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Original Contribution

Smoking and Risk of Incident Psoriasis Among Women and Men in the United States: A Combined Analysis

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The authors evaluated the association between smoking and the incidence of psoriasis among 185,836 participants from a cohort of older women (the Nurses' Health Study, 1996–2008), a cohort of younger women (the Nurses' Health Study II, 1991–2005), and a cohort of men (Health Professionals' Follow-up Study, 1986–2006). Information on smoking was collected biennially during follow-up. The authors identified a total of 2,410 participants with incident psoriasis. Compared with never smokers, past smokers had a relative risk of incident psoriasis of 1.39 (95% confidence interval (CI): 1.27, 1.52) and current smokers had a relative risk of 1.94 (95% CI: 1.64, 2.28). For current smokers who smoked 1–14 cigarettes/day, the relative risk was 1.81 (95% CI: 1.38, 2.36); for those who smoked 15–24 cigarettes/day, the relative risk was 2.04 (95% CI: 1.68, 2.47); and for those who smoked 25 or more cigarettes/day, the relative risk was 2.29 (95% CI: 1.74, 3.01). There was a trend toward an increased risk of psoriasis with increasing pack-years or duration of smoking ($P_{trend} < 0.0001$). The risk was highest among smokers who had 65 or more pack-years of smoking (relative risk = 2.72, 95% CI: 2.05, 3.60) and among those with a smoking duration of 30 or more years (relative risk = 1.99, 95% CI: 1.75, 2.25). The authors observed a graded reduction of risk with an increase in time since smoking cessation ($P_{trend} < 0.0001$). In this study, smoking was found to be an independent risk factor for psoriasis in both women and men. Psoriasis risk was particularly augmented for heavy smokers and persons with longer durations of smoking.

cohort studies; psoriasis; smoking

Abbreviations: HPFS, Health Professionals' Follow-up Study; NHS, Nurses' Health Study; NHS II, Nurses' Health Study II.

Psoriasis is a T-cell-mediated inflammatory disease (1–3). It is now recognized as a systemic inflammatory disorder, and inflammation and increased prevalence of unhealthy lifestyle factors in psoriasis have been independently associated with diabetes, hypertension, and cardiovascular disease (4–6).

Smoking has an impact on the immune system and disturbs endogenous antioxidant defenses (7–13). Previous studies have shown that smoking has adverse effects on the skin (14, 15). A correlation between smoking and the risk of psoriasis was demonstrated in past cross-sectional studies and case-control studies, providing evidence of a dose-effect relation between smoking and psoriasis; however, the specific effects on women and men are still unknown (16–26).

Data from prospective studies on smoking and the risk of psoriasis are sparse. In 2007, a preliminary analysis of data from the Nurses' Health Study II (NHS II) showed that smoking was associated with an elevated risk of incident psoriasis among young women (27). We now have access to the complete data set of women with psoriasis from the study implementation until 2005. We also had the opportunity to evaluate the risk of psoriasis among older women and men. It is interesting to note that elevated estrogen levels have been correlated with improvement in psoriasis, whereas smoking has been implicated to have an antiestrogen effect (24, 28–30). Moreover, younger women tend to have higher rates of type 1 psoriasis, and smoking may play different roles in different types of psoriasis (3). Hence, evaluating the association between smoking and risk of psoriasis in older women or men is necessary because no prospective data are currently available. We had the opportunity to probe into the overall effect

of smoking on the risk of psoriasis in a combined data set with different genders and age distributions.

In the present study, we investigated the associations between smoking status, quantity, duration, and cessation and exposure to environmental tobacco smoke and the risk of incident psoriasis in a total population of 185,836 participants from the Nurses' Health Study (NHS), NHS II, and Health Professionals' Follow-up Study (HPFS).

MATERIALS AND METHODS

Study cohort

Study participants were from 3 ongoing longitudinal cohort studies: the NHS, NHS II, and HPFS. In brief, the NHS was established in 1976 when 121,701 married female registered nurses who were 30–55 years of age and living in the United States were enrolled using a mailed questionnaire that included questions about their medical histories and lifestyle practices. The NHS II began in 1989 when 116,430 female nurses who were 25–42 years of age completed a mailed questionnaire. The HPFS consisted of 51,529 male health professionals who completed their baseline questionnaire in 1986. Information on lifestyle factors and medical histories was collected biennially via mailed questionnaires. The follow-up rates exceed 90% in all 3 studies.

The present study was approved by the institutional review board of Partners Health Care System (Boston, Massachusetts). We consider the participants' completion and return of the self-administered questionnaire to be informed consent.

