The Longterm Outcome of Osteoarthritis: Rates and Predictors of Joint Space Narrowing in Symptomatic Patients with Knee Osteoarthritis

FREDERICK WOLFE and NANCY E. LANE

ABSTRACT. ***Objective.*** To determine the rate of progression of radiographic joint space narrowing (JSN) and the factors that predict it in symptomatic clinic patients with knee osteoarthritis (OA).

Methods. In total 1507 patients with knee OA were studied with extended weight-bearing anterior-posterior views of the knee as part of a longitudinal study of longterm outcomes of osteoarthritis (OA). Baseline demographic and severity measurements included body mass index (BMI), pain, global severity, Health Assessment Questionnaire disability, and erythrocyte sedimentation rate. Rates and predictors of progression were obtained by Kaplan-Meier survival analyses and Cox regressions using a JSN score of 3 as "failure."

Results. For the 1232 patients who had not reached the endpoint narrowing score of 3 when first evaluated, the 75th and 50th survival times (time to JSN = 3) were 11.27 and 17.84 years for those with JSN = 0 at onset, 7.41 and 12.03 years for those with JSN = 1 at onset, and 4.49 and 7.44 years for those with JSN = 2 at onset. The corresponding yearly incidence rates for the 3 initial groups were 0.017, 0.032, and 0.077. In multivariate Cox models, initial JSN, BMI, symptom duration, and global severity were predictors of progression, but only JSN was a strong predictor. BMI predicted JSN in those with JSN = 0 at onset, but not in patients with more severe disease. Although contralateral JSN predicted progression, it was only of value with initial homolateral JSN scores of 0. Assessment of homolateral osteophytes aided prediction in patients with initial JSN = 0, but was of much less help when JSN had a higher severity score.

Conclusion. The risk of progression in clinical OA patients with radiographic abnormalities is substantial. Nonradiographic predictors of OA progression (e.g., BMI) are weak predictors of radiographic progression compared to current radiographic status. Rates of progression are greatest in those with established radiographic abnormalities. Osteophytes are of limited additional values once JSN = 2 is present. Contralateral radiographic abnormalities are useful predictors only in those with JSN = 0. Intervention studies to prevent radiographic progression probably should utilize joints where evidence of abnormality already exists. At a clinical level, current radiographic status predicts future status, with 50% of patients with JSN = 1 and 50% of patients with JSN = 2 progressing to complete joint space loss in 12.03 and 7.44 years, respectively. (J Rheumatol 2002;29:139–46)

Key Indexing Terms:
OSTEOARTHRITIS PROGRESSION RADIOGRAPHS

Knee osteoarthritis (OA) is a common disorder that is associated with significant morbidity, disability, and medical costs, particularly in its advanced stages when total joint replacement may be required and functional disability may be severe[1-4]. In contrast to knee OA as defined in populations, where radiographic abnormality may occur in the absence of pain[5], pain is an essential component of clinical OA and is a requirement of the American College of Rheumatology (ACR) knee OA criteria[6].

It is of considerable interest to identify the person with OA who will "progress." Progression is usually identified radiographically, particularly in population based studies[7-9]. Such approaches have provided useful information into the epidemiology and etiology of OA in populations. The clinical situation is somewhat different in that it deals only with symptomatic patients who have sought medical care for their symptoms. Only a few studies have addressed progression in this group of patients, and for a number of reasons[10-14]. First, it is difficult to do such studies because OA may take years, or even decades, to progress. It is also made more difficult, and sometimes impossible, when radiographs are obtained using different views and techniques. Finally, it is sad to note that, except for research projects, films may be destroyed or sold

From the National Data Bank for Rheumatic Diseases and University of Kansas School of Medicine, Wichita, Kansas; and the University of California at San Francisco, San Francisco, California, USA.

Supported in part by grants from Roche Global Pharmacoeconomic Research and the Rosalind Russell Research Fund.

F. Wolfe, MD, National Data Bank for Rheumatic Diseases and University of Kansas School of Medicine; N.E. Lane, MD, University of California at San Francisco.

Address correspondence to Dr. F. Wolfe, National Data Bank for Rheumatic Diseases, 1035 N. Emporia, Suite 230, Wichita, KS 67214. E-mail: fwolfe@arthritis-research.org

Submitted April 24, 2001; revision accepted July 25, 2001.

for their silver content. The consequence of these factors is that there have been few longterm studies of clinical OA.

Risk factors for knee OA have been identified in a number of studies[8,11,14-29]. But as noted by Cooper, *et al*, risk factors for incident cases may differ from risks associated with progression[8]. We investigated in symptomatic patients (1) the rate of progression of joint space narrowing (JSN) and (2) the factors that predict progression. In contrast to previous studies, we use life table analysis and Cox regression to determine the rate and risk factors associated with advanced JSN (i.e., JSN = 3). Even though pain and disability are not well correlated with JSN, a JSN score of 3 has particular clinical importance because in the United States it usually is a requirement for total joint replacement surgery and thus is associated with increased direct and indirect medical costs.

