RHEUMATOLOGY

Original article

Systemic sclerosis (scleroderma) and cancer risk: systematic review and meta-analysis of observational studies

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Abstract

Objectives. A higher incidence of cancer in scleroderma patients compared with the general population has been suggested by several observational studies, reporting, however, different estimates. Therefore, we aimed to perform a systematic review and meta-analysis to definitely assess this association.

Methods. We searched MEDLINE and Embase for all original articles of observational studies on cancer incidence in scleroderma patients without language restriction published up to December 2011. Two independent authors reviewed all titles/abstracts and retrieved detailed full-text of potentially relevant articles to identify studies according to predefined selection criteria. Summary estimates were derived using random-effects model and reported as relative risk (RR). Publication bias was evaluated by trim and fill analysis.

Results. From articles initially identified, 16 original studies, involving more than 7000 patients, were included in the present review. Compared with the general population, the summary RR to develop all invasive cancers in scleroderma patients was 1.75 (95% CI 1.41, 2.18). The results for selected cancer sites indicated a strong association with lung cancer (RR 4.35; 95% CI 2.08, 9.09), and a significant increased risk also for haematological neoplasms (RR 2.24; 95% CI 1.53, 3.29). The relation with breast cancer, suggested in some previous epidemiological studies, was not confirmed (RR 1.05; 95% CI 0.86, 1.29).

Conclusion. The present meta-analysis, the first on scleroderma and cancer risk, provides definite estimates on the association between scleroderma and cancer.

Key words: scleroderma, systemic sclerosis, cancer, risk, systematic review, meta-analysis.

Introduction

SSc is a rare, immune-mediated, multi-system disorder characterized by microvasculature damage, circulating autoantibodies and fibroblast activation leading to fibrosis of the skin and visceral organs [1]. Because of the low frequency and the lack of uniform clinico-epidemiological approach, data on its prevalence and incidence are conflicting. According to a recent systematic review of the literature the prevalence of scleroderma ranges from 7/million to 489/million and its incidence from 0.6/million/year to 122/million/year with appreciable geographical variations [2].

Scleroderma carries an increased risk of death compared with the general population, with standardized mortality ratios ranging between 1.5 and 7.2 [3], with pulmonary fibrosis and pulmonary arterial hypertension being responsible for more than half of all scleroderma-related deaths [4]. Furthermore, an increased incidence of cancer in these patients compared with the general population has been suggested based on case reports and series

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[5–7] and, more recently, several observational studies were performed to address this relevant issue. Although most of the investigations confirmed the presence of an overall higher risk to develop invasive malignancies, the estimates varied greatly among studies, in particular for cancer subtype, reflecting differences in sample size, duration of follow-up and study design. Therefore, we conducted a systematic review to detect all data available on cancer incidence in scleroderma patients and performed a meta-analysis of included results to definitely assess this association.

Materials and methods

Search strategy and study selection

We searched MEDLINE and Embase for all original articles of observational studies on cancer incidence in patients with scleroderma without language restriction published up to December 2011, using a combination of free text and MeSH terms related to scleroderma/SSc, cancer and observational studies. The electronic search was supplemented by checking related citations in MEDLINE and hand searching the bibliography of relevant articles. Experts in the field were also contacted for further published or unpublished data.

The following criteria were established for inclusion: (i) cohort study of patients with scleroderma reporting relative risk (RR)—or any ratio comparing the observed with the expected numbers of cancer cases in general population—and the corresponding CIs or sufficient information to calculate them; (ii) case–control study of cancer estimating the odds ratios (ORs) relative to history of scleroderma; (iii) studies reporting cancer cases ascertained by histological examination; (iv) studies with diagnosis of cancer following the diagnosis of systemic sclerosis; when a study included cancer cases diagnosed both before and after the onset of scleroderma, we considered data for the latter group only. If not available separately, we attempted to directly contact the authors by mail or postal address.

First, two independent authors reviewed all titles/abstracts. A second sift was based on full-text review of potentially relevant articles and disagreements were resolved by discussion. When we were unable to retrieve the full text of papers, we directly contacted the corresponding authors through mail or postal address. When multiple reports were published on the same study, the more complete information was extracted.

Methodological quality assessment

We assessed the selected studies for methodological quality using the Newcastle–Ottawa Scale [8].

Information on adequacy of definition of cases or cohorts, representativeness of the sample, selection and evaluation of controls, comparability, ascertainment of exposure and outcome were evaluated for cohort and case–control studies. The risk of bias was regarded as low if a study obtained four stars for selection, two for comparability and three for ascertainment of exposure.

The risk of bias was considered to be medium in studies with two or three stars for selection, one for comparability and two for exposure. Any study scoring one or zero stars for selection, comparability or exposure was deemed to have a high risk of bias.

Data extraction and statistical analysis

Two reviewers independently extracted information on study design, country, sex, number of subjects (cases, controls or cohort size), duration of follow-up, cancer sites considered, years between diagnosis of scleroderma and cancer (when available), variables adjusted for in the analysis, RR estimates and the corresponding 95% CIs.

The measure of interest was the RR, estimated by the OR in case–control and by the standardized incidence ratio (SIR) in cohort studies. We generated forest plots, in which all the meta-analytic estimates were derived using random-effects models [9]. We assessed the heterogeneity among studies using the χ^2-test [9], defining a significant heterogeneity as a $P < 0.10$, and quantified the inconsistency using the I^2-statistic [10]. We performed a sensitivity analysis in order to verify the influence on the summary estimates of case–control studies and to evaluate potential differences in RRs when the studies excluding/including cancer cases diagnosed within the first year from diagnosis of scleroderma were analysed separately.

To evaluate publication bias, we used the funnel plot, applying the trim and fill method [11], which assesses potential asymmetry in the funnel plot, imputes the suspected missing studies and recalculates a pooled estimate, adjusting for the effect that the hypothetical RRs of non-published (imputed) studies may have on the measured outcome.