Assessment of main exposure

Starting in 1976 (NHS), 1989 (NHS II), and 1986 (HPFS), the smoking status (never, past, or current) and number of cigarettes smoked among current smokers was assessed biennially by self-reported number of cigarettes per day divided into 6 categories (1–4, 5–14, 15–24, 25–34, 35–44, or $\geq$45 cigarettes/day). In 1976, current and past smokers in the NHS were asked about the age at which they began smoking, whether they had ever stopped smoking for 6 or more months, and the age at which they quit. A question about the quantity of past smoking (cigarettes smoked per day) was asked in 1976. In 1989, NHS II participants were asked about their lifetime history of smoking 20 cigarettes or more (1 pack contains 20 cigarettes) and if they had quit, how many years had elapsed since cessation ($<$1 or $\geq$1 year). The average number of cigarettes smoked per day at different ages ($<$15, 15–19, 20–24, 25–29, 30–35, and 36–42 years) was assessed and divided into the above-mentioned 6 categories. In 1986, HPFS participants were asked about their lifetime history of smoking 20 cigarettes or more and if they had quit, how many years had elapsed since cessation ($<$1, 1–2, 3–5, 6–9, or $\geq$10 years). The number of cigarettes smoked per day at different ages ($<$15, 15–19, 20–29, 30–39, 40–49, 50–59, or $\geq$60 years) was assessed and divided into the above-mentioned 6 categories. Data on passive smoking as a child (having parents who smoked at home before the participant was 18 years of age) or as an adult (living $>$1 year with a smoker after 18 years of age) were collected in 1982 (NHS), 1999 (NHS II), and 2004 (HPFS).

Duration, pack-years of smoking, and years since quitting were derived based on answers to the biennial questionnaires. Duration of smoking was calculated as the difference between age at smoking initiation and current age for current smokers and between ages at onset and cessation for past smokers. Years since cessation were obtained for past smokers by deducting the ages at which they quit smoking from their current ages. We multiplied the number of packs of cigarettes smoked per day by the number of years of smoking to estimate pack-years of smoking.

We had detailed biennial smoking information for 106,158 participants in the NHS beginning in 1996, including smoking status, intensity, and duration and time of smoking cessation. We had information for 115,770 participants in the NHS II and 47,336 in the HPFS. There were no marked differences in the main characteristics between participants for whom we had complete information about smoking and those for whom information was missing in the 3 cohorts.

Assessment of main outcome (psoriasis)

The outcome of interest was a diagnosis of psoriasis. In 2008, NHS participants responded to an item on the questionnaire that asked about any history of clinician-diagnosed psoriasis and the date of diagnosis (1997 or before, 1998–2001, 2002–2005, 2006–2007, or 2008). Of the 69,243 participants who responded, 2,161 reported having been diagnosed with psoriasis, and 827 of those diagnoses occurred after 1997. In 2005, NHS II participants were asked about clinician diagnoses of psoriasis and the date at which they occurred (before 1991, 1991–1994, 1995–1998, 1999–2002, or 2003–2005). Of the 97,476 participants who responded, 2,529 reported being diagnosed with psoriasis, and 1,151 of those diagnoses occurred after 1991. In 2008, HPFS participants responded to questions about whether they had clinician-diagnosed psoriasis and, if so, the date of diagnosis (before 1986, 1986–1990, 1991–1995, 1996–2000, 2001–2004, or 2005 or later). In all, 26,549 men responded, and 1,171 reported psoriasis. A total of 571 diagnoses occurred after 1986.

We confirmed a subset of patients with self-reported psoriasis in NHS and NHS II using a psoriasis screening tool, a 1-page self-administered questionnaire that comprises 7 questions (31). Three questions were about the type of medical provider that made the diagnosis and the other 4 inquired about the phenotypes of psoriasis. A pilot study showed that the psoriasis screening tool had a sensitivity of 99% and a specificity of 94% for identifying psoriasis. The confirmation rate of self-reports reached 92%.

Assessment of covariates

Race/ethnicity was reported in 1992 (NHS), 1989 (NHS II), and 1986 (HPFS). Information on height was collected in 1976 (NHS), 1989 (NHS II), and 1986 (HPFS). Weight was assessed biennially. A high correlation between self-reported and measured body weight was reported (32). We calculated body mass index as weight in kilograms divided by height in meters squared. Physical activity level was determined in 1996, 1998, 2000, and 2004 for NHS participants, in 1991, 1997, 2001, and 2005 for NHS II participants, and in each biennial questionnaire for HPFS participants. Validation studies

Table 1. Age-Standardized Baseline Characteristics of Study Participants by Smoking Status in the Nurses' Health Study (1996–2008), the Nurses' Health Study II (1991–2005), and the Health Professionals' Follow-up Study (1986–2006)[a]

