con il patrocinio di

CIPOMO

rete oncologica

APPROCCI INTERDISCIPLINARI IN REUMATOLOGIA

5ª edizione

REUMATOLOGIA E MALATTIE NEOPLASTICHE

Sclerosi Sistemica

Torino, 13-14 ottobre 2017

S.C. Reumatologia AO Città della Salute e della Scienza di Torino

S. PARISI

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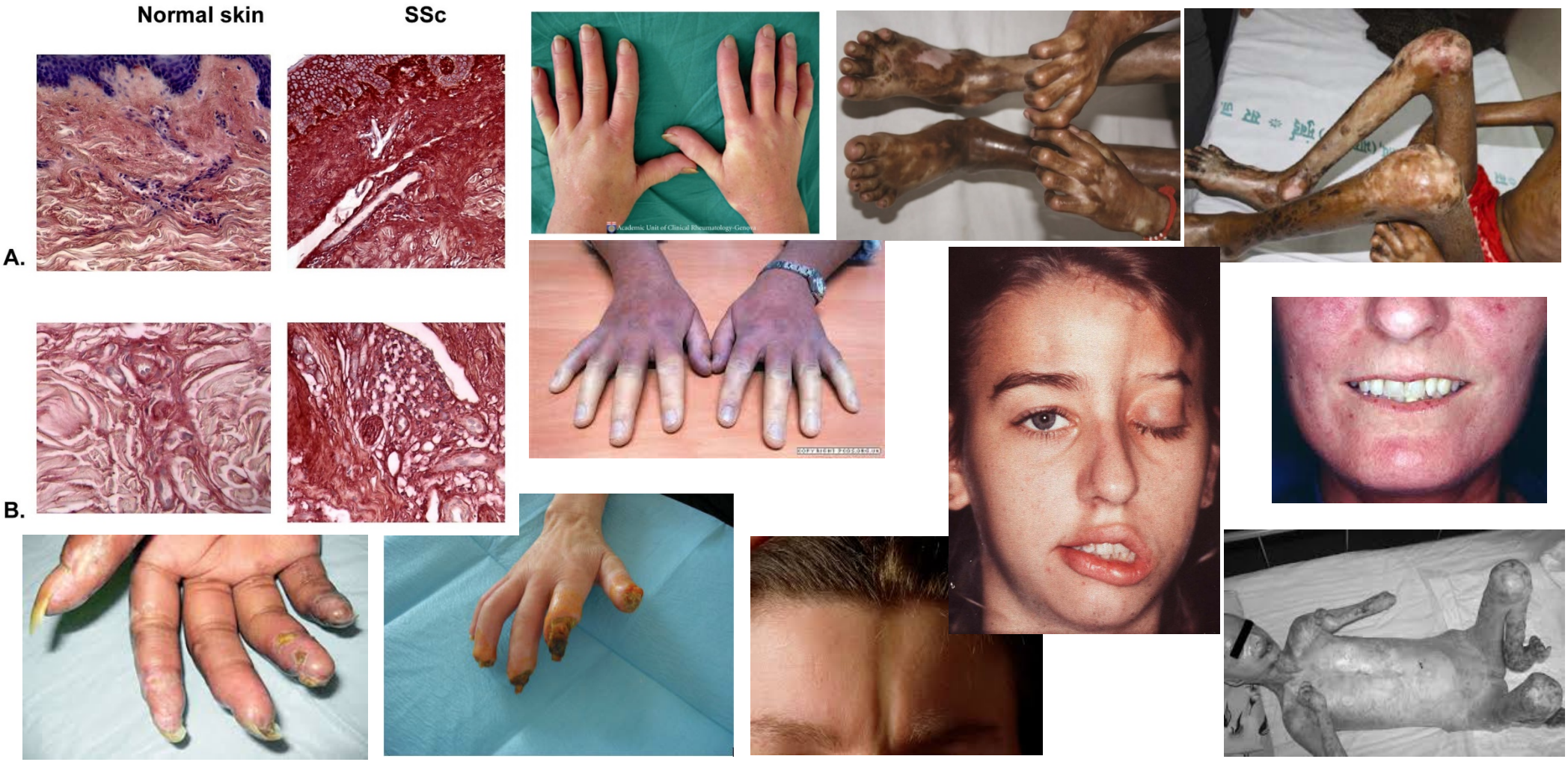
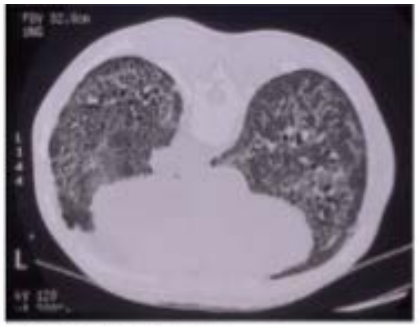
Cutaneous involvement

