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Smoking and risk of incident psoriatic arthritis in US women

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Abstract

Objectives—Psoriatic arthritis (PsA) is an inflammatory arthritis that is associated with psoriasis. Previous studies have found an association between smoking and psoriasis, but the association with PsA is unclear. We aimed to evaluate the association between smoking and risk of incident PsA in a large cohort of women.

Methods—A total of 94,874 participants were included from the Nurses Health Study II over a 14-year time period (1991-2005). Information on smoking was collected biennially during follow-up. Incidence of clinician-diagnosed PsA was ascertained and confirmed by self-reported questionnaires.

Results—During 1,303,970 person-years' follow-up, we identified 157 incident PsA cases. Among total participants, smoking was associated with an elevated risk of incident PsA. Compared with never smokers, the relative risk (RR) was 1.54 for past smokers (95% confidence interval (CI): 1.06-2.24), and 3.13 for current smokers (95% CI: 2.08-4.71). With increasing smoking duration or pack-years, risk of PsA increased monotonically (*P* for trend <0.0001). The increase in risk was particularly significant for PsA cases with more severe phenotypes. Secondary analysis among participants developing psoriasis during the follow-up replicated the association, demonstrating an increased risk of PsA among psoriasis cases, especially for those with higher cumulative measures of smoking or PsA cases with more severe phenotypes.

Conclusion—In this study of US women, we found that smoking was an independent risk factor for PsA and cumulative measures of smoking were also associated with a higher risk of PsA.

Keywords

smoking; psoriatic arthritis; epidemiology

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Participants consent Obtained.

Ethics approval The institutional review board of Partners Health Care System approved this study.

Role of the Sponsors None

Introduction

Psoriatic arthritis (PsA) is an inflammatory joint condition affecting an estimated 520,000 individuals in the US population[1]. As a pleomorphic clinical entity characterized by the development of arthritis in patients with psoriasis, PsA occurs in 6% to 42% of patients with psoriasis and the onset of joint symptoms usually does not happen until 8-10 years' duration of psoriasis skin lesions[1, 2].

A delayed diagnosis and treatment of PsA may lead to an erosive arthropathy and impair quality of life due to physical disability and lost productivity[1, 3]. PsA has been shown to augment the risk of incident diabetes and cardiovascular disease beyond the effect of psoriasis (unpublished data). Moreover, the pathogenetic link between skin and joint disease still appears tenuous[1, 4]. Therefore, prevention and early detection is warranted by understanding the causes and risk factors for PsA.

The unfavorable cutaneous and joint effects of smoking have been suggested from past studies due to the impact on the immune system and induction of oxidative stress[5-9]. However, only sparse evidence regarding the association between smoking and PsA has been reported [10-13]. One study showed that smoking may accelerate the onset of PsA in patients with psoriasis while delay the onset of PsA in healthy participants[11]. Another case-control study did not find an increased risk of PsA among smokers with psoriasis[12]. Another study even indicated smoking as a protective factor in the development of PsA among psoriasis patients[13]. To the best of our knowledge, no prospective data on smoking and psoriatic arthritis has been reported thus far.

In this study, we investigated the association between smoking status, duration, intensity, and incidence of PsA in 94,874 participants from the Nurses' Health Study II (NHS II).

METHODS

Study cohort

Our study participants were included from NHS II, an ongoing longitudinal cohort of women. In brief, this cohort was initially established in 1989 when 116,430 female nurses aged 25-42 completed and returned a baseline questionnaire inquiring about their medical history and lifestyle. Biennially, cohort members receive a questionnaire regarding diseases and health-related factors. The follow-up rate exceeds 90%.

Assessment of main exposure

In 1989, participants responded to question on the lifetime history of smoking 20 packs (1 pack=20 cigarettes) of cigarettes or more and if they were a past smoker, how many years had passed since quitting smoking (<1 or ≥1 year). The questionnaire also inquired about the quantities of smoking at different ages (<15, 15-19, 20-24, 25-29, 30-35, and 36-42 years) in the 6 categories (1-4, 5-14, 15-24, 25-34, 35-44, and 45 or more). On the baseline and following questionnaires biennially, participants reported whether they were never, past or current smokers. These questionnaires also inquired about the quantity of smoking in current

smokers by self-reported number of cigarettes per day in the same aforementioned 6 categories.

