

LETTER TO THE EDITOR

CANCER IN ITALIAN PATIENTS WITH SYSTEMIC SCLEROSIS

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The association between cancer and systemic sclerosis (SSc) is known, although the underlying mechanisms remain unclear and epidemiological data is conflicting. Since no data exist on cancer in Italian SSc, we examined the frequency and characteristics of cancer in an Italian cohort of SSc patients to examine whether clinical and/or laboratory SSc-specific features represent a risk for developing malignancies in these patients. A retrospective chart review was carried out of 112 Italian SSc patients of whom 109 were women and 3 were men, aged 63 ± 13 years; 81 patients had limited SSc, 25 had diffuse SSc and 6 had sine scleroderma SSc. Fifteen cancers were found in 14 patients. The majority (60%) occurred after SSc onset (average 16 years), 40% occurred before the onset of SSc (average 14 years). The most frequent was breast cancer (prevalence: 4.5%, relative prevalence: 33.3%), followed by uterine cancer and lymphomas (prevalence: 2.7%, relative prevalence: 20% each). Lung cancer was not observed. Cancers were unrelated with SSc type, autoantibodies, organ involvement and treatments. In conclusion, clinical features do not seem to be linked with the risk of developing cancer in SSc patients. Interestingly, and in contrast with published data, no lung cancer was present in our patients, although lung involvement was observed in the majority of them. This finding, consistent with a lower prevalence of lung cancer in the Italian female general population, and the absence of associations between SSc-specific features and cancer, suggests that genetic and environmental factors might play a pivotal role in cancer risk in these patients.

The association between cancer and connective tissue diseases, including systemic sclerosis (SSc), is well known, but epidemiologic data are conflicting and the underlying mechanisms are still elusive. While in an earlier series, cancer incidence in SSc was estimated comparable to that in the general population (1), subsequent data showed a significant increase of cancer in these patients of up to 20.4% (2), especially of the lung and breast (2-3). The major risk for SSc-associated lung cancer, which in these patients may occur in the absence of history of tobacco use, has been reported to be pulmonary fibrosis (3), while SSc-

associated breast cancer has been often related to the effects of chemo- and radio-therapy (4).

We retrospectively evaluated the prevalence and the specific types of malignancy in 112 Italian SSc patients, searching in the meantime for possible associations between cancers and clinical and/or laboratory features of SSc. To our knowledge there are no data on SSc and cancer in a large Italian case series.

MATERIALS AND METHODS

We retrospectively reviewed the complete medical

Key words: cancer, systemic sclerosis, Italian population, lung cancer, breast cancer

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charts of 112 Italian patients who fulfilled the ACR criteria for SSc (5) [109 women and 3 men, aged 63 ± 13 years; 81 patients with limited cutaneous SSc (lcSSc), 25 with diffuse cutaneous SSc (dcSSc) and 6 with sine scleroderma SSc (ssSSc)], seen from 2004 until November 2009 at the Rheumatology Unit of IRCCS Istituto Clinico Humanitas, Università degli Studi di Milano, Milan, Italy. All patients had body mass index (BMI) less than 25.

For each patient the following aspects of SSc were considered: SSc type, digital ulcers, organ involvement, autoantibodies, in particular anticentromere (ACA) and anti Scl-70, and therapy. In particular, for heart involvement arrhythmias, conductance abnormalities, ischemic features, and/or pulmonary arterial hypertension, were considered by means of EKG, Holter EKG, echocardiocolorDoppler and heart catheterization when necessary; for the lung we evaluate the presence of ground glass and/or fibrosis on High Resolution CT scan, forced vital capacity (FVC) $< 80\%$ with normal forced expiratory volume at one second (FEV1)/FVC on spirometry, diffusion of carbon monoxide (DLCO) $< 80\%$; for gastro-esophageal involvement we considered symptoms such as reflux-related and evaluated esophageal motor disturbances, oesophagitis or gastric disease by means of standard X-ray and oesophagogastrroduodenoscopy (Table I).

Statistical analysis

The Stat-View statistical package was used. Continuous data were expressed as averages (standard deviation, range). Differences between mean values were examined using the Student *t* test. Differences in the contingency table were examined using the *chi*-square test. Differences between continuous data and nominal variables were studied using ANOVA. A *p* value < 0.05 was considered significant.