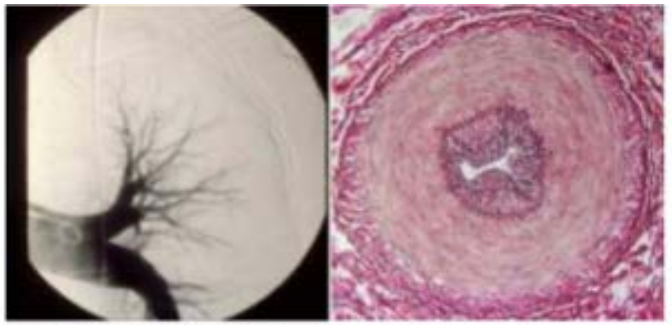


Systemic involvement

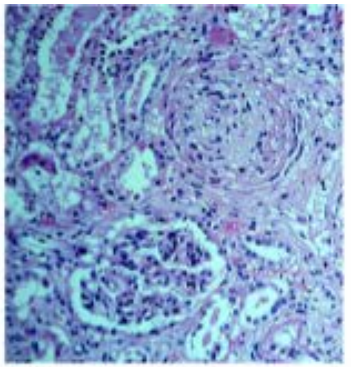
Oesophagus



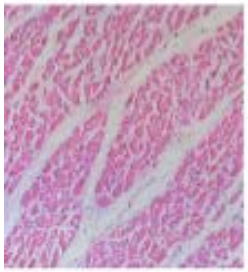
Lung fibrosis



Pulmonery hypertension



Renal crisis



Cardiac fibrosis

Bowel

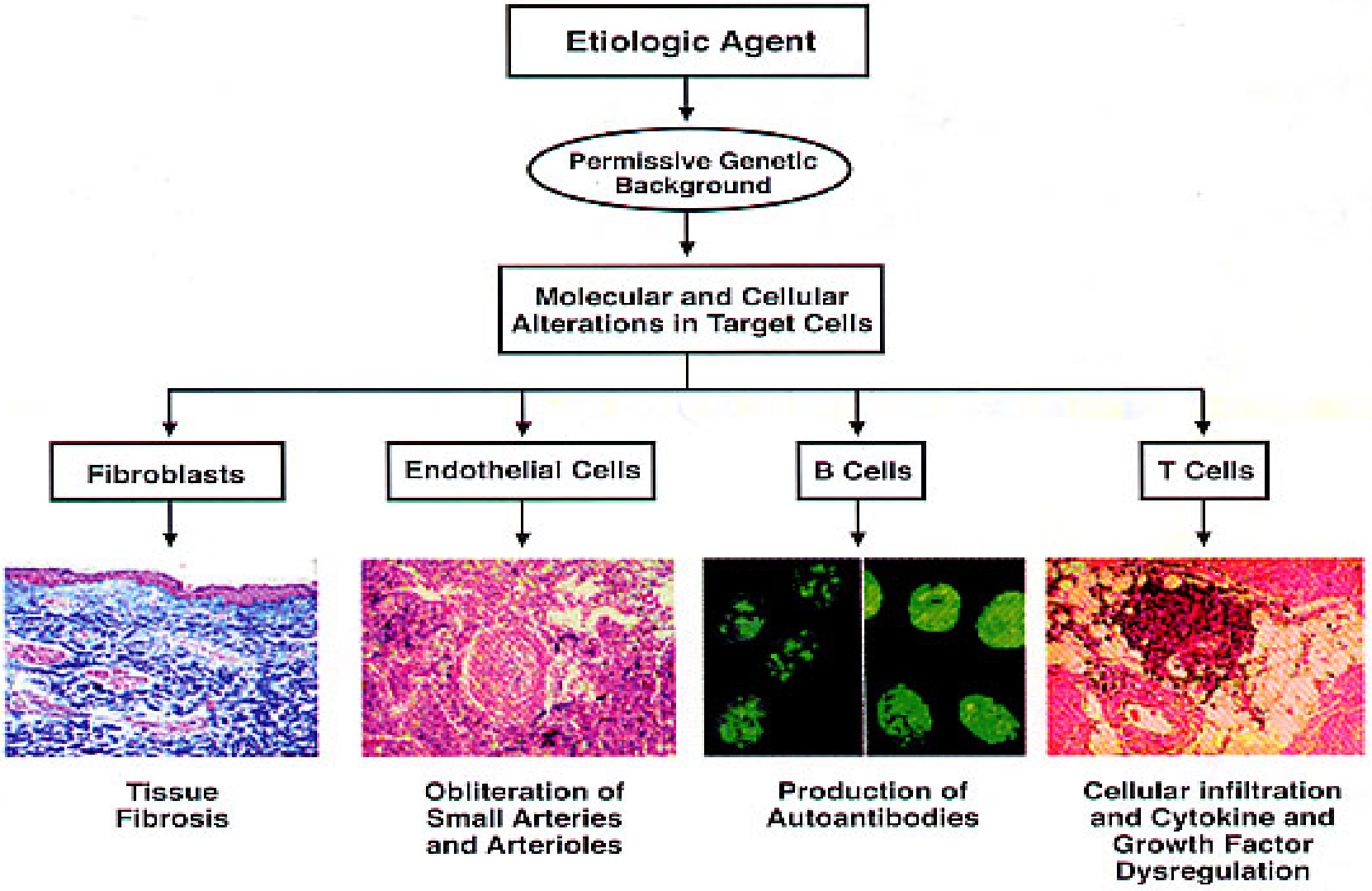
Abdomen

Hand contracture

Calcinosis

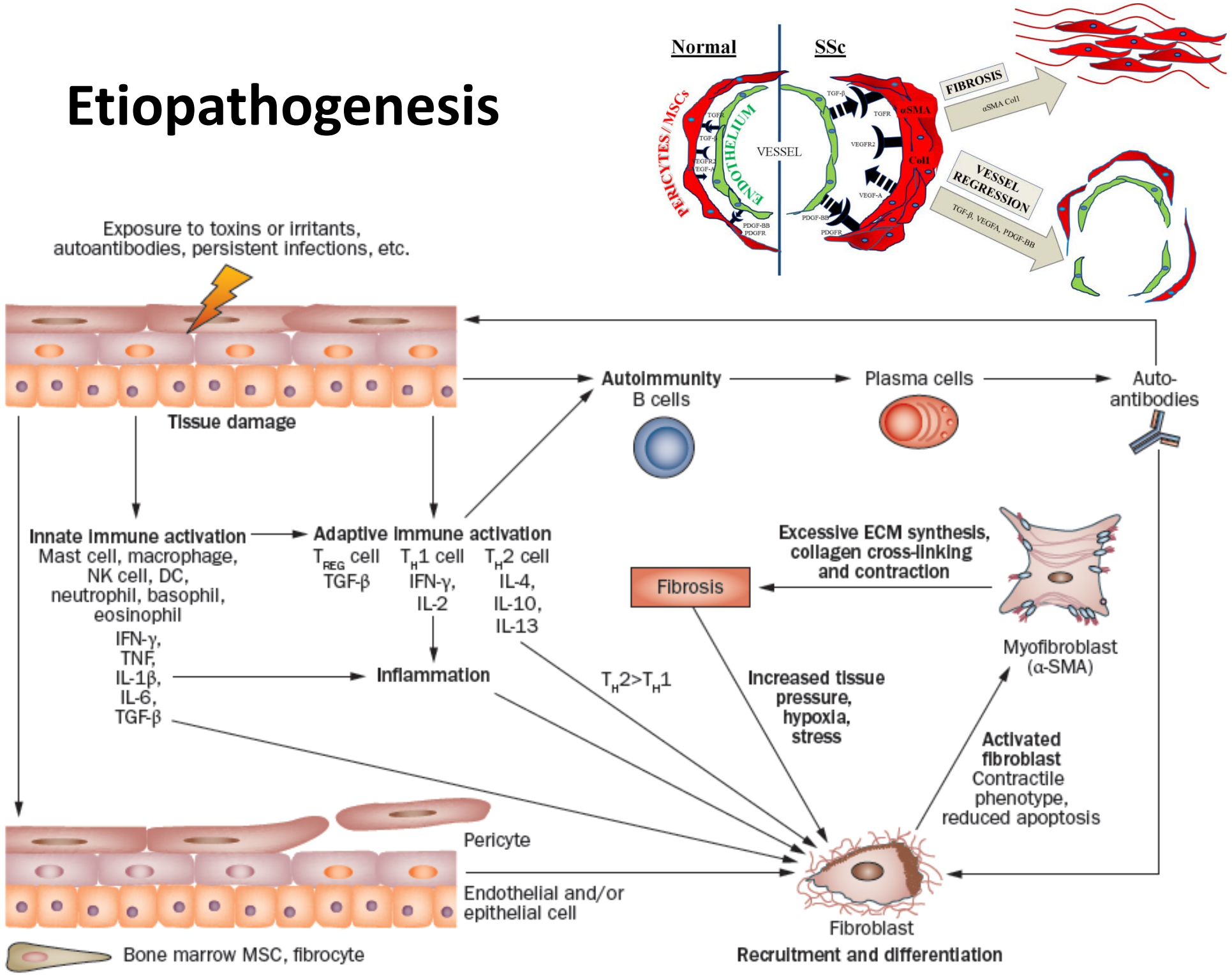
Severe Raynaud's with gangrene

Etiopathogenesis



John Varga et al Ann Int Med 2004

Etiopathogenesis



LUNG CANCER

Clinico-serological features of scleroderma patients with/without lung cancer.

	All patients	Patients with lung cancer	Patients without lung cancer	p value*
	No = 318	No = 16	No = 302	
Age (mean ± SD)	51.5 ± 14.5	42.3 ± 15.4	51.9 ± 14.2	0.0094
M/F	31/287	5/11	26/276	0.011
Dis. duration (years) (mean ± SD)	10.3 ± 6.5	14 ± 9.6	10.1 ± 6.3	0.0175
Smoke habit	97 (30.5%)	5 (31.2%)	92 (30.5%)	ns
Cutaneous subsets (L/D)^	278/40	14/2	264/38	ns
Skin ulcers	123 (38.7%)	6 (37.5%)	117 (38.7%)	ns
ACA	140 (44%)	1 (6.2%)	139 (46%)	0.0042
Anti-Scl70	105 (33%)	12 (75%)	93 (30.8%)	0.0007
ANoA	45 (14%)	3 (18.7%)	42 (13.9%)	ns
Interstitial lung disease (X-ray)	152 (47.8%)	13 (81.2%)	139 (46%)	0.0127
FVC% (mean ± SD)	96.4 ± 22.9	71 ± 24.6	97.9 ± 21.9	<0.0001
FVC < 75%	40 (12.6%)	9 (56.2%)	31 (10.3%)	0.0001
Paps > 35 mm Hg	54 (17%)	5 (31.2%)	49 (16.2%)	ns
Therapy with CFX*	36 (11.3%)	7 (43.7%)	29 (9.6%)	0.0001

^L = limited; D = diffuse; *CFX = cyclophosphamide.
Serology: Scl70 = anti-Scl70, ACA = anticentromere, ANoA = anti-nucleolar, ANA = anti-nuclear autoantibodies.
*Statistical evaluations between patients with and without lung cancer.

The presence of interstitial lung disease was supposed to be a pre-condition for cancer development

Chronic inflammation may facilitate at least the propagation of lung cancer, through a deregulated cytokine signaling, such as TGF-beta and PDGF, which are known to be implicated both in carcinogenesis and SSc lung fibrosis.

Colaci M al. Autoimmunity Reviews 12 (2013) 374–379

Daniels CE et al. Curr Opin Pulm Med 2005;11:431–7

Lung cancer and systemic sclerosis: review of the literature.

Authors	Year (ref.)	Country	Study design	No pts	No lung cancer	%	Follow-up (years)	Associations
Peters-Golden M et al.	1985 (14)	Michigan (USA)	Cohort-based	71	3	4.2	Mean 5	All pts with ILD
Roumm AD et al.	1985 (15)	Pittsburgh area (USA)	Cohort-based	262	8	3	1335 pt-years	ILD
Rothfield N et al.	1992 (16)	Connecticut (USA)	Cohort-based	148	4	2.7	Not indicated	Scl70
Abu-Shakra M et al.	1993 (17)	Canada	Cohort-based	248	7	2.8	2001 pt-years	ILD, age
Rosenthal AK et al.	1993 (18)	Sweden	Registry-based	233	5	2.1	Average 5.1	No
Rosenthal AK et al.	1995 (19)	Sweden	Cohort-based	917	15	1.6	7403 pt-years	No
Nishioka K et al.	1996 (20)	Japan	Cohort-based[a]	496	13	2.6	5–20	No
Kyndt X et al.	1997 (21)	France	Cohort-based	123	3	2.4	Median 4	No
Hesselstrand R et al.	1998 (13)	Sweden	Registry-based[a]	249	7	2.8	Mean 5.8 ± 4.2	No
Hill CL et al.	2003 (22)	South Australia	Registry-based	441	12	2.7	5.5 ± 3.1 (M) 6.1 ± 2.8 (F)	No
Chatterjee S et al.	2005 (23)	Detroit area (USA)	Registry-based	538	10	1.8	>2	No
Kang KY et al.	2009 (24)	Korea	Cohort-based	112	4	3.5	Mean 8.9	All female pts
Siau K et al.	2009 (25)	South-West England	Cohort-based	68	0	0	Not indicated	No
Joven BE et al.	2009 (26)	Spain	Cohort-based	275	2	0.7	Not indicated	No
Olesen B et al.	2010 (27)	Denmark	Registry-based	2040 (1731[b])	40 (31[b])	1.8	6.4 (2.2–11.5)	No
Szekanecz E et al.	2012 (28)	Hungary	Cohort-based	218	2	0.9	Not indicated	No
Kuo CF et al.	2012 (29)	Taiwan	Registry-based	2053	21	1	1996–2008	No
Present series	2012	Italy	Cohort-based	318	16	5	3270 pt-years	Scl70, FVC<75%

Legend: ILD = interstitial lung disease; Scl70 = anti-Scl70 autoantibodies.
[a] Evaluation of causes of death.
[b] Patients with disease duration >12 months.

- A variable prevalence of lung cancer is reported by previous studies in SSc patients' series from different countries (range 0–4.2%).

- Increased frequency of lung cancer among SSc patients (5%), compared to sex- and age-matched general population from the same Italian region.

- This malignancy is significantly associated with the presence of serum anti-Scl70 antibodies and abnormally reduced FVC (<75%), expression of clinically overt lung fibrosis.

- Male sex and longer disease duration might be considered as adjunctive parameters, able to identify a peculiar subset of SSc patients with higher risk to develop lung cancer.

Daniels CE et al. Curr Opin Pulm Med 2005;11:431–7
Colaci et al. Autoimmun Rev. 2013 Jan;12(3):374-9

CERVICAL AND VULVAR MALIGNACIES

Clinical features and pap test screening findings in 80 SSc patients.

	SSc series ($n = 80$)	Normal A ($n = 55$)	Inflammation B ($n = 20$)	Atypical cells/cancer C ($n = 5$)	p values (A versus C)	p values (A + B versus C)
Age at onset	51.2 ± 12	51.2 ± 12	51.2 ± 12	65 (46–67)	0.052	0.06
SSc duration	7.9 ± 5.8	8 ± 5.8	8 ± 5.8	6 (1–13)	0.45	0.45
Skin subsets						
Limited	72 (90%)	50 (90.9%)	18 (90%)	4 (80%)	0.42	0.42
Diffuse	8 (10%)	5 (9%)	2 (10%)	1 (20%)	0.42	0.42
Serology						
Anti-Scl70	23 (28.7%)	17 (30.9%)	2 (10%)	4 (80%)	**0.046**	**0.022**
ACA	37 (46.2%)	28 (50.9%)	8 (40%)	1 (20%)	0.35	0.37
ANoA	14 (17.5%)	6 (10.9%)	8 (40%)	0	1	0.58
Digital ulcers	29 (36.2%)	21 (38.2%)	7 (35%)	1 (20%)	0.64	0.65
Interstitial lung disease	30 (37.5%)	22 (40%)	8 (40%)	0	0.15	0.15
FVC < 70%	4 (5%)	3 (5.4%)	0	1 (20%)	0.30	0.23
DLCO < 70%	46 (57.5%)	32 (58.2%)	12 (60%)	2 (40%)	0.65	0.65
PAH	0					
History of smoking	27 (33.7%)	16 (29.1%)	9 (45%)	2 (40%)	0.63	1
History of immunosuppressant	5 (6.2%)	4 (7.3%)	1 (5%)	0	1	1
Pap test						
Negative	55 (68.7%)					
Inflammatory alterations	20 (25%)					
Atypical cells/cancer	5 (6.2%)					

Colaci M et al.Int J Rheumatol. 2015;2015:761867

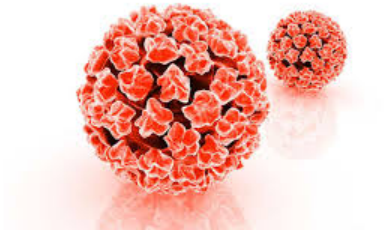
Cervical or vulvar cancers in SSc patients: review of the literature.

