Acta Medica et Biologica
Vol. 53, No. 1, 1-11, 2005

Epidemiology of Knee Osteoarthritis

Go OMORI

Center for Transdisciplinary Research, Niigata University, Niigata, Japan

Received 19 January 2005; accepted 11 March 2005

Summary. **Osteoarthritis (OA) is the most common form of aging of the joints. The knee joint is the key structure in the lower extremity and has much influence on activities of daily life (ADL) and the quality of life (QOL) in elderly persons. These include standing, walking, running, jumping, stair climbing, deep knee bending, such as squatting or sitting Japanese style, and other lower extremity tasks. Approximately 10 to 15% of people aged 60 years and older have symptomatic knee OA[1]. Therefore, knee OA is a major source of chronic disability and is becoming a serious public health problem. In order to clarify the pathomechanics of this disease and to determine suitable preventive strategies, detailed knowledge of the prevalence, progression, and the risk factors associated with knee OA is essential. This review focuses on the epidemiology and impact of knee OA.**

Key words—knee osteoarthritis, epidemiology, risk factors.

Historical and representative epidemiological study of knee osteoarthritis (OA) in the world

Studies evaluating the prevalence and risk factors of knee OA in subjects from different races and countries are essential to understand the disease etiology. There have been several large population-based cross-sectional or longitudinal epidemiological studies in the world, primarily in the United States and European countries, and recently in other areas including Japan and other Asian countries.

In 1958, Lawrence investigated the prevalence of OA in people in the Leigh and the Wensleydale areas of Northern England. The total number of the subjects was 2296 (males: 1098, females: 1198). This cross-sectional study included the evaluation of not only the knee joint but also the hand, feet, cervical and lumbar spine, and hip joint. The X-rays were evaluated according to Kellgren's classification and the prevalence of OA was analyzed using decennial age groups from 15-64 years. From this study, Lawrence reported that the prevalence of radiographic knee OA was 14% in males and 22% in females. He also found obesity was associated with knee OA in women, and a knee injury was associated in men[2,3].

Hernborg examined 244 knee OA patients in Malmo, Sweden, and evaluated the relationship between osteophytes and knee OA. He reported that the presence of osteophytes in knee joints was primarily related to age and was not necessarily an early sign of knee OA, but was frequently observed in cases of developed knee OA. Hernborg longitudinally investigated 94 knees OA over an 18-year period (1950-1968). In most cases, there was a marked radiological deterioration, and 56% of the subjects had more severe symptoms at the time of follow up than on initial examination. He concluded that the natural course of untreated knee OA was unfavorable and that the prognosis of the disease seemed worse than in hip OA[4,5,6].

From 1975 to 1978, 422 people in the Dutch town of Zoetmeer were surveyed to study the prevalence of knee OA and associated risk factors. Data were collected by a self-administered questionnaire, physical examination, radiographs, and serum analysis. A follow-up study was performed in 1988-1989, and 73% of the subjects were re-evaluated. In this longitudinal study, cartilage loss on the knee radiograph was found in 34% of the subjects over a 12-year period. The adjusted odds ratio was 11.1 in for a body mass index (BMI) greater than 27, and 3.8 for an age older than 60 years. There was no relationship with respect to gender, menisectomy, knee injury, uric acid concentration, or smoking [7].

Correspondence: Go Omori, M.D., Center for Transdisciplinary Research, Niigata University, 2-8050 Igarashi, Niigata 950-2181, Japan.

Abbreviations-BMI, body mass index; OA, osteoarthritis.

The Framingham osteoarthritis study[8-15]

The Framingham Heart Study started in 1948 and was designed to investigate factors associated with cardiovascular disease in the adult population of Framingham, Massachusetts in the USA. During the period of the eighteenth biennial examination, between 1983 and 1985, a total of 1424 subjects (males: 591, females: 833) were cross-sectionally examined by use of medical history, physical examination, and standing radiograph of the knee joint. The mean age of the cohort at the baseline study was 73 years (range: 63-94 years). Felson reported that the incidence of radiographic knee OA increased with age, from 27% in subjects younger than age 70 years of age, to 44% in subjects aged 80 years or older; further, it was noted that the prevalence was higher in women than in men (Fig.1). The prevalence of symptomatic disease was 9.5% (11.4% in female and 6.8% in male subject). This study focused mainly on elderly Caucasian people, and the same cohort was longitudinally evaluated in 1992-1993 at biennial examination 22. From this study, the natural history as well as many risk factors associated with the incidence or progression of knee OA were reported. The occurrence of incident radiographic and symptomatic disease and the progression of prevalent knee OA were as follows; approximately 2% of the women per year developed incident radiographic disease, 1% per year developed symptomatic, and 4% per year experienced progressive deterioration; these values were 1.5%, 0.5%, and 3%, respectively, in men. The rate of incident knee OA was 1.7 times higher in women than in men. Obesity was a major risk factor in women, but the relationship was not as strong as in men. Major knee injury also had a strong relationship to knee OA, and the relative risk was 3.46 in men and 2.18 in women. Smoking had an unexpectedly modest protective effect against the development of radiographic OA, but the biological reasons for which smoking may have protected against OA are unclear. Occupational knee bending and physical demands contributed to the development of structural OA in older men. As for the associations of osteoporosis and knee OA, high bone mineral density (BMD) was associated with an increased risk of incident radiographic OA but a decreased risk of progression of the disease. Recently, Felson categorized previously reported risk factors as systemic factors, intrinsic joint vulnerabilities, and extrinsic factors acting on joints, and described their interactions in causing knee OA.

