Osteoarthritis and Cartilage (2003) **11,** 29–35
 1063–4584/03/$30.00/0
doi:10.1053/joca.2002.0857

Osteoarthritis and Cartilage

International Cartilage Repair Society

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Smoking and osteoarthritis: Is there an association? The Clearwater Osteoarthritis Study

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Summary

Objective: To evaluate the association between cigarette smoking and the subsequent development of osteoarthritis (OA) at four separate sites: knee, hand, foot and cervical spine.

Methods: This cohort study examined 2505 men and women aged 40 years and older participating in the longitudinal Clearwater Osteoarthritis Study (1988–current). Biennial physical exams, including serial radiographs, as well as historical information, were collected. The Lawrence and Kellgren ordinal scale was used to determine radiological evidence of the study outcome, OA. Self-reported history of smoking behavior was used to determine the study exposure. Smoking was classified using four approaches: (1) ever/never, (2) former/never, (3) current/never, and (4) dose.

Results: Among the individuals at study entry, radiologically confirmed incident OA was detected during the follow-up period at four sites: knee (32%), hand (49%), foot (28%), and cervical spine (52%). Approximately 11% were self-reported current smokers. Unadjusted analyses indicated that individuals classified as current smokers demonstrated significant levels of protection from OA at all four sites investigated. However, adjusted point estimates ranging from 0.60–1.48 were suggestive of no association between smoking and the development of OA at any of the four sites investigated.

Conclusion: Based upon the findings of this prospective study, smoking does not appear to convey a clinically significant level of protection against the development of radiologically-confirmed OA. While these findings corroborate previous studies indicating no association between smoking and OA, anecdotal evidence warrants investigation into the role that cigarette smoking may play in the symptomatology of OA.

Key words: Osteoarthritis, Smoking, Risk factor, Prospective.

Introduction

Osteoarthritis (OA) affects more than 21 million Americans and is a leading cause of disability in the US[1]. Studies within the past 10 years have suggested that cigarette smoking may play a modestly protective role in the development of OA. Four previous studies have examined specifically the relationship smoking shares with OA[2–5]. Conflicting results have been reported. While cigarette smoking and its association with OA is largely unexplored, past studies have reported point estimates spanning both sides of the null value, ranging from 0.11 to 2.27[2]. Perhaps one of the earliest studies to investigate specifically the OA-smoking relationship was conducted based upon an unexpected finding of a modest, protective effect during analysis of the first Health and Nutrition Examination Survey (HANES I)[6]. In 1989, Felson *et al.*[3] further explored this association using the Framingham Osteoarthritis Study data. Results from their case-control study noted an adjusted, protective influence on OA among heavy smokers relative to never smokers (OR=0.81; *P*-value <0.05)[3]. Subsequently, two case-control investigations examined this relationship noting a similar protective influence. Hart and Spector reported protective effects in some joint groups, while reporting cigarette smoking as a risk factor for knee OA[4]. The current cohort investigation is studying the hypothesis: among men and women aged 40 years and older, those individuals who smoke are no more likely to develop OA (knee, hand, foot and cervical spine) than are those individuals who do not smoke.

Received 1 April 2002; revision accepted 17 September 2002.

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Patients and methods

In 1988, the Arthritis Research Institute of America (ARIA) located in Clearwater, Florida, initiated The Clearwater Osteoarthritis Study (COS). The COS is an on-going, prospective cohort study designed to identify major risk factors for the development of OA, differentiate risk factors for localized and generalized primary OA, as well as to identify risk factors for the progression of OA. Currently in its fifteenth year, the twenty-five year longitudinal study collects demographic, historical, clinical, and radiological data. ARIA is located appropriately in Pinellas County, Florida drawing upon a population with a large percentage of residents aged 65 years and older (22.5%)[7]. The study sample of this older community comprises volunteer participants who are recruited by various methods. These include invitational letters, television and radio announcements, newspaper articles publicizing the COS

study, articles posted in community organizations' bulletins, and seminars held at community clubs and organizations.