Results

Search results and characteristics of included studies

The first search identified 1597 references (supplementary Fig. S1, available as supplementary data at *Rheumatology Online*). After initial screening, 1488 papers were excluded because they were not relevant (i.e. laboratory studies, animal studies, case reports, review article) and the remaining 109 articles were retrieved for detailed full-text evaluation. Twenty-two papers were case reports/series, 17 were review articles, 49 were observational studies that failed to meet the inclusion criteria, such as studies on prevalence, or comparing cancer incidence between scleroderma patients and those with other autoimmune diseases [12], or including also cancer cases diagnosed before the onset of scleroderma [13]. Of the remaining papers, two were excluded since they reported data republished in more informative articles [14, 15], one was rejected as the data had already been reported in another paper by the same author [16], and another one because its statistical results were not clearly interpretable [17]. No further studies were identified by hand search or contacts with experts.

Thus, 16 original studies were included in the present review. Their main characteristics are summarized in Table 1.

TABLE 1 Case–control and cohort studies on the association between scleroderma and cancer risk

| Study	Country	Sex	No. of cases	Total no. of scleroderma patients	Period of enrolment/ duration of follow-up	Cancer site	Years between diagnosis of scleroderma and cancer	Variables adjusted for in the regression models	RR (95% CI)	Notes
Case–control										
Landgren et al. [42]	Sweden/ Denmark	MF	1	4	1958–98	HL	Not reported	Date of diagnosis, age, sex, country	0.60 (0.10, 6.20)	The analyses do not include all patients diagnosed with cancer within the first year from the initial diagnosis of scleroderma
Gadalla et al. [43]	USA	F	64	128	1993–2002	B	Not reported	Age, year of selection, race, mammography, region of residence, income, immunosuppressive therapy	0.96 (0.65, 1.44)	
Kristinsson et al. [44]	Sweden	MF	3	23	1958–2005	MPN	Not reported	Date of diagnosis, age, sex, country	0.60 (0.2, 2.0)	The analyses do not include all patients diagnosed with cancer within the first year from the initial diagnosis of scleroderma
Cohort										
Black et al. [45]	Australia	MF, M, F	2	27 (PR) 90 (PY)	1968–80	All	Not reported	Age, sex	6.45 (0.78, 23.29)	
Peters-Golden et al. [24]	USA	MF	3	71 (PR) 349 (PY)	1972–79 (average years of follow-up: 5)	Lu	8.33 (1 within first year, 2 after 10 years)	Calendar year, age, sex, race	16.50 (3.40, 48.20)	
Roumm and Medsger [25]	USA	MF, M, F	14	262 (PR) 1135 (PY)	1971–82 (average years of follow-up: 4.3)	All, Lu, B, Ga	All: 9.2 Lu: 18.8 B: 0.1	Age, sex	All: 1.81 (0.99, 3.04) Lu: 4.40 (1.20, 15.27) B: 0.62 (0.02, 3.45) Ga: 0.92	All cancers does not include non-melanoma skin cancers
Rosenthal et al. [14]	Sweden	MF, M, F	69	917 (PR) 7403 (PY)	1965–83 (average years of follow-up: 8)	All, Lu, B, Sk, Li, L, Le, U	All: 2–4: 22; 5–9: 38; >10: 9 Lu: 2–4:3; 5–9: 11; >10: 1 B: 2–4: 3; 5–9: 3; >10: 2 Ha: 2–4: 5; 5–9: 1; >10: 1	Calendar period, age, sex	All: 1.50 (1.20, 1.90) Lu: 4.90 (2.80, 8.10) B: 1.10 (0.50, 2.10) Sk: 4.20 (1.40, 9.80) Li: 3.30 (1.10, 7.60) L: 2.90 (0.80, 7.40) Le: 2.10 (0.20, 7.40) U: 1.0 (0.20, 3.10)	The analyses do not include all patients diagnosed with cancer within the first year from the initial diagnosis of scleroderma
Higuchi et al. [46]	Japan	MF	7	43 (PR) 383 (PY)	1982–96, (average years of follow-up: 6)	All	All: contemporary: 4 >10: 3	Calendar period, age, sex	5.10 (1.70, 10.80)	

Table 1 Continued

Study	Country	Sex	No. of cases	Total no. of scleroderma patients	Period of enrolment/ duration of follow-up	Cancer site	Years between diagnosis of scleroderma and cancer	Variables adjusted for in the regression models	RR (95% CI)	Notes
Hill *et al.* [23]	Australia	MF, M, F	47	441 (PR)	1993–2000 (years of follow-up: 5.5 for men, 6.1 for women)	All, Lu, B, Bl, Pr, Ga, Ha, Ot	Not reported	Calendar period, age, sex	All: 1.99 (1.46, 2.65) Lu: 5.90 (3.05, 10.31) B: 1.62 (0.70, 3.19) Bl: 3.42 (0.71, 9.99) Pr: 2.41 (0.50, 7.03) Ga: 0.92 (0.25, 2.36) Ha: 1.15 (0.14, 4.14) Ot: 1.96 (1.10–3.23)	All cancers does not include non-melanoma skin cancers
Chatterjee *et al.* [15]	USA	MF, M, F	45	538 (PR) 5766.14 (PY)	1973–2004	All, Lu, B, Li, NHL, Ce, Pr	Not reported	Age, sex	All: 0.91 (0.66, 1.22) Lu: 1.23 (0.59, 2.25) B: 0.81 (0.37, 1.53) Li: 7.35 (1.52, 21.49) NHL: 1.18 (0.14, 4.28) Ce: 1.37 (0.28, 4.01) Pr: 1.23 (0.25, 3.59)	
Derk *et al.* [20]	USA	MF, M, F	62	769 (PR) 3775 (PY)	1987–2002 (average years of follow-up: 4.9)	All, Lu B, C, NHL, Oe, Or, Ov, Ce, T	All: 3	Calendar period, age, sex	All: 1.55 (1.16, 1.93) Lu: 1.55 (0.54, 2.56) B: 0.99 (0.41, 1.57) C: 0.76 (−0.09, 1.61) NHL: 19.04 (0.38, 37.70) Oe: 15.90 (4.20, 27.60) Or: 9.63 (2.97, 16.29) Ov: 2.63 (−0.67, 5.25) Ce: 7.14 (0.15, 14.13) T: 4.34 (−1.66, 10.34)	
Brown *et al.* [47]	USA	M	6	—	1969–96	My	My: 2–4: 1 5–9: 4; >10: 1	Age, visits, calendar year, latency, race	2.41 (1.08, 5.36)	The analyses do not include all patients diagnosed with cancer within the first year from the initial diagnosis of scleroderma
Kang *et al.* [18]	Korea	MF, M, F	9	112	1990–2007 (average years of follow-up: 5.8)	All, Lu, P, Li, Oe, St	All: 8.66 Lu:7	Age, sex	All: 4.20 (2.30, 6.10) Lu: 18.60 (13.80. 23.40) P: 23.50 (14.30, 32.70) Li: 4.90 (3.0, 6.90) Oe: 35.0 (33.60, 36.40) St: 3.0 (1.90, 4.10)	

