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Review

Association between smoking and risk of knee osteoarthritis: a systematic review and meta-analysis

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SUMMARY

Objective: To investigate the association between smoking and the risk for knee osteoarthritis (OA).
Design: Cohort, case–control, and cross-sectional studies were obtained from the Medline, Embase, and Web of Science databases. Estimates were calculated using a random-effects model. Subgroup analyses and meta-regression models were performed to investigate potential sources of heterogeneity. We further analyzed the dose–response relationship between cigarette consumption and risk of knee OA.
Results: Thirty-eight independent observational studies that included 481,744 participants were analyzed. Those who had ever smoked had a significantly decreased risk of developing knee OA relative to those who had never smoked (RR = 0.80; 95% CI 0.73–0.88). This was unaffected by study design, and the pooled relative risks (RRs) were 0.79 (95% CI, 0.65–0.96), 0.71 (95% CI, 0.61–0.84) and 0.83 (95% CI, 0.73–0.94) for cohort, case–control, and cross-sectional studies, respectively. Analysis of subgroups stratified by gender reduced the heterogeneity from moderate to low in both males and females. The lower risk for developing knee OA was more apparent in male smokers (RR = 0.69; 95% CI 0.58–0.80) than female smokers (RR = 0.89; 95% CI 0.77–1.02) and dose–response analysis showed a linear decrease in knee OA with increased cigarette consumption.
Conclusions: We found an inverse association between cigarette smoking and risk of knee OA, irrespective of study design. This association was more apparent in males. However, we have not demonstrated a causal relationship between smoking and OA, and further investigations are needed.

Introduction

Osteoarthritis (OA) is a common, complex, and painful disorder that, when severe, can limit joint motion. It is now recognized that angiogenesis and inflammation play an important role in the pathophysiology of OA[1]. In older people, the knee is one of the joints most frequently affected by OA[2,3]. With the rising problem of global population aging in both developed and developing regions, the prevalence of knee OA will continue to increase worldwide. It is, therefore, important to better understand the factors associated with the occurrence knee OA.

Smoking is known to be related to chronic diseases such as cancer[4], diabetes[5], and cardiovascular disease[6]. It is also a recognized risk factor for many chronic musculoskeletal disorders, including low back pain[7], rheumatoid arthritis[8], and degenerative disc disease[9]. However, cigarette consumption is inversely associated with Parkinson's disease[10] and ulcerative colitis[11]. The relationship between smoking and knee OA has not yet been definitively determined.

The results of previous studies investigating the association between smoking and knee OA have been variable. Some studies found that smoking protected against knee OA[12,13], while others failed to detect any significant association between them[14,15]. A meta-analysis conducted by Hui *et al.*[16] concluded that previous epidemiological studies are likely to be affected by selection bias, and thus the protective effect of smoking against OA may be false. However, their conclusion is based on analyses that included not only knee OA, but also hand, hip and spine OA. OA may develop by different mechanisms in different joints, and OA studies that combine the knee with other joints may underestimate the overall effect of smoking on the risk of knee OA. In addition, the study by Hui *et al.* was conducted in 2009 and included only 28 studies that analyzed knee OA. More recent studies may provide new information.

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At present, the association between smoking and risk of knee OA is unclear. Thus, the aims of this meta-analysis were: (1) to assess whether there is an association between smoking and the risk of knee OA, irrespective of study design; (2) to evaluate the relationship between smoking and knee OA after adjusting for potential confounding factors such as gender, smoking status, and definition of OA; and (3) to determine whether there is a linear dose–response relationship between cigarette consumption and the risk of knee OA.

Materials and methods

Literature search and inclusion criteria

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[17]. We searched the Medline (via PubMed, 1966 to April 20, 2016), Embase (1950 to April 20, 2016), and Web of Science (1970 to April 20, 2016) databases using the MeSH terms "knee", "osteoarthritis", "smoking", and the individual corresponding free terms (Supplementary File 1). Studies were restricted to those published in English and those using human subjects. The articles resulting from these searches and the relevant references cited in those articles were also reviewed.

Only those studies containing enough information to estimate the relative risk (RR) of knee OA associated with smoking were included in this meta-analysis. To get comprehensive information, all types of observational studies that were published as original articles, including cohort studies, case–control studies, and cross-sectional studies[18], were included. If several publications reported on the same population or subpopulation, we used the data from the most informative reports.

