	1,312 (87.5)‡
K/L grade ≥2	1,164 (51.5)	296 (38.8)	868 (57.9)‡
K/L grade ≥3	355 (15.7)	75 (9.8)	280 (18.7)‡
Knee pain, no. (%)	478 (21.1)	111 (14.6)	367 (24.5)‡
Previous knee injury, no. (%)	217 (9.6)	52 (6.8)	165 (11.0)‡
Smoking, no. (%)	212 (9.4)	165 (21.6)	47 (3.1)‡
Alcohol, no. (%)	831 (36.7)	483 (63.3)	348 (23.2)‡

* Except where indicated otherwise, values are the mean ± SD. BMI = body mass index; OA = osteoarthritis; K/L = Kellgren/Lawrence.

† $P < 0.05$ versus men, by Student's unpaired t-test.

‡ $P < 0.05$ versus men, by chi-square test.

analysis to be sufficient for assessment ($\kappa = 0.86$ and $\kappa = 0.80$, respectively).

For the purposes of this study, we defined 4 knee OA outcomes. First, a subject was defined as having incident K/L grade ≥1 radiographic knee OA if both knees had less than grade 1 disease at baseline and if at least one knee had grade 1 or higher disease at followup. Second, a subject was defined as having incident K/L grade ≥2 radiographic knee OA if both knees had less than grade 2 disease at baseline and if at least one knee had grade 2 or higher disease at followup. Third, incident K/L grade ≥3 radiographic knee OA was defined as less than grade 3 disease in both knees at baseline and grade 3 or higher disease in at least one knee at followup. Fourth, progressive knee OA was defined as K/L grade 2 and K/L grade 3 knee OA at baseline (because K/L grade 4 knee OA cannot progress) and an increase by at least 1 grade in the affected knee at followup.

Statistical analysis. Odds ratios (ORs) and 95% confidence intervals (95% CIs) are provided. The differences in age, height, weight, BMI, and grip strength between men and women were examined using Student's unpaired t-test. To compare the prevalence of radiographic knee OA and knee pain between men and women, we performed the chi-square test. A logistic regression analysis was used to determine the association of incident radiographic knee OA, progressive knee OA, and incident knee pain with age in men and women. To determine risk factors for incident knee OA and progressive knee OA, a univariate generalized estimating equation (GEE) logistic regression analysis was used. Furthermore, to determine independent risk factors, multiple GEE logistic regression analysis was used with significant risk factors in a univariate GEE logistic regression analysis model as independent variables. Incident knee pain was defined as no knee pain in both knees at baseline and knee pain in at least one knee at followup. To determine risk factors for incident knee pain, a univariate GEE logistic regression analysis was used. Furthermore, to determine independent risk factors, multiple GEE logistic regression analysis was used with significant risk factors in a univariate logistic regression analysis model in addition to regions as independent variables. When we analyzed risk factors for incident knee OA, progressive knee OA, and incident knee pain, K/L grade at baseline, knee pain at baseline, and previous knee injury were defined for the knee which had the incident OA, progressive OA, and incident pain, respectively. Data analyses were performed using SAS software, version 9.0 (SAS Institute).

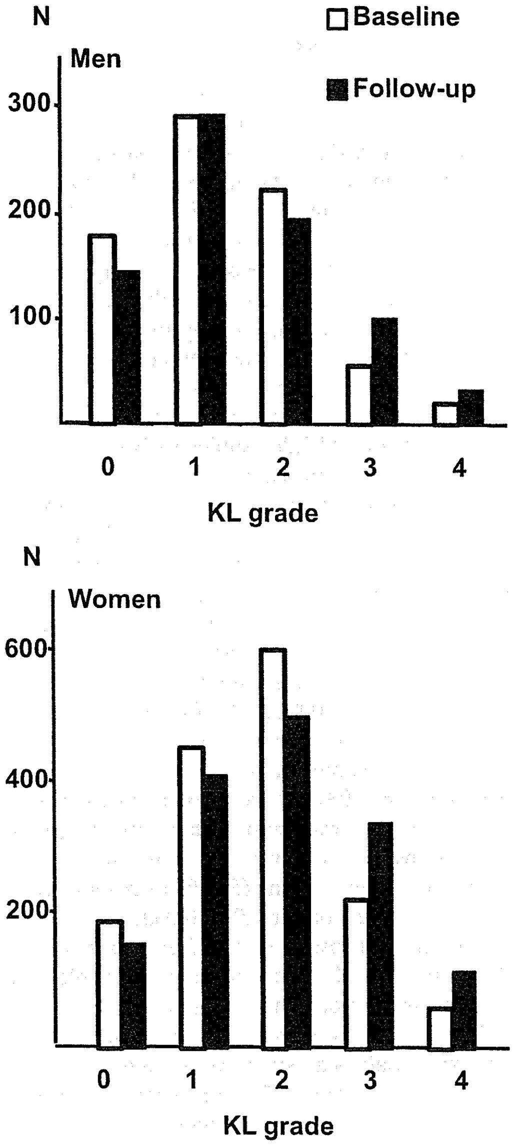

Figure 1. Number (N) of male and female subjects by Kellgren/Lawrence (K/L) grade at baseline and followup.

Table 2. Incidence of radiographic knee OA, progressive knee OA, and knee pain according to sex*

	K/L grade ≥1		K/L grade ≥2		K/L grade ≥3		Progressive knee OA		Knee pain	
	No. at risk	Cumulative incidence, no. (%)	No. at risk	Cumulative incidence, no. (%)	No. at risk	Cumulative incidence, no. (%)	No. at risk	Cumulative incidence, no. (%)	No. at risk	Cumulative incidence, no. (%)
Overall	364	70 (19.2)	1,098	107 (9.7)	1,907	228 (12.0)	1,084	229 (21.1)	1,784	447 (25.1)
Men	177	35 (19.8)	467	32 (6.9)	688	58 (8.4)	276	49 (17.8)	652	138 (21.2)
Women	187	35 (18.7)	631	75 (11.9)†	1,219	169 (13.9)†	808	180 (22.3)	1,132	309 (27.3)†

* See Table 1 for definitions.
† $P < 0.05$ versus men, by chi-square test.

