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## CONCISE REPORT

## Risk factors for lung cancer in patients with scleroderma: a nested case-control study

Eliza K Pontifex, Catherine L Hill, Peter Roberts-Thomson

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**Objectives:** To study potential risk factors for the development of lung cancer in patients with scleroderma and explore the chronological relationship between onset of scleroderma symptoms and subtypes of lung cancer.

**Method:** Linkage of two population-based registers to identify lung cancer cases and gender-matched controls with scleroderma, followed by retrospective case note review for clinical details.

**Results:** Patients with scleroderma who smoke are seven times more likely to develop lung cancer than non-smokers ( $p=0.008$ ). Smokers with scleroderma and cancer smoke more than smokers with scleroderma without cancer ( $p=0.019$ ). Pulmonary fibrosis and anti-topoisomerase antibody do not increase the risk of lung cancer. Peripheral lung tumours occur earlier after the onset of scleroderma symptoms than bronchogenic tumours ( $p=0.05$ ).

**Conclusions:** Smokers with scleroderma should be monitored for the presence of lung cancer and counselled to quit smoking. The earlier development of peripheral lung tumours is not consistent, with pulmonary fibrosis being an aetiological factor.

Most, but not all, population-based studies of cancer in scleroderma have shown an increased incidence of all cancers and, most consistently, an increased risk of lung cancer.<sup>1–4</sup> The relationship between these two diseases remains unclear. It has been suggested that the common link between lung cancer and scleroderma is pulmonary fibrosis; however, this has not been formally tested in a cohort study.<sup>5</sup>

## METHODS

## Scleroderma ascertainment

Patients with scleroderma were identified from the South Australian Scleroderma Registry (SASR), which has been described elsewhere.<sup>6</sup> The registry was established in 1993 and aims to identify all residents with scleroderma in South Australia (SA).

Patients were ascertained from hospital discharge indices, state immunodiagnostic laboratories (all positive centromeres and Scl-70 were pursued), referrals from SA rheumatologists and other specialist clinics. Scleroderma was validated according to the American Rheumatology Association criteria<sup>7</sup> by examining referring clinical letters, case notes and autopsy reviews. Patients were subdivided into three clinical variants—namely limited, diffuse or overlap scleroderma—according to the extent of skin involvement and other criteria according to LeRoy *et al.*<sup>8</sup> Patients with localised scleroderma were not included. Written consent was obtained from all patients before confidential enrolment, and the registry's use for analyses of this type had the approval of human ethical committees of all teaching hospitals in SA. Although complete ascertainment cannot be guaranteed, a high ascertainment rate in our population was inferred by the fact that scleroderma prevalence

in SA, a statistic derived from the SASR, was high when compared with other regional world studies.<sup>6</sup>

## Cancer ascertainment

There is compulsory notification of cancer in SA to the South Australian Cancer Registry (SACR)<sup>9</sup> from pathology laboratories, hospital medical record departments, radiotherapy departments and oncologists, with 95% completeness verified by multiple electronic searches of SA laboratory and hospital records each year. In addition, the International Agency for Research on Cancer checks the quality of the SACR data every 5 years.

Using Automatch software (Matchware Technologies, Kennebunk, Maine, USA), all subjects on the SASR were linked to the SACR to identify all cases of lung cancer among these patients prior to 1 January 2003. Case notes were then reviewed for confirmation of lung cancer histology, presence of pulmonary fibrosis and method of diagnosis, smoking history and year of onset of scleroderma symptoms including Raynaud's phenomenon. Gender-matched controls were selected using computer-generated random numbers from the remainder of the SASR and their case notes similarly reviewed. Odds ratios for risk factors for lung cancer in scleroderma were determined, and categorical variables were analysed using  $\chi^2$ , Fisher's exact and *t* tests.

## RESULTS

There were 632 patients on the SASR as of 1 January 2003 and 20 lung cancers were identified in 19 of them (table 1). One individual developed two histologically distinct tumours in different lobes. The average age at diagnosis of cancer was similar for all subtypes (squamous cell, mean 65.3 years; large cell, 64.3 years; adenocarcinoma, 60.7 years; small cell, 65.3 years; and bronchoalveolar cell (BAC), 72.5 years). Of those patients with lung cancer, 90% were smokers. Only two patients were non-smokers, both of whom developed BAC. There were 5 (20%) cases of PF in the patients with lung cancer (2 squamous cell, 1 BAC, 1 large cell and 1 small cell lung cancer).

