



Standardized incidence ratios and risk factors for cancer in patients with systemic sclerosis: Data from the Spanish Scleroderma Registry (RESCLE)

Cristina Carbonell^a, Miguel Marcos^{a,*}, Alfredo Guillén-del-Castillo^b, Manuel Rubio-Rivas^c, Ana Argibay^d, Adela Marín-Ballvé^e, Ignasi Rodríguez-Pintó^f, Maria Baldà-Masmiquel^g, Eduardo Callejas-Moraga^h, Dolores Colungaⁱ, Luis Sáez-Comet^j, Cristina González-Echávarri^k, Norberto Ortego-Centeno^l, Begoña Marí-Alfonso^h, José-Antonio Vargas-Hitos^m, José-Antonio Todolí-Parraⁿ, Luis Trapiellaⁱ, María-Teresa Herranz-Marín^o, Mayka Freire^p, Antoni Castro-Salomó^q, Isabel Perales-Fraile^r, Ana-Belén Madroñero-Vuelta^s, María-Esther Sánchez-García^t, Manuel Ruiz-Muñoz^u, Andrés González-García^v, Jorge Sánchez-Redondo^w, Gloria de-la-Red-Bellvis^x, Alejandra Fernández-Luque^y, Alberto Muela-Molinero^z, Gema-María Lledó^{aa}, Carles Tolosa-Vilella^h, Vicent Fonollosa-Pla^b, Antonio-Javier Chamorro^{a,1}, Carmen-Pilar Simeón-Aznar^{b,1}, on behalf of RESCLE Investigators, Autoimmune Diseases Study Group (GEAS)²

^a Department of Internal Medicine, Hospital Universitario de Salamanca, Universidad de Salamanca-IBSAL, Salamanca, Spain

^b Unit of Autoimmune Diseases, Department of Internal Medicine, Hospital Universitario Vall d'Hebron, Barcelona, Spain

^c Unit of Autoimmune Diseases, Department of Internal Medicine, Hospital Universitario de Bellvitge-IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain

^d Unit of Systemic Autoimmune Diseases and Thrombosis, Department of Internal Medicine, Complejo Hospitalario Universitario de Vigo, Vigo, Pontevedra, Spain

^e Unit of Autoimmune Diseases, Department of Internal Medicine, Hospital Clínico Universitario Lozano Blesa, IIS Aragón, Zaragoza, Spain

^f Department of Internal Medicine, Hospital Universitario Mútua Terrassa, Terrassa, Barcelona, Spain

^g Unit of Systemic Autoimmune Diseases, Department of Internal Medicine, Consorci Hospitalari de Vic, Vic, Barcelona, Spain

^h Department of Internal Medicine, Parc Taulí, Hospital Universitario, Sabadell, Barcelona, Spain

ⁱ Department of Internal Medicine, Hospital Universitario Central de Asturias, Oviedo, Asturias, Spain

^j Department of Internal Medicine, Hospital Universitario Miguel Servet, Zaragoza, Spain

^k Autoimmune Diseases Research Unit, Department of Internal Medicine, Biocruces Bizkaia Health Research Institute, Hospital Universitario Cruces, University of the Basque Country, Barakaldo, Spain

^l Inst Invest Biosanitaria Ibs Granada. Department of Internal Medicine, Unit of Systemic Autoimmune Diseases. Department of Medicine, Facultad de Medicina. Hospital Universitario San Cecilio. Granada. Spain

^m Department of Internal Medicine. Hospital Universitario Virgen de las Nieves. Granada, Spain

ⁿ Department of Internal Medicine. Hospital Universitario y Politécnico La Fe. Valencia, Spain

^o Department of Internal Medicine. Hospital General Universitario "J.M. Morales Meseguer", Murcia, Spain

^p Unit of Autoimmune Diseases, Department of Internal Medicine. Hospital Clínico Universitario de Santiago. Santiago de Compostela, A Coruña, Spain

^q Department of Internal Medicine. Hospital Universitario Sant Joan. Reus, Tarragona, Spain

^r Department of Internal Medicine. Hospital Universitario Rey Juan Carlos. Móstoles, Madrid, Spain

^s Department of Internal Medicine. Hospital General San Jorge. Huesca, Spain

^t Department of Internal Medicine. Hospital Universitario Virgen de Valme. Sevilla, Spain

^u Department of Internal Medicine. Hospital Universitario Fundación Alcorcón. Alcorcón, Madrid, Spain

^v Department of Internal Medicine. Hospital Universitario Ramón y Cajal. Madrid, Spain

^w Department of Internal Medicine. Hospital Universitario de Móstoles. Móstoles, Madrid, Spain

^x Unit of Systemic Autoimmune Diseases, Department of Internal Medicine. Fundació Hospital de l'Esperit Sant. Santa Coloma de Gramenet, Barcelona, Spain

^y Department of Internal Medicine. Hospital de Mollet. Mollet del Vallès, Barcelona, Spain

^z Department of Internal Medicine. Complejo Asistencial Universitario de León. León, Spain

^{aa} Department of Autoimmune Diseases. Hospital Clinic. Barcelona, Spain

* Corresponding author.

E-mail address: mmarcos@usal.es (M. Marcos).

¹ Both authors are co-senior authors of this manuscript.

² See Appendix 1 for members of the RESCLE Registry.

ARTICLE INFO

Keywords:

Systemic sclerosis
Cancer
Anticentromere antibody
Primary biliary cholangitis

ABSTRACT

Aim: Patients with systemic sclerosis (SSc) are at increased risk of cancer, a growing cause of non-SSc-related death among these patients. We analyzed the increased cancer risk among Spanish patients with SSc using standardized incidence ratios (SIRs) and identified independent cancer risk factors in this population.

Material and methods: Spanish Scleroderma Registry data were analyzed to determine the demographic characteristics of patients with SSc, and logistic regression was used to identify cancer risk factors. SIRs with 95% confidence intervals (CIs) relative to the general Spanish population were calculated.

Results: Of 1930 patients with SSc, 206 had cancer, most commonly breast, lung, hematological, and colorectal cancers. Patients with SSc had increased risks of overall cancer (SIR 1.48, 95% CI 1.36–1.60; $P < 0.001$), and of lung (SIR 2.22, 95% CI 1.77–2.73; $P < 0.001$), breast (SIR 1.31, 95% CI 1.10–1.54; $P = 0.003$), and hematological (SIR 2.03, 95% CI 1.52–2.62; $P < 0.001$) cancers. Cancer was associated with older age at SSc onset (odds ratio [OR] 1.22, 95% CI 1.01–1.03; $P < 0.001$), the presence of primary biliary cholangitis (OR 2.35, 95% CI 1.18–4.68; $P = 0.015$) and forced vital capacity $< 70\%$ (OR 1.8, 95% CI 1.24–2.70; $P = 0.002$). The presence of anticentromere antibodies lowered the risk of cancer (OR 0.66, 95% CI 0.45–0.97; $P = 0.036$).

Conclusions: Spanish patients with SSc had an increased cancer risk compared with the general population. Some characteristics, including specific autoantibodies, may be related to this increased risk.

1. Introduction

Systemic sclerosis (SSc) is a systemic autoimmune disease characterized by vascular and immunological changes that alter the normal architecture of tissues and lead to the development of fibrosis [1,2]. The leading causes of death related to SSc are mainly secondary to lung involvement, including pulmonary hypertension and interstitial lung disease (ILD). However, improvement of the management of patients with SSc and the increase in survival in recent decades have contributed to the reduction of SSc-related causes of death in favor of non-SSc-related deaths in this population. Among the most frequent of these is death from cancer, the rate of which ranges from 5% to 30% [3–7].

Recent series show a temporal trend of an increasing cancer prevalence among patients with SSc. Although conflicting results have been reported, likely due to the heterogeneity of study designs and differences among study populations, most authors describe breast, lung, and hematological cancers as most prevalent. Several studies have shown that the incidence of these neoplasias is higher among patients with SSc than in the general population [8–10], likely due to factors such as the existence of a hyperinflammatory chronic state, genetic factors, use of immunosuppressive therapies, and the presence of SSc-related autoantibodies [11,12].

Several cancer risk factors among patients with SSc have been identified, although evidence is scarce. For instance, anti-polymerase RNA III (anti-RNAP III) and anti-Scl-70 antibodies have been described as risk factors for lung cancer in several cohorts of patients [13–18], but evidence for many other factors has not been consistently reproduced. In addition, patients' sex, geographical location, and ethnic background should be considered when analyzing the risk of cancer, reinforcing the need for further and more precise epidemiological studies of the risk of SSc-related cancer in different regions [19,20]. Such data will aid the development of preventive programs and identification of susceptible patients at risk of specific cancers.