RESULTS

Of the 3,040 subjects in the baseline study in 2005–2007, 125 (4.1%) had died by the time of the review 3 years later, 123 (4.0%) did not participate in the followup study due to bad health, 69 (2.3%) had moved away, 83 (2.7%) declined the invitation to attend the followup study, and 155 (5.1%) did not participate in the followup study for other reasons. Among the 2,485 subjects who did participate in the followup study, 175 (5.8%) did not undergo plain radiography and 18 (0.6%) provided incomplete pain questionnaires; these were excluded. We also excluded 30 subjects (1.0%) who underwent total knee arthroplasty before the followup study, leaving a total of 2,262 subjects (74.4%) (763 men and 1,499 women) from whom paired radiographs and complete pain histories were obtained. Their mean ± SD age at followup was 72.2 ± 11.4 years. The mean ± SD duration of followup between initial and second radiographs was 3.3 ± 0.6 years. Those participating in the followup study were younger than those who did not survive or who did not participate for other reasons (mean age 68.6 years for responders versus 75.1 years for nonresponders; $P < 0.0001$). The followup study participants also were more likely to be women (66.3% of responders were women and 61.8% of nonresponders were women; $P = 0.03$) and were less likely to have knee OA at the baseline examination than either those who did not survive to followup or those who did not participate for other reasons (51.5% of responders versus 60.9% of nonresponders; $P < 0.0001$).

The characteristics of the 2,262 participants at baseline in the ROAD study are shown in Table 1. Men were significantly older than women, while BMI was higher in men than in women. The prevalence of knee OA and knee pain was significantly higher in women than in men at baseline. The proportion of previous knee injuries was also higher in women than in men. The number of subjects with each K/L grade at baseline and at followup is shown in Figure 1.

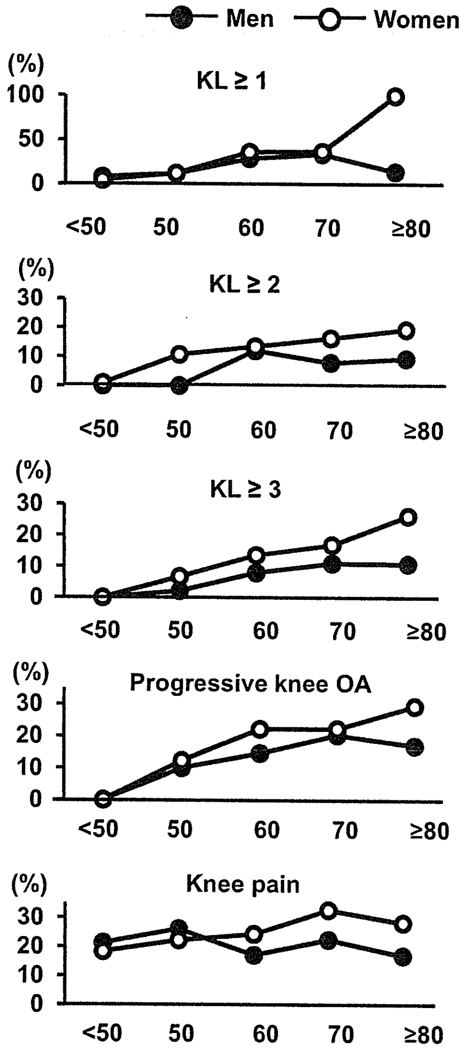

Figure 2. Percentage of subjects with incident radiographic knee osteoarthritis (OA) (Kellgren/Lawrence [K/L] grade ≥1, ≥2, or ≥3), progressive knee OA, and incident knee pain in each age stratum (<50 years, 50–59 years, 60–69 years, 70–79 years, and ≥80 years).

Table 3. Risk factors for incident radiographic knee osteoarthritis*

	K/L grade ≥2			K/L grade ≥3		
	No./total no. (%) of subjects	Crude OR (95% CI)	Adjusted OR (95% CI)	No./total no. (%) of subjects	Crude OR (95% CI)	Adjusted OR (95% CI)
Age (+5 years)	–	1.26 (1.15–1.39)	1.31 (1.15–1.49)	–	1.33 (1.23–1.44)	1.25 (1.13–1.39)
BMI (+5 kg/m^2)	–	2.00 (1.49–2.69)	2.43 (1.76–3.39)	–	1.67 (1.36–2.04)	1.68 (1.35–2.11)
Grip strength (+1 kg)	–	0.96 (0.94–0.98)	1.01 (0.97–1.04)	–	0.95 (0.94–0.97)	1.00 (0.97–1.02)
Sex						
Men	32/467 (6.9)	Referent	Referent	58/688 (8.4)	Referent	Referent
Women	75/631 (11.9)	1.83 (1.20–2.86)	2.76 (1.50–5.18)	169/1,219 (13.9)	1.75 (1.28–2.41)	1.42 (0.88–2.29)
K/L grade at baseline						
0	–	Referent	Referent	–	Referent	Referent
1	–	4.11 (2.33–7.83)	2.48 (1.35–4.87)	–	1.91 (0.69–5.43)	1.29 (0.45–3.80)
2	–	–	–	–	5.69 (2.38–14.30)	5.94 (1.07–35.83)
Knee pain at baseline						
No	–	Referent	–	–	Referent	Referent
Yes	–	0.91 (0.32–2.24)	–	–	3.77 (2.44–5.73)	2.53 (1.59–4.00)
Previous knee injury						
No	–	Referent	–	–	Referent	–
Yes	–	4.08 (0.66–18.8)	–	–	1.24 (0.45–3.11)	–
Smoking						
No	99/958 (10.3)	Referent	–	213/1,713 (12.4)	Referent	Referent
Yes	8/140 (5.7)	0.53 (0.23–1.04)	–	14/194 (7.2)	0.55 (0.30–0.93)	1.07 (0.55–1.94)
Alcohol use						
No	68/627 (10.9)	Referent	–	158/1,171 (13.5)	Referent	Referent
Yes	39/471 (8.3)	0.74 (0.49–1.12)	–	69/736 (9.4)	0.66 (0.49–0.89)	0.96 (0.67–1.36)

* Adjusted odds ratios (ORs) were calculated by multiple generalized estimating equation logistic regression analysis after adjustment for all other variables in addition to regions. We show all variables we analyzed in the present study. K/L = Kellgren/Lawrence; 95% CI = 95% confidence interval; BMI = body mass index.

