Chapter 4
Epidemiology and Environmental Risk Factors

Jammie K. Barnes and Maureen D. Mayes

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Systemic sclerosis (SSc) is an autoimmune connective tissue disease characterized by excessive collagen deposition in the skin and internal organs with associated vasculopathy and autoantibody production [1]. Classification of SSc is divided into two main groups: limited and diffuse cutaneous disease [2]. The limited form is characterized by skin thickening that is confined to areas distal to the elbows and knees and generally is associated with less severe internal organ involvement. The diffuse form involves skin thickening proximal to the elbows and the knees as well as distal areas and is associated with more severe organ damage. This chapter will focus on the epidemiology of systemic sclerosis including both limited and diffuse cutaneous forms.

Incidence and Prevalence of SSc

Reported incidence rates (number of new cases per year) and prevalence estimates (number of total cases) vary widely depending on geographic location and methods of case ascertainment. In 1980, the American Rheumatism Association (ARA, now the American College of Rheumatology or ACR) developed classification criteria to distinguish SSc from other connective tissue diseases and to standardize reporting [3]. The absence of a standard classification system for SSc prior to 1980 makes it problematic to interpret occurrence figures for SSc in reports prior to this time.

Reported prevalence figures for definite SSc vary greatly from 30 cases/million (New Zealand, 1979) [4] to 443 cases/million (Canada, 2009) [5]. Accordingly, the annual incidence rates also vary widely between 1.96 cases/million from the time period 1950 to 1973 (New Zealand) [6] to 23 cases/million from the time period 1988 to 2006 (Spain) [7]. Table 4.1, modified from Chifflot et al. [8], summarizes multiple reports of incidence rates and prevalence figures from different geographic locations and time periods [4–7, 9–25]. Only studies that included men and women are shown and only figures for systemic sclerosis are reported, excluding "scleroderma spectrum disorders."

It is clear from these studies that there are regional variations in reported disease occurrence. This may reflect differences in case definition and/or differences in how complete methods of case ascertainment were. However, the differences may also arise from true variations among regions and this in turn could be due to differences in exposures to environmental triggers or due to population differences in frequency of susceptibility genes.

J.K. Barnes, MD (✉) • M.D. Mayes, MD, MPH
Internal Medicine, Division of Rheumatology and Immunogenetics,
University of Texas Health Science Center – Houston, Houston, TX, USA
e-mail: Jammie.k.barnes@uth.tmc.edu; maureen.d.mayes@uth.tmc.edu

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Table 4.1 Variations of incidence and prevalence of systemic sclerosis by region and time (Modified from Chifflot et al. [8])

Publication: First author, journal, year [reference]	Region	Case ascertainment method	Inclusion criteria (n = number of cases)	Study period	Incidence (per million/year)	Prevalence (per million)	Female/male ratio
North America							
Medsger, Ann Intern Med, 1971 [9]	Tennessee	Hospital record review	Study specific (n=60)	1947–1952	0.6	–	1.5/1
				1953–1968	4.5		
				1947–1968	2.7 (entire period)		
Michet, Mayo Clin Proc, 1985 [10]	Minnesota	Diagnostic retrieval system	ICDA (7th) (n=13)	1950–1979	10	138	12/1
Steen, Arthritis Rheum, 1997 [11]	Pennsylvania	Hospital record review	ACR + study specific (n=444)	1963–1972	9.6	–	3/1
				1973–1982	18.7	–	
				1963–1982	13.9 (entire period)	–	
Maricq, Arthritis Rheum, 1989 [12]	South Carolina	Multistage population survey	ACR + study specific (n=2)	1989	–	286	–
Mayes, Arthritis Rheum, 2003 [13]	Michigan	Multiple sources (CR)	ACR and CREST (n=706)	1989–1991	21	276	4.6/1
Robinson, Cur Med Res Op, 2008 [14]	USA	2 Medical/drug claims datasets	ICD diagnostic codes	2001–2002	–	300	–
Bernatsky, Arth Rheum, 2009 [5]	Quebec	Hospital and physician billing databases	ICD diagnostic codes	2003	–	443	–
Australia							
Wigley, Soc Sci Med, 1980 [4]	New Zealand	Hospital record review	Study specific	1950–73	1.96	–	–
Eason, Aust NZ J Med, 1981 [6]	New Zealand	Hospital record review and specialist practices	ACR(n=50)	1970–79	6.3	30	3/1
Englert, Aust NZ J Med, 1999 [15]	Sydney	Hospital record review	ACR + study specific	1974–88	12	45.2 (1975)	2.3/1
						86.2 (1988)	
Chandran, Aust NZ J Med, 1995 [16]	South Australia	Hospital record review	ACR + study specific + overlap syndrome (n=215)	1987–1993	–	208	4/1
Roberts-Thomson, Int Med J, 2001 [17]	South Australia	Multiple sources	ACR + study specific + overlap syndrome (n=548)	1993	15.1	200	4/1
				1999	22.8	233	
Roberts-Thomson, Int Med J, 2006 [18]	South Australia	Multiple sources	ACR + study specific + overlap syndrome (n=353)	1993–02	20.4	232.2	–
Japan							
Tamaki, Arch Dermatol Res, 1991 [19]	Tokyo	Public health system	ACR (n=629)	1987	7.2	38	14/1
UK and Europe							
Silman, Br J Rheumatol, 1988 [20]	England (West Midlands)	Multiple sources	Study specific (n=128)	1986	3.7	31	–
Allcock, Rheumatology, 2004 [21]	England (Newcastle)	Multiple sources	ACR + Leroy/Medsger (n=80)	2000	–	88	5.2/1