The first national health and nutrition examination survey (NHANES-I) [16-22]

NHANES-I was a US national survey (conducted by the National Center for Health Statistics) that was designed to be representative of the white and black civilian, non-institutionalized population in the USA. This study was performed in 1975-1979, and both the interview and examination segments were completed by 6,913 persons aged 25-74 years. The data obtained from NHANES-I included X-rays of knees, hips, and sacroiliac joints, laboratory tests, anthropometric measurements, and questionnaires about medical history and activities of daily life (ADL). Many studies investigating the etiology of knee OA have been reported. The prevalence of knee OA was 4.9% in women and 2.6% in men, and the relative risk increased with age. The prevalence of knee OA was 8.3% in men and 18% in women aged older than 65 years (Fig.1). Bilateral knee OA was more prevalent (4.9%) than unilateral knee OA (1.5%), and bilateral knee OA was twice as prevalent in women. The cross-sectional associations between radiographic knee OA and a variety of putative risk factors were also evaluated. Obesity was significantly associated with knee OA in both genders. The relative risk of a BMI of more than 30 was 4.8 in men and 5.5 in women. There was a higher prevalence among black people than white people, especially in black women. Diabetes was not significantly associated with knee OA for either gender, and uric acid levels had a slight association in women. Jobs demanding knee-bending increased the risk of knee OA predominantly in those age 55 years and over. The adjusted odds ratio for the association of radiographic knee OA with knee-bending demands of a job in persons aged more than 55 years was 2.5 in men and 3.5 in women. Smoking habits had a modest protective effect against the development of knee OA. The prevalence of knee OA was 7.6% in non-smokers, 2.2% in heavy smokers, and 0.8% in very heavy smokers. Knee injury also increased the incidence of radiographic knee OA, and this association was especially found in unilateral cases. The effects of metabolic factors, such as serum cholesterol, serum uric acid, blood sugar level, body fat distribution, bone density, and blood pressure were analyzed in NHANES-I, but they remain unclear. In 1982-1984, NHANES-I epidemiological study follow-up (NHEFS-I) was performed, and the data from NHANES-I was then longitudinally evaluated. The mean follow-up rate of NHEFS-I was 94%. In NHEFS-I, persons who reported knee pain and had knee OA on radiography in NHANES-I were more likely to report difficulties with functional activity 10 years later than those without pain. The effect of chronic diseases---such as obesity, hypertension, heart disease, and pulmonary disease---on the association of knee OA with subsequent difficulty in physical function was also longitudinally evaluated. The strongest association with subsequent disability was with heart disease, followed by pulmonary disease, and then obesity. Recently NHANES- III was performed in

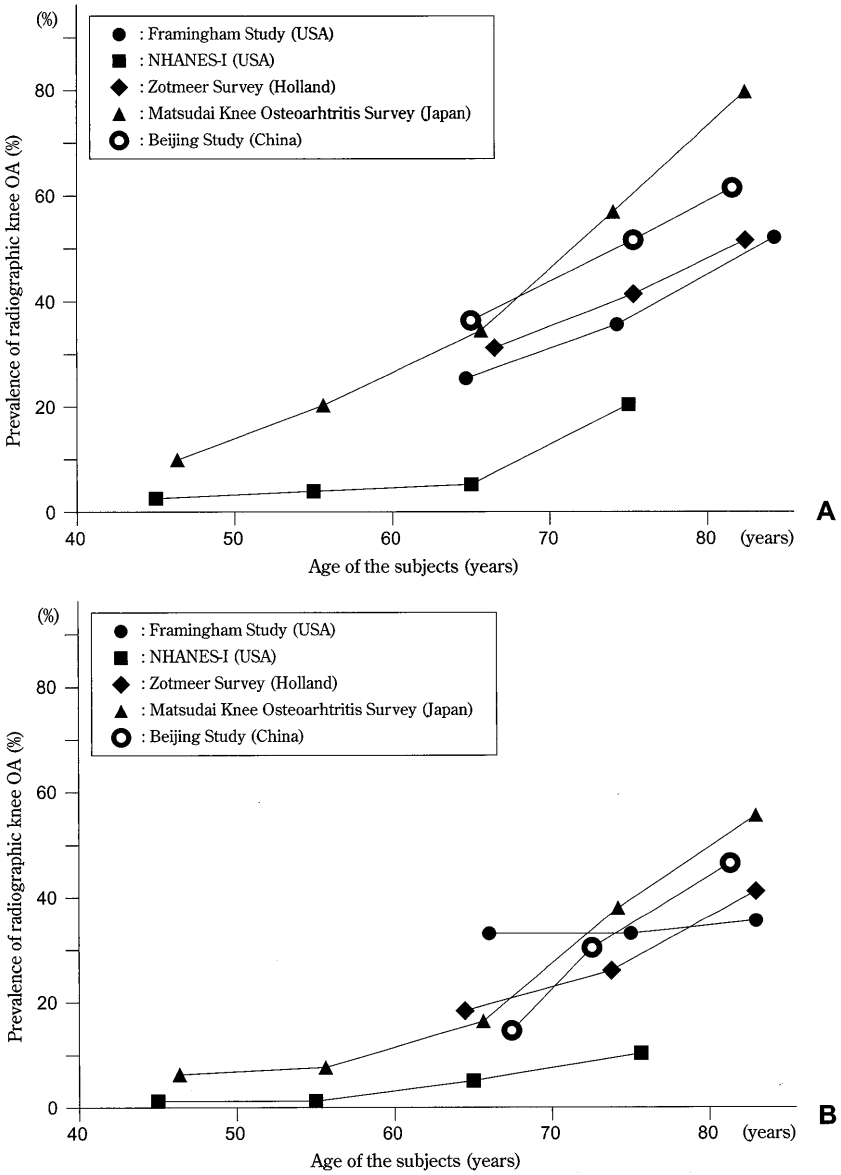

Fig. 1. The prevalence of radiographic knee OA in reported epidemiological studies. Knee OA was defined if a radiographic grade–according to the original or modified Kellgren-Lawrence scale–of II or higher was detected. **A.** The prevalence in women. **B.** The prevalence in men.

1992-1998, and longitudinal data concerning the etiology of knee OA will soon be available.