Males and female, aged 40 or older, are eligible for the COS study. Individuals with and without radiographic OA are eligible to enroll. To date, 3489 individuals have been enrolled in the COS study, with less than 30 individuals screened, but not subsequently enrolled. The following study subjects were excluded from enrollment: individuals with self-reported rheumatoid arthritis or variants (lupus erythematosus, ankylosing spondylitis, etc.); gout; history of methotrexate shots; disabling neuralgic disease; those confined to a wheelchair; and lastly, those mentally incompetent. Among the 3489 individuals that were enrolled in the COS study, 984 were excluded from the current analyses due to the following reasons: no follow-up time recorded (N=859); incomplete data (N=26); and individuals with prevalent OA at all four sites (N=99). Accordingly, the current analyses evaluated 2505 individuals.

At initial contact with participants, a description of study procedures was given, followed by a screening questionnaire, detailing inclusion and exclusion criteria. After eligibility was determined and informed consent was obtained, participants were asked to complete a self-administered, mostly pre-coded form, the COS History Questionnaire. This instrument collected detailed information including demographics, family history, diet, occupation, physical activity, injuries, and medical conditions. To improve study follow-up, participants were asked the name, the phone number, and address of a relative or a friend who could provide location information in the event that institute personnel were unable to contact the subject.

At the initial and all subsequent ARIA appointments, a physical exam was conducted including X-rays. The COS Physical Examination was completed at that time by the institute clinicians. The physical examination had an emphasis on clinical and functional joint evaluation. Height and weight measurements were taken with the subjects wearing stockings and indoor clothing. Study participants were re-evaluated biennially, updating both the history questionnaire and the clinical examination information.

For the purpose of this investigation, four distinct study outcomes were defined: OA of the knee, hand, foot, and cervical spine. Serial X-rays were taken initially at baseline and subsequently every two years. A case was defined when radiographic structural evidence of disease was found. Each radiograph was graded 0 to 4 for OA by the ordinal criteria of Kellgren and Lawrence[8]: 0, absent; 1, questionable osteophytes and no joint space narrowing; 2, definite osteophytes with possible joint space narrowing; 3, definite joint space narrowing with moderate multiple osteophytes and some sclerosis; 4, severe joint space narrowing with cysts, osteophytes and sclerosis present. The c-spine radiograph view was lateral, and the knees (weight bearing) hands and feet views were anterior-posterior. Hand OA was defined as evidence of disease in one or more of the hand joint sub-groups (right and left second DIP, third PIP, and first CMC). Diagnosis of foot OA was based on radiological evidence of disease in the metatarso phalangeal joints. A licensed X-ray technician using standard exposure techniques took X-rays, including anterior weight-bearing knee radiographs. X-rays were interpreted by a board-certified radiologist. Subjects whose X-rays were interpreted as grades 0 or 1 were considered disease-free for OA; subjects whose radiographs were interpreted as grades 2, 3, or 4 were classified as cases. At baseline, if an individual was free of OA at all four sites, they were included in each of the four smoking-OA studies: hand, knee, foot, and spine. At baseline, if they were free of, for example, hand and knee OA, they were included in the hand and knee OA studies. In addition to examining OA, severe radiographic OA (grades 3+) was considered when investigating the relationship between smoking and OA. To assess inter-reader validity, every tenth subject's assembled films were independently interpreted by a non-affiliated radiologist who was blinded to the results of the first reading. The study radiologist, as well as the independent radiologist, was blinded to information about the individual study participants.

