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Smoking and the Risk of Psoriasis in Women - Nurses' Health Study II

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SUMMARY

Background—Psoriasis is a common, chronic, inflammatory skin disorder. Smoking may increase the risk of psoriasis, but no prospective data are available on this relation.

Methods—We prospectively examined over a 14-year time period (1991–2005) the relation between smoking status, duration, intensity, cessation and exposure to second hand smoke, and incident psoriasis in 78,532 women from the Nurses Health Study II. The primary outcome was incident, self-reported, physician-diagnosed psoriasis.

Findings—We documented 887 incident cases of psoriasis. Compared to those who had never smoked, the multivariate relative risk (RR) of psoriasis was 1.78 (95% CI, 1.46–2.16) for current smokers and 1.37 (95% CI, 1.17–1.59) for past smokers. Compared to nonsmokers, the multivariate RR of psoriasis was 1.60 (95% CI, 1.31–1.97) for those who had smoked 11–20 pack-years, and 2.05 (95% CI, 1.66–2.53) for those who had smoked ≥ 21 pack-years. Compared to never smokers, the multivariate RR of psoriasis was 1.61 (95% CI, 1.30–2.00) for those who quit smoking <10 years ago, 1.31 (95% CI, 1.05–1.64) for 10–19 years ago, and 1.15 (95% CI, 0.88–1.51) for ≥ 20 years ago. Prenatal and childhood exposure to passive smoke was associated with an increased risk of psoriasis.

Interpretation—In this prospective analysis, current and past smoking, and cumulative measures of smoking were associated with the development of psoriasis. The risk of incident psoriasis among former smokers decreases nearly to that of never smokers 20 years after cessation.

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Contributors

A R Setty and H K Choi contributed to the conception and design of the study, obtaining of funding, administrative support, collection and assembly of data, interpretation of the data and critical revision of the article. A R Setty did the statistical analyses and drafted the paper. G Curhan contributed to the conception and critical revision of the article.

Conflict of interest statement

None declared.

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Keywords

Psoriasis; cigarette; smoking; pack-years; cessation; passive; risk factors; prospective; cohort

INTRODUCTION

Psoriasis is a chronic, inflammatory disease of the skin that affects approximately 2% of the population^{1–4} and poses a lifelong burden for those affected.³ A survey by the National Psoriasis Foundation found that 75% of patients with psoriasis reported a moderate to large negative impact of the disease on the quality of their life with an alteration of every day activities.⁵ The negative impact of psoriasis may not be limited to its cutaneous or psychosocial manifestations. A recent large cohort study based on the General Practice Research Database in the United Kingdom found psoriasis to be an independent risk factor for myocardial infarction.⁶

Previous cross-sectional and case-control studies have suggested a link between cigarette smoking and psoriasis, but no prospective data are available.^{7–9} Cigarette smoke contains many potentially toxic materials and may affect the immunopathogenesis of psoriasis including T cell activation and overproduction of pro-inflammatory cytokines (e.g. tumor necrosis factor α [TNF- α], interleukin [IL]-2, IL-6, IL-8, and γ -interferon).¹⁰ Furthermore, a significant association between the intensity and duration of smoking and clinical severity of psoriasis has also been reported.¹¹ Thus, an accurate understanding of the impact of smoking on psoriasis is important from the public health perspective and perhaps for comprehensive management of the condition.

To examine these issues, we prospectively evaluated the relation between smoking status, duration, intensity, cessation and exposure to second hand smoke, and incident psoriasis, in a cohort of 78,532 women without a history of psoriasis.

METHODS

The Nurses Health Study II (NHS II) is an ongoing longitudinal study of 116,608 female registered nurses from fifteen states between the ages of 25 and 42 years at baseline who completed and returned an initial questionnaire in 1989. The NHS II focuses on women's health outcomes in a population younger than the original Nurses' Health Study I cohort. The NHS II is followed with biennial questionnaires and the follow-up rate exceeds 90% for each 2-year period. In 2005, we asked participants if they had ever received a physician diagnosis of psoriasis and if so, the date of the diagnosis. Of the 79,628 participants for whom we have data, we excluded 1,096 women with prevalent psoriasis that occurred prior to our baseline of 1991. For this study we started follow-up in 1991, as this is the year for which we have corresponding information regarding smoking status and alcohol intake.