(continued)

TABLE 1 Continued

Study	Country	Sex	No. of cases	Total no. of scleroderma patients	Period of enrolment/duration of follow-up	Cancer site	Years between diagnosis of scleroderma and cancer	Variables adjusted for in the regression models	RR (95% CI)	Notes
Landgren et al. [19]	USA	M	60	—	1969–96	OC, Oe, St, C, R	Not reported	Age, visits, calendar year, latency, race, alcoholism (for buccal, oesophagus, liver)	Oc: 1.41 (0.90, 2.22) Oe: 2.86 (1.72, 4.74) St: 1.04 (0.39, 2.77) C: 1.01 (0.56, 1.83) R: 0.81 (0.34, 1.96)	The analyses do not include all patients diagnosed with cancer within the first year from the initial diagnosis of scleroderma
Olesen et al. [21]	Denmark	MF, M, F	186	2040 (PR) 16 003 (PY)	1977–2006 (average years of follow-up: 6.4)	All, Lu, B, Oe, P, C, R, K, Bl, NHL, Le, Ce, Me, Non Me Sk, CU, Ov, Pr, Ot	Not reported	Calendar period, age, sex	All: 1.40 (1.20, 1.60) Lu: 2.10 (1.40, 3.0) B: 1 (0.70, 1.50) Oe: 2.0 (0.20, 7.10) P: 1.60 (0.5, 3.7) C: 0.90 (0.40, 1.80) R: 0.40 (0.10, 1.60) K: 1.0 (0.10, 3.70) Bl: 1.70 (0.80, 3.40) NHL: 2.50 (1.20, 4.60) Le: 2.90 (1.20, 6.0) Ce: 1.50 (0.70, 2.80) Me: 1.70 (0.60, 3.60) Non Me Sk: 1.30 (0.9, 1.90) CU: 0.8 (0.20, 2.0) Ov: 1.0 (0.30, 2.50) Pr: 1.0 (0.20, 2.80) Ot: 1.30 (0.80, 2.0)	The analyses do not include all patients diagnosed with cancer within the first year from the initial diagnosis of scleroderma
Kuo et al. [22]	Taiwan	MF, M, F	83	2053 (PR) 12 118 (PY)	1996–2008	All, Lu, B, Ha, Or, Ga, Ce, Ot	M: 4 F: 3,4	Calendar period, age, sex	All: 1.63 (1.31, 2.01) Lu: 4.20 (2.67, 6.42) B: 1.38 (0.72, 2.39) Ha: 3.50 (1.53, 6.92) Or: 3.67 (1.83, 6.56) Ga: 0.53 (0.26, 0.97) Ce: 1.0 (0.32, 2.41) Ot: 1.91 (1.21, 2.87)	

B: breast; Bl: bladder; C: colon; Ce: cervix; E: endometrium; F: female; Ga: gastrointestinal; Ha: haematological; HL: Hodgkin lymphoma; K: kidney; L: lymphoma; Le: leukaemia; Li: liver; Lu: lung; M: male; Me: melanoma; MF: male and female; MPN: myeloproliferative neoplasms; My: myeloma; NHL: non-Hodgkin lymphoma, Non Me sk: non-melanoma skin cancer; OC: oral cavity; Oe: oesophagus; Or: oropharynx; Ot: other; Ov: ovarian; P: pancreas; Pr: prostate; PY: person-year; PR: prevalence ratio; R: rectal; Sk: skin; St: stomach; T: thyroid; U: uterus; Uc: corpus of uterus.