Geirsson, Ann Rheum Dis, 1994 [22]	Iceland	Multiple sources	ACR + CREST ($n = 18$)	1975–1990	3.8	71	8/1
Kaipiainana, J Int Med, 1996 [23]	Finland	Multiple sources	ACR + CREST ($n = 4$)	1990	3.7	–	–
Le Guern, Rheumatology, 2004 [24]	France (Seine-St-Denis)	Multiple sources (CR)	ACR + Leroy/Medsger ($n = 15$)	2001	–	158	11/1
Alamanos, Semin Arthritis Rheum, 2005 [25]	Greece (North-West)	Multiple sources	ACR + Leroy/Medsger ($n = 109$)	1981–2002	11	154	8.9/1
Arias-Nunez, Medicine, 2008 [7]	Spain (northwest)	Two-stage hospital based survey	ACR + Leroy/Medsger ($n = 78$)	1988–2006	23	277	–

ACR American College of Rheumatology, *CR* capture–recapture method, *CREST* calcinosis Raynaud's phenomenon esophageal involvement sclerodactyly telangiectasia, *ICD* International Classification of Diseases, *ICDA* International Classification of Diseases, Adapted

Temporal Changes in Incidence Rates

Studies by Medsger et al. [9] and Steen et al. [11] reported changes in the incidence rate (number of new SSc cases per year) over time. Using a hospital record review approach in Tennessee [9], the incidence of SSc was reported to have increased from 0.6 cases/million/year for the years 1947–1952 to 4.5 cases/million/year for the period 1953–1968. Applying a similar approach in Pennsylvania, the incidence of SSc was observed to almost double from 9.6/million/year for the period 1963–1972 to 18.7/million/year for the next decade (1973–1982). However, this latter figure of almost 19/million/year was quite similar to the incidence rate reported in Michigan [13] of 21 new cases/million/year for the study period of 1989–1991 suggesting that the increase in incidence did not continue.

Similarly, incidence figures from New Zealand and Australia suggest an increase over time with an observed incidence that increased from 1.96 for the period 1950 to 1973 to 6.3 in the 1970s, to 12.0 in the period 1974–1988 to 15.1 in 1993, and to 22.8 in 1999 (all incidence figures are per million per year). However, case ascertainment methods also improved during this period making it problematic to interpret these results.

Although taken as a whole these reports are suggestive of increasing incidence, it is difficult to reliably conclude that this is the case, as other changes such as better physician and patient awareness and the establishment of classification criteria for SSc could also account for the apparent increase in identified cases.

Geographic Variations in SSc Occurrence

Higher prevalence figures have been consistently reported in North America and Australia as compared to Japan and Europe. Three recent US studies [12–14] covering the time period 1989–2002 have reported quite similar prevalence figures of 286, 276 and 300 cases/million, respectively, in spite of using dissimilar methods of case ascertainment. The South Carolina study [12] was population based and used a questionnaire with a physical exam done among the positive responders. This resulted in an estimated prevalence of 286 cases/million for systemic sclerosis (SSc) and an estimate of 3,790 cases/million "scleroderma spectrum disease" in 1989. This latter prevalence figure is likely related to the inclusion of overlap syndromes and/or primary Raynaud's disease because the questionnaire focused on Raynaud's phenomenon symptoms. The Michigan study [13] used five different sources for case finding and used a capture-recapture method of analysis to adjust for incomplete case ascertainment. Based on fairly conservative assumptions for this model, the prevalence estimate was 276 cases/million as of 1991. A US population-based survey by Robinson et al. [14] which identified cases based on the International Classification of Diseases Version 9 (ICD-9) diagnostic codes as well as two medical and drug claims datasets reported a prevalence of 300 cases/million in 2002.

In contrast to these three similar estimates, Bernatsky et al. [5] reported a considerably higher prevalence of 443 cases/million in 2003 in the province of Quebec, Canada, using physician billing and hospitalization databases and applying statistical modeling to address issues related to incomplete case ascertainment. Although the use of such administrative databases has value in epidemiology research, it is not yet clear that appropriate statistical models have been developed to provide reliable prevalence estimates.

Similar to the recent US figures noted above, recent studies from Australia have reported a prevalence of 200 cases/million and 233 cases/million for 1993 and 1999, respectively, using surveys conducted by the same group [17, 18]. However, an earlier study from Sydney [15] had reported a much lower prevalence of 45/million for 1975 and 86/million for 1988. This rather large difference may be explained by different methods of case finding as the earlier figures were based on hospital record review while the latter used multiple sources.

