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Relationship between cigarette smoking and radiographic knee osteoarthritis in Chinese population: a cross-sectional study

Yi Zhang · Chao Zeng · Hui Li · Tuo Yang · Zhen-han Deng · Ye Yang · Xiang Ding · Dong-xing Xie · Yi-lun Wang · Guang-hua Lei

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Abstract The purpose of this paper was to estimate the cross-sectional association between cigarette smoking and radiographic knee Osteoarthritis (OA) in Chinese population. A total of 3,789 subjects (1,796 females and 1,993 males) participated in this study. A subject was diagnosed with radiographic knee OA if Kellgren–Lawrence (K–L) grade ≥2 in at least one leg. The smoking status was classified into four levels based on the daily smoking habit: (1) 0/day; (2) 1–10/day; (3) 11–20/day; and (4) >20/day. Linear trend and multivariable logistic regression were conducted for statistical analysis. The prevalence of radiographic knee OA was 28.4 % among the subjects of this study. An inverse association was observed between cigarette smoking and radiographic knee OA in the linear trend test. Such association remained valid after adjusting the factors of age, gender, body mass index, betel quilt chewing status, physical activity, alcohol drinking status, mean total energy intake and educational level in the multivariable logistic regression. This study suggested a negative association between cigarette smoking and radiographic knee OA in the Chinese population. The findings of this study need to be confirmed by further prospective research.

Keywords Radiographic knee osteoarthritis · Cigarette smoking · Cross-sectional · Association

Yi Zhang and Chao Zeng have contributed equally to this article.

Y. Zhang · C. Zeng · H. Li · T. Yang · Z. Deng · Y. Yang · X. Ding · D. Xie · Y. Wang · G. Lei (✉)
Department of Orthopaedics, Xiangya Hospital, Central South University, #87 Xiangya Road, Changsha 410008, Hunan Province, China
e-mail: lgh9640@sina.cn

Introduction

Osteoarthritis (OA) is a multifactorial, age-dependent, degenerative disease characterized by articular cartilage loss, osteophyte formation and subchondral bony sclerosis. The etiology of OA is not completely clear. A variety of factors are well known to be associated with the development of OA, such as age, sex, body mass index (BMI), occupational exposure, physical activity and the genetic factor [1, 2]. OA of the knee is a chronic disease with a high prevalence among the elderly. Its symptoms are expressed as the increasing disabling and painful situation [3, 4]. In view of the shortage of prevention and early treatment for OA, arthroplasty is the primary therapy for terminal OA patients, which accounts for a huge healthcare burden [5–7]. Therefore, an in-depth understanding of the pathogenesis and risk of OA will be greatly helpful for its early prevention.

A report from Global Adult Tobacco Survey (GATS) showed that the overall cigarette smoking rate of the Chinese population (>15 years old) is 28.1 %, including 52.9 % of the male and 2.4 % of the female [8]. Cigarette smoking is commonly recognized as a risk factor for many well-known chronic diseases, such as diabetes, cancer and cardiovascular diseases [9]. It is also believed to be related to some chronic musculoskeletal conditions such as rheumatoid arthritis [10–12], low back pain [13, 14] and degenerative disc disease [15]. However, on the other hand, an inverse association was observed between cigarette smoking and Parkinson's disease [16], ulcerative colitis [17] as well as Alzheimer's disease [18]. The Framingham study, a prospective cohort study established in 1948 to explore cardiovascular disease, is perhaps one of the earliest studies that investigated the OA–smoking relationship [19]. This study speculated that cigarette smoking may be protective

for OA while the reason remained unknown. Up to nowadays, the relationship between cigarette smoking and OA is still controversial and inconclusive [20–27].

