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INCIDENCE AND RISK FACTORS FOR RADIOGRAPHIC KNEE OSTEOARTHRITIS IN MIDDLE-AGED WOMEN

The Chingford Study

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Objective. **To examine the natural history, role of risk factors, and incidence of knee osteoarthritis (OA) in a prospective study of women from a population cohort.**

Methods. **Women from the Chingford Study who had been recruited in 1989 were followed up with knee radiographs 4 years later. A total of 715 paired radiographs (71% of the original sample) were graded for osteophytes and 644 for joint space narrowing (JSN). Women whose radiographs had been graded as 0 in 1989 and as ≥14 years later were classified as having incident disease. Incident cases were compared with controls for associations with a number of risk factors.**

Results. **Eighty-one women (12.6%) developed JSN of the knee, equating to an incidence of 3.1% per year. No clear risk factors for JSN were identified. Reproducibility of measures of joint space is poor, however, leading to inaccuracy of definition. Incident knee osteophytes developed in 95 women (13.3%), equating to an incidence of 3.3% per year. Compared with controls, women with incident knee osteophytes were older, heavier, and had more hand OA and knee symptoms. Women in the top tertile of obesity (body mass index >26.4) had a significantly increased risk of incident knee osteophytes (odds ratio [OR] 2.38, 95% confidence interval [95% CI] 1.29–4.39). Incident knee osteophytes increased by 20% per 5-year age increase. A nonsignificant protective effect for incident knee osteophytes was seen with current estrogen replacement therapy (ERT) (OR 0.41, 95% CI 0.12–1.42). No effect was associated with smoking, physical activity, hysterectomy, or previous knee injury.**

Conclusion. **Obesity and aging are associated with a high risk of new knee OA developing in women. Evidence of a protective effect of ERT was seen. No clear association was found for incident JSN, suggesting that different etiologic mechanisms are operating or that standard radiographs are an inaccurate measure of incident narrowing.**

Osteoarthritis (OA) is one of the most common causes of disability in the elderly. While genetic studies have suggested that genetic factors may account for 40–60% of the disease (1), a large environmental component undoubtedly remains. With the advent of a number of large, population-based cross-sectional studies, specific risk factors—particularly for prevalent knee OA—are now being consistently identified. However, little is understood of the natural history of the disease, and there are very few studies on disease incidence and predictive factors for incident knee OA. Recent consensus on classification and criteria for disease definition has enabled some cohort studies to longitudinally examine the incidence of knee OA (2–4). Such studies generally have focused on elderly subjects (age >70 years), however, and extrapolation of the risk factor findings to younger age groups is problematic.

Many risk factors and their association with knee OA have been reported in several different cross-sectional or retrospective studies. Well-recognized factors associated with knee OA include the female preponderance and the effects of obesity and age. In addition, there is consistent evidence supporting the theory of an inverse relationship between bone density and OA. However, speculation continues regarding the role of other reported risk factors, such as excessive

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physical activity in males; a possible association with a number of metabolic factors such as hypercholesterolemia, increased blood glucose level, and hypertension; and a protective effect of current estrogen use in postmenopausal women (5). Further studies are needed to confirm these associations.

We have reported factors associated with the prevalence of knee OA in cross-sectional studies of a large, well-described cohort of middle-aged women with mild disease (6–9). In the present study, women in this general population sample were followed up after 48 months to determine (a) the incidence of OA in a middle-aged group and (b) whether age, weight, smoking, hysterectomy, knee injury, or estrogen replacement, implicated in previous case–control studies, could be confirmed as risk factors for OA in a longitudinal incidence study.