First author, year [ref.]	Country	Type of study	patient-years[1] (pts/follow-up)	Cervical cancer	Vulvar cancer
Duncan, 1979 [9]	Mayo Clinic, USA	Cohort study	(2,141/n.d.[2])	10	1
Lee, 1983 [10]	Canada	Cohort study	(95/7.3 ± 6.6)	2	0
Kyndt, 1997 [11]	France	Cohort study	(123/median 4)	1	0
Hill, 2003 [12]	South Australia	Registry-based	(441/6.1 ± 2.8)	5	0
Chatterjee, 2005 [13]	Detroit area, USA	Registry-based	4,908	3 (2 *in situ*)	0
Derk, 2006 [14]	Pennsylvania, USA	Cohort study	3,775	4	1
Olesen, 2010 [15]	Denmark	Registry-based	16,003	9	0
Airo', 2011 [16]	Italy	Cohort study	4,041	1	1
Belloli, 2011 [17]	Italy	Cohort study	(112/n.d.[3])	3[4]	0
Szekanecz, 2012 [18]	Hungary	Cohort study	(218/n.d.)	1	0
Moinzadeh, 2014 [19][5]	United Kingdom	Cohort study	(2,177/median 12.8)	17 "gynaecological" cases	
Shah, 2015 [20][6]	John Hopkins H, USA	Cross-sectional	(1,044/1990–2012)	3	1
Present series	*Italy*	*Cohort study*	*560*	0.48 *2 (1 in situ)*	*2 (1 in situ)*

High frequency of cancerous lesions of the cervix (2 cases).

A significant association between gynaecological malignancies and anti-Scl70 autoantibodies

+ HPV persistence?



- Screening Adherence

Colaci M et al.Int J Rheumatol. 2015;2015:761867

HAEMATOLOGICAL MALIGNACIES

First author/year	Number cases	Study type (country)	Age/sex	Dis. duration	Skin subset	Serology	Visceral inv.	Ass. Sjogren	History notes	Clinical picture	Hematological malignancy	Outcomes
Agard/2000	1	CR (France)	62 F	14	L	ACA	None	No	MGUS	Spleno/lymphoadenop., ascites	Small B cell NHL	Improved with CHOP
Airo'/2011	1	CS (360 Italian pts)	nd	nd	nd	ACA	nd	nd	nd	nd	NHL	nd
Alacacioglu/2005	1	CR (Turkey)	57 M	3	nd	nd	nd	nd	nd	Bilateral upper/lower eyelid hernias	Orbital marginal zone NHL	Improved with chemo/radiotherapy
Angeli/1991	1	CR (France)	42 F	4	L	ACA	nd	No	nd	Splenomegaly	CLL	nd
Arai/2009	1	CR (Japan)	31 F	1	nd	nd	nd	nd	nd	None	Thymic large B-NHL	Remission with CHOP
Arnaud/2006	1	CR (France)	76 F	11	L	nd	E	nd	*H. pylori* +	nd	Gastric MALT lymphoma	nd
Bachleitner-Hofmann/2002	1	CR (Austria)	73 F	14	L	ACA	L, E	nd	MGUS	nd	MM	Marked and sustained improvement with therapy for MM and SSc
Baldini/1994	1	CR (Italy)	59 F	1	nd	ANA	nd	nd	nd	nd	Lymphocytic Ly of intermediate diff.	Improved
Bellis/2014	1	CR (France)	37 M	1	L	ANA	nd	nd	nd	Right axillary lymphoadenopathy	CD30+ anaplastic Ly	Lymphoma and SSc remission with BMT
Ben Ghorbel/2005	1	CR (Tunisy)	70 F	6	L	Scl70	L	No	nd	Generalized lymphoadenopaties	Follicular B NHL	Improved with CHOP
Bielefeld/1996	5	CS (21 French pts)	39 F, 56 F, 69 F, 12 M, 71 M	0, 6, 6, 9, 2	nd	nd	nd	nd	nd	nd	CML, AML, immunocytoma, Burkitt's Ly, Waldenstrom d.	nd
Bistue/1990	1	CR (Argentina)	36 F	nd	D	nd	L	No	nd	Dyspnea, splenomegaly, and fever	Myelofibrosis	nd
Cavallero/1994	1	CR (Italy)	79 M	nd	D	ANA	nd	nd	Carpenter	Purpura of legs	Hairy cell leukemia	Died for pneumonia after 3 months
Charlanne/2004	1	CR (France)	72 F	<1	L	ACA	No	Yes	Overlap RA-SS	Neutropenia and lymphocytosis	Large granular lymphocyte leukemia	Sustained (>1 year) improvement with MTX 7.5/week for leukemia and autoimmunity
Chatterjee/2005	5	RS (538 US pts)	2 NHL are F	nd	2 NHL: 1 L, 1 D	nd	nd	nd	nd	nd	NHL (2); MM (2); leukemia (1)	nd
Čolović/2011	1	CR (Serbia)	55 F	20	L	nd	nd	nd	nd	Intense facial pruritus, paraproteinemia	MM	Remission for SSc and MM
Comer/1992	1	CR (UK)	31 F	1	L	ANA	E, L, H	No	nd	Neck/mediastinum lymphadenopathy	IIb-staged HL	HL remission (MOPP), SSc evolution by 1 year
Constans/1993	1	CR (France)	65 F	0	L	ACA	CREST	No	nd		Hairy cell leukemia	nd
Derk/2003	1	CR (USA)	66 M	2	D	Scl70	E	No	nd	Expanding mass at the tongue base	Large B-NHL	Remission with CHOP
Doyle/1985	5	CS (USA)	10; 22; 31 54; 70 F	4; 9; 9; 40; 57	L	nd	CREST	nd	nd	nd	HL; MM (2); "malignant Ly"; CLL	Variable outcomes

Colaci et al. Case Rep Rheumatol. 2017;2017:6230138

HAEMATOLOGICAL MALIGNACIES

First author/year	Number cases	Study type (country)	Age/sex	Dis. duration	Skin subset	Serology	Visceral inv.	Ass. Sjogren	History notes	Clinical picture	Hematological malignancy	Outcomes
Duggal/2002	1	CR (India)	42 M	nd	nd	nd	nd	nd	nd	nd	HL	nd
Duncan/1979	7	CS (2,141 USA pts)	50–79 F	2, 0, 1, 3, 0, 61, 1	nd	nd	nd	nd	nd	nd	CLL (3), MM, lymphosarcoma (2), CMML	Died by 1 year (2), alive > 5 years (4)
Dupond/1989	1	CR (France)	73 F	nd	L	ACA	CREST, L	Yes	nd	Splenomegaly	CMML	nd
Ferroir/1991	1	CR (France)	42 M	2	nd	ANA	nd	No	nd	nd	Mixed follicular Ly	Diagnosis at autopsy
Frigui	1	CR (France)	56 F	10	L	Scl70	L, K	No	nd	Skin lesion	Cutaneous B-cell Ly (supraorbital)	Regression after radiotherapy but relapse
Gisser/1979	1	CR (USA)	29 F	4	nd	nd	L, H	nd	Previous chlorambucil treat.	Anemia	CML	Died for bronchopneumonia
Hall/1978	1	CR (USA)	22 F	14	nd	nd	E calcinosis	No	Generalized lipodystrophy	Diffuse lymphoadenopathies	Nodular sclerosing HL	nd
Hasegawa/1999	1	CR (Japan)	43 M	<1	D	ANoA	nd	No	nd	Neck/armpits lymphoadenopathies	Diffuse large T cell NHL	Lymphoma and SSc remission (CHOP 4 cycles)
Haviv/1997	1	CR (Israel)	72 F	1, 5	L	ANA	L, K	No	nd	Fever, wasting, and arthralgias	Diffuse small cell NHL	Death for sepsis
Hill/2003	2	RS (441 Australian pts)	F	nd	nd	nd	nd	nd	nd	nd	Not better specified	nd
Hoshida/2004	7	CS (Japan)	57 (56–65), 2/5 M/F	2.2 (0–12)	nd	nd	nd	2/7	nd	nd	HL (2); diffuse large B cell Ly (5)	All died by 1 year
Kaşifoğlu/2006	1	CR (Turkey)	50 F	7	L	Scl70	L	SSA+	nd	Weakness, weight loss	CML	Improved with HU
Kaşifoğlu/2016	3	CS (340 Turkish pts)	nd	nd	nd	nd	nd	nd	nd	nd	MM, CML, follicular NHL	nd
Katz/1979	1	CR (USA)	57	11	nd	ANA	nd	nd	Pemphigus v.	nd	Diffuse histiocytic Ly	nd
Kyndt/1997	1	CS (123 French pts)	76 F	8	nd	Scl70	L	Yes	nd	nd	CMML	nd
Kojima/2006	2	CS (Japan)	nd	nd	nd	nd	nd	nd	nd	nd	B cell follicular Ly	nd
Kuo/2012	6	RS (2,053 Taiwanese pts)	1 M, 5 F	nd	nd	nd	nd	nd	nd	nd	Ly (3), myeloprolif. dis. (2), CML (2)	nd
Lee/2001	1	CR (Korea)	56 F	15	L	ACA	CREST	No	Porphyria c.t.	Splenomegaly	Myelofibrosis	nd
Marto/2014	1	CR (Portugal)	76 F	0	L	ACA	L	No	Multiple polyps of the colon	Multiple adenop., diarrhea, and rectorrhagia	IIIb-staged mantle cell NHL of the colon	Ly remission with R-CHOP
Miyamoto/2000	1	CR (Japan)	55 F	17	nd	nd	nd	No	nd	Fever, fatigue, pancytopenia, and splenomegaly	Myelofibrosis	Treated with pulse steroids and transfusions
Olesen/2010	18	RS (2,040 Danish pts)	M/F 9/9	2/18 : <1	nd	nd	nd	nd	nd	nd	NHL (10); leukemia (7)	nd

Colaci et al. Case Rep Rheumatol. 2017:2017:6230138

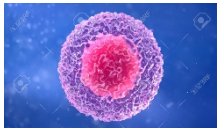
Table 1: Continued.