The Chingford study[23,24,25]

The Chingford study was established in 1988 in outer London UK, and 1003 women were studied with standing knee X-rays and questionnaires about their medical condition. The age range of the cohort was 45-64 years, and 98% of the people were Caucasian. The prevalence of radiographic knee OA was 12%, and 22% progressed in the index joint in a 2-year interval (Fig.1). Obesity at the baseline study was the most important factor related to incident disease. No clear effects were observed for age, physical activity, trauma episode, or the presence of hand OA. The Chingford study also analyzed the association between metabolic risk factors and knee OA. Raised blood glucose, blood cholesterol, hypertension, and the use of diuretics were significantly associated with knee OA. Odds ratios for those risk factors were 1.95, 2.06,

3.02, and 2.27, respectively. No association was found with raised triglyceride or HDL levels. The Chingford study cohort was longitudinally evaluated in 1994, four years after the baseline study, and 71% of the original subjects were followed up with knee radiographs again. Incident joint space narrowing was 12.6%, equating to 3.1% per year, and incident osteophytes developed in 13.3%, equating to 3.3% per year. No clear risk factors for joint space narrowing were identified, but obesity was strongly associated with osteophyte formation.

Epidemiological study of knee OA in the Asian countries

Recently, a few epidemiological studies of knee OA were conducted in the Asian population.

The Beijing OA study was conducted from 1997 to 2001 in Beijing, China and 1858 subjects, 755 men and 1103 women, were included. This cross-sectional study reported that the prevalence of radiographic knee OA was 21.5% in men and 42.8% in women over the age of 60 (Fig.1). The prevalence of symptomatic knee OA was 5.6% in men and 15% in women. The prevalence of radiographic knee OA of both genders increased with age. The prevalence of lateral knee OA in women was significantly higher than that of the Framingham study, and prolonged squatting was a strong risk factor for knee OA among elderly Chinese people in Beijing[26,27,28].

In the urban community of the Bangkok, Thai, an epidemiological study of knee OA was conducted in 1997, and 392 elderly people, aged more than 60 years, were studied. The prevalence of radiographic knee OA was 34.5% and increased as a function of age. Women were more often affected than men[29].

From 1993 to 1995, the prevalence of knee OA was studied in Al-Qaseem, Saudi Arabia. A total of 5894 adult subjects were evaluated. The prevalence of knee OA was 13% and increased with age, amounting to 30.8% of those aged 46-55 years and 60.6% in the age group 66-75 years. The associations of clinical OA of the knee with females and obesity BMI were significant[30].

Epidemiological study of knee OA in Japan[31-34]

In Japan, there have been several cross-sectional studies on the prevalence and risk factors of knee OA and, recently, a comparative study between Japanese and Caucasians was reported. Yoshida compared the prevalence of radiographic knee OA between women in the Nagasaki area and in Framingham, USA from 1998 to 1999. In this study, 358 Japanese women and 655 Caucasian women aged 63 years or older were compared. The age-specific prevalence of knee OA in Japanese women was 35.8% in the 63-69 year range, 54% in the 70-79 year range, and 63.3% in the 80-89 year range. The age-specific prevalence in American women was 26.5%, 36.4%, and 52.3% respectively. The age adjusted odds ratio of Japanese women in reference to American women was 1.96. Yoshimura analyzed the risk factors for knee OA in the Wakayama area and the results were compared with the study using the same methods in the UK in 2000. In this study, 101 Japanese women were interviewed and heavy weight, previous knee injury, and occupational activities were associated with incident radiographic knee OA. The odds ratio was 4.42 for obesity, 7.11 for previous knee injury, and 1.05 for occupational activity.

Matsudai Knee Osteoarthritis Survey[35-39]

We conducted an extensive survey of knee OA in order to investigate the prevalence and risk factors of the disease in a rural Japanese population in the Niigata area. The Matsudai Knee Osteoarthritis Survey was a population-based historical cohort study. A baseline survey was performed in 1979, and 1327 people (1075 women and 252 men) aged between 40 and 65 were evaluated. The same cohort was longitudinally followed at every 7 years from 1979 to 2000, resulting in a total of 4 surveys with 21 years of follow-up. Data were collected by questionnaire, physical examination, and anteroposterior standing radiographs of both knee joints. The questionnaire included age, gender, work history, knee injury, or trauma of the lower extremity,

Table 1. Demographic data of the Matsudai Knee Osteoarthritis Survey

	Age range	Total subjects number	Women	Men	Follow-up rate
Baseline study (1979)	40-65	1327	1075	252	81(%)
Second study (1986)	47-72	1015	831	184	80
Third study (1993)	54-79	1562	907	655	87
Fourth study (2000)	61-86	1260	711	549	73

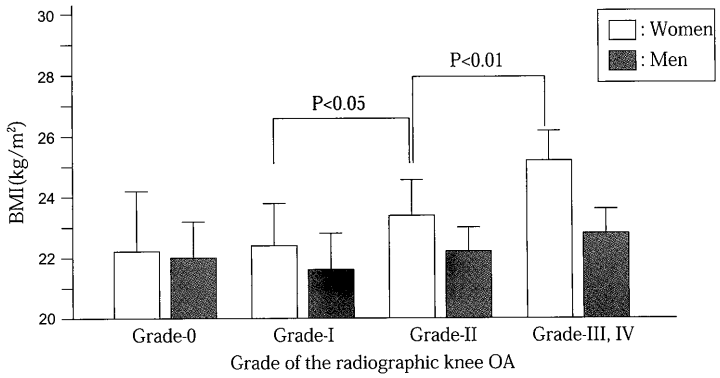

Fig. 2. The association between BMI and radiographic knee OA from the cross-sectional data in the fourth Matsudai Knee Osteoarthritis Survey. BMI was significantly increased with the progression of knee OA, especially in women.

