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Title: Smoking in Systemic Sclerosis: a Longitudinal European Scleroderma Trials and Research Group Study

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ABSTRACT

Objectives: Data on the role of tobacco exposure in systemic sclerosis (SSc) severity and progression are scarce. We aimed to assess the effects of smoking on the evolution of pulmonary and skin manifestations in the EUSTAR database.

Methods: Adult SSc patients with data on smoking history and a 12-24 months follow-up visit were included. Associations of severity and progression of organ involvement with smoking history and the comprehensive smoking index (CSI) were assessed using multivariable regression analyses.

Results: 3,319 patients were included (age 57 years; 85% female), 66% were never smokers; 23% ex-smokers and 11% were current smokers. Current smokers had a lower percentage of anti-topoisomerase autoantibodies than previous or never smokers (31% *vs.* 40% and 45%, respectively).

Never smokers had a higher baseline forced expiratory volume in one second/forced vital capacity (FEV1/FVC) ratio than previous and current smokers ($p<0.001$). The FEV1/FVC ratio declined faster in current smokers than in never smokers ($p=0.05$) or ex-smokers ($p=0.01$).

The baseline modified Rodnan skin score (mRSS) and the mRSS decline were comparable across smoking groups.

Although heavy smoking (more than 25 pack years) increased the odds of digital ulcers by almost 50%, there was no robust adverse association of smoking with digital ulcer development.

Conclusion: The known adverse effect of smoking on bronchial airways and alveoli is also observed in SSc patients; however robust adverse effects of smoking on the progression of SSc-specific pulmonary or cutaneous manifestations were not observed.

Systemic sclerosis (SSc) is a rare, multisystem autoimmune disorder [1]. Hypoxia and oxidative stress have been implicated in the pathophysiology of its generalized microangiopathy and fibrosis [1]. Although smoking does not appear to confer a risk for SSc development [2], it has vasoconstrictive effects and increases free radical exposure, and together with other proinflammatory and immunomodulatory effects may exacerbate SSc manifestations [3]. Data on the role of tobacco exposure with regards to the severity of SSc organ manifestations and progression are however scarce and at times contradictory [4]. A Canadian cohort study of 606 patients for example reported an increased frequency of digital ulcers (DU) in smokers [4], whereas a study of 172 Australian patients, found no association of smoking history with vascular characteristics [5].

Larger studies and robust data assessing the possible effect of smoking on SSc presentations and importantly SSc progression are lacking. We therefore assessed the association of tobacco exposure with the prevalence and evolution of SSc organ manifestations.

PATIENTS AND METHODS

This study is based on the multinational, longitudinal European Scleroderma Trials and Research (EUSTAR) database [6]. Each center obtained local ethical committee approval; each patient provided written informed consent. Data collection started in 2004. The smoking module, however, was introduced to the database in 2013; hence smoking data were only collected from that date onwards. Data for this study were exported in May 2017.

Patients were included if they were older than 18 years, fulfilled the 1980 ACR or 2013 ACR/EULAR criteria for SSc, and if the smoking status was known; additionally, patients were required to have a follow-up visit 12-24 months after baseline. Information about the core data collected in EUSTAR can be found elsewhere [6]. The EUSTAR smoking module collects patient-reported smoking status (never/previous/current smoker), the number of pack-years, and the smoking start and cessation dates.

The influence of smoking behavior was assessed on several disease parameters: forced expiratory volume in one second/forced vital capacity ratio (FEV1/FVC), FVC, single breath diffusing capacity for monoxide (DLCO/sb), systolic pulmonary arterial pressure as estimated by echocardiography (PAPsys), modified Rodnan skin score (mRSS) and digital ulcers (DU). Further information about outcome measures as well as variables describing the study population can be found in Supplementary Table 1.

Outcome progression was downscaled to 'rate of change per 12 months' unless otherwise stated.

Statistical analysis

Frequencies/percentages or means/standard deviations (SD) were calculated; groups were compared using X^2-tests/Fisher's exact tests or t-tests/ANOVA. Multiple linear and logistic regression analyses were applied to adjust outcome/exposure associations with *a priori* defined potential confounding factors (age, sex, time since the onset of Raynaud's phenomenon [RP] and since the first non-RP manifestation, antibody status, and skin involvement). As the SSc specific antibodies might be on the causal pathway between smoking and SSc organ involvement we additionally analyzed the data without adjustment for antibody status, these results can be found in the supplementary (Supplementary Tables 2, 3, 4).

