Smoking Behaviour and the Progression of Organ Manifestations in Systemic Sclerosis: a Longitudinal European Scleroderma Trials and Research Group Study

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KEYWORDS

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WORD COUNT

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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 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.

Never-smokers had a higher baseline FEV/FVC ratio than previous and current smokers ($p<0.001$). The FEV/FVC ratio declined faster in current smokers than in never-smokers ($p=0.05$) or ex-smokers ($p=0.01$).

The baseline mRSS and the mRSS decline were comparable across smoking groups. The baseline prevalence of DUs was similar in smokers/non-smokers. Incident DUs were negatively associated with current smoking (OR 0.5, $p=0.03$), but not with ex-smoking (OR 1.1, $p=0.7$).

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.

INTRODUCTION

Systemic sclerosis 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 in 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 SSc,[4] whereas a study of 172 Australian patients, found no association of a detailed smoking history with vascular characteristics.[5]

Larger studies and robust prospective data assessing the possible effect of smoking on SSc presentations and importantly SSc progression are not available. We therefore aimed to assess the association of tobacco exposure with the incidence and evolution of SSc organ manifestations in a large prospective study.

METHODS

This study is based on the multinational, longitudinal European Scleroderma Trials and Research (EUSTAR) database.[6,7] Each EUSTAR centre obtained ethical approval by its local ethics committee; each patient provided written informed consent. EUSTAR data collection started in 2004, however, smoking data was collected from 2013 onwards, though retrospective data entry into the smoking module was possible. Data for this study were exported in May 2017.

Patients were included in this analysis if they were older than 18 years, fulfilled either the 1980 ACR or the 2013 ACR/EULAR criteria for SSc,[8,9] and if the smoking status was known; additionally, patients were required to have a EUSTAR follow-up visit 12-24 months after the baseline visit. Information about the core data collected in the EUSTAR database can be found elsewhere.[6,7] The EUSTAR smoking module collects information on the patient-reported smoking status (never/previous/current smokers), the number of pack-years smoked, the smoking start and cessation dates.

The influence of the patients' smoking behaviour on the following disease characteristics were assessed: forced expiratory volume/forced vital capacity ratio (FEV/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). A possible influence of smoking on the baseline characteristic and on the progression in the outcomes between baseline and the follow-up visit was assessed; the progression was downscaled to rate of change per 12 months.

Statistical analysis

Frequencies/percentages or means/standard deviations (SD) were calculated and groups were compared using X^2-tests/Fisher's exact tests or t-tests/ANOVA. Multiple linear and logistic regression analyses were applied for the adjustment of the outcome/exposure association with *a priori* defined potential confounding factors (age, sex, time since RP and since first non-RP manifestation, antibody status, and skin involvement).

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.[10,11] 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.

Missing data were imputed using multiple imputation with chained equations.[12] All regression results are based on the imputed data. Analyses were performed with Stata/IC 13.1 (StataCorp, USA).

RESULTS

Patient and smoking characteristics

Of the 12,912 adult SSc patients within EUSTAR, 3,319 (26%) patients fulfilled the inclusion criteria. The included patients had similar demographic and disease characteristics than the excluded patients (data not shown). On average, a follow up visit was recorded 1.4 years (SD 0.33) after the baseline visit. Patients were on average 57 years old and 85% were female. Demographic and disease characteristics are shown in Table 1.

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; FEV-1, forced expiratory volume; 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".

Characteristics of the study population		**Never smokers** % or mean (SD)	**Ex-smokers** % or mean (SD)	**Current smokers** % or mean (SD)	**p-value**
N		2205	752	362	
Age; years		57.5 (14.1)	57.2 (12.1)	52.5 (11.2)	<0.001
Male sex		8	27	29	<0.001
Disease characteristics					
Time since RP onset; years		14.9 (11.7)	13.4 (11.3)	13.3 (11.8)	0.001
Time since first non-RP manifestation; years		11.7 (8.8)	10.5 (8.7)	8.9 (7.8)	<0.001
Skin involvement	Sine	7	8	15	<0.001
	Limited	64	62	58	
	Diffuse	29	30	27	
mRSS		7.7 (7.4)	7.8 (7.9)	6.9 (7.3)	0.14
Follow up mRSS*		7.4 (7.2)	7.2 (7.1)	6.9 (6.9)	0.40
Change in mRSS**		-0.3 (3.4)	-0.6 (4.0)	-0.2 (3.3)	0.12

