

## Smoking Interacts With Family History With Regard to Change in Knee Cartilage Volume and Cartilage Defect Development

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**Objective.** To describe the effects of smoking on change in knee cartilage volume and increases in knee cartilage defects, and to test for interaction between smoking and family history of osteoarthritis (OA).

**Methods.** Subjects with at least 1 parent having severe primary knee OA (offspring) and randomly selected controls without this history (a total of 325 subjects with a mean age of 45 years) were measured at baseline and 2.3 years later. Knee cartilage volume and defect score (on a 0–4 scale) were determined using T1-weighted fat-saturated magnetic resonance imaging. Smoking status and duration and number of cigarettes were recorded by questionnaire.

**Results.** In offspring, smoking was associated with annual change in medial and lateral tibial cartilage volume ( $\beta = -2.20\%$  and  $\beta = -1.45\%$ , respectively, for current smokers versus former smokers and those who had never smoked;  $\beta = -0.07\%$ /pack-year at both tibial sites, for smoking severity) in multivariate analysis. Smoking was also associated with increases (change  $\geq 1$ ) in medial and lateral tibiofemoral cartilage defect scores (odds ratio [OR] 4.91 and OR 2.98, respectively, for current smokers versus those who had never smoked; OR 9.90 and OR 12.98, respectively, for heavy smoking [total of >20 pack-years] versus never smoking) (all  $P < 0.05$ ). In contrast, smoking was not associated with any of the above in controls except for

change in lateral tibial cartilage volume. There was significant interaction between smoking and offspring–control status for change in medial tibial cartilage volume ( $P = 0.047$ ) and increases in medial ( $P = 0.03$ ) and lateral ( $P = 0.049$ ) tibiofemoral cartilage defects.

**Conclusion.** Smoking leads to knee cartilage loss and defect development primarily in individuals with a family history of knee OA. This provides evidence for a gene–environment interaction in the etiology of knee OA.

Osteoarthritis (OA), characterized by gradual loss of articular cartilage, is a slowly progressive disease that has a multifactorial origin. It is well established that several environmental factors, including obesity, acute joint injury, and occupation, as well as genetic factors play an important role in the pathogenesis of OA (1,2). There is conflicting evidence regarding the role of cigarette smoking in the pathogenesis of OA. While investigators in several studies have reported that smoking is not associated with development of radiographic OA (3–6), findings of most studies have suggested that smoking has a protective effect against prevalent and incident radiographic knee or hip OA (7–14). In contrast, there have been reports linking smoking with a higher prevalence of Heberden’s nodes (3), more severe spinal osteophytosis (15), and incident knee pain (16). These inconsistencies may reflect what actually happens or may more likely reflect the 2-dimensional (2-D) nature of radiographic measurement and the variability in measurement introduced by factors such as joint position. Furthermore, the radiographic joint space consists of not only articular cartilage but also menisci.

Magnetic resonance imaging (MRI) can visualize joint structure directly and is recognized as a valid and reproducible tool to measure articular cartilage defects (17) and cartilage volume (2,17–20). A recent study using MRI documented that men with OA who were

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current smokers had an increased risk of knee cartilage loss (an increase of  $\geq 1$  in the cartilage defect score) compared with nonsmokers and former smokers (21). However, an increase in knee cartilage defects is unlikely to lead to sufficient change in cartilage volume to result in a change on radiographs, even though it is significantly associated with the subsequent rate of change in knee cartilage volume (19). So far, there are no reports about the effects of smoking on change in knee cartilage volume. Therefore, the aim of this longitudinal MRI-based study was to describe the association between smoking and changes in knee cartilage volume and/or defects, and, when results were not consistent in the whole sample, to further test for interaction between smoking and family history of OA.

