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**Noriko Yoshimura · Hirofumi Kinoshita · Noriaki Hori
Taira Nishioka · Masahiko Ryujin · Yoshihiko Mantani
Mariko Miyake · Tatsuya Takeshita · Masao Ichinose
Munehito Yoshiida · Hiroyuki Oka · Hiroshi Kawaguchi
Kozo Nakamura · Cyrus Cooper**

Risk factors for knee osteoarthritis in Japanese men: a case-control study

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Abstract Risk of knee osteoarthritis (OA) was assessed in a population-based case-control study of Japanese men. The study covered three health districts in Wakayama and Osaka prefectures, Japan. Subjects were male individuals ≥45 years old diagnosed radiographically with knee OA, and who did not display any established causes of secondary OA. Controls selected randomly from the general population were individually matched to cases for age, sex, and residential district. Subjects were interviewed using structured questionnaires to determine medical history, physical activity, socio-economic factors, and occupation. Interviews were obtained from 37 cases and 37 controls. In univariate analysis, heaviest weight in the past and physical work such as factory, construction, agricultural, or fishery work as the principal occupation significantly raised the risk of male knee OA ($P < 0.05$). Odds ratios (OR) were determined using conditional logistic regression analysis mutually adjusted for potential risk factors using the results of univariate analysis. Heaviest weight in the past (OR 6.01, 95% confidence interval (CI) 1.18–30.5, $P < 0.05$), past knee injury (OR 6.25, 95% CI 1.13–34.5, $P < 0.05$), and physical work as the principal occupation (OR 6.20, 95% CI 1.40–27.5, $P < 0.05$) represented independent factors associated with knee OA after controlling for other risk factors. Physical work is associated with knee OA, demonstrating the influence of working activity on the development of OA. The present study suggests that risk factors for knee OA in men resemble those in women.

Key words Case control study · Heavy weight · Knee joint · Osteoarthritis (OA)· Physical work

N. Yoshimura (✉) · H. Oka
Department of Joint Disease Research, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
Tel. +81-3-5800-9178; Fax +81-3-5800-9179
e-mail: yoshimuran-ort@h.u-tokyo.ac.jp

H. Kinoshita
Department of Orthopaedic Surgery, Wakayama Medical University Kihoku Hospital, Wakayama, Japan

N. Hori
Hori Hospital, Sennan, Japan

T. Nishioka
Nishioka Orthopaedic Hospital, Arita, Japan

M. Ryujin
Ryujin Clinic, Wakayama, Japan

Y. Mantani
Tamai Orthopaedic Hospital, Hannan, Japan

M. Miyake
Yamomoto Clinic, Shimotsu, Japan

T. Takeshita
Department of Public Health, Wakayama Medical University School of Medicine, Wakayama, Japan

M. Ichinose
Second Department of Internal Medicine, Wakayama Medical University School of Medicine, Wakayama, Japan

M. Yoshiida
Department of Orthopaedic Surgery, Wakayama Medical University School of Medicine, Wakayama, Japan

H. Kawaguchi · K. Nakamura
Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, Tokyo, Japan

C. Cooper
MRC Epidemiology Resource Centre, University of Southampton, Southampton General Hospital, Southampton, UK

Introduction

Since osteoarthritis (OA) is a frequent cause of pain and disability in elderly individuals, the recent World Health Organization report on the global burden of disease indicated knee OA as an increasingly important cause of disability in both men and women, suggesting that strategies for preventing OA are urgently required.[1] In Japan, knee OA seems to represent a frequent cause of pain and disability, but few epidemiological studies have examined associated factors.

Several investigations regarding risk factors for hip and knee OA performed in Western populations have

suggested obesity, previous injury, polyarticular joint involvement, and occupational activities as important risk factors for the disorder.[2–8] However, few studies of risk factors for OA in Japanese populations have been performed. Our earlier case-control study of hip OA identified some variations in risk factors in Japan.[9] In the previous case-control study of hip OA, occupational lifting was identified as a risk factor and sedentary work as a protective factor for hip OA. In addition, obesity was not identified as a risk factor for Japanese hip OA. For contrast, an identical case-control study was performed for knee OA in women in a Japanese population.[10] In the female study, risk factors of obesity, previous knee injury, and period of total work were identified, and sedentary work as the initial occupation represented a preventive factor.[10] The results from these two investigations suggest various similarities and differences in risk factors between hip and knee OA in Japanese populations.