Characteristics of the study population		Never smokers % or mean (SD)	Ex-smokers % or mean (SD)	Current smokers % or mean (SD)	p-value
Oesophageal symptoms		60	66	58	0.010
Stomach symptoms		23	23	21	0.68
Intestinal symptoms		27	30	29	0.24
Dyspnoea; NYHA functional class	1	57	54	63	0.001
	2	33	34	31	
	3	9	10	5	
	4	1	2	1	
Digital ulcers, ever		46	48	45	0.56
LVEF; %		62.3 (6.1)	61.7 (6.3)	63.0 (5.8)	0.015
FEV/FVC ratio		97.5 (13.5)	95.4 (15.2)	92.8 (15.0)	<0.001
Follow up FEV/FVC ratio*		97.1 (12.0)	95.4 (14.5)	90.5 (12.7)	<0.001
Change in FEV/FVC ratio**		-0.3 (10.1)	0.4 (9.4)	-1.6 (7.7)	0.065
FVC; % of predicted		96.1 (22.0)	96.7 (21.3)	98.3 (19.7)	0.25
Follow up FVC*; % of predicted		95.5 (22.8)	96.3 (22.5)	99.3 (18.8)	0.037
Change in FVC**; % of predicted		-0.6 (8.5)	-0.4 (7.7)	0.1 (9.4)	0.45
DLCO/sb; % of predicted		69.8 (19.6)	66.4 (20.4)	67.1 (17.8)	<0.001
Follow up DLCO/sb*; % of predicted		67.5 (20.0)	65.6 (20.0)	64.4 (18.1)	0.021
Change in DLCO/sb**; % of predicted		-2.0 (9.1)	-1.7 (9.2)	-2.0 (7.8)	0.86
PAPsys; mmHg		28.8 (16.9)	26.0 (1.0)	24.3 (12.5)	<0.001
Follow up PAPsys*; mmHg		29.2 (13.6)	28.5 (14.1)	24.7 (11.6)	<0.001
Change in PAPsys**; mmHg		0.6 (10.5)	1.6 (8.5)	0.2 (8.1)	0.18
Laboratory parameters					
ACA positive		47	47	61	
Scl-70 positive		45	40	31	<0.001
RNAP-III positive		3	6	6	
ESR; mm/hr		22.8 (18.4)	18.9 (16.7)	18.0 (14.5)	<0.001

66% of patients were never smokers, 23% ex-smokers and 11% were current smokers. 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).

FEV/FVC ratio

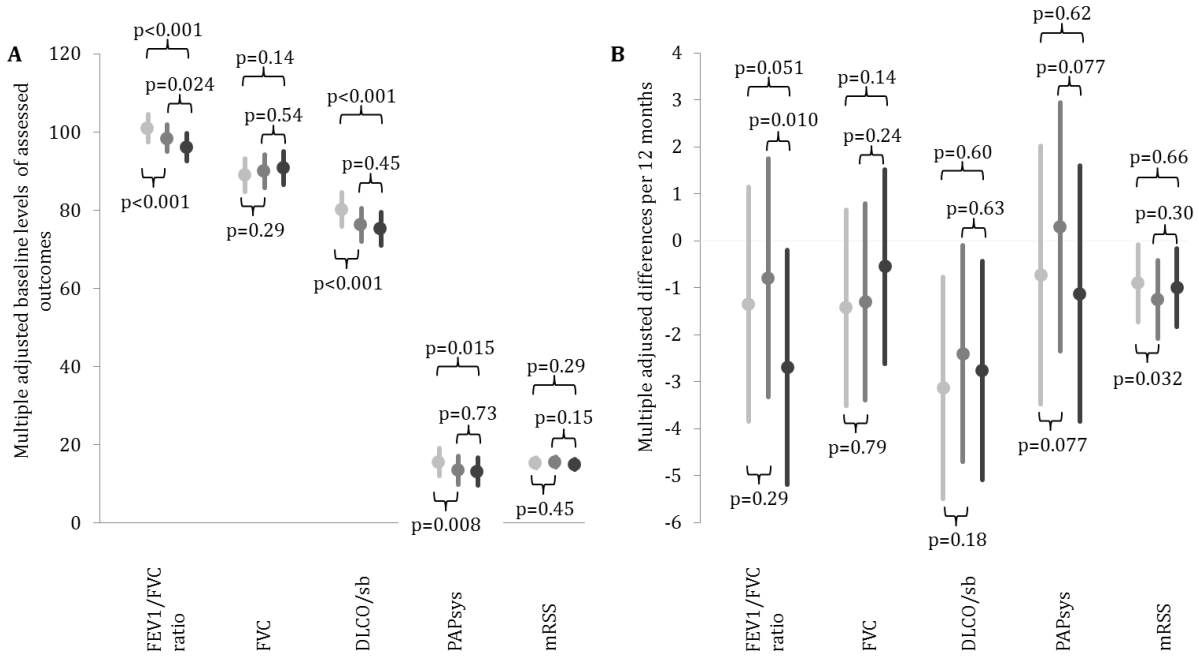
Never-smokers had a significantly higher baseline FEV/FVC ratio (97.5%) than previous (95.4%) and current smokers (92.8%, p<0.001; Table 1). These differences in baseline FEV/FVC ratio were