PATIENTS AND METHODS

The Chingford study population, established in 1988–1989, is a well-described cohort of 1,003 women seen annually and described in detail previously (6–8). The response rate at initial recruitment was 78%. The area from which the cohort was recruited is predominantly middle-class, with a range of all social groups. Ninety-eight percent of the women are white. A socioeconomic profile was performed using the Acorn classification system, which is based on each subject's postal code (CACI International, London, UK). This system classifies subjects into 4 socioeconomic categories. The majority of the women studied (42%) belonged to group C1 (middle to lower class, white-collar workers), 32% belonged to group A/B (professional workers), 17% to group C2 (manual/skilled [blue-collar] workers), and 8% to group D/E (manual/nonskilled workers). The women in the study were similar to UK normal subjects in terms of smoking statistics, hysterectomy rates, heights, and weights (6).

At baseline, all women had an anteroposterior (AP) radiograph of the hands and a weight-bearing AP radiograph of the knees taken with the legs in full extension. All radiographs were taken by the same technician using the same equipment. Views were standardized with the back of the knees in contact with the cassette, the patella centralized over the lower end of the femur, and the beam centered 2.5 cm below the apex of the patella, with a tube-to-film distance of 100 cm. Subjects were contacted 4 years later and invited to undergo repeat screening for knee OA; 868 women responded. All women had a repeat AP extended-view weight-bearing knee radiograph, taken by the same technician using the same equipment and methods as at baseline in order to maximize standardization.

The paired films were read side by side by a trained examiner for the presence of knee osteophytes and joint space narrowing (JSN) in each knee compartment, using a validated atlas (10). Severity was graded on a 0–3 scale. Subjects with a grade of at least 1 (definite presence of an osteophyte or JSN) were classified as cases. Subjects were classified as having incident radiographic OA if they had a radiographic grade of 0 at baseline and subsequently developed at least a grade 1 osteophyte or JSN. Baseline hand radiographs were also graded for OA, using the same radiographic criteria for the presence of distal interphalangeal joint osteophytes. Fifty-three subjects were classified as having prevalent hand OA, defined as 2 or more fingers affected with osteophytes.

Reproducibility of the radiographic grading system was confirmed using films from 50 women (100 knees), with 2 observers reading the films 2 weeks apart. Longitudinal reproducibility was studied by using readings of the most experienced observer, in films from 20 women (40 knees). Films were first read with the observer blinded to time sequence, and were then read side by side. Kappa coefficients were calculated as a measure of intra- and inter-observer agreement.

Both at baseline and at followup, all subjects completed a standardized nurse-administered medical history questionnaire for a number of known risk factors for knee OA. Height and weight were also recorded. Details of smoking status, duration of smoking (years), and average number of cigarettes consumed per day were recorded. All women who were undergoing ERT at the time of the first examination and continued it throughout the 48-month followup period were classified as current ERT users. Former users were those women who had undergone ERT for at least 60 months, but not during the 12 months prior to baseline. Subjects who were undergoing ERT at baseline but stopped during the 48-month followup period were excluded from analysis. Women were asked to provide details about any knee injury that was severe enough to require resting of the leg for at least 1 week. Knee pain was assessed using the National Health and Nutrition Examination Survey definition of knee pain lasting more than 1 month. Following a hand examination using standardized methods (11), the presence of clinically palpable Heberden's nodes was recorded.

Women with incident knee OA were compared with women with no OA. Subjects were analyzed individually for associations of risk factors with incident osteophytes and incident narrowing as separate outcomes. All women with knee OA at baseline were excluded from analysis. Relative risks and 95% confidence intervals (95% CI) were calculated and adjusted for potential confounders by logistic regression using EGRET software. For continuous variables, analysis of covariance with the package SPSSpc was used to adjust for confounders.