Smoking duration and pack-years were derived based on information from the baseline and biennial questionnaire. Duration was obtained by deducting the age at smoking onset from current age for current smokers, or from age of cessation for past smokers. The pack-years were evaluated as the number of packs per day multiplied by the number of years of smoking.

Assessment of main outcome (PsA)

In 2005, NHS II participants responded to a question on clinician-diagnosed psoriasis and the diagnosis date (before 1991, 1991-1994, 1995-1998, 1999-2002, or 2003-2005). Of the 97,476 responders of this item, 2,529 women reported psoriasis; 1,151 occurred since 1991.

We confirmed self-reported psoriasis by using the Psoriasis Screening Tool (PST) questionnaire, which inquired about the type of clinicians making the diagnosis and the phenotypes of psoriasis [14]. We developed scoring algorithms based on multiple *a priori* hypotheses to assign a diagnosis of psoriasis according to the response. The PST reached 99% sensitivity and 94% specificity for psoriasis screening in our pilot study[14]. This questionnaire was mailed to all NHS II participants with self-reported clinician-diagnosed psoriasis and the response rate was 87%, among which the confirmation rate was 92% (unpublished data).

The diagnosis of PsA was confirmed by using the Psoriatic Arthritis Screening and Evaluation (PASE) questionnaire, a self-administered questionnaire having a symptom scale with seven items and a function scale with eight items[15]. Details of the instrument design and pilot studies have been described in previous publications[15, 16]. For each item, participants chose one of five categories relating to agreement (strongly agree to strongly disagree). A total score of ≥47 has been shown in our pilot study to identify PsA with 82% sensitivity and 73% specificity[15].

Statistical analysis

We performed two sets of analyses for the association study given the close relationship between psoriasis and PsA. One was analyzed among the total participants. Secondary analysis was also performed by only including all individuals developing psoriasis to evaluate the risk of PsA associated with smoking among individuals with psoriasis. Of the 97,476 responders, for both the two sets of analyses, we excluded participants with the psoriasis item passing through (N=58), PsA or psoriasis cases which occurred before 1991 (N=1,376), self-reported psoriasis cases who were not confirmed (N=97) or did not responded to the PST or PASE questionnaire (N=467), PsA cases lack of diagnosis date (N=2), and participants with missing information on smoking (N=506). For the first set of analysis, we excluded incident psoriasis cases without joint phenotypes in the first follow-up period (N=96), therefore 94,874 participants remained. For the second set, we excluded all participants who did not develop psoriasis (N=94,389), 581 participants with psoriasis remained.

Person-years of follow-up were calculated for each participant by deducting the return date of baseline questionnaire (1991) from the date of diagnosis of PsA, or June of 2005, whichever came first.

Information on smoking was updated with the follow-up interval. Smoking status was categorized as never, past and current. The quantities of current smokers were evaluated in the following categories of cigarettes per day: 1-14 or ≥15. Other variables on smoking were categorized as smoking duration (<25 or ≥25 years) and pack-years (<20, 20-44, or ≥45 pack-years).

Stratified by age and follow-up interval, we performed Cox proportional hazards analysis to calculate the age and multivariate-adjusted relative risk (RR) and 95% confidence interval (CI) for the association of smoking with incidence of PsA. For multi-categorical measures of smoking, trend tests were carried out by using the median in different categories. Adjusting for multiple variables, population-attributable risk (PAR) of smoking and the corresponding 95% CI were calculated.