seen in all three smoking models in multivariable regression (Figure 1; Table 2; Supplementary 1). Medium and heavy smokers had lower baseline FEV/FVC ratios than never-smokers and light smokers (all p<0.001; Supplementary 1).

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); FVC, forced vital capacity (% of predicted); mRSS, modified Rodnan skin score; PAPsys, systolic pulmonary artery pressure as estimated by echocardiography (mmHg).



The change in the FEV/FVC ratio per 12 months was similar across smoking groups in univariable analysis (p=0.065); in multivariable analysis, the FEV/FVC ratio however declined faster in current smokers (Figure 1).

FVC

There was no significant difference in baseline FVC between the three smoking status groups (Table 1). The 12-months change of FVC was similar in the 3 smoking groups (p=0.45). This lack of a robust effect of smoking on the baseline FVC and on the FVC change was also observed in multivariable analysis in all three models (Figure 1; Table 2; Supplementary 1).

Table 2. Regression analysis comparing 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. *Outcome variables were analysed by logistic regression. The OR values represent the increase in odds for the presence of the outcome variable per unit CSI increase. Positive OR values indicate that increased smoking increased the likelihood of occurrence of the outcome.

CI, confidence interval; DLCO/sb, single breath diffusing capacity for monoxide; DU, digital ulcers; 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)	-2.71	-3.46 to -1.97	<0.001
FVC	0.34 (0-5.12)	0.41	-0.39 to 1.22	0.32
DLCO/SB	0.27 (0-2.94)	-4.38	-5.89 to -2.88	<0.001
PAPsys	0.23 (0-2.61)	-2.08	-3.57 to -0.58	0.006
mRSS	0.40 (0-7.05)	0.20	-0.03 to 0.43	0.088
DU current*	0.35 (0-7.94)	1.19	1.07 to 1.32	0.002
Follow-up				
FEV1/FVC	0.33 (0-6.69)	-0.45	-0.93 to 0.02	0.059
FVC	0.46 (0-6.36)	0.32	-0.01 to 0.66	0.059
DLCO/SB	0.43 (0-4.02)	0.37	-0.16 to 0.90	0.17
PAPsys	0.35 (0-6.19)	-0.21	-0.76 to 0.34	0.45
mRSS	0.43 (0-6.36)	-0.16	-0.29 to -0.02	0.021
DU new btw visits*	0.30 (0-8.37)	0.83	0.68 to 1.00	0.056

DLCO/sb

Smokers had a lower baseline DLCO/sb levels (current smokers 67.1% of predicted, ex-smokers 66.4% of predicted) than never-smokers (69.8% of predicted, p<0.001; Table 1); an association of smoking with DLCO/sb levels was also observed in multivariable analysis in all three models (Figure 1;Table 2; Supplementary 1).

The DLCO/sb declined similarly across the three smoking behaviour groups (Table 1). This lack of association was also seen in the three regression models (Figure 1; Table 2; Supplementary 1).

PAPsys

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

The PAPsys increased similarly in all groups over 12 months in univariable (Table 1) as well as in multivariable analysis (Figure 1; Table 2; Supplementary 1).

Skin involvement

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

Within 12 months, the mRSS decreased slightly by 0.3 in never-smokers, 0.6 in ex-smokers and by 0.2 in current smokers (p=0.12). No clinically meaningful difference in mRSS was observed after adjusting for potential confounding factors (Figure 1; Table 2; Supplementary 1).

DU

14% of the never-smokers, 14% of the ex-smokers and 16% of the current smokers had DUs present at baseline (p=0.7). Heavy smokers had a greater likelihood of DUs than never-smokers in multivariable analysis (OR=1.6, p=0.02; Supplementary 1); also, a higher CSI was associated with the presence of DUs at baseline in multivariable analysis (OR=1.2, p=0.002; Table 2).

In between the two visits, 14% of never-smoking, DU naive patients developed new DUs, compared to 16% ex-smokers and 8% current smokers (p=0.05). Ex-smokers had comparable odds than never-smoking patients to develop DU during the observation period (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 1).