RESULTS

Fourteen patients (12.5%), all women, had cancer; one patient developed both breast cancer and melanoma. Breast cancer was the most frequent cancer (4.5% of patients, 33.3% of all cancers), followed by uterine cancer and lymphomas (20% of all cancers, each) (Fig. 1). No lung cancers were found, although lung involvement (alveolitis and/or fibrosis) was observed in 68% of patients. Cancers were unrelated with the type of SSc (12% of dcSSc and 13.6% of lcSSc patients had cancer), although no malignancies were detected in patients with ssSSc.

The majority of malignancies (60%) developed

after the diagnosis of SSc (average 16 years, range 4-56 years), considering Raynaud's phenomenon as the first manifestation of the disease; 6 malignancies (40%) appeared before the onset of SSc (average 14 years, range 2-27 years).

One patient developed oesophagus adenocarcinoma on a Barrett's oesophagus, although Barrett's oesophagus was found in five SSc patients. No associations were found between malignancies heart or lung involvement, nor with digital ulcers or autoantibodies (Table II).

Six cancer patients underwent radio- and chemotherapy; seven patients had surgery and one patient had laser-therapy for an adenocarcinoma on Barrett's oesophagus. In none of them the characteristics of SSc were consistent with a paraneoplastic phenomenon (Raynaud's phenomenon and autoantibodies were present in all patients and no remissions were found after treatments).

None of the 17 patients who received at least one immunosuppressive drug (cyclophosphamide, azathioprine, cyclosporine A, methotrexate) developed cancer. None of the 112 patients received hormonal drugs.

DISCUSSION

To our knowledge this is the first study carried out on a large cohort of Italian patients to address the

Table I. Clinical and laboratory characteristics of SSc patients.

	number (%)
SSc type	
lcSSc	81 (72.3)
dcSSc	25 (22.3)
ssSSc	6 (5.3)
Visceral involvement	
lung	76 (67.9)
heart *	20 (17.9)
gastrointestinal	80 (71.4)
Digital ulcers	52 (46.4)
Autoantibodies	
ACA	64 (57.1)
anti-Scl-70	14 (12.5)
no autoantibodies **	4 (3.6)

* including pulmonary arterial hypertension

** all types

Table II. Clinical and laboratory characteristics of SSc patients with (14 patients) or without (98 patients) cancer.

	SSc patients with cancer number (%)	SSc patients without cancer number (%)	p
SSc type			
lcSSc	11 (78.6)	70 (71.4)	n.s.
dcSSc	3 (21.4)	22 (22.4)	n.s.
ssSSc	0	6 (6.1)	n.s.
Visceral involvement			
lung	10 (71.4)	66 (67.3)	n.s.
heart *	6 (42.9)	14 (14.3)	n.s.
gastrointestinal	9 (64.3)	71 (72.4)	n.s.
Digital ulcers	6 (42.9)	46 (46.9)	n.s.
Autoantibodies			
ACA	8 (57.1)	56 (57.1)	n.s.
anti-Scl-70	4 (28.6)	10 (10.2)	n.s.
no autoantibodies **	0	4 (4.1)	n.s.

* including pulmonary arterial hypertension

** all types

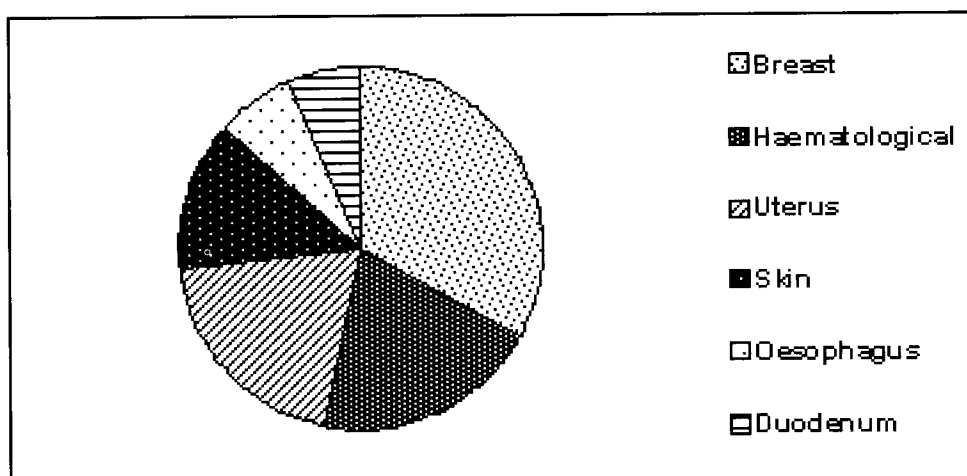


Fig. 1. Site and relative frequency of cancer in 112 Italian SSc patients: breast 5 (33.3%), haematological 3 (20%), uterus 3 (20%), skin 2 (13.3%), oesophagus 1 (6.7%), duodenum 1 (6.7%).