## SUBJECTS AND METHODS

**Subjects.** The study was carried out in southern Tasmania, primarily in the capital city of Hobart, from June 2000 until December 2001. The followup study was conducted  $\sim 2$  years later. Subjects were selected from 2 sources. Half of the subjects were the adult children (offspring) of patients who had undergone knee replacement surgery for primary knee OA at any Hobart hospital in the years 1996–2000. This diagnosis was confirmed by reference to the medical records of the orthopedic surgeon and the original radiograph when possible. The family structure of the 163 offspring was as follows: 1 offspring per family ( $n = 48$ ), 2 offspring per family (35 families,  $n = 70$ ), 3 offspring per family (9 families,  $n = 27$ ), 4 offspring per family (3 families,  $n = 12$ ), and 6 offspring per family (1 family,  $n = 6$ ). The other half of the subjects were controls selected at random from the state Electoral Roll, a comprehensive population listing. Those selected were eligible to participate if they had no parent with either a history of symptomatic knee OA or a knee replacement for OA. Subjects from either group were excluded on the basis of contraindications to MRI (including metal sutures, the presence of shrapnel, iron filings in the eye, and claustrophobia). This study was approved by the Southern Tasmanian Health and Medical Human Research Ethics Committee, and all subjects provided informed written consent.

**Anthropometrics.** At the beginning of each clinic visit, weight was measured to the nearest 0.1 kg (with shoes, socks, and bulky clothing removed) using a single pair of electronic scales (Delta Model 707; Seca, Hamburg, Germany) calibrated using a known weight. Height was measured to the nearest 0.1 cm (with shoes and socks removed) using a stadiometer. The body mass index (BMI; weight [kg]/height [m<sup>2</sup>]) was also calculated.

**Smoking.** At baseline, all subjects were asked questions regarding cigarette smoking. Smoking status (never, former, and current) and years of smoking were determined from the following questions: “Have you ever smoked cigarettes on a regular basis?”; “If yes, at what age did you start smoking regularly?”; “Do you currently smoke cigarettes?”; and “If you have given up smoking, at what age did you stop?” The number of cigarettes smoked each day was recorded for current and

former smokers. The total number of cigarettes (in pack-years) was calculated as follows: (number of years smoking  $\times$  number of cigarettes each day)/20. Smoking severity was defined semiquantitatively, as follows: 0 = no smoking, 1 (slight) =  $>0$ –5 pack-years, 2 (moderate) =  $>5$ –20 pack-years, and 3 (heavy) =  $>20$  pack-years.

**Knee pain assessment.** Knee pain at baseline was assessed by questionnaire and was defined as pain for  $>24$  hours in the last 12 months or daily pain on  $>30$  days of the last year (2).

**Physical activity measures.** Physical activity measures included lower limb muscle strength, endurance fitness, and questionnaire items (days of either strenuous activity or light activity for  $>20$  minutes in the last 2 weeks, daily television watching in the last week, and number of competitive sports in the last 12 months) as previously described (2,22,23).

**Radiography.** A standing anteroposterior semiflexed view of the right knee was obtained in all subjects at baseline and scored individually for osteophytes and joint space narrowing, as previously described (24).

**Knee cartilage volume and defects measurement.** An MRI scan of the right knee was obtained at baseline and followup using the same machine and the same protocol (T1-weighted, fat-saturated) as described previously (17,18,23). Knee cartilage volume was determined by means of image processing on an independent workstation at baseline and followup. The volumes of individual cartilage plates (medial tibia and lateral tibia) were isolated from the total volume by manually drawing disarticulation contours around the cartilage boundaries on a section-by-section basis. These data were then resampled by means of bilinear and cubic interpolation (area of  $312 \times 312 \mu\text{m}$  and 1.5-mm thickness, continuous sections) for the final 3-D rendering. The coefficients of variation for cartilage volume measurements were 2.1–2.6% (23). The percent change in cartilage volume per year was calculated as follows:  $100 \times ([\text{cartilage volume at followup} - \text{cartilage volume at baseline}]/\text{cartilage volume at baseline})/\text{time between scans in years}$ .