As far as we know, a large number of studies have examined the association between OA and smoking, but most of them regarded cigarette smoking as the secondary exposure (i.e., a covariate or confounding factor). Only in case–control studies where control samples were recruited from a hospital setting (e.g., a cardiovascular clinic), cigarette smoking was found to be inversely associated with OA since the control group had a higher exposure to smoking [28]. In addition, only a small number of related researches have been conducted for the Chinese population, most of which regarded cigarette smoking as the secondary exposure as well. There is one exception: a large-sample prospective cohort study conducted by Leung [29] showed that there was a negative association between cigarette smoking and total knee replacement for severe osteoarthritis with a clear dose–response relationship among Singaporean Chinese, rather than Chinese from Mainland China. From the literature research above, it seems that the previous studies are subject to many limitations. In this project, a cross-sectional study, which regarded cigarette smoking as the primary exposure with adjustment of major confounding factors, was performed on a sample of Chinese participants recruited from Hunan province of China. All subjects were apparently healthy and selected from the general public in order to minimize the selection bias of hospital-based case–control studies. The purpose of this study was to clarify the association between cigarette smoking and radiographic knee OA in Mainland China and to test the hypothesis that cigarette smoking is negatively associated with radiographic knee OA.

Materials and methods

Sample

The Xiangya Hospital Health Management Center Study (XYHMCS) included a cohort consisting mainly of apparently healthy Chinese people from general public for health screening. Routine health checkups are very common in China, because the Chinese government encourages people to take periodic medical examinations. Registered nurses interviewed all participants during the examination using a standard questionnaire, with the purpose to collect information on demographic characteristics and health-related habits. Subjects were selected according to the following inclusion criteria: (1) aged 40 years old or above; (2) undergoing weight-bearing bilateral anteroposterior radiography of the knee; (3) availability of the health-related habit information; and (4) availability of all basic characteristics, including age, gender, BMI, physical activity, betel quilt chewing status, alcohol drinking status, mean total energy intake, educational level and smoking status, etc. Initially, a total of 7,343 participants who underwent routine checkups including weight-bearing bilateral anteroposterior radiography of the knee at the Department of Health Examination Center Xiangya Hospital, Central South University in Changsha, Hunan Province, China, from October 2013 to May 2014 were recruited. Then, individuals with other joint diseases with radiographic evidence, such as osteochondroma or old fracture ($n = 65$), or with missing data of certain characteristics or physical examinations, such as BMI and waistline ($n = 201$), or younger than 40 years old ($n = 704$), were excluded. The overall response rate was 59.5 %, with 2,584 participants not reporting their health-related habit information. As shown in Table 1, there was no significant difference between participants who reported and who did not report their health-related habit information in terms of the prevalence of radiographic knee OA and the characteristics including age, sex and BMI. This study was approved by the ethics committee of Xiangya Hospital of Central South University. All participants gave written informed consent at the time of recruitment.

Table 1 Characteristics of participants who were included versus non-participants who refused to report health-related behavior

Variable	Participants ($n = 3,789$)	Non-participants ($n = 2,584$)	$P^{\#}$
Knee OA (%)	28.4	29.8	0.214
Age (years)	53.0 (7.7)	53.5 (9.3)	0.909
Male (%)	52.6	50.3	0.068
BMI (kg/m^2)	24.5 (3.1)	24.5 (3.0)	0.600
Waistline (cm)	83.1 (8.8)	83.1 (8.6)	0.944

Data are mean (standard deviation), *n* number

$^{\#}$ $P < 0.05$ was considered to be statistically significant

Radiographic assessment of knee OA

All subjects had a weight-bearing bilateral anteroposterior radiograph of the knees. All radiographs were taken by the same technician using the same equipment and were independently assessed by two senior orthopedists who were blinded to the subjects' clinical symptoms. Subjects with inconsistent opinions were recalled after the survey and resolved by discussion. Each radiograph was graded from 0 to 4 for OA based on the ordinal criteria of Kellgren and Lawrence [30]. 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. Radiographic knee OA was defined as Kellgren and Lawrence grade ≥2 in one or both knees.