Table 2 shows the rates of incident and progressive knee OA and incident knee pain in the overall population and subgroups classified by sex. The incidences of K/L grade ≥2 and K/L grade ≥3 knee OA and knee pain were significantly higher in women than in men, while there were no significant differences in the incidence of K/L grade ≥1 knee OA and the progression of knee OA between men and women. The incidence and progression rate of knee OA tended to increase with age in men and women (for 5-year increase: K/L grade ≥1, OR 1.22 [95% CI 1.06–1.43] and OR 1.52 [95% CI 1.29–1.84], respectively; K/L grade ≥2, OR 1.35 [95% CI 1.12–1.67] and OR 1.29 [95% CI 1.15–1.45], respectively; K/L grade ≥3, OR 1.34 [95% CI 1.15–1.58] and OR 1.35 [95% CI 1.24–1.49], respectively; progressive knee OA, OR 1.15 [95% CI 0.95–1.42] and OR 1.15 [95% CI 1.0–1.28], respectively) (Figure 2). Interestingly, the incidence rate of knee pain was age-dependent in women (OR 1.10 [95% CI 1.04–1.17]), while it was not age-dependent in men (OR 0.97 [95% CI 0.90–1.06]). Furthermore, in subjects age <60 years, the incidence of knee pain was similar between women and men (OR 1.12 [95% CI 0.88–1.42]), while in subjects age >60 years, the incidence of knee pain was significantly higher in women than in men (OR 0.78 [95% CI 0.68–0.88]) (Figure 2).

Table 3 shows the baseline risk factors for incident radiographic knee OA. Univariate logistic regression analysis showed that age, BMI, grip strength, sex, and K/L grade were associated with incident K/L grade ≥2 knee OA. Age, BMI, grip strength, sex, K/L grade, knee pain at baseline, previous knee injury, smoking, and alcohol consumption were associated with incident K/L grade ≥3 knee OA. We then determined independent risk factors using a multiple logistic regression analysis that included the above significant factors in the univariate model in addition to regions as independent variables. The results showed that age and BMI were risk factors for incident K/L grade ≥2 and incident K/L grade ≥3 knee OA. Female sex was a risk factor for incident K/L grade ≥2 knee OA, while being female was not significantly associated with incident K/L grade ≥3 knee OA. A more severe K/L grade at baseline was strongly associated with incident K/L grade ≥2 and incident K/L grade ≥3 knee OA. Knee pain at baseline was significantly associated with incident K/L grade ≥3 knee OA.

Univariate logistic regression analysis showed

Table 4. Risk factors for progressive knee OA and incident knee pain*

	Progressive knee OA			Knee pain		
	No./total no. (%) of subjects	Crude OR (95% CI)	Adjusted OR (95% CI)	No./total no. (%) of subjects	Crude OR (95% CI)	Adjusted OR (95% CI)
Age (+5 years)	–	1.14 (1.04–1.25)	1.17 (1.05–1.30)	–	1.05 (1.01–1.10)	1.01 (0.95–1.07)
BMI (+5 kg/m^2)	–	1.47 (1.20–1.80)	1.43 (1.16–1.77)	–	1.60 (1.37–1.88)	1.54 (1.30–1.82)
Grip strength (+1 kg)	–	0.98 (0.96–1.00)	0.99 (0.96–1.01)	–	0.98 (0.97–1.00)	1.00 (0.98–1.02)
Sex						
Men	49/276 (17.8)	Referent	–	138/652 (21.2)	Referent	Referent
Women	180/808 (22.3)	1.33 (0.94–1.90)	–	309/1,132 (27.3)	1.40 (1.11–1.76)	1.32 (0.94–1.84)
K/L grade at baseline						
0 and 1	–	–	–	–	Referent	Referent
2	–	–	–	–	1.89 (0.80–4.49)	1.58 (0.65–3.85)
3 and 4	–	–	–	–	3.17 (1.95–5.17)	2.54 (1.52–4.24)
Knee pain at baseline						
No	–	Referent	Referent	–	–	–
Yes	–	2.87 (1.99–4.14)	2.63 (1.81–3.81)	–	–	–
Previous knee injury						
No	–	Referent	–	–	Referent	Referent
Yes	–	0.79 (0.31–1.86)	–	–	3.09 (1.34–7.23)	2.91 (1.26–6.82)
Smoking						
No	219/1,016 (21.6)	Referent	–	411/1,603 (25.6)	Referent	–
Yes	10/68 (14.7)	0.63 (0.30–1.19)	–	36/181 (19.9)	0.72 (0.49–1.04)	–
Alcohol use						
No	168/746 (22.4)	Referent	–	281/1,093 (25.7)	Referent	–
Yes	61/338 (18.1)	0.76 (0.54–1.04)	–	166/691 (24.0)	0.91 (0.73–1.14)	–

* Adjusted ORs were calculated by multiple generalized estimating equation logistic regression analysis after adjustment for all other variables in addition to regions. We show all variables we analyzed in the present study. OA = osteoarthritis (see Table 3 for other definitions).

that age, BMI, grip strength, and knee pain at baseline were associated with progressive knee OA. We then included age, BMI, grip strength, and knee pain at baseline in addition to regions as independent variables in a multiple logistic regression analysis to determine independent risk factors (Table 4). Age and BMI at baseline were risk factors, but their adjusted ORs for progressive knee OA were lower than those for incident K/L grade ≥2 knee OA (Table 4). Knee pain was significantly associated with progressive knee OA.

We further investigated risk factors for incident knee pain (Table 4). Univariate logistic regression analysis showed that age, BMI, grip strength, sex, K/L grade, and previous knee injury were associated with incident knee pain. To determine independent risk factors for knee pain, multiple logistic regression analysis was used with age, BMI, grip strength, sex, K/L grade, and previous knee injury in addition to regions as independent variables. BMI was significantly associated with incident knee pain, but female sex was not associated with incident knee pain. Subjects with K/L grade ≥3 knee OA at baseline had an ~2.5-fold increased risk for incidence of knee pain compared with K/L grade 0 and K/L grade 1 knees. Previous knee injury was also significantly associated with incident knee pain.

DISCUSSION

This is the first population-based study to examine the incidence and progression of knee OA and risk factors for incident and progressive knee OA among Japanese men and women. We also examined the incident rate of knee pain and its risk factors. The present study showed high rates of incident knee OA, progressive knee OA, and incident knee pain.

Few population-based studies have examined incident radiographic knee OA (6–9). In the Framingham Osteoarthritis Study (6), given the ~8.1-year followup, the incident rate of K/L grade ≥2 knee OA was 11.1% and 18.1% (1.4% and 2.2% per year) in Caucasian men and women, respectively. A population-based study in the UK (18) showed that given the ~5.1-year followup, the incident rate of K/L grade ≥2 knee OA was 18.5% (2.3% per year), but men and women were not separated in the analysis. In the present study, the incidence of K/L grade ≥2 OA was 2.0% and 3.7% per year in men and women, respectively, which is a little higher than that in previous epidemiologic studies in the US and Europe (6,8), implying that the incidence is higher among Japanese than in Caucasians. This is compatible with our findings regarding prevalence of K/L grade ≥2 knee OA in our previous study (2), which showed that the prevalence of K/L grade ≥2 knee OA was much higher in Japanese people than in Caucasians (10,11).

