

## EXTENDED REPORTS

# Incidence and progression of osteoarthritis in women with unilateral knee disease in the general population: the effect of obesity

Tim D Spector, Deborah J Hart, David V Doyle

## Abstract

**Objectives**—The natural history of knee osteoarthritis (OA) is poorly understood. The principal aim was to assess the rate of contralateral knee OA in middle aged women in the general population with existing unilateral disease and to identify the major factors that influence this rate.

**Methods**—Fifty eight women aged (45–64) from a general population study cohort were identified with unilateral knee OA diagnosed radiologically (Kellgren and Lawrence 2+) (K&L). Follow up AP films were obtained at 24 months and compared with the baseline for K&L grade and individual features of osteophytes and joint space.

**Results**—Twenty women (34%) developed incident disease in the contralateral knee (based on K&L 2+ or osteophyte changes) and 22.4% (n = 13) of women progressed radiologically in the index joint. Obesity at baseline was the most important factor related to incident disease, 47% of women in the top BMI tertile developed OA, compared with 10% in the lowest tertile: relative risk 4.69 (0.63–34.75). No clear effect was seen for age, physical activity, trauma or presence of hand OA.

**Conclusions**—Over one third of middle aged women with unilateral disease will progress to bilateral knee OA within two years and a fifth will progress in the index joint. Obesity is a strong and important risk factor in the primary and secondary prevention of OA. These natural history data provide a useful estimate for planning therapeutic intervention trials.

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Osteoarthritis is one of the commonest causes of disability and knee disease is the commonest site leading to loss of function and pain.<sup>1</sup> The natural history of knee osteoarthritis is poorly understood. In hospital based patients one study collected information on 360 patients for a year<sup>2</sup> and only a few small studies have examined progression for more than five years.<sup>3–5</sup> Data on the outcome of milder cases in the community is even more scanty; the only information coming from the Zootomeer Study which obtained at follow up radiograph after 12 years in 142 patients with knee OA at

baseline and identified several poor prognostic indicators.<sup>6</sup> Knowledge about the prognosis of patients, the likelihood and predicted speed of progression in individuals is important in order to provide clear information to the patient, and it may also influence therapeutic approaches. A further reason for obtaining an estimate of rates of progression is for sample size estimates in the planning of clinical trials. To our knowledge no study has looked at the rates of incident OA in the contralateral knee in a general population sample. Using data from the Chingford population study we have identified individuals who were found at the baseline screening examination to have unilateral OA of the knee. Two year follow up films of these women have been obtained to assess the incidence of OA in the contralateral knee and progression in the index knee and the factors that influence this rate.

## Patients and methods

A sub-sample of women participating in the Chingford population study with unilateral knee OA were identified. The Chingford study population, established in 1988, is a well documented cohort of 1003 women who are seen annually.<sup>7</sup> The response rate at the initial recruitment from age/sex register at a general practice was 78%. All the women live within five miles of the general practice and 98% of the women are white. The area is predominantly middle class but with a range of all social groups. A socio-economic profile was performed using the Acorn classification system which is based on each subject's postcode and residence (CACI International, London). These codes were linked to one of four socio-economic categories. The majority of the women (42%) belonged to group C1 (mid to lower middle class, white collar workers), 32% were A/B, 17% C2 and 8% D/E. The women in the study are also similar to UK normals in terms of smoking statistics, hysterectomy rates and heights and weights.<sup>7</sup>

At baseline all women had a weight bearing AP film of the knees taken in the fully extended position by the same technician on the same equipment. Baseline films were graded blind to clinical details using the method of Kellgren and Lawrence (K&L) and the atlas of standard radiograph.<sup>8</sup> Individuals with grade 2 changes or more in one knee only (interpreted as the presence of a definite osteophyte) were

Department of  
Rheumatology,  
St Thomas' Hospital,  
London,  
United Kingdom  
T D Spector  
D J Hart

Department of  
Rheumatology,  
Whipp's Cross  
Hospital,  
London,  
United Kingdom  
D V Doyle

Correspondence to:  
Dr T D Spector,  
Department of  
Rheumatology,  
St Thomas' Hospital,  
London SE1 7EH,  
United Kingdom.

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identified and defined for the purposes of this study as having unilateral osteoarthritis. A follow up AP radiograph was performed on these women in the same manner 24 months later.

