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## Original Contribution

# Cigarette Smoking and Risk of Incident Rosacea in Women

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The relationship between smoking and rosacea is poorly understood. We aimed to conduct the first cohort study to determine the association between smoking and risk of incident rosacea. We included 95,809 women from Nurses' Health Study II (1991–2005). Information on smoking was collected biennially during follow-up. Information on history of clinician-diagnosed rosacea and year of diagnosis was collected in 2005. We used Cox proportional hazards models to estimate age- and multivariable-adjusted hazard ratios and 95% confidence intervals for the association between different measures of smoking and risk of rosacea. During follow-up, we identified 5,462 incident cases of rosacea. Compared with never smoking, we observed an increased risk of rosacea associated with past smoking (multivariable-adjusted hazard ratio = 1.09, 95% confidence interval: 1.03, 1.16) but a decreased risk associated with current smoking (hazard ratio = 0.65, 95% confidence interval: 0.58, 0.72). We further found that increasing pack-years of smoking was associated with an elevated risk of rosacea among past smokers ($P$ for trend = 0.003) and with a decreased risk of rosacea among current smokers ($P$ for trend < 0.0001). The risk of rosacea was significantly increased within 3–9 years since smoking cessation, and the significant association persisted among past smokers who had quit over 30 years before.

cohort studies; rosacea; smoking

Abbreviations: CI, confidence interval; OC, oral contraceptive; UV, ultraviolet.

Rosacea is a chronic skin disorder characterized by variable flushing, erythema, telangiectasia, edema, papules, and pustules on the cheeks, nose, and central forehead, in addition to rhinophyma and ocular involvement (1–3). It affects approximately 16 million people in the United States and is most frequently observed in people with fair skin (1, 2). At present, an understanding of the pathophysiology of rosacea remains limited. Most experts believe that rosacea is primarily an inflammatory disease (2, 4). Dysfunction in the innate and adaptive immune systems (including an exaggerated response to *Demodex* mite colonization), dysregulation of the vascular and nervous systems, and their interplay with the inflammatory response have been implicated in the development of rosacea (1–3, 5–7). A number of rosacea triggers have been proposed, such as heat, stress, menses, alcohol consumption, sun exposure, and spicy foods (8, 9). Family history of rosacea has been related to rosacea risk (10), suggesting a genetic predisposition of the pathophysiology.

Cigarette smoking has been associated with an increased risk of multiple inflammatory diseases, such as psoriasis and Crohn's disease, in past prospective studies (11–15). In contrast, smoking may have beneficial effects on other inflammatory diseases (14), such as ulcerative colitis and sarcoidosis (15–18). The dichotomous associations of smoking with various inflammatory diseases can be explained by a number of mechanisms. Smoking's impact on the immune system includes promoting immunosuppressive responses and disturbing endogenous antioxidant defenses (11, 14, 19). Nicotine, a major component of tobacco, influences the skin microcirculation, causing vasoconstriction, thereby reducing the partial pressure of oxygen on tissues and stimulating angiogenesis (4). On the basis of these properties, smoking may influence the risk of rosacea, an inflammatory disease with a prominent vascular component.

The direction and magnitude of the association between smoking and rosacea remain unclear based on prior cross-sectional

and case-control studies (4, 20–24). One large case-control study in 2012 found an increased risk of rosacea among past smokers and a decreased risk among current smokers (23). However, another recent case-control study showed significantly increased prevalence of rosacea among smokers (4). No cohort studies have examined the associations between smoking and the risk of rosacea thus far.

In the present study, we investigated the association between smoking status, quantity of smoking, and smoking cessation and the risk of incident rosacea in 95,809 participants from Nurses' Health Study II.

## METHODS

### Study cohort

Nurses' Health Study II was established in 1989, when 116,430 US female nurses aged 25–42 years completed a baseline questionnaire on medical history and lifestyle practices. Participants have received a study questionnaire biennially, and a response rate exceeding 90% has been achieved during follow-up.

The study was approved by the institutional review boards of Brigham and Women's Hospital and Harvard School of Public Health (Boston, Massachusetts). Participants' completion and return of the questionnaire were considered informed consent.