For incident K/L grade ≥3 knee OA, to the best of our knowledge no population-based studies have been previously reported. In the Chingford Study (7), knee OA was not defined according to K/L grade but according to osteophytosis and joint space narrowing. The Chingford Study showed that given the ~4-year followup, the incidence of joint space narrowing was 12.6% (3.2% per year) in women, which may be comparable to our results for incident K/L grade ≥3 knee OA, considering the K/L grade definition; however, a closer comparison provides quite limited accuracy.

In the present study, the incident rate of K/L grade ≥3 knee OA was 4.1% per year in Japanese women, which was also a little higher than that seen in Caucasian women. However, this higher incident rate of K/L grade ≥3 may be partly explained by the definition of K/L grade ≥3 knee OA, because by considering any knees that start at K/L grade <3 as eligible for this outcome, we combined incident (e.g., knees starting at K/L grade 0–1) and progressive (knees starting at K/L grade 2) disease. In the present study, we also examined progression of knee OA, and we found that the progression rate of knee OA was 5.2% and 6.3% per year in Japanese men and women, respectively, which was also higher than that in other studies in the US and the UK (2.2–3.9%) (6,8). The higher incidence of radiographic knee OA in Japan could also be due to lifestyle factors, because the traditional Japanese lifestyle includes sitting on the heels on a mat and using Japanese-style lavatories, requiring squatting and kneeling, which are associated with knee OA (31–33). These positions may cause mechanical stress to the knee joint and possibly lead to the acceleration of OA.

Although the rate of incident radiographic knee OA and progressive knee OA increased with age in both sexes, that of knee pain was age-dependent in women but not in men. This may be due to the fact that elderly men generally retire from their occupations at age ~60–70 years, and thus the load on the knees may be lighter in men age >60 years compared with those age <60 years, whereas women must often continue to do household chores even after age 70 years, and thus the load on the knees may not be lighter in women age >70 years compared with those age <70 years.

The present study also showed that age and BMI are risk factors for incident radiographic knee OA, consistent with findings of previous epidemiologic studies (5,7,8). Previous studies have shown that obesity is a strong risk factor for incident knee OA (34), possibly due to the accumulation of mechanical stress on the knee joint. More severe K/L grade was also a risk factor for incident radiographic knee OA in the present study, which is also consistent with findings of previous studies (7,8). Female sex was also a strong risk factor for incident K/L grade ≥2 knee OA, as in previous studies (6,8), possibly implicating the involvement of muscle strength to compensate for mechanical stress, as women are known to have less muscle strength than men in all decades of life (35). However, female sex was not a significant risk factor for incident K/L grade ≥3 knee OA or progressive knee OA. Furthermore, age and BMI at baseline were risk factors for progressive knee OA, but their ORs for progressive knee OA were lower than those for incident K/L grade ≥2 knee OA.

This discordance between the determinants of incidence of K/L grade ≥2 and K/L grade ≥3 knee OA or between those of incidence and progression of knee OA using K/L grade suggests that different mechanisms might influence the initiation of osteophytosis (the principal abnormality in K/L grade 2 disease) and joint space narrowing (the principal abnormality in K/L grade 3 disease). However, since K/L grade was defined by a categorical method, which is comparably insensitive to change, this discordance might simply be a function of the scoring system. Nevertheless, there is also accumulating evidence from previous studies that osteophytosis and joint space narrowing have distinct etiologic mechanisms. A recent cross-sectional study has shown that osteophytosis is unrelated not only to joint space narrowing on plain radiographs, but also to cartilage loss measured by quantitative magnetic resonance imaging (36). Furthermore, our study of an experimental mouse model of OA has identified a cartilage-specific molecule, carminerin, that regulates osteophytosis without affecting joint cartilage destruction during OA progression (37,38). Our most recent findings have implications for our understanding of the pathogenesis of knee OA, as well as for preventive strategies.

In the present study, knee pain was a risk factor for incident K/L grade ≥3 knee OA and progressive knee OA. Subjects with knee pain may tend not to go out or exercise because of the pain, which may lead to lower quadriceps strength. This may be one of the reasons why knee pain is a risk factor for incident and progressive knee OA, as quadriceps weakness has been previously associated with radiographic knee OA (39).

For incidence of knee pain, age was not a risk factor after adjustment for BMI, sex, and K/L grade at baseline. Knee pain occurrence may be mainly due to environmental factors rather than individual factors. As described above, elderly men generally retire from their occupations at ages 60–70 years, and thus the load on the knees may be lighter in men age <60 years compared with those age >60 years, which may partly explain the lack of significant association between age and incidence of knee pain. BMI was a risk factor for incident knee pain even after adjustment for K/L grade at baseline, indicating that obesity is a strong risk factor not only for incident radiographic knee OA but also for incident knee pain. In addition, knee OA at baseline was a risk factor for knee pain, but the ORs for knee pain of K/L grade 2 knee OA and K/L grades 3 and 4 knee OA were just 1.6 and 2.5, respectively. In fact, the proportion of subjects with knee pain of those with K/L grade 2 knee OA and K/L grades 3 and 4 knee OA was just 28.0% and 47.1%, respectively, indicating that ~70% of subjects with K/L grade 2 knee OA who had no knee pain at baseline and ~50% of subjects with K/L grades 3 and 4 knee OA who had no knee pain at baseline also had no knee pain after 3 years.

Previous cross-sectional studies have also demonstrated that correlation of knee pain with radiographic severity of knee OA is not as strong as one would expect (2,40–42), most likely because knee pain may arise from a variety of structures other than joint cartilage, such as the menisci, synovium, ligaments, bursae, bone, and bone marrow (43–47). Hence, comprehensive mechanistic studies of knee pain taking various tissues in and around the knee joint into consideration will be needed to elucidate the relationship between radiographic OA and symptomatic OA.