Thus, the aims of this study were to examine the increased risk of cancer among Spanish patients with SSc through the analysis of standardized incidence ratios (SIRs), and to define independent risk factors for cancer in this population.

2. Material and methods

2.1. Study design

We analyzed data from a nationwide multicenter observational SSc registry in Spain (*Registro Español de eSCLerodermia [RESCLE]*), managed by the Autoimmune Diseases Study Group of the Spanish Society of Internal Medicine.

2.2. Patients and data collection

Included patients with SSc met the 2013 American College of Rheumatology/European League Against Rheumatism criteria [21] and/or the modified criteria proposed by LeRoy and Medsger [22] in 1988, to avoid missing patients with sclerosis sine scleroderma who did not meet the former. Data were collected retrospectively until 2006 and prospectively thereafter until October 2018. Forty hospitals nationwide contributed to the registry during this period. All participating centers obtained local ethics committee approval.

According to the RESCLE protocol, data on patients' demographic and clinical characteristics, mortality, specific and other SSc-related autoantibodies, diagnostic procedures, SSc-related treatments, and cancer were collected when patients were included in the study and updated annually. Disease onset was defined as the appearance of the first clinical manifestation of SSc, and each SSc diagnosis was recorded on the date on which the first physician determined the presence of the disease. ILD was defined by the detection of a pulmonary interstitial pattern by high-resolution computed tomography [23]. Pulmonary hypertension (PH) was defined as systolic pulmonary arterial pressure (PAP) > 40 mmHg, detected by Doppler echocardiography or when mean PAP ≥ 25 mmHg by right catheterization, which was the definition in use during the study period [24]. Detailed definitions of SSc cutaneous subsets, clinical features, organ involvement, nailfold capillaroscopy patterns, immunological features, and SSc- and non-SSc-related causes of death have been published elsewhere [25].

The performance of autoantibody analysis depended on the availability of analytical tools in each participating center. To analyze relationships between pharmacological treatments and cancer development, data on the treatments used for conditions related to autoimmune disease prior to neoplasm appearance were collected. Data regarding the cancer location, histological type, and date of diagnosis were also collected. Multiple neoplasias were those that appeared in more than one location in the same patient, but data on the time elapsed between their appearance were not available. Cancer-associated scleroderma was defined as tumor occurrence from 3 years before to 3 years after scleroderma onset [16].

2.3. Statistical analyses

Data are presented as means and standard deviations (SDs) for normally distributed continuous variables, as medians with interquartile ranges for non-normally distributed continuous variables, and as numbers and percentages for categorical variables. Qualitative variables were compared using χ^2 and Fisher's exact-tests, and quantitative variables were compared using Student's *t*-test and the Mann-Whitney *U* test. SIRs with exact Poisson 95% confidence intervals (CIs) were

calculated as ratios of cancer incidence in patients with SSc (observed cases) to that in the general Spanish population (expected cases), weighted according to age and sex. Cancer incidence data for Spain were obtained from the GLOBOCAN database of incident cancers (September 2018 version) of the Global Cancer Observatory platform of the International Agency for Cancer Research [26]. Univariable and multivariable logistic regression was used to determine the associations of different variables with cancer. Variables with P values <0.05 in the univariable analysis and those deemed to be of clinical significance to the outcome were included in the multivariable logistic regression analysis. Kaplan–Meier curves and Mantel–Cox analysis were used to estimate cumulative survival from the time of the first SSc symptom in SSc patients with cancer compared with patients without this diagnosis. Two-tailed P values ≤ 0.05 were considered to be significant.

3. Results

3.1. Characteristics of patients with SSc with and without cancer

The cohort consisted of 1930 patients with SSc, of whom 206 (10.7%) had neoplasias (Table 1). The mean age at the time of cancer diagnosis was 62.0 (SD 12.9) years, and patients with cancer had a mean age at the time of SSc diagnosis of 57.8 (SD 13.9) years. Those who developed cancer were older than those who did not at the times of SSc onset (49.3 [SD 17.0] vs. 45.9 [SD 16.1] years, $P = 0.001$) and SSc diagnosis (57.8 [SD 13.9] vs. 51.9 [SD 15.6] years, $P < 0.001$). In addition, the time from symptom onset to SSc diagnosis was longer in patients with cancer.

3.2. Cancer locations and temporal associations between cancer and SSc

The most frequent malignancies were breast ($n = 47$ [22.8%]), lung ($n = 29$ [14.1%]), hematological ($n = 20$ [9.7%]), colorectal ($n = 18$ [8.7%]), and uterine ($n = 14$ [6.8%]) cancers. Locations for which fewer than 10 cancer cases were recorded included the kidney, prostate, ovary, brain, stomach, esophagus, pancreas, oropharynx/larynx, and bladder. Overall, adenocarcinoma was the most common histological type ($n = 78$ [42.3%]), followed by squamous carcinoma ($n = 17$ [10.8%]). Fig. 1 shows the temporal relationship between cancer occurrence and both the clinical onset of SSc and SSc diagnosis. Considering clinical onset of SSc, 34 (18.9%) tumors were considered to be cancer-associated scleroderma (Fig. 1A). One hundred thirty-three (70%) cases of cancer were diagnosed after the diagnosis of SSc and two temporal trends were noted: 48 (25.2%) tumors developed three years after SSc diagnosis and 49 (26%) tumors developed 10 years after SSc diagnosis (Fig. 1B).

3.3. Risk of cancer among patients with SSc compared with the general population

The global cancer risk was greater in our cohort of patients with SSc than in the general population (SIR 1.48, 95% CI 1.36–1.60; $P < 0.001$; Table 2). In addition, the incidences of lung (SIR 2.22, 95% CI 1.77–2.73; $P < 0.001$), breast (SIR 1.31, 95%CI 1.10–1.54; $P = 0.003$), and hematological (SIR 2.03, 95% CI 1.52–2.62, $P < 0.001$) cancers were higher in the SSc cohort. No overall increased risk was observed for colorectal cancer (SIR 1.12, 95% CI 0.84–1.45; $P = 0.388$). An increased risk of colorectal cancer was noted for women (SIR 1.57, 95% CI 1.17–2.04; $P = 0.004$), whereas men had no increased risk of colorectal (SIR 0.94, 95% CI 0.71–1.19; $P = 0.643$) or hematological (SIR 0.94, 95% CI 0.62–1.33; $P = 0.829$) cancer.

3.4. Cancer risk factors

Regarding lung involvement, these patients also had more PH (41.1% vs. 28.6%, $P = 0.010$) and ILD (52.7% vs. 40.5%, $P < 0.001$). Patients with cancer had worse respiratory function test results,

Table 1

Demographic and clinical characteristics of patients with SSc with and without cancer.