association between cancer and SSc. A clinical study from 1974 reported that 2 of 15 Italian SSc patients developed cancer (oesophageal cancer and bone metastases of unknown origin) (6).

The frequency of cancer in our SSc patients (13.4%) lies in between the wide reported range (3.6%-20.4%) (1-2). There were no differences between lcSSc and dcSSc, in agreement with certain (7), although not all studies (2, 8). No published data exist on cancer in ssSSc.

The most frequent type of cancer in our series was breast cancer, with a prevalence (4.5%) similar to the

national average (4.2%) calculated from the Italian National Cancer Registry (9), and in agreement with previous data reporting a frequency in SSc from 2% to 5.4% (3, 7).

Uterine cancer and lymphomas were the second most frequent malignancy in our patients. Reports of uterine malignancies in SSc are few (10-11), although they represented 6.7% of all malignancies in the Chatterjee series (12).

Our data are in agreement with the reported increased risk of SSc patients for haematological malignancies, including NHL and HL (13-14). It

deserves to be mentioned that one of our 3 patients with SSc and NHL, had Sjögren's Syndrome (SS), since SS is a known risk for lymphoma (15).

No relationship was found between cancer and organ involvement, and, although it is still debated whether Barrett's oesophagus is a risk for oesophageal cancer (16), ours and previously reported data (17) do not seem to indicate Barrett's oesophagus as a risk for cancer in SSc.

Interestingly, and in contrast with the majority of the reported data (3, 18), no lung cancer was present in our patients, although lung involvement (alveolitis and/or fibrosis) was observed in 68% of them. It is worthy of mention that there is a lower prevalence of lung cancer in the Italian female general population (19) compared with that of other European regions (20).

This finding, coupled with several reported data, including the recent observation of a high frequency of lung cancer in non-smoker Asian women (21), the lack of cancer risk in SSc patients living in the Detroit area (12), the low or even absent risk for breast cancer in SSc French or Swedish populations (13-14, 22), the high risk of gastrointestinal cancer in Japan (23) and in Japanese SSc (24), suggests that genetic and/or environmental factors might play a pivotal role in SSc-associated cancer.

We did not find any link between cancer and immunosuppressive treatments, nor could the SSc of any of our patients be considered a paraneoplastic phenomenon, since Raynaud's phenomenon and autoantibodies were present in all patients and no remissions were found after chemotherapy, radiotherapy or surgery (25).

Our study has several limitations; in particular, we were unable to evaluate family history or other risk factors, including smoking and pregnancy/nulliparity.

In conclusion, the absence of association between SSc clinical features and malignancies, and the absence of lung cancer in our series, which is consistent with a low prevalence of lung cancer in the Italian female general population, suggest that the risk of developing cancer might be rather related to genetic and/or environmental factors.

More studies on large sample sizes in different countries are needed to allow a better definition of SSc-related risk of cancer and to improve our

knowledge on the mechanisms linking autoimmune diseases and cancer.