The present study sought to clarify risk factors for knee OA among men in Japan, by performing a survey identical to that used in the previous female knee OA study. Results for men were compared to those from the female study.[10] Risk factors were then compared between knee OA and hip OA to address differences in risk factors for constitutional and mechanical factors between OA at different sites. Finally, risk factors for knee and hip OA were compared to those identified in a British study[11,12] that used identical methods to the Japanese studies, to clarify differences in risk factors for OA between Japanese and Western populations.

Patients and methods

Methods of data collection in the present study were basically identical to those of the case-control studies for female knee OA and hip OA reported previously.[9,10] A brief summary is provided here. Cases were identified from the registration systems of the six hospitals participating in the study, which were located in three cities in Japan (Wakayama City and Arita City in Wakayama Prefecture, and Sennan City in Osaka Prefecture).

Cases comprised men ≥45 years old who suffered knee pain and walking difficulties, and who were first diagnosed by an orthopedic surgeon as displaying a tibiofemoral joint with radiographic grade of ≥3 on the Kellgren and Lawrence scale[13] within the year preceding the start of the study. Cases with a history of knee injury in the previous year, rheumatoid arthritis, or ankylosing spondylitis were excluded.

For each case, a single control was randomly selected from among men of the same age and district of residence on city registers of the local population, which are updated as residents move into or leave the city. Controls who had suffered knee OA were excluded from the study.

All eligible cases and controls were initially approached using a letter to determine willingness to participate in the study. After providing informed consent, cases and controls were interviewed by the same trained interviewer.

An identical questionnaire to that used in the British case-control study was used to ascertain risk factors of knee OA.[11,12] The questionnaire was translated and back-translated from Japanese to English. Subjects completed a structured questionnaire that requested details of medical history, socio-economic status and education, cigarette smoking and alcohol consumption, functional status, and lifetime history of leisure activities. Lifetime history of leisure activities included participation in sports such as soccer, swimming, tennis, cricket, and golf, in addition to frequency and duration of less physical activities, such as gardening. Information about eight types of occupational physical activity was requested, namely: standing; sitting; climbing stairs; kneeling; squatting; driving; walking; and heavy lifting. Information on these activities was obtained for the initial job, defined as the earliest job reported, and for the principal job, defined as the job at which the subject had worked longest. For each job, the questionnaire enquired whether work entailed lifting weights (≥10 kg, ≥25 kg, or ≥50 kg) more than once during an average working week. Information regarding use of transport, including frequency and duration of cycling and motorcycling was obtained. Information was also requested on the involvement of other joints, including hands, shoulders, and hips. Furthermore, questions were added about back pain and stiffness, which were not included in the British study. Once heaviest reported weight after 25 years old was obtained, height and weight of each subject was measured at the time of the interview.

After analysis to clarify risk for male knee OA, results were compared between men and published results for women.[10] Risk factors for knee OA and hip OA were also compared to address differences in constitutional and mechanical risk factors between OA at different sites. Finally, risk factors for knee and hip OA were compared to the findings of the British study, which used identical methods to the Japanese studies.

Data were calculated using McNemar's Chi-square test and conditional logistic regression tests for matched sets. Results were summarized as odds ratios (OR) with 95% confidence intervals (CI). Odds ratios were calculated for categories of exposure, and tests of trend were performed across these categories. Statistical analyses were performed using SPSS statistical software (SPSS, Chicago, IL, USA) and the STATA statistical package (STATA, College Station, TX, USA).

Results

A total of 40 men ≥45 years old fulfilled the entry criteria for the study. Among these eligible cases, 37 men (92.5%) agreed to participate after information was provided. Unilateral knee OA ($n = 21$) was more common than bilateral disease ($n = 16$). Among the 21 men with unilateral disease, OA tended to be right-sided ($n = 13$) more often

than left-sided (n = 8), but no significant difference was identified.

For controls, we approached age-, sex-, and residence-matched candidates for each case. To recruit the 37 matched controls, we approached 70 subjects (overall response rate 52.9%).

Table 1 shows background characteristics for the 37 case-control pairs in the present study. Mean body weight was significantly greater for cases than for controls ($P < 0.05$). Furthermore, body mass index was significantly higher for cases than for controls ($P < 0.05$). No differences in personal habits such as smoking or drinking were noted between cases and controls.