First author/year	Number cases	Study type (country)	Age/sex	Dis. duration	Skin subset	Serology	Visceral inv.	Ass. Sjogren	History notes	Clinical picture	Hematological malignancy	Outcomes
Owlia/2014	1	CR (Iran)	58 M	15	L	nd	E	No	smoker (30 p-y)	Lumbar pain (extensive bony infiltration)	MM	Death 2 years after VAD/bortezomib
Ozturk/2006	1	CR (Turkey)	54 F	5	L	nd	CREST	No	nd	Sweet syndrome	Myelofibrosis	Improved with steroids and hydroxyurea
Parma/1996	1	CR (Italy)	68	3	nd	nd	nd	nd	nd	Primitive muscle and bone involv.	Large multilobated B-cell NHL	Improved
Prochorec-Sobieszek/2004	1	CR (Poland)	22 F	<1	L	PmScl	nd	No	nd	Parotid swelling	Parotid MALToma	nd
Rodrigues/1989	1	CR (Brazil)	nd	nd	nd	nd	nd	nd	Concom. thyroid adenoca.	nd	Ileal B-cell Ly	Rapid deterioration until death
Rosenthal/1993	3	RS (233 Swedish pts)	nd	<1 (1)	nd	nd	nd	nd	nd	nd	NHL (2), not better specified hematological cancer (1)	nd
Rothfield/1992	1	CS (148 USA pts)	nd	nd	nd	Scl70	nd	nd	nd	nd	Lymphocytic Ly	nd
Roumm/1985	3	CS (262 USA pts)	33 F, 50 F, 71 F	3.5, 6.5, 5.5	nd	nd	nd	nd	nd	nd	CML, AML, and histiocytic Ly	nd
Ryczek/2013	1	CR (Poland)	nd	nd	nd	nd	nd	nd	nd	nd	CML	nd
Schnack/1954	1	CR (Austria)	53 F	8	D	nd	nd	nd	nd	nd	MM	nd
Senel/2006	1	CR (Turkey)	65 F	0	D	Scl70	L, K	No	nd	Weakness, sweating, and weight loss	CML	nd
Shvidel/2002	1	CS (Israel)	71 F	nd	nd	nd	nd	nd	nd	nd	T large granular lymphocytic leukemia	nd
Siau/2011	5	CS (68 UK pts)	nd	0 (case of PC)	L	nd	nd	nd	nd	nd	MM (2), diffuse large B-NHL, thyroid NHL, solitary IgM PC	nd
Sidi/1990	2	CS (Israel)	47 M, 77 M	20; 11	L	nd	CREST	No	nd	Generalized lymphoadenopathy	B-CLL	Alive up to 2 years; death for bronchopneumonia and paralytic ileus
Sugai/1987	1	CR (Japan)	67 F	11	D	ANA	E, L	Yes	nd	Parotid swelling and generalized lymphadenopathy	IIIb-staged NHL	Death after 3 COPP cycles for complicating interstitial pneumonitis
Suzuki/1994	1	CR (Japan)	68 M	3	D	ANA	nd	No	nd	Gait disturbance, anemia, and hemorrhagic stroke	Brain diffuse large B-NHL	Death for pneumonitis during BACOPP chemotherapy
Szekanecz/2008	3	CS (218 Hungarian pts)	53; 67; 69 F	2; 1.9; 0.7	D	Scl70;	L-H-E; none; L-H-K-E	nd	nd	nd	(2) b-CLL; (1) chronic small lymphocytic B NHL	Surviving > 5 years

Table 1: Continued.

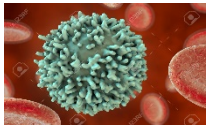
First author/year	Number cases	Study type (country)	Age/sex	Dis. duration	Skin subset	Serology	Visceral inv.	Ass. Sjogren	History notes	Clinical picture	Hematological malignancy	Outcomes
Talbott/1979	2	CS (USA)	64 M; 73 M	<1; 10	L; D	nd	None; L-H	Probable	Pt number 1 coal miner	Backache; generalized weakness	MM	Rapid deterioration and death
Vettori/2010	1	CR (Italy)	45 F		Sine sclerod.					Progressive weight loss	Gastric B-cell Ly	
Watanabe/1994	1	CR (Japan)	44 F	nd	nd	nd	nd	nd	nd	Leukocytosis, thrombocytosis	CML	CML remission and SSc improvement with therapy
William/2011	1	CR (USA)	61 M	30	L	ACA	E, L	No	nd	Thrombocytopenia, cervical adenopathy	Small lymphocytic B-NHL	Remission with FCR
Wooten/1998	1	CR (USA)	nd	3	L		CREST	nd	Porphyria c.t.	nd	CML	nd
Yamamoto/2005	1	CR (Japan)	72 M	5	D	Scl70	L	nd	nd	Multiple lymphoadenopathy	Angioimmunobl. T cell Ly with EBV-assoc. B cell lymphoprol. dis.	Died 6 months after CHOP therapy because of sepsis, initially improved
Present study	2	CR (Italy)	37 M; 72 F	2; 28	D; L	SSA/SSB ACA	E, L; CREST + L	Yes; no	nd; previous breast cancer	Weakness, sweating, and weight loss; asymptomatic	Diffuse large B-NHL; marginal B-NHL	Died few months after during R-CHOP therapy; lung lobe resection and remission
Total	130 pts											

T Cell



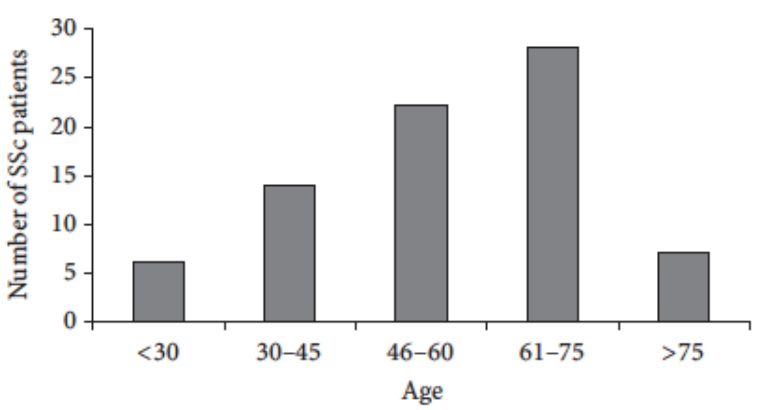
- > prevalence of thymic hyperplasia in SSc (during the first years)
- Pathological alteration of T ly maturation could lead to a deficient or incomplete T cell maturation, immunological alterations of SSc etiopathogenesis
- The autoreactivity of T cells strictly involves also B cells that produce a number of different autoantibodies,which in turn stimulate fibroblasts' toll-likereceptors-4 and induce endothelial dysfunction.

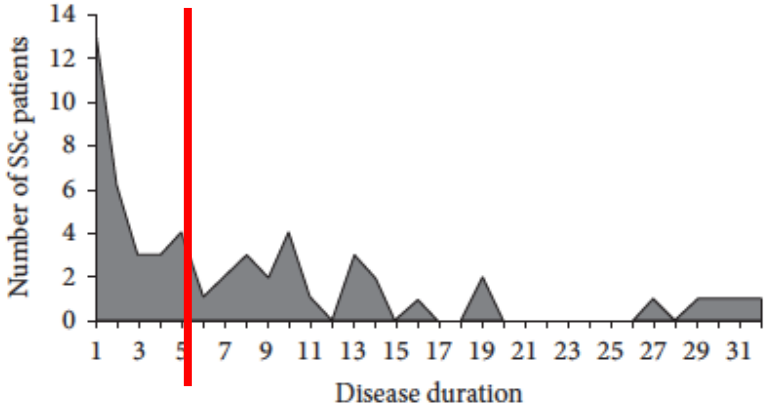
B Cell



- Autoreactive Bcells are more prone to undergo malignant transformation.
- In parallel, the chronic activation of the inflammatory response due to autoantigen-driven immune stimulation in specific organ tissues (i.e.in Sjogren's syndrome) is associated with an increased risk of lymphomas.
- Consistently, in SSc, prevalence of B cells versus the T cells cancers, suggesting that the systemic autoimmune activation plays a pivotal role in the carcinogenetic evolution.

Colaci et al. Case Rep Rheumatol. 2017;2017:6230138





The Peripheral B lymphocytes activated →altered percentage of apoptotic cells compared to HC

The levels of histone acetylation and methylation (> gene transcription) in Bcells from SSc correlate with disease activity

Concentrations of BAFF and APRIL, cytokines regulating B cell activity, survival, and proliferation, are found elevated in SSc in comparison with healthy controls, particularly in patients with active or severe disease

The amplification of the percentage of less mature B lymphocytes understandably leads to a major risk for lymphoid carcinogenesis.

The possibility that cancer mutations might trigger SSc itself, at least in patients with anti-RNApolymeraseIII autoantibodies

More frequently, B cells-derived lymphomas and leukaemias may be diagnosed in the first years of the disease and represent a significant warning for patients' prognosis

> Activity > Risk < Time

T. Sanges Guerrier et al. *Rev Med Interne*, 2016
Y.Wang et al. Clinical Immunology, vol. 149, no. 1, pp. 46–54, 2013

BREAST CENCER

Clinico-serological features of scleroderma patients with/without breast cancer.

	All patients	Patients with breast cancer	Patients without breast cancer	p value
	No = 318	No = 12	No = 306	
Age (mean ± SD)	51.5 ± 14.5	52.7 ± 12.7	51.4 ± 14.6	ns
M/F	31/287	1/11	30/176	ns
Smoke habit	97 (30.5%)	4 (33.3%)	93 (30.4%)	ns
Cutaneous subset (L/D)	278/40	12/0	266/40	ns
Skin ulcers	123 (38.7%)	6 (50%)	117 (38.2%)	ns
ACA	140 (44%)	6(50%)	134 (43.8%)	ns
Anti-Scl70	105 (33%)	4 (33.3%)	101 (33%)	ns
ANoA	45 (14%)	2(16.7%)	44 (14.4%)	ns
Interstitial lung disease (X-ray)	152 (47.8%)	8 (66.7%)	144 (47%)	ns
PAPs >35 mm Hg	54 (17%)	4 (33.3%)	50 (16.3%)	ns
FVC <75%	40 (12.6%)	2 (16.7%)	38 (12.4%)	ns
Therapy with CYC	36 (11.3%)	1 (8.3%)	35 (11.4%)	ns

Legend: L = limited; D = diffuse; CYC = cyclophosphamide. Interstitial lung disease was diagnosed by means of chest X-ray and/or HRCT.

Interestingly, found a close temporal relationship between SSc onset and breast cancer diagnosis, differently from previous findings regarding lung cancer (median 2.5)

Paraneoplastic manifestation?

Alternatively, a pathophysiological link between SSc and breast cancer could be present, i.e. the endothelial cell activation. VEGF PDGF FGF over expression→ promote new vessel formation, thus explaining the defective angiogenesis in the disease.

CYC is one of the treatments of SSc that hypothetically could increase the occurrence of breast cancer? Absence of a direct oncogenetic role

Colaci M et al. Autoimmun Rev. 2014 Feb;13(2):132-7

Diot E et al. Occup Environ Med 2002;59:545–9

BREAST CENCER

SSc and breast cancer: review of the literature.

