ORIGINAL ARTICLE

Smoking and Hand Dermatitis in the United States Adult Population

Yi Chun Lai[1], Yik Weng Yew[1,2]

[1]Harvard T.H. Chan School of Public Health, Harvard University, Boston, MA, USA, [2]National Skin Centre, Singapore, Singapore

Background: Hand dermatitis is a common chronic relapsing skin disease resulting from a variety of causes, including endogenous predisposition and environmental exposures to irritants and allergens. Lifestyle factors such as smoking have been implicated in hand dermatitis. **Objective:** To evaluate the association between tobacco exposure and hand dermatitis using the 2003~2004 National Health and Nutrition Examination Survey (NHANES) database. **Methods:** Data were retrieved and analyzed from 1,301 participants, aged 20~59 years, from the 2003~2004 NHANES questionnaire study who completed health examination and blood tests. Diagnosis of hand dermatitis was based on standardized photographs of the dorsal and palmar views of the hands read by two dermatologists. **Results:** There were 38 diagnosed cases of active hand dermatitis out of the 1,301 study participants (2.9%). Heavy smokers (>15 g tobacco daily) were 5.11 times more likely to have active hand dermatitis (odds ratio [OR], 5.11; 95% confidence interval [CI], 1.39~18.88; p=0.014). Those with serum cotinine >3 ng/ml were also more likely to have active hand dermatitis, compared with those with serum cotinine ≤3 ng/ml (OR, 2.50; 95% CI, 1.26~4.95; p=0.007). After adjusting for confounding factors such as age, atopic diathesis, occupational groups, and physical activity, the association between tobacco exposure and active hand dermatitis remained significant. **Conclusion:** Smoking has a significant association with the presence of active hand dermatitis. It is important to consider smoking cessation as part of management of hand dermatitis. (Ann Dermatol 28(2) 164~171, 2016)

-Keywords-
Dermatitis, Eczema, Epidemiology, Smoking

INTRODUCTION

Hand dermatitis, an inflammatory condition of unknown mechanism, is a common skin disease with a point prevalence of 4%, 1-year prevalence of 10%, and a lifetime prevalence of 15%~20%[1-3]. As a chronic relapsing disease, hand dermatitis incurs tremendous health-care costs and significantly decreases one's quality of life[4]. Hand dermatitis results from a combination of causes, including genetic predisposition (loss-of-function mutations in the filaggrin gene[5-7] and atopic diathesis[8,9]) and exogenous factors (contact with irritants/allergens and wet work[8-11]). Lifestyle factors such as cigarette smoking have been implicated in hand dermatitis[12,13]. Smoking plays an important role in mediating various inflammatory skin conditions, such as psoriasis[14], systemic lupus erythematous[15], palmoplantar pustulosis[16], contact allergy[17,18], infectious eczematoid dermatitis[19], and hidradenitis suppurativa[20]. Smoking *per se* may promote the onset of hand dermatitis[21], disturb the healing process[21], or be directly involved in the inflammatory process via cytokines and oxidative stress[22]. A positive association between hand dermatitis and cigarette smoking has been reported by numerous studies[21-29], whereas other studies failed to corroborate such a relationship[30-36]. To our knowledge, no population-based study regarding the association between hand dermatitis and cigarette smoking has been conducted in the United States

(US).

In this study, we aimed to evaluate the association between cigarette smoking and hand dermatitis among adult males using the National Health and Nutrition Examination Survey (NHANES) database. In addition, a possible dose-dependent relationship between tobacco exposure and hand dermatitis was also investigated by correlating it with measured serum cotinine, an alkaloid found in tobacco and a metabolite of nicotine.

MATERIALS AND METHODS

Study population

NHANES is a periodic annual population survey that targets the civilian noninstitutionalized US population. It utilizes a stratified multistage probability sampling design. In our analysis of interest, randomly selected males aged 20~59 years are interviewed in their homes about the variables of interest, such as demographics variables, smoking and alcohol drinking status, physical activities and history of atopy. A total of 1,301 participants subsequently completed health examination and blood tests. Data on hand dermatitis diagnosis and questionnaire as well as laboratory parameters on tobacco smoking exposure in the cycle year 2003~2004 were retrieved and analyzed. This information was not available in other cycle years.

Clinical information and laboratory data of the NHANES were available from the publicly accessible US Centers for Disease Control database. The NHANES was approved by the Institutional Review Board (#98-12), and documented consent was obtained from participants.