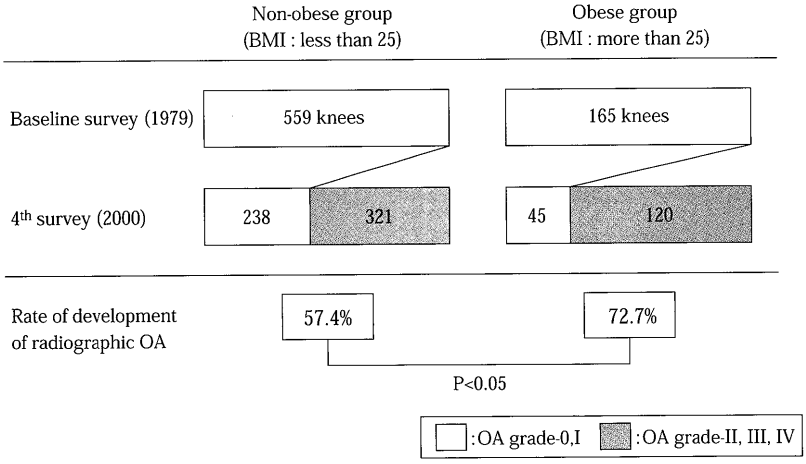

Fig. 3. The effect of BMI on the development of radiographic knee OA from the longitudinal analysis of the Matsudai Knee Osteoarthritis Survey. The incidence of radiographic knee OA was significantly increased in the obesity group in women subjects.

walking ability, and medical history of other diseases. The physical examination included body weight, height, range of motion of joints (knee, ankle, and hip joint), stability of the knee joint, and evaluation of the gait. BMI was calculated as a parameter of obesity. A weight-bearing knee radiograph was obtained and graded according to a modified Kellgren-Lawrence scale, and knee OA was defined if a radiographic grade of 2 or higher was detected.

A total of 5164 subjects, 3524 women and 1640 men, were involved in this survey, and the mean follow-up rate was 80.3% (73-87%) (Table 1). Of the 5164 subjects, 558 people— 494 women and 64 men, participated in all four surveys. The age-specific prevalence of radiographic knee OA in women was 10% in the 40-50 year range, 20% in the 50-60 year range, 35% in the 60-70 year range, 58% in the 70-80 year range, and 80% in subjects aged more than 80 years. In the case of men, the results were 5%, 7%, 15%, 35%, and 55%, for the respective age groups (Fig.1). While the prevalence of radiographic knee OA increased with age in both men and women, significantly higher levels were observed for women in all age-specific groups. BMI was calculated as an indicator of obesity, and a cross-sectional analysis of the 4th survey showed that BMI significantly increased with subsequently higher grades of radiographic knee OA in women (Fig.2). In this study, obesity was defined if BMI was greater than 25.0 according to the World Health

Table 2. Summary of reported risk factors, its influences on the knee OA, and range of relative risk

Risk factor	Influence on the prevalence of radiographic knee OA	Relative risk
Occupational activity	Heavy knee demand, heavy lifting work	1.7-3.4
Sports activity	High level, elite former athlete	1.3-6.5
	Low level, recreational sports (↓ risk)	Insufficient data
Knee injury	Ligament, cartilage, meniscus	5.2-14.0
	Surgical menisectomy	2.6-4.8
Knee alignment	Varus alignment (med knee OA)	4.0
	Valgus alignment (lat knee OA)	2.0
Muscle strength	Low quadriceps strength (↑ risk)	Insufficient data
Smoking	Average smoking	0.7
Race	Black women	2.1
	Japanese	1.9
	Chinese (women/men)	1.5/0.9
Obesity	High BMI	3.2-34.7
Bone	High BMD	1.1-2.3
Nutrients	Vitamin C intake	0.3
	Betacarotine	0.4
	Low vitamin D	1.02-2.9
Sex hormone	Estrogen use	0.3-3.3

Organization. We longitudinally evaluated 724 women subjects who participated in both the 1st and 4th surveys. All subjects had a 0 or 1 of radiographic grade of the knee joint, and they were subdivided according to their BMI during the 1st survey. The non-obese group was defined as BMI < 25 and the obese group as BMI > 25. The prevalence of radiographic knee OA over a 20 year period was significantly higher in the obese group (72.7%) than in the non-obese group (57.4%) (Fig.3). These cross-sectional and longitudinal data indicated that age, gender, and obesity were risk factors for knee OA. At this point, there are few epidemiological studies of knee OA with longer follow up periods than the Matsudai Knee Osteoarthritis Survey.

Discussion

The global aim of an epidemiological study is to clarify the pathogenesis and risk factors for a disease and to develop preventive strategies for both its incidence and progression. Many studies have suggested that the etiology of knee OA is complex and multifactorial. Previously reported risk factors for knee OA have been classified into two categories of local factors and systemic factors. Local factors, which are specific to joint sites and joint compartments, have received increasing attention in natural history studies of knee OA. Local factors may be further characterized as extrinsic or intrinsic to the knee joint. Extrinsic factors include physical activity and injury of the knee joint. Intrinsic factors include knee alignment, muscle strength, joint laxity, and proprioception. Systemic factors include obesity, bone, nutrients, hormone related issues, and genetic factors[15,40,41]. In the past, epidemiological studies mainly focused on the extrinsic factors but, in recent years, intrinsic factors and systemic factors have begun to receive more attention (Table 2).

Extrinsic factors in specific local factors

Physical activity:

Heavy physical work and prolonged knee bending, squatting, or kneeling work are strongly associated with knee OA[10,11,17,42]. Occupations such as coal miners[43], dockers[44], male carpenters and floor layers[45] have reported increased risk factors. A relationship between sports or recreational physical activity and the risk of knee OA has not been clearly demonstrated. Previous cross-sectional and longitudinal studies indicated that individuals who had normal joints and participated in low-impact exercises such as jogging, walking, and swimming, did not have an increased risk of knee OA, but former elite athletes with high impact to the knee joint, such as soccer players, weight lifters, and other jumping sports athletes, may have an increased risk[46-50]. Recently, a study in an Arabian country suggested that a range of motion exercises may help to preserve the motion arch in knee OA[51].