The cartilage defects were graded on 2 occasions at the medial tibial and femoral sites and at the lateral tibial and femoral sites as previously described, with excellent reproducibility (17,18). A ranked ordinal scale was used, where grade 0 = normal cartilage, grade 1 = focal blistering and intracartilaginous area with low signal intensity and an intact surface and bottom; grade 2 = irregularities on the surface or bottom and loss of thickness of  $<50\%$ , grade 3 = deep ulceration with loss of thickness of  $>50\%$ , and grade 4 = full-thickness chondral wear with exposure of subchondral bone. A prevalent cartilage defect was defined as a cartilage defect score  $\geq 2$  at any site within the medial or lateral tibiofemoral compartment. Changes in tibial or femoral cartilage defects were calculated by subtracting tibial or femoral cartilage defect scores at baseline from tibial or femoral cartilage defect scores at followup. A change in cartilage defects  $\geq 1$  at any site was defined as an increase in cartilage defects in the corresponding compartment, as previously reported (18,19).

**Statistical analysis.** Linear regression analysis was used to examine the associations between the annual percent change in cartilage volume (all subjects included regardless of their increase or decrease in cartilage volume) and smoking (status and pack-years) before and after adjustment for explan-

**Table 1.** Characteristics of the study participants\*

Characteristic	Never smoker	Former smoker	Current smoker
<b>Offspring group</b>			
No. of subjects	75	47	40
Women, %	55	60	65
Age, years	45.0 ± 6.3	45.6 ± 7.0	45.0 ± 6.3
BMI, kg/m <sup>2</sup>	27.8 ± 5.4	28.7 ± 5.1	26.9 ± 4.4
Radiographic OA, %	23	13	18
Knee pain, %	45	47	53
Previous knee injury, %	20	17	13
Lower limb muscle strength, kg	123.1 ± 45.1	127.4 ± 51.8	116.6 ± 43.4
Physical work capacity, W/kg	3.1 ± 1.3	2.8 ± 1.1	3.1 ± 1.0
Strenuous physical activity, 1–5†	2.1 ± 1.4	1.8 ± 1.2	1.7 ± 1.3
Light physical activity, 1–5†	4.4 ± 1.1	4.6 ± 0.7	4.2 ± 1.2
Television watching, 1–5‡	2.7 ± 0.7	2.8 ± 0.8	2.6 ± 0.8
Baseline medial tibial cartilage volume, ml	2.2 ± 0.5	2.2 ± 0.5	2.3 ± 0.5
Baseline lateral tibial cartilage volume, ml	2.6 ± 0.7	2.6 ± 0.6	2.7 ± 0.8
Baseline medial cartilage defect prevalence, %	23	26	15
Baseline lateral cartilage defect prevalence, %	19	19	25
<b>Control group</b>			
No. of subjects	95	38	30
Women, %	60	61	50
Age, years	45.3 ± 6.3	46.5 ± 7.3	43.3 ± 5.6
BMI, kg/m <sup>2</sup>	26.4 ± 4.2	26.6 ± 3.1	25.4 ± 5.9
Radiographic OA, %	18	11	17
Knee pain, %	22	18	27
Previous knee injury, %	23	13	27
Lower limb muscle strength, kg	127.9 ± 44.6	126.1 ± 48.6	135.9 ± 59.9
Physical work capacity, W/kg	2.8 ± 0.9	3.0 ± 1.0	3.1 ± 0.9
Strenuous physical activity, 1–5†	2.1 ± 1.2	2.1 ± 1.2	1.7 ± 1.3
Light physical activity, 1–5†	4.3 ± 1.0	4.4 ± 1.1	4.6 ± 0.9
Television watching, 1–5‡	2.7 ± 0.7	2.8 ± 0.8	2.5 ± 1.0
Baseline medial tibial cartilage volume, ml	2.2 ± 0.6	2.2 ± 0.5	2.1 ± 0.5
Baseline lateral tibial cartilage volume, ml	2.5 ± 0.7	2.6 ± 0.7	2.5 ± 0.5
Baseline medial cartilage defect prevalence, %	13	11	7
Baseline lateral cartilage defect prevalence, %	16	13	7

\* Except where indicated otherwise, values are the mean ± SD. There were no significant differences between the groups. BMI = body mass index; OA = osteoarthritis.

† Days of activity for >20 minutes in the last 2 weeks (1 = none, 2 = 1–2 days, 3 = 3–5 days, 4 = 6–8 days, 5 = ≥9 days).