Outcome

Diagnoses of active hand dermatitis were identified from the 2003~2004 NHANES examination data. All study participants had standardized photographs of the dorsal and palmar views of the hands. These photographs were read by two dermatologists for the presence of hand dermatitis. When the findings of the two dermatologists disagreed, the software program ISIS (Westat Inc., Rockville, MD, USA) required a third consensus reading. For the consensus readings, both dermatologists reviewed the image simultaneously and came to a unified decision.

Exposure

Exposure to tobacco was assessed using questionnaire items in NHANES, including smoking at least 100 cigarettes in their lifetime, current tobacco smoking, exposure to someone smoking at home, and exposure to tobacco smoke at work. Among current smokers, the amount of to-

bacco in grams was estimated by equating one cigarette to 1 g of tobacco. This information was used to dichotomize smoking status into >15 g daily for heavy smokers and $\leq$ 15 g daily for light smokers[26]. In addition, serum cotinine was measured to serve as a biomarker for both active smoking and "passive smoking" or environmental tobacco smoke exposure. Cotinine is a major metabolite of nicotine and is generally a preferred biomarker[37,38]. It is measured through isotope dilution high-performance liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometry[39]. A cutoff value of 3 ng/ml was used to dichotomize smokers (>3 ng/ml) and nonsmokers ($\leq$3 ng/ml) for further analysis[40].

Questionnaire data variables

Demographic variables such as age, ethnic groups, marital status, education status, family poverty income ratio (PIR), working status, and occupational group types were included for analysis as possible confounding factors.

Ethnic groups were categorized into "Mexican American," "other Hispanic," "non-Hispanic white," "non-Hispanic black," and "other race." Education status was separated into four categories of "<9th grade," "9th to 11th grade," "high school graduate/general education development," and "college, graduate or above." The family PIR is the ratio of family income to poverty threshold, which serves as a marker of socioeconomic status. Working status was dichotomized into "working" and "not working" based on the questions in the NHANES. Occupation text data from the questionnaire were coded using the standards of the National Center for Health Statistics and constructed according to the pattern established for NHANES III. Occupational groups such as "construction laborers," "mechanics and repairers," "waiters and waitresses," "cooks," and "cleaners" were classified as occupation with frequent manual and wet work.

Other possible confounding factors, such as alcohol consumption and engaging in moderate or vigorous physical activities, personal and family history of asthma, were also considered in the analysis. The alcohol consumption variable was dichotomized into "yes" or "no" based on whether the study participant consumed at least 12 drinks for the past 1 year. Engagement in moderate/vigorous physical activity was based on a "yes" or "no" response to whether one engaged in moderate or vigorous physical activity over the past 30 days. As there were no direct questions for any personal history of atopic diatheses, a positive response to personal or family history of asthma or a recent history of hay fever was assigned a positive history of atopic diathesis.

Data analysis

Analysis of the association between hand dermatitis and cigarette smoking was done using χ^2 or Fisher exact tests. Using two-sample t-test and Mann-Whitney U-test, serum cotinine levels were compared between those with and without hand dermatitis. To examine the potential confounding effect of selected variables, we performed multivariate logistic regression with hand dermatitis as the dependent variable and the aforementioned confounding factors as the independent variables.

The Statistical Package for the Social Sciences (IBM SPSS version 22; IBM, Armonk, NY, USA) was utilized to perform the analysis. Odds ratio (OR), 95% confidence interval (CI), and p-values were calculated to test the null hypotheses of the association between tobacco smoking exposure and diagnosis of hand dermatitis.

Table 1. Distribution of potential risk factors to the prevalence of current smokers

Characteristic	Odds ratio	95% confidence interval	p-value
Age	0.96	0.95~0.97	<0.0001
Ethnic group			0.174
Mexican American	0.81	0.56~1.17	
Other Hispanic	0.80	0.36~1.78	
Non-Hispanic White	1.00		
Non-Hispanic Black	1.45	0.96~2.18	
Other race	1.13	0.57~2.22	
Marital status			
Single/divorced/widowed	2.61	1.87~3.63	<0.0001
Married/attached	1.00		
Education status			<0.0001
<9th grade	1.24	0.75~2.04	
9~11th grade	2.56	1.65~3.96	
High school graduate/GED	1.55	1.09~2.20	
College, graduate or above	1.00		
Family poverty income ratio	0.81	0.74~0.89	<0.0001
Working status			
Working	0.54	0.38~0.76	<0.0001
Not working	1.00		
Occupational group*			
Frequent manual/wet work	2.17	1.53~3.08	<0.0001
Minimal manual/wet work	1.00		
Alcohol consumption			
Yes	1.18	0.74~1.88	0.477
No	1.00		
Body mass index	0.96	0.93~0.98	<0.0001
Vigorous physical activity			
Yes	0.81	0.59~1.10	0.174
No	1.00		
Moderate physical activity			
Yes	0.75	0.56~1.01	0.058
No	1.00		
Atopic diathesis			
Yes	0.77	0.56~1.06	0.112
No	1.00		

GED: general education development. *Construction laborers, mechanics and repairers, waiters and waitresses, cooks, and cleaners.