We were unable to detect an association between knee injury and incident OA in the present study. Other cross-sectional studies of OA prevalence have observed strong association with previous knee injury (48), while the incidence data from the Zoetermeer Study, Framingham Study, and Chingford Study (5–7) also showed a slight increase in risk with interim knee injury but were based on small numbers; no significant association with past knee injury was seen in those groups. In the present study, K/L grade ≥2 knee OA in subjects with previous knee injury was not significantly associated with previous knee injury, which suggests that the association of incident radiographic knee OA with previous knee injury may be weak, although the number of subjects with incident K/L grade ≥2 knee OA who had previous knee injury was just 12. Thus, the small number may partly explain the lack of statistical significance. The present study showed that previous knee injury is a risk factor for incident knee pain. As mentioned above, the correlation of knee pain with radiographic severity of knee OA is not as strong as expected (2,40–42), as knee pain may arise from a variety of structures other than joint cartilage, such as menisci, synovium, ligaments, bursae, bone, and the bone marrow (43–47), and these tissues may have been damaged by a previous knee injury, which may lead to the incident knee pain.

We were unable to detect an association between smoking/drinking alcohol and incident knee OA or knee pain. The association between smoking and incident knee OA is controversial. The Zoetermeer Study showed that smoking has no association with incident knee OA (5), while incidence data from the Framingham Study showed that smoking protects against incident knee OA (49). We were also unable to show any effect of physical activity in this incidence study. However, the numbers and power were too low to examine this group and to confirm or exclude such effects on incidence.

The present study has several limitations. First, the radiographic investigators did not have readers calibrate their readings to those from other studies. Although we reported a higher incidence of radiographic knee OA than in previous studies, differences in radiographic acquisition, scoring techniques, and methodology across studies limit strict comparisons between our results and previous reports. Differences across studies in the thresholds used by readers to define osteophytes may have had a substantial impact on their incidence. The high incidence of knee OA in our study compared to that in other populations may be due to such differences. Second, our analysis did not include patellofemoral joint radiographs, which would likely increase the concordance between radiographic knee OA and its pain. Third, we defined knee pain as present or absent, rather than as a continuous measure such as the Western Ontario and McMaster Universities Osteoarthritis Index (50) or visual analog scale score. Categorical methods are statistically less powerful than continuous methods. Thus, the association between knee pain and other variables might have been underestimated in the present study.

In conclusion, the present longitudinal study, using a large-scale population from the ROAD study, revealed a high incidence of radiographic knee OA in Japan compared with previous studies. Age, BMI, and female sex influence incidence more than radiographic progression of knee OA, indicating that different mechanisms might influence the initiation of osteophytosis and joint space narrowing. Knee pain was a risk factor for radiographic knee OA. Knee injury was not significantly associated with radiographic knee OA, but was a risk factor for incident knee pain. Further progress, along with continued longitudinal surveys within the ROAD study, will elucidate the environmental and genetic backgrounds of knee OA.

ACKNOWLEDGMENTS

The authors thank Drs. Seizo Yamamoto, Hideaki Ishibashi, and Yorito Anamizu and members of the Department of Orthopedics, and Mr. Yuji Kutsuma and other members of the Department of Radiology at Tokyo Metropolitan Geriatric Medical Center; Mrs. Tomoko Takijiri and other members of the Public Office in Hidakagawa, Japan; and Mrs. Tamako Tsutsumi, Mrs. Kanami Maeda, and other members of the Public Office in Taiji, Japan, for their assistance in the location and scheduling of participants for examinations.

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.

Study conception and design. Muraki, Akune, Oka, Ishimoto, Nagata, Yoshida, Tokimura, Nakamura, Kawaguchi, Yoshimura.

Acquisition of data. Muraki, Akune, Oka, Ishimoto, Nagata, Yoshimura.

Analysis and interpretation of data. Muraki, Akune, Oka, Yoshimura.

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Osteoarthritis and Cartilage 20 (2012) 712–718

Osteoarthritis
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Incidence and risk factors for radiographic lumbar spondylosis and lower back pain in japanese men and women: the ROAD study

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ARTICLE INFO

Article history:
Received 16 November 2011
Accepted 14 March 2012

Keywords:
Spondyloarthritis
Epidemiology
Lower back pain

SUMMARY

Objective: To determine the incidence of radiographic lumbar spondylosis (LS)and lower back pain, and their risk factors in Japan using a large-scale population from the nationwide cohort Research on Osteoarthritis/osteoporosis Against Disability (ROAD) Study.

Methods: Participants in the ROAD study who had been recruited between 2005 and 2007 were followed up with lumbar spine radiography for 3 years. A total of 2,282 paired radiographs (75% of the original sample) were scored using Kellgren and Lawrence (KL) grades, and the incidence and progression rate of radiographic LS was analyzed. The incidence of lower back pain was also examined. In addition, associations between risk factors and incident and progressive radiographic LS as well as incident lower back pain were tested.

Results: Given a 3.3-year follow-up, the incidence of $KL \geq 2$ radiographic LS was 50.0% and 34.4% (15.3% and 10.5% per year), while that of $KL \geq 3$ LS was 15.3% and 23.7% (4.6% and 7.2% per year) in men and women, respectively. The progression rate of LS was 20.5% and 27.4% (6.2% and 8.3% per year) in men and in women, respectively. In addition, the incidence of lower back pain was 28.3% and 31.2% (8.6% and 9.5% per year) in men and women. Lower back pain was not significantly associated with incident radiographic LS, while a more severe KL grade at baseline was associated with incident lower back pain.

Conclusion: The present longitudinal study revealed a high incidence of radiographic LS in Japan.

Introduction

Lumbar spondylosis (LS) and lower back pain are considered a major public health issue causing chronic disability of the elderly in most developed countries[1,2,3–8]. The prevalence of radiographic LS is high in Japan[3], with an estimated 37,900,000 individuals aged $\geq$40 years being affected by radiographic LS[9]. According to the recent National Livelihood Survey of the Ministry of Health, Labour and Welfare in Japan, lower back pain is rated first among symptoms that send men to the hospital[10]. Despite the urgent need for strategies to prevent and treat this condition, several cross sectional studies have investigated the prevalence of radiographic LS[3,9,11–16], but only a few have examined the incidence and progression of radiographic LS or their risk factors[17–21]. In addition, although lower back pain is believed to be the principal clinical symptom of LS, the correlation is not as close as would be expected, and the findings of cross sectional studies have often indicated a disconnect between them[3,11]. However, the incidences of radiographic LS and lower back pain have never been simultaneously analyzed in a longitudinal study.

The objective of the present study was to clarify the incidence and progression rate of radiographic LS as well as the incidence rate of lower back pain in Japanese men and women using the large-scale, population-based cohort study known as Research on Osteoarthritis/osteoporosis Against Disability (ROAD). In addition, we examined risk factors for the incidence and progression of LS as well as the incidence of lower back pain.