	Nurses' Health Study						Nurses' Health Study II						Health Professionals' Follow-up Study					
	Never Smoker		Past Smoker		Current Smoker		Never Smoker		Past Smoker		Current Smoker		Never Smoker		Past Smoker		Current Smoker	
	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%
Age[b], years	61.6 (7.0)		61.6 (6.6)		59.9 (6.2)		35.8 (4.7)		37.0 (4.5)		36.6 (4.6)		50.1 (8.2)		52.1 (8.1)		49.7 (7.2)	
White race		95.1		96.2		96.6		94.4		97.2		96.8		95.7		96.2		95.4
Body mass index[c]	26.6 (5.2)		26.8 (5.2)		25.2 (4.5)		24.6 (5.3)		24.6 (5.2)		24.5 (5.2)		25.1 (3.0)		25.5 (3.0)		25.2 (3.1)	
Alcohol intake, g/day	3.2 (6.6)		6.3 (9.8)		7.4 (11.8)		2.4 (4.9)		4.3 (6.7)		5.3 (9.1)		8.5 (12.4)		14.3 (16.6)		18.4 (21.1)	
Physical activity, metabolic equivalent hours/week	18.5 (22.2)		19.3 (22.9)		15.8 (20.3)		20.4 (26.1)		22.5 (28.8)		19.7 (26.8)		22.3 (30.3)		22.3 (28.5)		16.7 (22.6)	
Mental Health Index-5 score $\leq$52[d]		4.7		5.4		8.1		12.2		13.1		18.7						
Antidepressant use[e]		5.2		6.6		6.2		9.2		11.8		14.5		0.8		1.0		1.9
Postmenopausal hormone use		86.7		87.2		91.1		3.2		3.0		4.4						
Personal history of a chronic disease																		
Diabetes mellitus		3.8		3.7		2.6		0.6		0.5		0.4		1.3		1.4		1.4
Cancer		5.5		6.0		4.9		1.2		1.7		1.5		2.2		2.2		1.5
Cardiovascular disease		4.2		5.3		4.1		0.4		0.4		0.5		1.2		2.3		1.9
Hypertension		28.3		29.2		23.1		3.4		3.1		3.0		15.6		17.7		13.6
Hypercholesterolemia		35.5		36.8		31.4		9.0		8.8		10.1		10.2		11.8		10.8

Abbreviation: SD, standard deviation.

[a] Values are standardized to the age distribution of the study population.

[b] Values are not age-adjusted.

[c] Weight (kg)/height $(m)^2$.

[d] Score determined in 1996 in the Nurses' Health Study and in 1993 in the Nurses' Health Study II.

[e] Antidepressant use was assessed in 1990 in the Health Professionals' Follow-up Study.

Table 2. Age- and Multivariate-Adjusted Relative Risks for Psoriasis by Smoking Status in the Nurses' Health Study (1996–2008), the Nurses' Health Study II (1991–2005), and the Health Professionals' Follow-up Study (1986–2006)

	No. of Cases	No. of Person-Years	Age-Adjusted		Multivariate-Adjusted[a]	
			RR	95% CI	RR	95% CI
Nurses' Health Study						
Never smokers	295	352,829	1.00	Referent	1.00	Referent
Past smokers	395	336,673	1.38	1.19, 1.61	1.32	1.13, 1.54
Current smokers	114	63,002	2.25	1.81, 2.80	2.26	1.81, 2.82
1–14 cigarettes/day	54	31,157	2.12	1.59, 2.84	2.19	1.63, 2.94
15–24 cigarettes/day	43	24,337	2.23	1.61, 3.07	2.22	1.60, 3.07
≥25 cigarettes/day	17	7,508	2.88	1.77, 4.71	2.65	1.61, 4.34
P_{trend}			<0.0001		<0.0001	
Nurses' Health Study II						
Never smokers	629	868,253	1.00	Referent	1.00	Referent
Past smokers	332	311,088	1.43	1.25, 1.63	1.40	1.22, 1.61
Current smokers	163	129,844	1.81	1.52, 2.15	1.80	1.51, 2.14
1–14 cigarettes/day	65	62,783	1.47	1.14, 1.89	1.49	1.15, 1.92
15–24 cigarettes/day	66	47,813	2.02	1.57, 2.61	2.00	1.55, 2.58
≥25 cigarettes/day	32	19,248	2.47	1.73, 3.52	2.33	1.63, 3.33
P_{trend}			<0.0001		<0.0001	
Health Professionals' Follow-up Study						
Never smokers	200	230,555	1.00	Referent	1.00	Referent
Past smokers	250	188,812	1.51	1.25, 1.82	1.47	1.22, 1.79
Current smokers	32	22,939	1.78	1.22, 2.58	1.71	1.17, 2.50
1–14 cigarettes/day	17	10,852	1.96	1.19, 3.22	1.92	1.16, 3.16
15–24 cigarettes/day	9	6,835	1.68	0.86, 3.28	1.61	0.82, 3.15
≥25 cigarettes/day	6	5,251	1.49	0.66, 3.37	1.40	0.62, 3.18
P_{trend}			0.03		0.04	
All studies combined						
Never smokers	1,124	1,451,637	1.00	Referent	1.00	Referent
Past smokers	977	836,573	1.43	1.31, 1.56	1.39	1.27, 1.52
Current smokers	309	215,785	1.95	1.68, 2.27	1.94	1.64, 2.28
1–14 cigarettes/day	136	104,792	1.79	1.38, 2.31	1.81	1.38, 2.36
15–24 cigarettes/day	118	78,985	2.06	1.70, 2.49	2.04	1.68, 2.47
≥25 cigarettes/day	55	32,007	2.45	1.86, 3.21	2.29	1.74, 3.01
P_{trend}			<0.0001		<0.0001	

Abbreviations: CI, confidence interval; RR, relative risk.