DISCUSSION

Our report is by far the largest study that prospectively investigated the effect of smoking on diverse SSc outcomes. Smoking was common in our patient population, however less than in the Canadian and in the Australian Scleroderma Cohorts and also much lower than the European average of 28%.[4,5,13]

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 fact that we did not find adverse effects on pulmonary hypertension the effect of smoking on diffusion capacity may reflect emphysema rather than precapillary vasculopathy. Adverse effects of smoking on pulmonary airway obstruction and diffusing capacity were also seen in two cohorts of 137 SSc and 19 smokers.[14,15] In line with one of these cohorts [14] but in contrast to the second study [15] the EUSTAR study found no association between lung compliance (FVC) and smoking status.

Our study also found no adverse effects of smoking on DU prevalence and incidence, similar to two smaller studies.[16,17] The EUSTAR cohort found even a negative association between tobacco exposure and DU development (OR=0.5). Although a 'healthy smoker effect' may have contributed to these findings, such bias should have been accounted for by the CSI in our study.[18]

Smokers had a low proportion of Scl-70 autoantibodies, raising the possibility that patients with an unfavourable prognosis may be less prone to give up smoking. It is however unlikely that this selection bias accounts for our results, given the fact that we had carried out multivariable adjustment. The inbalance in autoantibody status found in our study also contrasts with that found in another study, in which smokers had a higher prevalence of Scl-70 autoantibodies a finding that gave rise to speculations of a possible aetiopathological link between smoking and development of Scl-70 autoantibodies.[2]

Like all cohort studies the EUSTAR cohort has limitations. It had no means to verify the smoking information provided by the patients. The fact that the EUSTAR cohort was able to demonstrate known adverse effects of smoking on airway obstruction however suggests that the information provided by the patients was not random and that our study was powered to detect meaningful changes in other parameters.

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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ETHICS APPROVAL

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

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Supplementary 1. Linear and logistic regression analysis comparing outcomes in light, medium or heavy smokers with that of never-smokers 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 beta values represent the increase or decrease in the outcome variable of the light, medium or heavy smokers compared to never-smokers. *Outcome variables were analysed by logistic regression. The OR values represent the increase in odds for the presence of the outcome variable of light, medium or heavy smokers compared to never-smokers. The follow-up part of the table assesses the difference between baseline and the projected 12 months values of the outcomes.

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

Outcomes	**>0 to 10 pack-years**			**>10 to 25 pack-years**			**>25 pack-years**		
	β or OR	95%CI	p-value	β or OR	95%CI	p-value	β or OR	95%CI	p-value
Baseline									
FEV1/FVC	-1.50	-3.34 to 0.34	0.11	-3.65	-5.59 to -1.72	<0.001	-5.35	-7.56 to -3.15	<0.001
FVC (% of predicted)	2.5	0.33 to 4.67	0.024	1.39	-1.12 to 3.91	0.28	-1.12	-3.70 to 1.47	0.40
DLCO/SB (% of predicted)	-2.57	-4.71 to -0.44	0.018	-3.82	-6.33 to -1.31	0.003	-7.29	-9.92 to -4.65	<0.001
PAPsys (mmHg)	-1.84	-3.69 to 0.01	0.051	-2.83	-4.85 to -0.81	0.006	-1.97	-4.19 to 0.24	0.080
mRSS	-0.13	-0.79 to 0.53	0.71	-0.22	-0.94 to 0.51	0.55	0.54	-0.24 to 1.32	0.17
DU current*	0.89	0.63 to 1.26	0.52	1.16	0.80 to 1.70	0.43	1.59	1.08 to 2.34	0.019
Follow-up									
FEV1/FVC	-0.018	-1.35 to 1.31	0.98	-0.36	-1.72 to 1.00	0.60	0.35	-1.12 to 1.81	0.64
FVC (% of predicted)	0.43	-0.67 to 1.52	0.44	0.34	-0.96 to 1.63	0.61	0.26	-1.02 to 1.54	0.69
DLCO/SB (% of predicted)	0.63	-0.65 to 1.92	0.33	0.53	-0.81 to 1.86	0.44	0.68	-0.75 to 2.11	0.35
PAPsys (mmHg)	0.53	-0.83 to 1.88	0.45	0.92	-0.69 to 2.52	0.26	0.27	-1.56 to 2.10	0.77
mRSS	-0.34	-0.74 to 0.06	0.09	-0.01	-0.05 to 0.43	0.95	-0.44	-0.93 to 0.04	0.07
DU new btw visits*	0.80	0.49 to 1.30	0.37	0.99	0.58 to 1.69	0.97	0.90	0.52 to 1.58	0.72