### Assessment of main exposure

In 1989, participants were asked about their lifetime history of smoking 20 or more packs of cigarettes (1 pack contains 20 cigarettes). Information on smoking status (never, past, or current smoking) was updated biennially, and self-reported number of cigarettes smoked daily among current smokers was divided into 6 categories (1–4, 5–14, 15–24, 25–34, 35–44, or ≥45 cigarettes/day). In 1989, participants were also asked about their age at smoking initiation and, if they had quit smoking, how many years had elapsed since cessation (<1 year or ≥1 year). The average number of cigarettes smoked per day at different ages (ages <15, 15–19, 20–24, 25–29, 30–35, and 36–42 years) was assessed and divided into the above-mentioned 6 categories.

Pack-years of smoking and years since quitting smoking were derived on the basis of answers to the biennial questionnaires. For past smokers, number of years since cessation of smoking was obtained by subtracting the age at which they had quit smoking from their current age. We multiplied the number of packs of cigarettes smoked per day by the number of years of smoking to estimate pack-years of smoking.

### Assessment of main outcome (rosacea)

In 2005, participants were asked whether they had ever been diagnosed with rosacea by a clinician and, if so, the year of diagnosis (in 5 time intervals: before 1991, 1991–1994, 1995–1998, 1999–2002, or 2003–2005).

### Assessment of covariates

Race, ethnicity, and height were reported in 1989. Weight was assessed biennially by self-report. A high correlation between self-reported body weight and measured body weight has been reported (25). We calculated body mass index as weight in kilograms divided by height in meters squared, as well as biennial weight changes. Physical activity level, in metabolic equivalent of task hours per week, was determined in 1991, 1997, 2001, and 2005. Validation studies have indicated good validity and reproducibility for the physical activity self-reports (26). Alcohol intake and coffee consumption were assessed every 4 years beginning in 1991. Total caffeine intake was calculated by summing the caffeine content for a specific amount of each food during the previous year multiplied by a weight proportional to the frequency of its consumption (27). Information on menopausal status and personal history of postmenopausal hormone use, oral contraceptive (OC) use, major chronic diseases (cancer (including nonmelanoma skin cancer), diabetes mellitus, cardiovascular disease, hypertension, and hypercholesterolemia), and lung diseases (pneumonia, asthma, emphysema, and chronic bronchitis) was collected at baseline and updated in the biennial follow-up questionnaires. Cumulative ultraviolet (UV) radiation flux for each participant was calculated on the basis of biennially updated residence information over the course of follow-up, taking factors such as cloud cover, altitude, and latitude into account (28). Methods used for assessment of UV flux have been detailed previously (29). In addition to UV flux, detailed information on several other sun exposure and UV radiation-related variables was collected, including childhood or adolescent susceptibility to sunburn, number of teenage severe sunburns, and frequency of indoor tanning at high school/college age or ages 25–35 years (29). Information on diagnosis of depression/antidepressant medication use was collected biennially from 1993 onward. Phobic anxiety was assessed in 1993 using the Crown-Crisp Index and was measured by 8 self-rated questions on phobias and desire for avoidance (30). Information on ever use of nonsteroidal antiinflammatory drugs was collected in 1989, 1995, 1999, and 2003.

### Statistical analysis

Participants who responded to the 2005 questionnaire (when the question about lifetime diagnosis of rosacea was asked) served as the base population ($n$ = 97,476). Participants who reported rosacea that occurred before 1991 or reported a diagnosis of rosacea but did not give a diagnosis date were excluded from the present study ($n$ = 1,158), as were those with missing smoking information ($n$ = 509).

We calculated person-years from the return date of the 1991 questionnaire to the date of diagnosis of rosacea or the end of follow-up (June 2005), whichever came first.

Smoking status was categorized as never, past, or current smoking. Current smokers were categorized according to number of cigarettes smoked per day: 1–4, 5–14, 15–24, or ≥25 cigarettes/day. Pack-years of smoking were classified into 3 groups: <10, 10–24, or ≥25 pack-years. Years since smoking cessation were classified into 6 groups: ≤2, 3–9,

10–19, 20–24, 25–29, or ≥30 years. Age at smoking initiation was classified into 3 groups: <15, 15–19, or ≥20 years.

