

Adherence to recommendations for cervical and breast cancer screening in systemic sclerosis

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SUMMARY

The aim of the study was to evaluate the adherence of systemic sclerosis (SSc) female patients to cervix and breast cancer screening procedures, as suggested by local guidelines.

A cohort of 84 SSc women was asked if they had undergone mammography and Pap test during the previous 2- and 3-year intervals, as indicated according to the Italian recommendations. The results were compared with those collected in patients affected by other chronic rheumatic disorders and in the general population.

More than 85% of SSc women declared to comply with an age-related cervix and breast cancer screening schedule. The data were similar to those collected in patients affected by other chronic rheumatic disorders, whereas the subjects belonging to the general population reported to undergo breast cancer screening more frequently. Among SSc women, neither the educational level, nor the lung and skin involvement influenced their cancer screening program compliance. Only a positive history of ischemic digital ulcers seemed to interfere with mammography.

Our study reported a very high percentage of SSc female patients who adhered to programs for the early detection of cervical and breast cancer. The significant adherence to guidelines may be due to the schedule adopted by the local health public service, which regularly invites eligible subjects by mail to undergo cancer screening at no charge.

Key words: Systemic sclerosis, Chronic rheumatic diseases, Cervical cancer screening, Breast cancer screening.

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■ INTRODUCTION

In Italy, the current recommendations for the early diagnosis of the most frequent female cancers suggest screening women aged 25-64 years for cervical cancer with Papanicolaou (Pap) test at 3-year intervals and women aged 50-69 years at 2-year interval with mammography (1). The aim of cancer screening is to detect precancerous lesions or early neoplastic transformation, thereby resorting to earlier and potentially less invasive treatment than what is required for symptomatic and more advanced cancers. The benefit of cancer screening procedures in terms of lower incidence of the invasive disease and lower mortality has extensively been documented (2-5).

There are discordant data regarding adherence to cancer screening programs in

patients affected by systemic lupus erythematosus (SLE). A Canadian study showed that 53% of 48 SLE women aged 50-69 and 33% of 27 SLE women aged less than 30 years reported to have performed a mammogram and a Pap test, in the previous year. These figures compare with 74% and 56% of similarly aged control women, respectively. Moreover, among 51 SLE subjects aged 50 and older, only 18% reported screening for colorectal cancer compared to 48% in the general population. Non-white SLE patients, those with lower educational level, and with higher disease damage scores were less likely to undergo cervical Pap testing (6). It is not clear why SLE women are less careful in performing age-related cancer screening in agreement with recommendations. These results might be attributed to the tedious-

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ness of adhering to screening programs by patients who need to frequently perform medical examinations for the periodic assessment of their systemic disease. On the contrary, a more recent study performed in California reported that 70% of eligible SLE women underwent mammograms and Pap tests, in a similar percentage of control subjects and of patients with chronic non-rheumatic diseases (7). In keeping with the experience of Bernatsky et al. (6), it was observed that patients with lower educational attainment were less likely to undergo Pap tests. Similar data were collected in Italian SLE women concerning the adherence to cervical cancer screening: 66.4% of 140 patients declared to perform a Pap test at least every 3 years, as suggested by local guidelines, without significant difference in comparison with the general population (8). SLE women should be encouraged to regularly undergo Pap test considering that some studies reported a higher incidence of cervical dysplasia (9) and cervical cancer (10) in comparison with the general population. However, a recent review suggested that literature data are contrasting (11).

To the best of our knowledge there are no data concerning the adherence to recommendations for cervical and breast cancer screening in systemic sclerosis (SSc), a chronic systemic autoimmune disease, that, as SLE, may involve skin and visceral organs and that requires frequent examinations for follow up of the disease, early diagnosis of complications, and management of comorbidities.

The aim of the present study was to assess if SSc female patients underwent Pap test and mammography as suggested by current recommendations to the same extent of female patients suffering from other chronic rheumatic diseases and of the general population.

■ MATERIALS AND METHODS

Study population

Outpatient women affected by SSc aged 25-69 years followed at the Rheumatology Unit of Verona, Italy, were consecutively

enrolled for the present study between January and June 2013. All patients fulfilled the American College of Rheumatology (ACR) criteria for the diagnosis of SSc (12). The distinction between limited and diffuse cutaneous SSc was made according to the criteria by LeRoy et al. (13).

All patients underwent clinical examination and laboratory evaluation including antinuclear and anti-extractable nuclear antigen antibody detection by indirect immunofluorescence on human epithelial cell line 2 cells and enzyme-linked immunosorbent assay method, respectively. Every year the patients underwent investigations in order to evaluate heart and lung involvement. Pulmonary fibrosis and pulmonary artery hypertension were diagnosed by high-resolution computed tomography and right heart catheterisation, respectively. Heart and gastrointestinal involvement was defined in agreement with Medsger's proposal (14). Skin involvement was assessed by modified Rodnan skin score (15). Digital ulcers were defined as ischemic ulcers located at the digit tip.