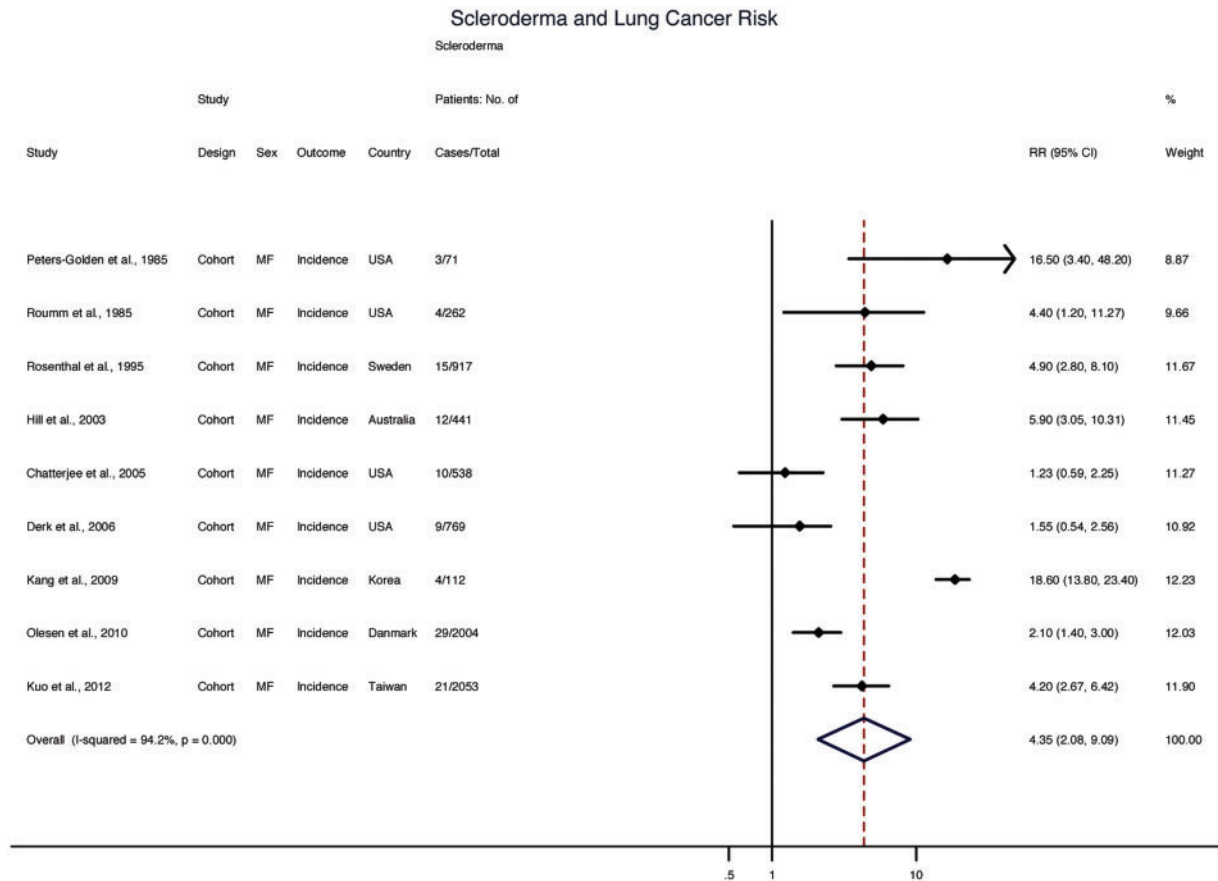Fɪɢ. 1 Summary RR for all invasive cancers in scleroderma patients.
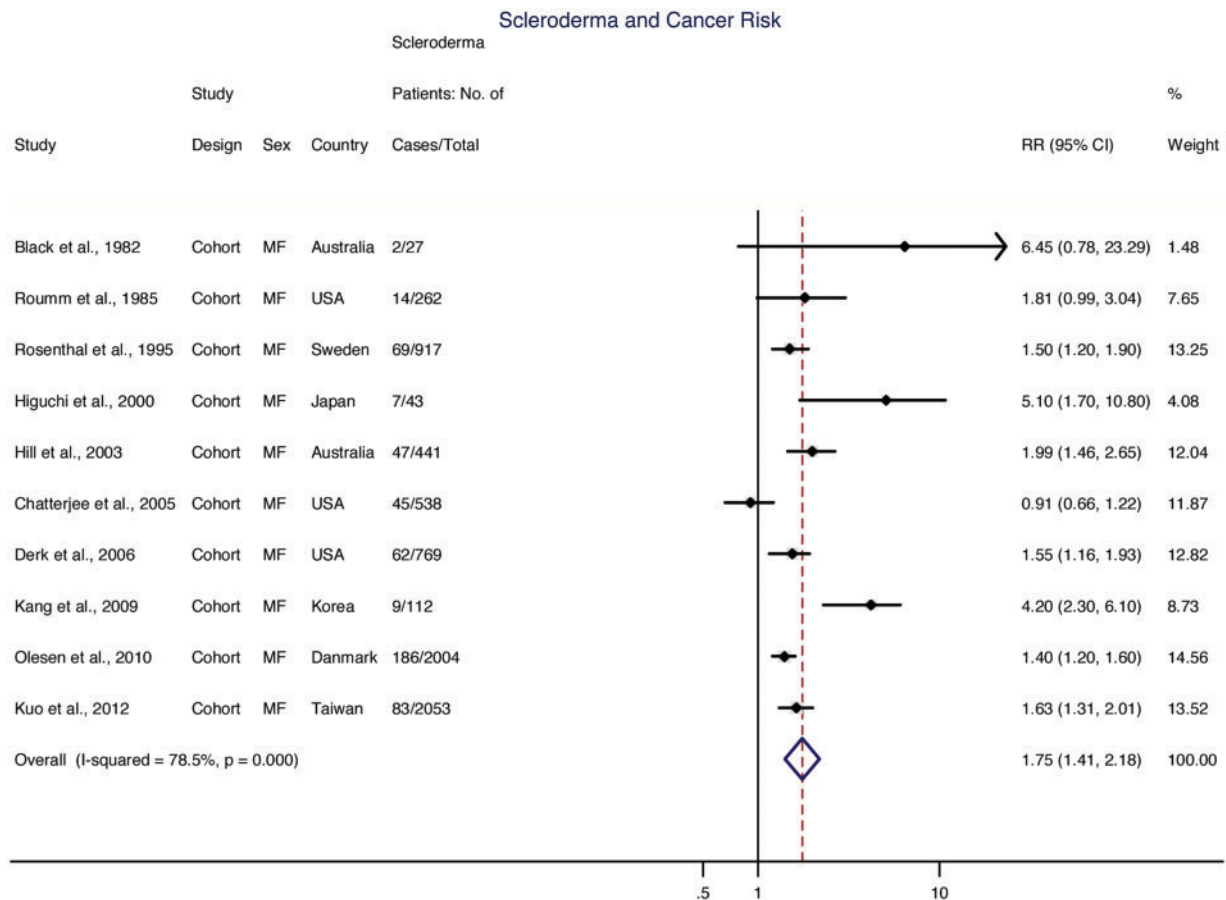
Thirteen were cohort studies, of which 2 were prospective and 11 retrospective, and 3 were case–control studies. Eight studies were conducted in America, four in Europe, two in Australia, one in Japan and one in Taiwan. Data for all cancers were provided by 10 studies, 9 of which also reported results by sex. With regard to selected cancer sites, risk of lung, breast and haematological neoplasms were presented respectively in 9, 8 and 11 studies.