[a] Adjusted for age (continuous variable), race (white, Asian, Hispanic, or black), body mass index (weight (kg)/height (m)^2; <18.5, 18.5–24.9, 25–29.9, 30–34.9, or ≥35), alcohol drinking (none, <4.9, 5.0–9.9, 10–14.9, 15–29.9, or ≥30.0 g/day), and physical activity level (metabolic equivalent hours/week in quintiles).

indicated good validity and reproducibility for the physical activity measurements (33). Data on alcohol intake were available every 4 years beginning in 1994 (NHS), 1991 (NHS II), and 1986 (HPFS). Menopausal status and personal history of postmenopausal hormone use, cancer, diabetes mellitus, cardiovascular disease, hypertension, and hypercholesterolemia were collected biennially. Depressive symptoms were assessed using the Mental Health Index-5 in both the NHS (1996 and 2000) and the NHS II (1993, 1997, and 2001). This index has been shown to have high sensitivity and specificity for major depression (34). Participants reported regular antidepressant medication use biennially from 1996 (NHS), 1993 (NHS II), and 1990 (HPFS).

Statistical analysis

Participants who reported psoriasis that occurred before the beginning of follow-up were excluded. We calculated

Table 3. Age- and Multivariate-Adjusted Relative Risks of Psoriasis by Pack-Years of Smoking in the Nurses' Health Study (1996–2008), the Nurses' Health Study II (1991–2005), and Health Professionals' Follow-up Study (1986–2006)

	No. of Cases	No. of Person-Years	Age-Adjusted		Multivariate-Adjusted[a]	
			RR	95% CI	RR	95% CI
Nurses' Health Study						
Never smokers	295	352,829	1.00	Referent	1.00	Referent
Pack-years of smoking in current and present smokers						
<10	115	133,475	1.03	0.83, 1.28	1.03	0.83, 1.28
10–24	119	113,660	1.24	1.00, 1.53	1.19	0.96, 1.48
25–44	149	93,231	1.90	1.56, 2.31	1.80	1.47, 2.20
45–64	81	42,409	2.23	1.74, 2.86	2.11	1.64, 2.71
≥65	45	16,900	3.10	2.26, 4.25	2.84	2.07, 3.91
P_{trend}			<0.0001		<0.0001	
Nurses' Health Study II						
Never smokers	629	868,253	1.00	Referent	1.00	Referent
Pack-years of smoking in current and present smokers						
<10	174	202,479	1.20	1.01, 1.41	1.20	1.02, 1.43
10–24	224	183,257	1.72	1.48, 2.01	1.68	1.43, 1.96
25–44	84	50,487	2.07	1.64, 2.61	1.97	1.56, 2.48
45–64	12	4,449	2.68	1.51, 4.77	2.56	1.44, 4.56
≥65	1	261	3.11	0.44, 22.05	2.93	0.41, 20.79
P_{trend}			<0.0001		<0.0001	
Health Professionals' Follow-up Study						
Never smokers	200	230,555	1.00	Referent	1.00	Referent
Pack-years of smoking in current and present smokers						
<10	60	46,570	1.45	1.09, 1.94	1.45	1.09, 1.94
10–24	101	87,463	1.34	1.05, 1.70	1.32	1.03, 1.68
25–44	78	55,374	1.66	1.27, 2.16	1.59	1.21, 2.08
45–64	32	17,225	2.21	1.51, 3.23	2.11	1.44, 3.10
≥65	11	5,117	2.40	1.30, 4.43	2.28	1.23, 4.24
P_{trend}			<0.0001		<0.0001	
All studies combined						
Never smokers	1124	1,451,637	1.00	Referent	1.00	Referent
Smokers by pack-years of smoking						
<10	349	382,524	1.19	1.01, 1.40	1.19	1.01, 1.41
10–24	444	384,380	1.44	1.16, 1.79	1.40	1.12, 1.74
25–44	311	199,092	1.89	1.65, 2.15	1.80	1.57, 2.05
45–64	125	64,083	2.27	1.87, 2.76	2.16	1.77, 2.63
≥65	57	22,278	2.94	2.23, 3.89	2.72	2.05, 3.60
P_{trend}			<0.0001		<0.0001	

Abbreviations: CI, confidence interval; RR, relative risk.

[a] Adjusted for age (continuous variable), race (white, Asian, Hispanic, or black), body mass index (weight (kg)/height $(m)^2$; <18.5, 18.5–24.9, 25–29.9, 30–34.9, or ≥35), alcohol drinking (none, <4.9, 5.0–9.9, 10–14.9, 15–29.9, or ≥30.0 g/day), and physical activity level (metabolic equivalent hours/week in quintiles).

person-years from the return date of baseline questionnaire (1996 for NHS, 1991 for NHS II, and 1986 for HPFS) to the date of diagnosis of psoriasis or the end of follow-up (June 2008 for NHS, June 2005 for NHS II, and January 2006 for HPFS), whichever came first.