Authors (year) [Ref.]	Country	Study design	No. of pts	Associations	Follow-up	SSc pts with BC	BC ≤12 months from SSc onset	BC before SSc onset	Comparison of breast cancer incidence vs general population
Duncan SC and Winkelmann RK (1979) [31]	Mayo Clinic, USA	Cohort-based	2141[a]		1959–1975[b]	13 (0.6%)	8 (0.4%)	5 (0.2%)	n.a.
Lee P et al. (1983) [24]	Toronto, Canada	Cohort-based	95		n.a.	2 (2.1%)	0	2 (2.1%)	n.a.
Roumm AD and Medsger TA Jr (1985) [4]	Pittsburgh area, USA	Cohort-based	262	Short dis. duration	1335 p/y	5 (1.9%)	4/5		Frequency not increased
Abu-Shakra M et al. (1993) [2]	Canada	Cohort-based	248	Short dis. duration	2001 p/y	5 (2%)	3/5		SIR 6.1 (6.0–6.2)
Rosenthal AK et al. (1995) [6]	Sweden	Registry-based	917		7403 p/y	10 (1.1%)	2/10		SIR 1.1 (0.5–2.1)[c]
Higuchi M et al. (2000) [7]	Japan	Cohort-based	43		383 p/y	0	0		n.a.
Hill CL et al. (2003) [8]	South Australia	Registry-based	441		6.1 ± 2.8 (female)	8 (1.8%)	the majority		SIR 1.62 (0.7–3.19)
Launay D et al. (2004) [29]	France	Cohort-based	203		1990–2002[a]	8 (3.9%)	6/8		n.a.
Chatterje S et al. (2005) [25]	Detroit area, USA	Registry-based	538		4908 p/y (female)	9 (1.8%)	n.a.		SIR 0.81 (0.37–1.53)
Derk CT et al. (2006) [9]	Pennsylvania, USA	Cohort-based	769	ILD	3775 p/y	11 (1.4%)	n.a.	13 (1.7%)	SIR 0.99 (0.41–1.57)
Lu TY et al. (2008) [21]	Australia	Registry-based	389	Family history, low incidence of HRT	n.a.	18 (4.6%)	2/18	3 (0.8%)	n.a.
Joven BE et al. (2009) [10]	Spain	Cohort-based	275		n.a.	8 (2.9%)	n.a.		n.a.
Siau K et al. (2009) [11]	South-West England	Registry-based	68		n.a.	5 (7.3%)	n.a.		SIR 3.07 (1.0–7.16)
Kang KY et al. (2009) [12]	South Korea	Cohort-based	112		1990–2007[a]	0	0		n.a.
Olesen AB et al. (2010) [13]	Denmark	Registry-based	2040		16,003 p/y	28 (1.4%)	2/28		SIR 1 (0.7–1.5)
Airò P et al. (2011) [30]	Italy	Cohort-based	360		4041 p/y	8 (2.2%)	0/8	5 (1.4%)	n.a.
Szekanecz E et al. (2012) [3]	Hungary	Cohort-based	218		n.a.	1 (0.4%)	0	1 (0.4%)	SIR 5.8 (n.a.)
Hashimoto A et al. (2012) [14]	Japan	Cohort-based	405	Heart involvement	4787 p/y	4 (1%)	n.a.		SIR 1.02 (0.02–2.02)
Kuo CF et al. (2012) [18]	Taiwan	Registry-based	2953		5.7 years (female)	11 (0.5%)	n.a.		SIR 1.28 (0.72–2.39)
Present series	Italy	Cohort-based	318	Short dis. duration	3270 p/y	12 (3.8%)	3/12	4 (1.2%)	SIR 2.1 (1.13–3.90)[d]

Legend: BC = breast cancer; pts = patients; n.a. = not available; ILD = interstitial lung disease; p/y = patient-year; HRT = hormone replacement therapy; SIR = standardized incidence ratio. Breast cancer 'concurrent to SSc' means that cancer diagnosis was made by 1 year the onset of SSc.

[a] The cohort included patients with localized scleroderma.

[b] Study time interval.

[c] Considering 8 cases of breast cancer.

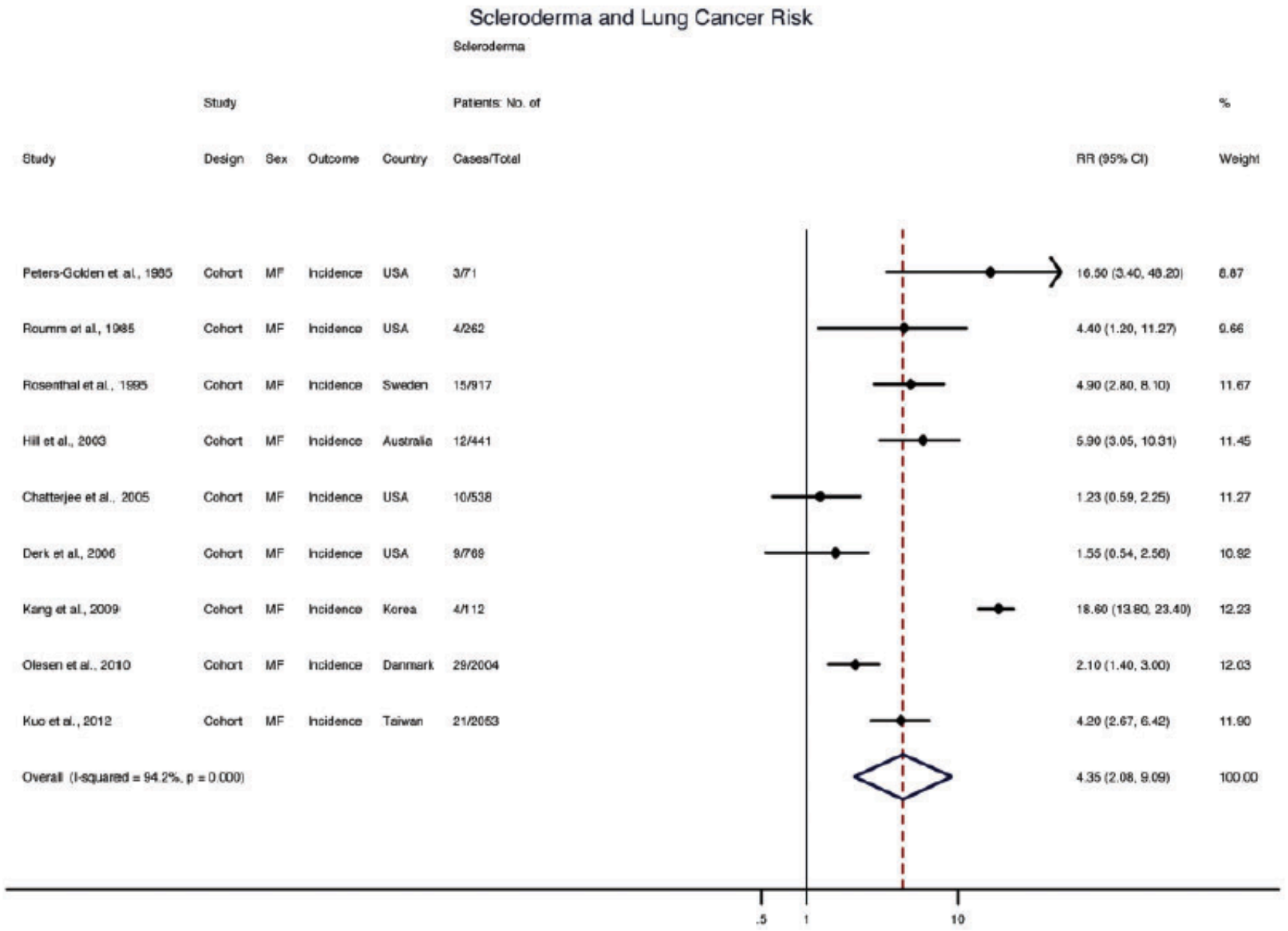
[d] SIR calculated with the incidence of breast cancer found on the series of 202 SSc patients from the same geographical area.

M. Colaci et al. / Autoimmunity Reviews 13 (2014) 132–137

- A significant increase of the incidence of breast cancer compared to sex- and age-matched general population
- The incidence of breast cancer in SSc reported in the literature is extremely variable
- Scleroderma patients with breast cancer presented a medially shorter SSc duration at the time of the malignancy appearance compared to another frequent neoplastic complication, namely lung cancer

SYSTEMATIC REVIEW AND META-ANALYSIS

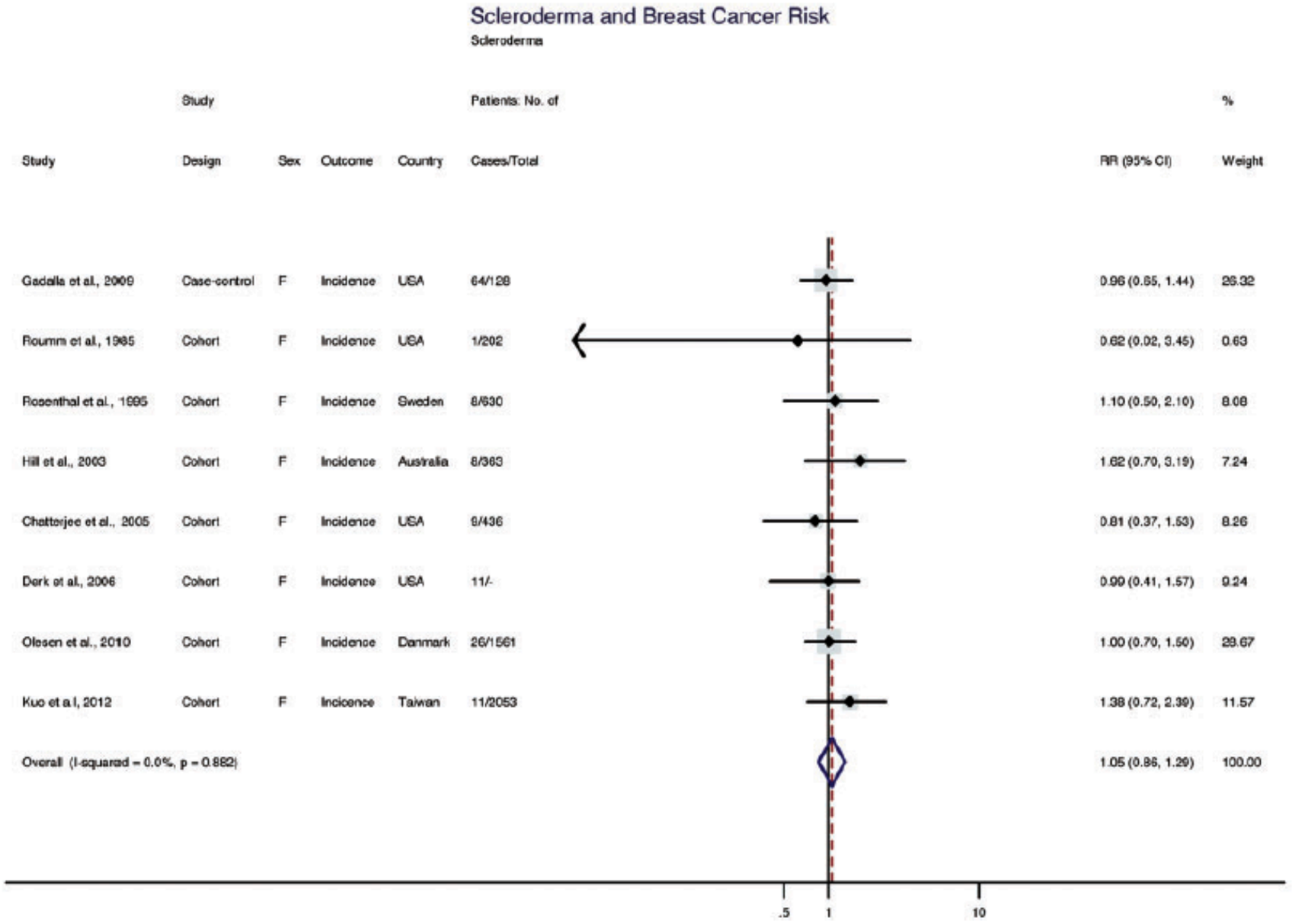
FIG. 2 Summary RR for lung cancer in scleroderma patients.