Data extraction

Data were independently extracted by two investigators and checked by the other authors. The concordance rate between the two investigators reached 87.5%. Discrepancies were resolved by consensus. The following information was extracted from the included publications: study design, name of first author, year, country, gender, number of patients, definition of OA, smoking status, and potential confounders. Odds ratios (ORs), RRs or hazard ratios (HRs), and their respective 95% confidence intervals (CIs) were either retrieved directly from the article or calculated from available data. In all cases, we used the most comprehensive post-adjustment risk estimates available.

Patients were classified into three smoking status categories: "ever", "current", or "former". Both "current" and "former" smokers were included in the "ever" category. Knee OA was classified as radiographic OA, symptomatic OA, severe OA, and other. Radiographs of the knees were evaluated using the Kellgren–Lawrence (KL) scoring system[19] (range 0–4). Radiographic OA was defined as having a KL grade $\geq$2 in one or both knees; symptomatic OA was having at least one knee with a KL grade $\geq$2 as well as knee pain; severe OA was defined as having a KL grade $\geq$3 or total knee arthroplasty (TKA) in one or both knees. Setting was defined according to the source population of the control group. If controls were selected from patients in a hospital setting, then the study was considered to be hospital-based; otherwise, it was classified as community-based[16].

As there is no standardized quality scoring system for both longitudinal and cross-sectional studies, quality scoring of the studies was not performed. However, we performed subgroup and sensitivity analyses to examine the effects of different quality aspects of the studies on our estimate of the association between smoking and risk of knee OA.

Statistical analysis

RRs with 95% CIs were used to present the relationship between smoking and the risk of knee OA except in case–control studies, from which ORs were used as estimates of the RRs[20]. Because significant heterogeneity was anticipated across studies, we used a random-effects model to calculate estimates except where otherwise specified. The distribution of RRs and 95% CIs was represented using a forest plot. The Cochran Q test was used to estimate the *P* value for heterogeneity. The I^2 statistic was calculated to assess heterogeneity across studies; studies with I^2 values of <25%, 25–50%, 50–75%, and >75% were considered to have no, low, moderate, and high heterogeneity, respectively[21].

Both subgroup analyses and meta-regression analyses were performed to investigate potential sources of heterogeneity. In the meta-regression analysis, the log values of RRs were used as dependent variables and study-level variables, including smoking assessed as a primary risk factor (yes/no), adjusted outcomes (yes/no), and study design (cohort, case–control, and cross-sectional study), were used as independent variables.

The dose–response analysis was done according to the method described by Greenland and Longnecker[22]. This method requires studies that present the total number of cases, person-years and dose of smoking, and the corresponding RRs with 95% CIs for at least three quantitative exposure categories. We used the mean value of the lower and upper boundaries of each category as the assigned dose. If the highest category was open-ended, 60 cigarettes per day was considered the maximum dose (for example, one study reported >40 cigarettes per day as an open range; we considered 50 cigarettes per day to be the smoking dose in this category). The dose–response analysis was conducted using linear models with dose increments of 10 cigarettes per day.

Publication bias was assessed with funnel plots and a combination of the Begg's[23] and Egger's[24] tests. We used STATA, version

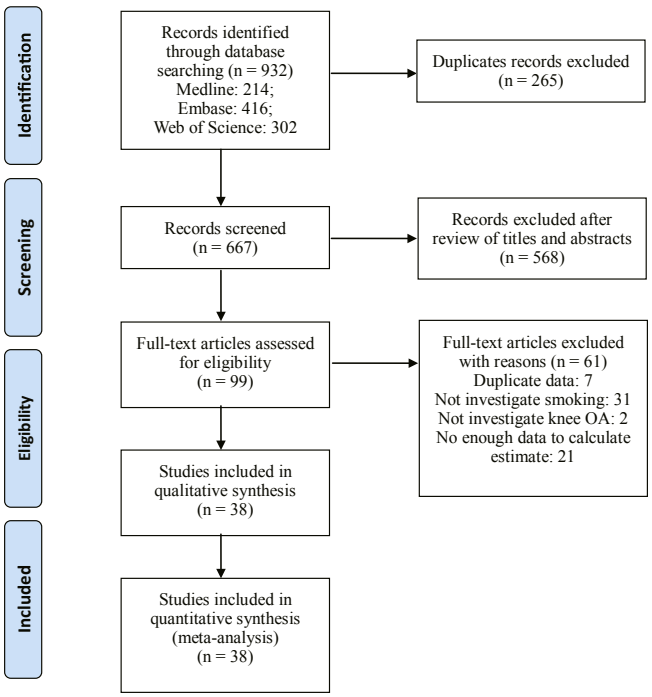

Fig. 1. PRISMA flow-chart illustrating the results of the search strategy.