The paired films were read 'blind' to time sequence and clinical details for K&L grade and for individual features for osteophytes and narrowing (JSN) for each compartment using a validated atlas on a 0-3 scale of severity.<sup>9</sup> On the basis of these results women were categorised into those who had developed incident disease in the contralateral knee and those that had progressed in the index knee. An outcome of knee replacement was categorised as an increase in osteophyte and narrowing grade. Hand radiographs were also obtained on all women at baseline and scored using the method of Kellgren & Lawrence, using grade 2 (presence of osteophyte) at the DIP joint to indicate disease. As a number of studies have found obesity to be the strongest known risk factor for knee OA,<sup>10</sup> women were divided into tertiles on the basis of the baseline body mass index (BMI) [ $\text{m/kg}^2$ ] of the whole study population and the frequency of incident and progressive disease compared. Relative risks and 95% confidence intervals were calculated for the middle and upper tertile groups compared with the lowest tertile and adjusted for potential confounders using the methods of Mantel-Haenzel and logistic regression using EGRET software.

## Results

At baseline 118 women were identified with at least K&L grade 2 in either knee. Of these, 67 had unilateral disease and of these 58 returned for the follow up radiograph, three had moved area, two refused and four were only examined clinically. The group in whom follow up radiographs were not obtained was similar to the others in terms of knee pain, age and BMI. The characteristics of this group at the baseline examination are given in table 1. The mean (SD) age was 56.8, and weighed a mean of 71

kg (range 52.7-100.7 kg). Forty five per cent of the women reported ever having had knee pain in either knee for an average recalled duration of 6.75 years and 38% had coexistent hand OA. Only three women were currently taking NSAIDs. Of the whole group 34% ( $n = 20$ ) had developed incident disease in the contralateral knee at follow up, based on K&L grade 2 or presence of osteophyte. Twelve women (21%) had developed joint space loss in addition to the presence of a definite osteophyte.

Progression in the index joint was noted in 22.4% using as a definition an increase in K&L grade, 32.8% using an increase in osteophyte size and 15.5% using a reduction in joint space in either the medial or lateral compartments. In one woman regression of a definite osteophyte, was noted although this was not confirmed on paired readings, being felt to be due to altered positioning. In four cases change from a 'doubtful' osteophyte (K&L 1) to normal (K&L 0) was noted.

The role of obesity as a risk factor in the contralateral knee was then examined (table 2). Only 10% of women in the lowest obesity group (BMI <23.4) developed OA defined by osteophyte, compared with 25% in the mid tertile (23.4-26.4) and 47% of those in the highest tertile (>26.4). The relative risk for the highest obesity category was 4.69 (95% CI 0.63-34.75) and for the middle category was 2.50 (95% CI 0.25-25.20). For each 5 kg increase in baseline weight, the risk of incident knee OA increased by 6.5%. Within the obese group the majority of incident disease was due to the presence of osteophytes alone (11.7%) with the remainder having both osteophytes and narrowing. When the definition of OA was altered to that of new joint space narrowing, the relative risks for obesity remained increased; for JSN in the top obesity tertile, being approximately 2.8 and for the mid tertile 1.9, although due to small numbers the confidence intervals included unity. For the whole group there was an average weight increase over the 24 months of 0.97 kg, with no marked differences between the three obesity groups. When weight change was added to the model, including baseline weight, no effect on risk of OA was seen.

Table 3 shows the effect of BMI on progression in the index joint. Numbers in the BMI group are small but a clear effect of obesity on progression of osteophyte score is seen with a relative risk of 4.69 (95% CI 0.63-34.75) for the upper tertile. Differences in joint space narrowing between the obesity groups were not seen clearly and progression in K&L grade, although higher, did not increase uniformly with obesity category.