MATERIALS AND METHODS

Patient population. The data of this study were the results of clinical and research practice at the Arthritis Research Center, where OA data collection began in July 1976. Beginning at that time and continuing through the present, consecutive patients with OA of the knee or hip who were seen for clinical care at the Arthritis Center had radiographic evaluations and were added to the data bank. In July 1996, a program was begun to recruit symptomatic patients with knee OA from the community. Through September 1999, 675 such patients were identified and enrolled into the databank. In addition to reassessments that occurred as part of clinical care, patients were invited to return for free evaluations, including radiography, on 3 occasions between 1985 and 1999. Overall, 2420 patients with knee or hip OA were enrolled. This report includes 1507 patients with OA of the knee who had 2445 paired knee radiographs. Of the 1507 patients, 1000 had only a single radiograph (at the first clinic visit) and 507 had more than one radiograph. A single radiograph refers to a single radiographic examination; this almost always refers to a film of the right and the left knee. Patients with a single radiograph examination had a mean of 3.6 (SD 4.3) observations and a duration of followup of 2.6 (SD 4.0) years at study termination. Patients with more than a single radiograph had a mean 8.5 (SD 8.3) observations and a duration of followup of 6.9 (SD 6.1) years.

Clinical criteria for OA rather than the ACR criteria[6] were used to identify patients so that early cases that might be missed by the ACR criteria could be included.

Clinical data. At each assessment demographic variables were recorded and body mass index (BMI) was calculated based on current weight as measured in the clinic. Clinical variables included the Stanford Health Assessment Questionnaire functional disability index (HAQ disability)[30,31], a visual analog scale (VAS) for pain, a VAS global disease severity, and the Arthritis Impact Measurement Scales (AIMS)[32,33] anxiety and depression scales[34,35]. Laboratory studies including the erythrocyte sedimentation rate (ESR) were obtained.

Data regarding total joint replacement were obtained at each clinic visit and, for patients who had consented to participate in a longterm OA outcome study, by mail or telephone.

Radiographic data. Although radiographic methods have changed over the years, extended weight-bearing anterior-posterior (WB-AP) views of the knee were used throughout this study. Although we are now using semiflexed views[36], we have continued to collect WB-AP views as well for backward compatibility. Films were scored according to the method of Altman, *et al*[37]. Briefly, for JSN and osteophytes (OP), scores ranged from 0 to 3. To account for instances when patients had a total joint replacement (TJR), but no film immediately prior to the TJR, we considered that a TJR indicated a JSN = 3.

Readers in this study had previously read radiographs together. After an additional training session, each of 2 readers read about half of the knee radiographs. Ten radiographs were selected and were read twice by each reader in a blinded fashion. Between-observer kappa values were 0.66 and 0.62 for JSN and OP, respectively. Overall within-observer values were 0.70 and 0.71, respectively.

Statistical methods. The right knee was used for outcomes. In some analyses we used left knee abnormalities to predict right knee outcomes, as described in the Results section. The primary study outcome was a right JSN score = 3. The 2 primary methods of analysis were Kaplan-Meier survival times, stratified by radiographic abnormalities, and Cox regression. The purpose of these analyses was to determine the rate of radiographic progression as well as the predictors of progression. In these analyses 275 patents had already reached a right knee narrowing score of 3 at the time of their first radiograph, and were excluded from analysis. For ease of understanding, we use the terms 75th, 50th, and 25th percent survival times to indicate that 75%, 50%, and 25% had not yet reached the endpoint of JSN = 3. Patients were censored at the time of the last radiographic examination.

The hazard ratio (HR) can be thought of as a measure of strength of effect, and is analogous to the odds ratio in its interpretation. HR of 1 means there is no effect. The HR for dichotomous variables, or for groups, compares those with the condition to those without the condition. For continuous variables the HR reflects a 1 unit change in the predictor variable.

All statistical tests were 2 tailed, and the level of significance was set at 0.05. These analyses were performed using Stata 6.0[38]. To enable use of clinical data in multivariate analyses, where missing data existed imputation was employed for pain, global severity, HAQ, and BMI[39]. Missing data were primarily caused by patients' observations being available before the HAQ disability and pain scales were developed, and ranged from 14.1% missing (HAQ) to 3.7% missing (BMI). After 1981 the HAQ missing rate was 3.6%. Because missing data were few, we replaced missing values with first-present values for individual patients. Where no previous values were available, we replaced with mean values for each sex.

RESULTS

Demographic and clinical characteristics. Table 1 gives demographic and clinical characteristics of the 1507 patients with knee OA at the time of their first observation. Overall,

Table 1. Demographic and clinical characteristics at the first radiographic assessment of 1507 patients with knee OA.