‡ Daily television watching in the last week (1 = none, 2 = ≤1 hour, 3 = 2–3 hours, 4 = 4–5 hours, 5 = ≥6 hours).

atory factors such as age, sex, BMI, offspring–control status, baseline cartilage volume, radiographic OA, knee pain, past knee injury, physical activity measures, and change in BMI and physical activity measures in the whole sample as well as separately in offspring and control groups. Logistic regression analysis was used to examine the associations between increases in cartilage defects (increase versus no increase) and smoking (status and pack-years) before and after adjustment for the above confounders and baseline prevalent cartilage defects in the whole sample as well as separately in offspring and control groups.

To take the relatedness of offspring subjects into account, subjects were grouped into family clusters, and the information sandwich variance estimator compiled over family clusters was used to obtain robust standard errors corrected for correlation between observations on siblings using the method described by Rogers (25,26). Standard diagnostic checks of model fit and residuals were routinely made, and data points with large residuals and/or high influence were investigated for data errors. Interactions between smoking and offspring–

control status were investigated by regressing the change in cartilage volume (or increases in cartilage defects) on a binary (0/1) term for offspring–control status within smoking strata (no smoking, former smoking, and current smoking) and assessed overall by testing the statistical significance of the coefficient of a (smoking × offspring–control score) product term, where the smoking scores assigned were no smoking = 0, former smoking = 1, and current smoking = 2, after adjustment for confounders.

*P* values less than 0.05 (2-tailed) or a 95% confidence interval not including the null point were considered statistically significant. All statistical analyses were performed using Stata statistical software, release 8 (College Station [TX]: Stata Corporation, 2003).

## RESULTS

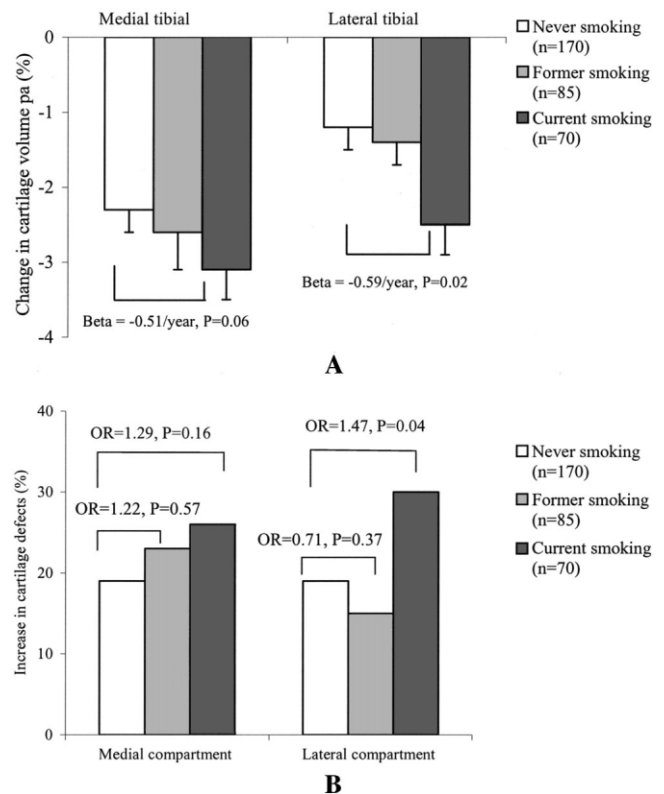
A total of 325 subjects (135 men and 190 women) completed the study (87% of those originally studied).

This sample comprised young individuals, with an average age of 45 years at baseline (range 26–61 years). The average time between visits was 2.3 years (range 1.8–2.6 years). Characteristics of all subjects combined are presented in Table 1. Former and current smokers and those who had never smoked were similar in terms of the proportion of women, baseline measurements including age, BMI, past knee injury, physical activity measures, radiographic OA, tibial cartilage volume, and prevalent tibial cartilage defects, with no significant differences in either offspring or control groups. In the control group, 23% and 18% of subjects were former and current smokers, respectively, and in the offspring group, 29% and 25% were former and current smokers, respectively ( $P = 0.10$ ). In the total sample, current smokers had a higher prevalence of knee pain compared with former smokers and those who had never smoked (41% versus 33%;  $P = 0.04$ ).