The effect of associated OA of the distal interphalangeal joint on rates of progression or incidence of disease at the knee was also examined. Twenty two women had radiological OA of at least one DIP joint, eight (40%) of those with incident disease and 14 (36.8%) of those with no new disease. The influence of obesity on progression and incident disease remained essentially unchanged after adjustment for age, hand OA, social class,

Table 1 Characteristics of 58 women with unilateral Kellgren & Lawrence (Grade 2+) at baseline

	Mean (SD) or No (%)
Age (years)	56.8 (5.9)
Weight (kg)	71 (12.0)
Height (m)	1.61 (5.5)
BMI $\text{kg/m}^2$	27.5 (4.1)
No (%) knee pain	26 (44.8)
No (%) hand OA	22 (37.9)
No (%) NSAIDs	3 (5.17)
No (%) K&L in 0	17 (29.3%)
'unaffected' knee 1	41 (70.6%)

Table 2 Incident knee OA in contralateral knee by BMI group

BMI group	Low (17-22.9) (n = 10)	Medium (23-25.9) (n = 16)	High (26+) (n = 32)	Total (n = 58)
Incident cases				
-Osteophyte (K&L2+)	1 (10%)	4 (25%)	15 (47%)	20 (34%)
-JSN	0	3 (18.8%)	9 (28%)	12 (20.7%)
Knee pain at baseline	3 (33%)	7 (43.7%)	16 (50%)	26 (44.8%)
Average weight change ( $\uparrow$ kg, SD)	1.14 (2.84)	0.95 (3.26)	0.92 (4.26)	0.97 (3.74)

Table 3 Progression of OA in index knee (N = 58) by increase in grade of K&L (0-4) and osteophyte (0-3) or joint space narrowing (JSN (0-3))

BMI group	Low (17-22.9) (n = 10)	Medium (23-25.9) (n = 16)	High (26+) (n = 32)	Total (n = 58)
K&L	0	4 (25.0%)	9 (28.1%)	13 (22.4%)
Osteophyte	1 (10%)	3 (18.75%)	15 (46.8%)	19 (32.8%)
JSN	1 (10%)	6 (37.5%)	2 (6.25%)	9 (15.5%)

Table 4 Baseline characteristics comparing progressors and non-progressors

No (%) or mean (SD)	Progressors (n = 20)	Non-progressors (n = 38)
Age	57.2 (5.23)	56.6 (6.29)
Weight	72.2 (11.22)	70.4 (12.52)
BMI	28.57 (3.39)	26.96 (4.31)
No (%) hand OA	8 (40%)	14 (36%)
No (%) knee trauma*	3/17* (15%)	8/32* (21%)
No (%) knee pain	9 (45%)	17 (44.7%)
No (%) physical activity top tertile	5 (25%)	14 (36.8%)

\*Based on 49 subjects.

previous knee injury and level of physical activity. A comparison of these factors for progressors and non progressors is given in table 4. Interestingly, women with the doubtful category of K&L grade 1 in the unaffected knee were much more likely to progress in that knee compared with those with grade 0 (8/8 compared with zero) and more likely to have incident disease 19/20 compared with 1/20 who had grade zero at baseline.

## Discussion

Our data show that in middle aged women with early unilateral osteoarthritis of the knee, a high percentage (34%) develop OA in the contralateral knee within two years and 22.4% progress radiologically in the index joint. It is likely therefore that over longer periods of time most women develop bilateral disease and cross-sectional studies suggesting that these are different subgroups should therefore be interpreted with caution. Obesity appears to have a marked effect on the incidence rates, with nearly a five-fold increase in overweight women compared with thin women. Obesity is the commonest and strongest risk factor identified to date for OA of the knee with numerous cross-sectional studies showing risks to be increased for women in the top tertile of BMI ranging from a 2 to 7-fold increase.<sup>10</sup> Data from the baseline examination of the Chingford Study showed a nearly 18-fold increased risk for bilateral disease.<sup>7</sup> Strangely the associations of obesity with hip OA are much weaker and inconsistent, suggesting that for the knee, the cause may not be purely mechanical. The association is likely to be causal rather than a secondary phenomenon, as shown by longitudinal data from the Framingham observational study.<sup>11</sup> Furthermore, data from the same group show the therapeutic potential of weight loss.<sup>12</sup>