Cigarette smoking was a risk factor for development of lung cancer (table 2), with smokers being seven times more likely to develop lung cancer than non-smokers. Having pulmonary fibrosis, diffuse disease or being anti-topoisomerase antibody positive did not increase the risk of lung cancer. Smokers with scleroderma and lung cancer were more likely to smoke larger quantities than controls with scleroderma who smoked. The number of pack years (1 pack year = 20 cigarettes per day for 1 year) smoked was known for 15 of the 18 (83%) cases of lung cancer in smokers, and in 18 of the 23 (78%) controls who smoked. The average number of pack years in the smokers who

**Abbreviations:** SASR, South Australian Scleroderma Registry; SACR, South Australian Cancer Registry

**Table 1** Characteristics of the patients with scleroderma and lung cancer

Lung cancer histology	Age at onset of scleroderma (years)	Age at diagnosis of cancer (years)	Interval (years)	Scleroderma subtype	Gender	Pulmonary fibrosis (method of diagnosis)	Smoking (pack years)
Squamous cell	58	59	>1	Unknown	M	Yes (CT)	100
Squamous cell	36	61	>25	L	M	Yes (CT)	30
Squamous cell	47	76	>29	L	F	no (CT)	50
Large cell	54	56	>2	L	M	Yes (biopsy)	40
Large cell	Unknown	72		Unknown	M	No (CT)	12 cig/day
Large cell*	60	65	>5	L	M	No (CT)	60
Adenocarcinoma*	60	65	>5	L	M	No (CT)	60
Adenocarcinoma	58	62	>4	L	F	No (CT)	58
Adenocarcinoma	28	46	>18	D	F	No (PFT)	20 cig/day
Adenocarcinoma	57	58	>1	O	F	No (CT)	25 cig/day
Adenocarcinoma	48	56	>8	L	F	No (CXR)	15
Adenocarcinoma	72	76	>4	O	M	No (CT)	50
Adenocarcinoma	29	62	>33	L	F	No (CT)	40
Small cell	51	57	>5	D	M	Yes (CT)	15
Small cell	26	65	>39	L	F	No (CT)	70
Small cell	50	72	>22	L	F	No (CXR)	40
Small cell	40	67	>27	L	M	No (CXR)	58
BAC	51	69	>18	L	F	Yes (CT)	0
BAC	60	76	>16	L	F	No (CT)	0
unspecified	62	81	>19	D	F	Unknown	14

BAC, bronchoalveolar carcinoma; CXR, chest x ray; D, diffuse; F, female; M, male; L, limited; O, overlap; PFT, pulmonary function test; pack years (1 pack year = 20 cigarettes per day for 1 year).

cig/day = number of cigarettes smoked per day, duration of smoking (years) unknown.

\*Patient with two histologically distinct lung tumours.

developed cancer (46.7 years) was significantly greater than in controls who smoked (29.6 years;  $p = 0.019$ ).

All lung cancers occurred after onset of scleroderma symptoms (fig 1). The median time to cancer after onset of scleroderma symptoms was 25 years (range 1–39 years) for the bronchogenic tumours (small and squamous cell) and 5 years (range 1–33 years) for the peripheral tumours (large cell, BAC and adenocarcinoma) ( $p = 0.05$ ). Only two of the seven bronchogenic tumours occurred early and both these patients had pulmonary fibrosis, whereas none of those with adenocarcinoma did.

## DISCUSSION

We have demonstrated a strong association between lung cancer and heavier smoking in patients with scleroderma, which is similar to that seen in the UK general population.<sup>10</sup> We found no association between lung cancer and pulmonary fibrosis, scleroderma subtype or anti-topoisomerase status. Furthermore, we have shown that peripheral lung tumours

occur earlier than bronchogenic tumours in the course of scleroderma.