In the whole group, smoking status was not associated with baseline tibial cartilage volume or prevalent tibiofemoral cartilage defects, before and after adjustment for age, sex, BMI, offspring–control status, physical activity, and radiographic OA (data not shown). Longitudinally, the associations between smoking status and rate of change in medial tibial cartilage volume (Figure 1A) and increase in medial tibiofemoral cartilage defects (Figure 1B) over 2.3 years were not significant or were of borderline significance in multivariate analysis; however, current smokers had a significantly higher rate of change in lateral tibial cartilage volume (Figure 1A) and significant increases in lateral tibiofemoral cartilage defects (Figure 1B) compared with individuals who had never smoked.

In the offspring group, smoking status was positively associated with baseline tibial cartilage volume (for medial tibia,  $\beta = 0.07$  ml,  $P = 0.08$ ; for lateral tibia,  $\beta = 0.10$  ml,  $P = 0.04$ ) but not with prevalent tibiofemoral cartilage defects, after adjustment for confounders (data not shown). Longitudinally, current smoking and pack-years were significantly associated with change in both medial and lateral tibial cartilage volume in multivariate analysis (Table 2). Furthermore, in unadjusted analyses, current smokers and heavy smokers had greater odds of an increase in cartilage defects in both medial and lateral tibiofemoral compartments than those who had never smoked, and these odds increased after adjustment (largely due to adjustment for radiographic OA) (Table 3).

In the control group, despite there being the same number of subjects as in the offspring group, smoking status was not significantly associated with



**Figure 1.** Association between smoking, annual change in tibial cartilage volume, and increases in cartilage defects over 2.3 years in the whole sample. **A**, Current smokers had greater medial and lateral tibial cartilage loss than those who had never smoked. **B**, Current smokers had a higher rate of increase in lateral tibiofemoral cartilage defects than those who had never smoked.  $P$  values were determined after adjustment for age, sex, baseline cartilage volume or baseline cartilage defect scores, radiographic osteoarthritis, knee pain, previous knee injury, and baseline and changes in body mass index and physical activity. Values are the mean and SEM (A) or the percentage (B). pa = per annum; OR = odds ratio.

baseline tibial cartilage volume and prevalent tibiofemoral cartilage defects before and after adjustment for confounders (data not shown). Longitudinally, there were no significant associations between smoking status and change in medial tibial cartilage volume or increase in medial tibiofemoral cartilage defects over 2.3 years (data not shown). Additionally, smoking status was not associated with change in lateral tibial cartilage volume or increase in lateral tibiofemoral cartilage defects (data not shown), but smoking pack-years was significantly associated with change in lateral tibial cartilage volume ( $\beta = 0.045$ /pack-year,  $P = 0.04$ ) in multivariate analysis.

The interaction between smoking and offspring–control status with change in medial tibial cartilage volume was significant after adjustment for confounders

**Table 2.** Associations between smoking and annual rate of change in knee cartilage volume in the offspring group\*

	Univariate $\beta$ (95% CI)	Multivariate $\beta$ (95% CI)†
Medial tibial cartilage volume change, %		
Ever smoking (current and former vs. never)	-1.28 (-2.39, -0.18)	-1.34 (-2.63, -0.06)
Current smoking (current vs. former and never)	-1.56 (-2.84, -0.29)	-2.20 (-3.69, -0.70)
Pack-years of smoking (per pack-year)	-0.04 (-0.09, 0.005)	-0.07 (-0.13, -0.01)
Lateral tibial cartilage volume change, %		
Ever smoking (current and former vs. never)	-0.67 (-1.65, 0.31)	-0.45 (-1.44, 0.53)
Current smoking (current vs. former and never)	-2.00 (-3.09, -0.91)	-1.45 (-2.77, -0.14)
Pack-years of smoking (per pack-year)	-0.07 (-0.12, -0.03)	-0.07 (-0.12, -0.02)

\* 95% CI = 95% confidence interval.