Patient characteristics	SSc patients without cancer	SSc patients with cancer	P
	n = 1729 n/N (%)	n = 206 n/N (%)	
Demographics			
Female	1534 /1724 (89.0)	177 /206 (85.9)	0.201
Age at SSc onset, years (SD)	45.9 (16.1)	49.3 (17.0)	0.007
Age Diagnosis of SSc	51.9 (15.6)	57.8 (13.9)	<0.001
Follow-up since first clinical manifestation, years (SD)	14.1 (11.5)	18.1 (14.5)	0.005
Years from onset SSc to diagnosis, years (SD)	6.3 (8.9)	8.7 (13.0)	0.017
Limited SSc	1019 (59.5)	128 (63.7)	0.255
Diffuse SSc	351 (20.5)	44 (21.9)	0.645
SSc sine scleroderma	184 (10.7)	21 (10.4)	1.000
Very early SSc	43 (2.5)	1 (0.50)	0.080
Pre-SSc	117 (6.8)	7 (3.5)	0.070
Smoking history			
Current	190 /1442 (13.2)	19 /190 (10.0)	0.249
Ex smoker	248 /1442 (17.2)	42 /190 (22.1)	0.106
Non smoker	1004 /1442 (69.6)	129 /190 (67.9)	0.616
Arterial hypertension	451 /1455 (31.0)	77 /190 (40.5)	0.010
Clinical manifestations			
Peripheral vascular involvement			
Raynaud's phenomenon	1641 /1713 (95.8)	191 /205 (93.2)	0.105
Digital ulcers	667 /1720 (38.8)	74 /205 (36.1)	0.495
Telangiectasias	975 /1713 (56.9)	122 /205 (59.5)	0.502
Acrosteolysis	96 /1161 (8.3)	14 /122 (11.5)	0.233
Musculoskeletal			
Calcinosis	351 /1717 (20.4)	45 /204 (22.1)	0.583
Arthritis	239 /1163 (20.6)	31 /122 (25.4)	0.242
Myositis	152 /1165 (13.0)	18 /123 (14.6)	0.578
Tendinitis	62 /1161 (5.3)	13 /123 (10.6)	0.026
Joint contractures	120 /639 (18.8)	20 /76 (26.3)	0.127
Digestive involvement			
Esophageal motility disorders	1001 /1702 (58.8)	126 /204 (61.8)	0.451
Barret's esophagus	41 /783 (5.2)	2 /90 (2.2)	0.303
Esophagitis	152 /506 (30.0)	25 /70 (35.7)	0.336
Gastritis	218 /1167 (18.7)	30 /142 (21.1)	0.496
Intestinal involvement	125 /1164 (10.7)	19 /142 (13.4)	0.323
Malabsorption	99 /1435 (6.9)	17 /159 (10.7)	0.105
Primary biliary cholangitis	72 /1708 (4.2)	18 /203 (8.9)	0.007
Lung involvement			
ILD	694 /1714 (40.5)	108 /205 (52.7)	<0.001
FVC (%) in ILD, mean (SD)	75.9 (23.0)	74.3 (23.6)	0.514
FVC <70% in ILD, mean (SD)	254/633 (40.1)	48/98 (49.0)	0.100
FVC (%), mean (SD)	87.0 (22.5)	82.4 (23.4)	0.042
DLCO (%), mean (SD)	77.4 (42.2)	66.1 (22.5)	0.430
DLCO / AV (%), mean (SD)	82.8 (42.7)	75.4 (22.7)	0.104
ILD with FVC < 70%	316 /1484 (21.3)	57 /171 (33.3)	<0.001
Ground glass pattern	370 /1040 (35.6)	65 /158 (41.1)	0.184
Reticular pattern	334 /1127 (29.6)	63 /163 (38.7)	0.023
PH (echocardiographic data)	262 /917 (28.6)	44 /107 (41.1)	0.010
PH (catheterization)	128 /176 (72.7)	23 /34 (67.6)	0.538
Cardiac involvement			

(continued on next page)

Table 1 (continued)

Patient characteristics	SSc patients	SSc patients	P
	without cancer	with cancer	
	n = 1729	n = 206	
	n/N (%)	n/N (%)	
LVEF <50%	30 /1304 (2.3)	6 /175 (3.4)	0.428
LVEF (%), mean (SD)	63.4 (6.9)	62.9 (8.2)	0.214
PAPs (mm Hg), mean (SD)	36.8 (17.6)	39.8 (15.4)	<0.001
TRV, mean (SD)	2.3 (0.9)	2.4 (0.9)	<0.001
VI diastolic dysfunction	345 /1037 (33.3)	60 /125 (48.0)	0.001
Pleural effusion	100 /1266 (7.9)	13 /172 (7.6)	1.000
Pericarditis	72 /823 (8.7)	9 /100 (9.0)	0.853
Ischemia	100 /826 (12.1)	19 /100 (19.0)	0.058
Conduction disturbances	177 /826 (21.4)	30 /99 (30.3)	0.055
Kidney involvement			
Scleroderma renal crisis	38 /1716 (2.2)	4 /204 (2.0)	1.000
Other manifestations			
Sicca syndrome	125 /1416 (8.8)	15 /185 (8.1)	0.890
Peripheral neuropathy	492 /1719 (28.6)	70 /203 (34.5)	0.087
Fulfilment of ACR SSc criteria	1359 /1480 (91.8)	174 /189 (92.1)	1.000

SSc, systemic sclerosis; SD, standard deviation; ILD, interstitial lung disease; FVC, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide; AV, alveolar volume; PH, pulmonary hypertension; LVEF, left ventricular ejection fraction; PAPs, systolic pulmonary artery pressure; TRV, ventricular repolarization disorder; ACR, American College of Rheumatology.

specifically a decrease in the forced vital capacity (FVC) to <70% of the expected value (33.3% vs. 21.3%, P < 0.001), and a greater frequency of the radiological reticular pattern (38.7% vs. 29.6%, P = 0.023). The frequency of arterial hypertension was greater among patients with SSc with than among those without cancer (40.5% vs. 31.0%, P = 0.010). Regarding cardiac involvement, a larger proportion of patients with cancer had left ventricular diastolic dysfunction (48.0% vs. 33.3%, P = 0.001). And at the digestive level, primary biliary cholangitis (PBC) was more common among patients with cancer (8.9% vs. 4.2%, P = 0.007). Patients with cancer had higher frequencies of positivity for anti-RNAP III (23.8% vs. 10.4%, P = 0.019) and anti-PM-Scl (13.4% vs. 7.0%, P = 0.024) antibodies, but a lower frequency of anti-centromere antibodies (ACAs; 40.8% vs. 49.3%, P = 0.033).

Among SSc treatments (used before the appearance of neoplasia in

cases of cancer), calcium antagonists (28.6% vs. 47.3, P < 0.001), proton pump inhibitors (PPIs; 33.0% vs. 47.9%, P < 0.001), antiplatelet drugs (18.4% vs. 27.3%, P = 0.006), specific vasodilators (9.7% vs. 22.4%, P < 0.001) and immunosuppressants (12.1% vs. 18.7%, P = 0.021), in particular azathioprine (2.4% vs. 5.8%, P = 0.049) and mycophenolate (4.9% vs. 9.7%, P = 0.021), were used significantly less frequently for patients with than for those without cancer (Table 3). No differences between SSc patients with and without cancer were detected according to SSc subtype or capillaroscopic pattern.

In the multivariable logistic regression analysis, variables significantly associated with higher risk of cancer were older age at the time of SSc onset (odds ratio [OR] 1.22, P < 0.001), and the presence of PBC (OR 2.35, P = 0.015), ILD with FVC < 70% of the expected value (OR 1.83, P = 0.002). The presence of ACAs (OR 0.66, P = 0.036), the use of calcium channel blockers (CCBs; OR 0.54, P = 0.002), and the use of pulmonary vasodilators (OR 0.46, P = 0.006; Table 4) were associated with a lower risk of cancer.

3.5. Risk factors for different types of cancer

Independent risk factors for cancer in patients with SSc by location are shown in Table 4.

3.5.1. Breast cancer

The breast was the most frequent tumor location; the prevalence in our cohort was 2.6% (n = 47, all female). Patients with breast cancer were older than those without cancer at the time of SSc onset (58.9 vs. 51.9 years, P = 0.004). In the multivariable logistic regression analysis, independent risk factors for the development of breast cancer were puffy hands as the first manifestation of SSc (OR 6.40, P = 0.005), the presence of PBC (OR 5.71, P < 0.001), ILD (OR 3.29, P < 0.001), the presence of anti-Ro antibody (OR 2.14, P = 0.048), less use of immunosuppressants (OR 0.19, P = 0.027), and less use of PPIs (OR 0.24, P < 0.001).

3.5.2. Lung cancer

The prevalence of lung cancer in the cohort was 1.2%. Twenty-seven (96.4%) cases of lung cancer occurred after SSc diagnosis. In the multivariable logistic regression analysis, lung cancer was associated with older age at the time of SSc onset (OR 1.06, P = 0.002) and the presence of anti-Scl-70 antibodies (OR 2.61, P = 0.049), whereas the

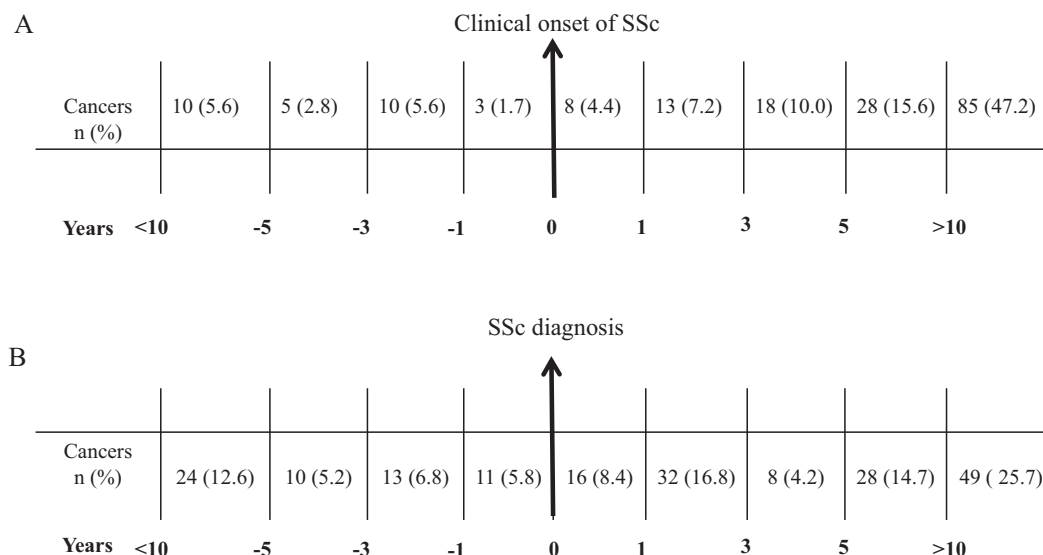


Fig. 1. A. Temporal relationship between cancer occurrence and the clinical onset of systemic sclerosis (SSc). B. Temporal relationship between cancer occurrence and SSc diagnosis.