We tested the proportional hazards assumption by means of likelihood ratio tests comparing the models with and without inclusion of terms for interaction between age and smoking-related variables and did not find any violations. We conducted Cox proportional hazards analysis stratified by age and 2-year interval to estimate age- and multivariable-adjusted hazard ratios for incident rosacea and 95% confidence intervals. Information on the exposure and the outcome was updated in 2-year questionnaire cycles, whenever available. Multivariable-adjusted hazard ratios were calculated after adjusting for age, race/ethnicity (non-Hispanic white or other), body mass index (continuous variable), physical activity (metabolic equivalent of task hours/week, in quintiles), alcohol intake (0, <4.9, 5.0–9.9, 10–14.9, 15–29.9, or ≥30.0 g/day), and menopausal and postmenopausal hormone use (premenopause, postmenopause, and never, current, or past use). We included these variables in the models to minimize potential residual confounding. An indicator was created for the missing data of each covariate. Trend tests for quantity of smoking, pack-years, age at smoking initiation, and years since smoking cessation were carried out using continuous measures of these variables by assigning the median value to each category.

Although understanding of epidemiologic risk factors for rosacea is still limited, several possible triggers for rosacea have been proposed (8, 9). In addition, rosacea has also been associated with several major chronic diseases (31–34). To address the concern of possible residual confounding by hormonal factors (35–37), sun exposure (8, 9), stress (8, 9), or other smoking-related disorders (31–34), we conducted a primary sensitivity analysis by additionally adjusting for OC use (never, past, or current use), cumulative UV flux (in quintiles), antidepressant medication use (ever or never), phobic anxiety (Crown-Crisp Index score of <2, 2, 3, or ≥4), personal history of systemic chronic diseases (including diabetes, cancer, cardiovascular disease, hypertension, and hypercholesterolemia), and lung diseases (including pneumonia, asthma, emphysema, and chronic bronchitis). We also considered potential residual confounding by medication use and additionally adjusted for use of nonsteroidal antiinflammatory drugs (ever or never). To further control for sun exposure, in a second sensitivity analysis we additionally adjusted for childhood or adolescent sunburn susceptibility, number of teenage severe sunburns, and frequency of indoor tanning. Because smoking is closely associated with coffee and caffeine intake (27) and weight change (e.g., smoking cessation leads to weight gain) (38), to address whether the association between smoking cessation and risk of rosacea might be confounded, we additionally adjusted for coffee consumption (0, 1–3 cups/month, 1 cup/week, 2–4 cups/week, 5–6 cups/week, 1 cup/day, 2–3 cups/day, 4–5 cups/day, or ≥6 cups/day) or caffeine intake (mg, in quintiles) and weight change (increase of ≥10 pounds (≥4.5 kg), increase of <10 pounds (<4.5 kg), no change, loss of <10 pounds, or loss of ≥10 pounds) in a third sensitivity analysis. For the analysis of years since smoking cessation, we conducted a fourth sensitivity analysis by additionally adjusting for smoking status (with cigarettes per day) or pack-years of smoking.

To address the concern of reverse-causation bias, we conducted a 4-year lag analysis by excluding rosacea cases that occurred before 1995. Because rosacea epidemiology clearly differs by race/ethnicity (39), we conducted secondary analyses by restricting the study participants to non-Hispanic whites. Secondary analyses were also conducted by restricting the data to participants without any OC or postmenopausal hormone use or restricting the data to persons without any chronic diseases.

All statistical analyses were conducted using SAS, version 9.4 (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 95,809 women were included in the analysis. Table 1 shows the characteristics of the participants in 1991. In terms of smoking status, 11.6% of the participants were current smokers, 22.3% were past smokers, and 66.0% had never smoked.

During 1,287,474 person-years of follow-up, we identified 5,462 incident cases of rosacea. We observed a significantly increased risk of rosacea among past smokers compared with never smokers but a significantly decreased risk of rosacea among current smokers (Table 2). After adjustment for other covariates, past smoking was associated with a hazard ratio for rosacea of 1.09 (95% confidence interval (CI): 1.03, 1.16), with a trend towards an elevated risk of rosacea with increasing numbers of cigarettes per day among past smokers ($P$ for trend = 0.001). Current smokers had a multivariable-adjusted hazard ratio of 0.65 (95% CI: 0.58, 0.72), with increasing numbers of cigarettes per day being associated with reduced risk of rosacea ($P$ for trend < 0.0001).