Three smoking metrics were modelled separately: (Model 1) never/previous/current smoking, (Model 2) smoking intensity (pack-years; never smokers = 0 pack-years, light smokers = 0-10 pack-years, medium smokers = 10-25 pack-years, heavy smokers = >25 pack-years), and (Model 3) comprehensive smoking index (CSI). The CSI is an index incorporating smoking duration, time since cessation and smoking intensity into a single variable [7,8]. The CSI depends on two parameters which are estimated for each outcome separately: the half-life, i.e. the rate at which the smoking's impact decays over time, and the lag-time, i.e. the delay between smoking and its impact.

Never smokers carry a CSI of 0 and higher CSI values indicate more smoking. The CSI values are estimated separately for each outcome variable and hence the CSIs including their ranges are different for each outcome variable. The results from the CSI regression analyses should be interpreted in the following way: The beta values represent the additive increase or decrease in the outcome variable per unit increase in the CSI. The odds ratio (OR) values represent the increase in odds for the presence of the outcome

variable per unit CSI increase. OR values larger than one indicate that increased smoking increases the likelihood of occurrence of the outcome.

Missing data were imputed using multiple imputation with chained equations [9]. The regression analyses shown in this paper are all based on imputed data; the results based on a complete case analysis are represented in Supplementary Table 6.

Analyses were performed with Stata/IC15.1 (StataCorp, USA).

RESULTS

Patient and smoking characteristics

Of the 12,912 adult SSc patients within EUSTAR, 6179 (48%) patients had no smoking data available; in 3414 (26%) patients had no follow-up visit in the required time frame. Therefore 3,319 (26%) patients fulfilled the inclusion criteria (Supplementary Figure 1). The included patients had clinically similar demographic and disease characteristics than the excluded patients (Supplementary Table 5). On average, a follow-up visit was recorded 1.4 years (SD 0.33) after baseline. Patients were on average 57 years old and 85% were female. Demographic and disease characteristics are shown in Table 1.

66% of patients were never smokers, 23% ex-smokers and 11% were current smokers; 13% of the current smokers (1.5% of patients) stopped smoking during the observation time on average 9 months after the baseline visit. The average ex-smokers had smoked 18 pack-years (SD 21) during a time of 19 years (SD 12) and ceased smoking 15 years (SD 13) ago. 49% of the ex-smokers had ceased smoking before RP onset and 58% had quit before the onset of the first non-RP manifestation. The average current smoker had smoked 27 pack-years (SD 30) during a time of 30 years (SD 13).

As patients with interstitial lung disease (ILD) might be more likely to cease smoking than patients without ILD there might be a higher percentage of ILD patients in the

previous smoker group possibly leading to worse trajectories in lung function measures. Therefore, in addition to analyzing the entire study population, we also analyzed the progression of lung function measures separately for patients with ILD on high resolution CT (HRCT) and patients without ILD on HRCT. Among all patients, 49% had signs of ILD on HRCT. The smoking behavior patterns were similar in patients with ILD and in patients without ILD; 68% of patients in both groups were never smokers, 23% of patients with and 20% of patients without ILD were previous smokers, and 9% of patients with and 12% of patients without ILD were current smokers (p=0.06).

FEV1/FVC ratio

Never smokers had a significantly higher baseline FEV1/FVC ratio than previous and current smokers (Table 1). These differences in baseline FEV1/FVC ratio were seen in all three smoking models (Figure 1; Table 2; Supplementary Table 7). As can be seen in Table 2, patients had a 2.7 unit lower FEV1/FVC ratio per unit increase in the CSI. Medium and heavy smokers had lower baseline FEV1/FVC ratios than never smokers and light smokers (all p<0.001; Supplementary Table 7).

In univariable analysis, the FEV1/FVC ratio declined similarly across smoking groups (p=0.065); in multivariable analysis, the FEV1/FVC ratio however declined faster in current smokers (Figure 1); this result was also observed when stratifying the study population into ILD and non-ILD patients (data not shown).

FVC

There was no significant difference in baseline FVC and in the FVC change between the three smoking groups (Table 1). This lack of a robust effect of smoking on the baseline FVC and on the FVC change was also observed in all three multivariable models (Figure

1; Table 2; Supplementary Table 7). This lack was also observed when assessing the FVC changes separately for ILD and non-ILD patients (data not shown).

