icant, except for squatting in women. Because men are known to have greater muscle strength than women of all ages and muscle strength has a protective effect on knee OA (36–38), it might be that the greater muscle strength obscures the harmful effects of kneeling and squatting on knee OA in men, resulting in lower ORs for knee OA than in women.

For K/L grade ≥2 lumbar spondylosis, there were no occupational activities associated with the increased prevalence except for heavy lifting in women. Few studies have focused on risk factors for lumbar spondylosis associated with occupational activity (25–28), and no increased risk of lumbar osteophytes due to physical activities has been reported (25,39,40).

In the present study, the occupational activity of sitting on a chair was inversely associated with both K/L grade ≥2 knee OA and lumbar spondylosis. For knee OA, our previous small-scale study showed that prolonged sitting on a chair at work was associated with a reduced prevalence of knee OA (34) (Table 5). Regarding the relationship between sedentary work and OA, the results of studies investigating the influence of sedentary work on knee OA are controversial (21,22). Although sitting on a chair clearly involves reduced load on many joints compared with other working activities, no other studies have reported a relationship between sedentary activity and knee OA. Sitting on a chair as a physical activity in the work place appears to represent a characteristic protective factor for OA in Japan.

Contrary to K/L grade ≥2 knee OA, occupational activities of kneeling and squatting were significantly associated with K/L grade ≥3 knee OA, whereas those of standing, walking, and climbing were not. Considering the definition of the K/L grade, this may suggest distinct risk factors between osteophytosis and joint space narrowing. In this population-based cohort study, the prevalence of K/L grade ≥2 knee OA was 45.6% in men and 61.2% in women, which was higher than that in whites, whereas that of K/L grade ≥3 was 16.8% and 26.5%, which is comparable with that in whites (41), suggesting that the Japanese lifestyle may be associated with osteophytosis rather than joint space narrowing. Therefore, regarding K/L grade ≥2 knee OA, the Japanese lifestyle could obscure the association between knee OA and occupational activities of kneeling and squatting as mentioned above. Furthermore, the discrepancy between risk factors for K/L grade ≥2 and K/L grade ≥3 knee OA may also be due to differences between the mechanism of osteophytosis and joint space narrowing. There is accumulating evidence that osteophytosis and joint space narrowing have distinct etiologic mechanisms (25,42–47). A previous prospective study using a large-scale OA cohort reported that there was no association between the 2 representative features of knee OA (44). A recent cross-sectional study also showed that osteophytosis was unrelated not only to joint space narrowing on plain radiographs, but also to cartilage loss measured by quantitative magnetic resonance imaging (45). Furthermore, our study on an experimental mouse model for OA has identified a cartilage-specific molecule, carminerin, which regulates osteophytosis without affecting joint cartilage destruction during OA progression (46,47). Further clinical and basic research will disclose the distinct backgrounds of these 2 features of OA.

There are several limitations in the present study. First, this is a cross-sectional study on factors associated with knee OA and lumbar spondylosis, so a causal association with occupational activity could not be determined. However, information collected included a lifetime occupational history and details of specific work place physical activities; therefore, ample evidence on the background of knee OA and lumbar spondylosis could be obtained. Second, information regarding past occupational exposures was obtained by self-report and there is a possibility that both self-selection bias and recall bias may have occurred. People with painful conditions may choose work that allows them to avoid aggravation of their conditions, so the impact of job titles and occupational activities on knee OA and lumbar spondylosis may be underestimated in the present study. Conversely, people with painful knee and lumbar conditions are likely to look for and assign a cause when asked about past work exposures. To determine the impact of working conditions on knee OA and lumbar spondylosis independently of the presence of pain at the examination, we analyzed the association of knee OA and lumbar spondylosis with job titles and occupational activities according to the presence of knee pain and low back pain at the baseline examination. The direction of association was similar regardless of the presence of pain, and the results between the overall population and the subpopulation without knee pain or low back pain were not different, suggesting that pain at the examination may not affect the results of the overall population very much in this study.

In conclusion, the present cross-sectional study using a large-scale population from the ROAD study revealed distinct risk factors of occupational activities for radiographic knee OA and lumbar spondylosis in Japanese subjects. Sitting on a chair was a significant protective factor for both radiographic knee OA and lumbar spondylosis. Other occupational activities of kneeling, squatting, standing, walking, climbing, and heavy lifting were risk factors for radiographic knee OA, but not for radiographic lumbar spondylosis. Further studies, along with longitudinal data in the ROAD study, will elucidate the environmental backgrounds of OA and spondylosis and clarify clinical evidence for the development of disease-modifying treatments.

AUTHOR CONTRIBUTIONS

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

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Prevalence of radiographic knee osteoarthritis and its association with knee pain in the elderly of Japanese population-based cohorts: The ROAD study

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Summary

Objective: We investigated the prevalence of radiographic knee osteoarthritis (OA) and knee pain in the Japanese elderly using a large-scale population of a nationwide cohort study, Research on Osteoarthritis Against Disability (ROAD), and examined their association.

Methods: From the baseline survey of the ROAD study, 2,282 participants ≥60 years (817 men and 1,465 women) living in urban, mountainous and seacoast communities were analyzed. The radiographic severity at both knees was determined by the Kellgren/Lawrence (KL) grading system. KL ≥ 2 and KL ≥ 3 knee OA were examined separately to assess osteophytosis and joint space narrowing (JSN).

Results: The prevalence of KL ≥ 2 OA (47.0% and 70.2% in men and women, respectively) was much higher than that of previous studies in Caucasians, while that of KL ≥ 3 OA was not much different in men. Age, BMI, female sex and rural residency were risk factors for radiographic knee OA, knee pain and their combination. The prevalence of knee pain was age-dependent in women, but not in men. Knee pain was more strongly associated with KL ≥ 3 OA than with KL = 2, and the association was higher in men than in women. Female sex was a strong risk factor even in the subgroup without radiographic knee OA (KL = 0/1).

Conclusion: The present cross-sectional study revealed a high prevalence of radiographic knee OA in the Japanese elderly. Knee pain was strongly associated with JSN especially in men, while women tended to have knee pain even without radiographic OA.

Key words: Osteoarthritis, Knee, Prevalence, Pain, Cross-sectional.

Introduction

Knee osteoarthritis (OA), characterized by pathological features including joint space narrowing (JSN) and osteophytosis, is a major public health issue causing chronic pain and disability of the elderly in most developed countries[1–3]. Despite the urgent need of strategies for the prevention and treatment of this condition, the prevalence overall and among demographic subgroups is not well characterized. The reported prevalence of radiographic knee OA differs considerably among previous population-based epidemiologic studies[4–14]. This may be due to a limitation of the sample size or a variability of age, ethnicity and radiological acquisition.

With the goal of establishing epidemiologic indexes to evaluate clinical evidence for the development of a disease-modifying treatment of OA, we set up a large-scale nationwide OA cohort study called Research on Osteoarthritis Against Disability (ROAD) in 2005. We have to date created a baseline database with detailed clinical and genetic information on three population-based cohorts in urban, mountainous and seacoast communities of Japan. The present study initially investigated the prevalence and distribution of knee OA according to age, gender and community using cohorts of 2,282 participants who were 60 years or older in the baseline survey of the ROAD study.

The most popular grading system for the radiographic severity of knee OA is the Kellgren/Lawrence (KL) system with classification into five-grade (0–4) scales. KL grade 2 is defined as osteophyte formation and grade 3 as JSN in addition to osteophyte formation; and KL ≥ 2 is generally thought to be the standard of the diagnostic criterion of knee OA[15,16]. However, accumulating evidence has shown that osteophytosis and JSN have distinct etiologic mechanisms and their progression is neither constant nor proportional[17–19]. Hence, to assess these two pathological features separately, the present study examined not only the prevalence of KL ≥ 2, but also that of KL ≥ 3 knee OA.

Arthritis is the most common cause of pain in the elderly, and knee pain is the principal clinical symptom of knee OA[20]. Although much effort has been devoted toward a definition of knee pain, the correlation with radiographic severity of the knee OA was not as strong as one would expect[21–23]. This study also examined the association of

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KL $\geq$ 2 and KL $\geq$ 3 knee OA separately with the presence of knee pain according to gender and age stratum.

Subjects and methods

SUBJECTS

The ROAD study is a nationwide OA prospective study constituted of population-based cohorts established in several communities in Japan. To date, we have completed creation of a baseline database including clinical and genetic information of 3,040 inhabitants (1,061 men and 1,979 women) ranging in age from 23–95 years (mean 70.6 years), who were recruited from listings of resident registration in three communities. Itabashi-ku, an urban community located in the east of Tokyo, had a population of 529,400/32 km^2 with 0.1, 25, and 75% of jobs in the primary industry (agriculture, forestry, fishing and mining), the secondary industry (manufacturing and construction), and the tertiary industry (service industry), respectively, and residents $\geq$65 years constituted 19.1% of the population. Hidakagawa-cho, a rural mountainous community located in the center of Wakayama, had a population of 11,300/330 km^2 with 29, 24 and 47% of jobs in the three industries above, and 30.5% were $\geq$65 years. Taiji-cho, a rural seacoast community located south of Wakayama, had a population of 3,500/6 km^2 with 13, 18, and 69% of jobs in the three industries, and those $\geq$65 years accounted for 34.9% of the total. Participants in the urban region were recruited from a cohort study[24] in which the participants were randomly drawn from the Itabashi-ward residents register database and the response rate in the age groups of 60 years or older was 75.6%. Participants in the mountainous and seacoast regions were recruited from listings of resident registration and the response rates in the age groups of 60 years or older were 68.4% and 29.3%, respectively. All participants provided written informed consent, and the study was conducted 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 occupational career, smoking habits, alcohol consumption, family history, medical history, physical activity, reproductive variables, and health-related quality of life. Anthropometric measurements included height, weight, arm length, bilateral grip strength and body mass index (BMI; weight [kg]/height^2 [m^2]). Medical information was taken by well-experienced orthopaedic surgeons (S.M. and H.O.) on systemic, local and mental status including information of knee, hip and low back pain, swelling and range of motion of the joints, and patellar and achilles tendon reflex. Knee pain was defined as that in and around the knee joint on most days during the past month. A self-recorded nutritional survey was also performed. Blood and urine samples were collected for biochemical and genetic examinations. Plain radiographs of knee, hip and lumbar spine were taken for all participants. Participants were confirmed to be comparable to the Japanese general population according to the national nutrition survey by the Ministry of Health, Labour and Welfare (Japan). Mean height was 162.5 and 149.7 cm in men and women, respectively, in the ROAD study vs 162.6 and 149.9 cm in the Japanese general population. Weight was 61.3 and 51.8 kg vs 61.6 and 53.8 kg. Percentage of the population with a smoking habit was 26.4 and 3.2% vs 29.4 and 4.0%. From the baseline data of the overall participants, the present study analyzed 2,282 (817 men and 1,465 women) aged 60 years or older, after excluding six subjects with total knee arthroplasty.