We further examined the association between cumulative smoking dose, measured by pack-years, and the risk of rosacea. Consistent with the findings for smoking status, we found that increasing pack-years was associated with an elevated risk of rosacea among past smokers ($P$ for trend = 0.003) and a reduced risk among current smokers ($P$ for trend < 0.0001) (Table 3). For age at smoking initiation, we found an earlier age of smoking initiation to be associated with an augmented risk of rosacea among past smokers ($P$ for trend = 0.005; see Web Table 1, available at https://academic.oup.com/aje). Current smoking starting in different age categories was significantly associated with reduced risk of rosacea ($P$ for trend = 0.81).

We also examined the association between time since smoking cessation and risk of rosacea. Corresponding with the increased risk of rosacea observed for past smokers, longer time since smoking cessation appeared to enhance the risk of rosacea ($P$ for trend < 0.0001) as compared with current smoking. The risk of rosacea was significantly increased within 3–9 years after smoking cessation, and the significant association persisted among past smokers who had quit over 30 years before, with the largest hazard ratio (hazard ratio = 1.82, 95% CI: 1.51, 2.20) being seen for the smoking cessation period of 25–29 years (Table 4).

We conducted a lag analysis by excluding cases documented within the first 4 years of each updated assessment of smoking status; this did not change the results materially. For

**Table 1.** Age-Standardized Characteristics of Participants in a Study of Smoking and Rosacea, by Smoking Status in 1991, Nurses' Health Study II[a]

| Characteristic | Smoking Status in 1991 | | | | | |
|---|---|---|---|---|---|---|
| | Never Smoker ($n$ = 63,266) | | Past Smoker ($n$ = 21,391) | | Current Smoker ($n$ = 11,152) | |
| | Mean (SD) | % | Mean (SD) | % | Mean (SD) | % |
| Age[b], years | 35.8 (4.7) | | 37.0 (4.5) | | 36.6 (4.6) | |
| Non-Hispanic white race/ethnicity | | 91.9 | | 94.8 | | 94.1 |
| Body mass index[c] | 24.6 (5.3) | | 24.6 (5.2) | | 24.5 (5.2) | |
| Alcohol intake, g/day | 2.4 (4.9) | | 4.3 (6.8) | | 5.2 (9.0) | |
| Physical activity, MET-hours/week | 20.4 (26.1) | | 22.5 (29.0) | | 19.7 (26.8) | |
| Postmenopausal hormone use | | 3.2 | | 3.0 | | 4.4 |
| Highest quintile of UV radiation flux | | 19.7 | | 16.9 | | 15.5 |
| Oral contraceptive use | | 82.0 | | 89.9 | | 90.6 |
| Nonsteroidal antiinflammatory drug use | | 18.1 | | 20.0 | | 23.5 |
| Antidepressant medication use | | 9.5 | | 12.3 | | 15.3 |
| Phobic anxiety (Crown-Crisp Index score ≥4) | | 26.3 | | 28.3 | | 33.5 |
| Major chronic diseases | | 12.0 | | 11.7 | | 12.9 |
| Major lung diseases | | 15.7 | | 16.8 | | 17.0 |

Abbreviations: MET, metabolic equivalent of task; SD, standard deviation; UV, ultraviolet.

[a] This table lists the covariates we adjusted for in the main analysis and the primary sensitivity analysis. Values are standardized to the age distribution of the study population.

[b] Values were not age-adjusted.

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

**Table 2.** Age- and Multivariate-Adjusted Hazard Ratios for Rosacea According to Smoking Status, Nurses' Health Study II, 1991–2005