Variable	Mean	SD			
Age, yrs	63.41	11.77			
Sex proportion, male	0.23				
High school graduates, yes/no	0.82				
Symptom duration at 1st observation	10.27	10.18			
Body mass index, kg/m^2	31.57	6.78			
Global severity, 0–100	43.16	22.42			
VAS pain, 0–3	1.47	0.66			
HAQ disability, 0–3	0.83	0.58			
Anxiety, 0–9.9	3.76	1.82			
Depression, 0–9.9	2.49	1.54			
ESR,mm/h	15.94	12.97			
WBC $\times 10^3$	7.05	1.99			
Hemoglobin, g	13.54	1.28			
Joint scores	0	1	2	3	
1st Right JSN score (0–3),%	38.4	28.6	14.1	19.0	
1st Left JSN score (0–3), %	38.2	28.4	15.1	18.4	
1st Right OP score (0–3), %	39.6	29.4	19.4	11.1	
1st Left OP score (0–3), %	41.0	26.6	20.6	11.8	

JSN: joint space-narrowing, OP: osteophyte

they displayed moderate clinical and radiographic severity. The mean age of the cohort was 63.4 years and 77% were women. Of importance, the BMI was elevated (31.57 kg/m^2). Of the bilateral joints, roughly 39% of joints had no radiographic abnormality, and 14% of patients had no JSN or OP abnormality. Right and/or left total joint arthroplasties were present at study start in 49 right knees and 31 left knees, respectively. By the conclusion, 87 additional right knee total joint arthroplasties and 70 left knee arthroplasties had been performed, for a total of 136 right knee total joint arthroplasties and 101 left knee total joint arthroplasties.

Rate of progression to maximum JSN. The rate of radiographic progression was studied using life table analysis and an endpoint of a JSN score = 3. As shown in Table 2 and Figure 1, the risk of progression to the maximum JSN is a function of the initial JSN score. Even among patients with no evidence of JSN at the first observation, the risk of maximum JSN is substantial, with 25% of patients in that group (the 0 group) estimated to progress that far in 11 years. The risk of progression is, as expected, greater in those with evidence of any JSN, with estimated 75% survival times of 7.4 and 4.5 years for those with JSN of 1 or 2 at first observation, respectively.

Factors associated with progression to maximum JSN. Table 3 presents the results of univariate Cox regressions. For ease of interpretation, the table is organized so that the strongest predictors, based on z scores and p values, are placed at the top. As shown in Table 3, initial JSN scores, global severity, BMI, pain, and ESR were significant univariate predictors of progression to maximum JSN. These variables were entered into a multivariate Cox regression. Four variables were statistically significant in the multivariate analyses. The final 4-variable model is shown in Table 4. The strongest effect was seen, as might be expected, for JSN at first assessment. To further elucidate the relationship of BMI and radiographic progression, the effect of BMI was studied in 2 ways: first controlling for the effect of initial JSN and displaying the result graphically (Figure 2), and then in Cox regressions, controlling for initial JSN (Table 5). Figure 2 shows little difference between tertile 1 and 2, after controlling for JSN at the initial observation. The 2nd tertile begins 27.4 and the 3rd tertile

Table 2. Risk of progression to maximum JSN score according to first knee radiograph for patients with knee OA. Time at risk and incidence rate are in years. Analyses refer to right knee. Patients who had reached a score of 3 at the 1st observation were excluded from analysis.

JSN at 1st Observation	Time at Risk, yrs	Incidence Rate, yrs	No. of Patients	Survival Time 75%	Survival Time 50%	Survival Time 25%
0	1657.32	0.017	583	11.27	17.84	
1	1139.13	0.032	434	7.41	12.03	15.55
2	503.38	0.077	215	4.49	7.44	9.35
Total	3299.83	0.032	1232	7.48	12.20	18.23

JSN: Joint space narrowing at first observation.

Table 3. Univariate hazard ratio for progression to maximum radiographic narrowing among patients with knee OA. Analyses refer to right knee. Patients who had reached a score of 3 at the 1st observation were excluded from analysis.

Variable	Hazard Ratio	SE	Z	p	95% Lower CI	95% Upper CI
1st Right JSN score = 2*	6.75	1.74	7.40	0.000	4.07	11.20
1st Right JSN score (0–3)	2.62	0.35	7.29	0.000	2.03	3.40
Global severity (0–100)	1.02	0.01	3.32	0.001	1.01	1.03
1st Right JSN Score = 1*	2.19	0.56	3.09	0.002	1.33	3.61
Body mass index, kg/m^2	1.04	0.01	2.69	0.007	1.01	1.07
VAS Pain, 0–3	1.55	0.29	2.33	0.020	1.07	2.24
Symptom duration in years at 1st observation	1.03	0.01	2.27	0.023	1.00	1.05
ESR, mm/h	1.01	0.01	2.04	0.042	1.00	1.03
WBC per 1000	1.08	0.06	1.60	0.110	0.98	1.20
HAQ disability, 0–3	1.34	0.25	1.57	0.117	0.93	1.93
Sex male/female, male = 1	0.73	0.18	–1.28	0.200	0.44	1.19
Depression, 0– 9.9	1.09	0.09	1.04	0.296	0.93	1.28
High school graduates, yes/no	1.25	0.33	0.86	0.388	0.75	2.08
Anxiety, 0–9.9	0.95	0.06	–0.72	0.471	0.84	1.08
Hemoglobin, g	0.98	0.08	–0.32	0.752	0.84	1.14
Age, yrs	1.00	0.01	0.05	0.961	0.98	1.02

*Reference group = JSN = 0. The scale for analysis is in the original units for the column 1 variable, except as indicated.