Table 2

Overall cancer risk and risk of cancer by location for patients with systemic sclerosis compared with the general population.

	Location	Observed cases	Expected cases	SIR	P*
Total	Global cancer	572.2	387.7	1.48 (1.36–1.60)	<0.001
	Lung	86.7	39.1	2.22 (1.77–2.73)	<0.001
	Breast	143.2	109.3	1.31 (1.10–1.54)	0.003
	Colorectal	54.4	48.5	1.12 (0.84–1.45)	0.388
	Hematological	56.4	27.8	2.03 (1.52–2.62)	<0.001
	Global cancer	548.4	322.5	1.70 (1.56–1.85)	<0.001
Woman	Lung	70.4	20.3	3.47 (2.69–4.36)	<0.001
	Breast	143.2	109.3	1.31 (1.10–1.54)	0.003
	Colorectal	52.8	33.7	1.57 (1.17–2.04)	0.004
	Hematological	55.5	22.4	2.48 (1.87–3.22)	<0.001
Men	Global cancer	783.0	469.2	1.67 (1.55–1.79)	<0.001
	Lung	191.0	61.0	3.13 (2.70–3.61)	<0.001
	Colorectal	61.5	65.6	0.94 (0.71–1.19)	0.643
	Hematological	29.0	30.9	0.94 (0.62–1.33)	0.829

SIR, standardized incidence ratio. Global cancer refers to the total number of cancers in all locations. *Null hypothesis, SIR = 1; alternative hypothesis, SIR \neq 1. The data on observed and expected values correspond to the incidence rate per 100,000 person-years.

presence of ACAs protected against lung cancer development (OR 0.15, $P = 0.018$).

3.5.3. Hematological cancer

The prevalence of hematological malignancies was 1.1%. In the multivariable logistic regression analysis, these malignancies were associated with older age at the time of SSc onset (OR 1.06, $P = 0.003$). The development of this neoplasia was associated with cardiac involvement, specifically a larger proportion of conduction disorders (5/7 [71.4%] vs. 177/826 [21.4%], $P = 0.007$), and left ventricular diastolic dysfunction (7/10 [70.0%] vs. 345/1037 [33.3%], $P = 0.036$), but these results could not be confirmed in the multivariate analysis.

3.5.4. Colorectal cancer

The prevalence of colon cancer was 1%. In the multivariable logistic regression analysis, colorectal cancer was associated with ILD with FVC < 70% of the expected value (OR 5.21, $P = 0.007$), whereas the use of PPIs protected against the development of this cancer (OR 0.18, $P = 0.031$).

3.5.5. Multiple neoplasias

Seventy-two patients had more than one type of neoplasm. Risk factors for multiple neoplasias were older age at the time of SSc onset (OR 1.05, $P < 0.001$) and ILD with FVC < 70% of the expected value (OR 2.72, $P < 0.001$), whereas the use of aspirin protected against multiple neoplasia development (OR 0.29, $P = 0.005$).

3.6. Mortality, causes of death, and survival

In total, 355 (18.4%) patients (284 [16.5%] without and 71 [34.5%] with cancer) died (Table 3). Of these deaths, 171 were considered to be SSc related, 163 were not, and the cause of death was unclear or

unknown in 21 cases. A total of 38 patients died because of cancer.

SSc-related deaths were slightly more common than non-SSc-related deaths (171/355 [48.2%] vs. 163/355 [45.6%]). The most prevalent cause of death was pulmonary involvement, specifically PH and ILD, representing 16.6% and 11.3% of deaths, respectively; cancer ranked third, representing 10.7% of all deaths.

The mortality rate was higher for patients with than for those without cancer (71/206 [34.5%] vs. 284/1724 [16.5%], $P < 0.001$). Significantly fewer SSc-related deaths occurred among patients with than among those without neoplasia (15/66 [22.7%] vs. 156/268 [58.2%], $P < 0.001$). The primary causes of death among patients with cancer were non-SSc related (77.3%), most commonly cancer (38/71 [53.5%]), followed by sepsis (3/71 [4.2%]). The primary causes of death among patients with SSc without cancer were SSc related (58.2%), most commonly PH (54/284 [13.4%]), ILD (38/284 [19.0%]), and PH with ILD (23/284 [8.1%]). Cumulative survival rates among patients with cancer declined from 92.5% at 5 years to 68.4% at 20 years and 53.0% at 30 years after the onset of the disease compared with those of patients without cancer (Table 3, Fig. 2).

4. Discussion

This report is the first description of the analysis of multicenter data on the characteristics of patients with cancer and SSc in Spain, and the evaluation of the risk of neoplasia in this population. We found an increased global risk of cancer among patients with SSc relative to that in the general population, as well as increased risks of specific cancer types (lung, breast, and hematological). Factors associated with the greater risk of cancer were the presence of PBC and moderate or severe ILD, whereas the presence of ACAs was associated with a reduced cancer risk.

Our findings agree with reports that the most prevalent cancers in patients with SSc are breast, lung, and hematological malignancies [8–10]. Most reports published before 2014 describe lung cancer as the most frequent neoplasm, followed by breast cancer [27–34]. This relationship is reversed in most recent studies, coinciding with our results [16,35–39]. The increased detection of breast neoplasia, facilitated by screening established in the last decade, may have contributed to this change. Hematological cancers have consistently ranked as the second or third most common cancer type in patients with SSc in many studies [13,27,28,34,35,39–43]. Colorectal cancer among patients with SSc is poorly represented in the literature [8], although it ranked fourth, as in the present study, in a recent multicenter Australian study with a large sample size [39]. In addition, cancer was the third leading cause of death in our series, and cancer diagnosis was associated with greater all-cause mortality. These findings are consistent with those from other cohorts, highlighting the relevance of this association [4,5,39].

According to our SIR calculation, patients with SSc had a 1.5-times greater risk of cancer compared with the general population in Spain. This increased risk was confirmed for lung, hematological, and breast cancers, and for colorectal cancer among women. Consistent with these results, the global risk of cancer has been reported to be increased in patients with SSc (by 1.5–4 times that in the general population), and increased risks of lung and hematological neoplasms have been reported [8–10]. Conflicting results have been found for breast cancer, with some studies showing an association [17,32,42] but others, including three meta-analyses [8–10], have failed to confirm this finding [28,39,44]. Differences in screening programs or inclusion criteria among studies may have contributed to this discrepancy.

In our analysis of the clinical manifestations of autoimmune disease, the presence of PBC was associated with cancer in general and with breast cancer in particular; such results have not been reported previously for an SSc cohort but the association of PBC and breast cancer have been noticed in the general population [45]. PBC and limited SSc are known to coincide as Reynolds syndrome [46]. The estimated prevalence of SSc in patients with PBC is 5–15%, and that of PBC in patients

Table 3
Immunological and treatment-related features, causes of death, and survival in patients with systemic sclerosis with and without malignancy.