RADIOGRAPHIC ASSESSMENT

All participants had radiographic examination of both knees using an anterior–posterior view with weight-bearing and foot map positioning. Fluoroscopic guidance with a horizontal anterior–posterior X-ray beam was used to visualize the joint space properly. Knee radiographs were read without knowledge of participant clinical status by a single well-experienced orthopaedist (S.M.), and KL grade was defined using the KL radiographic atlas for overall knee radiographic grades[15]. The higher KL grade in both knees was designated as that of a participant. The radiographic knee OA with pain was defined as: (1) a subject reporting knee pain lasting at least 1 month with pain having last occurred within the current or previous year; and (2) radiographic OA in that painful knee. To evaluate the intraobserver variability of the KL grading, 100 randomly selected radiographs of the knee were scored by the same observer more than 1 month after the first reading. One hundred other radiographs were also scored by two experienced orthopeadic surgeons (S.M. & H.O.) using the same atlas for interobserver variability. The intra- and inter variabilities evaluated for KL grade (0–4) were confirmed by the kappa analysis to be sufficient for assessment (0.86 and 0.80, respectively). Further, to determine the prevalence of medial and lateral knee OA, knee radiographs were also read for JSN in the medial and lateral compartment separately according to the Osteoarthritis Research Society International (OARSI) atlas by a single well-experienced orthopaedist (S.M.)[25]. Medial OA was defined as present when a knee had a KL grade $\geq$2 and medial JSN score of $\geq$1 on a 0–3 scale. Lateral OA was defined as being present when a knee had a KL grade $\geq$2 and lateral JSN score of $\geq$1 on a 0–3 scale.

STATISTICAL ANALYSIS

The differences of age and BMI between men and women were examined by non-paired *t*-test. Differences in age, height, weight and BMI among the urban, mountainous and seacoast communities were determined using one-way analysis of covariance and Scheffe's test. To compare the prevalence of radiographic knee OA between men and women, we performed logistic-regression analysis after adjustment for age and BMI. Association of prevalence with age was determined by logistic-regression analysis after adjustment for BMI. Association of the variables such as age, BMI, gender and community with radiographic knee OA was evaluated by multivariate logistic-regression analysis. Logistic-regression analyses were used to estimate odds ratio and the associated 95% confidence interval (CI) of KL = 2 and KL $\geq$ 3 knee OA for pain compared with KL = 0 or 1 after adjustment for age, BMI, and community. Data analyses were performed using SAS version 9.0 (SAS Institute Inc., Cary, NC).

Results

The characteristics of the 2,282 participants aged 60 years and older in the three cohorts of the ROAD study are shown in Table I. Men were significantly older than women in the overall population and in some communities. Although the seacoast residents tended to show higher body height and weight than the other two communities, BMI was comparable among the three communities and between genders.

Table II shows the prevalence of radiographic knee OA, knee pain and radiographic knee OA with pain in the overall population and subgroups classified by gender and community. In the overall population, prevalence of KL $\geq$ 2 and KL $\geq$ 3 OA was 61.9 and 20.6%, respectively, and that of knee pain was 32.8%. That of KL $\geq$ 2 and KL $\geq$ 3 OA with knee pain was 26.1% and 13.2%, respectively. The prevalence of unilateral and bilateral KL $\geq$ 2 knee OA was 12.3% and 49.5%, respectively, while the prevalence of unilateral and bilateral KL $\geq$ 2 knee OA with pain was 2.9% and 20.4%, respectively. We next analyzed the prevalence of

Table I
Characteristics of participants

	Men				Women			
	Overall	Urban	Mountainous	Seacoast	Overall	Urban	Mountainous	Seacoast
Number of subjects	817	396	266	155	1,465	740	433	292
Age, years	74.7 ± 6.1	77.3 ± 4.1	72.1 ± 6.2†	72.7 ± 7.4†	74.0 ± 6.4*	76.4 ± 4.8*	72.0 ± 7.0†	70.9 ± 6.8*†
Height, cm	161.3 ± 6.3	161.3 ± 5.9	160.3 ± 6.6	163.0 ± 6.1†	148.6 ± 6.2	148.6 ± 5.7	146.8 ± 6.4†	151.1 ± 5.9†
Weight, kg	60.1 ± 9.9	59.8 ± 8.3	59.3 ± 11.4	62.2 ± 10.6†	50.9 ± 8.9	50.7 ± 8.4	49.8 ± 9.7	53.0 ± 8.6†
BMI, kg/m^2	23.0 ± 3.3	23.0 ± 2.7	23.0 ± 3.8	23.3 ± 3.3	23.0 ± 3.7	22.9 ± 3.5	23.0 ± 4.1	23.2 ± 3.5

Data are means ± SD.
*$P < 0.05$ vs men in the corresponding group by non-paired *t*-test.
†$P < 0.05$ vs urban residents in the corresponding group by Scheffe's test.

Table II
Number (percentage) of participants with radiographic knee OA, knee pain, and their combination

	Overall	Men				Women			
		Overall	Urban	Mountainous	Seacoast	Overall	Urban	Mountainous	Seacoast
Radiographic knee OA									
KL ≥ 2	1,413 (61.9)	384 (47.0)	171 (43.2)	154 (57.9)	59 (38.1)	1,029 (70.2)*	521 (70.4)*	340 (78.5)*	168 (57.5)*
KL ≥ 3	470 (20.6)	110 (13.5)	27 (6.8)	45 (16.9)	38 (24.5)	360 (24.6)*	133 (18.0)*	139 (32.1)*	88 (30.1)*
Knee pain	748 (32.8)	197 (24.1)	100 (25.3)	76 (28.6)	21 (13.5)	551 (37.6)*	299 (40.4)*	176 (40.6)*	76 (26.0)*
Radiographic knee OA with pain									
KL ≥ 2	595 (26.1)	129 (15.8)	54 (13.6)	60 (22.6)	15 (9.7)	466 (31.8)*	237 (32.0)*	165 (38.1)*	64 (21.9)*
KL ≥ 3	301 (13.2)	63 (7.7)	21 (5.3)	29 (10.9)	13 (8.4)	238 (16.2)*	97 (13.1)*	93 (21.5)*	48 (16.4)*

*$P < 0.01$ vs men in the corresponding group by logistic-regression analysis after adjustment for age and BMI.

medial and lateral knee OA in the participants and found that they were 20.4 and 2.1% in men and 40.0 and 3.1% in women, respectively. Logistic-regression analysis after adjustment for age and BMI revealed that the prevalence of radiographic knee OA, knee pain, and their combination was significantly higher in women than in men. When the association of the prevalence with the age group (<65, 65–69, 70–74, 75–79 and ≥80) was examined, radiographic knee OA (KL ≥ 2 and KL ≥ 3) tended to increase with age in both genders [Fig. 1(A)]. Interestingly, the prevalence of knee pain was age-dependent in women, but not in men. Hence, that of radiographic OA with pain tended to be higher with age in women, but was affected little by age in men [Fig. 1(B)].

To examine the association of age, BMI, gender, and community with radiographic knee OA, knee pain, and their combination, we further performed logistic-regression analyses to estimate odds ratios and 95% CI (Table III). Age, BMI, and female sex were shown to be risk factors for all of them. Among the communities, mountainous area residents had a higher risk of KL ≥ 2 and KL ≥ 3 knee OA than urban residents, and seacoast area residents had a higher risk for KL ≥ 3 knee OA than urban residents.

We then evaluated the association between radiographic knee OA and knee pain in the designated knee. Figure 2 shows the percentage of subjects with knee pain in subgroups classified by radiographic OA severity: KL = 0/1, KL = 2, and KL ≥ 3. Although the percentage with pain was positively correlated with the radiographic severity, the difference between KL = 2 and KL ≥ 3 appeared to be greater than that between KL = 0/1 and KL = 2 in the overall population and all communities. When odds ratios of KL = 2 and KL ≥ 3 OA as compared to KL = 0/1 for the pain were estimated by logistic-regression analysis after adjustment for age, BMI, and community, KL = 2 OA was moderately but significantly associated with knee pain in both genders of the overall population (Table IV). However, KL ≥ 3 OA was much more strongly associated with knee pain not only in both genders of the overall population, but also in those of all age strata. Interestingly, although association of KL = 2 OA with pain was comparable between men and women, that of KL ≥ 3 OA with pain was stronger in

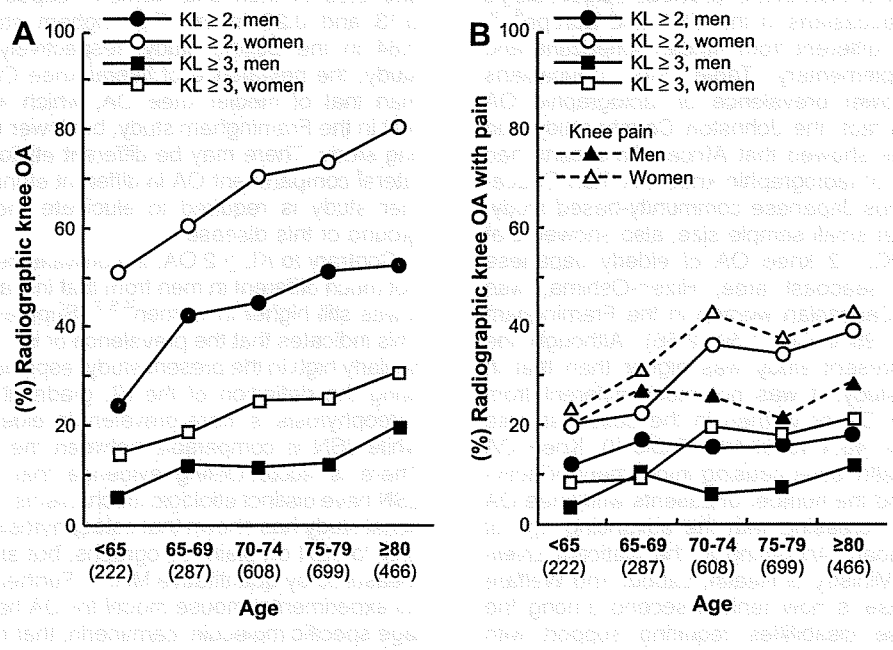

Fig. 1. (A) Percentage of subjects with radiographic knee OA (KL ≥ 2 or KL ≥ 3) in each age stratum (<65, 65–69, 70–74, 75–59 and ≥80). (B) Percentage of subjects with knee pain and radiographic knee OA (KL ≥ 2 or KL ≥ 3) with pain in each age stratum. The number of subjects in each age stratum is shown in parentheses.