RESULTS

Of the 1,003 women examined at baseline in 1989, 135 had been lost to followup in 1993: 40 had moved away, 11 had died, and 84 no longer wanted to participate. Baseline radiographs from 38 women from the original sample could not be located: therefore, these women were excluded from followup. Thus, paired films of 830 women (83% of the original sample) were available for analysis. Of these subjects, 115 had baseline OA defined by osteophytes and were excluded from further analysis, leaving 715 paired films of women who

Table 1. Baseline characteristics of the 830 women with paired radiographs*

Age, mean ± SD years	54.1 ± 5.9
Height, mean ± SD m	161.7 ± 6.1
Weight, mean ± SD kg	66.7 ± 11.5
BMI, mean ± SD kg/m^2	25.5 ± 4.1
Weight at age 20, mean ± SD kg	55.1 ± 8.0
Hysterectomy	192 (23.1)
Knee pain	198 (23.9)
Knee injury	92 (12.7)
ERT use	
Ever	110 (13.3)
Current	57 (6.9)
Smoker	
Ever	379 (45.7)
Current	190 (22.9)
Radiologic hand OA	53 (6.4)
Heberden's nodes	157 (19.0)
Social class†	
A/B	268 (32.2)
C1	348 (41.9)
C2	148 (17.8)
D/E	66 (8.0)

* Except where otherwise indicated, values are the number (%). BMI = body mass index; ERT = estrogen replacement therapy; OA = osteoarthritis.
† See Patients and Methods.

had been free of knee osteophytes at baseline. Because 186 of the 830 women with paired films had JSN at baseline, 644 remained for analysis of incident narrowing.

To examine whether the followup group was different in terms of selection, the rates of baseline OA in those who were included in the followup study and those not included in the followup study were compared. Of the 830 women with paired films, 88 (10.6%) had knee OA at baseline, compared with 20 (11.6%) of the 173 women not included in the followup; the 2 groups were similar in age and weight.

Studies of the reproducibility of the radiographic grading showed high intra-observer reproducibility for osteophytes and JSN ($\kappa = 0.88$ for osteophytes; $\kappa = 0.83$ for JSN), but only fairly good reproducibility for osteophytes ($\kappa = 0.69$) and moderate inter-observer reproducibility for JSN ($\kappa = 0.54$). For intra-observer reproducibility of grading of serial films, kappa values were 0.79 for osteophytes and 0.70 for JSN. There was little difference in the reproducibility results for readings done under blinded conditions versus those read side by side. The main radiographic analysis was thus performed using baseline and 48-month radiographs read side by side.

Analysis of paired films revealed that 95 of 715 women (13.3%) developed incident knee osteophytes within 4 years (incidence rate 3.3% per year); and 81 of 644 (12.6%) developed knee JSN (3.1% per year). Twenty women (2.8%) developed bilateral incident osteophytes within the time period, and 41 (6.4%) devel-

Table 2. Characteristics of the women with versus those without incident knee osteophytes*

	Incident OA (n = 95)	No OA (n = 620)	*P*
Age, mean ± SD years	55.3 ± 5.6	53.3 ± 5.9	0.003
Height, mean ± SD m	162.9 ± 6.1	161.6 ± 6.0	0.05
Weight, mean ± SD kg	69.9 ± 12.7	65.1 ± 10.4	<0.001
BMI, mean ± SD kg/m^2	26.3 ± 4.5	24.9 ± 3.7	0.001
Weight at age 20, mean ± SD kg	57.4 ± 7.5	54.8 ± 7.9	0.003
Hysterectomy	25 (26.3)	136 (21.9)	0.34
Knee pain	29 (30.9)	117 (18.9)	0.01
Knee injury	13 (13.7)	51 (8.2)	0.08
ERT use			
Ever	13 (13.7)	83 (13.4)	0.94
Current	5 (6.0)	48 (8.2)	0.42
Smoker			
Ever	39 (41.1)	287 (46.3)	0.33
Current	19 (20.0)	147 (23.7)	0.35
Radiologic hand OA	9 (9.5)	29 (4.7)	0.02
Heberden's nodes	19 (20.0)	103 (16.6)	0.23
Social class†			
A/B	38 (40.0)	190 (30.6)	0.07
C1	41 (43.2)	262 (42.3)	0.8
C2	7 (7.4)	118 (19.0)	0.005
D/E	9 (9.5)	50 (8.1)	0.6

* Except where otherwise indicated, values are the number (%). See Table 1 for definitions.
† See Patients and Methods.