Table 4. Multivariate hazard ratio for progression to maximum radiographic narrowing among patients with knee OA. Analyses refer to right knee. Patients who had reached a score of 3 at the 1st observation were excluded from analysis.

Variable	Hazard Ratio	SE	Z	p	95% Lower CI	95% Upper CI
JSN at 1st R knee radiograph, 0–3	2.53	0.34	6.86	0.000	1.94	3.31
Body mass index	1.03	0.01	2.11	0.035	1.00	1.06
Symptom duration in years at 1st observation	1.30	0.01	2.06	0.040	1.00	1.05
Global severity, 0–100	1.01	0.01	1.80	0.071	1.00	1.02

Table 5. Effect of body mass index on radiographic progression, controlling for joint space narrowing at the initial observation. Parameterization 1 compares the 2nd and 3rd tertile with the 1st tertile. This produces hazard ratios and statistics that compare the 2nd and 3rd tertiles, respectively, with tertile1. Parameterization 2 compares the 2nd tertile with the 1st and the 3rd tertile with the 2nd tertile. This *difference* parameterization compares one category to the next, as in tertile 2 to tertile 1 and tertile 3 to tertile 2. The 2nd tertile begins 27.4 and the 3rd tertile begins at 33.0.

Variable	Hazard Ratio	SE	Z	p	95% Lower CI	95% Upper CI
Parameterization 1						
2nd Tertile of BMI	1.21	0.33	0.67	0.500	0.70	2.08
3rd Tertile of BMI	1.65	0.42	1.96	0.050	1.00	2.71
1st JSN score	2.64	0.35	7.28	0.000	2.03	3.43
Parameterization 2						
2nd Tertile of BMI	1.21	0.33	0.67	0.500	0.70	2.08
3rd Tertile of BMI	1.37	0.31	1.36	0.174	0.87	2.14
1st JSN score	2.64	0.35	7.28	0.000	2.03	3.43

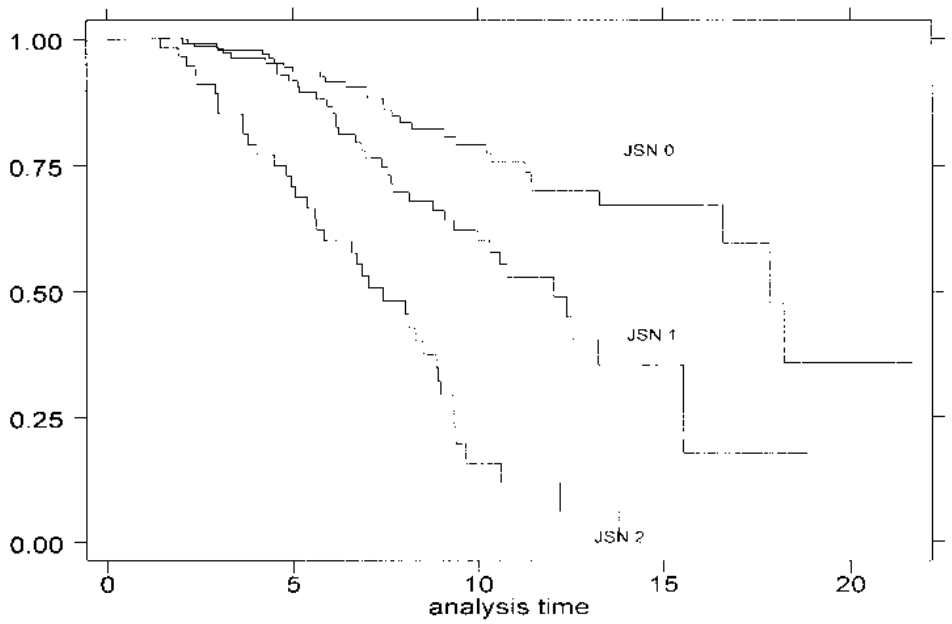

Figure 1. Kaplan-Meier survival estimates for patients with knee OA. "Failure" represents a JSN score = 3. The labels JSN 0, JSN 1, and JSN 2 represent JSN score at first observation. See Table 2 for numeric data. The *y*-axis represents the survival probability or probability of having a joint replacement.