Table III
Association of age, BMI, gender, and community with radiographic knee OA, knee pain and their combination

	Radiographic knee OA				Knee pain		Radiographic knee OA with pain			
	KL ≥ 2		KL ≥ 3				KL ≥ 2		KL ≥ 3	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age, years	1.09	1.07–1.11*	1.11	1.09–1.13*	1.04	1.02–1.06*	1.07	1.05–1.08*	1.09	1.07–1.12*
BMI, kg/m^2	1.14	1.11–1.18*	1.23	1.19–1.28*	1.18	1.14–1.21*	1.21	1.17–1.25*	1.24	1.20–1.29*
Women (vs Men)	3.28	2.71–3.97*	1.58	1.39–1.79*	2.05	1.68–2.51*	2.83	2.26–3.57*	2.59	1.92–3.53*
Community (vs Urban)										
Mountainous	2.64	2.08–3.35*	3.83	2.92–5.03*	1.27	1.02–1.58*	1.95	1.54–2.47*	2.84	2.09–3.85*
Seacoast	0.95	0.74–1.23	4.13	3.05–5.59*	0.56	0.42–0.73*	0.75	0.55–1.01	1.95	1.35–2.78*

The odds ratios were calculated by logistic-regression analysis after adjustment for all other variables.
*$P < 0.01$ OR = odds ratio, CI = confidential interval.

men. Considering that knee pain is more prevalent in women than in men (Tables II and III), we examined the association of gender with knee pain according to the KL grade. The odds ratio for knee pain of women compared with men estimated by a logistic-regression analysis after adjustment for age and BMI in the subgroup without radiographic knee OA (KL = 0/1) was comparable to or greater than that in those with radiographic knee OA (KL = 2 or KL ≥ 3) (Supplementary Table SI), suggesting independent backgrounds of knee pain between genders.

Discussion

The present study initially estimated the prevalence of knee OA in the Japanese elderly (≥60 years) using the baseline data of population-based cohorts in the ROAD study. The prevalence of KL ≥ 2 OA, the conventional diagnostic criterion of radiographic OA determined by the anterior–posterior view with standing position, was 47.0% and 70.2% in men and women, respectively (Table II), which was much higher than that of previous epidemiologic studies in elderly Caucasians in the USA and Europe[4–9], although not greatly different from African Americans and Chinese[10–12] (Supplementary Table SII). Caucasians seem to show a lower prevalence of radiographic OA than other races. In fact, the Johnston County study and the NHANES studies showed that African Americans had a higher prevalence of radiographic knee OA than Caucasians[6,8–10]. A previous Japanese community-based study, although with a rather small sample size, also showed that the prevalence of KL ≥ 2 knee OA of elderly Japanese women living in a seacoast area, Hizen-Oshima, was higher than that of Caucasian women in the Framingham study[13] (OR = 1.96, 95% CI = 1.50–2.56). Although the prevalence in the present study was higher than that in the Hizen-Oshima study, it was not much different from that of KL ≥ 2 knee OA of women in the seacoast area of the present study (46.4 vs 57.5%, Table II). Knee OA is a major public health issue causing impairment of activities of daily living and the number of patients with knee OA is suggested to be increasing with the advancing age of the population in Japan. According to the National Livelihood Survey of the Ministry of Health, Labour and Welfare in Japan, this disease is now ranked second among the diseases that cause disabilities requiring support with activities of daily living.

In the present study, the prevalence of unilateral and bilateral KL ≥ 2 knee OA was 12.3% and 49.5%, respectively, while it was 12.5 and 34.1% in the Beijing study and 15.2 and 19.7% in the Framingham study, respectively[11]. The high prevalence of bilateral OA in this study was comparable to that in the Beijing study, but higher than that in the Framingham study. The high prevalence of bilateral knee OA may indicate that environmental or ethnic factors have an important role in knee OA in Japan and China. Zhang *et al.* described that the higher prevalence of bilateral knee OA in China could be due to the much more physically active lifestyle of the Chinese compared with US whites, especially among those who are elderly[11]. The higher prevalence of bilateral knee OA in Japan could also be due to lifestyle factors, because the Japanese traditional lifestyle includes sitting on the heels on a mat and using Japanese-style lavatories; these positions may cause mechanical stress to the knee joint and possibly lead to the acceleration of OA[26,27]. On the other hand, the prevalence of medial and lateral knee OA in the present study was 20.4 and 2.1% in men and 34.0 and 3.1% in women, respectively. The ratio of lateral to medial knee OA was 0.10 and 0.09 in men and women, respectively, while it was 0.13 and 0.20 in the Framingham study and 0.80 and 0.64 in the Beijing study, respectively[28]. In the present study, the prevalence of lateral knee OA was much lower than that of medial knee OA, which was comparable to that in the Framingham study, but lower than that in the Beijing study. There may be different etiologies of medial and lateral compartment OA in different ethnic populations. Further study is required to elucidate the underlying background of this disease.

Contrary to KL ≥ 2 OA, the prevalence of KL ≥ 3 OA was not much different in men from that in Caucasians, although it was still higher in women[4,5,7] (Supplementary Table SII). This indicates that the prevalence of KL = 2 knee OA is particularly high in the present study, especially in men. Considering the definition of the KL grade, this may mean that osteophytosis is more prevalent in elderly Japanese men, while JSN is comparable between the two ethnic groups. There is accumulating evidence that osteophytosis and JSN have distinct etiologic mechanisms. A recent cross-sectional study has shown that osteophytosis was unrelated not only to JSN on plain radiographs, but also to cartilage loss measured by quantitative MRI[17]. Furthermore, our study on an experimental mouse model for OA has identified a cartilage specific molecule, carminerin, that regulates osteophytosis without affecting joint cartilage destruction during the OA progression[18,19]. Hence, there may be some risk factors that are specific to osteophytosis in elderly Japanese men.

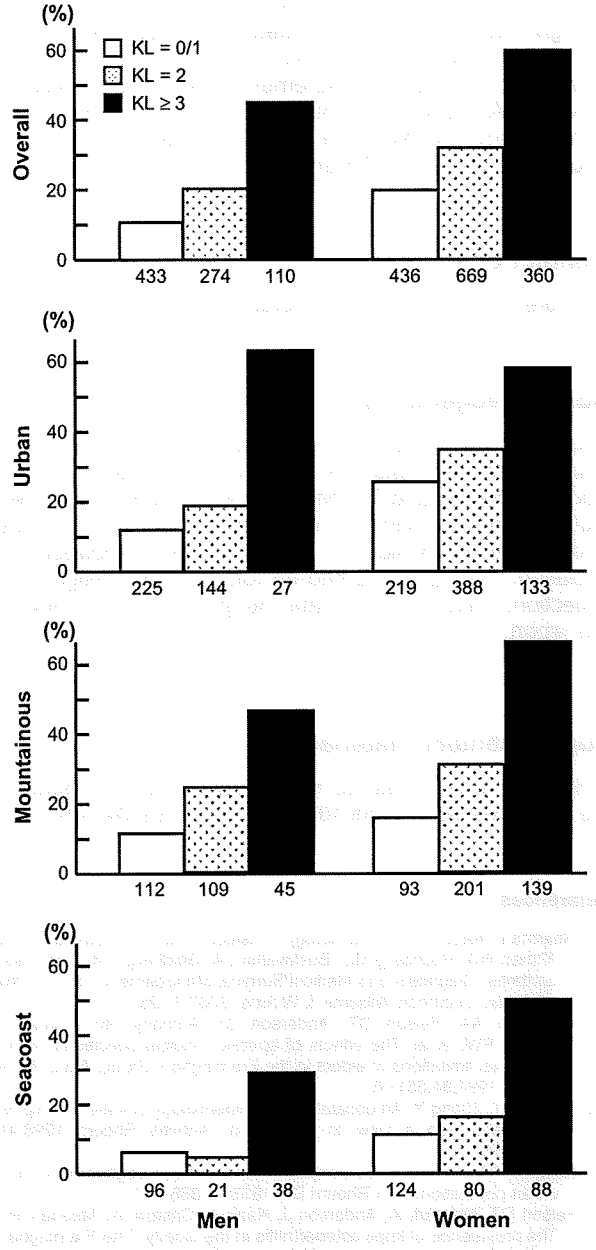

Fig. 2. Percentage of subjects with knee pain in each subgroup classified by the KL grade in the overall population and communities. The number of subjects in each subgroup is shown under the bars.