Injury of the knee joint:
A number of studies reported that previous knee injury is identified as the most important modifiable risk factor for subsequent knee OA. The effect of knee injury is more serious in men than in women, and more closely associated with unilateral OA than bilateral cases[18,52]. Injuries of the knee joint that include ligamentous rupture, meniscal tear, cartilage defect, or surgical menisectomy, often occur in the younger population and increase the risk of incident knee OA. Older age at the time of injury or surgery appears to predict a more rapid deterioration to OA of the involved knee[53,54].

Intrinsic factors in specific local factors

Knee alignment:
The varus-valgus alignment of the knee is a key determinant of load distribution. One study reported that the varus alignment was associated with medial knee OA and valgus alignment with lateral knee OA[55]. In the Matsudai Knee Osteoarthritis Survey, femoro-tibial angle (FTA) had a strong association with the radiographic grade of knee OA[39]. We believe that the varus alignment and laxity of the knee joint are the most important mechanical factors in knee OA.

Muscle strength:
Quadriceps weakness may increase the risk of knee OA, especially in women. Several studies reported that a lower strength of the quadriceps was associated with a higher incidence of knee OA but not with its progression. This notion remains controversial, and the influence of the muscle strength may differ between incidence and progression[56,57]. However, muscle exercise is recommended for prevention, suggesting that we have to consider the fact certain muscle forces may be associated with an increased joint reaction force[58,59].

Joint laxity:
Varus-valgus laxity leads to the coronal instability of the knee joint and may influence the loading condition of the tibio-femoral compartment[60]. For example, varus laxity will increase medial loading and result in deterioration of the articular cartilage of the medial compartment. The degeneration of the medial compartment will increase varus laxity. We found that a thrusting motion, or acute adduction motion in the early stance phase of the gait cycle, has a strong association with the radiographic grade of knee OA in the Matsudai Knee Osteoarthritis Survey[37]. In summary, these results are consistent with the possibility that varus-valgus laxity and a progression of knee OA form a vicious cycle.

Proprioception:
The proprioceptive function of the knee joint declines with age in healthy people, and is further impaired in elderly subjects with knee OA[61]. Even in a younger population, proprioception is impaired by injuries such as a rupture of the anterior cruciate ligament. Impaired proprioception will influence the joint position sense and is associated with physiological knee motion. Finally, prolonged abnormal knee motion may lead to joint degeneration resulting in the incidence of knee OA[62].

Systemic factors

Obesity:
Obesity is perhaps one of the strongest risk factors for the knee OA. This association is stronger in women than in men, and more often seen in bilateral cases[10,16,17,39]. Moreover, obese women with unilateral knee OA are at high risk for developing contralateral disease[23]. Obesity will have both mechanical and metabolic effects on the association with knee OA, and previous studies suggest that, at this point, the contribution of the mechanical effect is greater than the metabolic effect[18,19]. A recent study indicates that function in symptomatic knee OA is determined by pain and obesity rather than by structural change seen on the radiograph[25]. Therefore, weight reduction is a very important consideration for both treatment and prevention of the disease[63,64].

Bone:
Osteoporosis is the most important issue related to bone and knee OA[65]. It has been hypothesized that a stiffer subchondral bone, which is less deforming under loading, increases cartilage damage and leads to the development of knee OA[66]. Some studies reported that a high bone mineral density BMD increased the risk of incident knee OA but had a protective effect on the progression[13]. At present, there is no study to clearly account for the relationship between knee OA and osteoporosis.

Nutrients:
Nutrients may influence knee OA in at least two ways[67]. These include protection from excessive oxidative damage and biological actions related to bone and collagen synthesis. The focus of such studies has been the effect of the antioxidant vitamins A, C, and E. At this time there is no significant association of incident radiographic knee OA with any additional micronutrient. However, a significant reduction in the risk of progression is observed with vitamins C, E, and betacarotene intake[68]. Vitamin D may play a potentially important role in knee OA via bone mineralization and cell differentiation. As with the anti-oxidant study, there

is no effect of vitamin D on the risk of incident knee OA, but a low intake of vitamin D seems to be associated with an increase in the risk of knee OA progression. More research will be required to evaluate the importance of nutrition in the etiology, progression, and possible treatment of knee OA[69].

Hormone related issues:
Epidemiological evidence to clarify the effect of estrogen on the knee OA is still inconclusive. A descriptive epidemiological study showed that the risk of knee OA is comparable in men and women up to 50 years of age, but the incidence increases more rapidly in women than in men beyond this age[10,14]. Therefore, it has been thought that the postmenopausal changes in estrogen levels have an association with knee OA. Several cross-sectional studies report that estrogen replacement therapy (ERT) may protect against knee OA, while others show an inverse or lack of effect[70,71]. Recent longitudinal data suggest a non-significant protective effect of ERT on the development and progression of radiographic knee OA[72]. Further randomized prospective clinical trials are needed.

Genetic factors:
It is clear that a genetic component plays an important role in OA, and this issue is not specialized in knee OA[73,74]. However, there is the potential for many genes to contribute to a predisposition to OA because the development of OA represents the contribution of multiple cell types. Recently, many studies have addressed the contributions of genes. These include HLA-8, HLA-A1B8, collagen type II gene (COL2A1), Estrogen receptor gene, Interleukin-8 receptor, Vitamin D receptor, TGF-β1, and IGF- I gene[75,76,77]. More research will provide detailed information to determine the contributions of genes to knee OA.

Interaction of local and systemic factors:
In addition to the direct effects of local and systemic factors on knee OA, the risk factors may mediate each other in the mechanism of the disease. For example, knee alignment may play a mediating role in the relationship between obesity and knee OA. Varus alignment of the knee joint may increase the impact of body weight at the medial tibio-femoral compartment. A recent study suggests that BMI is related to the severity of medial knee OA. Furthermore, muscle strength will be associated with joint laxity and may enhance loading of the knee joint.