DLCO/sb

Smokers had lower baseline DLCO/sb levels than never smokers ($p<0.001$; Table 1); smoking was associated with low baseline DLCO/sb in all three models (Figure 1; Table 2; Supplementary Table 7).

The DLCO/sb declined similarly across all three smoking behavior groups in univariable (Table 1) and multivariable analysis (Figure 1; Table 2; Supplementary Table 7), these results were also true when looking at ILD and non-ILD patients separately (data not shown).

PAPsys

The average baseline PAPsys was slightly higher in never smokers than in current or ex-smokers (Table 1). These differences stayed apparent but to a lesser extent not only when assessing the smoking groups multivariably, but also evaluating smoking intensity and the CSI (Figure 1; Table 2; Supplementary Table 7).

The PAPsys increased similarly in the groups in univariable (Table 1) and multivariable analysis (Figure 1; Table 2; Supplementary Table 7).

Skin involvement

No association was evident between the severity of skin fibrosis and the smoking history regardless of the smoking matrices used (Table 1; Figure 1; Table 2; Supplementary Table 7). SSc sine scleroderma, however, was twice as prevalent in current as in ex- or never smokers (Table 1).

In all smoking models, no clinically significant difference in mRSS evolution was observed (Table 1; Figure 1; Table 2; Supplementary Table 7).

DU

The prevalence of DUs was comparable in the smoking behavior groups (Table 1). However, heavy smokers had a greater likelihood of DUs than never smokers in multivariable analysis (OR=1.6, p=0.02; Supplementary Table 7); also, a higher CSI was associated with the presence of DUs at baseline (OR=1.2, p=0.002, i.e. for a one unit increase in CSI, the odds of having DUs at baseline increases by a factor of 1.19; Table 2). In the sub-group of DU-naïve patients at baseline, 14% of never smokers developed new DUs in between the two visits, compared to 16% ex-smokers and 8% current smokers (p=0.05). Ex-smokers had comparable odds than never smokers to develop DU between the two visits (OR=1.1, p=0.7); current smokers developed DUs less often than never smoking patients (OR=0.5, p=0.031). The smoking intensity was not associated with incident DU during the observation period (Supplementary Table 7).

DISCUSSION

Our study is by far the largest prospectively investigating the effect of smoking on SSc outcomes. Smoking was common in our patients, however less than in Anglo-Saxon cohorts and also much lower than the European average of around 28% [4,5,10].

The EUSTAR cohort replicated the known adverse effect of smoking on bronchial airways in terms of a decline in FEV1/FVC and DLCO. Given the absence of discernible adverse effects of smoking on PAPsys the effect of smoking on diffusion capacity may reflect emphysema rather than precapillary pulmonary vasculopathy. Adverse effects of smoking on pulmonary airway obstruction and diffusing capacity were also seen in two

cohorts of 137 SSc and 19 smokers [11,12]. In line with one of these cohorts [11] but in contrast to the second study [12] we found no association between lung compliance (FVC) and smoking status.

Our study also found no robust effect of smoking on DU prevalence and incidence when assessing the smoking behavior itself or assessing the smoking intensity, similar to two smaller studies [13,14]. We even found a negative association between tobacco exposure and incident DU during the follow-up in a sub-group of DU naïve patients (OR=0.5). This effect could not be explained by differences in immunosuppressive and vasoactive medication (data not shown). However, when we assessed smoking using the CSI we did find an association of smoking on DU prevalence similar to another, however quite smaller study also using the CSI [4]. This difference could partially arise due to a 'healthy smoker effect', although this bias is partly been accounted for by the CSI [15]. Given these results, it is difficult to draw robust conclusions on the effect of smoking on DUs.

In our study, smokers had a lower prevalence of Scl-70 autoantibodies than previous and never smokers. This imbalance in autoantibody status is also in line with that found in another study, in which Scl-70 positive patients were more likely to be never smokers than ever smokers [2] raising the possibility of a aethiopathological link between smoking and Scl-70 positivity. The question, however, is if this imbalance is partly due to a link, maybe a causal one, between smoking and autoantibody status or if this imbalance is partly explained by a 'healthy smoker effect' especially as the prevalence of Scl-70 positivity in previous smokers is more comparable to the never smokers than to current smokers.