† Adjusted for factors including age, sex, baseline cartilage volume, radiographic osteoarthritis, knee pain, previous knee injury, and baseline and changes in body mass index and physical activity.

(Figure 2A), but the interaction with change in lateral tibial cartilage volume was not significant ( $P = 0.31$ ). There were also significant interactions between smoking and offspring-control status for increases in cartilage defects in both medial (Figure 2B) and lateral ( $P = 0.049$ ) tibiofemoral compartments after adjustment for confounders. Similar results were obtained for interactions between smoking severity and offspring-control status on change in knee cartilage volume or cartilage

defect development, or when men and women were analyzed separately (data not shown).

### DISCUSSION

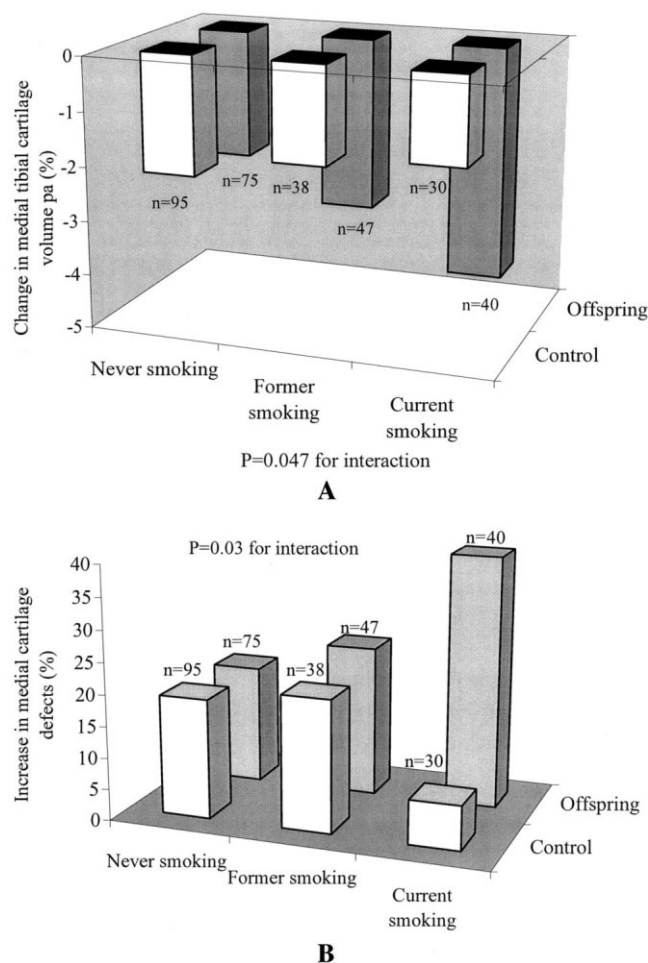
This study is the first to demonstrate harmful effects of smoking on both cartilage volume loss and cartilage defect development mainly in persons with a family history of severe knee OA. Our primary aim was

**Table 3.** Associations between smoking and increase in knee cartilage defects in the offspring group\*

	Univariate OR (95% CI)	Multivariate OR (95% CI)†
Increases in medial tibiofemoral cartilage defects		
Smoking (n)		
Never (75)	1	1
Former (47)	1.48 (0.60, 3.64)	2.61 (0.78, 8.74)
Current (40)	1.81 (1.17, 2.80)	4.91 (1.59, 15.13)
<i>P</i> for trend	0.010	0.005
Pack-years of smoking (n)		
0 (75)	1	1
>0-5 (19)	1.25 (0.36, 4.39)	9.84 (0.97, 99.44)
>5-20 (33)	1.56 (0.58, 4.25)	2.62 (0.45, 15.35)
>20 (31)	3.59 (1.40, 9.17)	9.90 (1.55, 63.04)
<i>P</i> for trend	0.009	0.015
Increases in lateral tibiofemoral cartilage defects		
Smoking (n)		
Never (75)	1	1
Former (47)	1.76 (0.64, 4.82)	6.09 (0.61, 60.93)
Current (40)	1.90 (1.17, 3.08)	2.98 (1.17, 7.56)
<i>P</i> for trend	0.014	0.022
Pack-years of smoking (n)		
0 (75)	1	1
>0-5 (19)	1.93 (0.52, 7.10)	17.80 (0.67, 469.70)
>5-20 (33)	2.41 (0.83, 6.96)	22.40 (0.88, 568.04)
>20 (31)	3.10 (1.09, 8.82)	12.98 (1.44, 116.95)
<i>P</i> for trend	0.020	0.020