| Smoking Status and Quantity Smoked, cigarettes/day | No. of Cases | No. of Person-Years | Crude Incidence Rate/100,000 Person-Years | Age-Adjusted | | Multivariable-Adjusted[a] | |
|---|---|---|---|---|---|---|---|
| | | | | HR | 95% CI | HR | 95% CI |
| Never smoker | 3,586 | 851,853 | 421 | 1.00 | Referent | 1.00 | Referent |
| Past smoker | 1,531 | 305,076 | 502 | 1.14 | 1.08, 1.22 | 1.09 | 1.03, 1.16 |
| 1–4 | 382 | 78,304 | 488 | 1.10 | 0.99, 1.23 | 1.06 | 0.96, 1.18 |
| 5–14 | 466 | 95,992 | 485 | 1.11 | 1.00, 1.22 | 1.07 | 0.97, 1.18 |
| 15–24 | 426 | 87,813 | 485 | 1.11 | 1.00, 1.23 | 1.05 | 0.95, 1.16 |
| ≥25 | 257 | 42,968 | 598 | 1.38 | 1.22, 1.57 | 1.29 | 1.13, 1.46 |
| $P_{trend}$ | | | | <0.0001 | | 0.001 | |
| Current smoker | 345 | 130,545 | 264 | 0.65 | 0.59, 0.73 | 0.65 | 0.58, 0.72 |
| 1–4 | 82 | 21,452 | 382 | 0.95 | 0.76, 1.18 | 0.91 | 0.73, 1.14 |
| 5–14 | 103 | 41,342 | 249 | 0.60 | 0.50, 0.73 | 0.61 | 0.50, 0.74 |
| 15–24 | 107 | 48,442 | 221 | 0.55 | 0.46, 0.67 | 0.55 | 0.45, 0.66 |
| ≥25 | 53 | 19,309 | 274 | 0.69 | 0.53, 0.91 | 0.67 | 0.51, 0.89 |
| $P_{trend}$ | | | | <0.0001 | | <0.0001 | |

Abbreviations: CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task.

[a] Adjusted for age (years; continuous variable), race/ethnicity (% non-Hispanic white), body mass index (weight (kg)/height $(m)^2$; continuous variable), postmenopausal hormone use (premenopausal, never use, current use, or past use), alcohol drinking (none, or <4.9, 5.0–9.9, 10–14.9, 15–29.9, or ≥30.0 g/day), and physical activity (MET-hours/week, in quintiles).

**Table 3.** Age- and Multivariate-Adjusted Hazard Ratios for Rosacea According to Pack-Years of Smoking, Nurses' Health Study II, 1991–2005

| Smoking Status and No. of Pack-Years | No. of Cases | No. of Person-Years | Crude Incidence Rate/100,000 Person-Years | Age-Adjusted | | Multivariable-Adjusted[a] | |
|---|---|---|---|---|---|---|---|
| | | | | HR | 95% CI | HR | 95% CI |
| Never smoker | 3,586 | 851,853 | 421 | 1.00 | Referent | 1.00 | Referent |
| Past smoker | | | | | | | |
| <10 | 821 | 174,269 | 471 | 1.10 | 1.02, 1.19 | 1.07 | 0.99, 1.15 |
| 10–24 | 603 | 113,896 | 529 | 1.18 | 1.08, 1.29 | 1.11 | 1.02, 1.22 |
| ≥25 | 107 | 16,911 | 633 | 1.27 | 1.05, 1.54 | 1.18 | 0.97, 1.43 |
| $P_{trend}$ | | | | <0.0001 | | 0.003 | |
| Current smoker | | | | | | | |
| <10 | 73 | 24,446 | 299 | 0.87 | 0.69, 1.10 | 0.85 | 0.67, 1.07 |
| 10–24 | 168 | 67,749 | 248 | 0.65 | 0.56, 0.76 | 0.64 | 0.55, 0.75 |
| ≥25 | 104 | 38,350 | 271 | 0.56 | 0.46, 0.68 | 0.56 | 0.46, 0.68 |
| $P_{trend}$ | | | | <0.0001 | | <0.0001 | |

Abbreviations: CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task.

[a] Adjusted for age (years; continuous variable), race/ethnicity (% non-Hispanic white), body mass index (weight (kg)/height $(m)^2$; continuous variable), postmenopausal hormone use (premenopausal, never use, current use, or past use), alcohol drinking (none, or <4.9, 5.0–9.9, 10–14.9, 15–29.9, or ≥30.0 g/day), and physical activity (MET-hours/week, in quintiles).

example, the hazard ratio for rosacea was 1.11 (95% CI: 1.03, 1.18) for past smokers ($P$ for trend < 0.0001) and 0.66 (95% CI: 0.59, 0.74) for current smokers ($P$ for trend < 0.0001). The secondary analyses excluding non-non-Hispanic white participants, restricting the data to persons without any OC or postmenopausal hormone use or restricting the data to those without major chronic diseases also yielded results similar to those of the primary analyses (data not shown).