These figures are in marked contrast to incidence and prevalence figures reported in Japan. Tamaki et al. [16] conducted a survey based on a medical database and reported an incidence rate of 7.2 cases/million/years with a prevalence of 38–53 cases/million.

In the UK, two studies have reported prevalence estimates of 31 cases/million in 1986 [20] and 88 cases/million in 2000 [21].

Two Scandinavian studies have reported remarkably similar incidence rates of 3.8 cases/million/year in Iceland [22] and 3.7 for Finland [23]. Only the Icelandic study calculated a prevalence figure of 71 cases/million.

Three studies in Europe have reported occurrence figures, with similar prevalence estimates for France [24] and Greece [25] at 158 and 154 cases/million, respectively. A recent study in northwestern Spain [26] reported a prevalence of 277/million suggesting that there may be a geographic north-south gradient.

Clusters

The phenomenon of clustering in epidemiology refers to a higher than expected number of cases in a confined geographic, occupational, or ethnic population. There have been multiple reports of SSc clustering. For example, Arnett et al. [26] reported a well defined population of Choctaw Indians in Oklahoma with a high prevalence of SSc reported as 658.6 cases/million. The prevalence of SSc in the Choctaw group was higher than that reported in other Native Americans in Oklahoma. In addition, SSc disease expression was more uniform among these cases than in the general population, with most Choctaw cases having diffuse cutaneous disease and pulmonary fibrosis. No common exposure was found but a particular Amerindian Histocompatibility locus antigen (HLA) haplotypes was identified suggesting a genetic predisposition to disease.

A higher SSc prevalence was also reported in boroughs close to major airports near London [27], with an estimated prevalence of 150 cases/million in the three boroughs near the airports, compared to a prevalence of 30.8 cases/million in more distant areas. Although the clusters were seen near the airports, they did not involve airport employees and factors responsible for the clustering were not identified.

Similarly, an increased prevalence of scleroderma was reported in the town of Woodstock, Ontario, Canada, compared to two nearby communities also in southwestern Ontario [28]. Explanatory factors in terms of occupation and health habits were not identified.

Two other clusters have been reported, one in Western Victoria, Australia, [29], and one in rural Italy [30], but both involved a relatively small number of cases such that population estimates based on these figures may be unreliable.

Survival

Survival rates have been recently been reported to have improved significantly compared to earlier published reports. According to Steen and Medsger [31] the 10-year cumulative survival rate improved in their Pittsburg cohort from 54% in the 1970s to 66% in the 1990s. Figure 4.1, adapted from Steen and Medsger, illustrates the changes in causes of systemic sclerosis-related deaths between 1972 and 2001.

Another survival study from a large Italian cohort showed similar improvement in survival rates with survival increasing from 60.6% in the period 1955–1985 to 78.6% during 1986–1999.

This improvement in survival is likely related to earlier diagnosis and improvement in treatment, particularly the early detection and effective therapy of scleroderma renal crisis. Steen and Medsger [31] reported changes in organ-specific

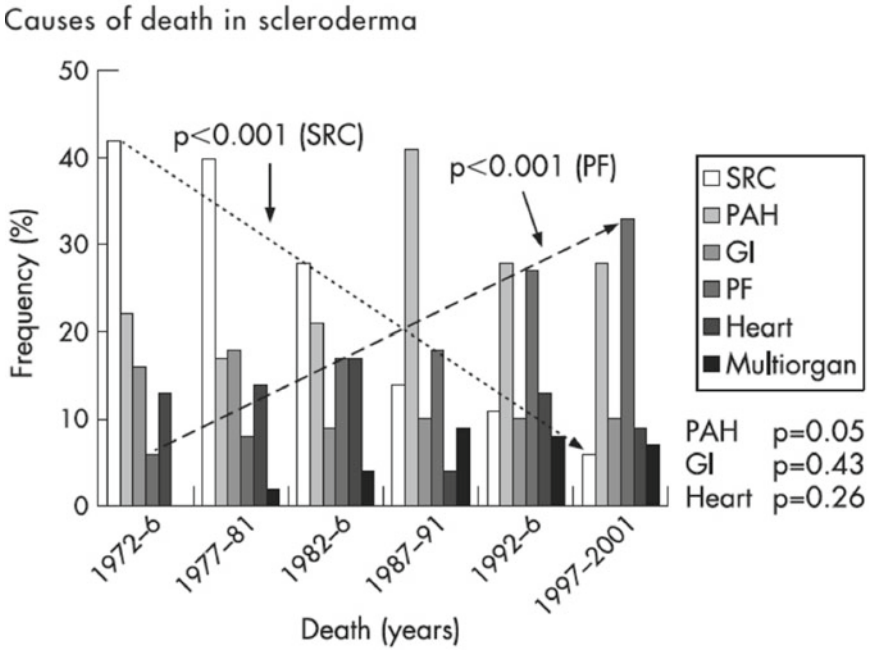

Fig. 4.1 Changes in causes of systemic sclerosis-related deaths between 1972 and 2001. *GI* gastrointestinal, *PAH* pulmonary arterial hypertension, *PF* pulmonary fibrosis, *SRC* scleroderma renal crisis (Adapted with permission from [31])

causes of mortality and found that pulmonary fibrosis and pulmonary hypertension have now become the leading causes of SSc-related deaths as opposed to SSc renal crisis following the introduction of treatment with angiotensin-converting enzyme inhibitors. Even with higher rates of survival found in these reports, overall survival in SSc remains considerable less than that predicted for age-, sex-, and race-matched controls [13].