The histological pattern was evaluated in six of eight studies investigating lung cancer risk and it appeared to be fairly heterogeneous, yielding a similar predominance of adenocarcinoma (32%) and squamous cell carcinoma (32%). The remaining cases were small cell lung cancer, undifferentiated non-small cell cancer and oat cell carcinoma, while bronchioloalveolar cell carcinoma was reported in only one patient. With reference to haematological neoplasms, the most common subtypes observed were non-Hodgkin lymphoma (19 cases overall) and leukaemia (9 cases); multiple myeloma was diagnosed in 6 patients, myeloproliferative neoplasms in 3 patients and Hodgkin lymphoma in 2 patients. Two studies did not specify which haematological subtypes were involved.

Other cancer sites (i.e. gastrointestinal, prostatic, renal, uterine, ovarian, etc.) were investigated in some of the studies included, but these were too few to perform a meta-analysis. Three studies assessed liver cancer incidence in scleroderma patients [14, 15, 18] and all reported a higher significant risk compared with the general population, with SIRs ranging from 3.30 to 7.35. Out of four studies evaluating oesophagus cancer risk, three [18–20] found a strong association with scleroderma (SIRs ranging from 2.86 to 35.0), while the other investigation [21], involving more than 2000 patients, did not reveal any significant increased risk (SIR 2.0; 95% CI 0.2, 7.10). Conflicting results were also reported for other cancer sites, as stomach [18, 19], pancreas [18, 21], skin [14, 21] and oral cavity [19, 22]. None of the studies reported a significant association with cancers of prostate [15, 21, 23], cervix [15, 21, 22], corpus uteri [14, 21], ovary [20, 21], colon [19–21], rectum [21, 22], bladder [21, 23], thyroid [20] and kidney [21].

Out of 13 cohort studies, 7 were judged to have low risk of bias, 3 medium and 3 high. All case–control studies were deemed to have low risk of bias. Six articles did not include patients diagnosed with cancer during the first year after being diagnosed with scleroderma and

Fɪɢ. 2 Summary RR for lung cancer in scleroderma patients.

Scleroderma and Lung Cancer Risk

Study	Study Design	Sex	Outcome	Country	Patients: No. of Cases/Total		RR (95% CI)	% Weight
Peters-Golden et al., 1985	Cohort	MF	Incidence	USA	3/71		16.50 (3.40, 48.20)	8.87
Roumm et al., 1985	Cohort	MF	Incidence	USA	4/262		4.40 (1.20, 11.27)	9.66
Rosenthal et al., 1995	Cohort	MF	Incidence	Sweden	15/917		4.90 (2.80, 8.10)	11.67
Hill et al., 2003	Cohort	MF	Incidence	Australia	12/441		5.90 (3.05, 10.31)	11.45
Chatterjee et al., 2005	Cohort	MF	Incidence	USA	10/538		1.23 (0.59, 2.25)	11.27
Derk et al., 2006	Cohort	MF	Incidence	USA	9/769		1.55 (0.54, 2.56)	10.92
Kang et al., 2009	Cohort	MF	Incidence	Korea	4/112		18.60 (13.80, 23.40)	12.23
Olesen et al., 2010	Cohort	MF	Incidence	Danmark	29/2004		2.10 (1.40, 3.00)	12.03
Kuo et al., 2012	Cohort	MF	Incidence	Taiwan	21/2053		4.20 (2.67, 6.42)	11.90
Overall (I-squared = 94.2%, p = 0.000)							4.35 (2.08, 9.09)	100.00

one specified the number of concurrent cases (diagnosed within the first 6 months), but included them in the analysis. In the majority of studies, the variables adjusted for in statistical analyses were age, sex and calendar period.

Meta-analysis

Figure 1 provides the forest plot for scleroderma and all cancer risk, based on a total of 524 cancer cases. There was a significant association, with a RR of 1.75 (95% CI 1.41, 2.18) to develop all cancers in scleroderma patients compared with the general population. There was significant heterogeneity ($P < 0.001$), although all studies, except one, estimated a risk above unity, significant in most cases.

With respect to selected cancer sites, we found a strong significant increase in lung cancer risk (Fig. 2). The RRs, derived from nine cohort studies, including 7167 patients with scleroderma and 107 lung cancer cases, was 4.35 (95% CI 2.08, 9.09). Again, there was a significant heterogeneity (I^2 94.2%, $P < 0.001$) among studies, although the RRs were above unity for all studies and significant for six.

The hematological cancer risk was provided by study design (Fig. 3). From nine cohort studies, the RR was 2.7

(95% CI 1.93, 3.76), with low heterogeneity (I^2 23.6%, $P = 0.219$). The RR from the two case–control studies was 0.6 (95% CI 0.22, 1.64). The overall RR was 2.24 (95% CI 1.53, 3.29).

There was no significant association between breast cancer and scleroderma (RR 1.05; 95% CI 0.86, 1.29) and no heterogeneity among studies (Fig. 4); the sensitivity analysis, excluding the case–control study did not change the overall result (RR 1.03; 95% CI 0.80, 1.34).

The sensitivity analyses including only studies that excluded cancer cases within the first year from the diagnosis of scleroderma provided significant increased risks both for all cancers (RR 1.43; 95% CI 1.26, 1.61) and for all the specific sites explored (lung cancer: RR 3.14, 95% CI 1.37, 7.20; haematological neoplasms: RR 2.07, 95% CI 1.36, 3.15) but not for breast cancer (RR 1.02, 95% CI 0.73, 1.43).