Control subjects

Patients affected by other chronic rheumatic disorders, which mainly affect female sex as SLE, rheumatoid arthritis, primary Sjögren's syndrome and fibromyalgia aged 25-69 years were consecutively enrolled as controls. The diseases were diagnosed in agreement with the most recent available criteria (16-19).

Moreover female subjects from the general population aged 25-69 years attending the office of a general practitioner were consecutively enrolled.

Cervical and breast cancer screening

During the periodic visits at the Rheumatology Unit, rheumatic patients aged 25-64 years were asked if they had undergone Pap test in the previous 3-year interval, except for patients previously hysterectomized. Female patients aged 50-69 years were asked if they had undergone mammography in the previous 2-year interval. A general practitioner asked the same questions to his female patients.

Both patients and subjects from the general population were also interviewed concerning their educational status; we ranked subjects in low and high educational level depending on whether they attended school for ≤ 8 or >8 years.

Statistics

Statistic workup was performed using SPSS 17.0 statistical package (SPSS Inc., Chicago, IL, USA). Population's characteristics are described as mean and standard deviation or median, as appropriate. The number of patients that underwent screening procedures was expressed as percentage. Differences between groups were calculated by t-test or Mann-Whitney test, according to the data characteristics. Differences of categorical variables between groups were analyzed by Fisher's exact test or Chi square test, as appropriate.

■ RESULTS

Demographic and clinical features

The cohort of SSc patients followed at the Rheumatology Unit of the University of Verona enrolled for the present study was composed of 84 subjects. Sixty-two patients were aged 25–64 years; after exclusion of 5 cases previously hysterectomized, the eligible patients for cervical cancer screening were 57. Sixty patients aged 50–69 years were eligible for mammography; only one of these was previously treated with quadrantectomy for breast cancer. All the subjects were of Caucasian origin and all but 2 of Italian origin.

Table I reports the main demographic and clinical features of SSc cases.

Cervical cancer screening

The age of SSc patients who were recommended to undergo Pap test was not different in comparison with patients affected by other chronic rheumatic disorders and with the sample of the general population.

Eight out of 57 SSc patients (14.0%) did not undergo the Pap test during the previous 3-year interval.

As to the other subgroups, 5 out of 103 pa-

Table I - Demographic and clinical characteristics of the 84 patients affected by systemic sclerosis.

Age (years)*	56.2 (9.9)
Disease duration (years)*	10.3 (5.8)
Disease pattern°	
Diffuse	24 (28.6%)
Limited	60 (71.4%)
Autoantibody pattern°	
ACA positivity	44 (52.4%)
Anti-Scl70 positivity	18 (21.4%)
ANA positivity (absent ACA and anti-Scl70)	22 (26.2%)
Pulmonary fibrosis°	17 (20.2%)
Pulmonary artery hypertension°	1 (1.2%)
Heart involvement°	31 (36.9%)
Gastrointestinal involvement°	70 (83.3%)
Digital ulcers°	21 (25%)

*Values expressed as mean and standard deviation; °values expressed as absolute number and percentages. ACA, anticentromere antibodies; Anti-Scl70, anti-Scl70 antibodies; ANA, antinuclear antibodies.

tients affected by other chronic rheumatic disorders (4.9%) and 3 out of 81 controls of the general population (3.7%) did not undergo Pap test during the previous 3-year interval.

The adherence to cervical cancer screening by SSc patients was not different in comparison with patients affected by other chronic rheumatic disorders and with the general population ($P=0.066$ and $P=0.051$, respectively).

These data are reported in table II.

Breast cancer screening

The age of SSc patients who were recommended to undergo Pap test was not different in comparison with patients affected by other chronic rheumatic disorders, whereas subjects from the general population were younger ($P=0.002$).

Eight out of 60 SSc patients (13.3%) did not undergo mammography during the previous 2-year interval.

Concerning the other subgroups 3 out of 76 patients affected by other chronic rheumatic disorders (4.9%) did not undergo mammography during the previous 2-year interval. Instead all controls of the general population reported to have regularly performed breast cancer screening.

The adherence to breast cancer screening

Table II - Frequency of adherence to cervical and breast cancer screening among patients affected by systemic sclerosis, other chronic rheumatic disorders (rheumatic patient controls), and subjects from the general population.

	Yes	No	Total	Comparison between SSc pts and other subgroups
Cervical cancer screening				
SSc	49 (86.0%)	8 (14.0%)	57	-
Rheumatic patient controls	98 (95.1%)	5 (4.9%)	103	P=0.066
General population	78 (96.3%)	3 (3.7%)	81	P=0.051
Breast cancer screening				
SSc	52 (86.7%)	8 (13.3%)	60	-
Rheumatic patient controls	73 (96.1%)	3 (3.9%)	76	P=0.060
General population	55 (100%)	0	55	P=0.006

SSc, systemic sclerosis; pts, patients.

by SSc patients was not different in comparison with patients affected by other chronic rheumatic disorders (P=0.060); on the contrary it was lower compared to that of the general population (P=0.006). These data are reported in Table II.

