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Review article

Association between cigarette smoking and impaired clinical symptoms in systemic sclerosis: A review

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ABSTRACT

It has been established that smoking has a profound impact on susceptibility and severity in some rheumatic diseases (e.g., rheumatoid arthritis), a mild impact in others (e.g., systemic lupus erythematosus) through epidemiological studies. And smoking is known to affect many inflammatory and autoimmune diseases through various mechanisms, including immunomodulation and chemical exposure. Although similar studies investigating the role of cigarette exposure in susceptibility to SSc have been rarely reported and specific mechanisms have never been established, the relationship between smoking and some SSc-related symptoms have been demonstrated during the last decade. However, due to the diversity of study designs, control populations, patient populations and the methodology used to determine smoking history, these results are contradictory in some respects. This paper will review current evidence on the association between smoking and SSc and summarize potential mechanisms.

1. Introduction

Systemic sclerosis (SSc) is a connective tissue disease which is characterized by the deposition of excess collagen in skin and multiple internal organs. Symptoms of this disease include diffuse vasculopathy, immune activation, low-grade inflammation and subsequent tissue fibrosis [1]. Clinically, SSc is mainly divided into two categories based on the extent of skin fibrosis: diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc (lcSSc). Like many other autoimmune and rheumatic diseases, the etiology of SSc is also considered to be multifactorial, with important contributions from multiple genetic and environmental factors, but the pathogenesis of SSc is not yet fully understood.

Since the first US Surgeon General's report in 1964, smoking has been recognized as one of the major risk factors for an ever-increasing number of diseases and conditions. It contains innumerable toxic chemicals that could cause genetic mutations and influence both cell-mediated and humoral immune responses harmfully [2]. These changes could eventually, in the course of years or decades, lead to the development of an autoimmune disease. Recently, smoking has been found to be an environmental risk factor for the development to autoimmune diseases, e.g., rheumatoid arthritis [3] and SLE [4]. However, few studies have shown that smoking is a risk factor for SSc, but the association between smoking and disease manifestations of SSc have been extensively noted during the last decade. For example, a study published in 2002 found that smokers were 3–4 times more prone to require treatment for digital ischemia [5]. However, conflicting results have been observed in these studies (see Table 1); these might be explained by small sample sizes or the heterogeneity of the study design, the definition of smoking, and the methods used to collect information about tobacco exposure as well as some inherent biases. If failure to account for these factors may lead to under- or overestimates of the association between smoking and disease outcomes. Therefore, this paper will review current evidence on the association between smoking and SSc to determine whether cigarette smoking worsens the progression and outcome of SSc from different aspects.

2. Search methods for identification of studies

For this review, we attempted to review the literature related to the association between smoking and the risk of SSc by searching for articles published from 1984 to 2017 in Medline via PubMed without any restriction on language. Systemic sclerosis OR scleroderma OR SSc individually with each of the following key descriptors of smoking: Smoking, smoke, cigarette, cigarette smoke, cigarette smoke extract, tobacco, tobacco smoke. This search strategy returned 296 primary references. But after carefully read the title and abstract, 21 articles

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Table 1
The association between cigarette smoking and various clinical symptoms of SSc patients.