Patient characteristics	SSc patients without cancer	SSc patients with cancer	P
	n = 1729	n = 206	
	n/N (%)	n/N (%)	
Autoantibodies			
Scleroderma-specific antibodies			
ANA determinations	1603 /1721 (93.1)	187 /205 (91.2)	0.312
Speckled pattern	523 /1559 (33.5)	59 /179 (33.0)	0.933
Centromeric pattern	511 /1559 (32.8)	53 /179 (29.6)	0.448
Homogeneous pattern	197 /1559 (12.6)	28 /179 (15.6)	0.289
Nucleolar pattern	222 /1559 (14.2)	22 /179 (12.3)	0.570
Nucleolar / speckled pattern	59 /1559 (3.8)	7 /179 (3.9)	0.838
Homogeneous / nucleolar pattern	47 /1559 (3.0)	10 /179 (5.6)	0.075
Topoisomerase I (Scl-70)	305 /1534 (19.9)	41 /190 (21.6)	0.566
Centromere	761 /1545 (49.3)	73 /179 (40.8)	0.033
RNAP III	39 / 376 (10.4)	10 / 42 (23.8)	0.019
PM-Scl	65 / 922 (7.0)	15 /112 (13.4)	0.024
Ro	214 /1528 (14.0)	31 /190 (16.3)	0.380
La	57 /1511 (3.8)	6 /191 (3.1)	0.839
Sm	16 /1483 (1.1)	3 /181 (1.7)	0.453
RNP	88 /1506 (5.8)	6 /184 (3.3)	0.174
Mitochondrial	96 / 837 (11.5)	16 /112 (14.3)	0.434
Thyroid	125 / 477 (26.2)	10 / 60 (16.7)	0.117
Ku	10 / 355 (2.8)	2 / 45 (4.4)	0.633
Rheumatoid factor	287 /1253 (22.9)	33 /153 (21.6)	0.760
Citrullinated anti-cyclic peptide	18 / 297 (6.1)	1 / 41 (2.4)	0.489
ANA positive and negative ATA, ACA, anti-RNAP III and anti-PM-Scl	89 / 308 (28.9)	9 / 33 (27.3)	1.000
Treatment			
Calcium antagonists	815/ 1724 (47.3)	59/ 206 (28.6)	<0.001
Antiplatelet	471/ 1724 (27.3)	38/ 206 (18.4)	0.006
ASA	426/ 1724 (24.7)	32/ 206 (15.5)	0.003
Anticoagulants	98/ 1724 (5.7)	10/ 206 (4.9)	0.749
Specific vasodilators	387/ 1724 (22.4)	20/ 206 (9.7)	<0.001
ERA	323/ 1724 (18.7)	17/ 206 (8.3)	<0.001
PDF-5	149/ 1724 (8.6)	6/ 206 (2.9)	0.003
PGL	109/ 1724 (6.3)	4/ 206 (1.9)	0.007
Antifibrotic	103/ 1724 (6.0)	14/ 206 (6.8)	0.642
Immunosuppressants	322/ 1724 (18.7)	25/ 206 (12.1)	0.021
Azathioprine	100/ 1724 (5.8)	5/ 206 (2.4)	0.049
Cyclosporine	8/ 1724 (0.5)	1/ 206 (0.49)	1.000
Phosphamide cycles	117/ 1724 (6.8)	12/ 206 (5.8)	0.767
Methotrexate	83/ 1724 (4.8)	6/ 206 (2.9)	0.290
Mycophenolate	168/ 1724 (9.7)	10/ 206 (4.9)	0.021
Tacrolimus	17/ 1724 (1.0)	1/ 206 (0.49)	0.712
Biological therapy	41/ 1724 (2.4)	2/ 206 (0.97)	0.313
Rituximab	33/ 1724 (1.9)	2 / 206 (0.97)	0.576
Anti-TNF	3/ 1724 (0.2)	0/ 206 (0)	1.000
PPI	826/ 1724 (47.9)	68/ 206 (33.0)	<0.001
Corticosteroids	431 (25.0)	42 (20.4)	0.170
NSAID	61 (3.5)	3 (1.5)	0.147
Antioxidants	79 (4.6)	7 (3.4)	0.591
Antimalarials	132 (7.7)	11 (5.3)	0.262
ACEI	251/ 1724 (14.6)	22/ 206 (10.7)	0.139
ARA II	171/ 1724 (9.9)	13/ 206 (6.3)	0.103
SSRI	115/ 1724 (6.7)	6/ 206 (2.9)	0.033
Causes of death			
Total deaths	284 /1724 (16.5)	71 /206 (34.5)	<0.001
SSc-related deaths	156 /284 (54.9)	15 /71 (21.1)	0.001
ILD	38 /284 (13.4)	2 /71 (2.8)	0.011
PH	54 /284 (19.0)	5 /71 (7.0)	0.013
PH and ILD	23 /284 (8.1)	3 /71 (4.2)	0.319
ILD/ PAH / PH and ILD	115 /284 (40.5)	10 /71 (14.1)	<0.001
Scleroderma renal crisis	17 /284 (6.0)	1 /71 (1.4)	0.140
Arrhythmias	4 /284 (1.4)	0 /71 (0)	0.588
Ischemic cardiomyopathy without CVRF	6 /284 (2.1)	1 /71 (1.4)	1.000
Sepsis	2 /284 (0.7)	0 /71 (0)	1.000
Other causes related to SSc	12 /284 (4.2)	3 /71 (4.2)	1.000
Non-SSc related deaths	112 /284 (39.4)	51 /71 (71.8)	0.05
Stroke	3 /284 (1.1)	0 /71 (0)	1.000
Chronic renal failure	3 /284 (1.1)	0 /71 (0)	1.000
COPD	2 /284 (0.7)	0 /71 (0)	1.000
Sepsis	19 /284 (6.7)	3 /71 (4.2)	0.587
Pulmonary embolism	4 /284 (1.4)	0 /71 (0)	0.588
Neoplasia	0 /284 (0)	38 /71 (53.5)	<0.001
Arrhythmias	2 /284 (0.7)	0 /71 (0)	1.000

(continued on next page)

Table 3 (continued)

Patient characteristics	SSc patients without cancer		SSc patients with cancer		P
	n = 1729		n = 206		
	n/N (%)		n/N (%)		
Ischemic cardiomyopathy	1	/284 (0.4)	0	/71 (0)	1.000
Other causes not related to SSc	78	/284 (27.5)	10	/71 (14.1)	0.021
Unknown	16	/284 (5.6)	5	/71 (7.0)	0.673

Cumulative survival since the first symptom of SSc (N = 1820)				
5 years	0.960	0.925	0.038	
10 years	0.919	0.878	0.073	
20 years	0.806	0.684	0.001	
30 years	0.682	0.530	<0.001	

SSc, systemic sclerosis; ANA, antinuclear antibody; RNP, ribonucleoprotein; RNAP III, RNA polymerase III; ATA, anti-topoisomerase antibody; ACA, anti-centromere antibody; ASA, acetylsalicylic acid; ERA, endothelin I receptor antagonist; PDF-5, phosphodiesterase 5 inhibitor; PGL, prostaglandins; TNF, tumor necrosis factor; PPI, proton pump inhibitor; NSAID, non-steroidal anti-inflammatory drugs; ACEI, angiotensin converting enzyme inhibitors; ARA II, angiotensin II receptor antagonist; SSRI, selective serotonin reuptake inhibitor; ILD, interstitial lung disease; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; CVRF, cardiovascular risk factors; COPD, chronic obstructive pulmonary disease.

Table 4

Independent risk factors for cancer in patients with SSc by location, as determined by multivariate analysis.

Cancer location	Risk factor	OR	95% CI	P
Global cancer (n = 206)	Increasing age at SSc onset	1.22	1.01–1.03	<0.001
	PBC	2.35	1.18–4.68	0.015
	ILD with FVC < 70%	1.83	1.24–2.70	0.002
	ACA	0.66	0.45–0.97	0.036
	Use of calcium channel blockers	0.54	0.37–0.79	0.002
	Use of specific vasodilators	0.46	0.26–0.80	0.006
Breast cancer (n = 47)	Puffy hands	6.40	1.73–23.64	0.005
	PBC	5.71	2.16–15.09	<0.001
	ILD	3.29	1.69–6.39	<0.001
	Anti-Ro antibody	2.14	1.01–4.56	0.048
	Use of immunosuppressants	0.19	0.04–0.83	0.027
Lung cancer (n = 29)	Use of PPI	0.24	0.11–0.54	<0.001
	Increasing age at SSc onset	1.06	1.02–1.10	0.002
	Anti-Scl-70 antibodies	2.61	1.00–6.79	0.049
	ACA	0.15	0.03–0.72	0.018
Hematological cancer (n = 20)	Increasing age at SSc onset	1.06	1.02–1.09	0.003
	Colorectal cancer (n = 18)	ILD with FVC < 70%	5.21	1.57–17.33
Multiple neoplasias (n = 72)	Use of PPI	0.18	0.04–0.85	0.031
	Increasing age at SSc onset	1.05	1.03–1.07	<0.001
	ILD with FVC < 70%	2.72	1.54–4.72	<0.001
	Use of ASA	0.29	0.12–0.68	0.005

SSc, systemic sclerosis; OR, odds ratio; CI, confidence interval; PBC, primary biliary cholangitis; ILD, interstitial lung disease; FVC, forced vital capacity; ACA, anti-centromere antibody; PPI, proton pump inhibitors; ASA, acetylsalicylic acid.

with SSc is 2–4.7%, higher than in the general population. Although we cannot explain the relationship between autoimmunity and overall or breast cancer, the presence of PBC in patients with SSc can be considered to be a risk factor for the development of cancer.