Smoking status was categorized as never, past, or current. Current smokers were categorized by the number of cigarettes smoked per day: 1–14, 15–24, or ≥25. We had the exact number of years since smoking cessation for women and classified it into 7 groups: ≤2, 3–5, 6–9, 10–19, 20–29, 30–39,

Table 4. Age- and Multivariate-Adjusted Relative Risks of Psoriasis by Smoking Duration in the Nurses' Health Study (1996–2008), the Nurses' Health Study II (1991–2005), and Health Professionals' Follow-Up Study (1986–2006)

	No. of Cases	No. of Person-Years	Age-Adjusted		Multivariate-Adjusted[a]	
			RR	95% CI	RR	95% CI
Nurses' Health Study						
Never smokers	295	352,829	1.00	Referent	1.00	Referent
Smokers' duration of smoking, years						
<10	50	73,803	0.81	0.60, 1.10	0.81	0.60, 1.10
10–19.9	86	88,807	1.15	0.90, 1.46	1.13	0.88, 1.43
20–29.9	102	79,502	1.53	1.22, 1.91	1.45	1.15, 1.82
≥30	271	157,564	2.02	1.71, 2.39	1.94	1.64, 2.30
P_{trend}			<0.0001		<0.0001	
Nurses' Health Study II						
Never smokers	629	868,253	1.00	Referent	1.00	Referent
Smokers' duration of smoking, years						
<10	52	60,344	1.20	0.90, 1.59	1.21	0.91, 1.61
10–19.9	224	231,677	1.37	1.18, 1.60	1.35	1.16, 1.58
20–29.9	153	118,082	1.85	1.55, 2.22	1.80	1.50, 2.15
≥30	66	30,829	2.08	1.60, 2.70	2.07	1.59, 2.69
P_{trend}			<0.0001		<0.0001	
Health Professionals' Follow-up Study						
Never smokers	200	230,555	1.00	Referent	1.00	Referent
Smokers' duration of smoking, years						
<10	68	62,442	1.25	0.95, 1.64	1.24	0.94, 1.64
10–19.9	70	53,423	1.52	1.16, 2.00	1.49	1.13, 1.96
20–29.9	56	46,386	1.40	1.04, 1.88	1.36	1.01, 1.84
≥30	88	49,500	2.09	1.62, 2.71	2.03	1.56, 2.64
P_{trend}			<0.0001		<0.0001	
All studies combined						
Never smokers	1,124	1,451,637	1.00	Referent	1.00	Referent
Smokers' duration of smoking, years						
<10	170	196,589	1.07	0.83, 1.39	1.07	0.83, 1.39
10–19.9	380	373,907	1.34	1.17, 1.53	1.32	1.15, 1.51
20–29.9	311	243,970	1.63	1.37, 1.92	1.56	1.31, 1.86
≥30	425	237,893	2.05	1.81, 2.32	1.99	1.75, 2.25
P_{trend}			<0.0001		<0.0001	

Abbreviations: CI, confidence interval; RR, relative risk.

[a] Adjusted for age (continuous variable), race (white, Asian, Hispanic, or black), body mass index (weight (kg)/height (m)^2; <18.5, 18.5–24.9, 25–29.9, 30–34.9, or ≥35), alcohol drinking (none, <4.9, 5.0–9.9, 10–14.9, 15–29.9, or ≥30.0 g/day), and physical activity level (metabolic equivalent hours/week in quintiles).

or ≥40 years. For HPFS participants, it was classified into 4 categories: ≤2, 3–5, 6–9, or ≥10 years. Other smoking variables that were analyzed included duration of smoking (<10, 10–19.9, 20–29.9, or ≥30 years) and pack-years of smoking (<10, 10–24, 25–44, 45–64, or ≥65 pack-years). Passive smoking (yes or no) was assessed as exposure to parental smoking before 18 years of age or passive smoking for 1 year or more after 18 years of age.

We conducted Cox proportional hazards analysis stratified by age and follow-up interval to estimate the age- and multivariate-adjusted relative risks and 95% confidence intervals. Trend tests were carried out using medians in different

Table 5. Age- and Multivariate-Adjusted Relative Risks of Psoriasis by Years Since Smoking Cessation in the Nurses' Health Study (1996–2008), the Nurses' Health Study II (1991–2005), and Health Professionals' Follow-up Study (1986–2006)

