Lung cancer risk in systemic sclerosis: data from an inception cohort and meta-analysis of published studies

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Abstract

Objective

Population-based cohort studies show an association between systemic sclerosis (SSc) and lung cancer; however, a Mendelian randomisation analysis refutes causality. Herein, lung cancer risk is analysed in an academic inception SSc cohort, complemented by a meta-analysis of published data.

Methods

Patients evaluated within 12 months of SSc onset, between January 1995 and December 2020, with regular follow-up until December 2024, were included. Clinical manifestations, laboratory parameters, treatments and comorbidities were prospectively recorded. Age-standardised incidence ratio (SIR) of lung cancer was estimated using the Global Cancer Observatory database. Lung cancer determinants were evaluated with Cox proportional hazards models. A systematic literature search for the association between SSc and cancer and a meta-analysis of lung cancer SIRs from eligible studies was conducted.

Results

Among 180 patients (2,110 person-years follow-up), lung cancer was diagnosed in 12, after a mean 10.2±5.9 years from SSc onset. Age-SIR was 5.1 (95% CI 4.7-5.4) for the entire cohort, 3.8 (95% CI 3.5-4.1) for male and 9.5 (95% CI 8.7-10.3) for female patients. Diffuse subtype [HR = 4.22, 95% CI: 1.03-17.35] and smoking history [HR=4.49, 95% CI: 1.14-17.69] were associated with lung cancer development, whereas digital ulcers were inversely associated [HR: 0.13, 95% CI: 0.03–0.63]. The meta-analysis of 17 studies (27,563 SSc patients) yielded a pooled lung cancer age-SIR of 3.85 [95% CI (2.63-5.63)].

Conclusion

Long-term follow-up data from an SSc inception cohort indicate a fivefold increased lung cancer risk in SSc, nearly doubled among female patients. Further studies are warranted to inform screening strategies.

Key word

systemic sclerosis, connective tissue diseases, autoimmune diseases, lung neoplasms

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Introduction

Systemic sclerosis (SSc) is a rare autoimmune rheumatic disease (ARD) characterised by immune and microvascular abnormalities, resulting in fibrosis of skin and internal organs (1). SSc carries significant morbidity and the highest cause-specific mortality of all ARDs (2, 3). Although mortality is primarily associated with cardiac and pulmonary complications of the disease, there is an increasing impact of comorbidities, especially cancer (4-7). SSc patients demonstrate an increased risk of malignancy development compared to the general population, with lung cancer being the most frequent type. Findings regarding lung cancer incidence in SSc are conflicting, while a two-sample Mendelian randomisation analysis disproved a genetic link between the two (8-10). Potential pathogenetic factors implicated in carcinogenesis include chronic inflammation, fibrosis, lymphocyte overactivation, vascular impairment and immunosuppression, alongside genetic contributions (8, 11, 12). Moreover, cancer development within a short interval from SSc onset has been interpreted as a paraneoplastic phenomenon termed 'cancer-associated scleroderma', which may correlate with specific serum autoantibody profiles (13-15).

To date, despite evidence of increased neoplasia risk in SSc, official malignancy screening guidelines are lacking, unlike in certain autoimmune rheumatic diseases such as inflammatory myopathies (14, 16, 17).

In the present study, the aim was to determine the risk of lung cancer in SSc by analysing original data from a single academic centre inception cohort with an observation period of over 30 years, as well as by performing an updated systematic review and meta-analysis of the relevant literature.

The present cohort study was approved by the Ethics Committee of Laiko General Hospital (Approval number 267/26-04-2021). All participants gave written, informed consent before enrolment. Participants' personal data were handled with confidentiality. The study was performed in accordance with the Declaration of Helsinki.

Methods

Original studies

All SSc patients evaluated at the Rheumatology Centre of the 1st Propaedeutic and Internal Medicine Department of Laiko General Hospital between January 1995 and December 2020 were screened for eligibility. Inclusion criteria were: (a) assessment within 12 months from SSc onset, defined as the occurrence of the first non-Raynaud manifestation; and (b) fulfilment of the 2013 ACR/EULAR classification criteria for SSc (18). Exclusion criteria comprised: (a) a documented diagnosis of lung cancer prior to SSc onset; and (b) lung cancer diagnosed concurrently with or within the same time frame as the first non-Raynaud SSc manifestation, in order to avoid inclusion of prevalent or paraneoplastic cases at baseline. Patients fulfilling these criteria constituted the inception cohort.

All included patients were prospectively and systematically followed through scheduled clinical visits and medical record review until December 2024 or until death.

Clinical manifestations of SSc, laboratory parameters, treatment modalities and comorbidities, including lung cancer, were prospectively recorded. Definitions for all clinical manifestations (*i.e.* interstitial lung disease, pulmonary hypertension, digital ulcers, renal crisis and others) were identical to those used in a previously published analysis of the same cohort, where the full diagnostic criteria are detailed (19).

The age standardised incidence ratio (SIR) of lung cancer in this cohort was estimated based on the incidence of lung cancer in the general Greek population according to the Global Cancer Observatory (GCO) database (https://gco.iarc.fr/en). Specifically, according to the GCO, cancer incidence in Greece is calculated from national mortality estimates via modelling, utilising mortality-to-incidence ratios from cancer registries of adjacent countries.