Smoking, the study exposure, was originally defined using four approaches: (1) ever/never, (2) former/never, (3) current/never, and (4) dose: light, moderate, and heavy. Differing methods of exposure quantification were utilized in an attempt to adequately summarize the smoking history of a given individual. The fourth method differentiated the quantities of cigarettes smoked per day among current smokers: light=1–19/day; moderate=20–39/day; and heavy=40+/day. The factors included in the final analyses were age at study entry, gender, body mass index (BMI), heredity, physical activity level, high risk occupation, and OA status at other sites. Heredity, a self-reported variable, was defined as a participant having one or more, siblings or parents who developed OA. Physical activity considered participants' both aerobic and weights resistance regimens. High risk occupation was determined by the categorization of the 22 possible responses from the COS History Questionnaire. The presence of OA at one site may be a risk factor for the development of OA at another site. Therefore, the presence of OA (grades 2+) at any of the other three sites was also included as a co-variate in the adjusted analyses.

Data entries were double-checked by an independent reviewer. During 1998, the inter-observer variability of X-ray interpretations was calculated using the kappa coefficient, measuring the amount of agreement between one reading and another that is above random chance[9]. The significance of the association between smoking status and the dichotomous outcome of OA was initially assessed using the Mantel–Haenszel chi-square test statistic[10]. Putative confounders for each association were identified and considered in the adjusted analyses. A factor was considered a confounder if it was associated with OA (outcome) and was differentially distributed between smokers (exposed) and non-smokers (non-exposed). The Student's t-test was the statistic employed for determining statistically significant differences between the continuous variables age and BMI[11]. As the study participants had been observed for unequal lengths of time and some observations were censored, proportional hazards regression (Cox's) was employed[12,13] to quantify the relationship between smoking and OA while simultaneously controlling for the influence of exogenous factors. The period of observation was the interval between study entry time and either: (1) the development of the outcome; (2) study withdraw; or (3) censoring. The exponentiated beta coefficients were used to calculate the point estimates (hazard ratios) for the final predictive models. Statistical Analyses Software (SAS), Version 8.12[14] was employed, specifically PROC PHREG, for the computer analysis of these data. Continuous co-variates in the analytic analyses (age and BMI) were kept as continuous variables. It should be noted that the results reported for the unadjusted analyses also used Cox's regression, with smoking as the only independent variable in the model. All point estimates

Table I
Evaluation of potential confounders and distribution of current smoking status by selected factors

	Smokers (*N*=265)	Never smokers (*N*=1198)
Age (mean)*	56.9	61.1
Female (%)	70.9	75.4
Mean BMI at entry	25.3	26.3
Mean BMI at age 45	23.6	24.2
Diabetes (%)	9.8	7.4
Knee injury (%)	1.1	1.6
Heredity (%)*	47.9	55.6
High risk occupation*	19.2	14.3
Physically active**	53.6	65.9

*P-value <0.05; **P-value <0.001.
The P-value notes the statistical significance of the association between current smoking status and the selected factors listed in the left column.

reported within are hazard ratios. Power calculations appropriate for time-to-survival study designs were conducted to determine sufficiency of sample size for detecting an association between smoking and OA[15,16]. This study had over 90% power to detect an association of 3.0 or higher, if indeed, one existed (α=0.05).

Results

Inter-observer variability by a second radiologist was high (93% agreement; kappa=0.85). Descriptive analyses revealed 11% of the study subjects were classified as current smokers. Efforts were made to identify those factors known to be associated with OA that were also differentially distributed by the factor of interest, smoking. Individuals who were free from OA in at least one site (knee, hand, foot, or cervical spine) were summarized with respect to their smoking behavior (*N*=2505). Stratified analyses noted that smokers were: (1) younger, (2) had a lower BMI at study entry and at age 45 years, (3) displayed a higher percentage of diabetes, (4) experienced a lower percentage of knee injury history, (5) had a lower heredity link with OA, (6) more likely to report a high risk occupation, and (7) less physically active (Table I). Additionally, statistically significant differences in age, heredity link, high risk occupation, and physical activity level were demonstrated between smokers and non-smokers. Next, the examination of the above factors' distribution between smoking groups was conducted separately for all four sites examined knee, hand, foot, and cervical spine (tables not shown). As the result of the evaluation for confounding in examining smoking and OA, age, BMI, gender, heredity, high risk occupation, physical activity, and OA status (yes/no) at any of the other three sites were considered in the adjusted analyses. These descriptive analyses indicated a similar distribution of factors by smoking behavior for all four sites. Table II displays the numbers and percentages of individuals that became incident cases of OA (site-specific) during the study period. Percentages ranged from a low of 27.5 % (foot) to a high of 51.5% (cervical spine). The percentage of participants that became incident cases of severe OA ranged from a low of 4.8% (foot) and a high of 17.3% (hand).