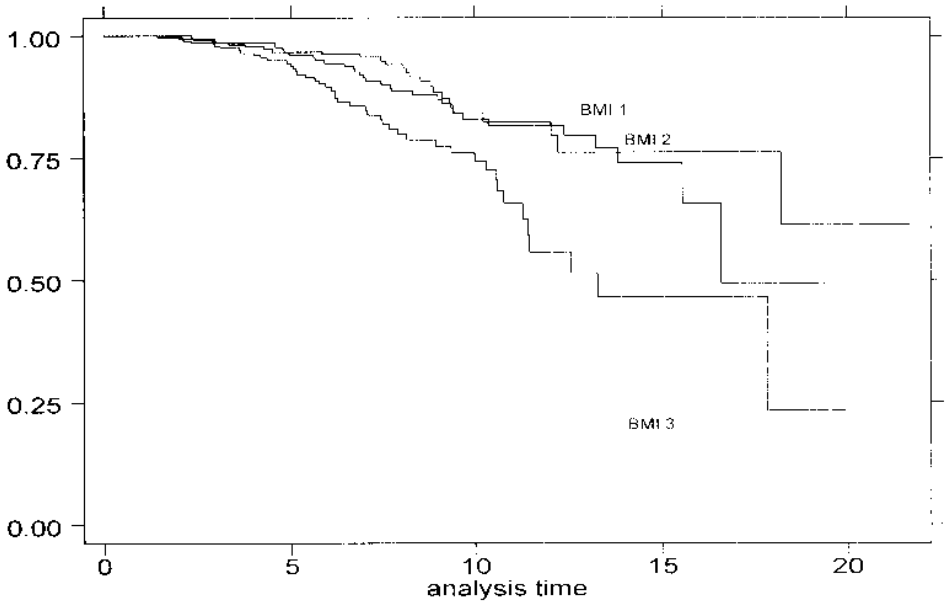

Figure 2. Kaplan-Meier survival estimates for patients with knee OA, by tertiles of BMI and adjusted to an initial JSN score = 1. "Failure" represents a JSN score = 3. The labels BMI 1, BMI 2, and BMI 3 represent tertiles of BMI at first observation. Tertile 3 begins at BMI of 33 kg/m^2. The *y*-axis represents the survival probability or probability of having a joint replacement.

begins at 33.0. In addition, the overall difference between the first and second tertiles is small. As shown in Table 5, compared to the reference category, patients in tertile 3 but not in tertile 2 are at significantly greater risk to progress. If the model is reparameterized so that each category is compared with the one before it (i.e., comparing 1 to 0 and 2 to 1), then the groups do not differ statistically. These analyses show that the effect of BMI is relatively weak when accounting for radiographic severity, and that simple cutpoints such as tertiles cannot be distinguished statistically.

How does the effect of JSN in one knee affect the other? To study this question, we held constant the starting value of the right knee JSN and examined the effect of various narrowing scores in the left knee. Because there were few observations in which left JSN was 3 and right JSN was 0, we combined left JSN of 2 and 3 into a single category. As shown in Table 6, left JSN scores of 2 or 3 were associated with an increased risk for progression in right knees that had scores of 0. BMI was not significant when added to this model. When the same analysis was performed with right JSN held to a score of 1 (Table 7), no significant effect of narrowing in the contralateral knee was found. In addition, BMI was not significant in the model of JSN = 0, but was significant when JSN = 1. These analyses indicate that abnormal scores in one knee predict the development of abnormal scores in the contralateral knee without JSN, but not in the contralateral knee with JSN. In addition, where radiographic abnormalities do not predict, as in Table 7, then BMI adds to the model.

Finally, the incidence rate for progression to maximum JSN in the right knee, given that the right knee score is 0, is 0.022 knees per year for a left JSN of 1 and 0.037 knees per year for a left JSN score of 2 or greater. By contrast (illustrated in Table 2), the rate for progression to maximum JSN in the right knee is 0.032 knees per year if the right knee initial score is 1 and 0.077 knees per year if the initial score is 2. While these data indicate that one knee predicts the other, the predicted rate of progression is greater if one simply identifies a unilateral abnormal knee.

The additive effect of JSN and osteophytes. In Cox regressions, right knee OP and right knee JSN were independently associated with progression to maximum JSN. The hazard ratio for OP was 1.54 (95% CI 1.16, 2.07), and it was 2.03 (1.50, 2.77) for JSN. The relative effects of these variables can be seen in Table 8, where the various combinations of JSN and OP are related to the incidence rate for maximum JSN. As expected, increasing JSN is associated with a greater rate of maximum JSN. OP added importantly to the risk of maximum JSN when initial JSN was 0, but played a much reduced role when JSN was present. The effect of contralateral OP was considerably less (data not shown).

DISCUSSION

The rate at which JSN progresses to a maximum value and the factors that influence this progression are of considerable interest. Developers of new therapeutic agents that might retard the progression of OA require information concerning rates of progression, knowledge of which patients will progress, and knowledge of what patient characteristics are most associated with progression. The situation is not different in the clinic, where it is common for clinicians to reassure

Table 6. Effect of initial left knee joint space narrowing on radiographic progression of right knee in patients with score of 0 in the right knee.

Variable	Hazard Ratio	SE	Z	p	95% Lower CI	95% Upper CI
Left knee JSN score = 1*	2.31	1.10	1.76	0.079	0.91	5.86
Left knee JSN score = 2*	4.07	1.88	3.04	0.002	1.65	10.05

* Compared with reference group with JSN score = 0.

Table 7. Effect of initial left knee joint space narrowing on radiographic progression of right knee in patients with score of 1 in the right knee.