Cox proportional hazards regression analysis was applied to evaluate the association between baseline demographic, clinical and laboratory variables, as presented in Table I, and the risk of incident lung cancer. Time-to-event was

defined as the interval between cohort entry and the diagnosis of lung cancer or censoring. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated. All candidate predictors (demographics, clinical manifestations, autoantibody status, lung function tests, treatment regimens, smoking history) were initially evaluated in univariate Cox proportional hazards models. Variables showing a statistically significant association with the outcome ($p<0.05$), were entered into the multivariable model.

Systematic review and meta-analysis

- Search strategy

A literature search was performed on PubMed and Cochrane Library databases until November 2025 using the following search combinations for identification of relevant studies: [("systemic sclerosis" OR "scleroderma" OR "SSc") AND ("cancer" OR "malignancy" OR "neoplasia")], as well as [("autoimmune disease" OR "rheumatic disease") AND ("malignancy" OR "cancer")]. Reviews and references of eligible articles were examined for identification of potentially undetected articles.

- Data screening and extraction

Deduplication was performed using Zotero reference managing software (Corporation for Digital Scholarship, USA). Study screening was conducted in the following steps: upon screening titles and abstracts, one author (A.M) excluded non-eligible records, and the remaining full texts were evaluated for eligibility. Second, another author (S.P.) confirmed the above decisions, and any disagreements were resolved after joint assessment of relevant studies.

Extraction of data from eligible studies was performed by two authors (A.M. and S.P.) and included the following information: first author, year, country, DOI, study design, total number of SSc patients, percentage of females, number of patients by SSc subtype, number of newly diagnosed cancers, standardised incidence ratio (SIR) of lung cancer, follow-up duration, mean time from disease onset to diagnosis, age at diagnosis, immunosuppression received.

Table I. Demographic and clinical characteristics of 180 patients with systemic sclerosis (SSc) stratified by lung cancer diagnosis.

	Without lung cancer n=168 (%)	With lung cancer n=12 (%)	*p* (t-test)
Sex, female	141 (84)	10 (83)	0.96
Age at SSc onset, years	49.2 ± 13.8	48.7 ± 15.6	0.94
Disease duration at last follow-up visit, years	11.7 ± 6.3	12.8 ± 7.8	0.53
Diffuse SSc	68 (41)	9 (75)	**0.020**
Anti-Topoisomerase antibody positivity	91 (57)	5 (56)	0.92
Smoking history	43 (26)	7 (57)	**0.026**
Alive at the end of follow-up	115 (69)	4 (33)	**0.013**
Interstitial lung disease	129 (77)	9 (75)	0.81
Pulmonary arterial hypertension	30 (18)	1 (8)	0.40
Oesophageal involvement	120 (71)	9 (75)	0.80
Digital ulceration	90 (53)	2 (17)	**0.015**
Calcinosis (x-ray positive)	25 (15)	2 (17)	0.91
Renal crisis	13 (8)	1 (8)	0.94
Any immunosuppressive therapy	126 (78)	10 (83)	0.490
mean duration of therapy, years	6.1 ± 3.7	6.2 ± 3.8	0.860

- Inclusion-exclusion criteria

The eligibility criteria for inclusion of studies in the current systematic review were formulated based on the PICOS (population, intervention/exposure, comparator, outcomes, and study design) study question format, as follows:

- Population: adult patients diagnosed with systemic sclerosis;
- Intervention/exposure: systemic sclerosis;
- Comparator: not applicable;
- Outcome: cancer diagnosis (after SSc onset);
- Study design: observational studies (prospective or retrospective).

Studies not fulfilling the above criteria or studies with the following characteristics were excluded: (a) SSc cohort of less than 100 participants; (b) data only on specific malignancies (except lung cancer); (c) no follow-up data (in person-years); (d) non-English language.

- Quality assessment and risk of bias

The NHLBI Study Quality Assessment Tool for Observational Cohort and Cross-sectional Studies 2021 was utilised for quality assessment of included studies (20). According to this tool, the internal validity of each study is appraised by assessment of 14 different domains (research question; study population; participation; population/inclusion-exclusion criteria; sample size; exposure; time frame; levels of exposure; measures of exposure; time of exposure assessment; outcome definition; blinding; follow-up; confounding). Critical appraisal was performed independently by A.M. and S.P., and consensus was reached after joint re-evaluation.

- Data analysis

A quantitative synthesis of eligible studies by means of meta-analysis was performed when data were sufficient and outcomes were comparable. Specifically, SIRs and their corresponding 95% CIs for lung cancer were collected from individual studies and were combined into a pooled estimate upon automatic conversion into the log scale and back-transformation. SIRs, alike other ratio measures, exhibit asymmetric CIs in the original scale which become symmetric after conversion into the log scale. Therefore, during back-transformation, the resultant CIs may differ slightly, but not significantly, from the original intervals (21). Heterogeneity was assessed through Cochran's Q test and the I^2 statistic; a value of <25%, 25–75%, or >75% in the I^2 test indicates low, moderate or high heterogeneity, respectively. A random-effects model or a fixed-effects model was utilised, depending on the level of heterogeneity. A funnel plot and an Egger's test were conducted to evaluate publication bias. Statistical calculations were performed using R Studio (metafor package) (R Foundation for Statistical Computing, Austria). A *p*-value <0.05 was recognised as statistically significant.

Results

Original studies

In total, 180 inception patients with SSc (151 women and 29 men, aged 49±14 (mean±SD) years, 77 with diffuse SSc, 96 anti-topoisomerase positive) were followed-up for 11.7±6.4 years and 2,110 patient-years were analysed. Demographics and disease characteristics are presented in Table I. The prevalence of interstitial lung disease, pulmonary arterial hypertension oesophageal involvement, digital ulcers and renal crisis was 76%, 17%, 71%, 51% and 8%, respectively. Overall, 76% of patients received immunosuppression therapy during follow-up (*i.e.* at least one agent, sequential therapy, or combination therapy with azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil, rituximab, or tocilizumab), for a mean duration of 6.1±3.8 years.

