A Cohort Study of Cancer Incidence in Systemic Sclerosis

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ABSTRACT. ***Objective.*** To describe the incidence of cancer in a large cohort of patients with systemic sclerosis (SSc) and compare it to the Surveillance Epidemiology and End Results (SEER) cancer registries.

Methods. Cancer risk in a large cohort of patients with SSc followed at our institution was assessed. A total of 769 patients with SSc who were followed between 1987 and 2002 were screened for the development of cancer. Standardized incidence ratios (SIR) for malignancies identified after diagnosis of SSc were calculated using the SEER cancer registries and stratified by sex.

Results. Ninety malignancies were diagnosed in 769 patients followed at our institution between 1987 and 2002. Sixty-two malignancies were diagnosed after diagnosis of SSc in a total of 3775 patient years of followup. Twenty-eight malignancies were diagnosed prior to diagnosis of SSc. The SIR for all cancers diagnosed after diagnosis of SSc was 1.55 (1.16-1.93). The SIR for esophageal cancer was 15.9 (4.2-27.6) while that of oropharyngeal cancer was 9.63 (2.97-16.29).

Conclusion. We identified an overall increase in the incidence of cancer in a cohort of patients with SSc compared to the general population, with statistically significant differences in the incidence of esophageal and oropharyngeal cancers. (First Release April 15 2006; J Rheumatol 2006;33:1113–6)

Key Indexing Terms:
SYSTEMIC SCLEROSIS SCLERODERMA MALIGNANCY
CANCER INCIDENCE TISSUE FIBROSIS

Systemic sclerosis (SSc) is a disease characterized by excessive collagen deposition in the skin and internal organs, alterations of the microvasculature, and humoral and cellular abnormalities[1]. The association between SSc and malignancy has been the focus of numerous studies. Two early studies with large cohorts of patients with SSc failed to show an association between SSc and neoplasia[2,3]. A subsequent epidemiological study with a cohort of 2,141 patients with SSc showed that the relative frequency of various types of malignancies in SSc was no different than that of the general population[4]. Several large epidemiological studies reevaluated this association more recently. Two studies showed an increased incidence of lung carcinoma among patients with SSc and, specifically, in patients who had long standing pulmonary fibrosis[5,6]. Subsequent epidemiological studies confirmed the increased incidence of lung carcinoma and also described higher incidence of non-melanoma skin cancer, breast cancer, and lymphoproliferative malignancies in SSc[7,8]. Two population based cohort studies, one in Australia and the other in Detroit, showed contradictory results[9,10]. The study in Australia suggested an increased risk of malignancy in patients with SSc and more specifically lung cancer. In contrast the Detroit study showed no increase in the risk of malignancy except for liver cancer.

We describe the incidence of cancer in a large population of patients with SSc followed at our institution over the past 16 years.

MATERIALS AND METHODS

Study patients. Following institutional review board approval, we evaluated the incidence of malignancy in 769 patients with SSc diagnosed with either diffuse or limited SSc. Our cohort was prospectively followed between 1987 and 2002 for the development of cancer at the Scleroderma Center of our institution. All patients fulfilled the American College of Rheumatology criteria for classification of SSc[11]. Three hundred and ninety-two (50.9%) patients had diffuse cutaneous SSc and 377 (49.1%) had limited SSc. Patients with mixed connective tissue disease, overlap syndrome, localized forms of scleroderma, and all forms of fasciitis were excluded from the study.

Data collection. Each consecutive patient was questioned in detail for the occurrence of cancer at the initial visit as well as at each followup visit (every 3 to 6 months). Following a report of the occurrence of a malignancy by the patient, the diagnosis was confirmed through a comprehensive review of medical records, communications with referring physicians and with physicians who made the diagnosis and/or treated the cancer, and review of pathology reports. Demographic and clinical data for this population were recorded and certain risk factors for the development of cancer were identified. The observation interval was defined by the entry date, which was the first recorded visit to the Scleroderma Center and the exit date, the last recorded visit to the Center, and the patient-year of followup was calculated by subtracting these 2 dates. To compare the demographic characteristics of the SSc patients with and without cancer, 150 patients were randomly selected from the SSc population who did not develop cancer.

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Statistical analysis. Quantitative data are presented as mean with standard deviation, while qualitative data are presented as a percentage of the total. The expected numbers of cancer in the study population were calculated by multiplying the number of person-years at risk by an age adjusted population during the same calendar years from the Surveillance Epidemiology and End Results Program (SEER) cancer registries[12]. Local registries were not used to analyze data because the patient population we studied is not exclusively from the surrounding demographic region, and the national SEER cancer registries were considered a better approximation of our study population. The annual incidence rate of each individual cancer was multiplied by the number of person-years of followup of the total SSc population to yield the expected cancer rates for the population studied. A standardized incidence ratio (SIR) was calculated from the ratio of observed to expected cases and a 95% confidence interval (CI) is given as described[13] for Poisson's parameters. To calculate the SIR it is necessary to include the exact length of followup for the cohort (patient-years of followup); therefore, only cases of cancer that developed after the diagnosis of SSc and only the first diagnosis of each specific cancer in each specific patient was used for analysis of cancer rates. To compare demographic characteristics of SSc patients with cancer to SSc patients without cancer, we used both an unpaired t test and Fisher's exact test.