Variable	Hazard Ratio	SE	Z	p	95% Lower CI	95% Upper CI
Left knee JSN score = 1*	1.25	0.55	0.49	0.621	0.52	2.97
Left Knee JSN score = 2*	1.42	0.64	0.78	0.433	0.59	3.45

* Compared with reference group with JSN score = 1.

Table 8. Incidence rates for maximum joint space narrowing according to JSN and osteophyte status at first observation in patients with knee OA. Time at risk and incidence rate are in years. Analyses refer to right knee. Patients who had reached a score of 3 at the 1st observation were excluded from analysis.

JSN at 1st Observation	Time at Risk	Incidence Rate	No. Patients	Survival Time 75%	Survival Time 50%	Survival Time 25%
JSN 0. OP 0	1140.75	0.015	371	71.84	18.23	—
JSN 0, OP 1	387.23	0.018	165	11.45	13.27	16.60
JSN 0, OP 2	126.34	0.040	44	7.90	9.09	—
JSN 1, OP 0	466.07	0.024	170	8.79	12.55	—
JSN 1, OP 1	451.73	0.033	170	6.70	12.03	15.55
JSN 1, OP 2	220.33	0.045	93	6.87	7.71	10.57
JSN 2, OP 0	55.72	0.054	29	4.81	5.85	—
JSN 2, OP 1	139.26	0.079	62	4.49	8.52	9.35
JSN 2, OP 2	301.30	0.083	123	4.95	6.88	9.31

JSN: Joint space narrowing at first observation.

patients that their illness may not progress, that osteophytes are not important, and to say often enough, in any event, that we can tell little about who will and won't progress.

There are a number of key results in this report. The first is the description and documentation of the rate of radiographic progression in clinical knee OA (Tables 2 and 8). Among symptomatic patients with OA of the knee, 25% with JSN of 1 and 2 will progress to complete joint obliteration in 7.41 and 4.49 years, respectively; and 50% are estimated to reach that endpoint in 12.03 and 7.44 years. These results indicate that as far as clinical OA is concerned any joint space narrowing represents a major risk factor for future complete joint narrowing. Further, we note that even in the absence of JSN, osteophyte formation of 2 or greater was associated with a score of 3 at 7.90 years and 9.09 years for 75th and 50th survival times, respectively.

We also found that unilateral JSN was by far the most important predictor of progression (Table 4), and that when radiographic damage was already present, BMI was a weak predictor of progression compared to when radiographs were not abnormal. It is not surprising that BMI, a key predictor of OA incidence and progression[11,20,29,40-49], should not perform as well when JSN or OP are included as predictors, for the identification of radiographic abnormalities defines the outcome that BMI will predict. But although BMI is significant in multivariate models, it contributes little additional risk for radiographic progression once radiographic OA is established (Table 5). This suggests that BMI and other factors are risk factors for incident knee OA, but that once OA is established, the illness progresses mostly, but not entirely, on its own. In this respect our findings are similar to those of Cooper, *et al*, who concluded that knee OA might be "initiated by joint

injury, but with progression being a consequence of impaired intrinsic repair capacity"[8].

Data from Table 8 also suggest that OP can be useful in predicting progression of JSN, but only when JSN is 0. With JSN values above 0, OP do not seem to contribute additionally to the risk of progression. Data such as these underscore the observation of this study that osteophytes are not harmless in symptomatic clinic patients.

This study also shows that contralateral knee abnormality predicts progression, but clearly not as well as does unilateral abnormality. Therefore if one were trying to identify persons who will progress for the purposes of an intervention study, the results of this study suggest that those with a unilateral JSN score = 1 or a unilateral OP score = 2 regardless of JSN score would be ideal candidates regardless of BMI. In recruiting for OA trials it is usual to require the presence of both JSN and OP, but it is not an infrequent finding to identify patients with only JSN. The data from this study suggest that using patients with JSN but not OP is associated with only a small penalty in the rate of progression.

For clinicians, our results suggest that the risk of progression should be taken seriously in the face of any radiographic abnormality and that such abnormalities, more than BMI and clinical symptoms, are the major identifiable predictors of progression in the clinic.

Limitations and indications. AP weight-bearing radiographs (WB-AP) are not the best plain film technique to study knee OA, and slightly more accurate results can be obtained using the posteroanterior semiflexed (MTP) and "schuss" views[36], methods that have become available over the last several years but were not available to this study. Although it has been our practice to use these newer views, we have continued to use the WB-AP view as well for reasons that include backward compatibility. Because the tibial plateau is not as level in the WB-AP, readings of radiographs taken with this method are slightly noisier than with the newer MTP views. In addition, except toward the end of the study when particular care was taken on standardized positioning, skewed alignment of the medial tibial plateau and x-ray beam may have introduced additional error. The consequence of these differences is to increase the imprecision of the analyses, although this is compensated by the large sample size of this study.