REFERENCES

1. Duncan SC, Winkelmann RK. Cancer and scleroderma. *Arch Dermatol* 1979; 115:950-5.
2. Hill CL, Nguyen AM, Roder D, Roberts-Thomson P. Risk of cancer in patients with scleroderma: a population based cohort study. *Ann Rheum Dis* 2003; 62:728-31.
3. Abu-Shakra M, Guillemin F, Lee P. Cancer in systemic sclerosis. *Arthritis Rheum* 1993; 36: 460-64.
4. Alexandrescu DT, Bhagwati NS, Wiernik PH. Chemotherapy-induced scleroderma: a pleiomorphic syndrome. *Clin Exp Dermatol* 2005; 30:141-5.
5. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. *Arthritis Rheum* 1980; 23:581-90.
6. Repetto E, Cerrato O, Spotorno N, Sorbi A. Studio clinico sull'incidenza di neoplasie maligne in corso di alcune malattie auto-immuni. *Reumatismo* 1974; 26:102-08.
7. Derk CT. Associations of breast cancer development in patients with systemic sclerosis: an exploratory study. *Clin Rheumatol* 2007; 26:1615-19.
8. Lu TY, Hill CL, Pontifex EK, Roberts-Thomson PJ. Breast cancer and systemic sclerosis: a clinical description of 21 patients in a population-based cohort study. *Rheumatol Int* 2008; 28:895-9.
9. Grande E, Inghelmann R, Francisci S, Verdecchia A, Micheli A, Baili P, Capocaccia R, De Angelis R. Regional estimates of breast cancer burden in Italy. *Tumori* 2007; 93:374-9.
10. Sattar MA, Cawley MI. Scleroderma and carcinoma of uterus. *Br J Clin Pract* 1983; 37:69-70.
11. Yamamoto M, Suzuki C, Naishiro Y, Tsukuda K, Murakami R, Yamamoto H, Takahashi H, Imai K. A case of pseudoscleroderma as paraneoplastic syndrome due to carcinoma of cervical uteri. *Nihon Rinsho Meneki Gakkai Kaishi* 2003; 26:293-8.
12. Chatterjee S, Dombi GW, Severson RK, Mayes MD.

- Risk of malignancy in scleroderma: a population-based cohort study. *Arthritis Rheum* 2005; 52:2415-24.
13. Rosenthal AK, McLaughlin JK, Gridley G, Nyrén O. Incidence of cancer among patients with systemic sclerosis. *Cancer* 1995; 76:910-4.
 14. Rosenthal AK, McLaughlin JK, Linet MS, Persson I. Scleroderma and malignancy: an epidemiological study. *Ann Rheum Dis* 1993; 52:531-3.
 15. Zintzaras E, Voulgarelis M, Moutsopoulos HM. The risk of lymphoma development in autoimmune diseases: a meta-analysis. *Arch Intern Med* 2005; 165:2337-44.
 16. Wood RK, Yang YX. Barrett's esophagus in 2008: an update. *Keio J Med* 2008; 57:132-8.
 17. Wipff J, Allanore Y, Soussi F, Terris B, Abitbol V, Rymond J, Chaussade S, Kahan A. Prevalence of Barrett's esophagus in systemic sclerosis. *Arthritis Rheum* 2005; 52:2882-8.
 18. Talbott JH, Barrocas M. Progressive systemic sclerosis (PSS) and malignancy, pulmonary and non-pulmonary. *Medicine* 1979; 58:182-207.
 19. Inghelmann R, Grande E, Francisci S, Verdecchia A, Micheli A, Baili P, Capocaccia R, De Angelis R. Regional estimates of lung cancer burden in Italy. *Tumori* 2007; 93:360-6.
 20. Micheli A, Mugno E, Krogh V, Quinn MJ, Coleman M, Hakulinen T, Gatta G, Berrino F, Capocaccia R. Cancer prevalence in European registry areas. *Ann Oncol* 2002; 13:840-65.
 21. Scagliotti GV, Longo M, Novello S. Nonsmall cell lung cancer in never smokers. *Curr Opin Oncol* 2009; 21:99-104.
 22. Kyndt X, Hebbard M, Queyrel V, Hachulla E, Hatron PY, Devulder B. Systemic scleroderma and cancer. Search for predictive factors of cancer in 123 patients with scleroderma. *Rev Med Interne* 1997; 18:528-32.
 23. Hamashima C, Shibuya D, Yamazaki H, Inoue K, Fukao A, Saito H, Sobue T. The Japanese guidelines for gastric cancer screening. *Jpn J Clin Oncol* 2008; 38:259-67.
 24. Fuse Y, Masuyama J, Yoshio T, Mimori A, Takeda A, Minota S, Kano S. Progressive systemic sclerosis (PSS) and cancer-increasing coincidence rate of cancer in 67 PSS patients. *Ryumachi* 1995; 35:25-31.
 25. Racanelli V, Prete M, Minoia C, Favoino E, Perosa F. Rheumatic disorders as paraneoplastic syndromes. *Autoimmun Rev* 2008; 7:352-8.