Evaluations of losses to follow-up were examined for each site: knee, hand, foot, and cervical spine (Table III). During the study period, 29–35% of the cohort was considered lost to follow-up at the time the data were censored for this study. Differences between those subjects that were lost to follow-up and those that were not lost were examined by smoking status. The number of person-years of follow-up differed by smoking status, as only 11% of our participants were current smokers. Overall, reasons for becoming lost to follow-up (death, relocation, or withdrawal) were fairly similar between our smokers and non-smokers.

Initially, we looked at the association between smoking and OA with smoking summarized as ever/never. The point estimates, ranging from 0.91–1.12 (all non-significant) approached the null value in many of the sites for both OA (2+) and severe OA (3+). This method of quantifying an individual's smoking history, as well as the former/never approach, proved to yield little predictive ability for both OA and severe OA (Tables IV and V). The third approach for summarizing an individual's smoking behavior, current/never, was analysed for an association with OA and severe OA. Unadjusted analyses for all four sites examined demonstrated current smoking to have a statistically significant protective effect against OA (Table VI). Those individuals classified as current smokers were 38% less likely to develop knee OA than were those who were never smokers (risk ratio=0.62; CI 0.46–0.83). A closely similar inverse relationship between smoking and OA was demonstrated for the following sites: hand (risk ratio=0.71; CI 0.54–0.92), foot (risk ratio=0.63; CI 0.46–0.87), and cervical spine (risk ratio=0.69; CI 0.54–0.88). We also investigated the effect current smoking may have with severe OA (Table VI). A greater protective effect was shown for severe hand OA relative to hand OA (grades 2+).

After adjusting for the influence of age, gender, BMI, heredity, occupation, physical activity level and OA status at other sites, risk estimates for OA and severe OA spanned both sides of the null value, ranging from 0.60 to 1.48 (Table VII). However, none showed significance in the relationship between current smoking and OA (or severe OA) at any of the four sites examined. While gender has been identified as an important factor in the epidemiology of OA, we assessed the possible role that gender may play in the smoking–OA relationship. Interaction terms evaluating such (smoking×gender) were calculated for all four sites, for both OA and severe OA. With the exception of severe knee OA (P=0.03), all corresponding P-values were non-significant, ranging from 0.17–0.80.

The dose–response relationship was analysed originally by categorizing the number of cigarettes smoked per day

Table II
Number of incident OA cases in knee, hand, foot, and spine

	Knee	Hand	Foot	Spine
Number of subjects free of OA at study entry	2212	1531	2106	1962
Number of incident cases, grades 2+ (%)	708 (32.0)	748 (48.9)	579 (27.5)	1011 (51.5)
Number of incident cases, grades 3+ (%)	205 (9.3)	265 (17.3)	101 (4.8)	309 (15.8)

Table III
Evaluation of losses to follow-up free of site-specific osteoarthritis at study entry

	Knee		Hand		Foot		Spine	
	Current smoker (*N*=249)	Never smoker (*N*=1059)	Current smoker (*N*=185)	Never smoker (*N*=710)	Current smoker (*N*=230)	Never smoker (*N*=998)	Current smoker (*N*=221)	Never smoker (*N*=934)
Person-years of follow-up time	1559	6314	1026	3827	1476	6021	1283	5188
Mean follow-up time (years)	6.28	6.07	5.61	5.46	6.47	6.14	5.86	5.64
Median follow-up time (years)	5.98	5.86	5.19	4.24	6.43	5.94	5.71	4.91
Number lost to follow-up (%)	87 (35.0)	317 (29.9)	56 (30.3)	195 (27.5)	76 (33.0)	299 (30.0)	72 (32.6)	271 (29.0)
Death	16 (6.4)	39 (3.7)	12 (6.5)	24 (3.4)	15 (6.5)	38 (3.8)	12 (5.4)	30 (3.2)
Relocation	16 (6.4)	86 (8.1)	10 (5.4)	60 (8.4)	15 (6.5)	81 (8.1)	15 (6.8)	72 (7.7)
Withdrawal	55 (22.1)	192 (18.1)	34 (18.4)	111 (15.6)	46 (20.0)	180 (18.0)	45 (20.4)	169 (18.1)