Table 2. Distribution of potential risk factors to the prevalence of hand dermatitis

Characteristic	Odds ratio	95% confidence interval	p-value
Age	1.02	1.00~1.06	0.101
Ethnic group			0.846
Mexican American	1.43	0.62~3.27	
Other Hispanic	0		
Non-Hispanic White	1.00		
Non-Hispanic Black	1.54	0.71~3.36	
Other Race	1.23	0.28~5.45	
Marital status			
Single/divorced/widowed	0.97	0.49~1.88	0.532
Married/attached	1.00		
Education status			0.167
<9th grade	1.93	0.61~6.10	
9~11th grade	1.91	0.74~4.92	
High school graduate/GED	2.32	1.07~5.00	
College, graduate or above	1.00		
Family poverty income ratio	0.84	0.69~1.03	0.099
Working status			
Working	1.40	0.61~3.21	0.562
Not working	1.00		
Occupational group*			
Frequent manual/wet work	8.03	2.43~26.5	<0.0001
Minimal manual/wet work	1.00		
Alcohol consumption			
Yes	0.86	0.37~1.97	0.657
No	1.00		
Body mass index	1.04	0.98~1.09	0.216
Vigorous physical activity			
Yes	0.38	0.17~0.83	0.012
No	1.00		
Moderate physical activity			
Yes	0.48	0.25~0.94	0.029
No	1.00		
Atopic diathesis			
Yes	0.44	0.18~1.07	0.062
No	1.00		

GED: general education development. *Construction laborers, mechanics and repairers, waiters and waitresses, cooks, and cleaners.

RESULTS

A total of 1,301 participants from the NHANES database of the cycle 2003~2004 who had complete standardized photography for diagnosis were included in the analysis. The median age of our study population is 38.0 years. Of the 771 respondents for current smoking, 34.4% were current smokers. Current smokers were more likely to be younger, non-Hispanic black, single, have lower education and socioeconomic status, engage in frequent manual/wet work, and have lower body mass index (BMI). Characteristics of current smokers and nonsmokers are summarized in Table 1.

There were 38 diagnosed cases (2.9%) of active hand dermatitis. Those who were diagnosed with active hand dermatitis were significantly more likely to engage in frequent manual/wet work but less likely to engage in physical activity. However, there was no significant evidence that other characteristics such as age, ethnic groups, marital, education, socioeconomic status, BMI, alcohol consumption, and atopic diathesis were related to hand dermatitis. Table 2 summarized the distribution of the participants' characteristics of hand dermatitis.

Current smokers were more likely to be diagnosed with active hand dermatitis (OR, 4.43; 95% CI, 1.31~14.90; $p=0.017$). Other measures of tobacco exposure were also associated with increased odds of having active hand dermatitis (Table 3). Compared with nonsmokers, light smokers ($\leq$15 g tobacco daily) had 4.27 times the odds of having active hand dermatitis (OR, 4.27; 95% CI, 1.12~16.33; $p=0.034$). Heavy smokers ($>$15 g tobacco daily) had 5.11 times the odds of having active hand dermatitis than nonsmokers (OR, 5.11; 95% CI, 1.39~18.88; $p=0.014$). Those with active hand dermatitis had a significantly higher median serum cotinine level of 115.0 ng/ml, compared with the median serum cotinine level of 0.477 ng/ml in those without this condition ($p=0.002$). Those with serum cotinine $>$3 ng/ml had increased odds of having active hand dermatitis, compared with those with serum cotinine $\leq$3 ng/ml (OR, 2.50; 95% CI, 1.26~4.95; $p=0.009$).

To adjust for possible confounding factors such as age, atopic diathesis, occupational groups, and physical activity, multivariate logistic regression analysis was performed. The adjusted ORs for hand dermatitis and different measures of tobacco exposure were summarized in Table 4. The positive association between current smokers and active hand dermatitis was still significant after adjusting for the abovementioned confounding factors. Heavy smoking remained significantly related with increased likelihood of having active hand dermatitis. In addition, exposure to tobacco smoke at home and smoking status based on serum cotinine levels remained significantly associated with the diagnosis of active hand dermatitis after adjustment for confounders.