The association between knee OA and heaviest reported body weight was analyzed. Under univariate analysis, mean heaviest reported body weight for cases was 72.1 kg (standard deviation (SD) = 13.0 kg), significantly higher than that for controls ($P < 0.01$) in men. Odds ratios for heaviest reported body weight were 1.07 (95% CI 1.02–1.13), suggesting that a 1-kg increase in heaviest reported body weight raised the risk of knee OA by 7%.

To more clearly address the influence of heaviest reported weight on development of knee OA, cases were categorized into the following three groups according to the distribution of heaviest reported weight: high, ≥72.0 kg; middle, 61.0–72.0 kg; and low, <61.0 kg. These categories were defined by dividing total distributions into equal thirds. Cases in the high group displayed a >4-fold elevation in risk compared with cases in the low group (OR 4.22, 95% CI 1.13–15.8 for high vs low, $P < 0.05$; OR 1.60, 95% CI 0.50–5.08 for middle vs low, $P = 0.43$) (Fig. 1).

The association between knee OA and history of injury in other joints was calculated. Under univariate analysis, although ORs exceeded a 2-fold increase, no significant difference was observed between cases and controls (OR 2.50, 95% CI 0.78–7.97 for yes vs no, $P = 0.12$).

The association between knee OA and methods of transportation was examined by comparing the frequency of regular bicycle use between cases and controls. Under univariate analysis, while OR was higher for men (OR 2.67, 95% CI 0.71–10.05), no significant differences were noted between cases and controls.

Associations between knee OA and occupational history were analyzed. The most frequent areas of employment for all subjects were factory/construction, agriculture/fishery, clerical/technical, and shop assistant/manager (Table 2). Distributions of initial and principal occupations differed

Table 1. Anthropometric and background characteristics of cases and controls for knee OA in men

	Men	
	Cases	Controls
No. of participants	37	37
Age (years)	70.0 ± 6.6	70.1 ± 7.0
Weight (kg)	64.1 ± 10.7*	59.3 ± 8.7
Height (cm)	162.5 ± 6.9	163.0 ± 6.7
Body mass index (kg/m^2)	24.2 ± 3.4*	22.4 ± 3.8
Heaviest weight in the past (kg)	72.1 ± 13.0**	64.0 ± 9.2
Age at the heaviest weight (years)	57.4 ± 15.1*	51.7 ± 17.8
Current smoking (%)	16 (43.2)	15 (40.5)
Current drinking (≥5 times/week, %)	20 (54.1)	22 (59.5)

Mean ± SD; percentage in parentheses
* $P < 0.05$, ** $P < 0.01$ cases vs controls

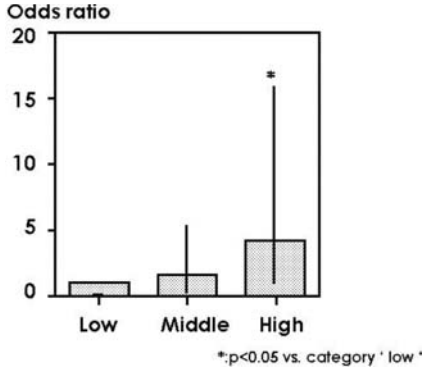

Fig. 1. Association of knee osteoarthritis with heaviest weight in the past. *Low*, lowest 3rd of the heaviest weight category, <61.0 kg; *Middle*, middle 3rd, ≥61.0 kg, <72.0 kg; *High*, highest 3rd, ≥72.0 kg. *Bar* represents 95% confidence interval

Table 2. Occupations reported as initial and principal jobs in men

	Initial occupation				Principal occupation			
	Cases	%	Controls	%	Cases	%	Controls	%
Total	37	100	37	100	37	100	37	100
Factory/construction workers	18	48.6	14	37.8	22	59.5	16	43.2
Agricultural/fishery workers	10	27.0	6	16.2	7	18.9	4	10.8
Clerical workers/technical experts	4	10.8	6	16.2	2	5.4	9	24.3
Shop assistants and managers	2	5.4	9	24.3	2	5.4	6	16.2
Clinical workers	2	5.4	0	0.0	1	2.7	0	0.0
Housekeepers	0	0.0	0	0.0	0	0.0	0	0.0
Hairdressers	0	0.0	0	0.0	0	0.0	0	0.0
Dressmakers	0	0.0	0	0.0	0	0.0	0	0.0
Teachers	0	0.0	0	0.0	2	5.4	0	0.0
Others (soldier, taxi driver, etc.)	1	2.7	2	5.4	1	2.7	2	5.4
No work, no answer	0	0.0	0	0.0	0	0.0	0	0.0