\* OR = odds ratio; 95% CI = 95% confidence interval.

† Adjusted for factors including age, sex, baseline prevalent cartilage defect, radiographic osteoarthritis, knee pain, previous knee injury, and baseline and changes in body mass index and physical activity.



**Figure 2.** Effects of interactions between smoking and family history on change in tibial cartilage volume and increases in tibiofemoral cartilage defects. There was a significant interaction between smoking and offspring–control status for tibial cartilage volume change (A) and increases in cartilage defects (B) in medial tibiofemoral compartments. *P* values were determined after adjustment for age, sex, baseline cartilage volume or baseline cartilage defect scores, radiographic osteoarthritis, knee pain, previous knee injury, and baseline and changes in body mass index and physical activity. pa = per annum.

to examine the association between smoking and loss of knee cartilage volume and increases in knee cartilage defects in the whole sample. However, when the data were not consistent, we then looked for a gene–environment interaction and found that the results were highly consistent in the offspring, in whom smoking was dose-dependently associated with change in medial and lateral tibial cartilage volume as well as with increases in medial and lateral tibiofemoral cartilage defect scores. However, in control subjects with no family history of knee OA, smoking pack-years was associated with change in lateral tibial cartilage volume only. Further-

more, there were significant interactions between smoking and offspring–control status with change in medial tibial cartilage volume and increases in tibiofemoral cartilage defect scores.

Although it is well known that cigarette smoking has been associated with an increased risk of some common diseases (27), such as cancer, cardiovascular diseases, respiratory diseases, stroke, and rheumatoid arthritis (RA) (28), to date reports of the effect of cigarette smoking on OA are conflicting. In 1989, Felson et al (7) explored the association between smoking and knee OA in the Framingham Osteoarthritis Study and found that heavy smokers had a modestly lower risk of developing knee OA than did nonsmokers (relative risk 0.81) after adjustment for confounders. Since then, several cross-sectional and longitudinal studies have confirmed a protective effect of smoking against knee or hip OA (8–14). However, some adequately powered studies have failed to confirm these associations between cigarette smoking and prevalent and incident knee OA (3–6).

In contrast, smoking has been revealed to be associated with prevalent Heberden's nodes (3), spinal osteophytosis (15), and incident knee pain (16). Investigators in a recent study reported that 61% of women awaiting knee replacement surgery due to knee OA were smokers, whereas 44% of matched controls who had no past knee injury and no knee pain in the past 3 years were smokers (29). These inconsistencies are probably due to variations in study samples (differing sample sizes, ages, and disease groups), but they may also reflect the inability to use joint space width on radiographs for detecting change in cartilage morphology.

Joint space narrowing was much less common than prevalence of cartilage defects in this study. Cartilage defects increase the rate of cartilage loss over time (19), but they do not immediately lead to loss of cartilage volume, suggesting that cartilage changes can be present long before radiographic changes appear. The cross-sectional results from the present study indicated that smoking was associated with less joint space narrowing (although this was not statistically significant) and greater tibial cartilage volume, suggesting that smoking is likely to have a protective effect against radiographic OA. However, a higher baseline cartilage volume at a given point in time may also represent cartilage swelling in the early stages of disease (2,18).