Studies of incidence and progression in OA are subject to many potential problems. The first is the generalisability of the subjects and the results. Using a population based screening

approach and reasonable response rate, it is unlikely that the women studied were a specially selected group. The cohort is similar to the national average in terms of a number of demographic variables and is therefore likely to be broadly representative of the UK female population. The definition of prevalent and incident disease as well as progression is a controversial subject. Although criteria exist for clinical cases which rely on signs and current symptoms, these have not been found to be sufficiently sensitive for epidemiological study.<sup>13</sup> Radiographic definitions are used for population studies and most authors use the presence of osteophytes and/or joint space narrowing.<sup>14</sup> We have shown in the Chingford population study, at least in the knee, that the presence of definite osteophytes is a reproducible feature that correlates better with knee pain than does joint space narrowing, suggesting it should be the primary diagnostic feature in epidemiological studies.<sup>15</sup> The relative merits of osteophytes and joint space in assessing progression remains to be tested in a rigorous manner and we therefore looked at both. Recently it has been argued that a proportion of knee pain can be explained by radiographic changes in the patello-femoral joint.<sup>16</sup> Although scoring changes in this joint are less reproducible,<sup>14</sup> we should have ideally included lateral or skyline views in our baseline protocol. The timing of disease onset is another problem; recall of duration of knee pain is likely to be highly unreliable and thus underlines the importance of longitudinal studies based on objective radiographic findings.

Our findings that the 'doubtful' grade 1 category of K&L appears to progress more than grade 0, raises difficult questions. The use of grade 1 is controversial and we are unaware of other prospective knee data. However, the reproducibility of detecting grade 1 K&L changes, is poor and some of the effect may be misclassification. Nevertheless, it suggests that even very minor osteophytes should not be overlooked and the best ways of measuring them needs to be further addressed.

Previous data on the natural course of knee OA is poor. A few small longitudinal studies indicate that between 30 and 50% of hospital treated cases of knee OA will deteriorate, but many remain stable, and a small number may actually improve.<sup>3-5</sup> Dougados *et al* collected radiographic data on 736 patients with symptomatic knee OA (the majority with bilateral disease) from a large number of French centres and radiographs were evaluated 12 months later on 360 (48%).<sup>2</sup> Of those re-attending 36.7% had progressed in terms of osteophytes but there was no significant decrease in joint space (which the authors used as the main outcome) and 41% of patients considered their overall disease had improved, compared with 28% who felt they had worsened.<sup>2</sup>

However, these studies were based on selected hospital-based patients and few studies have looked at the natural progression of knee OA in the general population. Some

data are available from the EPOZ study in Zoetermeer, The Netherlands, in which all people over 45 were x rayed. The authors examined 239 people who had x rays available at baseline and after a 12 year follow up period. Only 142, however, were considered to have knee OA when re-read at follow up, and a third of those cases had lost cartilage on knee x ray over the 12 year period.<sup>6</sup> Although the only study of its kind, there were considerable problems, primarily due to the large number (40%) who were lost to follow up and problems with disease definition in the original films.

Few studies have any detailed data on prognostic factors. In a small group of clinical cases followed up for 11 years, there were significantly more progressors in subjects that had knee pain on entry but there was no clear effect of obesity.<sup>5</sup> In the EPOZ study Schouten *et al* found that obesity, age, Heberden's nodes and valgus deformity were all associated with cartilage loss over a 12 year period.<sup>6</sup> He found no association with gender, chondrocalcinosis, injury, meniscectomy, smoking and occupation related factors. In a small eight year follow up study Massardo *et al* were unable to identify clear entry criteria that would predict outcome.<sup>4</sup> Factors related to joint space progression in the multicentre French study were obesity and number of affected joints.<sup>2</sup>

All these studies have suffered either from relatively small numbers, high numbers of non-responders and 'ad-hoc' design which have made the precise identification of risk factors for progression difficult. A follow up study by Doherty *et al* on patients who have had meniscectomy found that the presence of hand disease considerably increased the risk of subsequent contralateral knee OA and progression in the index joint, 25 years after the operation.<sup>18</sup> Data on the effect of obesity were not reported in this study.

Although this study underscores the importance of obesity as a potentially modifiable risk factor, the high rate of incident contralateral disease in this population lends support to the hypothesis that OA is a generalised disease and that unilateral disease usually progresses to other joint groups. Middle aged women are believed to have the highest incidence rates of OA and are more likely to have multiple joint involvement of greater

severity than men.<sup>19</sup> This has led to a number of hypotheses that systemic, metabolic and hormonal factors are responsible. These data suggest that patients with early unilateral knee OA are an ideal group for studying incident disease and therapeutic measures to retard or prevent the disease.

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