

Cigarette Smoking is not a Risk Factor for Systemic Sclerosis

Authors: Prateek Chaudhary¹, Xing Chen², Shervin Assassi¹, Olga Gorlova², Hilda Draeger³, Brock E. Harper⁴, Emilio Gonzalez⁴, Terry McNearney^{4,5}, Marilyn Perry¹, Frank C. Arnett¹, Maureen D. Mayes¹

Author Institution Affiliations: ¹University of Texas Health Science Center at Houston, ²University of Texas M.D. Anderson Cancer Center, ³University of Texas Health Science Center at San Antonio, ⁴University of Texas Medical Branch at Galveston, ⁵Eli Lilly, Indianapolis

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Corresponding Author: Prateek Chaudhary, DO, MPH. 5151 Edloe #5306, Houston, Texas 77005. Mobile: 281 840 1519. Email : prateek.chaudhary@gmail.com

Abstract

Background: The role of cigarette exposure in susceptibility to systemic sclerosis (SSc) has not been previously studied. Our objective was to investigate the association of smoking with susceptibility to SSc in a large well-defined patient population.

Methods: We conducted a review of 1,379 SSc patients enrolled in the Scleroderma Family Registry and DNA Repository and/or the Genetics versus Environment in Scleroderma Outcome Study (GENISOS) cohort. Smoking history was obtained from chart review or via telephone interview. SSc patients were subsequently categorized as never smokers or ever smokers. SSc patients with available smoking data were matched 2:1 by age, gender, ethnicity and state of residence to controls using the Behavioral Risk Factor Surveillance System.

Results: The majority of cases were White (74.2%) with Latinos and Blacks representing 11.3% and 9.7%, respectively. Most patients had limited disease type (54%). For our comparative analyses, 621 patients were matched to controls. There was no significant difference in age, gender, ethnicity and SSc disease type between matched versus unmatched patients. The majority of patients had never smoked (57%), while 43% of patients were ever smokers. The SSc patients did not differ in their smoking behavior from controls ($p=0.842$, OR: 1.020, 95% CI: 0.839-1.240). Anti-topoisomerase positive patients were more likely to be never smokers ($p=0.049$, OR=0.648, 95% CI=0.421-0.998) whereas no such association was found with the anti-centromere and anti-RNA Polymerase antibodies.

Conclusion: Unlike in rheumatoid arthritis, smoking does not confer a risk for development of SSc, though it may impact disease severity.

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Introduction

Systemic sclerosis (SSc) is a multisystem autoimmune disease. Although environmental factors have been implicated as contributors to the development of SSc in a genetically susceptible host (1), the exact role of environmental triggers in the etiology of SSc remains unclear. Smoking has been established as an important environmental contributor to rheumatoid arthritis (RA) through case control studies (2). Similar studies investigating the role of cigarette exposure in susceptibility to SSc have not been previously reported.

The most extensive research on the impact of cigarette smoking and rheumatic diseases involved RA. Over the past two decades, numerous studies have shown an association between cigarette smoking and rheumatoid factor (RF)- positive- and anti-cyclic citrullinated peptide (anti-CCP)-positive RA (3;4). These studies indicate that cigarette smoking not only serves as a risk factor for the development of RA, but also results in a more severe form of the disease (4). This association appears to be greatest for men and current smokers versus women and former smokers, respectively (3;5). In addition, while the duration of smoking seems to be more important than the actual number of cigarettes smoked, the effects of even moderate tobacco use appears to have an influence on RA for many years after smoking has ceased (6). While the exact role of tobacco use in the pathogenesis of RA remains under investigation, this research suggests that cigarette smoking serves as an environmental trigger for those with genetic susceptibility to RA (7).

The role of cigarette smoking as a risk factor for disease susceptibility in SSc has not been previously reported. However, a relationship between smoking and the severity

of SSc-related vascular disease has been demonstrated (8). This study found that SSc patients who were current smokers were three to four times more likely to experience digital vascular complications such as amputation and gangrene than persons with SSc who had never smoked (8).

More recently, a large Canadian study focused on cigarette smoking and the disease manifestations of SSc. This study found that cigarette smoking not only had negative effects on the vascular, gastrointestinal and respiratory outcomes of SSc, but that this impact exerted itself over a prolonged period of time (i.e. respiratory complications). Furthermore, this study also demonstrated that smoking cessation actually improved vascular complications of SSc (i.e. Raynaud's phenomenon) (9).