Survival: Prognostic Factors

In a recent analysis of 234 fatalities from the EUSTAR (EULAR [European League Against Rheumatism] Scleroderma Trials and Research) database, Tyndall et al. [33] reported the following independent risk factors for mortality: proteinuria, pulmonary arterial hypertension, restrictive pulmonary disease, dyspnea greater than New York Heart Association Class II, decreased pulmonary diffusion capacity, higher age at onset of Raynaud's phenomenon, and greater modified Rodnan skin score.

Similar results have been reported in studies from South Australia [34], in a meta-analysis from cases from the USA, Europe, and Japan [35], in French Canadians [36], and in cases from the UK. [37].

The studies listed above have also found that diffuse skin involvement is associated with a poor prognosis. A recent report by Domsic et al. [38] suggests that a higher rate of progression of skin thickening (skin thickness progression rate) is a predictor of mortality and early internal organ involvement particularly the development of renal crisis.

With respect to race, African-American patients have higher mortality compared to their white counterparts [13, 39] believed due to more aggressive disease and perhaps due to health care disparities between these groups.

Risk Factors for SSc

Risk factors for the development of SSc include gender, race, age, family history, birth order, and environmental factors including occupational exposures. As noted in Table 4.1, all epidemiology studies that have reported gender have noted that women outnumber men with female to male ratios usually being 4:1–6:1. The reason for this female preponderance is not well understood. There is speculation that the difference may be related to hormones, pregnancy-related events or gender-specific environmental exposures.

Risk Factors: Female Gender

There are relatively few published reports that have investigated the relationship of pregnancy with development of SSc. A Swedish population-based study found that nulliparity was associated with an increased risk of SSc (OR = 1.37, 95% CI = 1.22–1.55) whereas increasing parity was associated with a decreased risk [40]. However, the increased risk with lower parity could also be explained by infertility due to subclinical or early disease. A more recent study by Cockrill et al. [41] compared pregnancy histories of SSc patients ($n = 172$) with that of their healthy sisters ($n = 256$) and found a positive association between gravidity and the risk of SSc (OR = 2.8, 95% CI 1.62–6.61).

Microchimerism, the persistence of fetal cells in maternal tissues, has been proposed as a trigger for scleroderma or other autoimmune diseases [42] and it has been suggested as an explanation for the increased female to male ratio in these diseases. However, the mechanism responsible for this association has not been identified.

Risk Factors: Race

In the Michigan study previously noted above, Mayes et al. [13] reported a higher prevalence among African-Americans compared to European-Americans with an adjusted prevalence ratio of 1.15 (95% CI 1.02–1.30). In addition, the proportion of diffuse disease was higher in black patients versus white patients and age at diagnosis was earlier (43.8 years for black patients vs. 55.5 years for white patients, $p < 0.001$). In another study, pulmonary fibrosis was more severe at diagnosis among African-Americans than in other ethnic groups [43].

Similar findings were described by Le Guern et al. [24] who reported a prevalence of SSc for non-Europeans (Northern and sub-Saharan African, Asians, and Caribbean ancestries) as 210.8 cases/million versus the prevalence for European Caucasians at 140.2 cases/million. In addition as seen with prior studies, non-Europeans were more likely to have diffuse SSc (34% vs. 17%) and interstitial lung disease (53% vs. 33%).

Racial differences in disease susceptibility and expression can be a reflection of genetic differences among groups. Genetic risk factors are discussed in detail in another section of this book.

Risk Factors: Age at Onset

Systemic sclerosis is rare in childhood. In the Michigan study [13], African-American patients were significantly younger at the time of diagnosis compared with European-American patients ($p<0.001$). Figure 4.2 adapted from Mayes et al. [13] illustrates peak incidence by race and gender. The peak incidence occurred between the ages of 45 and 54 for African-American women, whereas the peak incidence among white women occurred in the 65–74-year age group. Peak incidence for African-American men was similar to that of African-American women. Among the European-American men, a gradually increasing incidence until the age of 75–84 years was observed.

Familial Risk

In any discussion regarding heritability of disease, it is worthwhile to compare disease frequency between monozygotic (identical) and dizygotic (fraternal) twins in order to distinguish genetic from environmental factors. This is difficult to do in a rare disease and only one such twin study has been done in SSc. Feghali-Bostwick et al. [44] studied 42 twin pairs (24 monozygotic twin pairs and 18 dizygotic pairs) in which at least one twin had SSc. They reported an overall concordance rate of 4.7% which did not differ between monozygotic and dizygotic twins. However, the number of twin pairs in this study was relatively small and may have underestimated the recurrence rate.

