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The Smoking Paradox in the Development of Psoriatic Arthritis among Psoriasis Patients – A Population-Based Study

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Abstract

Objectives—Smoking is associated with an increased risk of psoriatic arthritis (PsA) in the general population, but not among psoriasis patients. We sought to clarify the possible methodologic mechanisms behind this paradox.

Methods—Using 1995–2015 data from The Health Improvement Network, we performed survival analysis to examine the association between smoking and incident PsA in the general population and among psoriasis patients. We clarified the paradox using mediation analysis and conducted bias sensitivity analyses to evaluate the potential impact of index event bias and quantify its magnitude from uncontrolled/unmeasured confounders.

Results—Of 6.65 million subjects without PsA at baseline, 225,213 participants had psoriasis and 7,057 developed incident PsA. Smoking was associated with an increased risk of PsA in the general population (HR, 1.27; 95% CI:1.19to1.36), but with a decreased risk among psoriasis patients (HR 0.91; 95% CI:0.84to0.99). Mediation analysis showed that the effect of smoking on the risk of PsA was mediated almost entirely through its effect on psoriasis. Bias sensitivity analyses indicated that even when the relation of uncontrolled confounders to either smoking or

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PsA was modest (both HRs = ~1.5), it could reverse the biased effect of smoking among psoriasis patients (HR=0.9).

Conclusions—In this large cohort representative of the UK general population, smoking was positively associated with PsA risk in the general population, but negatively associated among psoriasis patients. Conditioning on a causal intermediate variable (psoriasis) may even reverse the association between smoking and PsA, potentially explaining the smoking paradox for the risk of PsA among psoriasis patients.

Keywords

Smoking; Psoriatic Arthritis; Epidemiology

INTRODUCTION

Psoriasis (PsO) is a chronic inflammatory and autoimmune skin disease that affects over 5 million Americans,[1] and psoriatic arthritis (PsA) is a progressive and often destructive joint disease that has been linked to premature cardiovascular (CV) events and mortality.[2–4] In most patients with PsA, symptoms do not appear until years after the onset of cutaneous psoriasis.[5] The high risk of PsA among psoriasis patients provides a unique opportunity to identify and prevent this serious arthropathy and its complications. However, few modifiable risk factors for PsA have been established among patients with psoriasis.

The evidence for smoking as a risk factor for PsA among psoriasis patients remains limited and contradictory. Several studies have shown that smoking is associated with an increased risk of psoriasis and PsA among the general population.[6,7] Yet, smoking was found to be inversely[8] or weakly associated with PsA in analyses restricted to patients with psoriasis[6] (i.e., smoking paradox). Given these conflicting data on this important risk factor on the risk of PsA, we sought to examine these associations in a general population context compared with that in psoriasis patients to clarify the methodological reason behind this potential smoking paradox.

The goals of our study were to examine the smoking and PsA paradox among psoriasis patients in a general population context, and clarify the possible methodologic mechanisms behind the paradox. We first estimated the effect of smoking on risk of PsA in the general population and then among psoriasis patients. We then clarified the underlying methodologic mechanisms using a unified mediation analysis and bias analysis.

METHODS

Study Population

Details of the Health Improvement Network (THIN) have been published previously.[9,10] Briefly, THIN is a database of computerized medical records from approximately 648 general care practices (GP) in the United Kingdom (UK). Most patients in the UK are registered with a general practitioner through the National Health Service. THIN is a population-based cohort of the general population representative of the UK population seen by general practitioners.[9] The database included anonymized health care data from

approximately 11 million patients, with information on patient demographics, diagnoses including details of the GP visits and specialists' referrals and hospital admissions, and additional health information such as height and weight, and lifestyle factors such as smoking and alcohol intake. Moreover, Read codes were used to specify medical diagnoses. For this current analysis, 7,247,774 million people from THIN population met our eligibility criteria which included men and women age 20 to 89 years, enrolled in THIN for at least 12 months between 1/1/1995 and 5/31/2015, free of PsA before study entry, and included both prevalent and incident psoriasis patients. Of these, 596,475 people (8.2%) had missing information on smoking; thus we included a subset of 6,651,299 participants for the current study. The Institutional Review Board at the University of Massachusetts Medical School and Boston University School of Medicine approved this study. We followed STROBE reporting guidelines for observational studies.