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doi:10.1016/j.joca.2012.03.009

Subjects and methods

Subjects

The ROAD study was a nationwide prospective study of bone and joint diseases (with osteoarthritis and osteoporosis as representative bone and joint diseases) in population-based cohorts established in several communities in Japan. A detailed profile of the ROAD study has already been described elsewhere[3,10,22,23], and thus a brief summary is provided here. Between 2005 and 2007, we created a baseline database that included clinical and genetic information about 3,040 inhabitants (1,061 men; 1,979 women) in the age range of 23–95 years (mean, 70.6 years), recruited from listings of 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 proceeded with the approval of ethics committees of the University of Tokyo and the Tokyo Metropolitan Institute of Gerontology. Participants completed an interviewer-administered questionnaire of 400 items that included lifestyle information such as smoking habits, alcohol consumption, family history, and medical history. Anthropometric measurements included height and weight, from which the body mass index (BMI) (weight [kg]/height^2 [m^2]) was calculated. . Experienced orthopaedists also asked all participants the question regarding lower back pain: "Have you experienced lower back pain on most days during the past month, in addition to now?" Those who answered "yes" were defined as having lower back pain based on previous studies[3].

Between 2008 and 2010, we attempted to trace and review all 3,040 participants by inviting them to attend a follow-up interview and undergo repeat radiography. The interviews included questions about current lower back pain and were conducted by the same trained orthopaedists who undertook the baseline study between 2005 and 2007. Anthropometric data including height and weight, were also obtained at follow-up.

Radiographic assessment

Plain radiographs of the lumbar spine at baseline and follow-up were taken in anteroposterior and lateral positions, and the images were downloaded into Digital Imaging and Communication in Medicine (DICOM) files to assess radiographic spondylosis. We used contrast-adjusted images to detect osteophytes and intervertebral spaces when the original images were obscure. Osteophytes were analyzed at endplates. LS at baseline and follow-up was read in pairs according to the Kellgren and Lawrence (KL) grading[24] (without blinding to baseline and follow-up status) at each intervertebral level from L1/2 to L5/S by a single experienced orthopaedist (S.M.), who was blinded to the background of each patient. The KL scale defines radiographic OA in 5 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 intraobserver variability of the KL grading, 100 randomly selected radiographs of the lumbar spine were scored by the same observer more than 1 month after the first reading. Furthermore, 100 other radiographs were scored by two experienced orthopaedic surgeons (S.M. and H.O.) using the same radiographic atlas to determine interobserver variability. Intra- and interobserver variability was evaluated by kappa analysis. These variabilities in the KL grading on lumbar radiographs were sufficient for assessment (0.84 and 0.76, respectively).

For the purposes of this study, we defined three LS outcomes. Incident KL ≥ 2 radiographic LS was defined if all vertebral interspaces had less than grade 2 disease at baseline, and if at least one vertebral interspace had grade ≥ 2 disease at follow-up. Incident KL ≥ 3 radiographic LS was defined if all vertebral interspaces had less than grade 3 disease at baseline, and if at least one vertebral interspace had $\geq$ grade 3 disease at follow-up. Progressive LS was defined as KL ≥ 2 LS at baseline, excluding subjects with KL $= 4$ LS at all vertebral interspaces because it cannot progress, and an increase of at least one grade in the affected vertebral interspace at follow-up.

Statistical analysis

Differences in age, height, weight, and BMI between men and women were examined using a non-paired Student's *t*-test. The prevalence of radiographic LS and lower back pain between men and women was compared the chi-squared test. We determined risk factors for incident and progressive LS and incident lower back pain using a univariate logistic regression analysis. Independent risk factors were determined by multiple logistic regression analysis with significant risk factors in a univariate logistic regression analysis with age, gender and BMI, as independent variables. Incident lower back pain was defined as no lower back pain at baseline and lower back pain at follow-up. Associations between the number of affected vertebral interspaces and incident lower back pain were assessed using the Cochran-Armitage test for trends. The odds ratio (OR) and 95% confidence interval (CI) of the number of affected vertebral interspaces with incident lower back pain compared with no affected vertebral interspaces was determined using a logistic regression analysis with adjustment for age and BMI. Data were analyzed using SAS version 9.0 software (SAS Institute Inc., Cary, NC).

Results

Of the 3,040 participants in the baseline study between 2005 and 2007, 125 (4.1%) had died by the time of the review 3 years later, 123 (4.0%) did not participate in the follow-up study due to bad health, 69 (2.3%) had moved, 83 (2.7%) declined the invitation to attend the follow-up study and 155 (5.1%) did not participate for other reasons. Among the 2,485 individuals who participated in the follow-up study, we excluded 186 (6.1%) who did not undergo plain radiography and 17 (0.6%) who provided incomplete pain questionnaires, leaving a total of 2,282 (74.4%; 758 men; 1,524 women) from whom paired radiographs and complete pain histories were obtained. Their median age at follow-up was 72.1 ± 11.5 years. The duration of follow-up between the initial and second radiographs was 3.3 ± 0.6 (mean ± SD) years. Those participating in the follow-up study were younger than those who did not survive or who did not participate for other reasons (responders 68.8 years, nonresponders 74.8 years; $P < 0.0001$). The follow-up study participants were also more likely to be women (responders 66.8% women, nonresponders 60.0% women; $P = 0.0007$) and were less likely to have LS at the baseline examination than either those who did not survive to follow-up or those who did not participate for other reasons (responders 68.1%, nonresponders 77.5%; $P < 0.0001$). The prevalence of lower back pain was similar between responders and nonresponders (responders 19.0%, nonresponders 18.7%; $P = 0.91$).

Table I shows the characteristics of the 2,282 participants at baseline in the ROAD study. Men were significantly older than women, and the BMI was higher in men than women. The prevalence of KL ≥ 2 LS was significantly higher in men than women at

Table I
Characteristics of participants at baseline

	Men	Women	*P*-values
Number of subjects	758	1,524	
Age at baseline, years	69.8 ± 11.0	68.3 ± 11.3	0.003
Height at baseline, cm	163.0 ± 6.6	150.4 ± 6.4	<0.0001
Weight at baseline, kg	62.0 ± 9.7	52.1 ± 8.6	<0.0001
BMI at baseline, kg/m^2	23.3 ± 3.0	23.0 ± 3.4	0.054
Grip strength at baseline, kg	34.3 ± 8.7	22.2 ± 6.1	<0.0001
Prevalence at baseline			
KL $\geq$ 2 (%)	79.9	62.3	<0.0001
KL $\geq$ 3 (%)	43.1	44.6	0.531
Lower back pain (%)	16.9	20.0	0.073
Smoking (%)	21.5	3.2	<0.0001
Alcohol (%)	63.2	23.0†	<0.0001

Except where indicated otherwise, values represent mean ± SD.
*$P < 0.05$ vs. men by non-paired Student's *t*-test; †$P < 0.05$ vs men by chi squared test.

baseline, while that of KL $\geq$ 3 LS and lower back pain was similar between men and women.