Although there are several reports of multicase SSc families, there are only four studies that have investigated heritability in a large case cohort of. Most recently, Frech et al. [45] studied 1,037 unique SSc cases and, linking the Utah Population Database and billing codes from the University of Utah Health Science Center Data Warehouse, reported a relative risk of SSc among first-degree relatives as 3.07 (95% CI 1.25–7.57, $p=0.0148$). In addition, increased relative risks were found for multiple other autoimmune diseases. An Australian study (18) of 353 SSc cases reported a relative risk for SSc among

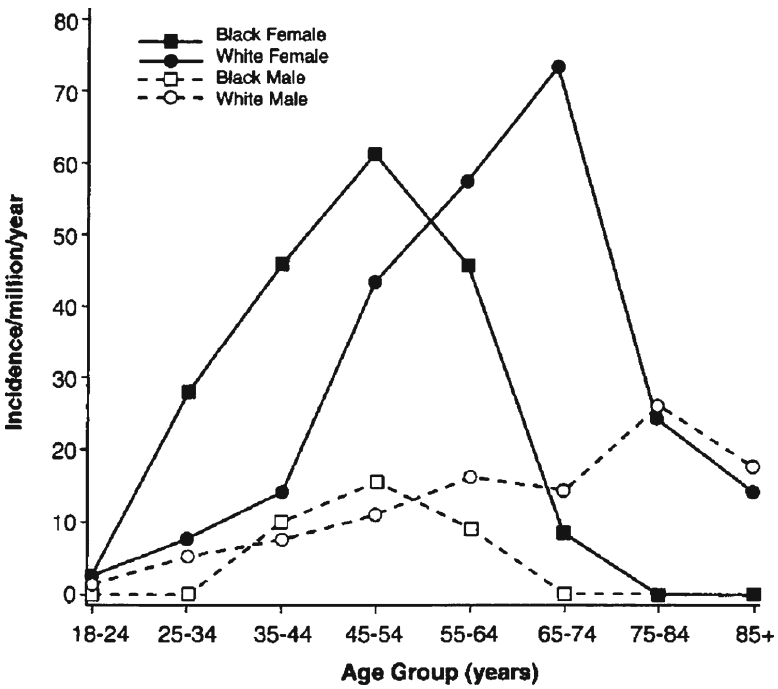

Fig. 4.2 Age-specific incidence of systemic sclerosis by race and sex (Adapted with permission from Mayes et al. [13])

first-degree family members of 14.3 (95% CI 5.9–34.5) which is remarkably similar to an earlier US study by Arnett et al. [46] of 703 families that found a relative risk of 13 (95% CI 2.9–48.6, $p<0.001$) for SSc among first-degree family members. In addition, the relative risk among African-American families was greater than among whites in this study but this difference did not reach statistical significance. A fourth study using cases from Canada and Columbia [47] found increased frequency of multiple autoimmune disease in family members but did not find an increased relative risk for SSc.

To determine if familiar scleroderma differed from spontaneously occurring disease, Assassi et al. [48] compared disease type, organ involvement, and autoantibody status among 18 familial SSc cases and 692 sporadic cases. SSc families tended to be concordant for SSc-specific autoantibodies and HLA haplotypes, but otherwise familial SSc did not appear to be a unique disease subset.

Birth Order

Birth order has been found to be a risk factor for allergy and atopy [49] with first-born offspring more likely to have atopic disease than subsequent children in the family. The role of birth order in SSc susceptibility was reported by Cockrill et al. [41] who studied 974 sibships and found that the opposite situation held in scleroderma. The risk of SSc increased with increasing birth order with an odds ratio of 1.25 (95% CI 1.06–1.50) for birth order 2–5, an odds ratio of 2.22 (95% CI 1.57–3.15) for birth order 6–9, and odds ratio of 3.53 (95% CI 1.68–7.45) for birth order 10–15. These findings suggest that immune development in early childhood and/or pregnancy associated maternal events play a role in SSc susceptibility.

Risk Factors: Environmental Triggers

Table 4.2 summarizes the well-documented environmental associations with SSc and SSc-like illnesses. Although there have been several case reports of SSc occurring after exposure to various other agents that are not listed here, this table is meant to highlight the few exposures that have been reported in multiple studies and for which an association with SSc can be considered established.