Lung cancer was diagnosed in 12 of 180 patients [10 with non-small-cell (8 with adenocarcinoma, 1 with squamous- and 1 with large- cell) and 2 with small-cell lung cancer, respectively], aged 59.4±10.8 years (range 43–77) and with SSc duration of 10.2±5.9 years (range 2–20) at the time of cancer diagnosis. Three of 12 cases had an SSc duration of less than 3 years. A temporal distribution of lung cancer diagnoses is visualised in Figure 1. Given that the estimated SIR of lung cancer in people aged 45–79 years in Greece is 114/100.000 (178/100.000 for males and 58/100.000 for females), the SIR of lung cancer in the entire inception cohort is 5.1 (95% CI 4.7–5.4). A sub-analysis according to sex revealed an SIR of 3.8 (95% CI 3.5–4.1) in male patients and 9.5 (95% CI 8.7–10.3) in female patients.

Cox proportional hazards models indicated diffuse cutaneous SSc and smoking history as independent predictors for lung cancer development. Specifically, patients with diffuse disease had more than a four-fold higher hazard compared with those with limited cutaneous involvement (HR=4.22, 95% CI: 1.03–17.35, p=0.046). Smoking history was also a significant predictor (HR=4.49, 95% CI: 1.14–17.69, p=0.032), suggesting an approximately four-fold increased hazard in ever-

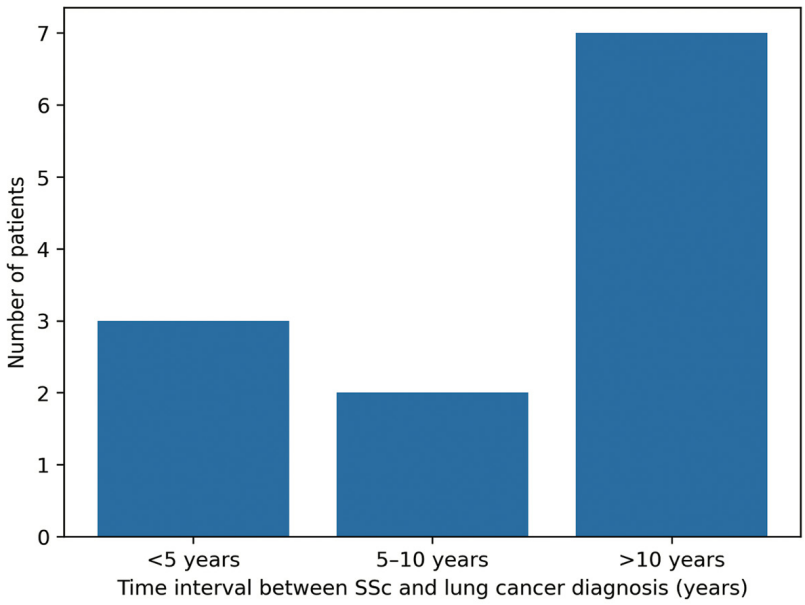

Fig. 1. Histogram showing the temporal distribution of lung cancer diagnoses among SSc patients.

Table II. Independent predictors of lung cancer development in systemic sclerosis (SSc).

Variable	Hazard ratio	95% Confidence interval	*p*-value
Diffuse SSc	4.22	1.03–17.35	0.046
Smoking (ever)	4.49	1.14–17.69	0.032
Digital ulcers	0.13	0.03–0.63	0.011

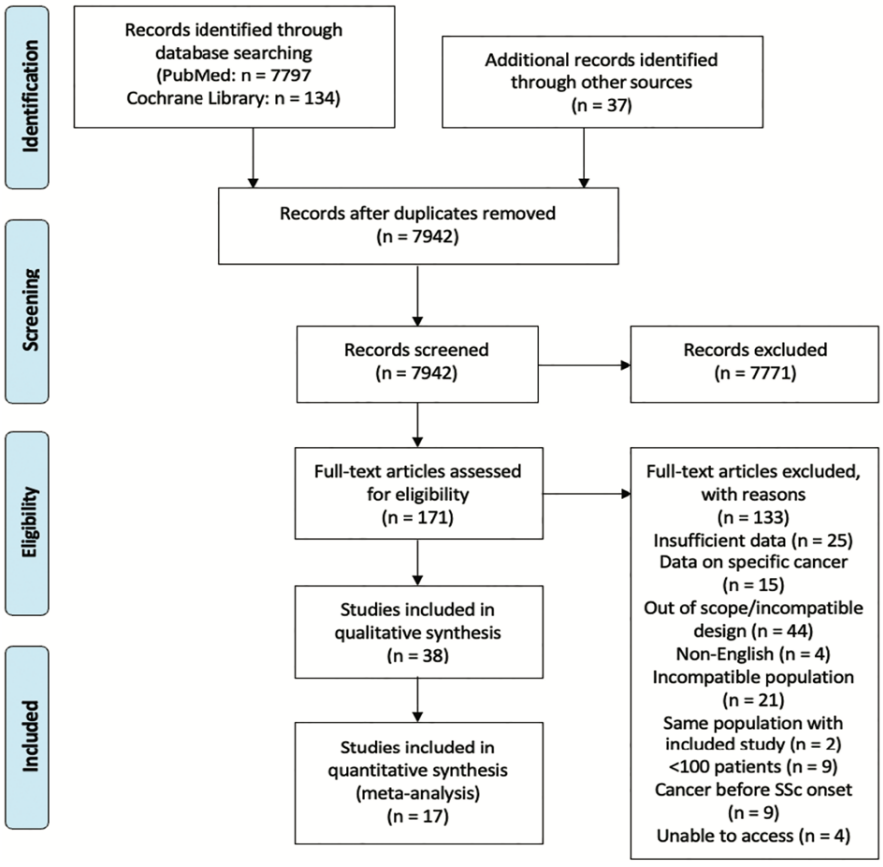

Fig. 2. PRISMA flowchart demonstrating the study selection process.