RESULTS

The study population comprised 769 patients diagnosed with either limited or diffuse cutaneous SSc and followed at the Scleroderma Center of our institution over the past 16 years. Each patient was questioned in detail for the occurrence of any type of malignancy at the initial visit as well as at each followup visit. The average length of followup was 4.9 ± 0.7 years, with a total followup of 3775 patient-years. From this population 77 patients (10.01%) were diagnosed with a malignancy either before or after diagnosis of SSc. A total of 90 neoplasms were diagnosed: 67 patients with a single neoplasm, 8 patients with 2 neoplasms, 1 patient with 3, and 1 patient with 4. Of the 90 malignancies, 28 occurred before and 62 occurred after the diagnosis of SSc. Of the 77 patients diagnosed with cancer, 32 (41.5%) had limited SSc and 45 (58.5%) had diffuse SSc. Mean age at cancer diagnosis was 53.1 ± 2.54 years. Sixty patients (77.9%) were women and 65 (84%) were Caucasian. Treatment with D-penicillamine was utilized in 44% of cases, and exposure to tobacco was identified in 40.2% of cases. A family history of cancer was recorded in 16.8% of cases (Table 1). When comparing SSc cancer patients to non-cancer patients there was a statistically significant difference in the age at SSc diagnosis between the 2 groups: SSc cancer patients were diagnosed with SSc about 5 years later than non-cancer SSc patients. Statistically significant differences among the 2 populations were also seen in the number of patients who used tobacco or who had a family history of cancer, with SSc cancer patients having a statistically significantly higher rate in both instances (Table 1).

The most prevalent cancers diagnosed before or after diagnosis of SSc were breast (25), lung (10), oropharynx (12), esophagus (7), and non-Hodgkin's lymphoma (7) (Table 2). A sub-analysis of the lung cancers diagnosed post-SSc diagnosis showed that 77% of these patients had long-standing SSc-related interstitial lung disease before they developed lung cancer. Another sub-analysis showed that 57% of patients who had developed breast cancer prior to SSc diagnosis had received radiation therapy as a therapeutic modality for their breast neoplasm.

The most commonly seen cancer after diagnosis of SSc in

Table 1. Demographics of patients with systemic sclerosis (SSc) and cancer compared to demographics of a randomly selected group of patients with SSc without cancer. Values are expressed as a percentage (number) unless otherwise indicated.

Clinical Feature	SSc and Cancer, (n = 77)	SSc with No Cancer (n = 150)	p
Age at SSc diagnosis, yrs, mean ± SD	50.1 ± 3.39	44.3 ± 2.4	0.01
Female	78 (60)	83.3 (125)	
Race			
Caucasian	84.4 (65)	84 (126)	
African American	11.6 (9)	12.6 (19)	
Oriental	2.6 (2)	0 (0)	
Hispanic	1.3 (1)	3.4 (5)	
Age at cancer diagnosis, yrs, mean ± SD	53.1 ± 2.54	NA	
Clinical subset of SSc			
Diffuse	58.4 (45)	48.6 (73)	
Limited	41.6 (32)	51.4 (77)	
Followup, yrs	6.86 ± 1.5	5.9 ± 0.9	
Radiation therapy	12.9 (10)	0	
Cytoxan	6.4 (5)	8 (12)	
D-penicillamine	44.1 (34)	40 (60)	
Methotrexate	6.4 (5)	6 (9)	
Tobacco	40.2 (31)	24 (36)	0.01
Alcohol	14.2 (11)	18 (27)	
Family history of cancer	16.8 (13)	6.6 (10)	0.02

NA: Not applicable.

Table 2. Type of cancer diagnosed in patients with SSc before or after diagnosis of SSc.

Carcinoma Site	Pre-SSc Diagnosis	Post-SSc Diagnosis	Total
Breast	14	11	25
Oropharyngeal	2	10	12
Lung	1	9	10
Non-Hodgkin's lymphoma	3	4	7
Esophageal	0	7	7
Colon	2	3	5
Cervical	0	4	4
Ovarian	1	3	4
Hodgkin's lymphoma	2	1	3
B cell lymphoma	2	1	3
Thyroid	0	2	2
Squamous cell (unknown primary)	0	1	1
Multiple myeloma	0	1	1
Bladder	0	1	1
Myelodysplasia	0	1	1
Vulva	0	1	1
Fallopian tubes	0	1	1
Neuroendocrine (unknown primary)	0	1	1
Parotid gland	1	0	1

our cohort of patients was breast cancer (11) although there was no increased relative risk. Other commonly seen cancers diagnosed after study entry included oropharyngeal (10), lung (9), esophageal (7), non-Hodgkin's lymphoma (4), cervical (4), ovarian (3), and colon (3).