Table IV
Unadjusted association between smoking and OA (and severe OA) in knee, hand, foot, and spine (ever vs never)

	Grades 2+		Grades 3+	
	RR	CI	RR	CI
Knee	1.01	0.87–1.17	1.09	0.83–1.43
Hand	1.04	0.90–1.20	0.91	0.72–1.16
Foot	0.96	0.82–1.13	1.12	0.75–1.65
Spine	1.07	0.94–1.21	0.94	0.75–1.18

RR=hazard risk ratio; CI=95% confidence interval.

Table V
Unadjusted association between smoking and OA (and severe OA) in knee, hand, foot, and spine (former vs never)

	Grades 2+		Grades 3+	
	RR	CI	RR	CI
Knee	1.12	0.96–1.31	1.24	0.93–1.64
Hand	1.14	0.98–1.33	1.07	0.84–1.38
Foot	1.06	0.89–1.25	1.16	0.77–1.75
Spine	1.18	1.04–1.35	1.01	0.80–1.28

RR=hazard risk ratio; CI=95% confidence interval.

Table VI
Unadjusted association between smoking and OA (and severe OA) in knee, hand, foot, and spine (current vs never)

	Grades 2+		Grades 3+	
	RR	CI	RR	CI
Knee	0.62*	0.46–0.83	0.58	0.32–1.04
Hand	0.71*	0.54–0.92	0.38*	0.22–0.67
Foot	0.63*	0.46–0.87	0.95	0.48–1.89
Spine	0.69*	0.54–0.88	0.67	0.43–1.04

**P*-value<0.05.
RR=hazard risk ratio; CI=95% confidence interval.

Table VII
Adjusted association between smoking and OA (and severe OA) in knee, hand, foot, and spine (current vs never)*

	Grades 2+		Grades 3+	
	RR	CI	RR	CI
Knee	0.97	0.71–1.31	1.08	0.58–2.00
Hand	0.99	0.75–1.31	0.60	0.33–1.08
Foot	1.16	0.83–1.63	1.48	0.71–3.08
Spine	0.86	0.67–1.11	0.84	0.53–1.32

*Adjusted for age, body mass index, gender, heredity, occupation, physical activity level, and presence of OA at any of the other three sites.
RR=hazard risk ratio; CI=95% confidence interval.

as: 1–19, 20–39, and 40+. Resulting values, notably smokers who developed OA, were too small for a meaningful analysis, necessitating the collapsing of the latter two categories (20+/day). The dosage data, available only from those participants completing four or more histories, afforded the ability to examine unadjusted OA. *Although all point estimates were non-significant*, the risk estimates among heavy smokers were lower (more protective) than those among light smokers at all four sites examined (Table VIII). However, none of the four sites displayed significance for a trend in the dose–response relationship.

Discussion

This study explored the association between smoking and its possible influence on incident OA at four different sites: knee, hand, foot, and cervical spine. This investigation produced adjusted point estimates suggestive of no association between smoking and OA. As additional research is conducted in the field of OA, it is important to have a commensurate increase in the understanding of which factors may play an influential role in predicting those who develop the disease and those who do not. If the current study had presented smoking to be strongly associated with OA, albeit inversely, then subsequent OA research would lend a greater level of concern to the ability to control for smoking status.