Table 3. Different measures of smoking vs. presence of hand dermatitis

Characteristic	Hand dermatitis	No hand dermatitis	Odds ratio	95% confidence interval	p-value
Current smoking					
Yes	22 (5.0)	419 (95.0)	4.43	1.31~14.90	0.009
No	3 (1.2)	253 (98.8)	1.00		
Smoking status					
Heavy smoker ($>$15 g daily)	10 (5.7)	165 (94.3)	5.11	1.39~18.88	0.014
Light smoker ($\leq$15 g daily)	8 (4.8)	158 (95.2)	4.27	1.12~16.33	0.034
Nonsmoker	3 (1.2)	253 (98.8)	1.00		
Smoked at least 100 cigarettes					
Yes	25 (3.6)	672 (96.4)	1.69	0.86~3.34	0.125
No	13 (2.2)	591 (97.8)	1.00		
Tobacco exposure at home					
Yes	19 (5.9)	303 (94.1)	3.12	1.63~5.97	$<$0.0001
No	19 (2.0)	946 (98.0)	1.00		
Tobacco exposure at work					
Yes	13 (4.8)	258 (95.2)	2.01	0.98~4.12	0.054
No	19 (2.5)	756 (97.5)	1.00		
Serum cotinine (ng/ml)					
$>$3 (smoker)	24 (4.4)	518 (95.6)	2.50	1.26~4.95	0.007
$\leq$3 (nonsmoker)	13 (1.8)	700 (98.2)	1.00		

Values are presented as number (%).

Table 4. Multivariate analysis between different measures of smoking exposure and hand dermatitis

Characteristic	Adjusted odds ratio*	95% confidence interval	p-value
Current smoking			
Yes	4.02	1.13~14.24	0.031
No	1.00		
Smoking status			
Heavy smoker (>15 g daily)	4.69	1.17~18.76	0.029
Light smoker (≤15 g daily)	3.82	0.89~16.36	0.071
Nonsmoker	1.00		
Smoked at least 100 cigarettes			
Yes	1.21	0.58~2.52	0.617
No	1.00		
Tobacco exposure at home			
Yes	2.80	1.37~5.73	0.005
No	1.00		
Tobacco exposure at work			
Yes	1.80	0.86~3.75	0.118
No	1.00		
Serum cotinine (ng/ml)			
>3 (smoker)	2.16	1.03~4.50	0.04
≤3 (nonsmoker)	1.00		

*Adjusted for age, atopic diathesis, occupational groups, physical activities.

DISCUSSION

In the present study, cigarette smoking was associated with increased likelihood of having active hand dermatitis. This is consistent with the findings of previous epidemiological studies[21-29].

This association between smoking and physician-confirmed hand dermatitis remained statistically significant whether the tobacco exposure was self-reported or objectively assessed via serum cotinine levels. As a major metabolite of nicotine, cotinine is a highly sensitive and specific marker of tobacco use. Cotinine acts as the preferred biomarker for tobacco exposure because of its longer half-life, compared with that of nicotine[40]. Compared with self-reported measures, which can potentially be subject to recall bias, serum cotinine provides an objective way to evaluate a possible dose-dependent relationship.

In our study, those who were diagnosed with active hand dermatitis had a significantly higher median serum cotinine levels than those without this condition. Compared with nonsmokers, both current light and heavy smokers had significantly higher odds of having active hand dermatitis, with ORs of 4.27 and 5.11, respectively, indicating a dose-dependent relationship. This result differs from the findings reported by Thyssen et al.[26], in which current

light smokers (≤15 g tobacco daily) had a higher prevalence of hand dermatitis than current heavy smokers (>15 g tobacco daily). Using regression analysis, Brans et al.[24] failed to find any association between the severity of occupational hand dermatitis and the amount of cigarettes smoked daily. In contrast, a dose-dependent association between cigarette smoking and hand dermatitis has been reported previously[29,35]. Meding et al.[29] reported a prevalence proportion ratio (PPR) of 1.10 for smokers with 1~7 cigarettes daily, 1.18 for smokers with 8~15 cigarettes daily, and 1.40 for smokers with >15 cigarettes daily. Furthermore, they reported a statistically significant PPR of 1.05 for the continuous variable of smoking habits, thus revealing a positive dose-response relationship between 1-year prevalence of hand dermatitis and level of smoking[29].