Ascertainment of psoriasis and PsA

We used THIN Read codes to define psoriasis and PsA. Validity of THIN Read codes for psoriasis and PsA has been previously reported.[10,11] Specifically, Read codes for psoriasis and PsA in THIN showed a positive predictive value (PPV) of 90% and 85% of clinical confirmation, respectively. Also, we performed sensitivity analyses where a person is defined as having PsA if there is a Read diagnostic plus use of disease-modifying antirheumatic drugs (DMARD) within one year of the Read code. However, the main definition remains Read code only, as DMARD data definitions only slightly improved the specificity for the diagnosis, but at the cost of a dramatic reduction in sensitivity.[12] Both psoriasis and PsA were classified as a dichotomous variable (Yes or No).

Assessment of Smoking and Covariates

Our exposure of interest was smoking recorded by physicians. Smoking status was divided into three categories: Non-, Ex-, or Current-Smoker. As a lifestyle exposure variable, smoking information in THIN has been collected prospectively and has been used successfully in previous analyses demonstrating anticipated relations of smoking to the risk of myocardial infarction[13], and the risk of lung cancer.[14] Occasionally, patients were coded in the database as a "nonsmoker" but also had a previous code for "smoker;" thus, would be recoded as an "Ex-Smoker." Covariates included age, sex, body mass index (BMI), alcohol and history of trauma at baseline.[12,13,15]

Statistical Analysis

Smoking and the Risk of PsA in the General Population vs Among Psoriasis Patients—First, we calculated the person-time of follow-up and incidence rates of PsA by smoking status. The study entry date in the general population was the date the subject free of PsA met our inclusion criteria for age, study calendar time, 12-month enrollment criteria and the first recorded smoking status, whichever comes last. Follow-up ended when participants developed PsA, became 90 years of age, died, transferred out of the GP practice, or the administrative end of follow-up (05/31/2015). Thus, for the purpose of studying incident PsA, patients did not have a Read code for PsA before the start of follow-up, and had a Read code for PsA during follow-up. We used Cox proportional hazards regression

models to estimate the hazard ratios for (HR) the effect of current or ex-smoking compared with never smoking on risk of incident PsA in the general population, adjusting for covariates. In addition to sex, covariates include age (continuous), BMI (continuous and defined as weight in kilograms divided by the square of height in meters), alcohol intake (current, ex, or non-drinker), and history of trauma (yes or no) from the most recent date before or on the follow-up start date. We took the same approach for our subgroup analysis to assess the association between smoking and risk of PsA restricted to patients with psoriasis. The psoriasis patients were included in the general population analysis. We also repeated the analyses using 5 sets of multiple imputation for missing BMI and alcohol data, where covariates for the multiple imputation model included age, alcohol, BMI, sex, trauma, smoking, PsA, and follow-up time.[16]

Assessing for Possible Misclassification of Smoking, Psoriasis, and Psoriatic Arthritis—To verify the robustness of the main study findings, we conducted several sensitivity analyses to determine the impact of possible misclassification. First, we used a different smoking classification to define smoking status, i.e., smoking was defined based on the last smoking status before diagnosis of PsA, as approximately 14% of individuals repeatedly quit then started smoking again over time. Second, we repeated the analysis by restricting study participants to those with incident psoriasis (instead of including both prevalent and incident psoriasis patients). Third, we used both Read code and DMARD use within one year of Readcode diagnosis to define PsA. Finally, we required the eligible population to be free of both PsA and psoriasis at start of follow-up (instead of being free of PsA only).

Methodologic Clarification of Smoking Paradox Using Mediation Analysis with Marginal Structural Models and Bias Sensitivity Analysis—Two major methodological reasons can explain this potential paradox: 1) the discrepancy between the intended research question and results obtained by the study design and analytic approach and 2) an index event bias (i.e., selection or collider bias), which is introduced when conditioning on a causal intermediate factor. Further details are provided in the Supplemental Methods.[18,22–25] To examine the role of the first explanation, we conducted mediation analysis using marginal structural models (MSM)[17] to partition the total effect of smoking on the risk of PsA into the indirect effect (i.e., the effect of smoking on the risk of PsA via psoriasis) and the direct effect (i.e., the effect of smoking on the risk of PsA independent of psoriasis) (See Supplemental Methods and Figure S1.a.). Then, to address the potential impact of index event bias and quantify its magnitude, we conducted a ‘bias sensitivity analysis’ as detailed in the Supplemental Methods.[25] Further rheumatic disease examples have also been reviewed in detail, including ‘obesity paradox.’[18]

All analyses were performed using SAS V9.3 (Raleigh, North Carolina, USA) and adjusted for sex, age, BMI, alcohol intake, and history of trauma at baseline.