Table 3. Multivariate analysis of continuous variables as risk factors for incident knee OA*

	Osteophytes			Joint space narrowing		
	Controls (n = 620)	Cases (n = 95)	P	Controls (n = 563)	Cases (n = 81)	P
Weight, kg†	65.1 ± 10.35	69.9 ± 12.7	<0.001	66.5 ± 11.56	68.1 ± 11.34	0.25
Height, cm‡	161.6 ± 6.04	162.9 ± 6.10	0.02	161.9 ± 6.01	162.0 ± 5.51	0.84
BMI†	24.9 ± 3.75	26.3 ± 4.48	0.002	25.4 ± 4.18	25.9 ± 4.20	0.24
Age, years§	53.3 ± 5.88	55.3 ± 5.55	0.003	53.9 ± 5.88	53.8 ± 6.35	0.77
Weight at age 20, kg†	54.8 ± 7.92	57.4 ± 7.47	0.004	55.7 ± 8.16	54.9 ± 7.44	0.46
Weight gain, kg†	10.3 ± 9.23	12.6 ± 11.40	0.04	10.8 ± 9.89	13.2 ± 10.34	0.05

* Values are the mean ± SD (adjusted for hysterectomy, ERT, smoking, physical activity, knee pain, and social class). See Table 1 for definitions.
† Also adjusted for age and height.
‡ Also adjusted for age and weight.
§ Also adjusted for height and weight.

oped bilateral incident narrowing. Only 9 women (1.3%) developed both osteophytes and narrowing (too few for accurate further analysis).

The main characteristics of the 830 women with paired films available, including those with baseline OA, are shown in Table 1. The mean ± SD age of the group was 54.1 ± 5.9 years at baseline and 58.1 ± 5.9 years at 4-year followup. Only 6% of the subjects had radiologic hand OA, with a greater number (19%) having clinically detectable Heberden's nodes.

Table 2 shows the mean differences between the women in whom incident disease developed, defined by incident knee osteophytes, and those who remained disease-free after 4 years. Women with incident knee osteophytes were significantly older, heavier by 4.8 kg (10 lb), slightly taller, more likely to have reported knee symptoms at baseline (30% versus 18%), and twice as likely to have had radiologic hand OA at baseline.

Table 3 shows the multivariate adjusted risk of developing incident osteophytes and JSN for the key continuous variables, adjusted for each other. No differences were seen between women with and those without incident narrowing, but weight, height, body mass index (BMI), age, weight gain, and weight at age 20 were all significantly different in those with osteophytes compared with controls.

The adjusted results for categorical variables are presented in Table 4. Comparison of the highest BMI tertile (>26.4) and the lowest (<23.4) showed a significant association with incident osteophytes (odds ratio [OR] 2.38, 95% CI 1.29–4.39). The risk of incident knee osteophytes increased by ~30% per 5-kg increase in weight. A similar result was seen in the highest age group (OR 2.41, 95% CI 1.11–5.24). The overall risk of OA defined by osteophytes increased by 20% per 5-year age increase. A nonsignificant protective effect of ERT was seen for the 57 current users (OR 0.41, 95% CI 0.12–1.42). Insufficient numbers were available to allow examination of a dose/duration effect. No effect was seen for hysterectomy, knee injury, smoking, or hand OA.

Although knee pain is not a predictor of radiographic disease, there was a significant difference in the frequency of reported symptoms between the group with and that without incident osteophytes. We therefore examined the relationship between baseline knee pain and incident osteophytes and found a significant association (crude OR 1.91, 95% CI 1.18–3.09), but no association was seen for narrowing (OR 0.78, 95% CI 0.43–1.44). None of the other variables measured showed any clear association with incident narrowing. A nonsignificant association between incident narrowing and the presence of radiologic hand OA was seen (OR 2.68, 95% CI 0.98–7.08), but this was based on only 8 cases in which OA was present at both sites.