While these studies have demonstrated that cigarette smoking is associated with worse disease manifestations once the diagnosis of SSc has been established, the role of smoking as a risk factor for disease development has not been investigated. In order to better understand this relationship, we conducted a case-control study to investigate the association of smoking with susceptibility to SSc in a large well-defined patient population.

Methods

We conducted a medical record review of 1,379 patients with SSc, enrolled in the *Scleroderma Family Registry and DNA Repository* and the *GENISOS* (Genes versus Environment in Scleroderma Outcomes Study) cohort (10).

The diagnosis of SSc was made according to the 1980 Criteria for the Classification of SSc (10-A) or if the patient had at least 3 out of 5 CREST (Calcinosis, Raynaud's phenomenon, Esophageal Dysfunction, Sclerodactyly, Telangiectasias) features. Patients were categorized according to the extent of skin involvement (11). Diffuse cutaneous involvement was defined as the presence of skin thickening proximal to elbows or knees. The remainder of patients was assigned to the group with limited cutaneous involvement. The disease duration was calculated from the first non-Raynaud's phenomenon as well as from the first symptom attributable to SSc. Anti-centromere antibodies were determined by the pattern of immunofluorescence on HEp-2 cells (Antibodies Inc, Davis, CA, USA) as part of antinuclear antibody testing. Anti RNA Polymerase III antibodies were determined by ELISA (MBL Co. Ltd, Nagoya, Japan) and anti-topoisomerase I antibodies were determined by passive immunodiffusion against calf thymus extract, (Inova Diagnostics, San Diego, CA, USA).

Smoking history was obtained from chart review and, in some cases, by telephone interview with patients, if sufficient information was not provided in the medical records.

The smoking history was obtained in majority of cases at the time of enrollment into the GENISOS or Scleroderma Family Registry Studies(1998-2009). Information extracted or asked included questions related to smoking status, duration and quantity (Supplementary Figure 1).

SSc patients were subsequently categorized as never smokers, past smokers or current smokers. This categorization was based upon smoking status at the time of enrollment.

Of the 1,379 patients with SSc, smoking data were available for 749 patients; 128 individuals did not have race or state of residence information leaving 621 who were matched 2:1 by age, gender, ethnicity, and state of residence to controls using the Behavioral Risk Factor Surveillance System (BRFSS, 1999-2009). BRFSS was created by the Centers for Disease Control (CDC) and is a state-based system of health surveys which collects information on health risk behaviors, including smoking via telephone surveys. Given the variation of smoking prevalence amongst various states, we felt it was important to control for geographic location in our analysis. The investigated outcome was frequency of ever smokers defined as past smokers and/or current smokers.

Sub-datasets were established to conduct the comparison of smoking status between subtypes of SSc and their matched controls (each SSc patient was assigned to two matched controls).

The comparison of smoking status between SSc cases and matched controls was conducted with a chi-square test. A multivariable nominal logistic regression model was utilized to adjust for age, gender, and ethnicity in the comparisons of smoking status among serological and clinical subtypes of SSc patients. Conservative Bonferroni correction (resulting in the nominal $p < 0.012$ being significant in the subset analysis) was also used to adjust for multiple testing.

Results

There were no significant differences in demographics between the 621 cases with smoking information and the rest of the SSc patients (data not shown). Table 1 lists the demographics of the 621 SSc cases used in our study and the 1,228 BRFSS controls.

Of the 621 cases, the mean age was 52.6 years, with 88.7% being female. The mean disease duration (standard deviation) was 9.07 years (8.35) from the first non-Raynaud's phenomenon symptom and 11.21 years (10.32) based on the first symptom attributable to SSc. Non-Hispanic Whites represented the largest ethnic group (74.2%), followed by Hispanics (11.3%) and Non-Hispanic Blacks (9.7%). Fifty seven percent of patients were never smokers, while 43% were categorized as ever smokers. Texas represented the most frequent state of residence (44.9%) with Michigan (7.4%) and Minnesota (5.5%) rounding out the top three.

Although current and past smokers were classified together as ever smokers for the purposes of this analysis, it is important to note that only 9.7% of cases were current smokers while 17.8% of controls were identified as current smokers.