	No. of Cases	No. of Person-Years	Age-Adjusted		Multivariate-Adjusted[a]	
			RR	95% CI	RR	95% CI
Nurses' Health Study						
Never smokers	295	352,829	1.00	Referent	1.00	Referent
Years since smoking cessation in past smokers						
≥40	49	47,299	1.11	0.82, 1.51	1.11	0.81, 1.50
30–39	71	81,524	1.03	0.79, 1.34	1.01	0.78, 1.31
20–29	81	70,767	1.37	1.07, 1.75	1.30	1.01, 1.67
10–19	109	81,441	1.60	1.28, 1.99	1.49	1.20, 1.87
6–9	41	25,292	1.97	1.42, 2.74	1.85	1.33, 2.57
3–5	32	19,123	2.01	1.40, 2.90	1.89	1.31, 2.73
≤2	12	11,228	1.34	0.75, 2.38	1.28	0.72, 2.28
P_{trend}[b]			<0.0001		<0.0001	
Nurses' Health Study II						
Never smokers	629	868,253	1.00	Referent	1.00	Referent
Years since smoking cessation in past smokers						
≥40	0	39				
30–39	14	8,986	1.00	0.58, 1.72	0.99	0.58, 1.70
20–29	79	74,649	1.12	0.88, 1.42	1.12	0.88, 1.42
10–19	126	130,123	1.50	1.24, 1.82	1.47	1.21, 1.79
6–9	39	41,270	1.43	1.04, 1.98	1.38	1.00, 1.91
3–5	41	31,475	1.90	1.38, 2.60	1.82	1.33, 2.50
≤2	33	24,548	2.02	1.42, 2.87	1.93	1.36, 2.74
P_{trend}[b]			<0.0001		0.0003	
Health Professionals' Follow-up Study						
Never smokers	200	230,555	1.00	Referent	1.00	Referent
Years since smoking cessation in past smokers						
≥10	208	155,158	1.48	1.22, 1.80	1.45	1.19, 1.78
6–9	21	13,778	1.99	1.27, 3.12	1.93	1.22, 3.04
3–5	10	9,950	1.33	0.70, 2.51	1.27	0.67, 2.42
≤2	11	9,716	1.50	0.82, 2.77	1.45	0.78, 2.67
P_{trend}[b]			0.38		0.50	

Table continues

categories. Population-attributable risk and its corresponding 95% confidence interval were calculated to estimate the percentage of cases of psoriasis that would be prevented by eliminating exposure to smoking. For the combined analysis, we tested the between-study heterogeneity and estimated the overall association from the random-effects model (weighted proportionately to the inverse of the sum of the study-specific variance plus the common between-study variance) and the fixed-effects model (weighted proportionately to the inverse of the study-specific variance) (35).

We performed updated analyses using the most recent data for each follow-up interval. Multivariate relative risks were calculated after adjusting for age, race (white, Asian, Hispanic, or black), body mass index (<18.5, 18.5–24.9, 25–29.9, 30–34.9, or ≥35), physical activity level (metabolic equivalent hours/week, in quintiles), and alcohol intake (0, <4.9, 5.0–9.9, 10–14.9, 15–29.9, or ≥30.0 g/day). In addition, level of depressive symptoms (Mental Health Index-5 scores of 86–100, 76–85, 53–75, or 0–52), antidepressant medication use (never, past, or current), menopausal status and postmenopausal hormone use (premenopausal, never user, or current/past user), and personal history of chronic diseases (yes or no, including cancer, diabetes, cardiovascular disease, hypertension, and hypercholesterolemia) were included in the sensitivity analysis. We included these variables in the models to minimize residual confounding because they were associated with psoriasis or could confound the association between smoking and psoriasis. For analysis of passive smoking, we

Table 5. Continued

	No. of Cases	No. of Person-Years	Age-Adjusted		Multivariate-Adjusted[a]	
			RR	95% CI	RR	95% CI
All studies combined						
Never smokers	1,124	1,451,637	1.00		1.00	
Years since smoking cessation in past smokers						
≥10	737	649,986	1.34	1.22, 1.48	1.31	1.19, 1.45
6–9	101	80,340	1.74	1.39, 2.17	1.66	1.34, 2.04
3–5	83	60,548	1.85	1.48, 2.32	1.77	1.41, 2.21
≤2	56	45,492	1.74	1.33, 2.28	1.67	1.27, 2.18
P_{trend}[b]			<0.0001		<0.0001	
Nurses' Health Study and Nurses' Health Study II						
Never smokers	924	1,22,1082	1.00		1.00	
Years since smoking cessation in past smokers						
≥40	49	47,338	1.11	0.82, 1.51	1.11	0.81, 1.50
30–39	85	90,510	1.02	0.81, 1.30	1.01	0.80, 1.27
20–29	160	145,416	1.23	1.01, 1.51	1.20	1.01, 1.43
10–19	235	211,564	1.54	1.33, 1.78	1.48	1.28, 1.72
6–9	80	66,562	1.68	1.23, 2.30	1.60	1.20, 2.12
3–5	73	50,598	1.95	1.53, 2.47	1.85	1.46, 2.35
≤2	45	35,776	1.75	1.20, 2.57	1.68	1.15, 2.46
P_{trend}[b]			<0.0001		<0.0001	

Abbreviations: CI, confidence interval; RR, relative risk.

[a] Adjusted for age (continuous variable), race (white, Asian, Hispanic, or black), body mass index (weight (kg)/height $(m)^2$; <18.5, 18.5–24.9, 25–29.9, 30–34.9, or ≥35), alcohol drinking (none, <4.9, 5.0–9.9, 10–14.9, 15–29.9, or ≥30.0 g/day), and physical activity level (metabolic equivalent hours/week in quintiles).

[b] Never smokers were excluded from the trend test.

evaluated the association between all participants and never smokers.

All statistical analyses were conducted using SAS, version 9.2 (SAS Institute, Inc., Cary, North Carolina). All statistical tests were 2-tailed, and the significance level was set at $P < 0.05$.