Table III. Characteristics of the studies included in the systematic review.

Author	Year	Country	SSc, n	Females, n	SSc subtype, n	Cancer, n (patients)	Follow-up (person-years)	Time from disease onset, mean (years)	Age at cancer diagnosis, mean (years)	Immunosuppression received by cancer patients, %
Airo	2011	Italy	360	335	dcSSc 83 Rest N/A	24	4041	N/A	N/A	N/A
Abu-Shakra	1993	USA	248	210	dcSSc 99 lcSSc 149	18	2001	7.8 ± 6	57.1±10.3	N/A
Bairkdar	2022	Sweden	1139	912	N/A	357	5695	N/A	N/A	N/A
Baysal	2025	Turkey	252	227	dcSSc 67 lcSSc 160 ssSSc 10	19	2132	8 ± 4.8	N/A	AZA 42.1 CYC 26.3 MMF 26.3 MTX 10.5
Bernal-Bello	2017	Spain	432	383	lcSSc 275 dcSSc 92 ssSSc 65	53	8726	9.6 ± 8.5	60.7 ± 17.7	AZA 7.7 CS 38.1 CYC 11.5 HCQ 5.8 MMF 8.2 MTX 0 RTX 3.8 TNFi 0
Chang	2014	Korea	274	84	N/A	16	2088	5.8 ± 3.5	55.5 ± 11.9	N/A
Chatterjee	2005	USA	538	473	lcSSc 317 dcSSc 187 ssSSc 9 Other 25	45	5766	N/A	N/A	N/A
Carbonell	2022	Spain	1930	1711	lcSSc 1147 dcSSc 395 ssSSc 205 Other 168	133	28,092	N/A	62 ± 12.9	AZA 2.4 CS 20.4 Cyclosporine 0.49 MTX 2.9 MMF 4.9 RTX 0.97 Tacrolimus 0.49 TNFi 0
Colaci	2013	Italy	318	287	lcSSc 278 dcSSc 40	16[a]	3270	14 ± 10	56.3	CYC 43.7 Rest N/A
Derk	2006	USA	769	N/A	lcSSc 377 dcSSc 392	62	3775	N/A	53.1 ± 2.5	CYC 6.4 D-penicillamine 44.1 MTX 6.4
Fairley	2025	Australia	2000	1700	dcSSc 540	319	8000	N/A	N/A	N/A
Hao	2016	Multicentre	3218/1070[¶]	2780 / 882[¶]	lcSSc 2086 / 622[¶] dcSSc 1006 / 431[¶]	417 / 108[¶]	22,526 / 3210[¶]	N/A	N/A	N/A
Hashimoto	2012	Japan	405	376	lcSSc 270 dcSSc 135	27	4787	8.0±1.8	57±1.7	N/A
Hemminki	2012	Sweden	7169	N/A	N/A	88[a]	90,023	N/A	N/A	N/A
Hill	2003	Australia	441	363	lcSSc 266 dcSSc 78	47	2643	N/A	N/A	N/A
Igusa	2018	USA	2383	1968	lcSSc 1470 dcSSc 913	205	37,686	10.9 ± 12.6	53.3 ± 19.7	N/A
Kang	2009	Korea	112	83	lcSSc 67 dcSSc 44	9	768	8.7	56.4 ± 8.5	AZA 32.3 CYC 31.5 D-penicillamine 71
Kasifoglu	2016	Turkey	340	314	lcSSc 175 dcSSc 165	28	1734	12.7	55.6 ± 8.4	CYC 48 Rest N/A
Kuo	2011	Taiwan	2053	1581	N/A	83	12,118	3.6 ± 3.5	58.4 ± 11.2	N/A
Lopez	2023	France	464	341	lcSSc 256 dcSSc 116 Other 92	40	4419	14.5 ± 6	69	AZA 10 CYC 22.5 HCQ 27.5 MTX 17.5 MMF 17.5 RTX 2.5
Mahajan	2025	USA	66,939	54,269	N/A	2896	214,205	N/A	N/A	N/A
Mahajan	2025	USA	2840	2274	N/A	109	11,370	N/A	N/A	MMF 50 RTX 50*
Moinzadeh	2014	UK	2177	1853	lcSSc 710 dcSSc 1358 Rest N/A	84	28,825	9.9±7.9	N/A	N/A