Table 3. Crude and adjusted odds ratios with risk factors for knee osteoarthritis in men

Men	Risk factors	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Heaviest reported weight[a]	Middle vs Low	1.60 (0.50–5.08)	1.25 (0.29–5.35)
	High vs Low	4.22 (1.13–15.8)*	6.01 (1.18–30.5)*
Past injury of either knee	Yes vs No	2.50 (0.78–7.97)	6.25 (1.13–34.5)*
Occupational factors	Physical work[b] as principal occupation (vs Others)	2.80 (1.01–7.77)*	6.20 (1.40–27.5)*

Adjusted odds ratio refers to values after mutual adjustment for other potential risk estimates
95% CI, 95% confidence interval
[a] Lowest 3rd, <61.0 kg; middle 3rd, ≥61.0 kg, <72.0 kg; highest 3rd, ≥72.0 kg in men
[b] Physical work meaning factory, construction, agriculture or fishery work
* $P < 0.05$

Table 4. Crude and adjusted odds ratios with risk factors for knee osteoarthritis in women (cited from ref. 10)

Women	Risk factors	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Heaviest reported weight[a]	Middle (vs Low)	1.68 (0.79–3.84)	3.33 (0.95–11.7)
	High (vs Low)	3.10 (1.26–7.98)*	3.92 (1.03–14.8)*
Past injury of either knee	Yes vs No	5.00 (2.44–10.2)*	7.51 (2.40–23.5)**
Transportation	Cycling almost every day for ≥12 months (vs Less)	1.88 (1.02–3.94)*	1.67 (0.61–4.57)
Occupational factors	Physical work[b] as initial occupation (vs Others)	2.54 (1.34–4.82)**	2.08 (0.88–5.61)
	Sitting ≥2 h/day at initial job (vs Less)	0.43 (0.23–0.78)**	0.44 (0.47–1.10)
	No. of jobs (1 job)	1.24 (1.02–1.50)*	0.91 (0.66–1.25)
	Total working period (1 year)	1.05 (1.03–1.07)***	1.05 (1.01–1.08)**

Adjusted odds ratio refers to values after mutual adjustment for other potential risk estimates
95% CI, 95% confidence interval
[a] Lowest 3rd, <55.0 kg; middle 3rd, ≥55.0 kg, <62.0 kg; highest 3rd, ≥62.0 kg in women
[b] Physical work meaning factory, construction, agriculture or fishery work
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

significantly between cases and controls. Physical work (factory/construction or agriculture/fishery) at the principal job was significantly more common among cases than controls (OR 2.80, 95% CI 1.01–7.77 for yes vs no). Mean age at commencement of the first job was 16.3 years (SD 3.8 years) compared to 16.6 years (SD 4.1 years) for controls, indicating no significant difference between cases and controls. Occupational activities including standing, climbing stairs, kneeling, squatting, driving, walking, sitting, and heavy lifting were not associated with increased risk of knee OA in men.

Table 3 shows ORs determined using conditional logistic regression analysis mutually adjusted for potential risk factors. Various risk factors were entered into the conditional logistic model, comprising: heaviest reported weight; previous knee injury; and physical work at the principal occupation in men. Heaviest reported weight in the past (OR 6.01, 95% CI 1.18–30.5, $P < 0.05$), past injury of the knee (OR 6.25, 95% CI 1.13–34.5, $P < 0.05$), and physical work at the principal occupation (OR 6.20, 95% CI 1.40–27.5, $P < 0.05$) represented independent factors associated with knee OA after controlling for other risk factors (Table 3).

Discussion

The results of the present case-control study indicate that heavy weight in the past and previous knee injury are associated with knee OA in men. Also in men, the proportion engaged in physical work (factory, construction, agriculture, or fishery work) was significantly higher among cases than controls. These risk factors for male knee OA are similar to those seen for female OA knees. Although we have already reported the results elsewhere,[10] we briefly compared results for men and women. Table 4 shows ORs in women determined using conditional logistic regression analysis mutually adjusted for potential risk factors. Various risk factors were entered into the conditional logistic model, comprising: heaviest reported weight in the past; previous knee injury; regular bicycle use; physical work in initial occupation; sedentary work in initial occupation; number of jobs; and total working period, summarizing all years of all jobs that subjects worked. Heaviest reported weight in the past, past injury of the knee, and total working period in women represented independent factors associated with knee OA after controlling for other risk factors. The results of the present case-control study indicate that heavy weight in the past and previous knee injury are associated with knee OA in both men and women.