A central concern that was particularly germane for this epidemiological investigation was the ascertainment of smoking exposure. The basis on which a given individual should be considered exposed was carefully considered. The decision involved defining the measurement of an individual's smoking exposure history that was relevant to the etiology of OA. Such a decision relies heavily on the understanding of the OA disease process, as well as any purported induction period involved. Clearly the current level of understanding of the etiology of OA, or lack thereof, has placed limits on the ability to do such. For example, when evaluating the relationship that smoking shares with lung cancer, the total duration and dose of smoking is considered etiologically important. However, when examining smoking and its influence on myocardial infarction, the current smoking behavior is the most relevant exposure[17]. Due to the paucity of smoking-OA studies, the most appropriate time window for the evaluation of smoking and its potential influence on OA is unclear. From our analyses, it is apparent the smoking exposure classification of ever/never utilizes information spanning too wide a period. This categorization scheme classifies individuals as smokers even if they had only a brief exposure early in life. In terms of teasing out the role smoking may play in OA, casting such a wide net did not afford the ability to make any valid inferences on the relationship. Given the dearth of OA studies examining smoking relative to other putative factors, our approach was to evaluate the data from various time windows of smoking exposure to gain information about the period that appears most relevant to OA.

Our findings do not confirm many results from previously published point estimates quantifying this relationship. The Framingham Osteoarthritis Study (FOS) noted an adjusted estimate of 0.78 (*P*-value <0.05) for knee OA. Controlling for the same factors of age, gender, and BMI, the current COS study indicated a knee OA point estimate, 0.83 (*P*-value >0.05, data not shown). It should be noted that the FOS exposure variable was smoking status at examination 1, while the OA assessment was subsequently conducted approximately 20 years later during the 18th examination. Information was unavailable to determine whether smoking status at the first visit continued at the same rate until radiological assessment of the knee at the 18th visit. Alternatively, the present study utilized current smoking

Table VIII
Unadjusted association between smoking and OA (grades 2+) by dose in knee, hand, foot, and spine (current vs never)*

	Knee		Hand		Foot		Spine	
	RR	CI	RR	CI	RR	CI	RR	CI
Never smokers	1.00	—	1.00	—	1.00	—	1.00	—
1–19/day	0.20	0.03–1.44	1.21	0.47–3.08	1.02	0.37–2.86	0.78	0.42–1.44
20+/day	0.15	0.02–1.10	0.81	0.29–2.27	0.18	0.02–1.29	0.67	0.37–1.22

*Average number of cigarettes smoked per day.
RR=hazard risk ratio; CI=95% confidence interval.

status queried prior to the OA diagnosis. Our results suggest a less protective effect by smoking for severe knee OA compared with the FOS findings (RR=0.82; *P*-value >0.05 and OR=0.71; *P*-value <0.05, respectively). The aforementioned estimates were adjusted for age, sex, and weight. The disparity in the point estimates between the COS and FOS data may be partially attributable to the aforementioned differences in the timing of exposure assessment. A portion of the difference may be explained by the current study's capability to exclude prevalent disease, thus considering only incident cases. The discrepancy cannot be explained by methods in X-ray attainment (for knee both used anteroposterior, weight-bearing), nor most likely by social class. COS and FOS study samples drew upon a predominantly white, middle-class population. In concurrence with our unadjusted dose–response findings, four of the five previously published studies examining the smoking–OA relationship[3–6] reported results confirming or suggesting a dose response.

This study has added to the body of OA literature through its contribution in four areas.

(1) Previous studies reporting results for this relationship were analysed using either cross-sectional or case-control epidemiological designs. The current prospective study has served to generate point estimates that benefit from the enhanced power of the cohort design. Prevalent OA cases at study entry were excluded from our analyses, allowing the ability to clearly establish the temporal relationship between smoking behavior (exposure) and *subsequent* OA (outcome). Previous studies have been unable to firmly establish the timing sequence between smoking and OA. For example, in previously published studies if an individual developed OA, then subsequently ceased smoking (possibly due to seeking a healthier life-style since developing OA), an investigator would not be able to discern which came first: the smoke-free behavior or the development of OA. This particular scenario would serve to artificially elevate the association between non-smokers and OA. The ability of the current study to make such a temporal distinction has afforded a clearer view of the smoking–OA relationship.