Cox regression analyses were updated because the outcome (PsA) and the independents are all time-varying. We calculated the RR and 95% CI after simultaneously adjusting for age (continuous variable), body mass index (<18.5, 18.5-24.9, 25-29.9, 30-34.9, or ≥35 kg/m^2), vigorous physical activity (metabolic equivalent hours/wk, in quintiles) and alcohol intake (0, <4.9, 5.0-9.9, 10-14.9, 15-29.9, or ≥30.0 g/d). Further, as a sensitivity analysis, postmenopausal hormone use (premenopausal, never, or current/past users), personal history of cancer, diabetes, cardiovascular disease, hypertension and hypercholesterolemia (yes or no) were concomitantly adjusted for. We also performed association analyses between smoking and risk of PsA with different severity scores (47-57, or ≥57). We set the cutoff value of severity scores as 57 because approximately 1/3 of the PsA cases had a score higher than 57.

Statistical Analysis System software (SAS, version 9.2; SAS Institute Inc, Cary, NC) was used to conduct all statistical analyses. All statistical tests were 2-tailed, and the significance level was set at P <0.05.

The participants' completion and return of the self-administered questionnaires was accepted as informed consent of the present study.

Results

The age-adjusted baseline characteristics of the cohort according to smoking status are reported in Table 1. Alcohol intake tended to increase from the never smokers to the current smokers.

During 1,303,970 person-years of follow-up, 157 were identified as PsA. Compared with never smokers, we observed an increased risk of incident PsA among past (multivariate-adjusted RR = 1.54, 95% CI: 1.06-2.24) or current smokers (RR = 3.12, 95% CI = 2.07-4.69). The risk for PsA was monotonically associated with increasing amounts of smoking among current smokers (P for trend <0.0001) (table 2). There was a graded

association between duration or pack-years of smoking and risk of PsA (*P* for trend <0.0001). The RR was 1.70 for duration <25 years and 3.12 for ≥25 years; 1.48 for <20 pack-years, 3.33 for 20-44 pack-years, and 3.91 for ≥45 pack-years. In this cohort, 25.9% (5.0-44.7%) of the incident PsA cases were attributable to having ever smoked.

We evaluated the association between smoking and PsA with different severity scores. The association appears much stronger for PsA with scores ≥57 (table 3).

We repeated the analyses after excluding all the participants without developing psoriasis during the follow-up to evaluate the risk of PsA among psoriasis cases. As is shown in Table 4, risk of PsA among psoriasis was monotonically elevated with increasing smoking quantities among current smokers. We also evaluated the association with smoking duration and pack-years. The risk was particular high among those with smoking duration ≥25 years (RR = 1.90, 95% CI: 1.09-3.33), and smoking ≥20 pack-years (RR = 2.02, 95% CI: 1.24-3.29).

Among psoriasis cases, risk for PsA with more severe phenotypes (PASE score ≥57) was remarkably elevated with the increasing smoking intensity or duration (*P* for trend <0.0001, table 5). However, we did not observe a significant association for PsA with PASE scores 47-57.

Secondary analyses were performed to adjust concomitantly the menopausal status and post-menopausal hormone use, as well as personal history of chronic diseases. The association was only slightly attenuated and remained significant. Secondary analyses were also performed by excluding baseline cancer, cardiovascular disease and diabetes, and no material change was observed for the association (data not shown).

Discussion

In this study, we observed that smokers were at an independently increased risk of developing PsA. The risk was increased with higher smoking amounts, longer duration of smoking or higher numbers of pack-years smoked.

PsA is a chronic inflammatory arthritis associated with psoriasis, which has been recognized as a systemic inflammatory disorder[1, 2, 17]. Psoriasis skin lesions usually precede the onset of joint symptoms by 8-10 years and PsA tend to have more extensive skin lesions[18, 19]. It has been postulated that smoking may play a role in the development of psoriasis skin lesions through a variety of mechanisms. Smoking induces oxidative stress and reduces anti-oxidant levels, leading to an imbalance of oxidants and anti-oxidants[8, 20]. The nicotinic cholinergic receptors in keratinocytes can be activated by smoking, subsequently stimulating calcium influx and accelerating cell differentiation[21, 22]. More importantly, smoking can adversely alter the immunological and inflammatory processes and elevated levels of autoantibodies have been detected among smokers[6, 23, 24].