Several limitations apply to the present study. Firstly, this investigation was based on a relatively small number of male cases and controls. Before the start of the research, we had calculated the sample size. We accumulated 155 pairs of cases and controls based on assumed values of a 0.05 level of significance, 80% statistical power, 2.0 risk ratio, and the 30% prevalence of cases. As a result, we succeeded in identifying 160 cases (40 men, 120 women) >45 years old

Table 5. Comparison of risk factors for hip and knee osteoarthritis (OA) in Britain and Japan (combined results for men and women)

	Risk factors	Britain	Japan
Hip OA	Obesity	Yes	No
	Past joint disturbance	Yes	No
	Occupational factors	Yes (lifting)	Yes (lifting)
Knee OA	Obesity	Yes	Yes
	Past joint disturbance	Yes	Yes
	Occupational factors	Yes (kneeling/squatting)	Yes (physical work, working period)

who fulfilled the entry criteria for the study. Of the eligible cases, 138 (86.3%; 37 men, 101 women) agreed to participate. However, the lack of gender balance for cases resulted in a small number of male subjects, which might reduce statistical power, and thus might not have detected other risk factors among lifestyle variables. This could be due to the use of identical case definitions for subject selection as the case-control hip OA and British studies. Cases were defined as those suffering knee pain and walking difficulties, who were first diagnosed by an orthopedic surgeon as displaying a tibiofemoral joint with a radiographic grade of ≥3 on the Kellgren and Lawrence scale. Our previous comparative study of OA in the lumbar spine indicated that OA in the general population tends to display lower prevalence and severity in Japan than in Britain.[14] In addition, the small number of male cases reflects gender differences in prevalence of knee OA in Japan. As a second limitation in the present study, the response rate for controls (52.8%) was lower than that for cases (92.0%). The present results may therefore be subject to some degree of overestimation.

Obesity has previously been shown to display strong associations with risk of knee OA,[2–8] and epidemiological studies performed in Japan have confirmed associations between obesity and knee OA.[15,16] In the present study, a history of heavy weight was shown to exert significant influences on risk of knee OA among men, resembling the results of women,[10] and consistent with previous studies. These findings indicate that the influence of heavy weight on knee OA is consistent across gender in both Japanese and Western populations.

The involvement of other joints is believed to play a role in increased risk of OA. In the British study paralleling the present study, presence of Heberden's node and previous knee injury were both strongly and independently associated with knee OA.[11,12] Although the present study did not seek information regarding the presence of Heberden's node, information was obtained about past history of the involvement of other joints and areas, as diagnosed by a medical doctor, indicating an independent association between previous knee injury and knee OA. In particular, site of knee OA was basically in accordance with the injured site among cases with previous knee injured (right side 91.7%, left side 100%). These findings were again consistent among men and women across Japanese and Western populations.

Mechanical stress represents another factor in the pathogenesis of OA at any joint site. In the present study, although occupational activities of standing, climbing stairs, kneeling, squatting, driving, walking, and heavy lifting were not associated with increased risk of knee OA in men, physical work at the principal occupation raised the risk of knee OA. Physical work represented by factory, construction, agricultural, or fishery work for long periods involved mechanical stress on the knee joints. The previous report utilized conditional logistic regression analysis without physical work, and identified sedentary work as a preventive factor in women.[10] These occupational activities influencing the risk of knee OA suggest that excess stress at the joint raises the risk, while reduced load on the joint decreases risk.

The present case-control study of knee OA paralleled our previous study of hip OA,[9] and was identical in format to some British studies.[17,18] Table 5 summarizes the results of studies using the same methods, indicating differences in risk factors between hip OA and knee OA, and between populations in Britain and Japan. Occupational factors clearly influence the development of both of hip and knee OA in Japan, as in Britain, although differences exist in specific activities exerting influence. Moreover, previous joint injury represented a risk factor for knee OA in Japan, as in the British studies. Conversely, obesity did not represent an independent risk factor for hip OA in Japan, but was a risk factor for both hip and knee OA in the British studies. This may be because local mechanical factors such as acetabular dysplasia might exert stronger influences on hip OA in Japan than other general mechanical factors such as adiposity. However, these results suggest that the pathogenesis of knee OA is similar in Japan and Western countries. Further studies of OA in other sites are required to characterize the risk profile in Japan.

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