Conclusions

The etiology of knee OA is complex and multifactorial. Local and systemic factors have direct effects and interact to cause knee OA. Previous well-established cross-sectional and longitudinal epidemiological studies have clarified many risk factors. Such research has mainly focused on local factors. There are still many unresolved issues with respect to systemic factors including metabolic and genetic factors. Further studies should pay more attention to the contribution by systemic factors and inter-relation of other factors so as to develop beneficial strategies for both the treatment and prevention of knee OA.

Acknowledgments. The author extends special thanks to Yoshio Koga M.D. for organizing the Matsudai Knee Osteoarthritis Survey. The author also thanks Yukio Endo M.D. for statistical support and members of the Rehabilitation Unit of Niigata Kobari Hospital for their assistance in analyzing the data.

References

1) Felson DT, Zhang Y: An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. *Arthritis Rheum* **41**: 1343-1355, 1998.
2) Kellgren JH, Lawrence JS: Osteoarthritis and disk degeneration in an urban population. *Ann Rheum Dis* **17**: 388-396, 1958.
3) Lawrence JS, Bremner JM, Brief F: Osteo-arthrosis. Prevalence in the population and relationship between symptoms and X-ray changes. *Ann Rheum Dis* **25**: 1-24, 1966.
4) Hernborg J, Nilsson BE: Age and sex incidence of osteophytes in the knee joint. *Acta Orthop Scand* **44**: 66-68, 1973.
5) Hernborg J, Nilsson BE: The relationship between osteophytes in the knee joint, osteoarthritis and aging. *Acta Orthop Scand* **44**: 69-74, 1973.
6) Hernborg J, Nilsson BE: The natural course of untreated osteoarthritis of the knee. *Clin Orthop* **123**: 130-137, 1977.
7) Schouten JSAG, Ouweland FA, Valkenburg HA: A 12 year follow up study in the general population on prognostic factors of cartilage loss in osteoarthritis of the knee. *Ann Rheum Dis* **51**: 932-937, 1992.
8) Felson DT, Naimark A, Anderson J, Kazis L, Castelli W, Meenan RF: The prevalence of knee osteoarthritis in the elderly. The Framingham osteoarthritis study. *Arthritis Rheum* **30**: 914-918, 1987.

9) Felson DT, Anderson JJ, Naimark A, Hannan MT, Kannel WB, Meenan RF: Does smoking protect against osteoarthritis? *Arthritis Rheum* **32**: 166-172, 1989.
10) Felson DT: The epidemiology of knee osteoarthritis: Results from the Framingham osteoarthritis study. *Semin Arthritis Rheum* **20**: 42-50, 1990.
11) Felson DT, Hannan MT, Naimark A, Berkeley J, Gordon G, Wilson PWF, Anderson J:Occupational physical demands, knee bending, and knee osteoarthritis: Results from the Framingham study. *J Rheumatol* **18**: 1587-1592, 1991.
12) McAlindon T, Zhang Y, Hannan M, Naimark A, Weismann B, Castelli W, Felson D: Are risk factors for patellofemoral and tibiofemoral knee osteoarthritis different? *J Rheumatol* **23**: 332-337, 1996.
13) Zhang Y, Hannan MT, Chaisson CE, McAlindon TE, Evans SR, Aliabadi P, Levy D, Felson DT: Bone mineral density and risk of incident and progressive radiographic knee osteoarthritis in women: the Framingham study. *J Rheumatol* **27**: 1032-1037, 2000.
14) Felson DT, Zhang Y, Hannan MT, Naimark A, Weissman BN, Aliabadi P, Levy D: The incidence and natural history of knee osteoarthritis in the elderly. *Arthritis Rheum* **38**: 1500-1505, 1995.
15) Felson DT: An update on the pathogenesis and epidemiology of osteoarthritis. *Radiol Clin North Am* **42**: 1-9, 2004.
16) Davis MA, Ettinger WH, Neuhaus JM, Hauck WW: Sex differences in osteoarthritis of the knee. The role of obesity. *Am J Epidemiol* **127**: 1019-1030, 1988.
17) Anderson JJ, Felson DT: Factors associated with osteoarthritis of the knee in the first National Health and Nutrition Examination Survey (NHANES 1). Evidence for an association with overweight, race, and physical demands of work. *Am J Epidemiol* **128**: 179-189, 1988.
18) Davis MA, Ettinger WH, Neuhaus JM, Cho SA, Hauck WW: The association of knee injury and obesity with unilateral and bilateral osteoarthritis of the knee. *Am J Epidemiol* **130**: 278-288, 1989.
19) Davis MA, Ettinger WH, Neuhaus JM: Obesity and osteoarthritis of the knee: evidence from the National Health and Nutrition Examination Survey (NHANES 1). *Semin Arthritis Rheum* **20**: 34-41, 1990.
20) Davis MA, Ettinger WH, Neuhaus JM, Mallon KP: Knee osteoarthritis and physical functioning: Evidence from the NHANES 1 epidemiologic follow-up study. *J Rheumatol* **18**: 591-598, 1991.
21) Ettinger WH, Davis MA, Neuhaus JM, Mallon KP: Long-term physical functioning in persons with knee osteoarthritis from NHANES 1: Effects of comorbid medical conditions. *J Clin Epidemiol* **47**: 809-815, 1994.
22) Grubber JM, Callahan LF, Helmick CG, Zack MM, Pollard RA: Prevalence of radiographic hip and knee osteoarthritis by place of residence. *J Rheumatol* **25**:959-963, 1998.
23) Spector TD, Hart DJ, Doyle DV: Incidence and progression of osteoarthritis in women with unilateral knee disease in the general population: the effect of obesity. *Ann Rheum Dis* **53**: 565-568, 1994.
24) Hart DJ, Doyle DV, Spector TD: Association between metabolic factors and knee osteoarthritis in women: the Chingford Study. *J Rheumatol* **22**: 1118-1123, 1995.
25) Hart DJ, Doyle DV, Spector TD: Incidence and risk factors for radiographic knee osteoarthritis middle-aged women: the Chingford Study. *Arthritis Rheum* **42**: 17-24, 1999.
26) Zhang Y, Xu L, Nevitt MC, Aliabadi P, Yu W, Qin M, Lui LY, Felson DT: Comparison of the prevalence of knee osteoarthritis between the elderly Chinese population in Beijing and whites in the United States. The Beijing osteoarthritis study. *Arthritis Rheum* **44**: 2065-2071, 2001.
27) Felson DT, Nevitt MC, Zhang Y, Aliabadi P, Baumer B, Gale D, Li W, Yu W, Xu L: High prevalence of lateral knee osteoarthritis in Beijing Chinese compared with Framingham Caucasian subjects. *Arthritis Rheum* **46**: 1217-1222, 2002.
28) Zhang Y, Hunter DJ, Nevitt MC, Xu L, Niu J, Jui LY, Yu W, Aliabadi P, Felson DT: Association of squatting with increased prevalence of radiographic tibiofemoral knee osteoarthritis. *Arthritis Rheum* **50**: 1187-1192, 2004;.
29) Kuptniratsaikul V, Tosayanonda O, Nilganuwong S, Thamalikitkul V: The epidemiology of osteoarthritis of the knee in elderly patients lining an urban area of Bangkok. *J Med Assoc Thai* **85**: 154-161, 2002.
30) Al-Arfaj AS, Alballa SR, Al-Salen SS, Al-Dalaan AM, Bahabry SA, Mou MA, Al-Sekeit MA: Knee osteoarthritis in Al-Quaseem, Saudi Arabia. *Saudi Med J* **24**: 291-293, 2003.
31) Nakajyo H, Endo H: Epidemiology of knee osteoarthritis in Tohoku area. *Tohoku J Orthop Traumatol* **10**: 23-27,1966. (in Japanese)
32) Takehi Y, Mitsuhashi T, Morita H: The results of knee joint survey in Kusatsu town. *Knee* **15**: 90-93, 1990. (in Japanese)
33) Yoshida S, Aoyagi K, Felson DT, Aliabadi P, Shindo H, Takemoto T: Comparison of the prevalence of radiographic osteoarthritis of the knee and hand between Japan and the United States. *J Rheumatol*