This study, the first analysis of the baseline data of the ROAD study, found that age and BMI were risk factors of radiographic knee OA (Table III), consistent with previous epidemiologic studies[1,29,30]. These factors may be related to the accumulation of mechanical stress on the knee joint. Female sex was also shown to be a strong risk factor, as in previous studies[4–8], possibly implicating an involvement of muscle strength to compensate the mechanical stress, as women are known to have less muscle strength than men in all decades[31]. Rural residency was also a risk factor of radiographic knee OA even after adjustment for age and BMI, indicating the involvement of other environmental factors like nutrition or occupation as well as genetic factors. In fact, the principle industries in the rural communities were

Table IV
Association of KL grade with knee pain according to age

	Overall		<65		65–69		70–74		75–79		≥80	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Men												
KL = 2	1.96	1.27–3.05†	4.16	0.61–31.78	1.31	0.37–4.49	2.51	1.12–5.74	2.87	1.29–6.82*	0.58	0.24–2.11
KL ≥ 3	8.55	5.00–14.84†	9.39	0.52–231.69	7.91	1.72–41.02†	5.44	1.77–17.02	13.49	4.91–39.86†	8.24	2.77–27.02†
Women												
KL = 2	1.55	1.15–2.09†	1.45	0.53–4.04	1.36	0.62–3.06	1.59	0.92–2.79	1.45	0.84–2.58	1.87	0.92–4.04
KL ≥ 3	4.37	3.09–6.21†	4.13	1.17–14.80*	3.16	1.18–8.73*	5.60	2.93–10.97†	2.82	1.49–5.43†	7.36	3.25–17.66†

The odds ratio was calculated by logistic-regression analysis compared with subjects with KL grade 0 or 1 after adjustment for age, BMI and communities.
*$P < 0.05$; †$P < 0.01$.

farming, forestry and fishing, each of which demands physical activity and repetitive laborious use of the knee joints. Because the database of the ROAD study includes such detailed information of environmental factors including occupational career, lifestyle, and physical activity, as well as genetic information, further analyses will allow us to elucidate the risk factors and backgrounds of knee OA in more detail.

The present study also showed that the odds ratio for knee pain of KL $\geq$ 3 OA was much higher than that of KL = 2 OA in both genders (Table IV), suggesting that JSN was more closely associated with the pain than osteophytosis. On the other hand, approximately 10% of men and 20% of women without radiographic knee OA (KL = 0/1) had knee pain. Although the prevalence of knee pain and radiographic OA with pain was approximately double in women what it was in men (Table II), the association of knee pain with radiographic knee OA, especially with KL $\geq$ 3 OA, was stronger in men (Table IV). Furthermore, the odds ratio for knee pain of women compared with men in the subgroup without radiographic knee OA (KL = 0/1) was comparable to or greater than that in those with radiographic knee OA (Supplementary Table SI). This suggests the existence of a cause of pain that is independent of OA in women, while the pain in men may be more dependent on JSN by OA. Radiographic JSN represents not only joint cartilage destruction, but also meniscal loss or extrusion. In addition, knee pain may arise from a variety of structures other than joint cartilage, like menisci, synovium, ligaments, bursae, bone and the bone marrow[32–36]. Hence, comprehensive mechanistic studies for the 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.

Although the prevalence of radiographic knee OA increased with age in both genders, that of knee pain was age-dependent only in women (Fig. 1). This might be due to the accumulated mechanical stress to the knee due to the Japanese traditional lifestyle and the decreased muscle strength as described above, both of which women may experience more than men. Alternatively, elderly men generally retire from their occupations around 60 to 70 years, while women must continue to do household chores even after the age of 70.

There are several limitations in this study. First, the radiographic investigators did not have readers calibrate themselves to readings from other studies. Although we reported higher prevalence of radiographic knee OA than in previous studies, 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 a substantial impact on their prevalence. The high prevalence 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 prevalence of radiographic outcomes and perhaps increase the concordance between radiographic knee OA and its pain. Third, because the KL system emphasizes osteophytosis, it is unclear how to handle knee OA with JSN but no osteophytosis. The investigation of the relationship among knee OA features including JSN and osteophytosis is the next task in the ROAD study.

In conclusion, the present cross-sectional study using a large-scale population from the ROAD study revealed a high prevalence of radiographic knee OA in the Japanese elderly. Knee pain was more strongly associated with KL $\geq$ 3 OA with JSN than with KL = 2 with osteophytosis, although it was distinctly associated with radiographic OA between genders. Further progress in developing an accurate method for surrogate measurement of the structural severity of knee OA, along with continued longitudinal survey in the ROAD study, will elucidate the environmental and genetic backgrounds of knee OA and its relation to knee pain.

Conflict of interest

There are no conflicts of interest.

Acknowledgements

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Supplementary material

Supplementary material for this article may be found, in the online version, at doi:10.1016/j.joca.2009.04.005.

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Prevalence of radiographic lumbar spondylosis and its association with low back pain in elderly subjects of population-based cohorts: the ROAD study

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ABSTRACT

Objectives: Although lumbar spondylosis is a major cause of low back pain and disability in elderly people, few epidemiological studies have been performed. The prevalence of radiographic lumbar spondylosis was investigated in a large-scale population study and the association with low back pain was examined.

Methods: From a nationwide cohort study (Research on Osteoarthritis Against Disability; ROAD), 2288 participants aged ⩾60 years (818 men and 1470 women) living in urban, mountainous and coastal communities were analysed. The radiographic severity at lumbar intervertebral levels from L1/2 to L5/S was determined by Kellgren/Lawrence (KL) grading.

Results: In the overall population the prevalence of radiographic spondylosis with KL⩾2 and ⩾3 at the severest intervertebral level was 75.8% and 50.4%, respectively, and that of low back pain was 28.8%. Although KL⩾2 spondylosis was more prevalent in men, KL⩾3 spondylosis and low back pain were more prevalent in women. Age and body mass index were risk factors for both KL ⩾2 and KL⩾3 spondylosis. Although KL = 2 spondylosis was not significantly associated with low back pain compared with KL = 0 or 1, KL⩾3 spondylosis was related to the pain only in women.

Conclusions: This cross-sectional study in a large population revealed a high prevalence of radiographic lumbar spondylosis in elderly subjects. Gender seems to be distinctly associated with KL⩾2 and KL⩾3 lumbar spondylosis, and disc space narrowing with or without osteophytosis in women may be a risk factor for low back pain.

Lumbar spondylosis is considered a major public health issue causing chronic disability of elderly people in most developed countries.[1 2] Despite the urgent need for strategies for the prevention and treatment of this condition, epidemiological data on lumbar spondylosis such as its prevalence and association with symptoms are sparse. With the goal of establishing epidemiological indices to evaluate clinical evidence for the development of disease-modifying treatment, we set up a large-scale nationwide cohort study for bone and joint disease called ROAD (Research on Osteoarthritis Against Disability) in 2005. We have to date created a baseline database with detailed clinical and genetic information on three population-based cohorts in urban, mountainous and coastal communities of Japan.

Lumbar spondylosis is characterised by disc degeneration and osteophytosis.[2 3] Although this disorder has been widely studied in a clinical setting, few population-based radiological studies have been attempted.[4–11] The reported prevalence of radiographic lumbar spondylosis differs greatly in these reports from about 40% to 85%. This may be due to limitation of the sample size and variability in age. The present study therefore initially investigated the prevalence and distribution of this disorder according to age, gender and community using cohorts of 2288 participants aged ⩾60 years in the baseline survey of the ROAD study.

The most popular grading system for the radiographic severity of osteoarthritis is the Kellgren/Lawrence (KL) system with classification into five grade scales (0–4) where KL⩾2 is the conventional standard of the diagnosis.[12] For lumbar spondylosis, KL grade 2 is defined as osteophyte formation and grade 3 as disc space narrowing in addition to osteophyte formation,[12] although few epidemiological studies have applied the KL system to evaluate the lumbar spine.[5 6 9] Hence, to assess osteophyte formation alone and disc space narrowing with or without osteophytosis separately, this study examined not only the prevalence of KL⩾2 spondylosis but also that of KL⩾3 spondylosis.

Although low back pain is believed to be the principal clinical symptom of lumbar spondylosis, its association with the radiographic severity remains unclear. The correlation was not as strong as one would expect, and there is often a disconnection between them.[7 8] In previous reports radiographic spondylosis was determined at the severest intervertebral level, but it is possible that other levels with milder spondylotic change might give rise to low back pain. This study therefore assessed the radiographic severity at all intervertebral levels of the lumbar spine by the KL system, and examined the association between radiographic severity and low back pain.

METHODS

Participants

The ROAD study is a nationwide prospective cohort study for bone and joint diseases consisting of population-based cohorts established in several communities in Japan. To date we have created a baseline database which includes clinical and genomic information of 3040 inhabitants (1061 men, 1979 women) in the age range 23–95 years (mean 70.6) in three 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 those of a cohort study[13] in which the participants were randomly drawn from the register database of Itabashi ward residents, with a response rate in the age group ≥60 years of 75.6%. Participants in the mountainous and coastal regions were recruited from resident registration lists, with response rates in the groups aged ≥60 years of 68.4% and 29.3%, respectively.

Participants completed an interviewer-administered questionnaire of 400 items which included 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, arm span, bilateral grip strength and body mass index (BMI, kg/m^2). Medical information was taken by experienced orthopaedic surgeons (SM and HO) on systemic, local and mental status including information on low back, knee and hip pain, swelling and range of motion of the joints, and patellar and achilles tendon reflex. All participants were interviewed regarding low back pain by asking: "In the past month, have you had pain on most days lasting?", and those who answered yes were defined as having low back pain. Blood and urine samples were collected for biochemical and genetic examinations. Plain radiographs of the lumbar spine, knee and hip were taken for all participants. Participants were confirmed to be comparable to the Japanese general population according to the national nutrition survey by the Ministry of Health, Labour and Welfare (Japan). The height of the men and women in the ROAD study was 162.5 cm and 149.7 cm, respectively, compared with 162.6 cm and 149.9 cm in the Japanese general population. Weight was 61.3 kg and 51.8 kg, respectively, compared with 61.6 kg and 53.8 kg. The percentage of the men and women in the study population with a smoking habit was 26.4% and 3.2%, respectively, compared with 29.4% and 4.0% in the general population. From the baseline data of the overall participants, the present study analysed 2288 subjects (818 men and 1470 women) aged ≥60 years.

Radiographic assessment

Plain radiographs of the lumbar spine were taken in the anteroposterior and lateral positions and the images were downloaded into Digital Imaging and Communication in Medicine (DICOM) format files to assess radiographic spondylosis. Contrast-adjusted images were used to detect osteophytes and intervertebral spaces when the original images were obscure. Osteophytes were analysed at endplates. The severity of lumbar spondylosis was determined according to the KL grading[12] at each intervertebral level from L1/2 to L5/S by a single experienced orthopaedic surgeon (SM) who was blind to the background of the patients. 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 1 month after the first reading. Furthermore, 100 other radiographs were scored by two experienced orthopaedic surgeons (SM and HO) using the same radiographic atlas for inter-observer variability. The intra- and inter-observer variabilities were evaluated by kappa analysis. The variability in KL grading of the lumbar radiographs was found to be sufficient for assessment (0.84 and 0.76, respectively).