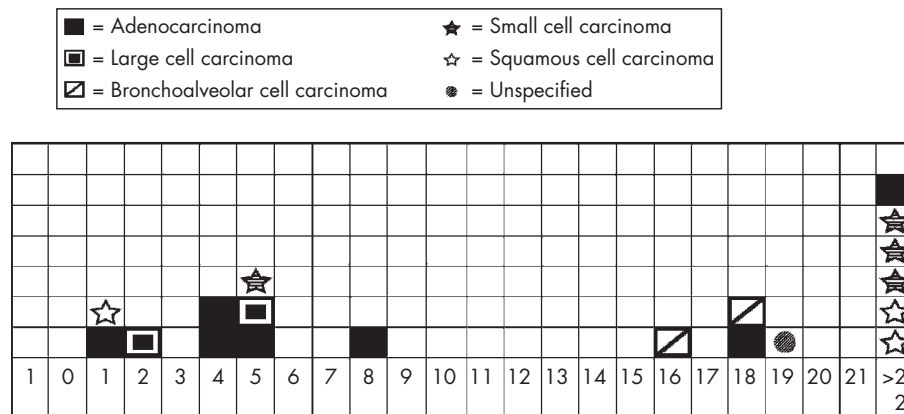
Three previous studies in the English literature have considered potential risk factors for lung cancer in scleroderma.<sup>11–13</sup> Similar but separate studies from Baltimore and Ontario that prospectively followed a total of 319 scleroderma outpatients found 10 patients who developed lung cancer, all of whom had evidence of pulmonary fibrosis and three of whom were smokers.<sup>11–12</sup> In a single-centre study from the Pittsburgh standard metropolitan statistical area,<sup>13</sup> four cases of lung cancer in 262 patients with scleroderma were identified. All had evidence of pulmonary fibrosis and one was a smoker. Conclusions regarding the lung cancer, smoking and pulmonary fibrosis relationship in scleroderma are difficult to draw from these studies owing to the lack of control groups and use of outpatient-based rather than population-based registers. The latter point is likely to lead to a higher proportion of patients with PF and smaller numbers of those with cancer. Patients on the SASR with diffuse scleroderma, the variant associated with pulmonary fibrosis, make up 22%. This is a low figure compared with many cohort studies, but reflects higher detection rates of limited and mild disease in our population.<sup>6</sup>

Although our pulmonary fibrosis ascertainment methods are similar to large cryptogenic fibrosing alveolitis cohorts<sup>14</sup> and the aforementioned scleroderma studies in which all patients with lung cancer had pulmonary fibrosis, the investigation used to demonstrate pulmonary fibrosis varies between patients in all these cohorts. A smaller prospective study would eliminate this variable, but lose the strength of complete cancer ascertainment. CT and biopsy results were available in 75% of our cancer cases, and although the prevalence of pulmonary fibrosis in our control group may be underestimated, this would not diminish, but would increase the significance of our findings. Data on immunosuppressant therapy in this cohort were incomplete and so not included, but this factor could potentially affect the incidence of cancer.

We have previously seen no difference in proportions of lung cancer subtypes in our cohort compared with the general SA population.<sup>2</sup> Peripheral lung cancers, however, occur earlier after the onset of scleroderma symptoms than traditionally smoking-related bronchogenic tumours. This contradicts the

**Table 2** Characteristics of lung cancer cases and gender-matched controls

	Cancer cases	Controls	
Number	20	41	
Male	9 (45%)	19 (46.3%)	
Mean age (years)	65	69	$p > 0.05$ , unpaired t test
Smokers	18 (90%)	23 (56%)	OR 7.04, $p = 0.008$ , $\chi^2$ square
Average pack years in smokers for whom value is known (table 1; years)	46.7	29.6	$p = 0.019$ , unpaired t test
Pulmonary fibrosis	5 (25%)	11 (27%)	OR 1.19, $p = 1$ , Fisher's
Diffuse	3 (15%)	7 (17%)	OR 0.86, $p = 1$ , Fisher's
scleroderma			
Anti-topoisomerase 0 (0%) antibody		6 (14.6%)	
Anti-centromere 3 (15%) antibody		17 (41.5%)	$p < 0.001$ , $\chi^2$ square



**Figure 1** Chronological relationship between onset of scleroderma symptoms and subtypes of lung cancer. 0, year of onset of scleroderma symptoms, subsequent number = years after onset of scleroderma that lung cancer was diagnosed.

hypothesis of scleroderma-induced pulmonary fibrosis leading to tumour development in the damaged lung as the time frame is inconsistent and none of the patients with adenocarcinoma had pulmonary fibrosis. A multitude of factors in a lung with scleroderma, including cytokines and disturbance of cellular immunity, may predispose an individual to peripheral tumours as well as pulmonary fibrosis, the former being a cause of death before the development of pulmonary fibrosis. Alternatively, the dominance of smoking as a risk factor in our study suggests that its effect may over-ride or synergise with that of scleroderma, making the smoking pattern, including year of cessation, important information to plot chronologically with diagnosis of lung cancer and of scleroderma symptoms onset. More detailed smoking histories are required and this information should be collected prospectively in scleroderma registries, followed by counselling to quit smoking. Different histological types of cancer may represent a heterogeneous end point and could also be a point for further study.

Using two population-based registries, we demonstrated a strong association between lung cancer and heavier smoking in patients with scleroderma. By contrast, we found no association with pulmonary fibrosis, scleroderma subtype and anti-topoisomerase status. Scleroderma registers should prospectively collect detailed smoking histories, and patients with scleroderma who smoke should be monitored for the presence of lung cancer, and strongly encouraged to quit.

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Competing interests: None.

The use of the SASR for studies such as this has the approval of ethics committees of all teaching hospitals in South Australia, and all patients with scleroderma are mailed a request to enrol on the confidential register.

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