First author, year	Type of study and methods	Patients	Smoke (past/present) (%)	Outcomes
Chaudhary [8]	Cross-sectional study; 621 cases and 1228 controls	1379	43/42.5	OR for SSc in smokers vs never smokers 1.020 (95% CI: 0.839–1.240).
Atteritano (2013)	Case-Control study; 54 cases and 54 controls	54	31.5/29.6	OR for SSc in smokers vs never smokers 1.091 (95% CI: 0.481–2.475).
Pischon (2016)	Case-Control study; 58 cases and 52 controls	58	53.4/40.4	OR for SSc in smokers vs never smokers 1.760 (95% CI: 0.823–3.766).
Caramaschi (2009)	Cross-sectional study; 29 digital ulcers and 56 without digital ulcers	85	34.5/8.9	Smoking was significantly associated with digital ulcers in SSc. P = 0.003, OR: 2.46 (1.45–4.15)
Alivernini [14]	Cross-sectional study; 34 skin ulcers and 96 without digital ulcers	130	8.8/14.6	Smoking was not a risk factor for skin ulcers. P = 0.274, OR: 0.64(0.22–1.88)
Khimdas [15]	Cross-sectional study;	938	71.6	Smoking was not a risk factor for digital ulcers. P = 0.909, OR:0.984
Harrison [2]	Cross-sectional study;	101	57.4	Current smokers are 3–4 times more likely than never-smokers to incur digital vascular complications. OR: 3.8(1.1–12.9) for Admission for IV Vasodilators; OR: 4.5 (1.1–18.3) for Digital Debridement; OR: 3.4 (0.8–15.1) for Digital Amputation;
Genevie'ye Gyger (2012)	Cross-sectional study	606	57.9	Smoking was significantly associated with less extensive skin disease in SSc. P = 0.0029, OR:0.84(0.75–0.95)
Broholm (2008)	Cross-sectional study; 30 pulmonary fibrosis and 125 non pulmonary fibrosis	155	43.3/55.2	Smoking was not associated with pulmonary fibrosis in SSc. P = 0.246, OR:0.68(0.36–1.30)
Pontifex (2007) [31]	Nested case-control study; 20 lung cancer and 41 gender-matched controls	61	90.0/56.1	Smoking was significantly associated with lung cancer in SSc patients. P = 0.016, OR = 7.04 (1.44–34.39)
Silvia (2008)	Cross-sectional study;	46	26.1	The smokers had a significantly higher TLC and RV/TLC as percentage of predicted (P = 0.036, P = 0.011, respectively.)
Steen [27]	Cross-sectional study; 137 smoking SSc and 165 nonsmoking patients	302	45.4	Smoking appears to have an additive deleterious effect on pulmonary function in SSc patients.(P < 0.05) OR for Restrictive 1.908 (95% CI: 1.003–3.628) OR for Obstructive 4.387 (95% CI: 2.131–9.035)
Mcnearney (2007) [30]	Cross-sectional study;	203	23.6	Higher obstructive and restrictive lung pattern in the current smokers compared with the nonsmokers.(P = 0.008, P = 0.062, respectively)
Kang (2009)	Cross-sectional study; 9 SSc with cancer and 103 without cancer	112	11.1/3.7	Smoking was not associated with cancer in SSc. P = 0.326,OR: 0.304(0.028–3.273)
Bernatsky (2009)	Cross-sectional study; 81abnormal Pap test and 239 without abnormal Pap test	320	25.9/13.4	Smoking was significantly associated with abnormal cervical cancer screening (Pap test) in SSc patients. P = 0.008, OR:2.43(1.23, 4.78)
Hudson [25]	Cross-sectional study;	606	57.9	The number of GI symptoms, poor appetite and FEV1/FVC showed statistical significant worsening with smoking. (P = 0.03, P = 0.03, P = 0.01, respectively)
Thombs (2009) [39]	Cross-sectional study;	659	15.9	Higher fatigue was significantly associated with current smoking (P = 0.018).
Milette [35]	Cross-sectional study;	70	15.7	Sleep disruption was associated with smoking (P = 0.025) in bivariate analyses.
Vemulapalli (2016)	Cross-sectional study; 133 SSc with diastolic dysfunction and 167 controls	300	47.4/32.9	Smoking was significantly associated with diastolic dysfunction in SSc patients. P = 0.011, OR:1.833 (1.147–2.930)
Santosa [10]	Cohort study; systemic sclerosis cohort Singapore (SCORE)	349	12.3	Multivariate analysis showed that smoking [(HR)4.0, 95% CI: 1.5–10.6] was independent predictors of mortality. (P = 0.016)
Hissaria [11]	Cohort study; South Australian Scleroderma Register (SASR)	786	47.7	Cox proportional hazards regression revealed that the significant HR of 1.53 (95% CI 1.02–2.30, P = 0.038) in smokers.