Cancer rates for our cohort of patients after diagnosis of SSc were compared to an age-matched population during the same calendar years from the SEER cancer registries. The standardized incidence ratio (SIR) for all cancer types was 1.55 (95% CI: 1.16-1.93), which was higher in men (1.88; 95% CI: 1.01-2.73) than women (1.6; 95% CI: 1.12-2.07). The highest and most significantly increased incidence ratio was for esophageal cancer (15.9; 95% CI: 4.2-27.6), again higher in men than women. Oropharyngeal cancer also reached a significantly increased incidence ratio (9.63; 95% CI: 2.97-16.29) and was also more frequent in men than in women. While lung, non-Hodgkin's lymphoma, ovarian, cervical, and thyroid cancer were also associated with increased relative risks they did not reach statistical significance owing to the small number of cases in each group (Table 3). From 28 cancers diagnosed before study entry, half were breast cancer (14); less common cancers included non-Hodgkin's lymphoma (3), oropharyngeal (2), colon (2), B-cell lymphoma (2), and Hodgkin's lymphoma (2).

DISCUSSION

Our results indicate that SSc is associated with an increased risk of malignancy and more specifically with esophageal and oropharyngeal cancer. While esophageal cancer is a type of malignancy we expected to observe in this population because of the associated risk of Barret's esophagus related to lower esophageal sphincter dysfunction, the observation that oropharyngeal carcinoma was found significantly more frequently was unexpected. We further analyzed patients with oropharyngeal carcinomas and found an increased incidence of squamous cell carcinoma of the tongue[14].

It is important to note that 10 (12.9%) patients in our cohort developed more than one primary malignancy during followup.

Cancer risk factors such as smoking and a family history of cancer were more commonly observed in the SSc patients who developed cancer, suggesting a multifactorial pathogenic mechanism involving both genetic contributions as well as other defined cancer risk factors.

The 2 most recent population based cohort studies evaluating risk of malignancy in SSc presented contradictory results. The study by Hill, *et al* in South Australia using the South Australia Scleroderma Registry found an increased incidence of malignancy with a SIR 1.99 (95% CI: 1.46-2.65), and more specifically a statistically significant increase risk of lung cancer (SIR 5.9; 95% CI: 3.05-10.31)[9]. In contrast, the study by Chatterjee, *et al* using the Michigan Scleroderma Registry did not find an overall increased risk of cancer in SSc patients compared to the local population with the exception of liver cancer, which had a SIR of 7.35 (95% CI: 1.52-21.49)[10].

Differences in the incidence of malignancy among different studies most likely relate to ascertainment and study design. Similar to our study design, previous studies of patients drawn from specialty clinics have suggested an increased risk of malignancy. Selection and referral bias clearly play a role in this type of study[6,7]. On the other hand, population based studies from scleroderma registries in which diagnosis of SSc is based only on medical records rather than on an accurate diagnosis of SSc from the patient's history, physical examination, and ancillary laboratory and other diagnostic tests may overestimate the local population of SSc patients.

Table 3. Standardized incidence ratios (95% confidence intervals) of SSc related cancers as compared to the SEER databases. Values in bold type are statistically significant differences.

Cancer Type	Female	Male	Total
All	**1.6 (1.12–2.07)**	**1.88 (1.01–2.74)**	**1.55 (1.16–1.93)**
Breast	0.99 (0.41–1.57)		
Lung	1.47 (0.29–2.65)	3.29 (–0.43–7.01)	1.55 (0.54–2.56)
Colon	0.73 (–0.28–1.74)	1.66 (–1.6–4.86)	0.76 (–0.09–1.61)
Non-Hodgkin's lymphoma		19.04 (0.38–37.7)	
Esophageal	13.3 (0.54–52.66)	**55.5 (6.85–104.1)**	**15.9 (4.2–27.6)**
Oropharyngeal	**9.8 (1.21–18.39)**	**23.8 (3–44.6)**	**9.63 (2.97–16.29)**
Ovarian	2.63 (–0.67–5.25)*		
Cervical	7.14 (0.15–14.13)*		
Thyroid	4.34 (–1.66–10.34)*		

* Too few cases to provide statistically significant differences.

Differences in study population demographics may also result in differences in cancer risk. Hill, *et al* included in their study both patients with overlap syndromes and patients with poorly-described cases of SSc, in contrast to our study in which these patients were not included in the final analysis owing to the potential difference in cancer risk. Other differences between the population described by Hill, *et al* and ours include an older age at study entry, which obviously changes the underlying cancer risk of the population, and a higher prevalence of limited SSc (60% vs 41.5%, respectively). This latter population characteristic was also higher in the study by Chatterjee, *et al*[10] than in our study, with 59% of their population having limited SSc.

Data analysis may also play a critical role in the differences seen among the different studies. Use of local cancer registries to define expected cancer cases in a scleroderma population may be valid in areas of the world where population movement is limited. However, we believe this not the case in the US, and that the best approximation of expected cancer cases would be to use national cancer rates.

Our findings add further evidence to the possible interrelationship between SSc and cancer, a pathogenic interrelationship that may suggest the presence of common factors predisposing to the development of both cancer and SSc.

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