Silica

As noted above, numerous environmental factors have been associated with SSc in case reports and small case series, but few have been verified in case-control studies. One of the most frequently reported exposures to be associated with SSc is silica. Occupational exposure to particulate silica or silica dust occurs in professions such as mining, sandblasting, and pottery. In fact, silica has been associated as a risk factor for several autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus, and small vessel vasculitis [50] in addition to SSc. In a meta-analysis published by McCormic et al. [51], the relative risk of developing SSc after exposure to silica was elevated only for men at 3.02 (95% CI, 1.24–7.35). This association was not seen in women with exposure to silica who had a minimal and insignificant elevation in relative

Table 4.2 Environmental exposures associated with SSc or SSc-like illnesses

Exposure	Disease	Evidence (reference)
Crystalline silica/silica dust	SSc	Meta-analysis [51]
Solvents	SSc	Meta-analysis [53]
Vinyl chloride monomer	Vinyl chloride disease	Investigation of outbreak [39]
Adulterated cooking oil	Toxic oil syndrome	Investigation of outbreak [55]
Tryptophan	Eosinophilic myalgia syndrome	Investigation of outbreak [57]
Gadolinium	Nephrogenic systemic fibrosis	Multiple case series (review [59, 60])
Drugs		
Bleomycin	Pulmonary fibrosis	Multiple observations (review [61])
Pentazocine	Localized dermal fibrosis at injection site	Multiple observations (review [62])

risk of 1.03% (95% CI, 0.74–1.44). Although this meta- analysis found considerable heterogeneity among the studies, it does indicate that silica exposure may be a significant risk factor for developing SSc at least in some men. However, this exposure does not explain the vast majority of cases including women who comprise over 80% of SSc cases and men who have had no such exposure.

Although, case reports suggested an association between silicone breast implants and SSc, multiple studies as described in a meta-analysis by Janowsky et al. [52] disproved this association.

Solvents

Since 1957, there have been over 100 published articles on the possible association between exposure to various chemical solvents and the subsequent development of SSc. A recent metaanalysis of 11 case-control studies by Kettaneh et al. [53] involving 1,291 cases and 3,335 controls was performed. The conclusion from this meta-analysis is that there is indeed an increased risk of SSc both for men and women, and that this risk was greater for male cases than for female cases; for men the odds ratio for solvent exposure was 2.96 (95% CI 1.893–4.64, $p<0.0001$) and for women the odds ratio was 1.75 (95% CI 1.48–2.09, $p<0.0001$). The authors were unable to conduct separate analyses for specific solvent subtypes, due to the limited number of studies for each solvent category. The mechanism underlying this association is unclear, but it is thought that solvents could alter native molecules to generate self-antigens that would in turn initiate an autoimmune response.

Exposures and Scleroderma-Like Syndromes

In addition to case reports of SSc occurring after contact with various chemicals, the impetus to study environmental exposures has come from reports of scleroderma-like diseases that have occurred in an epidemic fashion and that have resulted from an identified source.

Vinyl Chloride Disease

In the mid 1960s, a syndrome was described in factory workers employed in the plastics industry involving exposure to vinyl chloride. The workers developed paresthesias, Raynaud's phenomenon, skin thickening, edema of the hands and forearms, pseudo-acropachy, and phalanx acro-osteolysis [54]. The risk of developing these symptoms was related to cumulative exposure over time. Once the association was identified and changes made in the manufacturing process to protect workers, this syndrome has virtually disappeared.

Toxic Oil Syndrome

A review by Posada de la Paz et al. [55] described an epidemic illness that occurred in 1981 in Spain that was a progressive multisystem disease affecting over 20,000 people and resulting in hundreds of deaths. The causative agent was traced to rapeseed oil that had been contaminated with aniline and illicitly sold as cooking oil. People who consumed this toxic oil developed pulmonary edema, myalgias, rash, cardiomyopathy, vasculopathy, and pulmonary hypertension. Once the causative agent was identified and removed from the market, the epidemic resolved.

L-Tryptophan and Eosinophilia-Myalgia Syndrome

Another scleroderma-like illness, the Eosinophilia-Myalgia Syndrome [56, 57], occurred in the USA in 1984–1989 and was traced to a nutritional supplement containing L-tryptophan that had a contaminant introduced in the manufacturing process. Characteristics of the illness included sclerodermatous skin thickening, sensorimotor polyneuropathy, proximal myopathy, severe myalgias, and peripheral eosinophilia.

Again, once the causal agent was identified and removed from the market in 1989, the syndrome essentially disappeared.

Gadolinium and Nephrogenic Systemic Fibrosis (see chapter 13)

Nephrogenic Systemic Fibrosis (previously called Nephrogenic Fibrosing Dermopathy) was first reported by Cowper in 2000 ([58], for review see [59]) and characterized by rapidly progressive skin thickening with the early development of flexion contractures affecting the lower extremities more than upper extremities and typically sparing the face. There is also internal organ fibrosis of muscle, myocardium, and lung. It typically occurs following administration of gadolinium contrast material for magnetic resonance imaging in the setting of renal compromise.

Prevention is the best approach, with the avoidance of gadolinium containing agents in at-risk patients, since treatment of established disease is unsatisfactory. Although the underlying pathogenetic mechanism remains unclear, it is thought that fibrosis results from activation of the transforming growth factor beta (TGF-beta) pathway [60].

Bleomycin and Pulmonary Fibrosis

Bleomycin is an antineoplastic antibiotic drug used for several types of cancer. A known side effect of this drug is a pneumonitis which can be fatal [61]. The central event is endothelial damage to the pulmonary vasculature and those who survive this complication usually recover completely with normalization of pulmonary function.