Author	Year	Country	SSc, n	Females, n	SSc subtype, n	Cancer, n (patients)	Follow-up (person-years)	Time from disease onset, mean (years)	Age at cancer diagnosis, mean (years)	Immunosuppression received by cancer patients, %
Moon	2018	Korea	751	651	lcSSc 487 dcSSc 264	46	6983	N/A	N/A	N/A
Morrisroe	2020	Australia	1727	1483	lcSSc 1276 Rest N/A	245	7081	8.1 ± 14.7	57.7 ± 12.9	ABA 0.4 AZA 10.6 HCQ 15.9 CS 46.5 CYC 13.1 Cyclosporin 1.2 LEF 0.8 MMF 10.2 MTX 20.8 RTX 3.3 TCZ 0 TNFi 1.2
Na	2025	South Korea	6386	5123	N/A	910	49,916	N/A	N/A	AZA 12.8 CYC 10.1 HCQ 31.6 MMF 3.7 MTX 17.9 Tacrolimus 2.9
Olesen	2010	Denmark	1731	1586	N/A	222	16,003	0-0.5 years, n=23 0.5-1 years, n=13 >1 years, n=186	<30, n=2 30-49, n=25 50-69, n=122 >69 years, n=73	N/A
Pauling	2024	UK	1588/806¶	1354/667¶	N/A	206/90¶	19,292/5113¶	N/A	18-40, n<10/<5¶ 40-55, n=19/8¶ 50-70, n=90/40¶ 70-85, n=85/36¶ >85, n<10/<5¶	N/A
Pokeerbux	2019	France	625	493	lcSSc 104 dcSSc 42	49	2750	10	60	CYC 4.5 D-penicillamine 4.5 MTX 18
Rees	2021	New Zealand	164	142	lcSSc 104 dcSSc 42 Other 18	22	1476	9.4	46.9	CYC 4.5 D-penicillamine 4.5 MTX 18
Rosenthal	1993	Sweden	233	144	N/A	22	1195	< 1 year, n=6	69.4	N/A
Rosenthal	1995	Sweden	917	630	N/A	69	7403	N/A	20-40, n=2 40-60, n=23 >60, n=63	N/A
Roumm	1985	USA	262	202	N/A	13	1335	9.2	58.1	Chlorambucil 7
Sakr	2018	Canada	1560	1333	dcSSc 564 Rest N/A	18[a]	5519	N/A	N/A	AZA 5.6 CYC 0 MMF 0 MTX 11.1
Thomas	2000	UK	652	527	N/A	36	3179	N/A	N/A	N/A
Tonutti	2024	Italy	290	270	dcSSc 42 Rest N/A	46	2591	< 3 years, n=23 >3 years, n=23	N/A	N/A
Yu	2016	Taiwan	814	1353	N/A	79	12,408	<1 years, n=24 1-2 years, n=12 2-4 years, n=11 4-6 years, n=13 6-8 years, n=10 >8 years, n=9	<20, n=2 20-39, n=2 40-64, n=47 >64, n=28	N/A
Zhou	2022	China	375	305	N/A	27	1803	3.5±4.8	49.2±9.1	N/A

ABA: abatacept; AZA: azathioprine; CS: corticosteroids; CYC: cyclophosphamide; HCQ: hydroxychloroquine; LEF: leflunomide; MMF: mycophenolate mofetil; MTX: methotrexate; RTX: rituximab; TNFi: tumour necrosis factor inhibitor.
¶ Data from inception sub-cohort. [a] Data refer only to lung cancer cases. * All patients received either RTX or MMF.

smokers compared with never-smokers. In contrast, the presence of digital ulcers was associated with a markedly lower risk of lung cancer (HR: 0.13; 95% CI: 0.03–0.63; p=0.011) (Table II). Overall, the model showed statistically significant explanatory power (Omnibus test: χ^2=25.85, df=3, p<0.001).

Systematic review and meta-analysis - Study selection

The study selection process is summarised by the PRISMA flowchart, as

Table IV. Studies with data on incident lung cancer among systemic sclerosis patients.

Author	Year	SSc, n	Cancer, n (patients)	Follow-up (person-years)	Lung cancer, n (patients)	Lung cancer SIR (95% CI)
Abu-Shakra	1993	248	18	2001	7[#]	8.3 (7.2-9.6)
Baysal	2025	252	19	2132	5	N/A
Colaci	2013	318	16	3270	16	N/A
Chatterjee	2005	538	45	5766	10	1.23 (0.59–2.25)
Derk	2006	769	62	3775	9	1.55 (0.54–2.56)
Fairley	2025	2000	319	8000	39	N/A
Hashimoto	2012	405	27	4787	10	5.73 (2.18-9.29)
Hemminki	2012	7169	88	90,023	88	2.19 (1.76–2.70)
Hill	2003	441	47	2643	12	5.9 (3.05-10.31)
Igusa	2018	2383	205	37,686	30	1.18 (0.8-1.68)
Kang	2009	112	9	768	4	18.6 (13.8-23.4)
Kuo	2011	2053	83	12,118	21	4.2 (2.67–6.42)
Mahajan	2025	66,939	2896	214,205	557	N/A
Moon	2018	751	46	6983	11	N/A
Morrisroe	2020	1727	245	7081	25	2.12 (1.21-3.44)
Na	2025	6386	910	49,916	166	7.01 (5.99–8.17)
Olesen	2010	1731	222	16,003	29*	2.1 (1.4–3.0)
Pauling	2024	1588/806[¶]	206/90[¶]	19,292/5113[¶]	33/13[¶]	N/A
Rees	2021	164	22	1476	1	N/A
Rosenthal	1993	233	22	1195	5	7.8 (2.5-18.2)
Rosenthal	1995	917	69	7403	15	4.9 (2.8-8.1)
Roumm	1985	262	13	1335	4	4.4 (1.2-11.27)
Sakr	2018	1560	18	5519	18	N/A
Yu	2016	1814	79	12,408	N/A	2.4 (1.51-3.8)
Zhou	2022	375	27	1803	8	6.69 (2.89-13.18)