29: 1454-1458, 2002.
34) Yoshimura N, Nishioka S, Kinoshita H, Hori N, Nishioka T, Ryujin M, Mantani Y, Miyake M, Coggon D, Cooper C: Risk factors for knee osteoarthritis in Japanese women: heavy weight, previous joint injuries, and occupational activities. *J Rheumatol* **31**: 157-162, 2004.
35) Tamaki M, Koga Y: Osteoarthritis of the knee joint: A field study. *J Jpn Orthop Assoc* **68**: 737-750, 1994. (in Japanese)
36) Shiozaki H, Koga Y, Omori G, Yamamoto G, Takahashi HE: Epidemiology of osteoarthritis of the knee in a rural Japanese population. *The Knee* **6**: 183-188, 1999.
37) Shiozaki H, Koga Y, Omori G, Tamaki M: Obesity and osteoarthritis of the knee in women: results from the Matsudai Knee Osteoarthritis Survey. *The Knee* **6**: 189-192, 1999.
38) Omori G, Koga Y, Segawa H, Nagasaki K, Shiozaki H, Tamaki M: Epidemiology of osteoarthritis of the knee joint with 21 years follow-up. The Matsudai Knee Osteoarthritis Survey 2000. *Knee* **26**: 243-246, 2002. (in Japanese)
39) Omori G, Koga Y, Higano Y, Auda H, Nagasaki K, Tamaki M, Shiozaki H, Endo K: Epidemiological longitudinal study of the osteoarthritis of the knee joint: The Matsudai Knee Osteoarthritis Survey. *Bessatsu Seikeigeka* **42**: 7-11, 2002. (in Japanese)
40) Sharma L: Local factors in osteoarthritis. *Curr Opin Rheumatol* **13**: 441-446, 2001.
41) Sowers M: Epidemiology of risk factors for osteoarthritis: systemic factors. *Curr Opin Rheumatol* **13**: 447-451, 2001.
42) Coggon D, Croft P, Kellingray S, Barret D, McLarren M, Cooper C: Occupational physical activities and osteoarthritis of the knee. *Arthritis Rheum* **43**: 1443-1449, 2000.
43) Kellgren JH, Lawrence JS: Rheumatism in miners. Part-II. X-ray study. *Br J Int Med* **9**: 197-201, 1952.
44) Partridge RE, Duthie JJ: Rheumatism in dockers and civil servants. A comparison of heavy manual and sedentary workers. *Ann Rheum Dis* **27**: 559-568, 1968.
45) Kivimaki J, Riihimaki H, Hannien K: Knee disorders in carpet and floor layers and painters. *Scand J Work Environ Health*; **128**: 179-189, 1992.
46) Lane NE, Bloch DA, Jones HH, Marshall WHJ, Wood PD, Fries JF: Long-distance running, bone density, and osteoarthritis. *JAMA* **255**: 1147-1151, 1986.
47) Panush RS, Schmit C, Caldwel JR: Is running associated with degenerative joint disease? *JAMA* **255**: 1152-1154, 1986.
48) Spector TD, Harris PA, Hart DJ: Risk of osteoarthritis associated with long-term weight bearing sports: a radiologic survey of the hips and knees in female ex-athletes and populaton controls. *Arthritis Rheum* **39**: 988-995, 1996.
49) Kujala UM, Kettunen J, Paananen H: Knee osteoarthritis in former runners, soccer players, weight lifters, and shooters. *Arthritis Rheum* **38**: 539-546, 1995.
50) Sandmark H, Vingard E: Sports and risk for severe osteoarthritis of the knee. *Scand J Med Sci Sports* **9**: 279-284, 1999.
51) Szabo G, Lovasz G, Kustos T, Bener A: A prospective comparative analysis of mobility in osteoarthritic knees. Does lifestyle have an influence? *J Bone Joint Surg Br* **82**: 1167-1169, 2000.
52) Gelber AC, Hochberg MC, Mead LA: Joint injury in young adults and risk for subsequent knee and hip osteoarthritis. *Ann Intern Med* **133**: 321-328, 2000.
53) Roos H, Lauren M, Adalberth T, Roos EM, Jonsson K, Lohmander LS: Knee osteoarthritis after menisectomy: prevalence of radiographic changes after twenty-one years, compared with matched controls. *Arthritis Rheum* **41**: 687-693, 1998.
54) England M, Rose M, Lohmander L: Impact of type of meniscal tear on radiographic and symptomatic knee osteoarthritis. *Arthritis Rheum* **48**: 2178-2187, 2003.
55) Sharma L, Song J, Felson DT, Cahue S, Shamiyeh E, Dunlop DD: The role of knee alignment in disease progression and functional decline in knee osteoarthritis. *JAMA* **286**: 188-195, 2001.
56) Slemenda C, Brandt KD, Heilman DK, Muzzuca S, Braunstein EM, Katz BP: Quadriceps weakness and osteoarthritis of the knee. *Ann Intern Med* **127**: 97-104, 1997.
57) Slemenda C, Heilman DK, Brandt KD, Katz BP, Mazzuca SA, Braunstein EM, Byrd D: Reduced quadriceps strength relative to body weight. A risk factor for knee osteoarthritis in women? *Arthritis Rheum* **41**: 1951-1959, 1998.
58) Hurley MV: The role of muscle weakness in the pathogenesis of osteoarthritis. *Rheum Dis Clin North Am* **25**: 283-298, 1999.
59) Van Baar M, Assendelft WJ, Dekker J, Oostendorp RA, Bijlsma JW: Effectiveness of exercise therapy in patients with osteoarthritis of the hip or knee: A systemic review of randomized clinical trials. *Arthritis Rheum* **42**: 1361-1369, 1999.
60) Sharma L, Lou C, Felson DT: Laxity in healthy and osteoarthritic knees. *Arthritis Rheum* **42**: 861-870, 1999.
61) Pai Y-C, Rymer WZ, Chang RW: Effect of age and osteoarthritis on knee proprioception. *Arthritis Rheum* **40**: 2260-2265, 1997.