Assessment

Participants reported whether they were current, past, or never smokers on each biennial questionnaire. The initial questionnaire inquired about the average number of cigarettes smoked per day (1–4, 5–14, 15–24, 25–34, or ≥ 45) by current and past smokers in the following age categories: <15, 15–19, 20–24, 25–29, 30–35 and 36–42. All subsequent questionnaires assessed the intensity of smoking in current smokers using the same categories of cigarettes per day. Duration of smoking and years since quitting were calculated. We calculated the pack-years of smoking (the equivalent of smoking 20 cigarettes a day for 1 year) by multiplying the number of packs smoked per day by the number of years of smoking. All smoking variables were updated biennially. In 1999, women were asked to report on exposure to passive smoke.

They were asked if their mother smoked while pregnant with them. The second question asked whether their mother, father, or both smoked regularly inside the home when they were children. The following question asked the number of years the participant had lived with a smoker as an adult in the following categories: none or < 1 year, 1–4 years, 5–9 years, 10–19 years, 20–29 years and 30+ years. Participants were also asked about reproductive factors (age at menarche, regularity of menses, length of breast-feeding, parity, menstrual status and postmenopausal hormonal use) and husband's level of education.

The endpoint of the current study was a self-reported, physician diagnosis of incident psoriasis. The baseline and biennial follow-up questionnaires inquired about weight, height, and alcohol intake. The reproducibility and validity of the questionnaires have been previously documented in the Nurses Health Study cohort.^{12–14}

Statistical Analysis

We computed person-time of follow-up for each participant from the return date of the 1991 questionnaire to the date of diagnosis of psoriasis, death from any cause, or the end of the study period, whichever came first. We used Cox proportional hazards modeling to estimate the multivariate relative risk (RR) of incident psoriasis. We categorized smoking status as never, current and past. Cumulative exposure to smoking was assessed by pack-years in the following categories: never, 1–10, 11–20, ≥ 21 . Years since quitting smoking was assessed in the following categories: never smoked, < 10 years, 10–19 years, and ≥ 20 years. Intensity of smoking was analyzed in four categories of cigarettes per day: never, 1–14, 15–24, and ≥ 25 . Duration of smoking was categorized as never, <20 years, 20–29 years, ≥ 30 years for current smokers, and as never, <10 years, 10–19 years, ≥ 20 years for past smokers. Exposure to the different types of passive smoke was examined as an indicator variable (yes or no).

Multivariate models were adjusted for age (continuous), alcohol intake (7 categories: none, 1–4 g/d, 5–9 g/d, 10–14 g/d, 15–29 g/d, 30–49 g/d, 50+ g/d) and BMI (<21 kg/m², 21–22.9 kg/m², 23–24.9 kg/m², 25–29.9 kg/m², 30–34.9 kg/m² and ≥ 35 kg/m²). We evaluated the potential impact of reproductive factors (age at menarche, regularity of menses, length of breast-feeding, parity, menstrual status and postmenopausal hormonal use) and husband's level of education by entering each term into the multivariate model. Tests for linear trends were calculated using continuous values for the smoking exposure. We calculated the population-attributable risk, an estimate of the percentage of psoriasis cases in this population that would theoretically not have occurred if participants had never smoked, assuming a causal relation between smoking and incident psoriasis. For all RRs, we calculated 95% confidence intervals (CIs). All P values are two-sided. Statistical analyses were performed using SAS software, version 9.1 (SAS Institute Inc, Cary, NC).

The Partners Health Care System institutional review board approved this study. Return of a completed questionnaire was accepted by the institutional review board as implied informed consent.