CI: confidence interval; N/A: not applicable; SIR: standardised incidence ratio; SSc: systemic sclerosis.
Values refer to cancers diagnoses both during (concurrent) and after (subsequent) SSc diagnosis.
[¶] Data from inception sub-cohort.
*Values refer to cancers that developed after 12 months of SSc diagnosis.

presented in Figure 2. After entering the appropriate keyword combinations and upon deduplication, a total of 7942 records were identified. Following application of exclusion criteria to 171 full-texts, 38 articles were eligible for inclusion in the qualitative synthesis (14-16, 22-56), while 17 were used for the meta-analysis (15, 16, 23, 27, 30, 32-35, 37, 41, 44-46, 49, 50, 56).

- Study characteristics

Characteristics of the included studies are presented in Table III. Thirty-eight observational studies with 115,876 SSc patients (643,624 patient-years) and a total of 7105 malignancies after SSc onset were included. They were conducted between 1985 and 2025 in 15 different countries, and their follow-up ranged from 768 to 214,205 person-years. Available data suggest a mean age of 57.6 at cancer diagnosis, and a mean duration of 9 years between disease onset and cancer development. Finally, concerning immunosuppression, chronic use of cyclophosphamide ranged between 0 and 48% (12 studies) *versus* 0–26.3% for mycophenolate mofetil (8 studies) and 0.97–3.8% for rituximab (5 studies).

- Study outcomes

From the 25 studies with data on lung cancer, 1123 lung malignancies were diagnosed in 101,135 SSc patients with a follow-up of 517,588 person-years, while lung cancer SIRs ranged from 1.18 to 18.6 (Table IV). Available data from 4 studies suggest that most cancers (17 of 39) were diagnosed more than 10 years after SSc onset, whereas 15 were

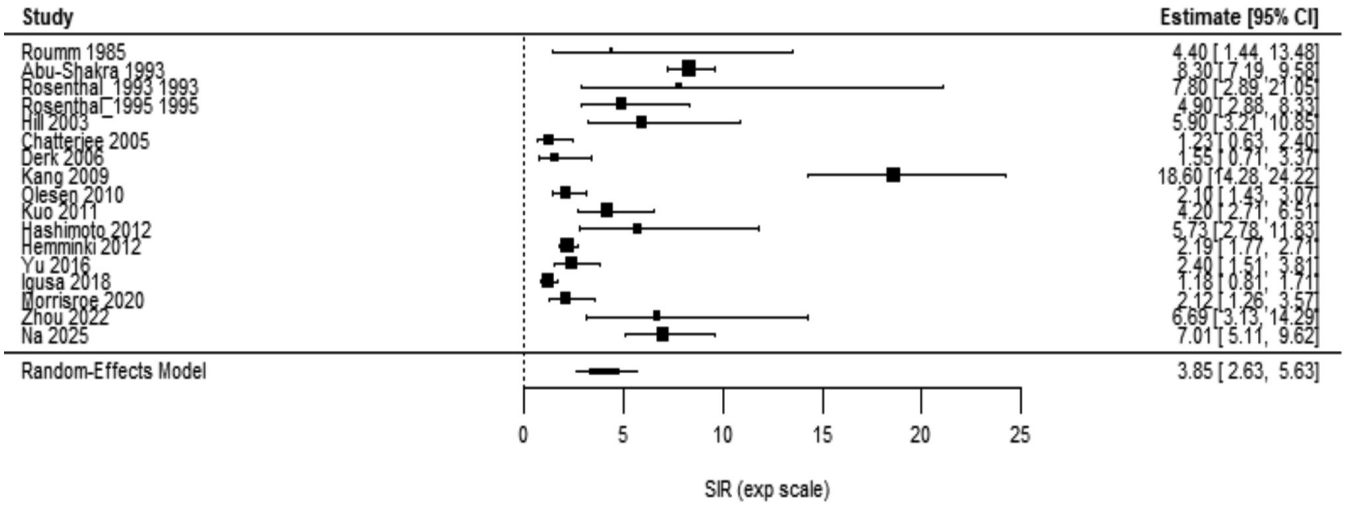

Fig. 3. Forest plot showing individual and pooled lung cancer standardised incidence ratios (SIR) with 95% confidence intervals (CI) in systemic sclerosis.

diagnosed between 5 and 10 years, and the remaining cases within 5 years of SSc diagnosis.

Of note, 6 out of 12 studies with available data demonstrated higher lung cancer SIRs in females *versus* males with SSc (32, 33, 35, 44, 50, 56) (Supplementary Table S1). Three of these 6 studies reported no lung cancer cases in male SSc patients (32, 35, 50).

Quality assessment by use of the NHLBI tool indicated relatively high quality of included studies, although results are not quantifiable (Suppl. Table S2).

The meta-analysis of lung cancer SIRs from 17 studies including 27,563 SSc patients revealed a pooled SIR of 3.85 (95% CI, 2.63–5.63; $p<0.0001$), as shown in the forest plot (Fig. 3). Significant inter-study heterogeneity was observed (Q=330.52, df=16, $p<0.0001$, $I^2=93.8\%$), and consequently, a random-effects model was used. To examine whether the asymmetry visible in the funnel plot (Fig. 4) is attributable to publication bias, Egger's test was performed. Its results (z=-1.41, $p=0.18$) point towards little chance of publication bias and, hence, heterogeneity can be ascribed to actual differences between studies. The Trim-and-Fill adjusted forest plot was identical to the initial forest plot, as expected.