RESULTS

We identified 225,213 participants with incident or prevalent psoriasis and 7,057 with incident PsA over a mean total of 7.0 years (median of 5.5 years) and 46,524,609 person-

years of followup. In the overall study population, the average age was 42 years, 53% were female, 13% were obese, and 62% were current drinkers at baseline. Approximately 56% participants were nonsmokers, 16% were ex-smokers, and 28% were current smokers. Among those with psoriasis, the average age was 45 years, 52% were female, 21% were obese, and 64% were current drinkers. Also, about 46% participants were non-smokers, 19% were ex-smokers, and 35% were current smokers (Table 1).

The Smoking Paradox for PsA

The associations between smoking and the risk of PsA in the general population and among psoriasis patients are shown in Table 2. The adjusted HR for the risk of incident PsA comparing current smoking with non-smoking in the general population was 1.27 (95% CI: 1.19 to 1.36), but the corresponding HR of the association among psoriasis patients was 0.91 (95% CI: 0.84 to 0.99), indicating a paradoxical phenomenon. Similar findings were also observed for ex-smokers. Results from multiple imputation of missing data were very similar (Table 2). Our results remained robust and inference did not change materially with the various sensitivity analyses, whether with using different definitions of smoking status, restricting the index group to people with incident psoriasis instead of including both incident and prevalent psoriasis, a more restrictive definition of PsA with DMARDS, or defining the overall study population to be free of both PsA and psoriasis at the start of follow-up (Appendix, Supplemental Results).

Clarification of the Smoking Paradox for PsA Using Mediation Analysis

Results from the mediation analysis to clarify the smoking paradox are shown in Table 3. The *total effect* or the net causal effect of current smoking compared with non-smokers on the risk of PsA in the general population was 1.27 (95%CI: 1.19 to 1.36), the *indirect effect* mediated through psoriasis status was 1.31 (95%CI: 1.26 to 1.37) and the *direct effect* independent of psoriasis status was 0.96 (95%CI: 0.93 to 1.00). The corresponding effect estimates for ex-smokers were 1.32 (1.22 to 1.43), 1.21 (95%CI: 1.17 to 1.26), and 1.08 (95%CI: 1.03 to 1.13), respectively.

Bias Sensitivity Analysis to determine Potential Impact of Index Event Bias

Bias sensitivity analyses indicated that even when the relation of uncontrolled confounders to either smoking or PsA was relatively modest (both HRs = ~1.5), it could reverse a 10% protective effect of smoking among psoriasis patients (i.e., HR=0.9) (Supplemental Figure S2 and Supplemental Results).

DISCUSSION

In this large cohort representative of the UK population, we found that current smoking was associated with a 27% increased risk of PsA in the general population. However, when we limited the study population to those with psoriasis, current smoking was associated with approximately a 10% lower (protective) risk of PsA, illustrating the smoking paradox[18]. Further analysis revealed that the effect of smoking on the risk of PsA was mediated almost entirely through the effect of smoking on psoriasis. Moreover, uncontrolled confounding even at a modest level could account for the collider bias resulting in the inverse association

between smoking and PsA when the study was restricted to an index event such as psoriasis. Together, our findings illustrate the smoking paradox associated with the risk of PsA among the psoriasis patients in a general population context and methodological limitations could potentially provide an enticing explanation for the seemingly paradoxical phenomenon.

