EXTENDED REPORT

Risk of cancer in patients with scleroderma: a population based cohort study

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Background: Previous studies have suggested an increased risk of cancer among patients with scleroderma.

Objective: To study a population based cohort of patients with scleroderma in South Australia.

Methods: Subjects with scleroderma were identified from the South Australian Scleroderma Registry established in 1993. All subjects on the scleroderma registry were linked to the South Australian Cancer Registry to identify all cases of cancer until 31 December 2000. Standardised incidence ratios (SIRs) for cancer for subjects with scleroderma were determined using the age- and sex-specific rates for South Australia.

Results: In 441 patients with scleroderma, 90 cases of cancer were identified, 47 of which developed after inclusion on the scleroderma registry. The SIRs for all cancers among these patients were significantly increased (SIR=1.99; 95% confidence interval (95% CI) 1.46 to 2.65) compared with the cancer incidence rates for South Australia. The SIRs for lung cancer (SIR=5.9; 95% CI 3.05 to 10.31) were also significantly increased. The SIRs for all cancers among the subgroups with diffuse scleroderma (SIR=2.73; 95% CI 1.31 to 5.02) and limited scleroderma (SIR=1.85; 95% CI 1.23 to 2.68) were significantly increased.

Conclusions: This population based cohort study provides evidence that scleroderma is associated with cancer, and in particular, lung cancer. In addition, both diffuse and limited forms of scleroderma are associated with a similarly increased risk of cancer.

Previous studies have noted an increased risk of cancer among patients with scleroderma (systemic sclerosis).^{1–4} The most common cancers in these studies appeared to be lung and breast cancers.^{3,5} By comparison, the most recent study using data from the Detroit Scleroderma Registry found no increased risk of cancer among those with scleroderma.⁶ Our study using data from the South Australian Scleroderma Registry and the South Australian Cancer Registry is designed to estimate the risks of cancer in a population based cohort of patients with scleroderma.

METHODS

Scleroderma ascertainment

Subjects with scleroderma were identified from the South Australian Scleroderma Registry, which has been described in detail elsewhere.⁷ Briefly, the registry was established in 1993 with the aim of identifying all known patients with scleroderma resident in South Australia. Patients were ascertained from the following sources:

- Hospital discharge indices of the major teaching hospital (these indices were established between 1983 and 1987) and corresponding indices for country hospital discharges
- State immunodiagnostic laboratories (all cases of positive centromere and Scl-70 were pursued)
- Patients of all rheumatologists practising in South Australia
- Death records of the South Australian State Births, Deaths and Marriages Registry (BDM)
- Patients self referred or referred by vascular surgeons or dermatologists
- Nailfold capillaroscopy clinic.

The creation of the register for analyses of this type has the approval of ethics committees of all teaching hospitals in South Australia, and all patients identified with scleroderma

have been mailed with a request to enrol on the confidential register. Validation of scleroderma in each patient, according to the American Rheumatology Association criteria, was made through an examination of referring clinical letters, case notes or necropsy review, with additional clinical, serological, and pathology information obtained from the case notes.⁸ In addition, patients were also included on the register if they had clinical evidence of sclerodactyly together with at least two of Raynaud's phenomenon, oesophageal dysfunction, calcinosis, telangiectasia, nailfold capillary abnormalities, or antinuclear antibodies, in order to include all subsets with calcinosis, Raynaud's disease, oesophageal motility disorders, sclerodactyly, telangiectasia (CREST) syndrome as discussed by Englert *et al.*⁹ Patients with localised scleroderma (such as morphoea) are not included on the register.

Patients were subdivided into three clinical variants—namely, limited (includes the CREST variant) scleroderma, diffuse scleroderma, and overlap scleroderma, according to the extent of skin involvement and other criteria as presented by LeRoy and colleagues.¹⁰ Ascertainment of patient deaths was made by (a) confirmation of death through the State BDM Register; (b) active follow up and personal communication with a relative of the deceased; (c) hospital case notes; and (d) necropsy results.