Information on demographic characteristics and health-related habits

The cigarette smoking status was evaluated by two questions "Do you smoke Y/N?" and "How many cigarettes do you smoke per day?" This study classified the quantity of cigarettes smoked per day into four groups with regarding cigarette smoking as the primary exposure: group 1: 0/day; group 2: 1–10/day; group 3: 11–20/day; and group 4: >20/day. The potential confounding factors were age, gender, BMI, betel quilt chewing status, physical activity, alcohol drinking status, mean total energy intake and educational level. The weight and height of each subject were measured, respectively, to calculate the BMI. Participants were requested to answer their average frequency of physical activity (never, one to two times per week, three to four times per week, five times and above per week.) and the average duration of physical activity (within half an hour, half an hour to one hour, one to two hours, more than two hours). The status of betel quilt chewing was also inquired by the question "Do you chew betel nut Y/N?" and "How many betel nut do you chew per day?"

Assessment of the state of dietary

A semiquantitative food frequency questionnaire (SFFQ) was specially designed for the population in Hunan Province of China to estimate the dietary intake of participants. This SFFQ contained 63 food items that were generally consumed in Hunan Province. Participants were requested to answer the frequency (never, once per month, two to three times per month, one to three times per week, four to five times per week, once per day, twice per day, or three times and above per day) they consumed each food item and the average amount they consumed for each time (<100, 100–200, 201–300, 301–400, 401–500, and more than 500 g) in the past 1 year. Color pictures showing food samples with labeled weights were provided in order to help participants make choices more easily and accurately. The total energy intake was calculated based on this SFFQ.

Statistical analysis

The quantitative data are expressed as mean ± standard deviation, and the qualitative data are expressed in percentage. The status of cigarette smoking was divided into four parts: 0/day, 1–10/day, 11–20/day and >20/day. Differences in continuous data were evaluated by the one-way classification ANOVA (normally distributed data) or the Kruskal–Wallis H test (non-normally distributed data), while differences in qualitative data were assessed by the Chi-square test. The relationship between OA and cigarette smoking was determined by liner trend Chi-square test. Multivariable logistic regression was also used to evaluate the association between cigarette smoking and OA. Association between each status of cigarette smoking and OA was adjusted for the following variables: age, gender, BMI, betel quilt chewing status, physical activity, alcohol drinking status, mean total energy intake and educational level. Test for linear trend was conducted by putting status of cigarette smoking as ranked data into the logistic regression model. All statistical analyses were also performed in subgroups stratified by sex. Data analyses were performed using SPSS 17.0; a P value <0.05 was considered to be statistically significant.

Result

In this cross-sectional study, the overall prevalence of radiographic knee OA was 28.4 % which applies only to this cohort based on the radiographic result. The characteristics of subjects according to the cigarette smoking status are briefly described in Table 2. For the Chinese population, subjects with the highest level of smoking status were more likely to be younger, male, alcohol drinker, betel quilt chewer, having higher BMI, taking less physical activity and having higher intake of total energy. The characteristics of smokers of the Chinese population are quite different from those in Western countries (lower social class, lower BMI, lower educational level, etc.).

An inverse association between cigarette smoking status and radiographic knee OA ($P = 0.019$) was suggested by the univariate analysis, and such association was confirmed by the multivariable logistic regression, which was adjusted by age, gender, BMI, betel quilt chewing status, physical activity, alcohol drinking status, mean total energy intake and educational level. Table 3 shows that the multivariable-adjusted ORs (95% CI) of radiographic knee OA across cigarette smoking status were 1, 0.91 (95% CI 0.68–1.21), 0.70 (95% CI 0.52–0.94) and 0.75 (95% CI 0.55–1.03), respectively, and P for trend was 0.010. When combining all the three smoking subcategories in a separate model on smoker (all categories) as compared to non-smoker after adjusted by the same variables, the negative relationship between smoking and radiographic knee OA still exists (OR 0.78; 95% CI 0.64–0.96; $P = 0.016$).