RESULTS

Baseline characteristics

We documented 887 incident cases of psoriasis during the 14 years of follow-up. The baseline characteristics of the cohort according to smoking status are shown in Table 1. Alcohol consumption tended to increase from the never to the current smoker group, as did duration of smoking and number of cigarettes smoked per day. Current smokers were more likely to have been exposed to passive smoking than were never and past smokers.

Smoking Status, Intensity, Duration and Risk of Incident Psoriasis

Compared to those who never smoked, the multivariate RR for incident psoriasis was 1.37 for past smokers and 1.78 for current smokers (Table 2). In age-adjusted and multivariate models, pack-years were associated with a graded increase in the risk for psoriasis. Compared to never smokers, the overall multivariate RR was 1.20 for 1–10 pack-years, 1.60 for 11–20 pack-years, and 2.05 for ≥ 21 pack-years. For current smokers, the multivariate RRs for the corresponding pack-year categories were 1.05, 1.57, and 2.25 (P for trend <0.001). A significant trend was also present with increasing pack-year categories among past smokers (P for trend <0.001) (Table 2). When we additionally adjusted for the female reproductive factors or husband's level of education to either the age-adjusted or the multivariate models, these RRs did not change materially.

Similarly, there was a graded association between smoking intensity and the risk of psoriasis (Table 3). For current smokers, as compared to nonsmokers, the multivariate RR for psoriasis was 1.40 for smoking 1–14 cigarettes a day, 2.00 for 15–24 cigarettes a day and 2.54 for 25 cigarettes a day. The corresponding multivariate RRs for past smokers were 1.34, 1.39 and 1.53. The significant trends persisted with smoking duration in both current and past smokers (Table 3).

Time since Quitting Smoking and Risk of Incident Psoriasis

There was a graded reduction in the risk of psoriasis with increasing years of smoking cessation and the risk of psoriasis became comparable to that of non-smokers, 20 or more years after smoking cessation (Table 4).

Passive Smoke and Risk of Incident Psoriasis

The age-adjusted RRs of incident psoriasis by exposure to passive smoke were 1.31 for those whose mother smoked while pregnant with them, 1.26 for those with exposure to passive smoking as a child, and 1.35 for those with passive smoke exposure after age 18 (Table 5). After additionally adjusting for BMI, alcohol consumption and self-smoking status, the multivariate RRs were attenuated to 1.21 (95% CI; 1.04–1.41), 1.18 (95% CI; 1.02–1.35), and 1.10 (95% CI; 0.95–1.28), respectively.

Population-Attributable Risk

In our cohort, 14% of the incident psoriasis cases were attributable to having ever smoked. For past smokers, 27% of the risk was attributable to smoking; for current smokers, 44% of the risk was attributable to smoking.

DISCUSSION

Our objective was to prospectively evaluate the relation between smoking and incidence of psoriasis in a large cohort of women. We found that both past and current smokers were at increased risk for developing psoriasis, and the risk was greater for current smokers. The risk was graded and increased with the duration, intensity and pack-years of smoking. Furthermore, the risk of incident psoriasis decreased with increasing years of smoking cessation reaching nearly that of never smokers 20 years after cessation. These associations were independent of other purported risk factors. The current study provides the first prospective evidence that smoking is a strong risk factor for incident psoriasis.

The impact of smoking on psoriasis has been evaluated in a cross-sectional study that compared 557 psoriatic patients attending the University of Utah Dermatology Clinics, with external population databases.⁹ The prevalence of smoking in the psoriatic patients was higher than in the general Utah population (37% vs 13%; $P < 0.001$) and higher than in the non-psoriatic