The sensitivity analysis excluding studies judged as having a high risk of bias did not significantly change the overall results (all cancer: RR 1.58; 95% CI 1.25, 1.99; lung cancer: RR 3.71, 95% CI 2.17, 6.32; haematological neoplasms: RR 2.2, 95% CI 1.56, 3.08; breast cancer: RR 1.06, 95% CI 0.85, 1.31).

Funnel plots to evaluate publication bias are summarized in Fig. 5. The graph regarding all cancer risk (Fig. 5A),

Fig. 3 Summary RR for haematological neoplasms in scleroderma patients.
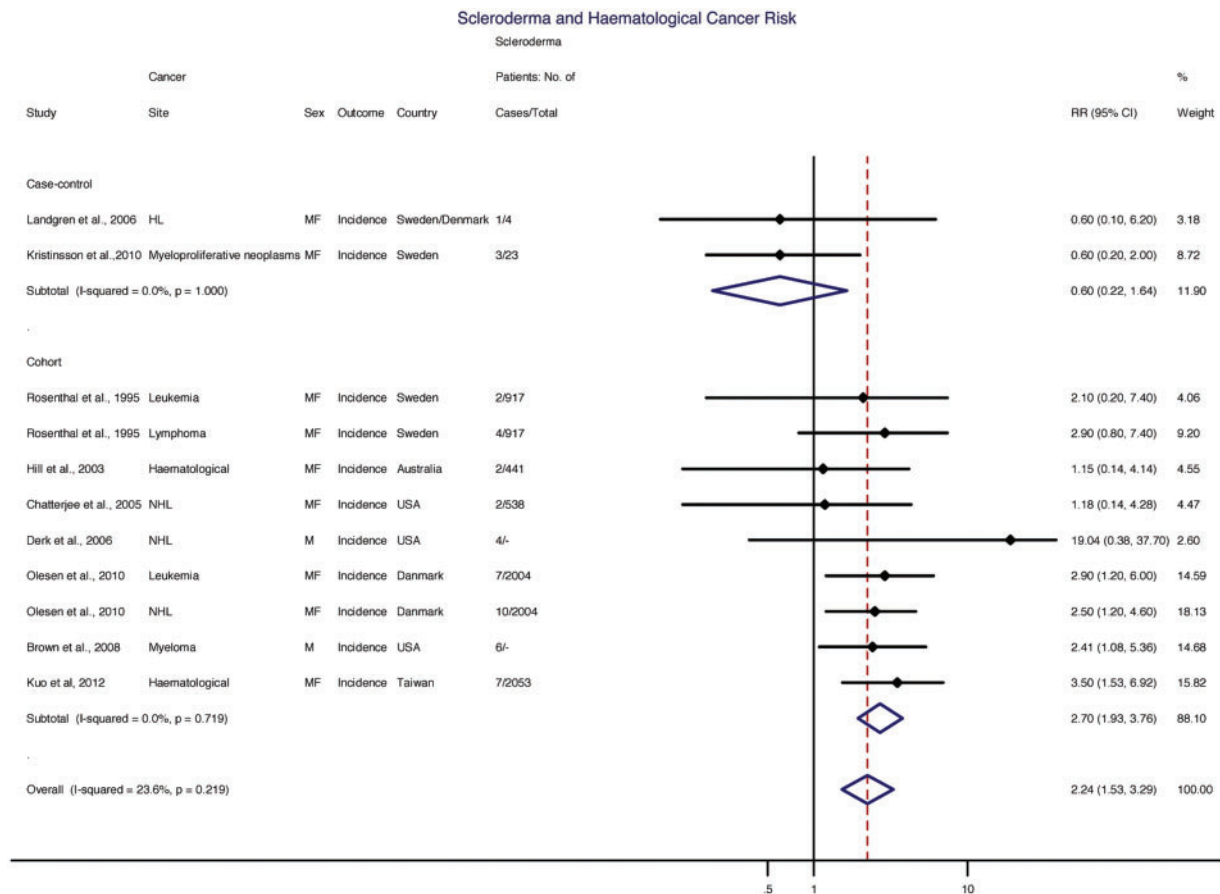
although fairly symmetric, provides a suspected missing study. We re-calculated RR estimates and the corresponding 95% CIs including the RR of this hypothetic study and we found no significant difference (RR 1.43; 95% CI 1.13, 1.80). A hypothetical missing study was reported also in the funnel plot for lung cancer (Fig. 5B), but the re-calculated RR did not significantly change (RR 4.35; 95% CI 2.01, 9.09). The graphs regarding breast and haematological neoplasms appear to be symmetrical, suggesting the absence of major publication bias (Fig. 5C and D).

Discussion

The present meta-analysis, the first on scleroderma and cancer risk, involving more than 7000 patients in various countries worldwide, provides definite estimates on the association between SSc and malignancy, showing an ~75% increased risk of developing all cancers in scleroderma patients compared with the general population (RR 1.75; 95% CI 1.41, 2.18).

The association is fairly specific, since lung cancer (RR 4.3) and, to lesser extent, haematopoietic cancers (RR 2.2) were significantly increased in scleroderma patients, while breast cancer, although suggested by previous epidemiological investigations, was not associated with scleroderma (RR 1.05; 95% CI 0.86, 1.29).

Although the studies we have analysed are heterogeneous, most of the RRs, derived from individual data, were significantly above unity. Moreover, even though funnel plots for all cancer and lung cancers suggested the existence of potential publication bias, the summary RRs, including also the results of hypothetical unpublished studies obtained through the trim and fill method (Fig. 5), did not significantly change, further confirming the robustness of the results.

The most important limitation of our study is the observational nature of the investigations, which is prone to bias of various sources and may ultimately be confounding. Specifically, the data in most studies were retrospectively retrieved from record linkage between various health care databases, such as hospital discharge data sets and national registers, which did not contain detailed clinical information. As a consequence, relevant confounding or modifying factors, such as smoking habit and previous immunotherapies (i.e. CYC, MTX), as well as information on scleroderma subtype and organ-specific involvements, could not be considered.