In our study, occupational groups and recent moderate or vigorous physical activities were noted to have significant relationships with the diagnosis of hand dermatitis. The association between hand dermatitis and tobacco exposure remained statistically significant even after adjustment for confounding variables. Similarly, the positive association between serum cotinine level and hand dermatitis remained relatively unchanged after multivariate regression analysis.

Cigarette smoking may be directly involved in the onset of hand dermatitis through the deleterious effects of its toxic constituents on the skin. For instance, nicotine itself has been demonstrated to activate dendritic cells and T cells[41]. In addition, it also leads to the development of acanthosis by increasing keratinocytes mitosis, migration, differentiation, and adhesion[42]. Alternatively, smoking may interfere with the process of wound healing or promote inflammatory cascades, thus aggravating preexisting hand dermatitis. Specifically, smoking is associated with an increased level of proinflammatory cytokines such as tumor necrosis factor α and interleukin 1 β and 6[43]. Furthermore, smoking also decreases the levels of anti-inflammatory cytokines such as interleukin 10[43]. These cytokines promote leukocyte adhesion to the capillary walls and infiltration of inflammatory cells to the dermis[44]. The healing process is disturbed by a substantial reduction in tissue blood flow, oxygen tension, and aerobic metabolism from cutaneous microvascular vasoconstriction related to tobacco exposure[45-47]. Free radicals in tobacco smoke induce oxidative stress, which causes tissue damage and has an immunomodulatory effect[44,48]. Furthermore, smoking has also been reported to be associated with nickel sensitization. The nickel in tobacco might stimulate individuals with nickel allergy[49], resulting in increased cases of hand dermatitis as seen among current smokers in our study.

In our study, the most commonly reported occupational groups among those diagnosed with hand dermatitis were "construction laborers," "mechanics and repairers," "waiters and waitresses," "cooks" and "cleaners." High-risk occupations such as bakers, hairdressers, dental surgery assistants, kitchen workers, health-care workers, and cleaners are commonly associated with hand dermatitis[50]. After adjusting for the types of occupational groups, however, smoking remained significantly associated with hand dermatitis. Smoking has been found to exacerbate the severity and prolong the duration of preexisting occupational hand dermatitis. Although it is unclear whether the negative effect of smoking is related to cigarette use or to other factors associated with smoking, Brans et al.[24] suggested that smoking itself was associated with the severity and course of occupational hand dermatitis, independent of risk factors in the work environment.

To our knowledge, studies evaluating the relationship between smoking and hand dermatitis were mainly conducted in Europe. This was the first US population-based, well-documented study that further supports the positive association between tobacco exposure and hand dermatitis. The diagnosis of hand dermatitis depends on physician diagnosis rather than the less reliable method of self-reporting. In addition, the NHANES database provides a detailed questionnaire on smoking status as well as various routes of tobacco exposure. An objective measure of tobacco exposure using serum cotinine level also allowed us to explore the possible dose-dependent relationship quantitatively. However, given the relatively small number of patients with hand dermatitis, the ORs should be interpreted with caution.

Data on personal/family history of atopy as well as total serum immunoglobulin E levels were not readily available from the NHANES database. Therefore, we used personal/family history of asthma and recent diagnosis of hay fever for the past 1 year to serve as a proxy for atopic diathesis. Other important information such as contact allergies and habits of frequent hand washing was not available either. The diagnosis of hand dermatitis relied on assessment of standardized photographs by two dermatologists. Although this can be a specific screening method, there are other mimickers of hand dermatitis such as palmoplantar psoriasis, tinea manuum, and keratoderma. It may also be less sensitive in detecting cases of hand dermatitis that were mild or relapsing infrequently. Instead of identifying past diagnoses of hand dermatitis, the photographs probably reflected the more current condition of the hands. Therefore, hand dermatitis identified in this study likely represented a more severe and persistent form. However, there was no information available on the type of hand dermatitis and duration of the condition for each case. Given that the more severe and persistent form of hand dermatitis were identified, the results of this study could be generalized to those with more chronic and occupation-related hand dermatitis.

In conclusion, smoking, whether self-reported or objectively assessed, has a significant association with the presence of active hand dermatitis. It is therefore important to consider smoking cessation for all cases of hand dermatitis. This is especially important for manual workers who are also heavy smokers, given their environmental risk factors at work. A dose-dependent relationship between tobacco exposure and hand dermatitis was also observed. An observational longitudinal cohort study with objective assessments of tobacco exposure and hand dermatitis severity would be useful in further characterizing this dose-dependent association.

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