Another relevant finding of this study is the association in a multivariable analysis between cancer and ILD with FVC < 70% of the expected value. Other authors have reported worse SSc prognoses with more severe lung disease [47] and a greater risk of lung cancer in patients with ILD and SSc [12,28,30,32]. As lung disease is caused by endothelial cell injury and subsequent vascular damage, cancer development in this setting may be related to increased inflammation, although more data are needed to confirm this association.

The main result of our multivariable analysis of antibody associations with cancer was that the presence of ACAs was significantly less frequent in patients with SSc and cancer than it was in those without cancer. This finding is consistent with the results of Igusa et al. [16] among patients with SSc, who reported that patients with ACA positivity had a lesser risk of cancer development during follow-up (SIR 0.59, 95% CI 0.44–0.76). Other authors have also reported that the presence of ACAs reduces the cancer risk compared with the presence of other autoantibodies [13]. In contrast, Higuchi et al. [48] identified this autoantibody as a risk factor for cancer, although their sample was small (45 patients, of whom 7 had neoplasias). Overall, the data clearly suggest that ACAs are associated with a reduced risk of cancer among patients with SSc. As the presence of this autoantibody has been correlated with a less severe form of SSc and improved survival, the presence of less severe organ damage and reduced inflammation may explain the association [49–51].

Anti-RNAP III has also been reported to be a risk factor for cancer [13–16,52,53]. Given the small number of patients with this autoantibody in our cohort, assessment of its significance in a multivariable analysis in this study was difficult. Our multivariable analysis revealed the novel finding that anti-Ro was a risk factor for breast cancer, and that anti-Scl-70 was a risk factor for lung cancer, confirming previously reported associations [17,18,28]. Although the significance of these relationships was limited by the sample size and the performance of multiple comparisons, the detection of certain autoantibodies or combinations thereof may aid the identification of patients at greater risk of cancer [15,16,54]. We also identified the late onset of SSc as a risk factor for neoplasia, as reported previously [15,32,42]. This relationship may be explained by the likelihood that immunosenescence favors carcinogenesis in the context of this disease.

Finally, we found several associations between certain drugs (CCBs, PPIs, and acetylsalicylic acid [ASA]) and a reduced risk of cancer. We observed an inverse association between CCB use and the risk of cancer; other authors have reported otherwise [39]. Bernal Bello et al. [55] noted that CCB use among patients with SSc and cancer has rarely been analyzed, whereas several studies have analyzed the relationship between CCB use and breast cancer in general populations; controversial results have been reported, and no clear pathogenic explanation can be offered for either finding. The observed protective effect of ASA against multiple neoplasias in our cohort aligns with the protective effect of this drug against cancer in the general population [56] and other SSc cohorts [35,57]. Aspirin may inhibit eicosanoid pathways, leading to the reduced release of thromboxane-mediated tumor growth factors that modulate apoptosis and cell proliferation [58]. Further studies are needed to analyze the role of this drug in carcinogenesis among patients

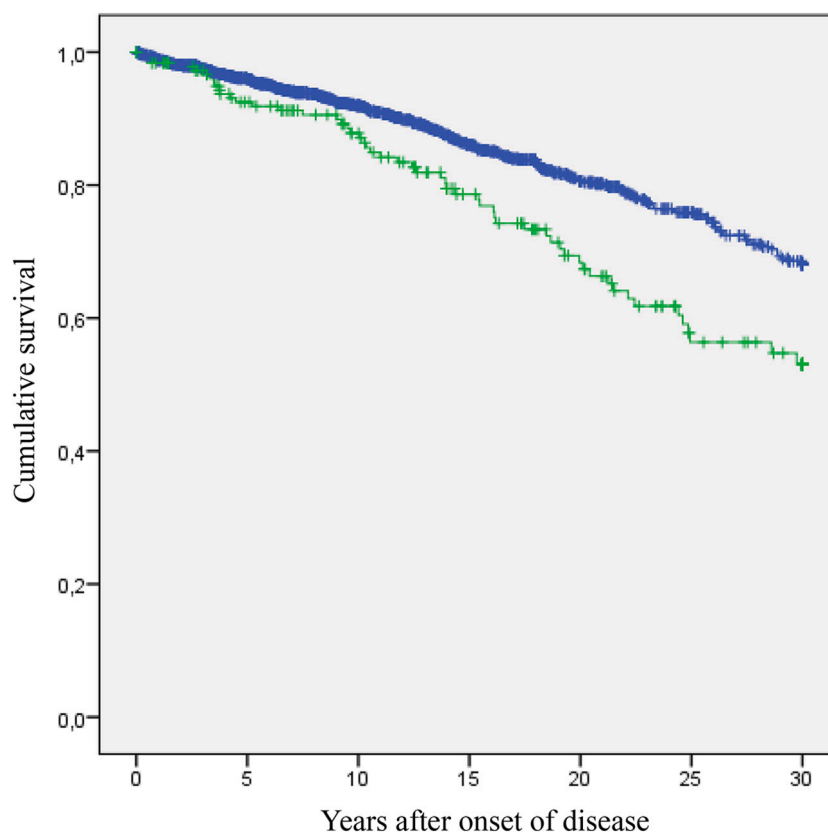


Fig. 2. Kaplan–Meier survival curves for patients with systemic sclerosis with (green) and without cancer (blue). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

with SSc.

Apart from the limitations mentioned above, including the small samples available for some neoplasias, we acknowledge that data on some potential risk factors for specific cancers (e.g., alcohol use or family history of cancer) were not collected in this study. Despite these limitations, the main strength of our study lies in the multicentric design, the overall large sample relative to those of other observational studies, and, to our knowledge, the first use of SIRs to examine a cohort of Spanish patients with scleroderma and cancer.

In summary, our work clearly shows that patients with SSc have an increased risk of cancer compared with the general population. Patients with late-onset SSc, those with moderate ILD defined as FVC < 70%, and those with ACA negativity are at increased risk of cancer. These data may help to identify SSc patients at high-risk of cancer for screening.

Author contributions

Conceptualization, formal analysis, methodology, supervision, writing-review: CPS and AJC. Data curation, formal analysis, investigation, writing original draft: CC. Formal analysis, supervision, writing-original draft and review: MM. Data curation and writing-review: AGC, MRR, AA, AMB, IRP, MBM, ECM, DC, LSC, CGE, NOC, BMA, JAVH, JATP, LT, MTHM, MF, ACS, IPF, ABMV, MESG, MRM, AGG, JSR, GRB, AFL, AMM, GML, CTV, VFP. All authors revised the manuscript for critical important content and approved the final version.

Funding

This work was financed in part by the Autoimmune Diseases Study Group of the Spanish Society of Internal Medicine.

Declaration of Competing Interest

The authors declare that they have no conflict of interest, including any financial, personal, or other relationship within 3 years of beginning this research with a person or organization that could have inappropriately influenced, or be perceived to influence, this work.

Appendix 1. RESCLE Registry members

Argibay A, Callejas-Moraga E, Carbonell-Muñoz C, Castro-Salomó A, Chamorro AJ, Colunga-Argüelles D, De-la-Red-Bellvis G, Espinosa G, Estévez-Gil M, Fernández-Luque A, Fonollosa-Pla V, Freire M, García-Hernández FJ, González-García A, Guillén-Del-Castillo A, González-Echavarrri C, Gracia-Tello BC, Herranz-Marín MT, Iniesta-Arandia N, Lledó GM, López-Rodríguez M, Lorenzo-Castro R, Madroñero-Vuelta AB, Marí-Alfonso B, Marín-Ballvé A, Ortego-Centeno N, Patier JL, Perales Fraile I, Pestaña-Fernández M, Pla-Salas X, Ríos-Blanco JJ, Rodríguez-Carballeira M, Rodríguez-Pintó I, Rubio-Rivas M, Ruiz-Muñoz M, Sáez-Comet L, Salvador-Cervelló G, Sánchez-García ME, Sánchez-Redondo J, Sánchez-Trigo S, Simeón-Aznar CP, Tarí-Ferrer E, Todolí-Parra JA, Tolosa-Vilella C, Trapiella-Martínez L, Vargas-Hitos JA, Vega-González VJ.