Patients in clinical care and clinical studies, in contrast to those in epidemiological studies, are systematically different in that they self-select for greater severity and may have different sociodemographic characteristics than will be found in the community. Therefore the data of this study cannot and should not be extrapolated to the general population. It refers only to symptomatic patients receiving and who have received clinical care for knee OA. In addition, patients in this study do not represent a complete sample. Although many patients returned for followup clinical care and research evaluations, many patients did not return. This problem is not unique to studies that span 22 years, but suggests the possibility of biases that cannot be fully understood. For example, it is possible that some patients chose to participate because they were doing poorly or "progressing," while others may have participated for the opposite reason.

In summary, the risk of progression in clinical OA patients with radiographic abnormalities is substantial. Nonradiographic predictors of OA progression (e.g., BMI) are weak predictors of progression compared to current radiographic status. Rates of progression are greatest in those with established radiographic abnormalities (JSN = 1 or OP = 2). Osteophytes are of limited additional value once JSN of 2 is present. Contralateral radiographic abnormalities are useful predictors only in those with JSN = 0, but are not as powerful as unilateral predictors. Intervention studies to prevent radiographic progression probably should utilize joints where evidence of abnormality already exists (JSN = 1 or OP = 2) if the desire is to utilize the most susceptible group. At a clinical level, current radiographic status predicts future status, with 50% of patients with JSN = 1 and 50% of patients with JSN = 2 progressing to complete joint space loss in 12.03 and 7.44 years, respectively.

REFERENCES

1. MacLean CH, Knight K, Paulus H, Brook RH, Shekelle PG. Costs attributable to osteoarthritis. J Rheumatol 1998;25:2213-8.
2. Gabriel SE, Crowson CS, Campion ME, O'Fallon WM. Indirect and nonmedical costs among people with rheumatoid arthritis and osteoarthritis compared with nonarthritic controls. J Rheumatol 1997;24:43-8.
3. March LM, Bachmeier CJM. Economics of osteoarthritis: a global perspective. Baillieres Clin Rheumatol 1997;11:817-34.
4. Liang MH, Cullen KE, Larson MG, et al. Cost-effectiveness of total joint arthroplasty in osteoarthritis. Arthritis Rheum 1986;29:937-43.
5. Davis MA, Ettinger WH, Neuhaus JM, Barclay JD, Segal MR. Correlates of knee pain among United States adults with and without radiographic knee osteoarthritis. J Rheumatol 1992;19:1943-9.
6. Altman R, Asch E, Bloch DA, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986;29:1039-49.
7. Schouten JSAG, Van den 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 1992;51:932-7.
8. Cooper C, Snow S, McAlindon TE, et al. Risk factors for the incidence and progression of radiographic knee osteoarthritis. Arthritis Rheum 2000;43:995-1000.
9. Felson DT, Zhang YQ, Hannan MT, et al. The incidence and natural history of knee osteoarthritis in the elderly: The Framingham Osteoarthritis Study. Arthritis Rheum 1995;38:1500-5.
10. Pavelka K, Gatterova J, Altman RD. Radiographic progression of knee osteoarthritis in a Czech cohort. Clin Exp Rheumatol 2000;18:473-7.
11. Ledingham J, Regan M, Jones A, Doherty M. Factors affecting radiographic progression of knee osteoarthritis. Ann Rheum Dis 1995;54:53-8.
12. Massardo L, Watt I, Cushnaghan J, Dieppe P. Osteoarthritis of the knee joint: an eight year prospective study. Ann Rheum Dis