Cancer ascertainment

There is compulsory notification of cancer in South Australia to the South Australian Cancer Registry,¹¹ from pathology laboratories, medical record departments of hospitals, radiotherapy departments, and oncologists. The registrar of births, deaths, and marriages also provides details of deaths affecting all people notified to the cancer registry, irrespective of cause of death. Non-melanoma skin cancers are not included on the registry. Cancer cases on the cancer registry were checked for completeness by multiple electronic searches each year of records of all South Australian pathology and haematology

Table 1 Characteristics of the patients with scleroderma

	Men	Women
Number	78	363
Scleroderma type		
Diffuse	23	65
Limited	38	228
Other*	17	70
Age at entry (mean (SD) [range])	58.7 (14.4) [18–86]	56.4 (15.5) [15–87]
Years of follow up (mean (SD))	5.5 (3.1)	6.1 (2.8)
Total cancer cases		
Before registry inclusion	8	35
After registry inclusion	16	31

*"Other" includes subjects with scleroderma overlap syndrome and scleroderma of unknown type.

Table 2 Standardised incidence ratios (SIRs) and 95% confidence intervals (CI) of cancer

Type (ICD-9 code)	Men		Women		Total	
	Obs	SIR (95% CI)	Obs	SIR (95% CI)	Obs	SIR (95% CI)
All cancer sites (140–208)	16	2.79 (1.59 to 4.53)	31	1.73 (1.18 to 2.46)	47	1.99 (1.46 to 2.65)
Lung (162)	8	9.32 (4.02 to 18.37)	4	3.41 (0.93 to 8.72)	12	5.9 (3.05 to 10.31)
Breast (174)			8	1.62 (0.7 to 3.19)		
Prostate (185)	3	2.41 (0.5 to 7.03)				
Bladder (188)	1	2.71 (0.08 to 15.07)	2	3.93 (0.47 to 14.19)	3	3.42 (0.71 to 9.99)
Haematological (200–208)	0	0.00 (0.00 to 7.98)	2	1.56 (0.19 to 5.64)	2	1.15 (0.14 to 4.14)
Gastrointestinal (150–154)	0	0.00 (0.00 to 3.49)	4	1.22 (0.33 to 3.13)	4	0.92 (0.25 to 2.36)
Remainder	4	2.29 (0.63 to 5.87)	11	1.86 (0.93 to 3.33)	15	1.96 (1.10 to 3.23)

laboratories and public and private hospitals. In addition, the International Agency for Research on Cancer also checked the quality of the South Australian Registry data every five years. Automatch software (Matchware Technologies, Inc) was used to link all subjects on the scleroderma registry with the South Australian Cancer Registry to identify all cases of cancer among these subjects before 1 January 2001. Analyses were undertaken at the cancer registry such that the release of identified data on cancer cases was not required.

Analysis

A historic cohort analysis was undertaken, using STATA 6.0 software (STATA Corporation, College Station, Texas 1999). Patients with scleroderma were followed up from their date of entry onto the scleroderma registry until either their death or 31 December 2000, whichever came first. Each month of follow up was classified by calendar year and by sex of patients and age at that time.

The number of cancers expected in this cohort was calculated by applying the cancer incidence rates for South Australia, classified by calendar year, age, and sex, to these months of follow up. Indirectly standardised incidence ratios (SIRs) were obtained by dividing the numbers of cancers observed with the numbers expected, and deriving 95% confidence intervals (95% CI) of these ratios from the Poisson distribution.

Analyses were undertaken for all cancer sites collectively and for individual sites (using ICD-9 codes) where numbers were sufficient or previous published evidence had suggested an association with scleroderma. Analyses were performed to assess cancer risk in all types of scleroderma collectively, and in three subgroups classified as diffuse, limited, and "other" (included overlap scleroderma and those subjects who were not otherwise classified).

Cancers which were diagnosed before inclusion of the patient on the scleroderma register were identified and classified according to cancer site (using ICD-9 codes) and by number of years before inclusion on the scleroderma register.

RESULTS

Four hundred and forty one subjects (78 (17.7%) men, 363 (82.3%) women) were included in the study. The mean age at entry was 58.7 years for men and 56.4 years for women (table 1). A total of 90 cancers were identified in 84 subjects, of which 47 developed after entry to the scleroderma registry. Thus, 19.0% were diagnosed with cancer either before or after entry. There was no sex difference in those patients with cancer diagnosed before or after entry to the scleroderma registry (table 1; χ^2 $p=0.10$). There were also no age differences between those who developed cancer before inclusion on the scleroderma registry (60.7 years) compared with after inclusion (62.3 years, $p=0.51$).