Table II shows the rates of incident and progressive radiographic LS as well as that of incident lower back pain. Given the 3.3-year follow-up, the rates of incident KL $\geq$ 2 and $\geq$3 LS and progressive LS, and incident lower back pain were 38%, 21%, 25%, and 30%, respectively. The incidence of KL $\geq$ 2 LS was significantly lower, but that of KL $\geq$ 3 LS was significantly higher in women than in men. The rate of progressive LS was also significantly higher in women than men. The rate of incident and progressive LS increased with age in men and women ($P < 0.05$) (Fig. 1). The rate of incident lower back pain was not age-dependent in either men or women ($P = 0.44$ and 0.85, respectively) (Fig. 1). We also showed incidence and progression of LS at each vertebral interspace in Supplementary Table. Among the vertebral interspaces, the incident rate of KL $\geq$ 2 LS was highest at the L2/3 interspace. While, the incident rate of KL $\geq$ 3 LS was highest at the L4/5 interspace.

Table III shows baseline risk factors for radiographic LS. Multiple logistic regression analysis showed that age was a risk factor for KL $\geq$ 2 and KL $\geq$ 3 LS and that higher BMI was a risk factor for KL $\geq$ 2, but not for KL $\geq$ 3. Female gender was a protective factor against the incidence of KL $\geq$ 2 LS but was a risk factor for the incidence of KL $\geq$ 3 LS. A higher KL grade at baseline was a risk factor for KL $\geq$ 3 LS. Lower back pain at baseline, smoking and alcohol consumption were not associated with incident KL $\geq$ 2 or KL $\geq$ 3 LS. We further examined the risk factors for progressive LS in individuals with KL $\geq$ 2 LS, excluding those with KL = 4 LS at all vertebral interspaces (Table IV). Age and female gender were also risk factors for progressive LS, whereas BMI, lower back pain at baseline, smoking and alcohol consumption were not associated with progressive LS. A grade of KL $\geq$ 3 at baseline was a risk factor for progressive LS compared with KL = 2.

We next examined the risk factors for incident lower back pain (Table IV). KL $\geq$ 3 LS was associated with incident lower back pain compared with KL = 0 or 1, whereas age, BMI, gender, smoking and alcohol consumption were not associated with incident lower back pain. We next examined the association between KL grade at each vertebral interspace and incident lower back pain (Table V). In women, KL $\geq$ 3 LS at L2/3, 3/4, 4/5, and 5/S and the most severely affected interspaces were significantly associated with incident lower back pain compared with KL < 3 at the corresponding interspaces. KL $\geq$ 3 LS at L2/3, 3/4, 4/5 and 5/S in men tended to be associated with incident lower back pain compared with KL < 3 at the corresponding interspaces, but these findings did not reach statistical significance except for the L3/4 and L5/S interspaces. KL $\geq$ 3 LS at the L1/2 interspace was not associated with incident lower back pain in men or women. Thus, we further examined the number of KL $\geq$ 3 vertebral interspaces among L2/3, 3/4, 4/5 and 5/S interspaces (Supplementary Fig. 1). The Cochran-Armitage test for trends showed that the incidence rate of lower back pain significantly increased as the number of affected vertebral interspaces increased in women ($P < 0.001$), but not in men ($P = 0.09$). In addition, multiple logistic regression analysis after adjustment for age and BMI showed that having three or more KL $\geq$ 3 vertebral interspaces was significantly associated with incident lower back pain in men (OR 1.69 95% CI 1.03–2.76) and in women (OR 1.77, 95% CI 1.34–2.34).

Discussion

This is the first population-based study to examine the rates of incident and progressive radiographic LS as well as incident lower back pain, and their risk factors in Japanese men and women. We found high rates of incident and progressive LS and incident lower back pain in Japanese men and women.

Few population-based studies have examined incident radiographic LS [17,18]. Symmons *et al.* examined radiographic changes in the lumbar spines of Dutch women (mean age, 54 years) using KL grade[17] and found that 4.2% per year of individuals with no disc degeneration (KL grade 0/1) but with recurrent back pain, and 3.2% per year of those with no disc degeneration and no back pain at baseline, had disc degeneration at follow-up. The present study found a 27.6% incidence rate of KL $\geq$ 2 LS in women aged in their 50s over a period of 3.3 years (9.0% per year), and thus the incidence of KL $\geq$ 2 LS is apparently considerably higher in Japanese than Caucasian women, although a strict comparison may be limited because of differences in definition of the incidence of LS. Considering the definition of the KL grade, this may suggests that the incidence of osteophytosis is higher in Japanese women than in Caucasian women.

Regarding progression of radiographic LS, Symmons *et al.* reported that 63.1% (7.0% per year) of individuals with disc degeneration and with recurrent back pain, and 55.4% (6.2% per year) of those with disc degeneration but without back pain at baseline, had worse disc degeneration at follow-up[17]. The present

Table II
Incidence of radiographic LS and progressive LS as well as incidence of lower back pain

	KL $\geq$ 2 LS		KL $\geq$ 3 LS		Progressive LS		Lower back pain	
	No. at risk	Incidence (%)	No. at risk	Incidence (%)	No. at risk	Incidence (%)	No. at risk	Incidence (%)
Overall	727	274 (37.7)	1,276	266 (20.8)	1,530	378 (24.7)	1,849	558 (30.2)
Men	152	76 (50.0)	431	66 (15.3)	599	123 (20.5)	630	178 (28.3)
Women	575	198 (34.4)*	845	200 (23.7)*	931	255 (27.4)*	1,219	380 (31.2)

Incident KL $\geq$ 2 and $\geq$3 radiographic LS at the overall vertebral interspace was defined as all vertebral interspaces having less than grade 2 or 3 disease at baseline, and if at least one vertebral interspace was grade 2 or higher or grade 3 or higher at follow-up, respectively.
Progressive LS in the overall inter spaces was defined as KL $\geq$ 2 LS at baseline, excluding subjects with KL = 4 LS at all vertebral interspaces because it cannot progress, and an increase by at least 1 grade in the affected vertebral interspace at follow-up.
Incident lower back pain was defined as no lower back pain at baseline and lower back pain at follow-up.
*$P < 0.05$ vs men by chi square test.