RESULTS

A total of 185,836 participants were enrolled in our study, including 66,241 from the NHS, 95,531 from the NHS II, and 24,064 from the HPFS. Characteristics of the participants by updated smoking status during follow-up are listed in Table 1. Current smokers tended to have higher alcohol intakes.

In the 2,503,994 person-years of follow-up, there were 2,410 documented cases of incident psoriasis. Compared with never smokers, current and past smokers had significantly higher incidences of psoriasis. The relative risks are shown in Table 2. Combined analysis showed a trend toward increased risk of developing psoriasis overall with increasing smoking intensity in current smokers.

A marked trend was found with increasing pack-years. Compared with never smokers, smokers had a multivariate relative risk that was augmented from 1.19 for less than 10 pack-years of smoking to 2.72 for 65 or more pack-years of smoking (Table 3). We observed a gradual elevation in the incidence of psoriasis that corresponded to a longer duration of smoking. Especially for those who smoked for more than 30 years, the risk was increased approximately 2-fold (Table 4).

We calculated the population-attributable risk assuming smoking as the exposure that was linked with psoriasis, although there could be other factors on the causal pathway. In the NHS, 20% of the cases of incident psoriasis might have been prevented by the elimination of smoking. Similarly, the population-attributable risk was 15% in the NHS II and 19% in the HPFS. For all participants, 17.5% of the incidents of psoriasis were attributable to having ever smoked.

Combined analysis indicated an inverse association between years since quitting smoking and the risk of psoriasis. Both male and female past smokers had an augmented risk after having quit for more than 10 years. Further analysis demonstrated that after having quit for 20–29 years, the risk was still significantly higher for women (Table 5).

Analysis on passive smoking showed a slightly increased risk of psoriasis associated with exposure to parental smoking during childhood (relative risk = 1.10, 95% confidence interval: 1.00, 1.21). However, we observed a positive association with adulthood exposure to passive smoking only for men (relative risk = 1.27, 95% confidence interval: 1.04, 1.56).

Secondary analyses were performed using only confirmed cases of psoriasis (NHS and NHS II) and replicated findings obtained from self-reported cases (data not shown). Sensitivity analyses were applied to adjust simultaneously for the level of depressive symptomatology (NHS and NHS II) and antidepressive drug use. We did not observe a material change of the results (Web Tables 1–4, available at http://aje.oxfordjournals.org/). We also adjusted for personal history of chronic diseases in all participants and menopausal status and postmenopausal hormone use in women and reached very similar results.

DISCUSSION

In the present study, we investigated the association between smoking and incident psoriasis in pooled cohorts of women and men. We observed a significantly elevated risk of developing psoriasis associated with smoking, and the risk increased with higher cumulative measures. Further, 15%–20% of the incident psoriasis cases could be attributed to past or current smoking, providing evidence that smoking increases the risk of the development of psoriasis among women and men.

Although it is difficult to identify the agents in tobacco smoking that are responsible for the increased risk of psoriasis, a variety of mechanisms may be involved (7, 36, 37). Chronic inhalation of smoke has been shown to alter a wide range of immunologic and inflammatory processes, including innate and adaptive immune responses, which may have an impact on psoriasis (7, 8). Smokers have increased levels of autoantibodies, which account for their higher susceptibility to autoimmune diseases (9). Smoking may induce T-cell proliferation through an increased capacity of antigen-presenting cells caused by nicotine (38) and has been correlated with production of proinflammatory cytokines associated with psoriasis (8, 39). In addition, smoking has been shown to modify the morphology and function of psoriatic polymorphonuclear cells, which constitute the predominant inflammatory infiltrates in psoriasis (37, 40, 41). Cigarette smoking can deliver oxidants directly, induce oxidative stress, and reduce antioxidant levels, which may play a role in the pathogenesis of psoriasis (10–13). Keratinocytes have nicotinic cholinergic receptors that can stimulate calcium influx and accelerate cell differentiation, which could be another possible mechanism (42, 43). Moreover, individuals with psoriasis, especially those with late-onset disease, have a specific psychological profile of elevated depression and anxiety and may be using smoking as a form of ''self-medication'' (44).

Previous cross-sectional and case-control studies have pointed to a link between smoking and psoriasis and reported more cases of psoriasis, more severe phenotypes, and adverse outcomes among smokers (16–25, 45, 46). A preliminary analysis reported the association between incident psoriasis and smoking status, as well as cumulative measures of smoking in younger women (27). Our combined analysis provides further evidence regarding the increased risk of incident psoriasis that is associated with updated smoking measures during follow-up among women and men.

Evidence from past association studies seemed to indicate a stronger association between smoking and psoriasis in women than in men (24, 26). Because of the potential immunologic effect of estrogen in autoimmune diseases and the improvement in psoriasis caused by increasing estrogen levels, the antiestrogen effect of smoking has been postulated as a possible reason for this association (24, 28–30). The differential effect might also be partly explained by differences in psychological stress in individuals with psoriasis, with women reporting higher rates (44). However, the present study did not show material differences in the association among younger versus older women or between women and men. In the 3 cohorts, more than 15% of the incident cases of psoriasis were attributed to smoking, demonstrating the significant role of smoking in pathogenesis of psoriasis. Further, when we accounted for the potential comorbid conditions of smoking-related psoriasis, menopausal status, and depression or carried out secondary analyses including only confirmed psoriasis, the magnitudes of effect estimates were very similar.