Statistical analysis

The non-paired *t* test was used to examine the difference in age and BMI between men and women. To compare the percentage of patients with radiographic spondylosis (KL≥2 or ≥3 at the severest level) and low back pain between men and women, logistic regression analysis was performed after adjustment for age and BMI. The differences in prevalence among the age groups were determined using one-way analysis of covariance and Scheffe's test after adjustment for BMI. The association of the variables such as age, BMI, gender and community with radiographic spondylosis and low back pain was evaluated by multivariate logistic regression analysis. The association of radiographic spondylosis at each intervertebral level with low back pain was determined by logistic regression analysis after adjustment for age and BMI. The association of the number of intervertebral level with KL≥3 with low back pain was determined by multiple regression analysis after adjustment for age and BMI. Data analyses were performed using SAS Version 9.0 (SAS Institute, North Carolina, USA).

RESULTS

Table 1 shows the overall characteristics of the 2288 participants aged ≥60 years in the three cohorts of the ROAD study. Although the men were significantly older than the women in the overall population and in some communities, BMI was comparable between them.

Table 2 shows the prevalence of radiographic lumbar spondylosis and low back pain in the overall population and subgroups classified by gender and age strata. In the overall population the prevalence of radiographic spondylosis with KL≥2 and ≥3 at the severest intervertebral level was 75.8% and 50.4%, respectively, and that of low back pain was 28.8%. The prevalence of osteoporotic fracture at the lumbar spine was 10.7%. Logistic regression analysis after adjustment for age and BMI showed that the prevalence of radiographic spondylosis with KL≥2 was higher in men than in women, while the prevalence of KL≥3 radiographic spondylosis and low back pain was higher in women than in men. When the prevalence was

Table 1 Characteristics of study participants

	Men				Women			
	Overall	Urban	Mountainous	Coastal	Overall	Urban	Mountainous	Coastal
No of subjects	818	397	266	155	1470	742	434	294
Age (years)	74.7 (6.1)	77.3 (4.1)	72.1 (6.2)	72.7 (7.4)	74.0 (6.4)*	76.4 (4.8)*	72.1 (7.1)	70.9 (6.8)*
Height (cm)	161.3 (6.3)	161.2 (5.9)	160.3 (6.6)	163.0 (6.1)	148.6 (6.2)	148.6 (5.8)	146.8 (6.4)	151.2 (5.9)
Weight (kg)	60.1 (9.9)	59.8 (8.3)	59.3 (11.4)	62.2 (10.6)	50.9 (9.0)	50.7 (8.4)	49.8 (9.8)	53.1 (8.8)
BMI (kg/m^2)	23.0 (3.2)	23.0 (2.7)	23.0 (3.8)	23.3 (3.3)	23.0 (3.7)	22.9 (3.4)	23.1 (4.2)	23.2 (3.5)
Current smoker (%)	24.6	25.2	26.3	20.0	3.1*	3.1*	4.4*	1.0*
Current drinker (%)	61.2	60.0	67.0	54.8	20.2*	21.0*	22.1*	15.3*

Data are mean (SD).
*$p<0.05$ vs men in the corresponding group by the non-paired *t* test.
BMI, body mass index.

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Table 2 Number (%) of participants with radiographic lumbar spondylosis and low back pain according to gender and age

		Radiographic lumbar spondylosis		
		KL≥2	KL≥3	Low back pain
Overall	2288	1728 (75.8)	1149 (50.4)	659 (28.8)
Men	818	688 (84.1)	383 (46.8)	201 (24.6)
<70	154	114 (74.0)	51 (33.1)	35 (22.7)
70–79	491	419 (85.3)*	232 (47.3)*	119 (24.2)
≥80	173	155 (89.6)*	100 (57.8)*	47 (27.2)
Women	1470	1040 (70.7)†	766 (52.1)†	458 (31.2)†
<70	356	196 (55.1)	128 (36.0)	80 (22.5)
70–79	818	612 (74.8)*	456 (55.7)*	273 (33.4)*
≥80	296	232 (78.3)*	182 (61.5)*	105 (35.5)*

Radiographic spondylosis was determined at the severest level among L1/2–L5/S1.
*p<0.05 vs subjects aged <70 years by Scheffe's test after adjustment for body mass index.
There was no significant difference between ages 70–79 and ≥80 in both genders.
†p<0.05 vs men by logistic regression analysis after adjustment for age and body mass index.
K/L, Kellgren/Lawrence grading.

compared among the generations, radiographic spondylosis (KL≥2 and ≥3) and low back pain tended to increase with age. Interestingly, the difference was greater between ages <70 and 70–79 years than between 70–79 and ≥80 years.

To identify risk factors for the radiographic spondylosis and low back pain, we further performed the logistic regression analysis to estimate odds ratios and confidence intervals (table 3). Age and BMI were significantly associated with radiographic spondylosis. Male sex was confirmed to be a risk factor for KL≥2 spondylosis while female sex was a risk factor for KL≥3 and low back pain. Among the communities, residents of the mountainous area had a lower risk for KL≥3 spondylosis than urban residents.

We then examined the association between radiographic spondylosis and low back pain. Considering that intervertebral levels other than the severest level of radiographic spondylosis might possibly cause low back pain, spondylosis at all intervertebral levels from L1/2 to L5/S was evaluated: KL≥2 spondylosis was found to be comparably prevalent at L2/3, L3/4 and L4/5 while KL≥3 spondylosis was remarkably prevalent at L4/5 in both men and women (table 4). In fact, among the five levels L4/5 was most frequently determined to be the severest level in both genders (men: L1/2 49.4%, L2/3 59.5%, L3/4 58.0%, L4/5 64.5%, L5/S 48.3%; women: L1/2 49.5%, L2/3 58.0%, L3/4 58.6%, L4/5 65.5%, L5/S 44.3%). We then looked at the percentage of subjects with low back pain in three groups: KL = 0 or 1, KL = 2, and KL≥3, at each intervertebral level and the severest level in the overall population and the three communities (fig 1). When odds ratios of KL = 2 and KL≥3 spondylosis compared with KL = 0 or 1 for pain were estimated by logistic regression analysis after adjustment for age and BMI, KL = 2 spondylosis was not significantly associated with pain in either gender at any intervertebral level (table 5). However, KL≥3 spondylosis was related at all levels in women while in none of the levels in men. Furthermore, the number of intervertebral levels with KL≥3 spondylosis was significantly associated with low back pain in women (p<0.01) but not in men by multiple regression analysis after adjustment for age and BMI. The association between KL≥3 spondylosis at the severest level and low back pain in women was evident at younger ages (<70 and 70–79 years; see table 1 in online supplement) and in the urban community (see table 2 in online supplement).

DISCUSSION

This study showed that the prevalence of radiographic lumbar spondylosis with KL≥2 and KL≥3 in elderly people (≥60 years) was 75.8% and 50.4%, respectively, and that of low back pain was 28.8% in the overall population. Although KL≥2 spondylosis was more prevalent in men (84.1%) than in women (70.7%), KL≥3 spondylosis and low back pain were more prevalent in women. This study also showed that KL = 2 spondylosis was not significantly associated with low back pain compared with KL = 0 or 1, while KL≥3 spondylosis was related to the pain only in women.

Most previous epidemiological studies on lumbar spondylosis focused on middle-aged or younger populations, reporting the prevalence to be 46.5–83.7%.[4 6–8 10 11] Our previous small-scale study on a younger population reported the prevalence to be 76.3% and 37.4%.[9] Interestingly, the subjects were living in a mountainous area in Japan, which was shown to have a lower risk for spondylosis in the present study. The variability may therefore be due to the differences in age, community, the sample size and ethnic variation. In fact, a study on elderly people (≥65 years) showed that the prevalence of KL≥2 spondylosis was 84.8% and 70.6%, similar to the present results, although in a relatively small number of subjects.[5] We have reported a different prevalence of lumbar spondylosis in Japan and the UK in a small-scale comparative study,[9] which may in part relate to ethnic variation. It should be noted that this is the first population-based study to investigate the age-related prevalence of lumbar spondylosis in elderly people. Although KL≥2 and KL≥3 spondylosis tended to increase with age, a significant difference was detected between the 60s and the 70s, but not thereafter. However, this cross-sectional

Table 3 Association of gender and community with radiographic lumbar spondylosis and low back pain

	Radiographic lumbar spondylosis		
	KL≥2	KL≥3	Low back pain
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age (years)	1.07 (1.06 to 1.09)†	1.05 (1.04 to 1.07)†	1.02 (1.00 to 1.04)*
BMI (kg/m²)	1.06 (1.03 to 1.09)†	1.04 (1.01 to 1.06)†	1.02 (0.99 to 1.05)
Women (vs men)	0.68 (0.61 to 0.76)†	1.13 (1.03 to 1.23)†	1.19 (1.08 to 1.31)†
Community (vs urban)			
Mountainous	0.82 (0.65 to 1.04)	0.56 (0.45 to 0.69)†	0.87 (0.69 to 1.08)
Coastal	1.24 (0.93 to 1.66)	1.06 (0.84 to 1.34)	0.86 (0.66 to 1.11)

Radiographic spondylosis was determined at the severest level among L1/2–L5/S1.
The odds ratios were calculated by logistic regression analysis after adjustment for all other variables.
*p<0.05; †p<0.01.
BMI, body mass index; KL, Kellgren/Lawrence grading; OR, odds ratio; CI, confidence interval.