References

- [1] Allanore Y, Simms R, Distler O, Trojanowska M, Pope J, Denton CP, et al. Systemic sclerosis. *Nat Rev Dis Primers* 2015;1:15002. <https://doi.org/10.1038/nrdp.2015.2>.
- [2] Denton CP, Khanna D. Systemic sclerosis. *Lancet* 2017;390:1685–99. [https://doi.org/10.1016/S0140-6736\(17\)30933-9](https://doi.org/10.1016/S0140-6736(17)30933-9).
- [3] Elhai M, Meune C, Avouac J, Kahan A, Allanore Y. Trends in mortality in patients with systemic sclerosis over 40 years: a systematic review and meta-analysis of cohort studies. *Rheumatology* 2012;51:1017–26. <https://doi.org/10.1093/rheumatology/ker269>.

- [4] Tyndall AJ, Bannert B, Vonk M, Airo P, Cozzi F, Carreira PE, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR scleroderma trials and research (EUSTAR) database. *Ann Rheum Dis* 2010;69:1809–15. <https://doi.org/10.1136/ard.2009.114264>.
- [5] Simeón-Aznar CP, Fonollosa-Plá V, Tolosa-Vilella C, Espinosa-Garriga G, Campillo-Grau M, Ramos-Casals M, et al. Registry of the Spanish network for systemic sclerosis: survival, prognostic factors, and causes of death. *Medicine (Baltimore)* 2015;94:e1728. <https://doi.org/10.1097/MD.0000000000001728>.
- [6] Rubio-Rivas M, Royo C, Simeón CP, Corbella X, Fonollosa V. Mortality and survival in systemic sclerosis: systematic review and meta-analysis. *Semin Arthritis Rheum* 2014;44:208–19. <https://doi.org/10.1016/j.semarthrit.2014.05.010>.
- [7] Hao Y, Hudson M, Baron M, Carreira P, Stevens W, Rabusa C, et al. Early mortality in a multinational systemic sclerosis inception cohort. *Arthritis Rheum* 2017;69:1067–77. <https://doi.org/10.1002/art.40027>.
- [8] Onishi A, Sugiyama D, Kumagai S, Morinobu A. Cancer incidence in systemic sclerosis: meta-analysis of population-based cohort studies: cancer incidence in SSc. *Arthritis Rheum* 2013;65:1913–21. <https://doi.org/10.1002/art.37969>.
- [9] Bonifazi M, Tramacere I, Pomponio G, Gabrielli B, Avvedimento EV, La Vecchia C, et al. Systemic sclerosis (scleroderma) and cancer risk: systematic review and meta-analysis of observational studies. *Rheumatology* 2013;52:143–54. <https://doi.org/10.1093/rheumatology/kes303>.
- [10] Zhang J, Wan Y, Peng W, Yan J, Li B, Mei B, et al. The risk of cancer development in systemic sclerosis: a meta-analysis. *Cancer Epidemiol* 2013;37:523–7. <https://doi.org/10.1016/j.canep.2013.04.014>.
- [11] Zeineddine N, Khoury LE, Mosak J. Systemic sclerosis and malignancy: a review of current data. *J Clin Med Res* 2016;8:265–32. <https://doi.org/10.14740/jocmr2606w>.
- [12] Shah AA, Casciola-Rosen L. Mechanistic and clinical insights at the scleroderma-cancer interface. *J Scleroderma Relat Disord* 2017;2:153–9. <https://doi.org/10.5301/jrsd.5000250>.
- [13] Moizadeh P, Fonseca C, Hellmich M, Shah AA, Chighizola C, Denton CP, et al. Association of anti-RNA polymerase III autoantibodies and cancer in scleroderma. *Arthritis Res Ther* 2014;16:R53. <https://doi.org/10.1186/ar4486>.
- [14] Saigusa R, Asano Y, Nakamura K, Miura S, Ichimura Y, Takahashi T, et al. Association of anti-RNA polymerase III antibody and malignancy in Japanese patients with systemic sclerosis. *J Dermatol* 2015;42:524–7. <https://doi.org/10.1111/1346-8138.12827>.
- [15] Shah AA, Hummers LK, Casciola-Rosen L, Visvanathan K, Rosen A, Wigley FM. Examination of autoantibody status and clinical features associated with cancer risk and cancer-associated scleroderma: age in scleroderma and cancer. *Arthritis Rheum* 2015;67:1053–61. <https://doi.org/10.1002/art.39022>.
- [16] Igusa T, Hummers LK, Visvanathan K, Richardson C, Wigley FM, Casciola-Rosen L, et al. Autoantibodies and scleroderma phenotype define subgroups at high-risk and low-risk for cancer. *Ann Rheum Dis* 2018. <https://doi.org/10.1136/annrheumdis-2018-212999>.
- [17] Colaci M, Giuggioli D, Sebastiani M, Manfredi A, Vacchi C, Spagnolo P, et al. Lung cancer in scleroderma: results from an Italian rheumatologic center and review of the literature. *Autoimmun Rev* 2013;12:374–9. <https://doi.org/10.1016/j.autrev.2012.06.003>.
- [18] Rothfield N, Kurtzman S, Vazques-Abad D, Charron C, Daniels L, Greenberg B. Association of anti-topoisomerase I with cancer. *Arthritis Rheum* 1992;35:724. <https://doi.org/10.1002/art.1780350621>.
- [19] Barnes J, Mayes MD. Epidemiology of systemic sclerosis: incidence, prevalence, survival, risk factors, malignancy, and environmental triggers. *Curr Opin Rheumatol* 2012;24:165–70. <https://doi.org/10.1097/BOR.0b013e32834ff2e8>.
- [20] Freire M, Rivera A, Sopena B, Tolosa Vilella C, Guillén-Del Castillo A, Colunga Argüelles D, et al. Clinical and epidemiological differences between men and women with systemic sclerosis: a study in a Spanish systemic sclerosis cohort and literature review. *Clin Exp Rheumatol* 2017;35(Suppl. 106):89–97.
- [21] van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. *Ann Rheum Dis* 2013;72:1747–55. <https://doi.org/10.1136/annrheumdis-2013-204424>.
- [22] LeRoy EC, Medsger TA. Criteria for the classification of early systemic sclerosis. *J Rheumatol* 2001;28:1573–6.
- [23] Walker UA, Tyndall A, Czirjak L, Denton C, Farge-Bancel D, Kowal-Bielecka O, et al. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR scleroderma trials and research group database. *Ann Rheum Dis* 2007;66:754–63. <https://doi.org/10.1136/ard.2006.062901>.
- [24] Galè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2016;37:67–119. <https://doi.org/10.1093/eurheartj/ehv317>.
- [25] Tolosa-Vilella C, Morera-Morales ML, Simeón-Aznar CP, Marí-Alfonso B, Colunga-Argüelles D, Callejas Rubio JL, et al. Digital ulcers and cutaneous subsets of systemic sclerosis: clinical, immunological, nailfold capillaroscopy, and survival differences in the Spanish RESCLE Registry. *Semin Arthritis Rheum* 2016;46:200–8. <https://doi.org/10.1016/j.semarthrit.2016.04.007>.
- [26] International Agency for Research on Cancer (IARC). Global cancer observatory (GCO). In: Cancer today [Internet]; 2018 [cited may 3, 2018]. Available from: <https://gco.iarc.fr/today/home>.
- [27] Roumm AD, Medsger TA. Cancer and systemic sclerosis. An epidemiologic study. *Arthritis Rheum* 1985;28:1336–40. <https://doi.org/10.1002/art.1780281204>.
- [28] Olesen AB, Svaerke C, Farkas DK, Sørensen HT. Systemic sclerosis and the risk of cancer: a nationwide population-based cohort study: systemic sclerosis and the risk of cancer. *Br J Dermatol* 2010;163:800–6. <https://doi.org/10.1111/j.1365-2133.2010.09861.x>.
- [29] Hill CL. Risk of cancer in patients with scleroderma: a population based cohort study. *Ann Rheum Dis* 2003;62:728–31. <https://doi.org/10.1136/ard.62.8.728>.
- [30] Hashimoto A, Arinuma Y, Nagai T, Tanaka S, Matsui T, Tohma S, et al. Incidence and the risk factor of malignancy in Japanese patients with systemic sclerosis. *Intern Med* 2012;51:1683–8. <https://doi.org/10.2169/intermalmedicine.51.7686>.
- [31] Chatterjee S, Dombi GW, Severson RK, Mayes MD. Risk of malignancy in scleroderma: a population-based cohort study. *Arthritis Rheum* 2005;52:2415–24. <https://doi.org/10.1002/art.21225>.
- [32] Abu-Shakra M, Guillemin F, Lee P. Cancer in systemic sclerosis. *Arthritis Rheum* 1993;36:460–4. <https://doi.org/10.1002/art.1780360405>.
- [33] Kang KY, Yim HW, Kim I, Yoon JU, Ju JH, Kim H, et al. Incidence of cancer among patients with systemic sclerosis in Korea: results from a single Centre. *Scand J Rheumatol* 2009;38:299–303. <https://doi.org/10.1080/03009740802642062>.
- [34] Kuo C-F, Luo S-F, Yu K-H, Chou I-J, Tseng W-Y, Chang H-C, et al. Cancer risk among patients with systemic sclerosis: a nationwide population study in Taiwan. *Scand J Rheumatol* 2012;41:44–9. <https://doi.org/10.3109/03009742.2011.618145>.
- [35] Bernal-Bello D, de Tena JG, Guillén-del Castillo A, Selva-O'Callaghan A, Callejas-Moraga EL, Marín-Sánchez AM, et al. Novel risk factors related to cancer in scleroderma. *Autoimmun Rev* 2017;16:461–8. <https://doi.org/10.1016/j.autrev.2017.03.012>.
- [36] Partouche L, Goulabchand R, Maria ATJ, Rivière S, Jorgensen C, Rigau V, et al. Biphasic temporal relationship between cancers and systemic sclerosis: a clinical Series from Montpellier University Hospital and review of the literature. *J Clin Med* 2020;9:853. <https://doi.org/10.3390/jcm9030853>.
- [37] Sargin G, Senturk T, Cildag S. Systemic sclerosis and malignancy. *Int J Rheum Dis* 2018;21:1093–7. <https://doi.org/10.1111/1756-185X.13311>.
- [38] Catano J, Guedon A, Riviere S, Carrat F, Mahevas T, Fain O, et al. Survenue de cancers au cours de la sclérodémie systémique: facteurs de risque, impact sur la survie et revue de la littérature. *Rev Médecine Interne* 2019;40:637–44. <https://doi.org/10.1016/j.revmed.2019.06.004>.
- [39] Morrisroe K, Hansen D, Huq M, Stevens W, Sahhar J, Ngian G, et al. Incidence, risk factors, and outcomes of cancer in systemic sclerosis. *Arthritis Care Res* 2020;72:1625–35. <https://doi.org/10.1002/acr.24076>.
- [40] Kaşifoğlu T, Yaşar Bilge Ş, Yıldız F, Özen G, Pehlivan Y, Yılmaz N, et al. Risk factors for malignancy in systemic sclerosis patients. *Clin Rheumatol* 2016;35:1529–33. <https://doi.org/10.1007/s10067-016-3288-8>.
- [41] Siau K, Laversuch CJ, Creamer P, O'Rourke KP. Malignancy in scleroderma patients from south West England: a population-based cohort study. *Rheumatol Int* 2011;31:641–5. <https://doi.org/10.1007/s00296-009-1348-y>.
- [42] Derk CT, Rasheed M, Artlett CM, Jimenez SA. A cohort study of cancer incidence in systemic sclerosis. *J Rheumatol* 2006;33:1113–6.
- [43] Duncan SC, Winkelmann RK. Cancer and scleroderma. *Arch Dermatol* 1979;115:950–5.
- [44] Rosenthal AK, McLaughlin JK, Gridley G, Nyrén O. Incidence of cancer among patients with systemic sclerosis. *Cancer* 1995;76:910–4. [https://doi.org/10.1002/1097-0142\(19950901\)76:5<910::aid-cnrc2820760528>3.0.co;2-t](https://doi.org/10.1002/1097-0142(19950901)76:5<910::aid-cnrc2820760528>3.0.co;2-t).
- [45] Bergasa NV. Primary biliary cirrhosis in patients with breast cancer: studying the link. *Med Hypotheses* 1998;50:465–72. [https://doi.org/10.1016/s0306-9877\(98\)90263-8](https://doi.org/10.1016/s0306-9877(98)90263-8).
- [46] Marí-Alfonso B, Simeón-Aznar CP, Guillén-Del Castillo A, Rubio-Rivas M, Trapiella-Martínez L, Todolí-Parra JA, et al. Hepatobiliary involvement in systemic sclerosis and the cutaneous subsets: characteristics and survival of patients from the Spanish RESCLE registry. *Semin Arthritis Rheum* 2018;47:849–57. <https://doi.org/10.1016/j.semarthrit.2017.10.004>.
- [47] Goh NSL, Desai SR, Veerarahgavan S, Hansell DM, Copley SJ, Maher TM, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. *Am J Respir Crit Care Med* 2008;177:1248–54. <https://doi.org/10.1164/rccm.200706-877OC>.
- [48] Higuchi M, Horiuchi T, Ishibashi N, Yoshizawa S, Niho Y, Nagasawa K. Anticentromere antibody as a risk factor for cancer in patients with systemic sclerosis. *Clin Rheumatol* 2000;19:123–6. <https://doi.org/10.1007/s100670050029>.
- [49] Hanke K, Becker MO, Brueckner CS, Meyer W, Janssen A, Schlumberger W, et al. Anticentromere-a and Anticentromere-B antibodies show high concordance and similar clinical associations in patients with systemic sclerosis. *J Rheumatol* 2010;37:2548–52. <https://doi.org/10.3899/jrheum.100402>.
- [50] Iniesta Arandia N, Simeón-Aznar CP, Guillén Del Castillo A, Colunga Argüelles D, Rubio-Rivas M, Trapiella Martínez L, et al. Influence of antibody profile in clinical features and prognosis in a cohort of Spanish patients with systemic sclerosis. *Clin Exp Rheumatol* 2017;35(Suppl. 106):98–105.
- [51] Pokeerbox MR, Giovannelli J, Dauchet L, Mouthon L, Agard C, Lega JC, et al. Survival and prognosis factors in systemic sclerosis: data of a French multicenter cohort, systematic review, and meta-analysis of the literature. *Arthritis Res Ther* 2019;21:86. <https://doi.org/10.1186/s13075-019-1867-1>.
- [52] Maria ATJ, Partouche L, Goulabchand R, Rivière S, Rozier P, Bourgeois C, et al. Intriguing relationships between cancer and systemic sclerosis: role of the immune system and other contributors. *Front Immunol* 2019;9:3112. <https://doi.org/10.3389/fimmu.2018.03112>.