1989;48:893-7.
13. Hernborg JS, Nilsson BE. The natural course of untreated osteoarthritis of the knee. Clin Orthop 1977;123:130-7.
14. Spector TD, Dacre JF, Harris PA, Huskisson EC. Radiological progression of osteoarthritis — An 11 year followup study of the knee. Ann Rheum Dis 1992;51:1107-10.
15. Hannan MT, Felson DT, Pincus T. Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee. J Rheumatol 2000;27:1513-7.
16. Hart DJ, Doyle DV, Spector TD. Incidence and risk factors for radiographic knee osteoarthritis in middle-aged women — The Chingford Study. Arthritis Rheum 1999;42:17-24.
17. Petersson IF. Developing knee joint osteoarthritis. Clinical, radiographical and biochemical features. Scand J Rheumatol 1998;27:238.
18. Roos H, Lauren M, Adalberth T, Roos EM, Jonsson K, Lohmander LS. Knee osteoarthritis after meniscectomy: Prevalence of radiographic changes after twenty-one years, compared with matched controls. Arthritis Rheum 1998;41:687-93.
19. Cicuttini FM, Spector T, Baker J. Risk factors for osteoarthritis in the tibiofemoral and patellofemoral joints of the knee. J Rheumatol 1997;24:1164-7.
20. Felson DT, Zhang YQ, Hannan MT, et al. Risk factors for incident radiographic knee osteoarthritis in the elderly: The Framingham Study. Arthritis Rheum 1997;40:728-33.
21. Lloyd ME, Hart DJ, Nandra D, et al. Relation between insulin-like growth factor-I concentrations, osteoarthritis, bone density, and fractures in the general population: the Chingford Study. Ann Rheum Dis 1996;55:870-4.
22. McAlindon T, Zhang YQ, Hannan M, et al. Are risk factors for patellofemoral and tibiofemoral knee osteoarthritis different? J Rheumatol 1996;23:332-7.
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 1994;53:565-8.
24. Schouten JS, Van den Ouweland FA, Valkenburg HA, Lamberts SW. Insulin-like growth factor-1: a prognostic factor of knee osteoarthritis. Br J Rheumatol 1993;32:274-80.
25. Bagge E, Bjelle A, Eden S, Svanborg A. Factors associated with radiographic osteoarthritis — results from the population study of 70-year-old people in Goteborg. J Rheumatol 1991;18:1218-22.
26. 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 1989;130:278-88.
27. Davis MA, Ettinger WH, Neuhaus JM. The role of metabolic factors and blood pressure in the association of obesity with osteoarthritis of the knee. J Rheumatol 1988;15:1827-32.
28. Anderson JJ, Felson DT. Factors associated with osteoarthritis of the knee in the first national Health and Nutrition Examination Survey (HANES I). Evidence for an association with overweight, race, and physical demands of work. Am J Epidemiol 1988;128:179-89.
29. Hochberg MC, Lethbridge-Cejku M, Scott WW, Reichle R, Plato CC, Tobin JD. The association of body weight, body fatness and body fat distribution with osteoarthritis of the knee: Data from the Baltimore Longitudinal Study of Aging. J Rheumatol 1995; 22:488-93.
30. Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the Health Assessment Questionnaire, disability and pain scales. J Rheumatol 1982;9:789-93.
31. Fries JF, Spitz PW, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137-45.
32. Meenan RF, Gertman PM, Mason JH, Dunaif R. The Arthritis Impact Measurement Scales. Arthritis Rheum 1982;25:1048-53.
33. Meenan RF. The AIMS approach to health status measurement: conceptual background and measurement properties. J Rheumatol 1982;9:785-8.
34. Hawley DJ, Wolfe F. Depression is not more common in rheumatoid arthritis: a 10 year longitudinal study of 6608 rheumatic disease patients. J Rheumatol 1993;20:2025-31.
35. Hawley DJ, Wolfe F. Anxiety and depression in patients with RA: A prospective study of 400 patients. J Rheumatol 1988;15:932-41.
36. Buckland-Wright JC, Wolfe F, Ward RJ, Flowers N, Hayne C. Substantial superiority of semiflexed (MTP) views in knee osteoarthritis: A comparative radiographic study, without fluoroscopy, of standing extended, semiflexed (MTP), and schuss views. J Rheumatol 1999;26:2664-74.
37. Altman RD, Hochberg M, Murphy WA Jr, Wolfe F, Lequesne M. Atlas of individual radiographic features in osteoarthritis. Osteoarthritis Cartilage 1995;3:3-70.
38. Stata Corporation. Stata statistical software: Release 6.0. College Station, TX: Stata Corporation; 1999.
39. Rubin DB. Multiple imputation for non-response in surveys. New York: John Wiley & Sons; 1987.
40. Sturmer T, Gunther KP, Brenner H. Obesity, overweight and patterns of osteoarthritis: the Ulm Osteoarthritis Study. J Clin Epidemiol 2000;53:307-13.
41. Oliveria SA, Felson DT, Cirillo PA, Reed JI, Walker AM. Body weight, body mass index, and incident symptomatic osteoarthritis of the hand, hip, and knee. Epidemiology 1999;10:161-6.
42. Sandmark H, Hogstedt C, Lewold S, Vingard E. Osteoarthrosis of the knee in men and women in association with overweight, smoking, and hormone therapy. Ann Rheum Dis 1999;58:151-5.
43. Heliovaara M, Makela M, Impivaara O, Knekt P, Aromaa A, Sievers K. Association of overweight, trauma and workload with coxarthrosis. A health survey of 7,217 persons. Acta Orthop Scand 1993;64:513-8.
44. Colville-Nash PR, Scott DL. Angiogenesis and rheumatoid arthritis — pathogenic and therapeutic implications. Ann Rheum Dis 1992;51:919-25.
45. Dougados M, Gueguen A, Nguyen M, et al. Longitudinal radiologic evaluation of osteoarthritis of the knee. J Rheumatol 1992; 19:378-84.
46. Felson DT, Zhang Y, Anthony JM, Naimark A, Anderson JJ. Weight loss reduces the risk for symptomatic knee osteoarthritis in women. Ann Intern Med 1992;116:535-9.
47. Davis MA, Neuhaus JM, Ettinger WH, Mueller WH. Body fat distribution and osteoarthritis. Am J Epidemiol 1990;132:701-7.
48. Sharp JT. Scoring radiographic abnormalities in rheumatoid arthritis. J Rheumatol 1989;16:568-9.
49. Davis MA, Ettinger WH, Neuhaus JM, Hauck WW. Sex differences in osteoarthritis of the knee. The role of obesity. Am J Epidemiol 1988;127:1019-30.