62) Sharma L, Pai Y-C, Holtkamp K: Is knee joint proprioception worse in the arthritic knee vs. the unaffected knee in unilateral knee osteoarthritis? *Arthritis Rheum* **40**: 1518-1525, 1997.
63) Slemenda CW: The epidemiology of osteoarthritis of the knee. *Curr Opin Rheumatol* **4**: 546-551, 1992.
64) Felson DT, Anderson JJ, Naimark A: Obesity and knee osteoarthritis: The Framingham study. *Ann Intern Med* **109**: 18-24, 1988.
65) Hart DJ, Mootoosamy I, Doyle DV: The relationship between osteoarthritis and osteoporosis in the general population: the Chingford study. *Ann Rheum Dis* **53**: 158-162, 1994.
66) Radin EL, Paul IL, Rose RM: Role of mechanical factors in pathogenesis of primary osteoarthritis. *Lancet* **749**: 519-522, 1972.
67) Sowers MF, Lachance L: Vitamins and arthritis: the role of vitamins A, C, D, and E. *Rheum Dis Clin North Am* **25**: 315-332, 1999.
68) McAlindon TE, Jacques P, Zhang Y: Do antioxidant micronutrients protect against the development and progression of knee osteoarthritis? *Arthritis Rheum* **39**: 648-656, 1996.
69) McAlindon TE, Felson DT, Zhang Y: Relation of dietary intake and serum levels of vitamin D to progression of osteoarthritis of the knee among participants in the Framingham study. *Ann Intern Med* **125**: 353-359, 1996.
70) Samanta A, Jones A, Regan M, Wilson S, Doherty M: Is osteoarthritis in women affected by hormonal changes or smoking? *Br J Rheumatol* **32**: 366-370, 1993.
71) Oliveria SA, Felson DT, Klein RA, Reed JI, Ealker AM: Estrogen replacement therapy and the development of osteoarthritis. *Epidemiology* **7**: 415-419, 1996.
72) Zhang Y, McAlindon TE, Hannan MT: Estrogen replacement therapy and worsening of radiographic knee osteoarthritis: the Framingham study. *Arthritis Rheum* **41**: 1867-1873, 1998.
73) Kellgren JH, Lawrence JS, Bief F: Genetic factors in generalized osteoarthrosis. *Ann Rheum Dis* **22** 237-255, 1963.
74) Spector TD, Cicuttini F, Baker J: Genetic influences on osteoarthritis in women; a twin study. *Br Med J* **312**: 940-944, 1996.
75) Knowlton RG, Katzenstein PL, Moscovitz RW: Genetic linkage of a polymorphism in the type II procollagen gene (COL2A1) to chondrodysplasia. *New Engl J Med* **322**: 526-530, 1990.
76) Huang J, Ushiyama T, Inoue K, Kawasaki T, Hukuda S: Vitamin D receptor gene polymorphisms and osteoarthritis of the hand, hip, and knee: a case-control study in Japan. *Rheumatology* **39**: 79-84, 2000.
77) Loughlin J, Sinsheimer JS, Mustafa Z: Association analysis of the vitamin D receptor gene, the type I collagen gene COL1A1, and the estrogen receptor gene in idiopathic osteoarthritis. *J Rheumatol* **27**: 779-784, 2000.