Moreover, the time relationship between clinical onset of scleroderma and diagnosis of malignancy, a crucial

FIG. 4 Summary RR for breast cancer in scleroderma patients.
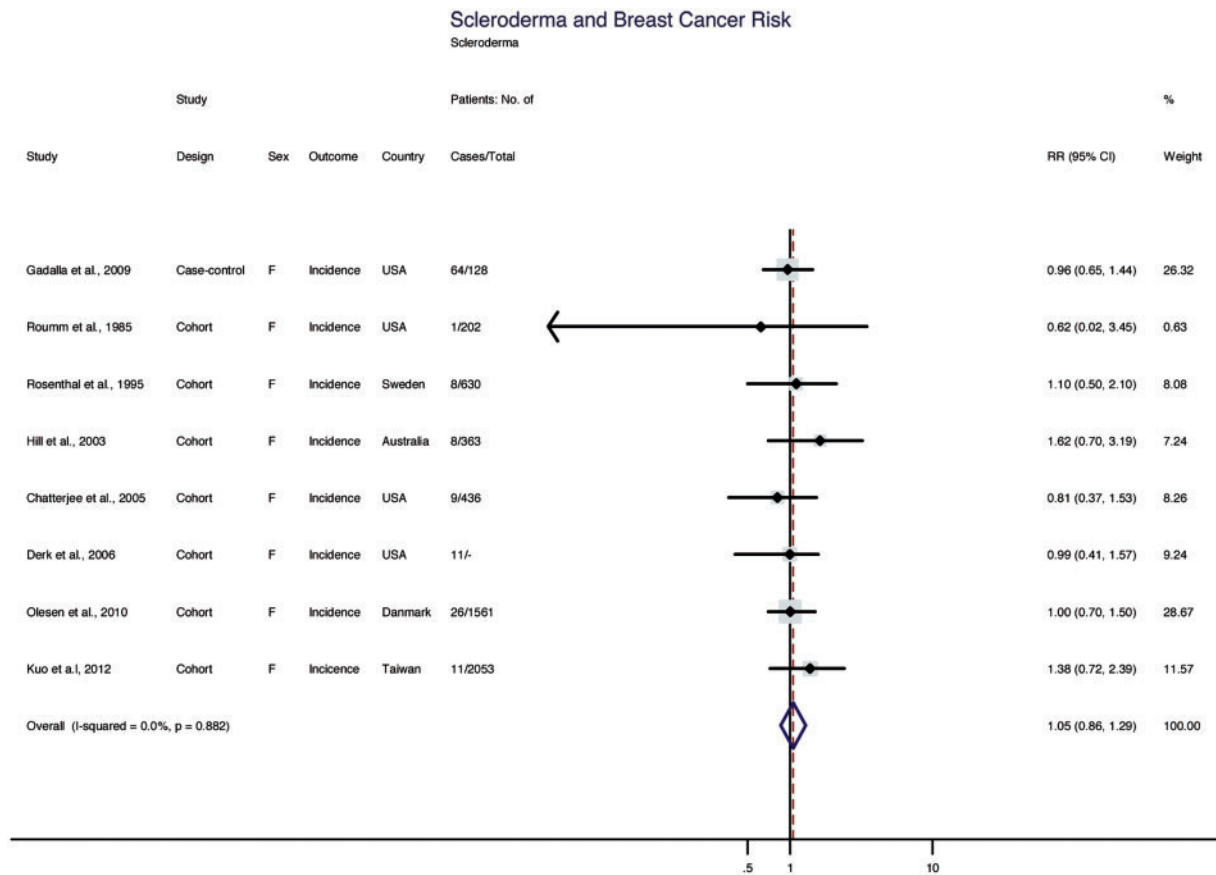
issue to understand possible underlying mechanisms, has not always been reported, and several investigations also included cancer cases ascertained within the first year after the diagnosis of scleroderma, which were more likely to be concomitant than subsequent diseases, leading to potential overestimate of summary risk. However, the sensitivity analyses excluding the latter studies showed significant, albeit slightly lower, increased risks for all and specific cancer sites explored, anyway.

Other potential sources of bias, especially for prospective design, include overdiagnosis bias, probably due to the closer surveillance in these patients with respect to the general population, and selection of reference cohorts, usually derived from data of national cancer registries, which do not always refer to the same interval time of studies.

These possible limitations, however, do not invalidate the specific association observed between scleroderma and risk of cancer, especially of the lungs. In particular, the reliability of data on scleroderma and lung cancer was also supported by the fact that, when evaluated, the average interval time between the onset of these two disease appeared to be >5 years [14, 18, 24, 25], and a close relationship with pulmonary fibrosis was reported. Furthermore, we also speculate that it is unlikely that

prevalence of smoking habits among scleroderma patients with pulmonary involvement could be higher than that observed in general population and accounts for the excess of risk. On the other hand, although bronchioloalveolar cell carcinoma was suggested as the most frequent pulmonary histotype in previous series of scleroderma patients [7, 26], there was no specific subtype correlation. However, details of pathological assessment were only available in about the half of cases included, making difficult any definite conclusion on this issue.