patients attending the same dermatology clinics (37% vs 25%; $P < 0.001$). A previous case-control study of 108 psoriasis cases from the dermatology department of South Glamorgan (UK), and 108 control patients from family practices of the same region, reported a similarly strong association between prior smoking and the risk of psoriasis (OR = 3.75; 95 % CI, 1.68–9.47).¹⁵ A recent Italian, multi-center, case-control study involving 318 men and 242 women with newly diagnosed psoriasis and 690 controls also reported that there was a significant association (multivariate OR = 1.9 [95 % CI, 1.3–2.7] for past smokers and 1.7 [95 % CI, 1.1–3.0] for current smokers). The same study reported that the risk of psoriasis was significantly higher in female current smokers, whereas the risk was not significant in female past smokers (OR, 1.2; 95% CI, 0.6–2.2).¹⁶ Furthermore, no graded response was observed across smoking intensity and duration, unlike our findings. Our prospectively obtained smoking history data, coupled with a larger sample size may explain the differences. While previous cross-sectional studies left uncertainty regarding the temporal relationship between smoking and psoriasis,^{9, 17} our prospective longitudinal data indicate that increased smoking precedes the occurrence of new cases of psoriasis. Furthermore, potentially biased recall of various facets of smoking history was avoided in this study because smoking data were collected prior to the data on incident psoriasis.

Psoriasis is a T cell immune-mediated disease that involves over-expression of proinflammatory cytokines and chemokines such as TNF- α , IL-2, IL-6, IL-8, and γ -interferon. There are several speculated mechanisms by which cigarette smoke could augment the risk of psoriasis. Cigarette smoke contains many potentially toxic materials such as nicotine, reactive oxygen species, nitric oxide, peroxy nitrite, and free radicals of organic compounds, and may affect the immunopathogenesis of psoriasis.¹⁰ Abnormalities in T-cell function,^{18, 19} reduction in natural killer cells,²⁰ impairment of humoral immunity,^{20–22} and elevated levels of inflammatory markers such as interleukin-6 and C-reactive protein^{23–25} have been observed in smokers. Specifically, nicotine may stimulate the functional capacity of antigen presenting cells leading to T-cell proliferation and release of proinflammatory cytokines,^{16, 26} which are thought to be involved in the pathogenesis of psoriasis. Some studies^{27–30} have also shown that cigarette smoking induces an overproduction of interleukin IL-1 β , and increases the production of TNF- α and transforming growth factor- β , which have been associated with psoriasis severity.

The constituents of cigarette smoke, including mutagenic, neurotoxic and fetotoxic agents can pass through the placenta and are detectable in the urine of newborns.^{31, 32} Maternal smoking is known to increase a woman's risk of spontaneous abortion, preterm delivery, and lower birth weight.^{31, 33} A previous study that evaluated the role of passive smoking in psoriasis did not find it to be a risk factor.¹⁶ However, the study did not evaluate separately for prenatal, childhood and adult exposure. Our study found passive exposure to serve as a risk factor in the first two groups. It is conceivable that for psoriasis, passive exposure to smoke has greater negative consequences earlier rather than later in life.

Conversely, smoking cessation may be an important target for prevention and management of psoriasis.^{34, 35} Smoking cessation may decrease the degree of smoke-induced inflammation by lowering the level of circulating inflammatory cytokines or restoration of T-cell impairments. Indeed, our study found that the risk for psoriasis in past smokers was consistently lower than it was for current smokers. The risk progressively decreased with increasing years of smoking cessation and became insignificant, 20 years after cessation. Furthermore, among patients with existing psoriasis, higher intensity and duration of smoking was associated with increased clinical severity of psoriasis.¹¹ These findings, along with well-established hazardous health effects of smoking, provide clear incentives for smoking cessation in those at risk for and suffering from psoriasis. Beyond the potential effect on psoriasis, smoking

cessation would lead to a better overall clinical outcome in psoriasis patients, who often suffer co-morbidities related to smoking.^{34, 36}