Bonifazi et al. Rheumatology (Oxford). 2013 Jan;52(1):143-54

SYSTEMATIC REVIEW AND META-ANALYSIS

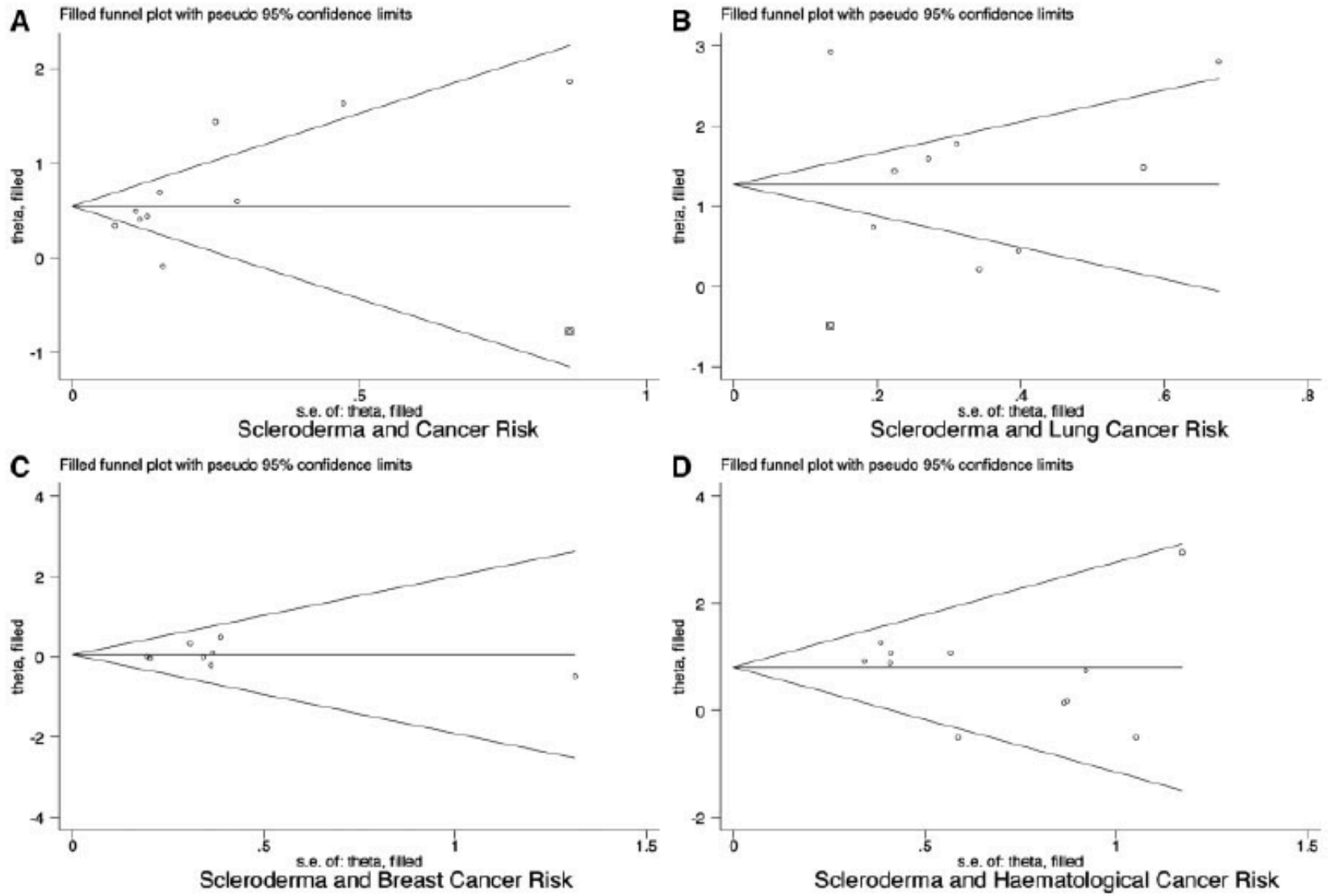
FIG. 4 Summary RR for breast cancer in scleroderma patients.



Bonifazi et al. Rheumatology (Oxford). 2013 Jan;52(1):143-54

SYSTEMATIC REVIEW AND META-ANALYSIS

FIG. 5 Trim and fill funnel plot of studies on the association between scleroderma and cancer risk..



The present meta-analysis provides definite estimates on the association between scleroderma and malignancy

The results indicated a strong association between scleroderma and lung and haematological cancers

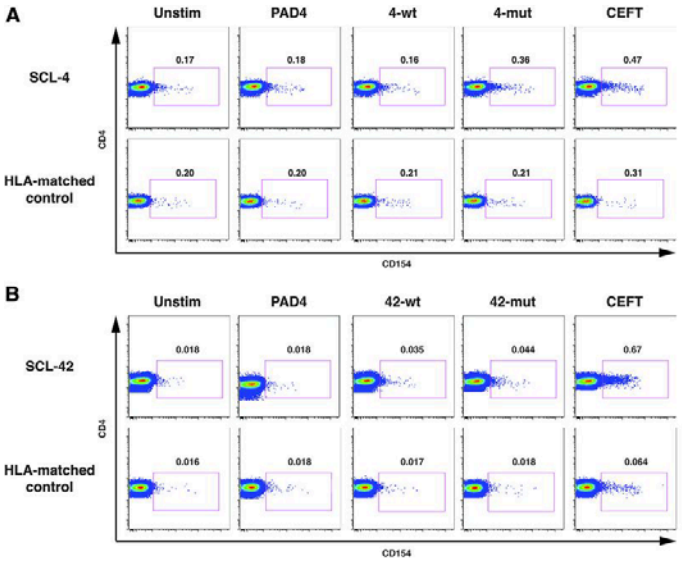
Bonifazi et al. Rheumatology (Oxford). 2013 Jan;52(1):143-54

Sciencexpress Research Articles

Association of the Autoimmune Disease Scleroderma with an Immunologic Response to Cancer

Christine G. Joseph,[1*] Erika Darrah[2,*] Ami A. Shah,[2*] Andrew D. Skora,[1*] Livia A. Casciola-Rosen,[2] Fredrick M. Wigley,[2] Francesco Boin,[2] Andrea Fava,[2] Chris Thoburn,[3] Isaac Kinde,[1] Yuchen Jiao,[1] Nickolas Papadopoulos,[1] Kenneth W. Kinzler,[1†] Bert Vogelstein,[1†] Antony Rosen[2†]

Fig. 1 Mutant and WT peptide-specific CD4+ T cells in patients SCL-4 and SCL-42.CD154 expression on CD4+ T cells was assayed after stimulation (18 hours) with patient-specific WT or mutant RPC1 peptides, PAD4 peptide (negative control), or a pool of peptides from infectious agent antigens (CEFT, positive control).



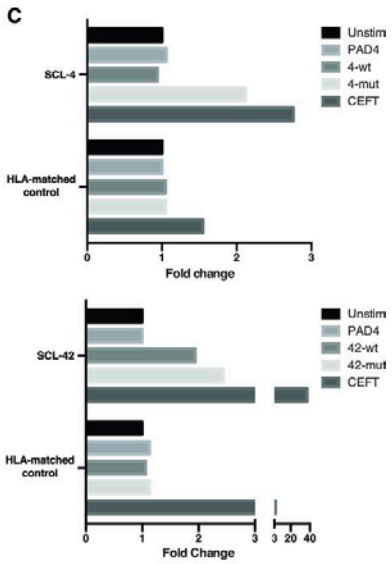
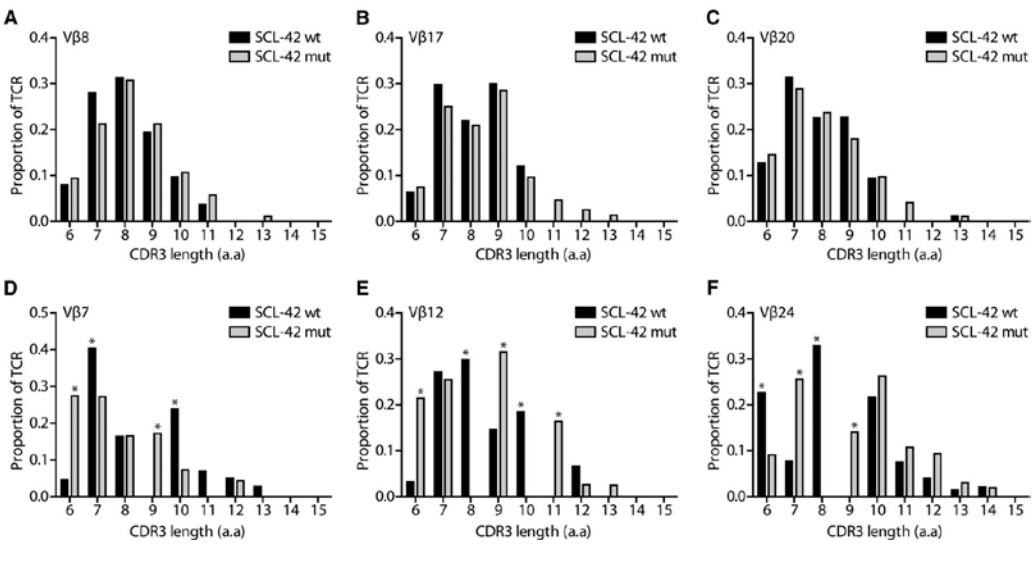


Fig. 2 Vβ-family usage and CDR3 length in patient SCL-42 PBMCs stimulated with WT or mutant peptides.SCL-42 PBMCs were stimulated for 6 days with patient-specific mutant (gray bars) and corresponding WT (black bars) RPC1 peptides.



Genetic alterations of POLR3A locus in pts with ab RPC1

Analyses of peripheral blood

lymphocytes and serum suggested that *POLR3A* mutations triggered cellular immunity and crossreactive humoral immune responses.