An increased risk of cancer has been also suggested for other autoimmune rheumatic diseases, including RA and SLE, though data on selected cancer sites have often been conflicting [27]. With reference to RA, a meta-analysis from observational studies reported a significant higher risk for specific malignancies, like lymphoma (SIR 2.08; 95% CI 1.80, 2.39), regardless of the subtype, and lung cancer (SIR 1.63; 95% CI 1.43, 1.87) [28]. On the other hand, a slight significant reduced risk was suggested for colorectal (SIR 0.77; 95% CI 0.65, 0.90) and breast cancers (SIR 0.84; 95% CI 0.79, 0.90), and the SIR for overall malignancies was 1.05 (95% CI 1.01, 1.09). Data from the largest international SLE cohort study [29] revealed a slight significant higher risk for all cancers (SIR

Fɪɢ. 5 Trim and fill funnel plot of studies on the association between scleroderma and cancer risk..
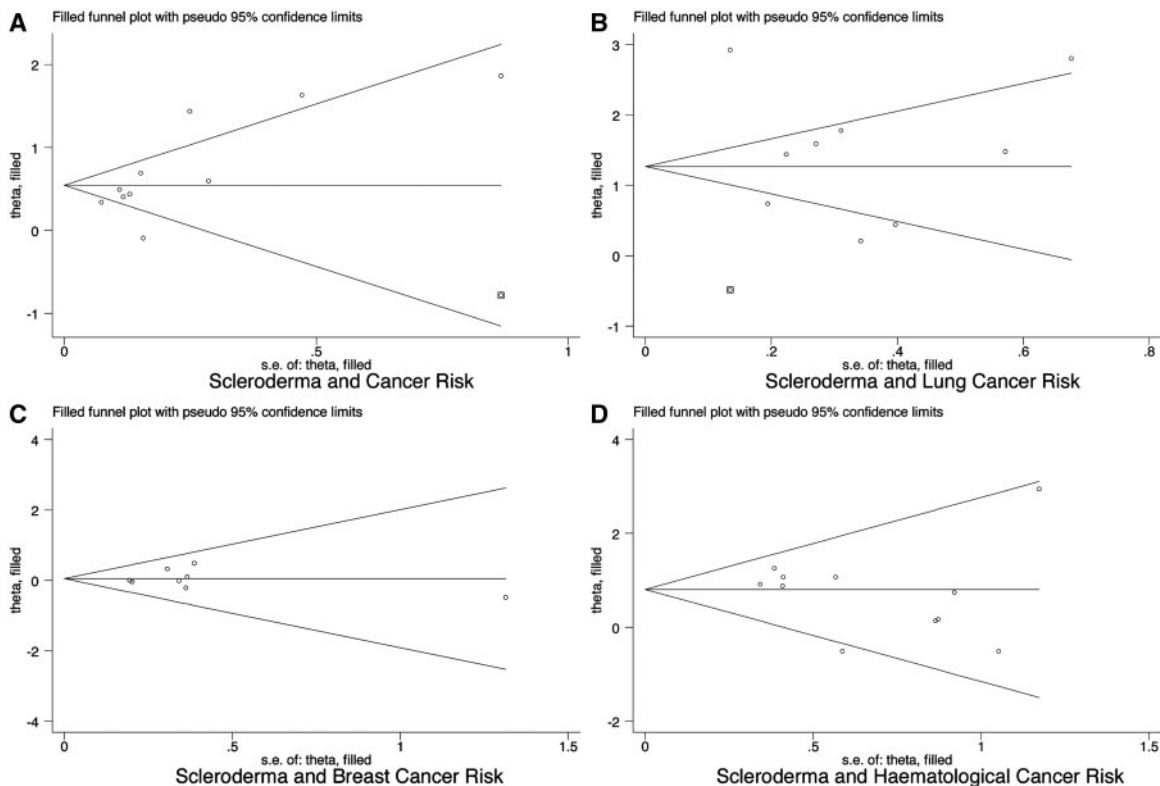
1.15; 95% CI 1.05, 1.27), with a strong association with haematological neoplasms (SIR 2.75; 95% CI 2.13, 3.49), mainly non-Hodgkin lymphoma (SIR 3.64; 95% CI 2.63, 4.93). Data also suggested an increased risk for lung (SIR 1.37; 95% CI 1.05, 1.76) and hepatobiliary (SIR 2.60; 95% CI 1.25, 4.78) cancers. In contrast, more recently, synthesis of data on breast, ovarian, endometrial [30] and prostate cancer [31] incidence among patients with SLE reported a significant decreased risk compared with the general population.

As to the mechanism underlying this association between scleroderma and higher cancer frequency, we suggest that DNA damage, induced by reactive oxygen species (ROS), both in mesenchymal and adjacent epithelial cells, is the primary cause of transformation [32–34]. A higher rate of chromosomal breakage has been reported in fibroblasts [33] and peripheral blood lymphocytes [35, 36]. Both fibroblasts and lymphocytes spontaneously release hydrogen peroxide, which diffuses through the membranes (D. Amico, S. Svegliati, M. Rovinelli, M. Serafini, G. D'Amico, T. Spadoni, L. De Gennaro, G. Moroncini, A. Gabrielli, manuscript in preparation) and may directly damage DNA. Lung and blood are the organs where these events triggered by fibroblasts can be amplified by activated mononuclear cells, which spend much of their time in these sites [37].

Mesenchymal cell, exposed to persistent ROS, undergo senescence, which leads to inhibition of replicative capacity and terminal differentiation (myofibroblasts and fibrosis) [38]. Epithelial cells adjacent to ROS-activated fibroblasts (in lung, for example) may succumb to apoptosis [39] or may require new phenotypes that selectively drive neoplastic progression. It is of interest that a DNA-damaging agent, such as bleomycin, initiates apoptosis of lung epithelial cells by ROS and simultaneously promotes local fibrosis [39].

The implications of this study are 2-fold. First, active surveillance of scleroderma patients for early detection of cancer is advisable and, with regard to the lung, specific guidelines would be welcomed to define modalities and timing of the screening with the benefit of a periodic CT scan of the lung, outweighing the risk posed by radiation. Secondly, alkylating agent should be used judiciously since they may predispose to cancer patients with an already fragile genome. CYC has been linked to increased risk of malignancy in patients with RA [40] and systemic vasculitis [41]. Unfortunately, the data retrieved by this study have not permitted this point to be addressed, which warrants further investigations.

> ### Rheumatology key messages
>
> - The present meta-analysis provides definite estimates on the association between scleroderma and malignancy.
> - The results indicated a strong association between scleroderma and lung and haematological cancers.

Supplementary data

Supplementary data are available at *Rheumatology* Online.

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