Educational level

There was no difference in educational level between SSc patients who did and who did not perform cervical and breast cancer screening, as well as in patients affected by rheumatic diseases other than SSc and in the general population.

Clinical features and cancer screening in systemic sclerosis

There was no difference in SSc between patients who did and who did not perform cervical and breast cancer screening in relation to age, disease duration, pattern of disease, autoantibody profile, skin and lung involvement.

Patients with a positive history for digital ulcers tended to be less prone to perform breast cancer screening than those without (P=0.059) (Table III). On the contrary there was no difference regarding cervical cancer screening.

Table III - Frequency of adherence to cervical cancer and breast screening among patients affected by systemic sclerosis, accordingly to the presence or not of ischemic digital ulcers, pulmonary involvement and type of cutaneous subset.

Digital ulcers		Yes	No	Total	Comparison between SSc subgroups
Breast cancer screening	Yes	9 (69.2%)	43 (91.5%)	52	P=0.059
	No	4 (30.8%)	4 (8.5%)	8	
Cervical cancer screening	Yes	14 (82.4%)	35 (87.5%)	49	n.s.
	No	3 (17.6%)	5 (12.5%)	8	
Pulmonary involvement		Yes	No	Total	Comparison between SSc subgroups
Breast cancer screening	Yes	12 (80%)	40 (88.9%)	52	n.s.
	No	3 (20%)	5 (11.1%)	8	
Cervical cancer screening	Yes	8 (88.9%)	41 (83.7%)	49	n.s.
	No	1 (11.1%)	7 (16.3%)	8	
Diffuse subset		Yes	No	Total	Comparison between SSc subgroups
Breast cancer screening	Yes	13 (86.7%)	39 (88.6%)	52	n.s.
	No	3 (13.3%)	5 (11.4%)	8	
Cervical cancer screening	Yes	14 (87.5%)	35 (85.4%)	49	n.s.
	No	2 (12.5%)	6 (14.6%)	8	

SSc, systemic sclerosis, n.s., not significant.

■ DISCUSSION AND CONCLUSIONS

Our study shows that the percentage of SSc female patients who adhere to programs for the early detection of cervical and breast cancer was high (>85% of the cases), even if the general population more frequently performed mammography. The elevated adherence to recommendations may be likely due to the organization of the local health public service, which regularly invites by mail eligible subjects to undergo cancer screening at no charge. The collected data were self-reported like in previous studies (6-8). This methodology is considered reasonable even if it may overestimate the adherence to screening procedures (20).

The adherence to screening programs was not influenced by the educational level, unlike what was reported in other studies in SLE (6, 7). Moreover there was no difference comparing SSc cases with and without lung involvement as well in relation to the severity of the skin involvement, whereas patients with a positive history of ischemic digital ulcers tended to undergo mammography less frequently than patients who never suffered from this manifestation. In recent years the negative impact of digital ulcers on disability, the social and economic burden and the quality of life received great attention (21-24). This painful clinical manifestation may predispose to severe complications like soft tissue infections, osteomyelitis and gangrene.

The prevalence of pulmonary fibrosis and pulmonary artery hypertension in our SSc population was low. This may be due to many reasons, including the great heterogeneity of the disease and the design of the study, which led to exclude male patients and women older than 69 years. Male sex is associated with a more frequent interstitial lung disease (25) and late age at scleroderma onset is a risk factor for development of pulmonary artery hypertension (26).

No other reports were published regarding adherence to cervical and breast cancer screening in SSc. A previous Italian study on SLE patients showed that two thirds of

eligible respondents regularly performed Pap test (8). A comparison with other experiences performed in other countries regarding age-related cancer screening procedures was not feasible on the grounds of the different local guidelines.

Recently, two meta-analyses were published about cancer incidence among SSc patients (27, 28). The relative risk to develop all invasive cancer was quantified in 1.75 (27). SSc men were more prone than women to develop neoplastic diseases (28). The results for selected cancers showed that SSc patients have in comparison with the general population a higher risk of developing lung and haematological neoplasms (27, 28), as well liver and bladder cancers (28). The incidence of breast cancer (27, 28) and cervix cancer (28) was not increased among SSc females in comparison with the general population, even if SSc women reported abnormal Pap test results more frequently than healthy controls (29). This indicates that SSc women should be pressed to undergo the age-related screening cancer programs recommended for the general population.

Our study showed that a high-quality prevention strategy for the early detection of the most frequent female cancers, like those implemented in our region, ensures a high level of adherence among a category of high-risk patients as those affected by SSc. We have seen that patients with severe complications, such as ischemic digital ulcers, are somewhat less prone to comply with breast cancer early detection strategies and this should prompt rheumatologists to devote greater attention to these patients.

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