Of the 115 women with osteophytes at baseline, only 1 appeared to have "improved" (a single grade 1 medial osteophyte was regraded as normal). Among the 186 women for whom JSN was noted at baseline, 11 appeared to improve (from grade 1 to 0 in all cases). Analysis of the minimum joint space width in millimeters, as measured by magnified reticule, confirmed that all 11 "improvers" had a measurably larger joint space at followup compared with baseline.

Of the 95 women with incident osteophytes, 89 were classified in radiologic grade 1, and 30% of those had knee symptoms. The remaining 6 women had grade 2 osteophytes, and 33% had current knee symptoms. Of the 89 graded as having mild disease, 32 (36%) had osteophytes in either both knees or in more than 1 tibiofemoral compartment. Of the 81 women with incident narrowing, all were classified as having grade 1

Table 4. Association of categorical risk factors with incident osteophytes and joint space narrowing of the knee, presented as the odds ratio (95% confidence interval)*

	Osteophytes	Joint space narrowing
Hysterectomy	1.36 (0.78–2.36)	1.32 (0.72–2.42)
Knee injury	1.85 (0.82–4.19)	1.03 (0.45–2.32)
BMI group		
1	1.00 (referent)	1.00 (referent)
2	1.69 (0.96–2.97)	1.28 (0.71–2.33)
3	2.38 (1.29–4.39)	1.58 (0.86–2.89)
Weight at age 20 group†		
1	1.00 (referent)	1.00 (referent)
2	1.67 (0.93–2.97)	0.97 (0.53–1.78)
3	1.76 (0.90–3.43)	0.88 (0.43–1.56)
Age group‡		
1	1.00 (referent)	1.00 (referent)
2	1.86 (1.01–3.41)	0.84 (0.41–1.69)
3	2.41 (1.11–5.24)	0.79 (0.41–1.56)
ERT use		
Ever	0.73 (0.32–1.67)	1.17 (0.59–2.33)
Current	0.41 (0.12–1.42)	1.88 (0.86–4.11)
Smoker		
Ever	0.90 (0.55–1.47)	1.38 (0.82–2.33)
Current	0.97 (0.52–1.81)	1.23 (0.66–2.31)
<10 per day	0.84 (0.29–2.41)	0.89 (0.25–3.15)
≥10 per day	1.02 (0.50–2.08)	1.35 (0.69–2.64)
Radiologic hand OA	1.84 (0.59–5.77)	2.53 (0.90–7.11)
Heberden's nodes	1.78 (0.80–3.96)	1.05 (0.50–2.20)
Social class§		
A/B	1.00 (referent)	1.00 (referent)
C1	0.58 (0.34–0.98)	1.04 (0.55–1.94)
C2	0.25 (0.10–0.60)	1.16 (0.55–2.43)
D/E	0.66 (0.27–1.60)	1.64 (0.67–4.01)
Physical activity		
Walking	0.60 (0.22–1.71)	0.38 (0.15–0.93)
Job	1.48 (0.34–5.64)	0.56 (0.18–1.79)
Sport	1.23 (0.54–2.81)	0.98 (0.42–2.30)

* Values adjusted for hysterectomy, ERT, smoking, physical activity, knee pain, and social class. See Table 1 for definitions.
† Also adjusted for age and height.
‡ Also adjusted for height and weight.
§ See Patients and Methods.

disease, and 41 (51%) had developed narrowing in both knees.

DISCUSSION

These data show that ~3% of middle-aged women will develop new knee osteophytes and narrowing of the joint space each year. Obesity and age seem to have the most marked effect on the incidence of knee osteophytes. A 2-fold increase in risk is seen in older women compared with women 20 years younger, and in moderately overweight women compared with thin or normal-weight women.