There are several strengths and limitations of our study. It is the largest, prospective assessment of multiple markers of smoking status, duration and intensity in relation to the risk of psoriasis. Similar to other population-based epidemiologic studies of psoriasis,^{3, 37, 38} we did not confirm the nurses' self-reported physician-diagnosis of psoriasis clinically with an examination by a dermatologist. A recent French study of a non-health professional population reported that the agreement between self-reported and dermatologists' diagnoses of psoriasis was moderate, although it was the second best among five common skin disorders.³⁹ While we expect the overall accuracy of self-reported physician-diagnosis of psoriasis to be higher among registered nurses, as was the case with other health data in our cohort, the corresponding accuracy against a dermatologist's examination is not available. However, when we additionally adjusted for self-reported physician-diagnosed co-morbidities associated with increased smoking such as asthma, chronic obstructive lung disease, cardiovascular disease, and hypertension, our results did not change materially. These data suggest that these co-morbidities associated with smoking did not contribute to an increased ascertainment of psoriasis among women smokers in our cohort. Furthermore, any non-differential misclassification of psoriasis would have biased the study results toward the null and would not explain the strong associations observed in this study. Nonetheless, confirmation of these results using more specific case definitions of psoriasis as well as evaluation of psoriasis subtypes would be valuable.

The restriction to registered nurses in our cohort is both a strength and a limitation. The cohort of well-educated women minimizes potential for confounding associated with socioeconomic status, and we were able to obtain high quality data with minimal loss to follow-up. Although the absolute rates of psoriasis and frequency of smoking may not be representative of a random sample of US women, the biological effects of smoking should be similar. Our findings would be most directly generalizable to Caucasian women with no history of psoriasis. Furthermore, between the reported bimodal peaks of psoriasis onset time (23 and 55 years),⁴⁰ the age range of our cohort during the follow-up tended to overlap more with the second peak of incidence. Thus, our results may be more applicable to the later-onset cases of psoriasis.

In conclusion, this prospective study suggests that the risk of incident psoriasis in women is increased in past and current smokers, and with increasing duration and intensity of smoking. The risk of incident psoriasis among former smokers decreases nearly to that of never smokers, 20 years after cessation. Smoking cessation may be a potentially important target for the prevention and management of psoriasis.

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Table 1
Baseline Characteristics within Categories of Smoking Status (1991) in the Nurses' Health Study II

	Never	Past	Current
Number	51779	17730	9023
Mean Age (yrs)	35.3	36.6	36.1
BMI (mean)	24.4	24.6	24.5
Alcohol (g/d)	2.4	4.4	5.4
Smoking Exposures			
Pack-Years	0	9.1	16.1
Average number of cigarettes per day	0	14.2	15.9
Duration of smoking (yrs)	0	12.3	19.6
Passive Smoking Exposures *			
Mother smoked while pregnant (%)	21.1	25.5	28.7
Parent smoked at home (%)	55.9	64.9	68.6
Lived > 20 years with a smoker (%)	3.5	7.8	34.6

* Ascertained in 1999

Table 2
Relative Risk of Psoriasis by Smoking Status and Pack-Years among Women

	Cases of Psoriasis	Person Years	Age adjusted RR (95% CI)	Multivariate RR* (95% CI)
Smoking Status				
Never	494	711823	1.00	1.00
Past	262	265298	1.40 (1.20–1.62)	1.37 (1.17–1.59)
Current	131	104804	1.82 (1.50–2.21)	1.78 (1.46–2.16)
<i>P for Trend</i>			<0.001	<0.001
Pack-Years				
Never	494	711823	1.00	1.00
1–10	158	190389	1.20 (1.00–1.43)	1.20 (1.00–1.44)
11–20	120	104463	1.67 (1.37–2.04)	1.60 (1.31–1.97)
≥ 21	115	73781	2.19 (1.78–2.70)	2.05 (1.66–2.53)
<i>P for trend</i>			<0.001	<0.001
Pack-Years for Current Smokers				
Never	494	711823	1.00	1.00
1–10	17	23655	1.06 (0.65–1.71)	1.05 (0.64–1.71)
11–20	37	34863	1.59 (1.14–2.23)	1.57 (1.12–2.20)
≥ 21	75	45359	2.35 (1.84–3.00)	2.25 (1.76–2.89)
<i>P for trend</i>			<0.001	<0.001
Pack-Years for Past Smokers				
Never	494	711823	1.00	1.00
1–10	140	165719	1.21 (1.00–1.46)	1.22 (1.01–1.47)
11–20	82	68857	1.69 (1.33–2.14)	1.61 (1.27–2.04)
≥ 21	37	27756	1.78 (1.27–2.50)	1.61 (1.14–2.26)
<i>P for trend</i>			<0.001	<0.001

* The multivariate model adjusts for age, BMI, and alcohol intake.