In the whole group, we found that current smokers and smokers with >20 pack-years had greater change in lateral tibial cartilage volume and increase in lateral tibiofemoral cartilage defects than those who had never

smoked, after adjustment for some important confounders such as age, sex, BMI, and physical activity. Current and heavy smokers also had greater change in medial tibial cartilage volume and/or increase in medial tibiofemoral cartilage defects than those who had never smoked, but the associations were of borderline significance. The associations between pack-years of smoking and change in lateral tibial cartilage volume were of similar significance in both offspring and controls, suggesting that heavy smoking may be associated with more lateral tibial cartilage loss regardless of a family history of OA. Similar results for knee cartilage focal loss were observed in a recent longitudinal study (21). However, the dose-response effect of smoking in women and the effects on change in knee cartilage volume have not previously been demonstrated.

A modest but significant genetic effect for radiographic knee OA has been demonstrated (1). We recently reported that changes in knee cartilage volume and cartilage defects were heritable (2,30,31). In the current sample, offspring of patients with severe knee OA had high annual knee cartilage loss and a greater increase in the tibiofemoral cartilage defect score than did controls, suggesting that both knee cartilage loss and cartilage defect development play roles in the genetic development of knee OA (2). We then tested the effect of smoking on knee cartilage loss and defect development in offspring and controls separately, due to inconsistent results in the total sample. Somewhat unexpectedly, we found evidence of a gene-environment interaction between smoking and family history of OA with cartilage damage, in which the effect of smoking was much stronger and more consistent in those with at least 1 parent with severe knee OA. Offspring who smoked had greater tibial cartilage volume change and greater increases in tibiofemoral cartilage defects than did nonsmoking offspring. There was also a dose-response association.

However, although the mechanism is unknown, there is evidence to support a gene-environment interaction of smoking for other complex diseases such as cardiovascular disease (32) and RA (28). There were significant effects of interactions between cigarette smoking and inflammation-related gene polymorphisms such as the interleukin-1 (IL-1) genotype (33,34) and IL-4 receptor genotype (35) on the risk of other diseases, and these genes may be relevant to knee OA (36). Interestingly, former smokers had less knee cartilage loss than current smokers, suggesting that smoking cessation may have benefits for knee cartilage health in offspring of patients with severe knee OA. In contrast,

the associations between smoking and cartilage changes in controls were weak and were significant only for change in lateral tibial cartilage volume. Our results suggest that knee OA is a complex disease in which environmental agents may interact with genetic factors that influence susceptibility to knee cartilage loss and cartilage defect development, and that smoking may be most harmful in persons at higher genetic risk. These findings need to be replicated, but they suggest a biologically plausible association, since there is a dose-response association. The exact biologic mechanism remains unknown, as does the mechanism for the gene-smoking interaction.

The loss to followup in this study was small, suggesting that nonparticipation is not a source of major concern; however, the study has a number of other potential limitations. First, we could not determine the possible susceptibility genes for knee OA, so we could not identify which gene(s) were interacting with smoking. This area is worthy of further study. Second, cigarette smoking was based on self-report and thus may be subject to reporting error, but studies have shown that self-report of smoking is accurate, and there is also fair agreement between self-reported smoking amount and the serum or urinary level of cotinine (a biochemical marker of cigarette smoking) (37). Third, although this is one of the largest MRI-based studies on knee cartilage health so far, the sample size of the individual smoking subgroups is small, which limits power for some items. Fourth, the left knee was not examined, and Heberden's nodes and hand OA were not recorded; therefore, we cannot comment on the effects of smoking on cartilage changes at the left knee, and we cannot exclude the possible modifying influence of generalized OA. Finally, while measurement error may have influenced the results, our measurements of knee cartilage volume and defects are highly reproducible (17,23), suggesting that this is unlikely.

In conclusion, the results of this longitudinal study suggest that smoking leads to knee cartilage loss and defect development primarily in persons with a family history of knee OA. This provides evidence for a gene-environment interaction in the etiology of knee OA.

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### AUTHOR CONTRIBUTIONS

Dr. Ding had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study design.** Ding, Cicuttini, Jones.

**Acquisition of data.** Ding, Jones.

**Analysis and interpretation of data.** Ding, Blizzard, Jones.

**Manuscript preparation.** Ding, Cicuttini, Blizzard, Jones.

**Statistical analysis.** Ding, Blizzard.

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