Risk of cancer in patients with scleroderma

J E Pearson, A J Silman

Risk of cancer may be slightly increased, but extra screening is not necessary

The first report linking cancer with scleroderma (Scl) was 50 years ago when a case of alveolar cell carcinoma was described.¹ Since then there have been several further case reports and series linking Scl with cancer at various sites.² The sites of cancer most frequently reported are the lung^{3,4} and breast⁵ (perhaps reflecting their prevalence in the general population), but cancers at other sites have also been reported.^{2,6} In this issue of the *Annals* there is a report of an Australian population study on Scl and cancer.⁷ The authors showed a doubling in the risk of all cancers over an average six year follow up period, with the lung being the site at greatest risk. It is thus timely to consider all the evidence suggesting this association is real and then explore some of the possible underlying explanations.

IS THERE AN ASSOCIATION?

It is necessary to compare the incidence of cancer occurring in patients with Scl with that occurring in an appropriately matched general population sample, typically derived from regional or national cancer registers. Studies, such as the current report from Australia, are

enhanced when they attempt to include all cases arising in a population to minimise the likelihood of a severity bias. Table 1 summarises the results of a number of such main population studies. In these studies the risk of cancer is expressed as standardised incidence ratios (SIRs) (equivalent to relative risks, which are calculated by dividing the number of observed cases of cancer in patients with Scl by the number of expected cases, allowing for the age and sex of the patients, in the general population occurring during the same period of follow up). Though the early studies reported no association,^{8,15} most of the more recent studies have found an increased risk (table 1), typically around twofold. However, a recent large study from the USA,¹⁴ although in abstract form only, reported no increased risk and this lack of consistency is a cause for caution. The lung is the site with the reported greatest risk with relative risks of up to 16.5.³ Consistent with the case reports there is also a frequently reported trend for an increase in breast cancer, which is not always statistically significant.⁷

There are few studies that have looked at the role of potential risk factors in Scl and cancer. A recent Japanese study¹³ suggested that anticentromere antibody positivity (linked with limited Scl) is a significant risk factor. Consistent with these observations is that the presence of antitopoisomerase I has been associated with cancer in patients with Scl only.¹⁶ In support of this the latest Australian study found that patients with diffuse involvement were at greater risk than those with limited cutaneous disease. This difference was modest and perhaps explains why others found no significant difference between disease subsets.⁹ Older age (>50 years) at diagnosis of Scl, not surprisingly, was a significant risk factor, although interestingly neither the sex of the patient nor smoking differed significantly.¹⁰

POSSIBLE EXPLANATIONS

If there is an increased association between Scl and cancer it is useful to consider the possible explanations. In brief, one disease may increase the risk of the other either as a direct complication or as a result of the treatment given. Alternatively, the two disorders may share common risk factors.

Scl as a risk factor for malignancy

Diseases such as Scl which are associated with lung damage have been linked to an increased risk of cancer compared with the general population.¹⁷ Pulmonary fibrosis resulting from non-Scl causes, such as silicosis, is a well recognised risk factor for malignancy.¹⁸ Thus it has been suggested that Scl related pulmonary fibrosis is a risk factor for subsequent lung cancer. In support of this a study from the USA showed that pulmonary fibrosis was present in 62% of the