Incidence studies of OA may be subject to a number of potential problems or biases. One of these is the generalizability of the results and the study population characteristics. Since the present study used a large population with a good response rate for followup (83% of the original sample), it is unlikely that preferential selection would have altered the results. The population has been shown to be broadly representative of the UK national population in terms of demographic variables. For example, the subjects are statistically similar to UK women in their age group in terms of height, weight, smoking, and rates of hysterectomy (6). It is possible that women who suspected they had OA may have been keener to return for followup, thereby influencing the incident OA rate, but the rate of baseline OA did not differ in this group compared with the 17% who did not return for followup. Bias in terms of selection of

subjects with symptoms was also unlikely because adjustment for symptoms in the analysis failed to affect the results.

Accepted criteria based on features of OA are now widely used in epidemiologic studies of prevalence (12). Use of these criteria for determining incident disease may lack sensitivity, however, particularly in terms of joint space using a global score of only 4 grades. Some studies of progression have used a magnified reticule to measure minimum joint space at the knee, which may be more sensitive to short-term change. However, we previously found that although short-term precision for the reticule (on the same radiograph) was good in this population (coefficient of variation [CV] 3–5.4%), long-term precision for serially obtained films was poor (CV 20–30%) (13). The main problem was variation in positioning of the patient, with changes such as slight flexion altering readings dramatically. This was observed in the current study, in which all 11 subjects whose JSN scores "improved" from baseline had larger reticule measures on followup studies. A visual global score appears more reproducible longitudinally, perhaps partially due to the subjective assessment of positioning, and may be a better method for large-scale epidemiologic studies.

These problems of definition are one explanation of why we could not confirm the associations found with incident osteophytes for incident JSN. However, we previously showed that osteophytes are a good correlate for knee symptoms and perform better as a primary diagnostic feature for cross-sectional epidemiologic studies of knee OA (14). Other possibilities include the fact that osteophytes may be a marker of disease severity, not reflected by small changes in narrowing. Nonetheless, redefining JSN using a grade of at least 2 to indicate the presence of this feature yielded only 9 cases, which was too few for accurate analysis. It is possible that narrowing may also be a different or independent process in OA; the associations we have examined may alter the development of bone remodeling involved in the osteophytic progression of OA, but thinning and alteration of cartilage may not be influenced by the same mechanisms or environmental factors. Nevertheless, the lack of increase of JSN with age (Figure 1) suggests, in our view, that inaccuracy of JSN measurement is the more likely explanation.

Comparisons of the incidence and cross-sectional data from this same population are also interesting. We confirmed the strong association between obesity and incident OA in middle-aged women, although the association was less strong than that with prevalent disease

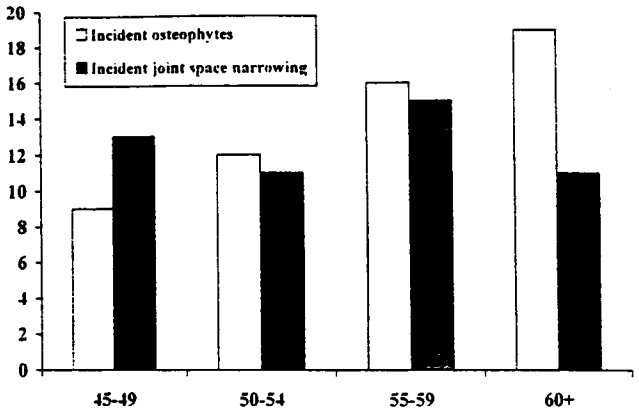

Figure 1. Incident knee osteophytes and joint space narrowing (%) in the study population, by 5-year age group.

(2-fold increase in risk for the top tertile for incident disease, versus 6-fold increase in risk for prevalent disease) (6). This finding suggests that part of the effect of obesity on prevalence may be secondary to the OA. We also showed that being overweight since age 20 years has a similar effect on both incident and prevalent disease.