Findings of the association between smoking and risk of PsA among people with psoriasis are limited and inconsistent. For example, Tey et al[19] found no association between smoking and PsA when comparing psoriasis patients with PsA (cases) and without PsA (controls). Results from Pattison et al[20] suggested that smoking protects against PsA among cases with PsA compared with psoriasis controls, i.e., smokers had about a 50% reduced risk for PsA. Similarly, Eder et al. suggested a protective effect of smoking on risk of PsA among psoriasis patients.[8] Li et al., however, found that smoking had an increased risk of PsA among psoriasis patients, but the magnitude of association was substantially smaller than that seen for the association between smoking and risk of psoriatic arthritis in the general population of the Nurses' Health Study II.[6] Explanations for the lack of consistent findings vary. For example, the biological explanation for the protective effect of smoking was hypothesized that smoking decreased expression of interleukin (IL) 1β, IL-8 and altered response of Toll-like receptor pathways to noxious agents.[8] It is unclear how smoking can have a protective effect among psoriasis patients but not in the overall general population. Another explanation may be that the effect estimate of smoking on the risk of PsA among the general population may be different from that of the traditional studies restricted to patients with psoriasis, owing to differences in risk of PsA among non-smokers in the general vs. psoriasis populations.

Our results suggest that smoking increased risk of PsA in the general population but smoking appeared protective among psoriasis patients. With the large sample size, both modest effects were statistically significant and we were able to clarify the paradox and showed that not only the measure of effect in those with psoriasis was that of the direct effect, but was also possibly biased by uncontrolled confounding. When studying the effect of smoking on the risk of PsA among patients with psoriasis, the goal is to assess the total effect of smoking on the development psoriatic arthritis. To obtain such an effect estimate, investigators could enroll a group of patients with psoriasis and assess how changes in smoking status (i.e., either smokers stopped smoking or non-smokers started smoking) after psoriasis diagnosis are associated with the risk of PsA. By doing so, the effect estimate of smoking change on the risk of PsA represents the total effect of smoking on the risk of PsA among patients with psoriasis. In contrast, traditional studies of the association between smoking and risk of PsA restricted to people with psoriasis often assess prevalent smoking status at baseline. If smoking is a risk factor for psoriasis and having psoriasis increases risk of PsA, then restricting a study to those with psoriasis would be conditioning on an intermediate in the causal pathway between smoking and PsA. Thus, the measure of effect represents the direct effect of smoking on risk of PsA (Supplemental Figure S1.a) independent of psoriasis. Furthermore, conditioning on an intermediate may also result in collider bias (Supplemental Figure S1.b).

Several limitations warrant discussion. First, general practitioners in THIN did not regularly record smoking status and other lifestyle factors. It may lead to under-reporting of smoking

status, especially among non-smokers or healthy people. Such under-reporting or misclassification of smoking status may result in the effect estimates being biased toward the null. We conducted additional analyses for possible misclassification of smoking and results did not change materially. Second, the diagnostic accuracy of PsA and psoriasis, and disease severity are potential concerns in this study using medical record data. However, validation studies have shown high positive predictive value for psoriasis (90%) in THIN[10] and PsA (>90%) in an electronic medical records database similar to THIN.[10,21] Our sensitivity analyses using both Read codes and DMARDs for classification of PsA did not change the inference, as was using incident psoriasis as compared with both incident and prevalent psoriasis provided similar inference. While excluding prevalent cases of psoriasis could better ensure the temporal relation between smoking and the onset of psoriasis, it will exclude a substantial proportion of individuals with a causal intermediate (i.e., prevalent psoriasis) for psoriatic arthritis endpoints. Furthermore, conditioning on causal intermediates (i.e., excluding prevalent psoriasis individuals) could then lead to potential selection bias. As such, we pursued both analyses, which resulted in very similar findings. Despite these limitations, our study was conducted using a large population-based cohort of the UK population; thus, our findings may apply to a general population. Also, we were able to perform various sensitivity analyses, and the study inference remained the same.