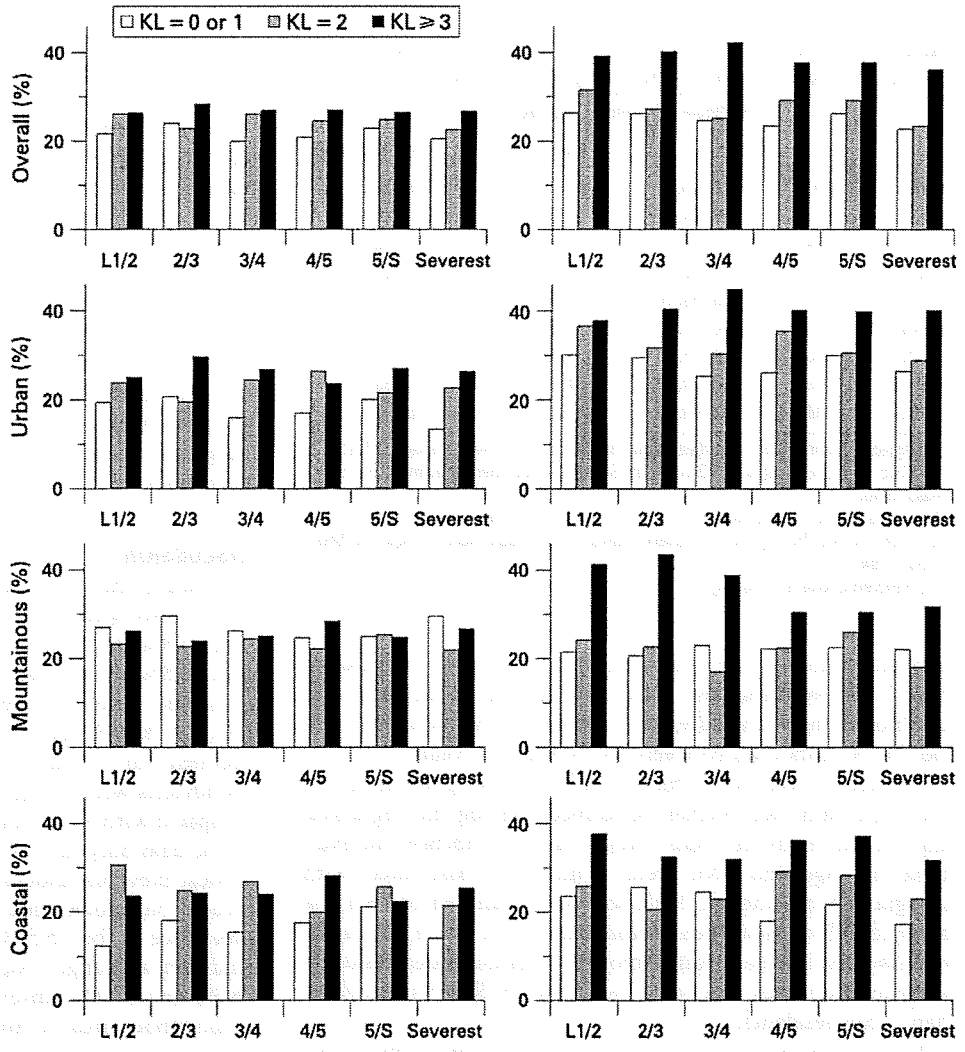

Figure 1 Percentage of subjects with low back pain according to the Kellgren/Lawrence (KL) grade in the overall population and in urban, mountainous and coastal communities.

analysis does not, of course, lead to the conclusion that individual lumbar spondylosis hardly progresses after 80 years. Since the ROAD study is a prospective cohort study of >10 years, the follow-up data will clarify the progression with ageing. Furthermore, there was a difference in prevalence between urban and mountainous communities. Considering that lumbar spondylosis is a common disease whose progression is governed by environmental and genetic factors, the regional difference is inevitable, as previously reported.[6] Although age and obesity are known to be representative risk factors for lumbar spondylosis,[2] the difference between communities in the present study was significant even after adjustment for age and BMI, indicating the involvement of other factors. Here again, a further longitudinal survey of the ROAD database including detailed environmental and genomic information will elucidate the underlying backgrounds.

Table 4 Number (%) of subjects with radiographic lumbar spondylosis at each intervertebral level in all cohorts

	KL⩾2		KL⩾3	
	Men	Women	Men	Women
L1/2	474 (57.9)	609 (41.4)	116 (14.2)	254 (17.3)
L2/3	541 (66.1)	749 (51.0)	164 (20.1)	355 (24.2)
L3/4	554 (67.7)	735 (50.0)	194 (23.7)	419 (28.5)
L4/5	523 (63.9)	736 (50.1)	306 (37.5)	605 (41.2)
L5/S	400 (48.9)	576 (39.2)	197 (24.2)	413 (28.1)

KL, Kellgren/Lawrence grading.

Interestingly, KL⩾2 spondylosis was more prevalent in men than in women, while KL⩾3 spondylosis was more prevalent in women. We and others also have reported that osteophytosis of the lumbar spine is more common in men than in women,[8 9] while disc space narrowing is more prevalent in women.[9] Based on the definition of the KL grading,[12] the discrepancy may be due to distinct aetiological mechanisms between osteophyte formation and disc space narrowing. A cross-sectional study which investigated the extent, prevalence and distribution of spinal spondylosis in women also showed that osteophytosis and disc space narrowing were significantly correlated, but each predicted only 19% of the variation in the other .[11] A previous prospective study in knee joints in the Chingford Study cohort found no association between osteophyte formation and joint space narrowing.[14] A recent study using quantitative magnetic resonance imaging (MRI) in knee joints also reported that osteophyte formation was unrelated to cartilage loss.[15] Furthermore, in an experimental mouse knee osteoarthritis model, we have identified a cartilage-specific molecule, carminerin, that induces only osteophyte formation without affecting cartilage degeneration during the progression of osteoarthritis.[16 17] Further clinical and basic research will disclose the distinct backgrounds of these two representative features of osteoarthritis.

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Table 5 Association of Kellgren/Lawrence (KL) grade at each intervertebral level with low back pain

	L1/2	L2/3	L3/4	L4/5	L5/S	Severest
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Men						
KL = 2	1.30 (0.92 to 1.84)	0.94 (0.65 to 1.36)	1.43 (0.98 to 2.11)	1.24 (0.82 to 1.89)	1.12 (0.75 to 1.65)	1.15 (0.70 to 1.92)
KL≥3	1.30 (0.79 to 2.11)	1.25 (0.80 to 1.94)	1.49 (0.96 to 2.32)	1.42 (0.97 to 2.08)	1.22 (0.82 to 1.81)	1.44 (0.89 to 2.38)
Women						
KL = 2	1.20 (0.91 to 1.57)	0.99 (0.75 to 1.31)	0.96 (0.71 to 1.30)	1.25 (0.82 to 1.88)	1.07 (0.73 to 1.54)	0.99 (0.69 to 1.42)
KL≥3	1.66 (1.23 to 2.24)*	1.74 (1.32 to 2.30)*	2.10 (1.62 to 2.72)*	1.88 (1.48 to 2.38)*	1.60 (1.25 to 2.06)*	1.80 (1.38 to 2.37)*

The odds ratio was calculated by logistic regression analysis compared with subjects with KL grade 0 or 1 after adjustment for age and body mass index.
*$p<0.01$.
OR, odds ratio; CI, confidence interval.

Symptomatic low back pain was associated with KL≥3 spondylosis in women but not in men, but not with KL≥2 spondylosis in either gender. Considering the definition of KL grading, this may suggest that disc space narrowing but not osteophytosis of the lumbar spine contributes to low back pain, which is consistent with previous reports.[18] Differences in the association between genders might be dependent on muscle strength to compensate for spinal instability due to disc space narrowing, since men are known to have greater muscle strength than women at all ages.[19] However, approximately 30% of participants without definite radiographic lumbar spondylosis (KL = 0 or 1) had low back pain, and the odds ratio of KL≥3 spondylosis for pain was 1.44 in men and 1.80 in women, which is much lower than the previously reported odds ratio of 8.5 for KL≥3 osteoarthritis in the knee joint for knee pain.[20] This may be because low back pain arises from a number of disorders other than disc space narrowing such as nociceptive stimuli, inflammation, muscle weakness and abnormal load on muscle, ligament or capsular tissues.[21] Indeed, disc degeneration was detected by MRI in at least one lumbar level in all but one asymptomatic volunteers aged 60–80 years.[22] Furthermore, pain is also influenced by psychological factors such as depression, since a significant association between low back pain and depression has been confirmed in many longitudinal studies.[23–25] A recent psychophysical study has shown that anxiety was linked to self-reported and induced low back pain in men but not in women.[26] This might be an alternative reason for the lower association between radiographic spondylosis and low back pain in men.

This study has several limitations. First, prevalence figures using a large-scale population-based sample of elderly people may be generalisable to the Japanese population. However, this study investigated elderly participants who lived independently rather than those who lived in institutional settings, so the calculated prevalence may be underestimated. Second, the definition of low back pain in the present study did not determine the severity. The association of lumbar spondylosis with the severity of low back pain could not be examined in this study. Third, the analyses did not include facet joint osteoarthritis or vertebral fracture, which would probably be associated with low back pain. This is the next factor to be investigated in the ROAD study. Fourth, since the KL system emphasises osteophytosis, it is unclear how to handle lumbar spondylosis with disc space narrowing but no osteophytosis. Since quantitative MRI is still too laborious and expensive to perform in general clinical practice, we are now developing a computer-aided diagnostic program which enables the fully automatic measurement of major features of lumbar spondylosis including disc space narrowing and osteophytosis on plain radiographs.

In conclusion, this cross-sectional study using a large-scale population from the ROAD study revealed a high prevalence of radiographic lumbar spondylosis in elderly people. The prevalence differed to some extent by age, gender and community. Gender seems to be distinctly associated with KL≥2 and KL≥3 lumbar spondylosis, and disc space narrowing with or without osteophytosis in women may be a risk factor for low back pain. Further progress, along with continued longitudinal survey in the ROAD study, will elucidate the environmental and genetic backgrounds of lumbar spondylosis and its relation with low back pain.

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Original article

Association of low dietary vitamin K intake with radiographic knee osteoarthritis in the Japanese elderly population: dietary survey in a population-based cohort of the ROAD study

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Abstract

Background. The present study sought to identify dietary nutrients associated with the prevalence of radiographic knee osteoarthritis (OA) in the Japanese elderly of a population-based cohort of the Research on Osteoarthritis Against Disability (ROAD) study.