The association between smoking and psoriasis has been evaluated in past epidemiologic studies[5, 9]. Our recent pooled analysis indicated smoking as an independent risk factor for incident psoriasis among women and men (unpublished data). Smoking is also an

established risk factor for rheumatoid arthritis[7]. These data suggest a possible role of smoking in development of PsA. However, the direct evidence regarding the association between smoking and PsA is sparse[10-12]. A study by Tey et al. did not point to a link between smoking and PsA in patients with cutaneous psoriasis[12]. Duffin et al. reported that smoking may modulate the effect of interleukin-13 polymorphisms on risk of PsA[10]. Our longitudinal data provide evidence regarding the association between smoking status, quantity, duration, pack-years, and the risk of PsA. Given the temporal sequence of smoking and incident PsA, our results indicate that smoking is an independent risk factor for development of PsA.

Past studies indicated a graded relationship between components of cigarette smoke and changes in the inflammatory response[6]. Previous evidence also showed that smoking impacts the occurrence or severity of psoriasis in a dose-response manner[5, 9]. In the present study, we observed a gradually elevated risk of developing PsA corresponding with the increasing of quantities of current smokers, smoking duration, and pack-years. Further, the effect of smoking appeared stronger for those with higher PsA severity scores.

Our study is the first large cohort study on the association between smoking and development of PsA. We evaluated multiple measures of smoking status, duration and intensity in association with risk of PsA. In our study, all the PsA cases had concomitant psoriasis. We performed secondary analyses by excluding or adjusting for psoriasis comorbidities for their possible association with smoking, and the association remained fairly consistent. We compared the effect of smoking on risk of PsA among total participants as well as only among psoriasis cases. These two sets of analyses observed consistently increased risk of PsA associated with smoking, providing further evidence on the role of smoking in the development of inflammatory psoriatic arthritis. However, PsA can affect individuals with very limited or no skin manifestations as well, though accounting for a quite small proportion[4, 25]. Further work is warranted on the role of smoking in such cases.

A marked strength of our study lies in the confirmation of self-reported clinician-diagnosed psoriasis and PsA by using PST and PASE questionnaires, compared with other population-based epidemiologic studies of psoriasis and PsA [1, 5]. Although we did not confirm the cases by reviewing the medical records, our participants are health professionals and we have designed a priori algorithms for the confirmation of diagnosis via supplementary questionnaires[14, 15]. Since our pilot study showed high accuracy of this algorithm, we expect an overall high validity of confirmation among registered nurses.

Physician-diagnosis of psoriasis was collected in 2005; therefore survival bias may exist because we cannot obtain information for individuals with psoriasis who died before the data collection. However, this is a younger women cohort. We found that the mean age of those responding to the 2005 psoriasis question was even a bit higher than non-responders; therefore it is less likely that our results were greatly distorted. Most of our study participants are Caucasian women younger than 60 years. The generalization to other ethnic populations or older women should be made cautiously considering there could be a different proportion of Type 1 and Type 2 psoriasis among younger versus older women[26], though still little is known about the difference between these two types.

In conclusion, our study suggests an increased risk of developing PsA associated with smoking. The risk elevated with the increasing duration and intensity of smoking. Our study has implications for public health, adding PsA to the long list of diseases that may be prevented by smoking cessation.

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Table 1

Age-Standardized baseline characteristics of study participants by smoking status, NHS II*

	Smoking status		
	Never	**Past**	**Current**
Age †, mean (SD), year	35.8 (4.7)	37.0 (4.5)	36.6 (4.6)
Body mass index, kg/m^2, mean (SD)	24.6 (5.3)	24.6 (5.2)	24.5 (5.1)
Alcohol intake, g/d, mean (SD)	2.4 (4.9)	4.3 (6.7)	5.2 (9.0)
Vigorous physical activity, metabolic equivalent hours/wk, mean (SD)	13.3 (21.9)	15.2 (24.8)	12.9 (22.2)
Post Menopausal (yes, %)	3.2	3.0	4.5
Personal history of chronic diseases (yes, %)			
Diabetes	0.6	0.5	0.4
Cancer	1.2	1.7	1.5
Cardiovascular disease	0.4	0.4	0.5
Hypertension	3.4	3.1	3.0
Hypercholesterolemia	9.0	8.8	10.1

*Characteristics of participants at the beginning of follow-up (return date of the 1991 questionnaire). Values are means (SD) or percentages and are standardized to the age distribution of the study population.