These results offer insight into the pathogenesis of

scleroderma and provide support for the idea that acquired immunity helps to control naturally occurring cancers

Science

AAAS

Christine G. Joseph et al. Science 2014;343:152-157

Table 2. Allelic ratios of SNP loci within and closely surrounding the *POLR3A* gene.

		Patients with RPC-1 antibodies								Patients without RPC-1 antibodies							
Chr 10 position	SNP ID	SCL- 1	SCL-2	SCL-4	SCL-13	SCL-35	SCL-42	SCL-81	SCL-82	SCL-5	SCL-8	SCL-11	SCL-12	SCL-19	SCL-24	SCL-32	SCL-85
79,213,314	rs1054608	55%	88%	102%	NI	NI	68%	83%	NI	NI	NI	99%	NI	99%	103%	NI	NI
79,222,098	rs2165046	52%	88%	99%	NI	NI	69%	76%	NI	NI	NI	99%	NI	94%	102%	NI	NI
79,222,113	rs1058203	NI	NI	NI	NI	100%	NI	78%	NI	NI	102%	NI	NI	NI	99%	NI	99%
79,222,157	rs1058202	50%	NI	102%	NI	NI	NI	NI	NI	NI	102%	NI	NI	NI	NI	NI	97%
79,230,809	rs10762763	53%	86%	103%	NI	NI	69%	85%	NI	NI	NI	102%	NI	102%	104%	NI	NI
79,235,661	rs2289311	55%	91%	103%	NI	NI	66%	88%	NI	97%	NI	104%	NI	100%	103%	NI	NI
79,260,691	rs10824579	NI	93%	97%	NI	NI	70%	73%	NI	NI	NI	96%	NI	97%	103%	NI	NI
79,323,400	rs1248888	80%	NI	NI	NI	102%	NI	87%	NI	101%	102%	NI	NI	NI	101%	NI	96%
79,406,970	rs2241547	78%	NI	NI	NI	104%	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	102%
79,415,741	rs12241228	NI	NI	NI	NI	NI	NI	NI	NI	100%	NI	NI	NI	NI	NI	NI	NI
79,415,795	rs3815891	70%	NI	NI	NI	NI	NI	NI	NI	103%	NI	NI	NI	NI	NI	NI	102%
79,419,810	rs7094028	79%	NI	NI	NI	NI	NI	NI	NI	98%	NI	NI	NI	NI	NI	NI	104%
79,424,105	rs2818827	75%	NI	104%	NI	100%	NI	NI	NI	NI	102%	NI	NI	NI	NI	NI	102%
79,424,140	rs12267816	NI	NI	NI	NI	NI	NI	NI	NI	104%	NI	NI	NI	NI	NI	NI	NI
79,442,860	rs2493568	76%	NI	96%	44%	101%	NI	91%	NI	NI	103%	NI	NI	NI	NI	NI	101%
79,514,037	rs67287610	NI	NI	NI	45%	100%	NI	95%	NI	99%	NI	NI	NI	NI	NI	NI	NI
79,514,072	rs4979801	85%	NI	NI	46%	101%	NI	95%	NI	NI	96%	NI	NI	NI	NI	NI	104%
79,546,360	rs2253909	NI	NI	94%	40%	102%	NI	76%	NI	102%	99%	NI	NI	NI	NI	NI	NI
79,549,686	rs2253513	78%	NI	102%	41%	102%	NI	88%	NI	NI	100%	NI	NI	NI	NI	NI	90%
79,573,735	rs2114907	82%	NI	103%	43%	104%	NI	78%	96%	NI	104%	100%	NI	NI	NI	NI	NI
79,615,946	rs1249134	86%	90%	98%	44%	102%	NI	85%	NI	NI	NI	99%	NI	104%	NI	NI	NI
79,618,728	rs1249126	75%	91%	103%	46%	101%	NI	74%	NI	NI	NI	NI	NI	98%	NI	NI	NI
79,654,802	rs2434123	NI	NI	NI	46%	NI	67%	NI	102%	NI	104%	NI	NI	NI	NI	NI	NI
Allelic ratio average*		71%	88%	99%	44%	101%	69%	83%	99%	99%	101%	100%	NI	99%	102%	NI	100%
Allelic ratio S.D. (%)		13%	4%	6%	2%	4%	3%	7%	4%	5%	3%	2%	NI	3%	2%	NI	4%

*Entries represent the allelic ratios of the indicated SNPs. The values in normal individuals were 100% +/- 3.10%. Allelic ratios less than 2 standard deviations (SD) from the mean (i.e., <94%) are highlighted in red. A tumor was considered to exhibit LOH if more than 3/4 of the informative SNPs exhibited alleic ratios <94%. NI: Non-informative, i.e., the SNP was not heterozygous in the normal cells of the patient (see Supplemental material, Materials and Methods).

Given the ubiquitous presence of somatic mutations in solid tumors, these new data add credence to the idea that immunoediting could play a major role in limiting the incidence of human cancer—an old hypothesis that has recently garnered more attention.

Matsushita H, et al. Nature. 2012; 482:400–404

A REVIEW OF CURRENT DATA

Autoantibodies	Many studies have found an association between the diagnosis of SSc and malignancy with specific antibodies, most commonly anti-RNA polymerase III.
Fibrosis	The scarring of pulmonary tissue can block the lymphatic channels and lead to accumulation of carcinogens. These carcinogens participate in the transformation of hyperplastic epithelium initially to metaplasia, then to neoplasia. Through this process, fibrotic tissue might be the nidus of cancer in SSc patients.
Lung	Young age at disease onset, the presence of ILD, and female gender are believed to confer higher risk of developing lung malignancy in patients with SSc.
Breast	There is a considerable amount of data suggesting an increased incidence of breast cancer in patients with SSc, but the evidence remains weak. Notably prolonged use of CCBs, increased collagen deposition, as well as the hormonal imbalance that were commonly seen in patients with SSc who developed breast cancer.
Esophagus	Although these results still need to be confirmed by larger cohorts with longer follow-up, the proposed risk suggests the need for close surveillance of SSc patients with BE.

Zeineddine et al. J Clin Med Res. 2016;8(9)625-632

A REVIEW OF CURRENT DATA

Squamous cell carcinoma of the skin	Patients with pansclerotic morphea are found to be at a higher risk for developing squamous cell carcinoma of the skin. A few cases have been reported in the literature of young patients with longstanding pansclerotic morphea developing recurrent squamous cell carcinoma highly refractory to treatment.
Non Hodgkin lymphoma	It has been suggested that chronic stimulation of polyclonal B cells, deficiency of T and NK cells, and the presence of HLA-DR5 genotype might be linked to an increased frequency of lymphomas and other hematological malignancies in patients with SSc. The development of lymphoma in these case reports can still be incidental.
Multiple Myeloma	Although multiple other case reports are available in the literature describing the concurrence of MM and scleroderma, there are no robust data to show an actual link between these two entities.
Cervical and Vulvar	No specific recommendations are available so far regardregarding the prevention or treatment of HPV in patients with SSc, but clinicians should be aware of the need to routinely screen for pre-invasive genital lesions before the introduction of biological or immunosuppressive agents.

Zeineddine et al. J Clin Med Res. 2016;8(9)625-632

Novel risk factors related to cancer in scleroderma

David Bernal-Bello, Jaime García de Tena, Alfredo Guillén-del Castillo, Albert Selva-O'Callaghan, Eduardo L. Callejas-Moraga, Ana María Marín-Sánchez, Vicent Fonollosa-Pla, Carmen Pilar Simeón-Aznar

PII: S1568-9972(17)30082-4
DOI: doi:10.1016/j.autrev.2017.03.012
Reference: AUTREV 1991

Table 2. Comparison of treatment-related features in systemic sclerosis patients with and without malignancy.

Treatment	Malignancy	No Malignancy	*p*
Immunosuppressive			
CS [n=421 (%)]	*16/42 (38.1)*	*16/379 (44.3)*	*0.440*
CYC [n=431 (%)]	*6/52 (11.5)*	*31/379 (8.2)*	*0.417*
MPA [n=428 (%)]	*4/49 (8.2)*	*50/379 (13.2)*	*0.318*
AZA [n=431 (%)]	*4/52 (7.7)*	*34/379 (9)*	*0.760*
MTX [n=432 (%)]	*0/53 (0)*	*17/379 (4.5)*	*0.116*
CI [n=432 (%)]	*3/53 (5.7)*	*15/379 (4)*	*0.632*
HQC [n=431 (%)]	*3/52 (5.8)*	*53/379 (14)*	*0.099*
TNFα-i [n=432 (%)]	*0/53(0)*	*3/379 (0.8)*	*1.000*
Rituximab [n=432 (%)]	*2/53 (3.8)*	*8/379 (2.1)*	*0.451*
IGs [n=432 (%)]	*0/53 (0)*	*9/379 (2.4)*	*0.257*
Non-Immunosuppressive			
ACEi [n=388 (%)]	*16/37 (43.2)*	*123/351 (35)*	*0.322*
ARB [n=309 (%)]	*8/29 (27.6)*	*52/280 (18.6)*	*0.243*
CCB [n=421 (%)]	*30/42 (71.4)*	*276/379 (72.8)*	*0.847*
Aspirin [n=423 (%)]	*14/44 (31.8)*	*186/379 (49.1)*	***0.030***
Non-aspirin antiplatelet agents [n=236 (%)]	*2/30 (6.7)*	*32/206 (15.5)*	*0.196*
PPI [n=415 (%)]	*31/36 (86.1)*	*302/379 (79.7)*	*0.355*
Statins [n=426 (%)]	*3/47 (6.4)*	*67/379 (17.7)*	*0.059*
Pentoxifylline [n=431 (%)]	*4/52 (7.7)*	*31/379 (8.2)*	*0.904*
ERAs [n=427 (%)]	*7/48 (14.6)*	*86/379 (22.7)*	*0.200*
PDE5i [n=427 (%)]	*5/50 (10)*	*54/377 (14.3)*	*0.405*
PGAS [n=430 (%)]	*1/51 (2)*	*39/379 (10.3)*	*0.068*

CS, corticosteroids; **CYC**, cyclophosphamide; **MPA**, mycophenolic acid; **AZA**, azathioprine; **MTX**, methotrexate; **CI**, calcineurin inhibitors; **HCQ**, Hydroxychloroquine **TNFα-i**, tumor necrosis factor alpha inhibitors; **IGs**, immunoglobulins **ACEi**, angiotensin-converting enzyme inhibitors; **ARB**, angiotensin receptor blockers; **CCB**, calcium channel blockers; **PPI**, proton-pump inhibitors; **ERAs**, endothelin receptor antagonists; **PDE5i**, phosphodiesterase-5 inhibitors; **PGAS**, prostaglandin analogues.