Table 1 Epidemiological studies on the risk of cancer in Scl

Ref	Year	Country	Mean follow up years	No of cases of Scl	All cancers, SIR (95% CI)			Sites of risk
					All	Male	Female	
8	1982	Australia	3.3	27	6.45 (0.78 to 23.29)	8.33 (0.21 to 46.28)	5.26 (0.13 to 29.22)	No significant risk found
9	1985	USA	4.3	262	1.81*	2.46*	1.58*	Lung
10	1993	Canada	4.6	248	7.90*			Lung
								Breast
11†	1993	Sweden	5.1	233	2.4 (1.5 to 3.6)	1.8*	2.9*	Lung
								Non-Hodgkin's lymphoma
12†	1995	Sweden		917	1.5 (1.2 to 1.9)			Lung
								Non-melanoma skin cancers
								Primary liver cancer
								Increase in haematopoietic cancers
13	2000	Japan	6	43	5.1 (1.7 to 10.8)			
14	2000	USA		490	0.75 (0.45 to 1.18)	1.14 (0.37 to 2.66)	0.77 (0.42 to 1.29)	Lung
								Breast
7	2003	South Australia	5.5 (male) 6.1 (female)	441	1.99 (1.46 to 2.65) Diffuse Scl 2.73 (1.31 to 5.02) Limited Scl 1.85 (1.23 to 2.68)			Lung

*CIs not presented; †there is some overlap between these two studies.

patients with Scl who developed lung cancer compared with 28% of those who remained cancer free.⁹ Others have also reported that lung cancer was associated with Scl related pulmonary fibrosis.¹⁰ However, a retrospective study from France of 123 cases of lung cancer in Scl subjects identified no clinical, immunological, or histological, including pulmonary fibrosis, predictors.¹⁹

"Most studies, but not all, show increased risk of lung cancer in Scl"

An alternative hypothesis is that immunosuppressive drugs used to treat Scl may predispose patients to cancer. There have been no studies to assess this, but there is evidence that immunosuppression, for example in those who have had a kidney transplant, may increase the risk of subsequent malignancy.²⁰ However, although sites recorded include the lung and breast, they are not the sites at greatest risk.²¹

Malignancy as a risk factor for Scl

Although there is no evidence that cancer itself increases the risk of Scl, there is reported evidence that some of the treatments used in cancer induce Scl or Scl-like reactions. Thus there have been reports of Scl-like skin after radiation therapy for breast cancer.²²⁻²³ In addition, there have been case reports of an Scl-like illness after the use of anticancer drugs, including docetaxel,²⁴ paclitaxel,²⁵ a combination of uracil and tegafur,²⁶ bleomycin²⁷ and carboplatin chemotherapy.²⁸ A recent case report has reported the development of Raynaud's phenomenon in a child after chemotherapy.²⁹ By contrast there have also been reports of Scl remission during chemotherapy.³⁰

"Some cancer treatments induce scleroderma"

An interesting hypothesis relates to the possibility that breast malignancy leads to a silicone implant, the latter causing an increased risk of Scl. Despite several case reports describing a link between silicone implants and Scl³¹⁻³² several large epidemiological studies have not shown any association between implants and Scl.³³⁻³⁴

Shared risk factors

The other explanation is that there are shared risk factors, either genetic or environmental, for the two diseases. There is an increased risk of cancer in first degree relatives of patients with Scl, suggesting that there may be a common genetic/environmental link.³⁵ Other indirect evidence suggesting a shared environmental link comes from a prospective

American study which found a high incidence of tongue and oral malignancies, raising the possibility that an ingested carcinogenic compound may possibly initiate Scl.³⁶ Smoking is not considered a risk factor for Scl, which would have been one obvious explanation for the increased number of lung cancers. By contrast, coal miners have an increased risk of both disorders, perhaps mediated through pulmonary fibrosis as suggested above.

Other environmental agents such as exposure to organic solvents has been linked independently to both cancer³⁷ and Scl³⁸ and may be of relevance, but there are no data on this. Scl has been associated with chromosomal damage/breakage,³⁹ and this may also possibly be linked to a role in cancer development.

SUMMARY

The data suggesting a link between Scl and cancer are not overwhelming, but there is probably a modest increase in risk, particularly of lung cancer, in patients with diffuse disease and associated pulmonary fibrosis. By contrast, there does not seem to be a convincing and biologically coherent case for a non-specific increased risk of malignancy in patients with Scl. Given that the lung status of patients with diffuse disease is already regularly monitored, these conclusions do not suggest any additional screening is necessary.

Ann Rheum Dis 2003;**62**:697-699

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