Like all registry-based studies the EUSTAR cohort has limitations. We had no means to verify the smoking information provided by the patients, however we were able to demonstrate known adverse effects of smoking on airway obstruction suggesting that the information provided by the patients was not random and that our study was powered to detect meaningful changes in other parameters.

By requiring the study population to have a follow-up visit there is a possibility that we excluded sicker patients, i.e. that we introduced a selection bias for healthier patients. However, at baseline the patients that were excluded due to the absence of a follow-up visit within the required time frame were not majorly worse off than the included patients (Supplementary Table 5) arguing against a major selection bias.

In summary, our study demonstrates an adverse effect of smoking on pulmonary airways, but no effects on SSc-specific pulmonary and cutaneous involvement. These data argue against a major role of tobacco associated free radicals, vasoconstrictory and immunomodulatory effects in the pathogenesis of SSc vasculopathy and fibrosis.

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ETHICAL APPROVAL

Ethics approval according to the Declaration of Helsinki has been obtained from all respective contributing local ethics committees.

DATA SHARING

Data is available from the EUSTAR group upon valid scientific request.

CONTRIBUTORSHIP

VKJ and UAW designed the study, analyzed and interpreted the data and wrote the manuscript, OD and YA advised in the study design. All authors were involved in data acquisition, and drafting of the article or revising it critically for important intellectual content. All authors approved the final version of the manuscript.

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Table 1. Baseline demographic and disease characteristics as well as outcome measures by smoking status.

ACA, anticentromere autoantibodies; DLCO/sb, single breath diffusing capacity for monoxide; ESR, erythrocyte sedimentation rate; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; LVEF, left ventricular ejection fraction; mRSS, modified Rodnan skin score; NYHA, New York heart association; PAPsys, systolic pulmonary artery pressure as estimated by echocardiography; RNAP-III, anti-RNA polymerase-III autoantibodies; RP, Raynaud's phenomenon; Scl-70, anti-topoisomerase autoantibodies.

*based on the follow-up visit, not the 12 months projection. **The changes in outcomes are given downscaled to "per 12 month". #Number of patients with available information for each variable.

Characteristics of the study population		**n#**	**Never smokers** % or mean (SD)	**Ex-smokers** % or mean (SD)	**Current smokers** % or mean (SD)	**p-value**
N			2205	752	362	
Age; years		3319	57.5 (14.1)	57.2 (12.1)	52.5 (11.2)	<0.001
Male sex		3319	8	27	29	<0.001
Disease characteristics						
Time since RP onset; years		3286	14.9 (11.7)	13.4 (11.3)	13.3 (11.8)	0.001
Time since first non-RP manifestation; years		2988	11.7 (8.8)	10.5 (8.7)	8.9 (7.8)	<0.001
Skin involvement	Sine	3106	7	8	15	<0.001
	Limited		64	62	58	
	Diffuse		29	30	27	

mRSS		2949	7.7 (7.4)	7.8 (7.9)	6.9 (7.3)	0.14
Follow-up mRSS*		2839	7.4 (7.2)	7.2 (7.1)	6.9 (6.9)	0.40
Change in mRSS**		2684	-0.3 (3.4)	-0.6 (4.0)	-0.2 (3.3)	0.12
Esophageal symptoms		3275	60	66	58	0.010
Stomach symptoms		3241	23	23	21	0.68
Intestinal symptoms		3250	27	30	29	0.24
Dyspnea; NYHA functional class	I	3114	57	54	63	0.001
	II		33	34	31	
	III		9	10	5	
	IV		1	2	1	
Digital ulcers, current		3125	14	14	16	0.7
Digital ulcers, ever		3125	46	48	45	0.56
LVEF; %		2448	62.3 (6.1)	61.7 (6.3)	63.0 (5.8)	0.015
FEV1/FVC ratio		2256	97.5 (13.5)	95.4 (15.2)	92.8 (15.0)	<0.001
Follow-up FEV1/FVC ratio*		1988	97.1 (12.0)	95.4 (14.5)	90.5 (12.7)	<0.001
Change in FEV1/FVC ratio**		1656	-0.3 (10.1)	0.4 (9.4)	-1.6 (7.7)	0.065
FVC; % of predicted		2720	96.1 (22.0)	96.7 (21.3)	98.3 (19.7)	0.25
Follow-up FVC*; % of predicted		2435	95.5 (22.8)	96.3 (22.5)	99.3 (18.8)	0.037
Change in FVC**; % of predicted		2166	-0.6 (8.5)	-0.4 (7.7)	0.1 (9.4)	0.45
DLCO/sb; % of predicted		2583	69.8 (19.6)	66.4 (20.4)	67.1 (17.8)	<0.001
Follow-up DLCO/sb*; % of predicted		2253	67.5 (20.0)	65.6 (20.0)	64.4 (18.1)	0.021
Change in DLCO/sb**; % of predicted		1977	-2.0 (9.1)	-1.7 (9.2)	-2.0 (7.8)	0.86
PAPsys; mmHg		2317	28.8 (16.9)	26.0 (1.0)	24.3 (12.5)	<0.001