Methods. From the baseline survey of the ROAD study, 719 participants ≥60 years of age (270 men, 449 women) of a rural cohort were analyzed. Dietary nutrient intakes for the previous 1 month were assessed by a self-administered brief diet history questionnaire. The radiographic severity at both knees was determined by the Kellgren/Lawrence (KL) system.

Results. The prevalence of knee OA of KL ≥2 was 70.8%. Age, body mass index, and female sex were positively associated with the prevalence. Among the dietary factors, only vitamin K intake was shown to be inversely associated with the prevalence of radiographic knee OA by multivariate logistic regression analysis. The presence of joint space narrowing of the knee was also inversely associated with vitamin K intake. The prevalence of radiographic knee OA for each dietary vitamin K intake quartile decreased with the increased intake.

Conclusions. The present cross-sectional study using a population-based cohort supports the hypothesis that low dietary vitamin K intake is a risk factor for knee OA. Vitamin K may have a protective role against knee OA and might lead to a disease-modifying treatment.

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Introduction

Osteoarthritis (OA) is a major public health issue causing disability of the elderly in most developed countries.[1] There is an urgent need for safe, effective strategies for preventing and treating this disease. Such strategies could come from dietary nutrition as studies have indicated an association of nutritional factors with OA.[2–7] Diet and nutritional factors are important because they are modifiable. However, epidemiological data on the relation between nutritional factors and OA are insufficient. We thus set up a population-based prospective cohort study named Research on Osteoarthritis Against Disability (ROAD) in 2005. The present study investigated the association of the prevalence of radiographic knee OA with dietary nutritional factors assessed by a self-administered brief diet history questionnaire (BDHQ) in the Japanese elderly living in a rural community participating in the ROAD study.[8]

Participants and methods

Participants

The ROAD study is a population-based prospective cohort study designed to clarify the environmental and genetic risk factors for OA. The participants of the ROAD study were recruited from the residents of three communities that have different characteristics: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a coastal region in Taiji, Wakayama.[9] The inclusion criteria were as follows: The patient (1) had to be able to walk to the clinic at

which the survey was performed, (2) provide self-reported data, and (3) understand and sign an informed consent form. Residents of the urban, mountainous, and coastal regions were recruited from the resident registration list of the relevant region.

The age of the participants recruited from the urban region was ≥60 years, and that of the participants from the two other regions was ≥40 years. In the urban, mountainous, and coastal areas, 99.8%, 84.3%, and 54.7% of the participants, respectively, were >60 years of age. Two-thirds of the participants were women, and their mean age was 1 year less than that of the male participants. The baseline survey of the Hidakagawa cohort was conducted from November 2005 to February 2006. The community has a population of 11300/330 km^2 and residents ≥65 years constitute 30.5% of the population. All participants provided written informed consent, and the study was conducted with approval of ethics committees of the institution. From the baseline data of 723 participants who were ≥60 years in the cohort, we analyzed 719 participants (270 men, 449 women) after excluding four individuals who had undergone knee surgery.

Dietary assessment

For the dietary survey, we used the BDHQ and investigated dietary nutrient intakes for the previous 1 month. A questionnaire was given to each participant with detailed explanations to fill it out at home and was addressed by well-trained interviewers when the participant visited the clinic. The BDHQ is a 4-page, structured questionnaire that inquires about the consumption frequency of a total of 56 food and beverage items, with specified serving sizes described in terms of a natural portion or the standard weight and volume measurement of servings commonly consumed in general Japanese populations. The BDHQ was developed based on a comprehensive (16-page) version of a validated self-administered diet history questionnaire[8] and is now widely used for the dietary survey in Japan.[10–12] Estimates of dietary intake for the 56 food and beverage items, energy, and selected nutrients were calculated using an ad hoc computer algorithm for the BDHQ, which was based on the Standard Tables of Food Composition in Japan. Dietary intake levels of total energy and 16 nutrient factors (animal protein; vegetable protein; animal fat; vegetable fat; carbohydrate; vitamins B_1, B_2, B_6, and B_{12}; niacin; vitamins C, D, E, and K; dietary fiber; salt) were analyzed.

Radiographic assessment

All participants had plain radiographic examinations of both knees with an anteroposterior view with weight-bearing and foot map positioning. Knee radiographs were read, without knowledge of the participants' clinical status, by a single well-experienced orthopedist using the Kellgren/Lawrence (KL) radiographic atlas, and a KL grade (0–4) was determined.[13,14] The higher KL grade in both knees was designated as that of the participant. To evaluate intraobserver variability of the KL grading, 100 randomly selected radiographs of the knee were scored by the same observer more than 1 month after the first reading. Furthermore, 100 other radiographs were scored by two experienced orthopedic surgeons using the same atlas for interobserver variability. The intra- and interobserver variabilities were evaluated by kappa analysis and were confirmed to be sufficient for assessment (0.86 and 0.80, respectively).

Statistical analysis

Differences in crude mean values of dietary nutrient intakes were examined by a nonpaired *t*-test between the KL = 0 or 1 group and the KL ≥2 group for each sex, and those with significant differences were further evaluated by multivariate logistic regression analysis after adjustment for age, sex, body mass index (BMI), and total energy to estimate the odds ratio (OR) and its associated 95% confidence interval (95% CI). Association of the presence of joint space narrowing of the knee defined as KL ≥3 with nutrient intakes was also examined by logistic regression analysis. The Cochran-Mantel-Haenszel test was used to determine the association of the prevalence of knee OA for each dietary nutrient intake quartile for linear trend. Data analyses were performed using SAS version 9.0 (SAS Institute, Cary, NC, USA). $P < 0.05$ was considered significant.

Results

Characteristics of the 719 participants are shown in Table 1. The prevalence of KL ≥2 knee OA was 70.8% (57.8% in men, 78.6% in women) and that of KL ≥ 3 was 25.9% (15.9% in men, 31.8% in women). Neither the age nor the BMI was significantly different between men and women in the overall population. Participants with KL ≥2 knee OA were older than those without it (KL = 0 or 1) in both sexes, and the BMI was higher in KL ≥2 than in KL = 0 or 1 in women.

We compared total energy and 16 dietary nutrient intakes between the groups with and without KL ≥2 knee OA (Table 2). Vegetable fat intake was significantly lower in the KL ≥2 group than in the KL = 0 or 1 group in women. Vitamin K intake was significantly lower in the KL ≥2 group than in the KL = 0 or 1 group in both sexes. Total energy and other nutrient intakes

Table 1. Characteristics of participants

	Men			Women		
	Overall	KL = 0 or 1	KL ≥2	Overall	KL = 0 or 1	KL ≥ 2
No. of participants	270	114	156	449	96	353
Age (years)	72.1 ± 6.3	70.4 ± 5.9	73.4 ± 6.3†	72.0 ± 7.0	68.8 ± 6.1*	72.8 ± 7.0†
Height (cm)	160.2 ± 6.2	160.1 ± 6.8	159.9 ± 5.8	146.9 ± 6.3*	148.5 ± 6.1*	146.8 ± 6.3*
Weight (kg)	58.9 ± 9.6	58.3 ± 9.6	59.2 ± 9.6	49.7 ± 8.5*	48.7 ± 6.7*	49.9 ± 8.9*
BMI (kg/m^2)	22.8 ± 2.9	22.5 ± 2.8	23.1 ± 3.0	22.9 ± 3.4	22.1 ± 2.6	23.2 ± 3.5†

Data are means ± SD
KL, Kellgren/Lawrence system; BMI, body mass index
* $P < 0.05$ vs. men in the corresponding group by nonpaired *t*-test
† $P < 0.05$ vs. KL = 0 or 1 in the corresponding group by nonpaired *t*-test

Table 2. Comparison of total energy and dietary nutrient intakes between participants with (KL ≥2) and without (KL = 0 or 1) radiographic knee OA according to sex

	Men		Women	
Parameter	KL = 0 or 1	KL ≥2	KL = 0 or 1	KL ≥2
Total energy (MJ/day)	9.77 ± 2.88	9.90 ± 2.73	7.07 ± 1.75	7.03 ± 1.78
Dietary nutrients				
Animal protein (g/day)	46.3 ± 20.7	48.4 ± 20.9	36.8 ± 12.9	37.4 ± 16.2
Vegetable protein (g/day)	34.1 ± 10.1	33.8 ± 9.4	27.2 ± 6.7	26.1 ± 6.8
Animal fat (g/day)	27.6 ± 13.3	28.7 ± 12.2	21.9 ± 7.8	22.1 ± 10.1
Vegetable fat (g/day)	21.2 ± 10.9	21.9 ± 10.4	19.7 ± 8.6	17.6 ± 8.1*
Carbohydrate, (g/day)	352 ± 116	356 ± 114	259 ± 72	261 ± 75
Vitamin D (μg/day)	22.0 ± 11.5	23.7 ± 13.0	16.7 ± 7.4	18.5 ± 9.9
Vitamin E (mgα-TE/day)	7.76 ± 3.43	7.89 ± 3.15	7.24 ± 2.51	6.84 ± 2.58
Vitamin K (μg/day)	266 ± 171	228 ± 131*	253 ± 125	213 ± 115*
Vitamin B_1 (mg/day)	0.81 ± 0.27	0.80 ± 0.24	0.71 ± 0.16	0.67 ± 0.19
Vitamin B_2 (mg/day)	1.09 ± 0.44	1.06 ± 0.37	0.97 ± 0.27	0.92 ± 0.33
Niacin (mgNE/day)	18.1 ± 6.9	18.0 ± 6.6	14.1 ± 4.1	13.6 ± 5.1
Vitamin B_6 (mg/day)	1.34 ± 0.49	1.32 ± 0.45	1.08 ± 0.29	1.05 ± 0.35
Vitamin B_{12} (μg/day)	12.1 ± 6.3	12.5 ± 6.5	9.2 ± 4.0	9.6 ± 4.9
Vitamin C (mg/day)	103 ± 43	96 ± 39	117 ± 45	113 ± 42
Dietary fiber (g/day)	11.7 ± 4.0	11.2 ± 3.3	11.0 ± 3.2	10.5 ± 3.0
Salt (g/day)	13.0 ± 4.1	12.5 ± 3.7	10.4 ± 2.6	10.4 ± 3.1

Data are the mean ± SD
TE, tocopherol equivalent; NE, niacin equivalent
* $P < 0.05$ vs. KL = 0 or 1 in each group by nonpaired *t*-test

were not significantly different between the groups in either sex. Logistic regression analysis was performed using the presence of KL ≥2 knee OA (1, yes vs. 0, no) as an objective variable and age, BMI, sex, total energy, vegetable fat, and vitamin K intakes (vs. +1 SD) as explanatory variables (Table 3). Age, BMI, and sex were associated with the presence of radiographic knee OA (KL ≥2). Although vegetable fat intake had no significant association, dietary vitamin K intake (OR = 0.75, 95% CI = 0.63–0.89 vs. +1 SD) was shown to be inversely associated with the presence of radiographic knee OA in the overall population.