Furthermore, sub-analyses were performed to examine potential sex-dependent differences regarding lung cancer risk in SSc patients; a meta-analysis of lung cancer SIRs among male SSc patients from 7 studies yielded a pooled SIR of 4.67 [95% CI (3.14–6.95), $p<0.0001$, $I^2=86.13$] (Fig. 5), whereas the respective meta-analysis among female patients from 10 studies demonstrated a pooled SIR of 5.07 [95% CI (3.06–8.39), $p<0.0001$, $I^2=94\%$] (Fig. 6).

Discussion

To the authors' knowledge, this is the first study analysing long-term data from an inception cohort regarding lung cancer risk among SSc patients, based on SIRs. The results presented herein support a fivefold increased risk of lung cancer (mostly non-small cell) in SSc patients compared to the general population, with female patients demonstrating a nearly double risk compared to their healthy counterparts. The above findings were corroborated by the present meta-analysis of 17 studies including 27,563 SSc patients, which demonstrated a significantly increased lung cancer risk in SSc patients, approximately fourfold higher than the general population. In line with these results, previous meta-analyses (9, 10, 57, 58) have reported a significant association between SSc and lung cancer, with SIRs ranging from 2.8 to 4.35.

Several mechanisms have been proposed to explain the association between SSc and cancer, mainly formulated into three hypotheses: (a) SSc is the primary event; (b) cancer is the primary event (*i.e.* SSc as a paraneoplastic syndrome); (c) SSc and cancer share common pathogenetic pathways (8). In the first hypothesis, chronic inflammation-mediated DNA damage, impaired tissue repair, and immunosuppressive agents have been linked to tumourigenesis; cyclophosphamide has been associated with bladder cancer, while azathioprine, cyclosporine and mycophenolate mofetil have also been implicated, however evidence remains conflicting (59). The paraneoplastic hypothesis is supported by a temporal proximity between SSc onset and malignancy, as well as disease remission secondary to anti-cancer treatment (11). Cancer-related SSc is strongly associated with anti-RNA polymerase III antibodies, and mutations of RNA-polymerase III genes have been detected in tumours of SSc patients (8, 60), while cancer immunotherapies, especially immune checkpoint inhibitors, may also induce SSc-like syndromes (61). Finally, shared mechanisms between SSc and neoplasia include environmental exposures such as silica, disturbances in common genetic and epigenetic pathways (8, 62) as well as epithelial-to-mesenchymal transition, triggered by the action of tumour growth factor beta, a central cytokine in SSc pathophysiology (63, 64).

According to the multivariate analysis of the present study, diffuse subtype and a history of smoking were independent predictors for lung cancer development in SSc. Diffuse cutaneous SSc is characterised by more intense immune activation, creating a microenvironment conducive to lung carcinogenesis. A recent study by Odintsov *et*

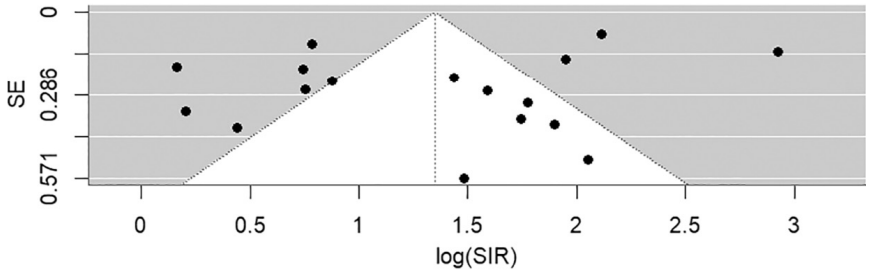

Fig. 4. Funnel plot of studies on the association between systemic sclerosis and lung cancer risk.

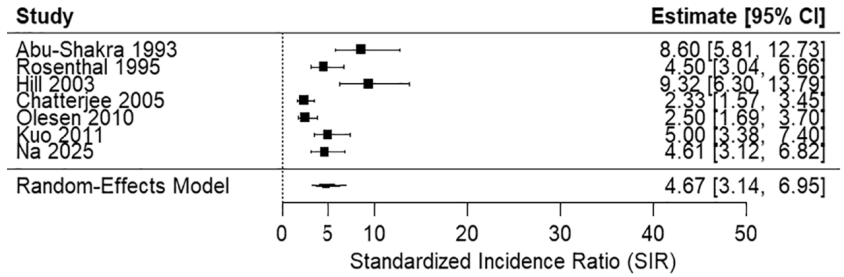

Fig. 5. Forest plot showing individual and pooled lung cancer standardised incidence ratios (SIR) with 95% confidence intervals (CI) among male patients with systemic sclerosis.

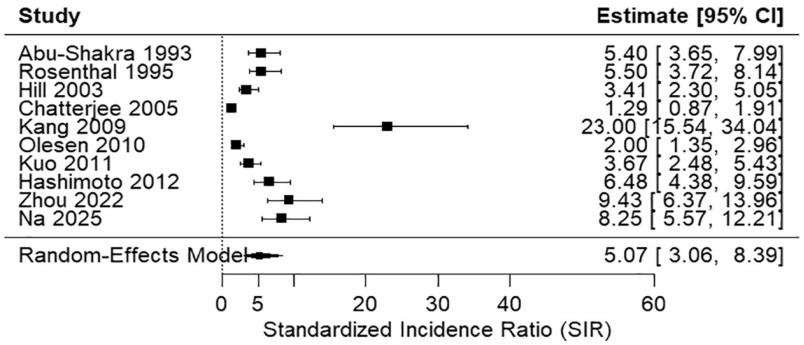

Fig. 6. Forest plot showing individual and pooled lung cancer standardised incidence ratios (SIR) with 95% confidence intervals (CI) among female patients with systemic sclerosis.

al. (65) showed that chronic inflammation/autoimmunity was associated with distinct genomic tumour characteristics in patients with SSc and non-small cell lung carcinoma, which was also the predominant subtype of lung cancer in the present cohort.