Follow-up PAPsys*; mmHg	2055	29.2 (13.6)	28.5 (14.1)	24.7 (11.6)	<0.001
Change in PAPsys**; mmHg	1706	0.6 (10.5)	1.6 (8.5)	0.2 (8.1)	0.18
Laboratory parameters					
ACA positive	2508	47	47	61	
Scl-70 positive		45	40	31	<0.001
RNAP-III positive		3	6	6	
ESR; mm/hr	2795	22.8 (18.4)	18.9 (16.7)	18.0 (14.5)	<0.001

Table 2. Regression analysis comparing outcomes at baseline and progression of outcomes according to the comprehensive smoking index (CSI) adjusted for age, sex, time since the onset of Raynaud's phenomenon, time since the first non-Raynaud's phenomenon manifestation, antibody status and extent of skin involvement.

The first column illustrates the mean and the range of each outcome's CSI based on the imputed dataset. Higher CSIs indicate more smoking; never smokers carry a CSI of 0.

The beta values represent the additive increase or decrease in the outcome variable per unit increase in the CSI. The OR values represent the increase in odds for the presence of the outcome variable per unit CSI increase. OR values larger than one indicate that increased smoking increased the likelihood of occurrence of the outcome.

The follow-up part of the table assesses the projected change per 12 months of the outcomes.

CI, confidence interval; DLCO/sb, single breath diffusing capacity for monoxide; DU, digital ulcers; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; mRSS, modified Rodnan skin score; OR, odds ratios; PAPsys, systolic pulmonary artery pressure as estimated by echocardiography.

Outcomes	**Mean CSI (range)**	**CSI** β or OR	95%CI	p-value
Baseline				
FEV1/FVC	0.45 (0-4.09)	β= -2.71	-3.46 to -1.97	<0.001
FVC	0.34 (0-5.12)	β= 0.41	-0.39 to 1.22	0.32
DLCO/sb	0.27 (0-2.94)	β= -4.38	-5.89 to -2.88	<0.001
PAPsys	0.23 (0-2.61)	β= -2.08	-3.57 to -0.58	0.006
mRSS	0.40 (0-7.05)	β= 0.20	-0.03 to 0.43	0.088

DU current	0.35 (0-7.94)	OR= 1.19	1.07 to 1.32	0.002
Follow-up				
FEV1/FVC	0.33 (0-6.69)	β= -0.45	-0.93 to 0.02	0.059
FVC	0.46 (0-6.36)	β= 0.32	-0.01 to 0.66	0.059
DLCO/SB	0.43 (0-4.02)	β= 0.37	-0.16 to 0.90	0.17
PAPsys	0.35 (0-6.19)	β= -0.21	-0.76 to 0.34	0.45
mRSS	0.43 (0-6.36)	β= -0.16	-0.29 to -0.02	0.021
DU new btw visits	0.30 (0-8.37)	OR= 0.83	0.68 to 1.00	0.056

Figure 1. Regression analysis comparing outcomes by smoking status adjusted for age, sex, time since the onset of Raynaud's phenomenon, time since the first non-Raynaud's phenomenon manifestation, antibody status and extent of skin involvement.

Panel A shows the multiple adjusted baseline levels of the outcome measures and corresponding 95% confidence intervals and panel B shows the multiple adjusted change rates in the outcome measures between baseline and the projected 12 months follow-up. Light grey represents never smokers, medium grey represents ex-smokers and dark grey represents current smokers.

DLCO/sb, single breath diffusing capacity for monoxide (% of predicted); FEV1, forced expiratory volume in one second; FVC, forced vital capacity (% of predicted); mRSS, modified Rodnan skin score; PAPsys, systolic pulmonary artery pressure as estimated by echocardiography (mmHg).