Discussion

The result showed that the overall prevalence of radiographic knee OA was 28.4 % in the study population. This

Table 2 Characteristics among 3,789 participants according to cigarette smoking status

Characteristics	Cigarette smoking status			
	0/day	1–10/day	11–20/day	>20/day
Participants (*n*)	2,930	289	312	258
Knee OA (%)	29.1	29.8	23.7	24.0
Age (years)	53.2	53.0	52.2	51.1
Male (%)	40.3	90.3	96.5	96.5
BMI (kg/m^2)	24.4 (3.1)	24.4 (3.3)	24.5 (3.2)	25.6 (3.3)
Alcohol drinking (%)	28.4	54.7	56.1	62.0
Betel quilt chewing (%)	2.1	8.7	13.5	10.1
Mean total energy intake (kcal/d)	1,651.9 (800.0)	1,789.1 (722.0)	1,934.4 (965.9)	1,926.3 (754.8)
Activity level (h/d)	0.3 (0.5)	0.3 (0.5)	0.3 (0.5)	0.3 (0.5)
High school background or above (%)	45.1	55.0	42.9	53.5

Data are mean (standard deviation), *n* number

Table 3 Multivariable-adjusted association of cigarette smoking and radiographic knee OA adjusted by age, gender, BMI, activity level, alcohol drinking status, betel quilt chewing status, mean total energy intake and educational level ($n = 3{,}789$)

Variable	Adjusted odds ratio	95 % CI	*P* value
Age	1.08	1.07–1.09	0.000
Gender	0.79	0.66–0.94	0.009
Smoking (0/day)	1.00	Reference	–
Smoking (1–10/day)	0.91	0.68–1.21	0.499
Smoking (11–20/day)	0.70	0.52–0.94	0.018
Smoking (>20/day)	0.75	0.55–1.03	0.074
BMI	1.39	1.20–1.62	0.000
Activity level	1.09	0.95–1.25	0.227
Alcohol drinking	1.07	0.90–1.28	0.429
Betel quilt chewing	1.03	0.69–1.54	0.880
Mean total energy intake	1.00	1.00–1.00	0.513
Educational level	1.10	0.95–1.28	0.214

study explored the association between cigarette smoking and radiographic knee OA, through univariate analysis and multivariable logistic regression with adjustment of age, gender, BMI, betel quilt chewing status, physical activity, alcohol drinking status, mean total energy intake and educational level. The findings confirmed the negative association.

To our knowledge, though many studies have explored the association between cigarette smoking and OA, a majority of them regarded cigarette smoking as the secondary exposure (i.e., a covariate or confounding factor), and very few data revealed this association in the Chinese population. This study suggested that the primary exposure of cigarette smoking was negatively associated with radiographic knee OA in the Chinese population, which was consistent with some previous researches [29, 40–43]. Two recent studies, including a large-sample prospective cohort study conducted by Mnatzaganian et al. [40, 41], considered total joint replacement (TJR) as a surrogate indicator of severe OA and demonstrated a strong inverse dose–response relationship between the duration of cigarette smoking and the risk of TJR. Another important large-sample prospective cohort study conducted by Leung [29] reported a very strong dose-dependent association between the increased duration and dosage of cigarette smoking and the decreased risk of total knee replacement (TKR) among active smokers. These studies provide important support to our findings.

Several Chinese epidemiological studies have explored the prevalence and risk factors for knee OA with regarding cigarette smoking as the secondary exposure. This may be the major reason why some of these studies did not reveal the negative OA–smoking association. Jiang et al. [31] believed that cigarette smoking might be a risk factor for knee OA in rural dwellers but not in urban residents based on a study in Heilongjiang Province. The difference between rural dwellers and urban residents may due to the inadequate control of confounding factors, such as air pollution, air ventilations of indoor places in rural China and second-hand smoking. Furthermore, the previous studies only classified subjects into active smokers, ex-smokers and non-smokers, which might be the cause of their limitations. Zeng et al. [32] supposed that cigarette smoking was not significantly related to knee OA based on a study in Taiyuan. This study only reported the obscure smoking history without description of the data collection method. A survey conducted in Pudong New District of Shanggang Community also showed that cigarette smoking was not significantly associated with the prevalence of knee OA [33]. A research covering six administration regions of China revealed that cigarette smoking was not the common risk factor for knee OA and the main risk factor for OA varied for different cities [34]. These two studies only analyzed the smoking status as qualitative data. In addition,

those researches did not compare the current and former smokers since Leung et al. [29] have nicely demonstrated in a prospective cohort study among Singapore Chinese that the negative association between smoking and severe OA requiring TKR quickly lost when subjects quit smoking. Moreover, although some epidemiological studies have investigated the prevalence of knee OA in some regions of China [35–39], this topic is still inconclusive.