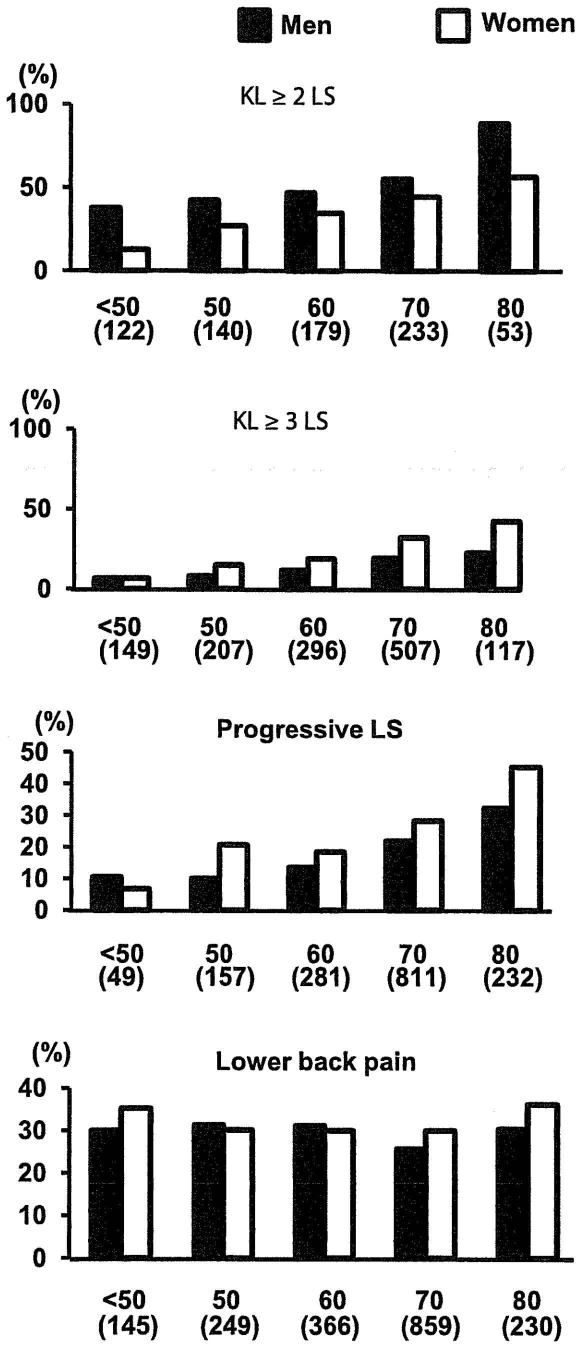

Fig. 1. Ratios (%) of individuals with incident radiographic LS (KL ≥ 2 and KL ≥ 3), progressive LS and incident lower back pain in each age stratum (<50, 50–59, 60–69, 70–79 and ≥80 years). Data in brackets are the number of individuals in each group.

study found that the progression rate of LS in women aged in their 50s was 20.9% over a period of 3.3 years (6.3% per year) and thus the progression rate of LS appears similar between Japanese and Caucasian women. In the present study, progression of radiographic LS was defined as KL ≥ 2 LS at baseline and an increase of at least one grade in the affected vertebral interspace at follow-up. Considering the definition of the KL grade, progression of radiographic LS may mean incidence or progression of disc space narrowing in subjects with osteophytosis, thus, our results may indicate that the incidence or progression of disc space narrowing is similar between Japanese and Caucasian women.

Furthermore, the present study included an investigation of KL ≥ 3 LS. To the best of our knowledge, incident KL ≥ 3 LS has never been investigated in a population-based study. LS was not defined according to KL grade but according to osteophytosis and disk space narrowing in the Chingford study[18]. That study showed that the progression of disk space narrowing was 3.2% per year in women whose mean age was 54 years at baseline. Our results regarding incident KL ≥ 3 LS might be comparable to these, considering the definition of KL grade, although a detailed comparison provides only limited accuracy. The incidence rate of KL ≥ 3 LS was 15.0% (4.5% per year) in Japanese women aged in their 50s at baseline in the present study, which was also higher than that in Caucasian women. This might in part be related to ethnic variations.

The incidence of KL ≥ 2 spondylosis was notably higher in men than in women, while that of KL ≥ 3 spondylosis was higher in women in the present study. Considering the definition of KL grade, this might mean that the incidence of osteophytosis is higher in men, whereas the incidence of disk space narrowing is higher in women. In fact, osteophytosis of the lumbar spine is more common in men than in women[11,12], whereas disc space narrowing is more prevalent in women[12]. A cross-sectional study that investigated the extent, prevalence and distribution of spinal spondylosis in women also showed that osteophytosis and disc space narrowing significantly correlated, but each predicted only 19% of the variation in the other[13]. This discordance suggests that different mechanisms influence the initiation of osteophytosis (the principal abnormality in KL grade 2 disease) and disk space narrowing (a principal abnormality in KL grade 3 disease). Our findings have implications for understanding of the pathogenesis of LS, as well as for designing preventive strategies.

In the present study, age, BMI, gender and KL grade at baseline were significantly associated with incident LS; this result differed from the findings of previous studies[19–21]. The UK twin spine study[19] using magnetic resonance imaging (MRI) showed that age, BMI and gender had no detectable effect on the progression of lumbar disc degeneration. The Finnish twin spine study also showed that body weight was not associated with progression of lumbar disc degeneration[20]. These differences may be explained not only by the differences in the definition of progressive LS, but also the ages of the subjects between these previous studies and the present study. The subjects in the UK twin study and Finnish twin study were quite younger at baseline than those in the present study (55 years, 49 years and 69 years, respectively). The association of these factors with LS may change among the age strata. In addition, racial differences may exist in the association of these factors with LS, because the prevalence or incidence of LS is different among races[3]. Age, BMI and female gender were not risk factors for lower back pain in the present study. Lower back pain occurrence might be mainly due to environmental, rather than to individual factors. Elderly men in particular generally retire at around age 60–70 years, and thus the load on the lower back might be greater in men aged below 60 years compared with those over 60 years, which might partly explain the lack of a significant association between age and the incidence of lower back pain. KL ≥ 3 LS was significantly associated with incident lower back pain compared with the absence of LS. Cross sectional studies have shown that the correlation between LS and lower back pain is not as strong as would be expected, and they are often disconnected[3,11]. However, this longitudinal study discovered that severe radiographic LS is a risk factor for lower back pain. We further found that the association between the number of KL ≥ 3 vertebral interspaces and the incidence of lower back pain differed between men and