We failed to confirm an association in either direction with smoking, using both incident and cross-sectional data; this is consistent with the results of some studies (15), but not others (16). Incidence data from the Framingham study found smoking to be protective, with a 50% reduction in risk for incident knee OA (2). However, we were unable to confirm this finding in our incidence data, with the lack of association being similar to our findings using prevalence data (7).

We have reported a 60% protective effect of current estrogen use (17) for prevalent knee OA, with a similar but nonsignificant protective effect for incident disease. A number of studies on ERT and its protective effect on OA have been published previously. A study of knee OA in the elderly suggested a weak, nonsignificant protective effect of ERT, but the numbers of ERT users were small because of the age of the subjects (mean 73 years) (18). A case–control study of knee OA by Samanta and colleagues examined ERT use as one of a number of potential risk factors and found a nonsignificant protective effect but did not distinguish the timing of hormone use (19). A recently published study by Nevitt et al, from the Study of Osteoporotic Fractures cohort of 4,366 white women, reported that in current estrogen users the risk of hip OA was 0.62 (95% CI 0.49–0.86), with a weak trend of increasing protection with disease severity (20). We know little of the mech-

anisms of action of estrogens on bone and cartilage; it may be that ERT may prevent the sharp perimenopausal changes that trigger OA. Whatever the real reason for the protective effect of estrogen, greater understanding of these mechanisms may potentially lead to new avenues for therapy.

We could not show an effect of being in the top tertile of physical activity in this incidence study. In our previous prevalence study we found an effect in the most active 5% of women (21); however, numbers and power were too low to examine this group and confirm or exclude such an effect on incidence.

We could not confirm an association between knee injury and incident OA, which translated to a 3-fold increase in risk for prevalent OA, although the number of subjects with injury and incident disease was small (n = 13) and confidence intervals wide. This is similar to the incidence data from the Framingham study, which showed a slight increase in risk with interim knee injury but were based on small numbers; no association with past knee injury was seen in that group (3). Other studies of OA prevalence confirm the strong association with previous knee injury (22,23), but, similar to the present findings, no clear relationship with knee injury has been found in other incidence studies, suggesting a possibility of recall bias.

Previous cross-sectional studies have shown obesity to be the most common and strongest modifiable risk factor for OA of the knee (24). There is little data on the role of obesity in incident disease. In a small subanalysis of the women who had unilateral knee OA at baseline in the Chingford study, nearly 50% of women in the top tertile of obesity developed incident knee OA in the contralateral knee after only 24 months (25). Recent incident data from the Framingham cohort 1992–1993 examination confirmed the association of knee OA with obesity in women (3). The rate of incident knee OA in the elderly Framingham population (mean age at followup 79 years) was 2% per year in women, compared with 3% per year among women in our current study. Unlike our current study, however, the Framingham study found no effect of age, but the cohort was elderly at the initiation of the study, and most susceptible subjects have already developed disease by this age. Preliminary results from the Framingham study reveal similar rates of protection against incident knee OA with current ERT as were found in the present study, with a 60% reduction of risk (*P* not significant) (26).

One of the only other studies of incident knee OA was carried out with 12-year followup of the Zoetomeer (The Netherlands) population (15). That study found that the incidence of knee OA was higher in women (mean age 64 years) than in men, and that obesity was also related to increased incidence. No association between OA and age, smoking, physical activity, knee injury, or Heberden's nodes was found. However, that study had several important limitations: a large percentage of subjects was lost to followup, only 135 of the women were disease-free at baseline, and only 36 incident cases were used for analysis.

In summary, the current findings demonstrate that ~3% of middle-aged women will develop radiologic knee OA every year and confirm the importance of obesity as the major modifiable risk factor for knee OA in middle-aged women. This study also provides evidence to support the notion of a protective effect of estrogen replacement therapy, which should stimulate further clinical trials in this area.

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