Table 3
Relative Risk of Psoriasis by Intensity and Duration of Smoking Among Past and Current Women Smokers (1991–2005)

	Cases of Psoriasis	Person-Years	Age-Adjusted RR (95% CI)	Multivariate RR (95% CI)*
Current smokers				
Smoking Intensity (cigarettes/day)				
Never	494	711823	1.00	1.00
1–14	50	51197	1.40 (1.05–1.87)	1.40 (1.04–1.88)
15–24	52	37124	2.06 (1.54–2.74)	2.00 (1.50–2.67)
≥ 25	28	14754	2.81 (1.92–4.11)	2.54 (1.73–3.73)
<i>P for trend</i>			<0.001	<0.001
Smoking Duration (y)				
Never	494	711823	1.00	1.00
<20	21	28047	1.09 (0.70–1.70)	1.07 (0.69–1.66)
20 to 29	67	51662	2.07 (1.60–2.68)	2.02 (1.56–2.62)
≥ 30	41	24636	2.05 (1.48–2.85)	2.00 (1.44–2.78)
<i>P for trend</i>			<0.001	<0.001
Past smokers				
Smoking Intensity (cigarettes/day)				
Never	494	711823	1.00	1.00
1–14	140	149011	1.33 (1.10–1.61)	1.34 (1.10–1.62)
15–24	76	74947	1.43 (1.13–1.83)	1.39 (1.09–1.77)
≥ 25	44	37057	1.68 (1.23–2.29)	1.53 (1.12–2.09)
<i>P for trend</i>			<0.001	<0.001
Smoking Duration (y)				
Never	494	711823	1.00	1.00
<10	41	50760	1.15 (0.83–1.58)	1.16 (0.84–1.59)
10–19	156	163423	1.38 (1.15–1.65)	1.36 (1.13–1.63)
≥ 20	62	49311	1.67 (1.28–2.19)	1.57 (1.19–2.06)
<i>P for trend</i>			<0.001	<0.001

*The multivariate model adjusts for age, BMI, and alcohol intake.

Table 4
Relative Risk of Psoriasis by Years since Quitting Smoking (1991–2005)

	Cases of Psoriasis	Person-Years	Age-Adjusted RR (95% CI)	Multivariate RR (95% CI)*
Never	494	711823	1.00	1.00
<10	103	87616	1.71 (1.38–2.11)	1.61 (1.30–2.00)
10–19	96	109760	1.33 (1.07–1.66)	1.31 (1.05–1.64)
≥ 20	63	67006	1.14 (0.87–1.49)	1.15 (0.88–1.51)
<i>P for trend</i>			0.004	0.007

*The multivariate model adjusts for age, BMI, and alcohol intake.

Table 5
Relative Risk of Psoriasis by Exposure to Passive Smoke (reported in 1999)

Exposure	Cases of Psoriasis	Person-Years	Age-Adjusted RR (95% CI)	Multivariate Adjusted Model RR (95% CI) *
Prenatal [†]				
No	496	651212	1.00	1.00
Yes	248	248952	1.31 (1.13–1.53)	1.21 (1.04–1.41)
Childhood [‡]				
No	316	440674	1.00	1.00
Yes	576	644984	1.26 (1.10–1.45)	1.18 (1.02–1.35)
Adult [§]				
No	402	567271	1.00	1.00
Yes	414	429580	1.35 (1.18–1.56)	1.10 (0.95–1.28)

[†] Mother smoked while pregnant with the participant

[‡] At least one parent smoked regularly at home during participants' childhood

[§] Lived at least one year with someone who smoked regularly inside the home after age 18

* Adjusted for age, updated BMI, alcohol consumption, and smoking status