Il complesso PM / Scl è composto da diverse proteine con attività ribonucleasica che possono agire come potenziali autoantigeni

Table 3. Independent risk factors for cancer in systemic sclerosis patients by logistic regression modeling

Risk factor	Univariate Analysis		Multivariate analysis	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Telangiectasies	*0.53 (0.29-0.97)*	*0.036*	-	*0.578*
Slow capillaroscopic pattern	*2,41 (1.04-5.59)*	*0.035*	-	*0.146*
Anti-PM/Scl antibodies	*3,13 (1.14-8.62)*	*0.021*	*3.90 (1,31-11.61)**	*0.014*
Aspirin	*0,48 (0.25-0.94)*	*0.030*	*0.33 (0.12-0.90)**	*0.031*

**p* results from logistic regression analysis with forward stepwise selection procedure are shown.

The chemopreventive role of aspirin against cancer may be related to an inhibition of some eicosanoids pathways involved in tumour development

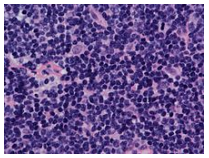
Bruni et al. 70 pts PM/Scl +, in 14 with cancer. L'anti-PM / Scl role of potential biomarker of more severe disease due to > frequency of malignant and renal crisis

Bruni C et al. Rheumatology 2016:kew382

CONCLUSION

LUNG

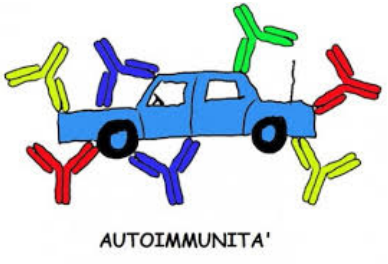
HAEMATOLOGICAL



RNA POL III

AUTOANTIBODIES

PM SCL?

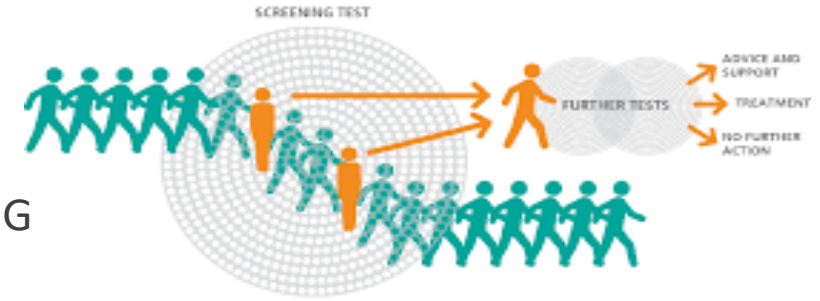


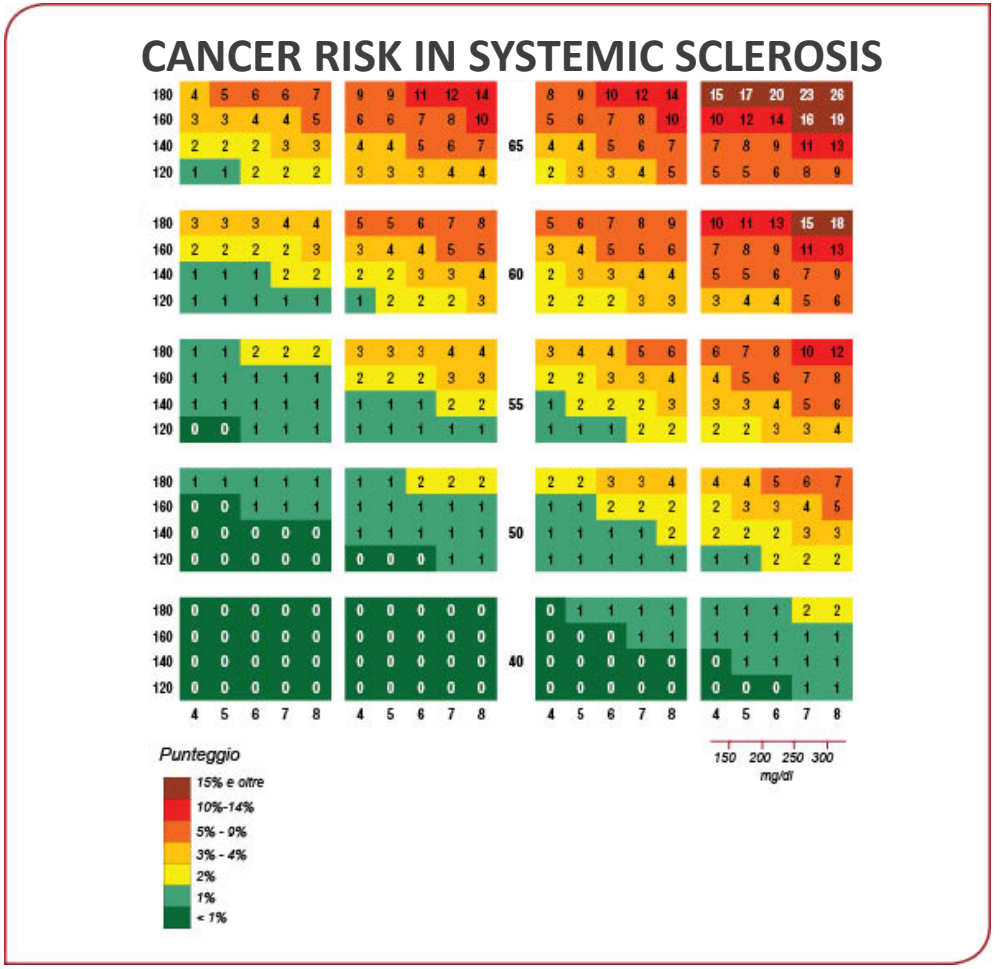
DISEASE ACTIVITY

TIMING OF ONSET

THERAPY

SCREENING





Purpose of Study

Adherence

Retrospective Analysis

>150 SSc female pts

Methods

Anamenstic and Clinical Evaluation

Serological and Antibodies Evaluation

Imaging

Specialistica Evaluation

- Pulmonary
- Cardiovascular
- Gastrointestinal
- Musculo-Skeletal
- Renal

Specific Questionnaire

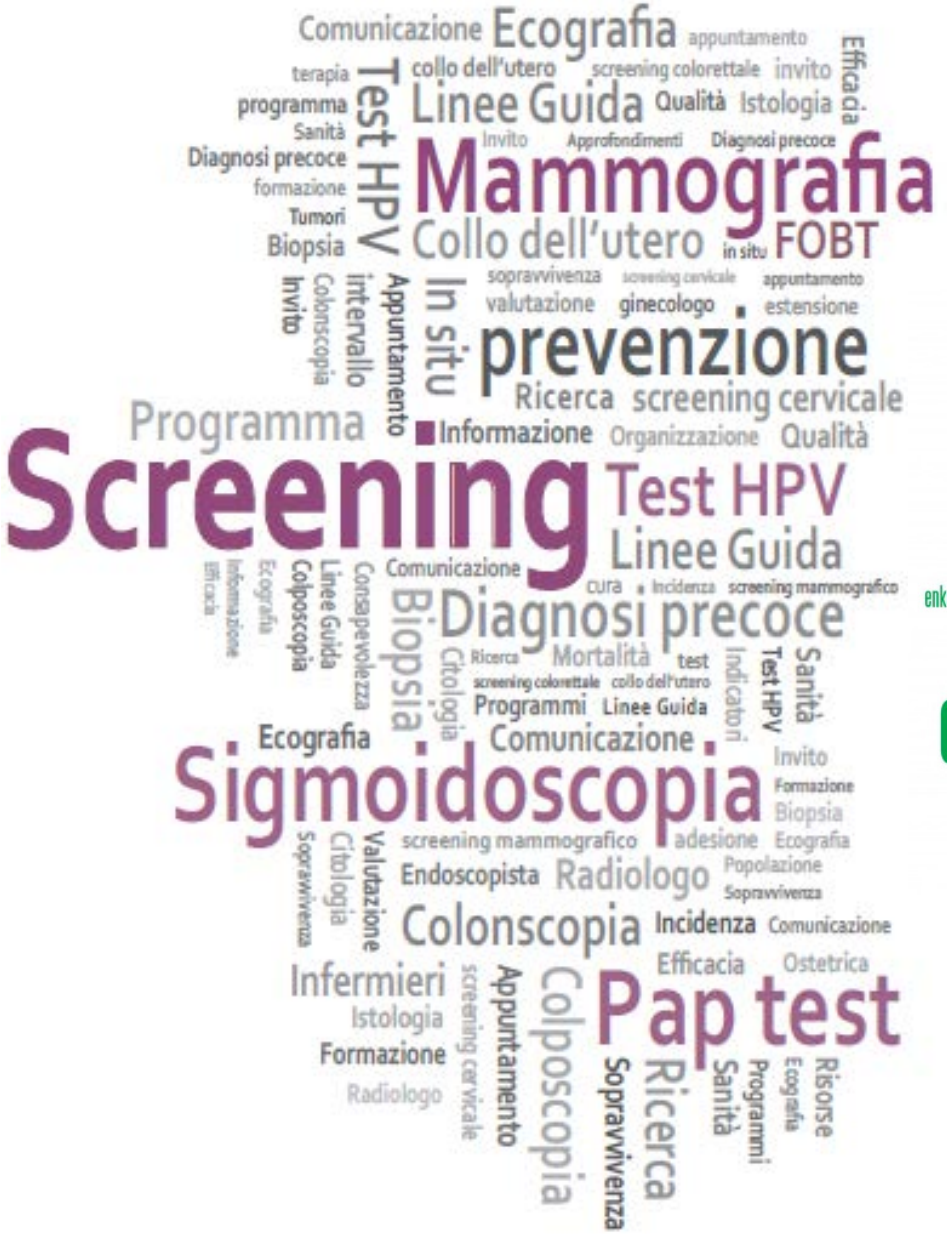
Mammografia per tumore alla mammella

Pap test o test HPV per il tumore del collo dell'utero

Sigmoidoscopia flessibile o FOBT per il tumore del colon-retto

The data obtained from the questionnaires will then be compared to those of the general population of the **PASSI Surveillance Program**

Courtesy of Nicotera A


Comunicazione
Ecografia
appuntamento
terapia
collo dell'utero
screening colorettale
invito
Efficacia
programma
Test HPV
Linee Guida
Qualità
Istologia
Sanità
Invito
Approfondimenti
Diagnosi precoce
Diagnosi precoce
Mammografia
formazione
Tumori
Collo dell'utero
FOBT
Biopsia
in situ
sopravvivenza
screening cervicale
appuntamento
valutazione
ginecologo
estensione
Invito
Colonscopia
intervallo
Appuntamento
In situ
prevenzione
Ricerca
screening cervicale
Programma
Informazione
Organizzazione
Qualità
Screening
Test HPV
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Comunicazione
Informazione efficacia
Ecografia
Colposcopia
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Incidenza
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Biopsia
Diagnosi precoce
Citologia
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Mortalità
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Indicatori
Sanità
Test HPV
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collo dell'utero
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Linee Guida
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Comunicazione
Invito
Sigmoidoscopia
Formazione
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Valutazione
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Sopravvivenza
Colonscopia
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Formazione
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Risorse
Radiologo
screening cervicale


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