Table 4 shows the association between KL grade and dietary vitamin K intake according to sex. Logistic

Table 3. Association of age, BMI, sex, and nutrient intakes with radiographic knee OA (KL ≥ 2) in the overall population

Parameter	OR	95% CI
Age (years)	1.11	1.07–1.14*
BMI (kg/m^2)	1.15	1.08–1.22*
Women (vs. men)	3.08	2.16–4.40*
Dietary nutrient intakes		
Vegetable fat[a] (SD)	0.93	0.78–1.10
Vitamin K[a] (SD)	0.75	0.63–0.89*

The odds ratios for KL ≥ 2 (vs. KL = 0 or 1) were calculated by logistic regression analysis
OR, odds ratio; CI, confidence interval
* $P < 0.01$
[a]Adjusted for age, sex, BMI, and total energy

Table 4. Association between KL grade and dietary vitamin K intake according to sex

	Overall		Men		Women	
Condition	OR	95% CI	OR	95% CI	OR	95% CI
KL ≥2 (vs. KL = 0 or 1)	0.75	0.63–0.89†	0.76	0.59–0.95*	0.74	0.58–0.96*
KL ≥3 (vs. KL ≤2)	0.67	0.53–0.84†	0.74	0.50–1.04	0.61	0.45–0.81†

Odds ratios were calculated by logistic regression analysis after adjustment for age, sex, BMI, and total energy
*$P < 0.05$
†$P < 0.01$

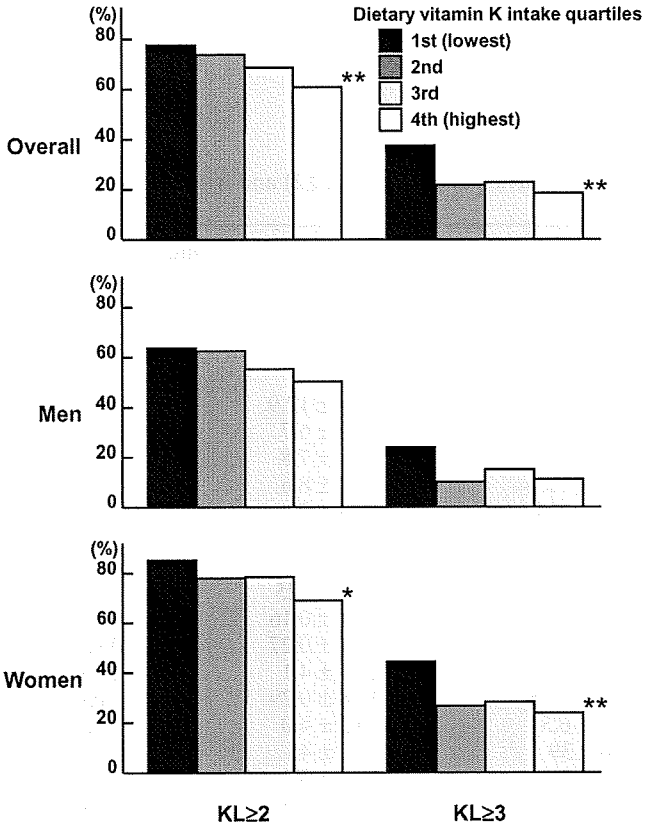

Fig. 1. Prevalence of KL ≥2 and KL ≥3 knee osteoarthritis per quartile of dietary vitamin K intake. The 25th, 50th, and 75th percentiles were, respectively, 141.4, 205.8, and 285.8 mg/day in the overall population; 145.0, 222.8, and 314.0 mg/day in men; and 137.4, 199.9, and 279.3 mg/day in women. *$P < 0.05$ and **$P < 0.01$ for linear trend

regression analysis using the presence of KL ≥2 knee OA as an objective variable showed that vitamin K intake was inversely associated with KL ≥2 knee OA in both sexes (OR = 0.76, 95% CI = 0.59–0.95 vs. +1 SD in men; OR = 0.74, 95% CI = 0.58–0.96 vs. +1 SD in women) as well as in the overall population. Furthermore, logistic regression analysis using the presence of KL ≥3 knees (vs. KL ≤2) as an objective variable revealed that KL ≥ 3 knees (vs. KL ≤2) were also inversely associated with vitamin K intake in the overall population (OR = 0.67, 95% CI = 0.53–0.84 vs. +1 SD) and in women (OR = 0.61, 95% CI = 0.45–0.81 vs. +1 SD), indicating that the presence of joint space narrowing of the knee was inversely associated with dietary vitamin K intake. Furthermore, we examined the prevalence of KL ≥2 and KL ≥3 knee OA for each dietary vitamin K intake quartile (Fig. 1), which decreased with ascending vitamin K intake. This tendency was significant in the overall population and in women.

Discussion

The present study investigated the association of radiographic knee OA with nutritional factors in a population-based cohort of the ROAD study. Total energy, protein, fat, and carbohydrate had no significant association with knee OA. Among dietary vitamin intakes, vitamin K was inversely associated with the prevalence of radiographic knee OA. Previous published epidemiological studies have suggested a relation between OA and vitamins.[2–7] Vitamin K includes vitamin K_1 or phylloquinone, which is contained in green leafy vegetables, and vitamin K_2 or menaquinone, which is synthesized by bacteria and abundantly contained in a traditional Japanese fermented soybean food called *natto*.[15,16] Vitamin K belongs to the fat-soluble vitamins, which may be the reason why vegetable fat intake was lower in the knee OA group in women, although it was not significant in the multivariate analysis. Plasma levels of phylloquinone has been reported to be inversely associated with the prevalence of OA in the hand and knee,[6] which is consistent with the results of the present study.

Vitamin K serves as an essential cofactor of γ-glutamyl carboxylase, an enzyme for the γ-carboxylation of vitamin K-dependent proteins including matrix Gla protein (MGP).[17] MGP is an extracellular matrix protein of the mineral-binding Gla protein family that includes osteocalcin, the growth arrest-specific protein 6 (Gas6). Gas6 is up-regulated in growth-arrested cells,[18] suggesting a role in protection from certain cellular stresses, such as apoptosis. In fact, many studies demonstrated the ability of Gas6 to promote cell survival and proliferation.[19–22] MGP is expressed by proliferative and late hypertrophic chondrocytes,[23,24] and mutations in MGP

are responsible for Keutel syndrome in which patients are affected by aberrant cartilage calcification.[25] Studies of MGP-deficient mice suggest that MGP is an inhibitor of extracellular matrix calcification in the epiphyseal growth plate.[26] Warfarin, a vitamin K-antagonist anticoagulant, is known to cause warfarin embryopathy characterized by abnormal calcification and decreased growth of the cartilage.[27,28] These data demonstrate that vitamin K plays an important role in cartilage metabolism as a inhibitor of extracellular matrix calcification as well as a promotor of cell survival and proliferation. Habitual low dietary vitamin K intake may exert an inhibitory effect on the vitamin K-dependent MGP and Gas6 functions and modulate the pathogenesis of OA by influencing the process of osteophytosis and cartilage destruction.

The minimum amounts of vitamin K intake recommended by the Japanese Ministry of Health, Labor, and Welfare are 75 and 65 μg/day for men and women, respectively. The percentages of participants who did not meet the criteria in this study were 8.5% in men, 3.6% in women, and 5.4% in the overall population—all of whom belonged to the 1st quartile (lowest) in Fig. 1. However, even in the 2nd through 4th quartiles, the prevalence of radiographic OA decreased with ascending vitamin K intake, suggesting that the recommended amount of vitamin K intake may not be sufficient for the prevention of knee OA.

The management of knee OA is largely palliative, focusing on the alleviation of symptoms, although it is a major public health issue causing disabilities in the elderly. The Osteoarthritis Research Society International (OARSI) current recommendations include a combination of nonpharmacological interventions and pharmacological treatments.[29] Considering that nonsteroidal antiinflammatory drugs (NSAIDs) with serious adverse effects caused by their long-term use remain among the most widely prescribed drugs for OA,[30] there is a need for safe, effective alternative strategies for the prevention and treatment of this disease. Such strategies could come from dietary nutrition, and vitamin K might have a preventive role against OA.

There are limitations in the present study. This is a cross-sectional study of the baseline data, and a causal relation could not be determined. In addition, the dietary survey in this study investigated dietary habits only for the pevious month, which did not necessarily reflect a long habit of several years, despite the fact that OA is a slowly progressing chronic disease. This dietary survey also investigated whether participants had changed their dietary habits. Those who answered yes comprised 9.6%; and 90.4% of participants answered they had not changed their dietary habits. Although it is likely that dietary habits in middle-aged and elderly people are usually quite different from those in children and young adults, there is a possibility that most of participants in this study had not changed their dietary habits for several years or for a longer time, which may have affected the disease process of OA. Furthermore, the dietary survey in the present study was conducted from autumn to winter although there are four seasons in Japan and diets may vary with the season. Therefore, the present study could give some bias for the effect of season on the nutritional quality of diets. This is a limitation in this study because we could not follow participants during all seasons to get a measure of average diets during the year. We are planning a follow-up study during the same season to minimize the variation caused by seasonal differences. Longitudinal data are required to confirm the relation between vitamin K and OA.

Conclusion

The present cross-sectional study using a population-based cohort supports the hypothesis that low dietary vitamin K intake is a risk factor for knee OA. Vitamin K may have a protective role against knee OA and might lead to disease-modifying treatment.

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We declare that we have no conflict of interest regarding the present manuscript.

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