There are also some epidemiological studies regarding cigarette smoking as the primary exposure. A large-sample prospective cohort study conducted by Jarvholm [42] indicated that smoking might reduce the risk of hip OA in men, but the effect was weak when compared to the BMI and age. Samanta [43] suggested that there was a negative association between cigarette smoking and large joint OA, but on the contrary, Wilder [20] confirmed clinically that cigarette smoking was not a protective factor for radiographic OA in knee, hand, foot and cervical spine. The Chingford study also found no clear evidence on the protective effect of cigarette smoking for hand and knee OA in women [44]. Vingard [45] revealed that smokers were in face of 1.54 times of risk of hip arthrosis than non-smokers. Moreover, the Chuvashian community-based study showed that there was no association between cigarette smoking and hand OA [46]. From what have been discussed above, the previous researches involved many sites of OA, such as knee, hip, hand, foot and spine, but consensus could not be achieved with respect to the smoking–OA association, and further studies are needed. The differences in etiology for OA at different body sites may be the main reason why the negative association was not shown when OA was analyzed as a whole. A meta-analysis performed by Hui clearly demonstrated that the negative association only existed in knee OA, rather than other sites, such as hip, hand and spine. In addition, the statistically significant inverse association was only reported in the case–control study, but not in the cross-sectional or cohort study [28].

OA is characterized by articular cartilage loss. At the experimental level, Gullahorn and Ying et al. [47–49] confirmed that nicotine was beneficial to the metabolism of chondrocytes. At the same time, some investigators demonstrated that nicotine might destroy the function of chondrocytes from intervertebral disk but not from knee articular cartilage [50–53]. A meta-analysis exploring the OA–smoking relationship suggested that the association between cigarette smoking and MRI cartilage loss was positive in both OA patients and normal subjects, but the studies of radiographic OA progression suggested a negative association [54]. Generally speaking, the research outcomes differed at the level of experiment, MRI and radiology.

The strengths of this cross-sectional study are mainly reflected from the following aspects: First of all, this is the first study aiming at the radiographic knee OA–smoking relationship in Chinese mainland population with regarding cigarette smoking as the primary exposure; the effects of confounding factors can be adjusted in the multivariable model. In this study, a considerable number of potentially confounding factors, such as age, gender, BMI, betel quilt chewing status, physical activity, alcohol drinking status, mean total energy intake and educational level, were adjusted to improve the reliability of the results. Secondly, on the basis of the outcomes of major previous studies, the inverse association between cigarette smoking and radiographic knee OA has been proved. Thirdly, this study was conducted on a large sample (3,789 subjects), which may improve the accuracy of the results.

Limitations of the present study should also be acknowledged. Firstly, the cross-sectional design precludes causal relationships, and thus, further prospective studies should be undertaken to establish a causal association between cigarette smoking and knee OA. Secondly, this study only explored the association between cigarette smoking and radiographic knee OA without concerning symptoms. Some other studies reported that cigarette smoking might lead to more severe knee pain [27], but this study cannot verify this issue. Thirdly, the present study only concerned the subjects' current smoking status without inquiring their smoking history, thus the effect of change in smoking habit cannot be addressed. It is worth mentioning that past smoking history and passive smoking can probably influence the results of this study. Fourthly, this study only excluded the participants with old fracture according to the radiographic evidence, since injury is appositively associated with secondary OA. Fifthly, this study did not collect comorbidities, such as heart disease and cancer which are expected to be more common among smokers. Sixthly, participants who refused to report their health-related habit information, including smoking status, were excluded from this study. Last but not the least, the population of this study may represent a more affluent group of people in the general population who can afford health screening program.

In conclusion, this study suggested a negative association between cigarette smoking and radiographic knee OA in the Chinese population. The findings of this study need to be confirmed by further prospective research.

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