This has led to the development of the bleomycin mouse model as an in vivo system to study pulmonary and lung fibrosis and to test potential agents for the treatment of human disease.

Pentazocine

Repeated injection of pentazocine, a synthetic narcotic analgesic, can cause a local fibrotic reaction affecting dermal, subcutaneous, and muscle layers in the area of administration [62]. This was first reported in 1975 [63] and since has been described in the setting of repetitive and prolonged use typically associated with narcotic abuse. The mechanism is not clear and the changes are usually irreversible.

Summary

Although incidence rates and prevalence estimates vary by region, these figures are fairly similar from recent reports for Europe, the USA, and Australia and suggest that prevalence is in the range of 150–300 cases/million with lower prevalence in Scandinavia, Japan, and the UK.

Incidence rates (number of new cases per year) have apparently increased from the 1940s to the present, but it is not clear if this represents a real increase in disease occurrence or if this is due to improved awareness and earlier diagnosis.

Survival in SSc has improved over time, and this improvement is largely related to the introduction of angiotensin converting enzyme inhibitors for the treatment of scleroderma renal crisis in the early 1980s. Interstitial lung disease and pulmonary vascular disease have replaced renal failure as the most common cause of death. SSc is more common in women than in men with most reports of female to male ratios of 4:1–6:1.

African American race and Choctaw Native American ancestry are risk factors for the development of SSc and African Americans have more severe disease with an earlier age at onset and worst prognosis.

Familial clustering clearly suggests a genetic contribution and multiple recent studies, described elsewhere in this book, have begun to identify these factors. The finding that increasing birth order predisposes to SSc is intriguing and suggests that early exposure to infection and/or other agents may contribute to the development of SSc.

Although the evidence for an association between SSc and environmental exposure to particulate silica and chemical solvents is relatively well-established, these exposures account for only a tiny percentage of all cases. Hence the environmental trigger(s) for the majority of cases remains unknown.

Several agents have been associated with scleroderma-like illnesses, but the relevance to spontaneously occurring systemic sclerosis is unclear.