†Values are not age-adjusted.

Table 2

Age- and multivariate-adjusted RRs for the association of smoking status with risk of psoriatic arthritis (PsA) among all participants*

	Cases	Person-years	Age-adjusted RR (95% CI)	Multivariate-adjusted RR # (95% CI)
Reference: Never smokers	76	865,189	1.00	1.00
Smoking status				
Past smokers	46	309,749	1.55 (1.07-2.23)	1.54 (1.06-2.24)
Current smokers	35	129,032	3.08 (2.06-4.61)	3.12 (2.07-4.69)
1-14 cigarettes/day	12	62,479	2.19 (1.19-4.02)	2.34 (1.27-4.33)
≥15 cigarettes/day	23	66,553	3.92 (2.45-6.27)	3.77 (2.35-6.06)
P for trend			<0.0001	<0.0001
Duration				
Duration, <25 years	55	366,471	1.68 (1.19-2.38)	1.70 (1.19-2.42)
Duration, ≥25 years	26	72,310	3.20 (2.02-5.07)	3.12 (1.96-4.97)
P for trend			<0.0001	<0.0001
Pack-years				
pack-years, <20	44	342,974	1.43 (0.99-2.08)	1.48 (1.02-2.16)
pack-years, 20-44	34	91,129	3.67 (2.42-5.56)	3.33 (2.19-5.06)
pack-years, ≥45	3	4,678	4.53 (1.41-14.56)	3.91 (1.21-12.59)
P for trend			<0.0001	<0.0001

* Psoriasis cases with only skin phenotypes were excluded during the follow-up.

Adjusted for age (continuous variable), body mass index (<18.5, 18.5-24.9, 25-29.9, 30-34.9 or ≥35 kg/m^2), alcohol drinking (no, <4.9, 5.0-9.9, 10-14.9, 15-29.9 or ≥30.0 g/d), vigorous physical activity (metabolic equivalent hours/wk, in quintile).

Table 3

Age- and multivariate-adjusted RRs for the association between smoking and risk of PsA with different severity scores*

	Person-years	Scores 47-57	Multivariate-adjusted RR# (95% CI)	Scores ≥57	Multivariate-adjusted RR# (95% CI)
Reference: Never smokers	865,189	54	1.00	22	1.00
Smoking status					
Past smokers	309,749	35	1.61 (1.04-2.48)	11	1.34 (0.64-2.79)
Current smokers	129,032	19	2.30 (1.35-3.91)	16	5.34 (2.78-10.28)
Quantity, 1-14 cigarettes/day	62,479	7	1.88 (0.85-4.16)	5	3.62 (1.36-9.65)
Quantity, ≥15 cigarettes/day	66,553	12	2.64 (1.40-4.98)	11	6.81 (3.27-14.16)
P for trend			0.002		<0.0001
Duration					
Duration, <25 years	366,471	42	1.80 (1.19-2.72)	13	1.43 (0.71-2.86)
Duration, ≥25 years	72,310	12	1.80 (0.95-3.43)	14	7.89 (3.81-16.35)
P for trend			0.002		<0.0001
Pack-years					
pack-years, <20	342,974	33	1.54 (0.99-2.40)	11	1.32 (0.64-2.75)
pack-years, ≥20	95,807	21	2.47 (1.47-4.17)	16	6.05 (3.08-11.89)
P for trend			0.001		<0.0001

*Psoriasis cases with only skin phenotypes were excluded during the follow-up. PsA cases were classified into two groups by the cutoff of scores at 57, picked to include those with the top 1/3 of the scores into one category.