Conclusion

Our study showed that traditional study design and analytic methods could result in a risk factor paradox in the context of smoking and risk of PsA among patients with psoriasis. Future work would need to determine appropriate study design and analysis to ascertain the total effect of smoking in the development of PsA among those with psoriasis, as this may have critical clinical implications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline Characteristics by Smoking Status, Overall and Restricted to Participants with Psoriasis

	THIN General Population			Among Psoriasis Patients		
	non-smoker	ex-smoker	current smoker	non-smoker	ex-smoker	current smoker
Subjects (n)	3,759,554	1,035,203	1,856,542	104,004	43,205	78,004
Age-mean (SD)	41.9 (18.2)	48.9 (18.4)	39.2 (15.5)	44.2 (17.8)	51.1 (17.4)	41.5 (15.4)
Female (n, %)	2,131,881 (56.7%)	499,916 (48.3%)	860,368 (46.3%)	57,823 (55.6%)	20,639 (47.8%)	39,233 (50.3%)
BMI-mean (SD)*	25.5 (5.1)	26.7 (5.2)	25.1 (5.0)	26.4 (5.3)	27.4 (5.4)	25.7 (5.2)
Alcohol (n, %) Missing	833,488 (22.2%)	196,028 (18.9%)	426,356 (23.0%)	22,327 (21.5%)	7,867 (18.2%)	17,716 (22.7%)
Non-drinker	702,569 (18.7%)	111,956 (10.8%)	221,084 (11.9%)	16,586 (16.0%)	4542 (10.5%)	9014 (11.6%)
Ex-drinker	19,482 (0.5%)	19,182 (1.9%)	24,225 (1.3%)	612 (0.6%)	786 (1.8%)	1071 (1.4%)
Current drinker	2,204,015 (58.6%)	708,037 (68.4%)	1,184,877 (63.8%)	64,479 (62.0%)	30,010 (69.5%)	50,203 (64.4%)
Trauma (n, %)	1,128,218 (30.0%)	356,190 (34.4%)	664,097 (35.8%)	38,483 (37.0%)	17,093 (39.6%)	32,140 (41.2%)

* Missing BMI data were 24.2% and 21.5% (non-smokers), 19.3% and 18.2% (ex-smokers), 25.5% and 22.7% (current smokers) in THIN general population and psoriasis patients, respectively.

Table 2

Association between Smoking and Psoriatic Arthritis in the General Population and among PsO Patients

	Non-Smokers	Ex-smokers	Current Smokers
General THIN Population	3,759,554	1,035,203	1,856,542
Number developing PsA	3,699	1,178	2,180
Total Follow-up (Person-Years)	26,961,014	6,599,380	12,964,215
PsA Incidence Rate (per 10,000 person-years)	1.4	1.8	1.7
Unadjusted HR (95% CI)	1.0	1.32 (1.24 to 1.41)	1.23 (1.17 to 1.30)
Adjusted HR * (95% CI)	1.0	1.32 (1.22 to 1.43)	1.27 (1.19 to 1.36)
Adjusted HR ** (95% CI)	1.0	1.30 (1.21 to 1.38)	1.23 (1.16 to 1.29)
Among PsO Patients	104,004	43,205	78,004
Number developing PsA	2,288	789	1,492
Total Follow-up (Person-Years)	951,097	329,631	697,500
PsA Incidence Rate (per 10,000 person-years)	24.0	23.9	21.4
Unadjusted HR (95% CI)	1.0	1.00 (0.92 to 1.08)	0.89 (0.83 to 0.95)
Adjusted HR * (95% CI)	1.0	1.07 (0.97 to 1.18)	0.91 (0.84 to 0.99)
Adjusted HR ** (95% CI)	1.0	1.03 (0.95 to 1.12)	0.88 (0.83 to 0.94)

* Adjusted for age, alcohol, BMI, sex, and trauma using complete case analysis.

** Adjusted for age, alcohol, BMI, sex, and trauma using multiple imputation for missing covariates.

Table 3

Partitioning the Total Effect into Components of Indirect and Direct Effects Using Mediation Analysis

	Partition of Effect of Smoking at Baseline on Risk of Psoriatic Arthritis		
	Non-Smokers HR (95% CI)	**Ex-Smokers* HR (95% CI)**	**Current Smokers* HR (95% CI)**
Total Effect	1.00 (Ref)	1.32 (1.22 to 1.43)	1.27 (1.19 to 1.36)
Indirect (through PsO)	1.00 (Ref)	1.21 (1.17 to 1.26)	1.31 (1.26 to 1.37)
Direct (not through PsO)	1.00 (Ref)	1.08 (1.03 to 1.13)	0.96 (0.93 to 1.00)

*Adjusted for age, alcohol, BMI, sex, and trauma