- [53] Shah AA, Laiho M, Rosen A, Casciola-Rosen L. Protective effect against cancer of antibodies to the large subunits of both RNA polymerases I and III in scleroderma. *Arthritis Rheum* 2019;71:1571–9. <https://doi.org/10.1002/art.40893>.
- [54] Xu GJ, Shah AA, Li MZ, Xu Q, Rosen A, Casciola-Rosen L, et al. Systematic autoantigen analysis identifies a distinct subtype of scleroderma with coincident cancer. *Proc Natl Acad Sci* 2016;113:E7526–34. <https://doi.org/10.1073/pnas.1615990113>.
- [55] Bernal-Bello D, García de Tena J, Simeón-Aznar C, Fonollosa-Pla V. Systemic sclerosis, breast cancer and calcium channel blockers: a new player on the scene? *Autoimmun Rev* 2014;13:880–1. <https://doi.org/10.1016/j.autrev.2014.03.003>.
- [56] Tsoi KKF, Ho JMW, Chan FCH, Sung JY. Long-term use of low-dose aspirin for cancer prevention: a 10-year population cohort study in Hong Kong. *Int J Cancer* 2019;145:267–73. <https://doi.org/10.1002/ijc.32083>.
- [57] Patrignani P, Patrono C. Aspirin and cancer. *J Am Coll Cardiol* 2016;68:967–76. <https://doi.org/10.1016/j.jacc.2016.05.083>.
- [58] Ulrych T, Böhm A, Polzin A, Daum G, Nüsing RM, Geisslinger G, et al. Release of sphingosine-1-phosphate from human platelets is dependent on thromboxane formation: thromboxane-dependent release of platelet S1P. *J Thromb Haemost* 2011;9:790–8. <https://doi.org/10.1111/j.1538-7836.2011.04194.x>.