The comparison of cases to controls revealed that there was no significant SSc risk associated with ever smoking ($p=0.842$, OR: 1.020, 95% CI: 0.839-1.240). A total of 337 (54%) had limited and 260 (41%) had diffuse cutaneous involvement. Disease type information was not available in 24 SSc patients (4%). As shown in Table 2, there was no significant difference in SSc subtype between ever and never smokers after adjustment for age, gender, and ethnicity.

There was no significant difference in anti-centromere or anti-RNA Polymerase III antibody positivity between never smokers and ever smokers among our patients. After adjusting for age, gender, and ethnicity, never smokers were more likely to be anti-topoisomerase I positive than ever smokers ($p=0.049$, OR=0.648, 95% CI=0.421-0.998). Thus, a relationship between autoantibody expression and smoking may be present.

However, this association was not significant after correcting for multiple comparisons (0.049>0.012). The comparison of serological and clinical subtypes of SSc to the matched controls is detailed in Table 3.

Discussion

Cigarette smoking has been established as having both pro-inflammatory and immunosuppressive effects on various disease processes, including rheumatic and other autoimmune diseases. Through mechanisms that are not entirely understood, cigarette smokers, both past and present have increased susceptibility to developing RA, Grave's hyperthyroidism (GH), Crohn's disease (CD), multiple sclerosis (MS), and primary biliary cirrhosis (PBC) (12). Furthermore, the course and severity of many of these disease processes are worsened by cigarette smoking. For instance, cigarette smoking is associated with increased joint involvement and rheumatoid nodules in RA, ophthalmopathy in GH, colonic involvement in CD and an overall worse clinical course in MS (12).

On the other end of the spectrum, current cigarette smoking has a protective effect on disease course in Behçet's disease (i.e. less aphthous ulcers) and on both susceptibility and disease course in ulcerative colitis (12).

The impact of cigarette smoking on systemic lupus erythematosus (SLE) may lie somewhere in the middle of this spectrum. The results are mixed in SLE, but a recent analysis of several studies concluded that current cigarette smoking may have a mild impact on both disease susceptibility and activity (i.e. more cutaneous manifestations)(13).

As for SSc, our study shows that there is no statistically significant difference in ever versus never smoking status between SSc cases and controls. Therefore, unlike in RA and some other autoimmune diseases, we cannot conclude that smoking confers an increased risk for the development of SSc, even though cigarette smoking has been associated with more deleterious disease outcomes (8;9). It is not entirely clear why smoking has a profound impact on susceptibility and severity in some rheumatic diseases like in RA, a mild impact on others like in SLE, and only an influence on severity as we propose for SSc. It is challenging to compare studies on the impact of cigarette smoking in autoimmune diseases because of the diversity of study designs, controls, patient populations and smoking history methodology used.

There are many proposed mechanisms for how cigarette smoking modulates disease susceptibility and severity in rheumatic diseases. One theory suggests that cigarette smoking modulates autoantibody expression. For instance a large study involving SLE patients found that current cigarette smokers had significantly higher titers of ant-double stranded DNA (dsDNA) in comparison to never smokers (14). However, while this study controlled for age and sex, it did not control for race/ethnicity.

In our study, there was no significant association between cigarette smoking and the expression of anti-centromere and anti-RNA Polymerase III antibodies. However, anti-topoisomerase positive patients were more likely to be never-smokers than anti-topoisomerase negative patients. This result might be a true finding or a spurious association resulting from multiple comparisons, and should therefore be interpreted with caution and as an exploratory finding until the association is replicated in other independent cohorts. The comparison of serological and clinical subtypes of SSc to

controls in regard to smoking status did not yield any significant results, indicating that smoking is also not associated with susceptibility to SSc in subtypes of disease.

The current sample size had a power of 76% to detect an odds ratio of 1.3 and a power of 86% to detect an odds ratio of 1.35. Therefore, we believe this study is well powered to detect a moderately strong association in the range of 1.3 to 1.35. However, the current sample size is underpowered for the detection of weaker associations.

The strengths of this study include both the large number of SSc patients examined as well as the careful consideration given to geographical location in the matching process, as smoking patterns differ on a state-by-state basis. In fact, the Morbidity and Mortality Weekly Report (MMWR), based on BRFSS found that in 2009, the prevalence of cigarette smoking was highest in Kentucky, West Virginia and Oklahoma (25.6%, 25.6% and 25.5%, respectively) and lowest in Utah, California, and Washington (9.8%, 12.9% and 14.9%, respectively)(15). The inclusion of geographic location in the matching process distinguishes this study from many others that did not take this into account.