The sensitivity analyses additionally adjusting for OC use, cumulative UV flux, antidepressant use, phobic anxiety, use of nonsteroidal antiinflammatory drugs, personal history of major chronic diseases, and personal history of lung diseases and the sensitivity analysis additionally adjusting for sunburn susceptibility, teenage severe sunburns, and frequency of indoor tanning did not change the results materially (data not shown). The sensitivity analyses for years since smoking

**Table 4.** Age- and Multivariate-Adjusted Hazard Ratios for Rosacea in Past Smokers According to Years Since Smoking Cessation, Nurses' Health Study II, 1991–2005

| Smoking Cessation Status and Years Since Smoking Cessation | No. of Cases | No. of Person-Years | Crude Incidence Rate/100,000 Person-Years | Age-Adjusted | | Multivariable-Adjusted[a] | |
|---|---|---|---|---|---|---|---|
| | | | | HR | 95% CI | HR | 95% CI |
| Current smoker | 345 | 130,544 | 264 | 1.00 | Referent | 1.00 | Referent |
| Past smoker | | | | | | | |
| ≤2 | 81 | 24,489 | 331 | 1.31 | 1.03, 1.67 | 1.27 | 0.99, 1.62 |
| 3–9 | 319 | 72,097 | 442 | 1.79 | 1.54, 2.09 | 1.73 | 1.48, 2.01 |
| 10–19 | 582 | 127,856 | 455 | 1.77 | 1.54, 2.02 | 1.71 | 1.49, 1.95 |
| 20–24 | 308 | 48,552 | 634 | 1.85 | 1.58, 2.16 | 1.80 | 1.53, 2.10 |
| 25–29 | 176 | 23,570 | 747 | 1.87 | 1.55, 2.26 | 1.82 | 1.51, 2.20 |
| ≥30 | 65 | 8,513 | 764 | 1.61 | 1.21, 2.13 | 1.56 | 1.17, 2.06 |
| $P_{trend}$ | | | | <0.0001 | | <0.0001 | |

Abbreviations: CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task.

[a] Adjusted for age (years; continuous variable), race/ethnicity (% non-Hispanic white), body mass index (weight (kg)/height $(m)^2$; continuous variable), postmenopausal hormone use (premenopausal, never use, current use, or past use), alcohol drinking (none, or <4.9, 5.0–9.9, 10–14.9, 15–29.9, or ≥30.0 g/day), and physical activity (MET-hours/week, in quintiles).

cessation that additionally adjusted for coffee consumption (or caffeine intake) and weight change or additionally adjusted for smoking status/pack-years did not yield different findings for the associations (data not shown).

## DISCUSSION

In this study, we comprehensively evaluated the risk of rosacea associated with smoking status, cumulative pack-years of smoking, and time since smoking cessation. To our knowledge, this represents the first cohort study on this topic. We found significant and contrasting associations between past and current smoking and rosacea. The risk of rosacea was significantly increased in past smokers but decreased in current smokers, with a trend towards elevated risk of rosacea with increasing numbers of cigarettes per day and increasing numbers of pack-years among past smokers and a trend towards decreased risk of rosacea among current smokers. The associations were independent of major confounders and remained robust in our sensitivity analyses.

Several cross-sectional or case-control studies have examined the associations between smoking and rosacea (4, 20–24). The first, a study from the United Kingdom, found that patients with rosacea smoked less frequently than the general population (20). In the second, a study from Estonia, Abram et al. (21) reported a higher prevalence of rosacea among ex-smokers than among current or nonsmokers. The third study, from France, did not show a significant difference in smoking between cases and controls but found that cessation of smoking was associated with increased odds of rosacea in comparison with current smoking or nonsmoking (22). While the above 3 studies were small-scale studies, a large case-control study (60,042 cases and 60,042 controls) based on the General Practice Research Database (United Kingdom) also found that current smokers had significantly reduced risk of rosacea (odds ratio = 0.64, 95% CI: 0.62, 0.67) and past smokers had increased risk of rosacea (odds ratio = 1.14, 95% CI: 1.10, 1.18) when compared with nonsmokers, with effect magnitudes very similar to our findings (23). However, in 1 case-control study, Kucukunal et al. (4) reported an increased risk of rosacea among active smokers, particularly for the erythematotelangiectatic (vascular) subtype of rosacea. Another recent cross-sectional study also suggested a positive association between pack-years of smoking and rosacea grading scores developing by the National Rosacea Society (24). Therefore, the available data on the association between smoking and rosacea have not been consistent.