#Adjusted for age (continuous variable), body mass index (<18.5, 18.5-24.9, 25-29.9, 30-34.9 or ≥35 kg/m^2), alcohol drinking (no, <4.9, 5.0-9.9, 10-14.9, 15-29.9 or ≥30.0 g/d), vigorous physical activity (metabolic equivalent hours/wk, in quintile).

Table 4

Age- and multivariate-adjusted RRs for the association between smoking and risk of PsA among participants with psoriasis

	Cases	Person- years*	Age-adjusted RR (95% CI)	Multivariate-adjusted RR* (95% CI)
Reference: Never smokers	76	2,356	1.00	1.00
Smoking status				
Past smokers	46	1,191	1.17 (0.77-1.78)	1.39 (0.89-2.16)
Current smokers	35	805	1.56 (0.98-2.47)	1.62 (1.00-2.63)
Quantity, 1-14 cigarettes/day	12	328	1.12 (0.55-2.29)	1.22 (0.58-2.56)
Quantity, ≥15 cigarettes/day	23	477	1.91 (1.11-3.27)	1.93 (1.09-3.40)
P for trend			0.004	0.006
Duration				
Duration, <25 years	55	1,680	1.18 (0.81-1.74)	1.35 (0.90-2.04)
Duration, ≥25 years	26	316	1.85 (1.08-3.17)	1.90 (1.09-3.33)
P for trend			0.024	0.012
Pack-years				
Pack-years, <20	44	1,453	1.08 (0.71-1.63)	1.22 (0.79-1.89)
Pack-years, ≥20	37	543	1.87 (1.17-3.01)	2.02 (1.24-3.29)
P for trend			0.084	0.082

*Adjusted for age (continuous variable), body mass index (<18.5, 18.5-24.9, 25-29.9, 30 34.9 or ≥35 kg/m^2), alcohol drinking (no, <4.9, 5.0-9.9, 10-14.9, 15-29.9 or ≥30.0 g/d), vigorous physical activity (metabolic equivalent hours/wk, in quintile).

Table 5

Age- and multivariate-adjusted RRs for the association between smoking and risk of PsA with different severity scores among participants with psoriasis*

	Person-years	Scores 47-57	Multivariate-adjusted RR# (95% CI)	Scores ≥57	Multivariate-adjusted RR# (95% CI)
Reference: Never smokers	2,356	54	1.00	22	1.00
Smoking status					
Past smokers	1,191	35	1.35 (0.78-2.35)	11	1.34 (0.64-2.79)
Current smokers	805	19	1.27 (0.68-2.39)	16	5.34 (2.78-10.28)
Quantity, 1-14 cigarettes/day	328	7	0.93 (0.35-2.47)	5	3.62 (1.36-9.65)
Quantity, ≥15 cigarettes/day	477	12	1.55 (0.73-3.28)	11	6.81 (3.27-14.16)
P for trend			0.146		<0.0001
Duration					
Duration, <25 years	1,680	42	1.32 (0.80-2.19)	13	1.43 (0.71-2.86)
Duration, ≥25 years	316	12	1.30 (0.61-2.79)	14	7.89 (3.81-16.35)
P for trend			0.259		<0.0001
Pack-years					
pack-years, <20	1,453	33	1.19 (0.69-2.03)	11	1.32 (0.64-2.75)
pack-years, ≥20	543	21	1.61 (0.85-3.06)	16	6.05 (3.08-11.89)
P for trend			0.592		<0.0001

*Psoriasis cases with only skin phenotypes were excluded during the follow-up. PsA cases were classified into two groups by the cutoff of scores at 57, picked to include those with the top 1/3 of the scores into one category.

#Adjusted for age (continuous variable), body mass index (<18.5, 18.5-24.9, 25-29.9, 30-34.9 or ≥35 kg/m^2), alcohol drinking (no, <4.9, 5.0-9.9, 10-14.9, 15-29.9 or ≥30.0 g/d), vigorous physical activity (metabolic equivalent hours/wk, in quintile).