Chronic exposure to benzo[a]pyrene, a chemical found in cigarettes, induces a dose-response reduction in the mass and cellularity of lymphoid tissues (7). Cigarette smoke that contains more tar and nicotine can induce faster immunologic changes (7). In the present study, we found a graded elevation of incidence of psoriasis that corresponded to increasing current smoking duration or intensity, underscoring smoking as an independent risk factor for psoriasis.

In our study, we evaluated the risk of psoriasis associated with smoking duration and cessation. Because current smokers may quit smoking over time and some past smokers may resume smoking, updating smoking exposure over time instead of using smoking status just before diagnosis ensured that we did not obscure the harms of continuing smoking and the benefits of cessation. Risk of psoriasis was monotonically increased with increasing duration of smoking and significantly elevated after a duration of 10 years or more, indicating that the accumulation of exposure played a role in psoriasis. Quitting smoking has been shown to decrease the risk of cancer, cardiovascular disease, and early death; however, the time periods required for risks to decrease to levels seen in nonsmokers vary (47, 48). In our study, the risk of developing psoriasis was higher in current smokers than in past smokers, indicating that quitting smoking could positively moderate the immune system and balance the oxidant-antioxidant equilibrium. We observed a monotonic decrease in risk with increasing years of smoking cessation compared with current smoking, with risks equivalent to those of never smokers after 30 years for women, which demonstrates that continuous risk induction would persist until the eradication of extra effect.

There has been growing concern about the harmful effect of inhalation of secondhand smoke because of the higher concentration of harmful compounds in sidestream smoke and exhaled mainstream smoke (7, 49, 50). Setty et al. (27) reported an increased risk of psoriasis associated with prenatal exposure to secondhand smoke. In our study, we observed

a moderately increased risk of psoriasis associated with secondhand smoke during childhood, adding to the knowledge about the negative impact of passive smoking.

On the basis of 3 large cohort studies, we found in a pooled analysis a consistent association between smoking and the risk of incident psoriasis, showing that smoking is an independent risk factor for psoriasis. Our study was reasonably powered. The health professional backgrounds of the participants accounted for the high validity of self-reported exposures and outcomes. We had access to the confirmed psoriasis databases in NHS and NHS II and performed all analyses using only confirmed psoriasis cases; the results remained significant and the effect estimation did not change appreciably. Different sensitivity analyses were applied to ensure precision. Mental health disorders have previously been linked to psoriasis (44, 51–53). Our descriptive analysis showed a higher percentage of participants who had depression and who were using antidepressant medications among smokers. Sensitivity analyses did not reveal material changes in the association between smoking and psoriasis, indicating a significant role of smoking that was independent of depression.

Given the relatively older age of the populations, most of the incident psoriasis cases in the NHS and the HPFS may be type 2 psoriasis, which tends to be less hereditary and less severe (3). Because most type 1 psoriasis occurs before 40 years of age, we stratified the NHS II population by updated age (40 years was the cutoff) but found no marked difference in the results between the 2 strata. The associations of smoking with different types of psoriasis did not seem materially different. Information on physician diagnosis of psoriasis was collected in 2005 or 2008, and therefore our study has retrospective characteristics. Misclassification was possible because we could not obtain information for participants with psoriasis who died before data collection. We compared the characteristics of participants who responded to psoriasis questions in the NHS and HPFS with those who did not respond because participants in those populations were older. The main characteristics were similar, such as body mass index and alcohol intake, although those who responded might be more physically active. However, this may only lead to an underestimation of the study effect. We also performed an analysis stratified by age (cutoff of 60 years) for NHS, and there was no marked difference in the associations in younger and older participants. Although the confirmation rate of self-reported psoriasis was beyond 92% in NHS II and we are very optimistic in the confirmation rate that would be reached in NHS and HPFS (validation ongoing), self-reports that we and others used to assess the outcome are still questionable. However, because we observed a very consistent association between smoking and psoriasis, we have confidence in the overall accuracy of our conclusions. Another limitation lies in the lack of confirmation of self-reported smoking, especially the quantitative and updated assessment of passive smoking, given the difficulty in assessment of exposure to environmental tobacco smoke. Most participants were white and the generalizability is therefore limited.

Although it has important public health implications, there is lack of awareness of the association between smoking and psoriasis. We provide further evidence showing that smoking is an independent risk factor for the development of psoriasis among US women and men. Further work is warranted on the postulated mechanisms underlying this association. Our study suggests that psoriasis is not directly linked to cardiovascular disease but rather is linked with smoking as a mediator. As psoriasis is highly prevalent in our population, broad public messaging that advises smokers to quit smoking or cut down on the intensity to minimize risk is warranted.

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