Although it is difficult to identify the specific agents in tobacco smoke that are responsible for its impact on rosacea, a variety of mechanisms may be involved. Vasodilatation caused by neurovascular dysfunction has been implicated in the pathogenesis of rosacea (40, 41). Cigarette smoking may lead to microvascular vasoconstriction, thus decreasing the vasodilatory signs and symptoms of rosacea (23, 42). In addition, the immunosuppressive effects of cigarette smoking may decrease the inflammatory component of rosacea (43). For past smokers, it is possible that there is a rebound of vasodilatation upon smoking cessation and nicotine withdrawal (21, 23), which may partly explain the increased risk of rosacea among past smokers. Other potential mechanisms may also be possible. Smoking has been shown to affect hormone function (44). Because hormone-related factors may be possible triggers for rosacea (35–37), further studies are warranted to investigate whether smoking-related alteration of hormone function may be associated with risk of rosacea. It is worth noting that a latency period of over 30 years after smoking cessation is quite long; future studies are needed to further address residual confounding and explore biological plausibility.

Our findings of an increased risk of rosacea associated with past smoking but a reduced risk of rosacea associated with current smoking are similar to the reported associations between smoking and risks of ulcerative colitis and sarcoidosis (15–18). In fact, nicotine patches have been used therapeutically in persons with ulcerative colitis (45) and diseases with cutaneous manifestations such as Behcet disease (46).

Our study had several strengths. Our assessments of cigarette smoking and other covariates were updated biennially during follow-up. Because current smokers may quit smoking over time and some past smokers may relapse, updating smoking exposure data over time ensured that we used the most accurate information for smoking, thus avoiding misclassification and permitting a detailed examination of the influence of smoking on rosacea. The large number of participants and long-term follow-up facilitated the documentation of a sufficient number of incident cases of rosacea for robust associations.

We acknowledge some limitations of our study. First, information on lifetime diagnosis of rosacea was self-reported in 2005, and no validation study was conducted. The retrospective collection of data on rosacea may have led to recall bias. However, the high educational level and health literacy of cohort participants allowed high-quality and valid information to be collected on self-administered forms. For example, our prior validation study indicated a very high validity of psoriasis self-reporting, with more than 90% of self-reported cases being confirmed (47). High validity of the rosacea self-reporting was expected. Selection bias may have occurred because all participants needed to be alive in order to respond to the questionnaire in 2005 to be included in our analysis. Because rosacea is a condition that is usually brought to the attention of clinicians by patients themselves due to cosmetic concerns, it is likely that smoking history would not affect patients' ability or desire to bring signs and symptoms of rosacea to a physician's attention. Smokers may have more medical comorbidity than nonsmokers, making them less likely to initiate a discussion about rosacea with their physicians. However, our analyses adjusting for major chronic diseases or excluding persons with major chronic diseases partly addressed this potential differential misclassification. We considered the possibility that the association between smoking and incident rosacea may reflect smoking among affected symptomatic subjects who had not yet received a physician-defined diagnosis. However, the 4-year lag analyses did not demonstrate a material change in the associations, which helps in classifying the temporal relationship between smoking and subsequent rosacea development. Therefore, it is less likely that our results were greatly distorted by rosacea self-reports.

Second, there may be etiological heterogeneity underlying different types of rosacea (1, 48). Because we did not have

information on rosacea subtypes, we were not able to examine the associations of smoking with each subtype. Third, our participants were female health professionals and most were non-Hispanic whites; therefore, extrapolation of our findings to the general US population requires caution. Fourth, an epidemiologic study cannot rule out the possibility of residual confounding due to unmeasured or imperfectly measured confounders. Although we comprehensively adjusted for potential confounders, it remains unclear whether the observed association between smoking and rosacea may still be partly attributable to other, unmeasured factors. For example, we lacked information on family history of rosacea.

In summary, based on a large, well-established cohort, we provide evidence in US women that past smoking is associated with an increased risk of rosacea, while current smoking is associated with a decreased risk of rosacea. Our study may have implications for rosacea etiology. Further investigations are warranted to elucidate the mechanisms underlying these associations, which may lead to a better understanding of rosacea pathogenesis. Because smoking is unequivocally linked with numerous health woes, dermatologists and other health practitioners should keep advising the public to quit smoking. Dermatologists may pay special attention to the prevention and early treatment of rosacea among past smokers.

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