For all cancer types, there was a twofold increase in risk of malignancy after entry onto the scleroderma registry (table 2). The SIR for men (2.79; 95% CI 1.59 to 4.53) was higher than for women (1.73; 95% CI 1.18 to 2.46). The greatest significantly increased relative risk was for lung cancer. However, although breast, bladder, and prostate cancers were also associated with increased relative risk, these did not reach statistical significance owing to the small numbers seen. The most commonly seen cancers after inclusion on the registry were lung (12) and breast (8) cancer and malignant melanoma (5). Other cancers seen were prostate (3), bladder (3), rectal (2), haematological (2), and one each of lip, mouth, oesophageal, stomach, liver, pancreas, ovary, kidney, and thyroid cancer and three of unspecified origin.

Differences in cancer risks were found between the scleroderma types, such that those with diffuse scleroderma had the highest relative risk of cancer (SIR=2.73; 95% CI 1.31 to 5.02) (table 3). In contrast, subjects with limited or other forms of scleroderma had similar increased risks (SIR=1.85, 95% CI 1.23 to 2.68 and SIR=1.85, 95% CI 0.85 to 3.52), respectively. Again, men had the marginally higher relative risk in all categories (table 3).

Forty three cancers were diagnosed before entry to the scleroderma registry. These included breast (10), lung (6), cervix (5), colorectal (4), and lip (2) cancers, and haematological (5) malignancies and malignant melanoma (4); and one each of

Table 3 Standardised incidence ratios (SIRs) and 95% confidence intervals (CI) of all cancers by scleroderma type

Type of scleroderma	Men		Women		Total	
	Obs	SIR (95% CI)	Obs	SIR (95% CI)	Obs	SIR (95% CI)
Diffuse scleroderma	4	3.53 (0.96 to 9.05)	6	2.37 (0.87 to 5.16)	10	2.73 (1.31 to 5.02)
Limited scleroderma	8	2.67 (1.15 to 5.26)	20	1.65 (1.01 to 2.55)	28	1.85 (1.23 to 2.68)
Other types	4	2.49 (0.68 to 6.36)	5	1.54 (0.50 to 3.59)	9	1.85 (0.85 to 3.52)

prostate, bladder, kidney, thyroid, mouth, uterus, and connective tissue cancers.

Of the 18 lung cancers identified both before and after entry to the scleroderma registry, 8 (44%) were adenocarcinomas, 3 (17%) were squamous cell cancers, 3 (17%) were large cell cancers, 3 (17%) were small cell carcinomas and 1 (6%) adenosquamous cell cancer. In the general South Australian population, 30% of the lung cancers are adenocarcinomas, compared with 44% of the lung cancers in the patients with scleroderma (Fisher's exact test, $p=0.20$).

We found no association between autoantibody status and risk of cancer in the 344 patients for whom we had autoantibody status. Anticentromere autoantibody was present in 15/38 (39%) patients with cancer, compared with 149/306 (49%) patients without cancer (χ^2 , $p=0.283$). Anti-Scl-70 autoantibody was present in 5/38 (13%) patients with cancer, compared with 35/306 (11%) patients without cancer (χ^2 , $p=0.761$).

DISCUSSION

We have shown that scleroderma is associated with an increased risk of malignancy. In addition, we have shown that all subtypes of scleroderma are associated with an increased risk of malignancy. There was a statistically significant increased risk of lung cancer. Our study, using data from two disease specific registries, has the advantage of being population based.

Previous studies have shown an increased risk of malignancy in scleroderma, but the patients with scleroderma have generally been drawn from outpatient clinics, with attendant selection and referral biases.^{1,2} A Swedish national population based study reported by Rosenthal *et al* also found that systemic sclerosis, including both the diffuse and limited variants, but not localised scleroderma, was associated with an increased risk of malignancy (SIR=1.5; 95% CI 1.2 to 1.9).³ The specific cancer sites associated with increased risk were lung (SIR=4.9; 95% CI 2.8 to 8.1), non-melanoma skin cancers (4.2; 95% CI 1.4 to 9.8), primary liver cancer (2.3; 95% CI 0.1 to 7.6), and haematopoietic cancers (2.3; 95% CI 0.9 to 4.8). There was no increased risk of breast cancer. However, as the patients with scleroderma were identified from hospital discharge diagnoses, some patients are likely to have been excluded because they had never been admitted to hospital. Most recently, data on malignancy in the Detroit Scleroderma Registry has been published in abstract form.⁶ This study showed no increased risk in cancer. Indeed, there was a non-significant reduction in risk of lung and breast cancer.⁶ Interestingly, this scleroderma registry corresponds most closely to ours in its comprehensive means of ascertaining cases of scleroderma.¹² A limitation of the current study is that we used inclusion on the scleroderma registry, rather than onset of scleroderma, as the starting point of the study. However, documenting the onset of scleroderma itself is problematic as patients often described symptoms long before a doctor diagnosed scleroderma. We have previously shown that Raynaud's phenomenon developed a mean (SD) of 9.2 (1.3) years before diagnosis of limited scleroderma and 1.1 (10.6) years before diffuse scleroderma.¹³ Therefore, we used inclusion on the

scleroderma registry as a similar, reliable date for all subjects. In many cases, inclusion on the registry would have been coincident with the doctor's diagnosis of scleroderma.