Conversely, a negative association between digital ulcers, a hallmark of SSc vasculopathy, and lung cancer development was demonstrated in multivariate regression analysis. Although such an association has scarcely been documented in the literature, Morrisroe *et al*. (16) report digital ulcers to be inversely correlated with early-onset cancer, whereas in a EUSTAR study (66) digital ulcers were also reported to be protective against "synchronous" (*i.e*. within 3 years from SSc onset) as well as "interceptable" (*i.e*. within or after 3 years of SSc onset) malignancy development. Several explanations for this association may be considered. First, vascular-dominant phenotypes may represent biologically distinct subsets with differing carcinogenic susceptibility. Second, patients with digital ulcers may receive earlier or more aggressive vasodilatory or immunomodulatory treatment, potentially modifying malignancy risk. Finally, patients with more severe vascular disease may experience earlier morbidity or mortality related to SSc, thereby reducing the time window for cancer to develop or be diagnosed. Consistently with previous studies (14, 25, 67), neither interstitial lung disease nor any specific immunosuppressive treatment proved to be significant determinants for lung cancer in the present study.

Available data regarding the association of sex with lung cancer in SSc are controversial. In the present study, female patients were at the highest risk for lung cancer, consistent with findings from previous studies (28, 29, 31, 40, 46) whereas other studies have suggested male sex as a risk factor (9, 10, 58). Moreover, a sub-analysis within the meta-analysis revealed a higher risk of lung cancer in female compared with male patients with SSc. However, the true risk may be underestimated, as studies reporting a lung cancer SIR of 0 in male subgroups were excluded from the present sub-analyses, as well as from previous analyses (9, 10, 58). Several factors may be considered when interpreting this finding. Hormonal influences appear important; oestrogens have immunomodulatory effects and may act as promoters of cell proliferation, influence carcinogen metabolism, and activate pathways linked to tumour invasion and angiogenesis, supported by the presence of oestrogen receptors (ERα, ERβ) in lung tissue (68). In addition, women generally exhibit stronger autoimmune responses and higher autoantibody production (69), which may lead to sustained immune activation and, over time, impaired tumour immune surveillance. Finally, male sex is a well-established risk factor for worse survival in SSc and such differences may allow greater cumulative exposure to carcinogenic processes in women with SSc (70). In the present cohort, most of lung cancer cases were adenocarcinomas, a type more frequently encountered in women (71).

The present study has several strengths; the inception cohort design with inclusion of patients within 12 months of symptom onset and a follow-up of over three decades minimises survivor bias (72) and allows for accurate temporal assessment between disease onset and malignancy development. As previously mentioned, it is the first SSc inception cohort reporting on lung cancer incidence in terms of SIRs, and the largest relevant meta-analysis to date. Furthermore, this study provides significant insights into the association between

SSc and lung cancer; it supports an increased risk of lung cancer among female patients and those with the diffuse subtype, representing the groups most affected within the SSc population. Additionally, it revealed an inverse association with SSc vasculopathy, which has rarely been documented in the literature and merits further investigation to better understand the potential biologic interplay between SSc vasculopathy and lung cancer.

However, some limitations should also be addressed. The relatively small number of lung cancer events (n=12) reduces statistical power and may result in wide confidence intervals and instability in multivariable Cox regression modelling. Significant associations are to be viewed as preliminary, warranting confirmation in larger, independently validated cohorts. On the same grounds, a single lung cancer diagnosis may overly impact the estimated pooled SIR. Another limitation relates to the estimation of SIR using GCO incidence data. For Greece, due to the paucity of explicit data on lung cancer incidence, incidence figures are partially derived through mortality-to-incidence modelling based on regional registry data. Such modelling may introduce imprecision in absolute incidence rates, potentially influencing SIR estimation. However, as SIR represents a relative comparison and the same reference source was uniformly applied, any potential misclassification is likely non-differential.

Regarding the data used in this meta-analysis, they were derived from observational studies, often retrospective and registry based. Despite being of relatively high quality according to the quality assessment, it is possible that they suffer from confounding, thereby introducing bias to the results. Additionally, the current meta-analysis exhibits high heterogeneity, although unrelated to publication bias. This can be potentially explained by inter-study differences in SSc classification criteria, publication year, sample sizes, follow-up duration, geographic distribution and inherent disease heterogeneity, as well as outcome ascertainment methods.

In conclusion, the results of the present study suggest an approximately fivefold increased risk of lung cancer among SSc patients compared to the general population. Female patients with diffuse SSc, a smoking history and absence of digital ulcers appear to be at highest risk. Identification of high-risk serological phenotypes and predictive biomarkers could help elucidate the temporal relationship between SSc and lung cancer. Moreover, further research is required to consolidate the direct relationship between the two entities and identify shared drivers, potentially through multi-omics techniques. Finally, development of evidence-based screening recommendations as per the inflammatory myopathy guidelines, deserves thoughtful consideration.

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