(2) Additionally, this study has provided an initial glimpse at the role smoking may play in OA of the foot and cervical spine. The venerable National Health and Nutrition Examination Survey[6], the Framingham Osteoarthritis Study[3], as well as the 1999 study by Sandmark *et al.*[5] added valuable insight to the smoking–knee OA relationship. The 1993 Chingford Study reported results for both the knee and the hand[4]. A review of the literature indicate that this is the first study to examine the smoking–OA relationship for the foot or cervical spine. In terms of ultimately determining causality, the ability to quantify the relationship at various sites will allow an increased understanding of what mechanisms may, or may not, be at play.

(3) This prospective study utilized a sample (*N*=2505) that was 77% larger than samples previously analysed for evaluating this association. If smoking, in reality, shares a very modest association with OA, it would take a substantial-sized sample to have the statistical power to detect such a relationship. (4) Lastly, this study has contributed by quantifying point estimates for the smoking–OA relationship for the knee and hand, thus providing a basis of comparison with previously published results in other investigations.

In evaluating these study results, it is important to consider whether study participants with any OA-risk factor *combination* (e.g. has OA and a history of smoking) were more or less likely to be selected than were others. One venue in which this type of selection bias can occur is when study recruits are aware of the details of the hypotheses under investigation. This is unlikely to have occurred for the Clearwater Osteoarthritis Study. Prospective participants were informed this would be a large-scale, longitudinal study attempting to identify various factors that may play a role in the development and progression of OA. However, participants were blinded as to the details regarding the hypotheses to be tested, including which specific risk factors were to be examined. The etiology of OA is largely an enigma among the scientific community. It can be assumed that the general public may have even less insight as to the factors that may be associated with OA, hence minimizing the likelihood of this form of selection bias.

It should be noted that the four primary hypotheses evaluated smoking and its relationship with knee, hand, foot, and cervical spine. A conventional level of alpha of 0.05 was selected a priori for the determination of the statistical significance of the resulting point estimate. The reader should be reminded that a significance level is a function of, among other factors, the number of hypotheses under investigation. If four separate analyses are conducted for each site (knee, hand, foot, and cervical spine), the probability of one or more significant results is 0.20 (4×0.05), under alpha=0.05. As suggested by Bonferroni[18], appropriate compensation for multiple comparisons is to decrease the alpha level by dividing it by the number of hypotheses studied. Thus, if we consider (four sites)×(two types of OA: 2+ and 3+), we reduce our acceptance level for any given hypothesis test precipitously to alpha=0.006. This is not an inherent limitation to this specific study, or to numerous other similarly conducted studies, but rather a fair caution to the reader to interpret these findings in a conservative, suitable manner. As this

study evaluates smoking as the primary exposure, competing causes of mortality were considered as a phenomenon possibly influencing the results. To introduce bias into these findings, the death rate of smokers *with* OA would need to be significantly different than the death rate of smokers *without* OA. The death rate among smokers *with* OA (4.7%) was lower than the death rate among smokers *without* OA (6.9%). However, it is suggested that this difference would not strongly influence the findings from this study.

No clear biologic explanation supports an inverse relationship between smoking and OA. However, theories have suggested that smoking may affect the cartilage directly, or when considering knee OA, it may act in an indirect manner by conveying protection through making the subchondral bone more deformable to impact loads[19]. Subsequent epidemiological studies employing the power of the cohort design will complement the results of this study. While these findings corroborate previous studies indicating no association between smoking and OA, anecdotal evidence warrants investigation into the role that cigarette smoking may play in the symptomatology of OA. Future research focusing on the inverse relationship between OA and osteoporosis (known to be positively associated with smoking) may serve to enhance our understanding of the mechanisms affecting the etiology of OA.

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