Previous case reports have noted the development of scleroderma synchronously with the diagnosis of breast cancer,¹⁴⁻¹⁶ with reports of worsening of scleroderma with cancer recurrence² and improvement with cancer treatment.¹⁵ These suggest that scleroderma may be a paraneoplastic phenomenon. We found no clear association between diagnosis of cancer and entry to the scleroderma registry. However, we used entry to the scleroderma registry as the starting point of this study, which in many subjects would not be coincident with onset of symptoms. Interestingly, most breast cancers were diagnosed before entry to the scleroderma registry and after entry for lung cancers. This is in keeping with the possibility that scleroderma may be a paraneoplastic phenomenon in breast cancer. In contrast, if lung cancer arises in damaged fibrotic scleroderma lung, it would develop later in the course of scleroderma.¹⁷ In only one patient did we observe the coincident onset of both breast carcinoma and scleroderma. This patient had the diffuse variant of scleroderma complicated with an acute renal crisis. She survived for only 12 months after her diagnosis.

Why should our patients with scleroderma have an enhanced cancer incidence? Previous observations have suggested that lung cancer in scleroderma may arise in previously damaged or fibrotic lung and is frequently of the bronchoalveolar or adeno type rather than the more common squamous cell type.⁵ Such an association is further supported by the observation that idiopathic lung fibrosis also appears to be linked to lung cancer.¹⁸ In the current study, we showed that adenocarcinoma was the commonest lung cancer observed. Bronchoalveolar carcinomas are not coded separately from adenocarcinoma in the South Australian Cancer Registry. Therefore, we were not able to determine if this rare form of adenocarcinoma was overrepresented in our subjects.

However, as we have shown in this study other common cancers also are seen more frequently in scleroderma. Is this because of exposure to environmental agents—for example, silicates and hydrocarbons, which may be common to both disorders, or is it due to other factors? It is not possible to come to any firm conclusion, although there is tantalising information which suggests that patients with scleroderma have evidence of prior genetic damage. This damage includes increased chromosomal breakage rates, deletions, and acentric fragments¹⁹; clastogenic activity in sera and cell extracts detected in patients with scleroderma²⁰; increased chromosomal breakage rate in first degree relations of patients with scleroderma²¹; and, finally, increased variable number random repeats in patients with scleroderma.²² Perhaps patients with scleroderma have a more fragile genome, and prior genetic damage may predispose to both scleroderma and cancer. In addition, it is possible that the use of immunosuppressive agents in patients with scleroderma might have predisposed them to development of cancer. Unfortunately, we cannot comment on the impact of immunosuppressive treatment of scleroderma on the risk of malignancy in this study because the records giving this information are incomplete. However, this is unlikely to have influenced the overall result as most

patients had limited scleroderma, which was not treated with immunosuppressive agents.

Of the connective tissue disorders, dermatomyositis has been most closely linked to malignancy. A recent study of dermatomyositis using population data from three Nordic countries showed a threefold increased risk of malignancy, with a 1.2-fold increased risk for polymyositis.²³ The increased risk shown in this study for scleroderma approaches that for dermatomyositis and is larger than for polymyositis. This suggests that clinicians should be as aware of the enhanced risk of malignancy, and in particular, lung cancer, in patients with scleroderma, as they are in patients with dermatomyositis. However, our study does not examine which patients with scleroderma are at highest risk of cancer or what are the most appropriate screening measures for cancer in scleroderma. We could not show any association with autoantibody status, but this issue requires further investigation. Although "atypical" cases of scleroderma are included on the South Australian Scleroderma Registry, it is possible that malignancy related scleroderma may have atypical features, which would lead to underregistration.

In conclusion, all disease variants (diffuse, limited, and overlap) of scleroderma are associated with an increased risk of malignancy, with the greatest increased risk being for lung cancer. This is the first population based study of scleroderma and malignancy which deals with the issue of the risks in both diffuse and limited scleroderma.

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