In the current study, the smoking history information from both patients and BRFSS controls was obtained in a similar time period. Therefore, we do not believe general changes in smoking habits over time have substantially influenced our results. Furthermore, the BRFSS data indicate that the prevalence of ever smoking in the last decade has remained stable though the prevalence of current smoking has decreased in the last 10 years.

We could not match or adjust for other potentially important variables such as income level or alcohol consumption because this information was not available in the Scleroderma Family Registry and BRFSS databases.

Our results could potentially have been influenced by the effect of SSc on smoking habits: namely that the diagnosis of SSc is a strong incentive for smoking cessation which does not exist for controls. This likely explains the disparity in the percentage of cases (9.7%) and controls (17.8%) who are current smokers. We categorized patients into ever and never smokers for the comparative analyses in order to avoid issues arising from this bias.

In the current study, information about smoking history was obtained in the majority of cases at the time of enrollment. We did not ask patients about their smoking history at the time of first symptom attributable to scleroderma. It is possible that a small group of patients started smoking after the disease onset and before the enrollment into the GENISOS/Registry. However, we believe this scenario will apply to a small group of the study subjects because the mean age at enrollment was 52.6 years and the average time from the first symptom attributable to SSc was 11.2 years.

The current study does not indicate that smoking influences the susceptibility to SSc. Larger studies are needed to evaluate the impact of cigarette smoking on autoantibody expression as well as whether the duration or quantity of cigarettes smoked (i.e. smoking intensity) has an impact on the susceptibility to SSc, thereby creating a threshold beyond which cigarette smokers are more susceptible to SSc. Regardless, there are significant data to support the deleterious effects of cigarette smoking on the severity

of SSc. Therefore, smoking cessation counseling should remain an important part of medical care in SSc.

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Table 1. Demographic characteristics and smoking status of SSc cases and BRFSS controls

	SSc Cases (n=621)	BRFSS Controls (n=1228)
Age (mean in years)	52.6	52.8
Sex		
Female	551 (88.7%)	1091 (88.8%)
Male	70 (11.3%)	137 (11.2%)
Race/Ethnicity		
Non-Hispanic White	461 (74.2%)	917 (74.7%)
Non-Hispanic Black	60 (9.7%)	118 (9.6%)
Asian/Pacific Islander	2 (0.3%)	4 (0.3%)
American Indian/Alaska Native	11 (1.8%)	21 (1.7%)
Other/non-Hispanic /multiracial	17 (2.7%)	33 (2.7%)
Hispanic	70 (11.3%)	135 (11.0%)
Smoking Status		
Never smokers	354 (57.0%)	706 (57.5%)
Ever Smokers	267 (43.0%)	522 (42.5%)
State of Residence*		
Texas	279 (44.9%)	552 (45.0%)
Michigan	46 (7.4%)	92 (7.5%)
Minnesota	34 (5.5%)	66 (5.4%)

*The remainder of the cases was distributed at lesser frequencies among the other U.S. states and territories

Table 2: Multivariable comparison of smoking status among clinical and serological subtypes of SSc after adjustment for age, gender, and ethnicity

	No of subjects (n=621)	P- value	OR	Confidence Interval	
				Lower	Upper
SSc Subtype (Limited/diffuse)	337/260†	0.291	1.211	0.849	1.728
Anti-RNA Polymerase III	126/495	0.115	0.715	0.471	1.085
Anti-centromere	175/446	0.279	1.232	0.844	1.798
Anti-topoisomerase	125/496	0.049	0.648	0.421	0.998

†Disease type information was not available in 24 patients

SSc/Smoking

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Table 3. Comparison of smoking status between subtypes of SSc and matched controls

	No of subjects	P-value	OR	Confidence Interval	
				Lower	Upper
Limited SSc subtype/ matched controls	337/674	0.408	1.118	0.859	1.455
Diffuse SSc subtype/ matched controls	260/520	0.540	0.909	0.671	1.232
Anti-RNA polymerase III /matched controls	126/252	0.494	0.585	0.554	1.330
Anti-centromere /matched controls	175/350	0.245	1.242	0.862	1.790
Anti-topoisomerase /matched controls	125/250	0.067	0.659	0.422	1.030