References

1. Bolster MB, Silver RS. Clinical features of systemic sclerosis. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology. 5th ed. Philadelphia: Mosby, Elsevier; 2011. p. 1373–86.
2. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger Jr TA, Rowell N, Wollheim F. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol. 1988;15(2):202–5.
3. 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 May;23(5):581–90. PMID: 7378088.
4. Wigley R, Borman B. Medical geography and the aetiology of the rare connective tissue diseases in New Zealand. Soc Sci Med Med Geogr. 1980;14(2):175–83.
5. Bernatsky S, Joseph L, Pineau CA, Belisle P, Hudson M, Clarke AE. Scleroderma prevalence: demographic variations in a population-based sample. Arthritis Rheum. 2009;61(3):400–4.
6. Eason RJ, Tan PL, Gow PJ. Progressive systemic sclerosis in Auckland: a ten year review with emphasis on prognostic features. Aust N Z J Med. 1981;11(6):657–62.
7. Arias-Nuñez MC, Llorca J, Vazquez-Rodriguez TR, Gomez-Acebo I, Miranda-Filloy JA, Martin J, Gonzalez-Juanatey C, Gonzalez-Gay MA. Systemic sclerosis in northwestern Spain: a 19-year epidemiologic study. Medicine (Baltimore). 2008;87(5):272–80.
8. Chifflot H, Fautrel B, Sordet C, Chatelus E, Sibilia J. Incidence and prevalence of systemic sclerosis: a systematic literature review. Semin Arthritis Rheum. 2008;37:223–35.
9. Medsger Jr TA, Masi AT. Epidemiology of systemic sclerosis (scleroderma). Ann Intern Med. 1971;74:714–21.
10. Michet Jr CJ, McKenna CH, Elveback LR, Kaslow RA, Kurland LT. Epidemiology of systemic lupus erythematosus and other connective tissue diseases in Rochester, Minnesota, 1950 through 1979. Mayo Clin Proc. 1985;60(2):105–13.
11. Steen VD, Oddis CV, Conte CG, Janoski J, Casterline GZ, Medsger Jr TA. Incidence of systemic sclerosis in Allegheny county, Pennsylvania. A twenty-year study of hospital-diagnosed cases, 1963–1982. Arthritis Rheum. 1997;40(3):441–5 PMID: 9082931.
12. Maricq HR, Weinrich MC, Keil JE, Smith EA, Harperl FE, Nussbaum AI, et al. Prevalence of scleroderma spectrum disorders in the general population of South Carolina. Arthritis Rheum. 1989;32:998–1006.
13. Mayes MD, Lacey Jr JV, Beebe-Dimmer J, et al. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. Arthritis Rheum. 2003;48:2246–55.
14. Robinson Jr D, Eisenberg D, Nietert PJ, Doyle M, Bala M, Paramore C, et al. Systemic sclerosis prevalence and comorbidities in the US, 2001–2002. Curr Med Res Opin. 2008;24:1157–66.
15. Englert H, Small-McMahon J, Davis K, O'Connor H, Chambers P, Brooks P. Systemic sclerosis prevalence and mortality in Sydney 1974–88. Aust NZ J Med. 1999;29:42–50.
16. Chandran G, Smith M, Ahern MJ, Roberts-Thomson PJ. A study of scleroderma in South Australia: prevalence, subset characteristics and nailfold capillaroscopy. Aust N Z J Med. 1995;25(6):688–94.
17. Roberts-Thomson PJ, Jones M, Hakendorf P, Kencana Dharmapatni AA, Walker JG, MacFarlane JG, Smith MD, Ahern MJ. Scleroderma in south Australia: epidemiological observations of possible pathogenic significance. Intern Med J. 2001;31(4):220–9 PMID: 11456035.
18. Roberts-Thomson PJ, Walker JG, Lu TY, Esterman A, Hakendorf P, Smith MD, et al. Scleroderma in South Australia: further epidemiological observations supporting a stochastic explanation. Intern Med J. 2006;36:489–97.
19. Tamaki T, Mori S, Takehara K. Epidemiological study of patients with systemic sclerosis in Tokyo. Arch Dermatol Res. 1991;283:366–71.
20. Silman A, Jannini S, Symmons D, Bacon P. An epidemiological study of scleroderma in the West Midlands. Br J Rheumatol. 1988;27(4):286–90.
21. Allcock RJ, Forrest I, Corris PA, et al. A study of the prevalence of systemic sclerosis in northeast England. Rheumatology (Oxford). 2004;43:596–602.
22. Geirsson AJ, Steinsson K, Guthmundsson S, Sigurthsson V. Systemic sclerosis in Iceland. A nationwide epidemiological study. Ann Rheum Dis. 1994;53(8):502–5.
23. Kaipiainen-Seppanen O, Aho K. Rare systemic rheumatic and connective tissue diseases in Finland. J Int Med. 1996;240:81–4.
24. Le Guern V, Mahr A, Mouthon L, et al. Prevalence of systemic sclerosis in a French multi-ethnic county. Rheumatology (Oxford). 2004;43:1129–37.
25. Alamanos Y, voulgari PV, Tsifetaki N, et al. Epidemiology of systemic sclerosis in northwest Greece 1981–2002. Semin Arthritis Rheum. 2005;34:714–20.
26. Arnett FC, Howard RF, Tan F, et al. Increased prevalence of systemic sclerosis in a native American tribe in Oklahoma: association with an Amerindian HLA haplotype. Arthritis Rheum. 1996;39:1362–70.
27. Silman AJ, Howard Y, Hicklin AJ, Black C. Geographical clustering of scleroderma in south and west London. Br J Rheumatol. 1990;29:93–6.
28. Thompson AE, Pope JE. Increased prevalence of scleroderma in southwestern Ontario: a cluster analysis. J Rheumatol. 2002;29(9):1867–73 PMID 12233880.
29. Englert H, Joyner E, Bade R, Thompson M, Morris D, Chambers P, Carroll G, Manolios N. Systemic scleroderma: a spatiotemporal clustering. Intern Med J. 2005;35(4):228–33.
30. Valesini G, Litta A, Bonavita MS, Luan FL, Purpura M, Mariani M, Balsano F. Geographical clustering of scleroderma in a rural area in the province of Rome. Clin Exp Rheumatol. 1993;1(1):41–7.
31. Steen VD, Medsger TA. Changes in the causes of death in systemic sclerosis, 1972–2002. Ann Rheum Dis. 2007;66:940–4.
32. Ferri C, Valentini G, Cozzi F, Sebastiani M, Michelassi C, La Montagna G, Bullo A, Cazzato M, Tirri E, Storino F, Giuggioli D, Cuomo G, Rosada M, Bombardieri S, Todesco S, Tirri G. Systemic Sclerosis Study Group of the Italian Society of Rheumatology (SIR-GSSSc). Systemic sclerosis: demographic, clinical, and serologic features and survival in 1,012 Italian patients. Medicine (Baltimore). 2002;81(2):139–53 PMID: 11889413.

33. Gurman AB, Damjanov N, Mueller A, Valentini G, Riemekasten G, Tikly M, Hummers L, Henriques MJ, Caramaschi P, Scheja A, Rozman B, Ton E, Kumánovics G, Coleiro B, Feierl E, Szucs G, Von Mühlen CA, Riccieri V, Novak S, Chizzolini C, Kotulska A, Denton C, Coelho PC, Kötter I, Simsek I, de la Pena Lefebvre PG, Hachulla E, Seibold JR, Rednic S, Stork J, Morovic-Vergles J, Walker UA. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. Ann Rheum Dis. 2010;69(10):1809–15 PMID: 20551155.
34. Hissaria P, Lester S, Hakendorf P, Woodman R, Patterson K, Hill C, Ahern MJ, Smith MD, Walker JG, Roberts-Thomson PJ. Survival in scleroderma: results from the population based South Australian Register. Intern Med J. 2010;41(5):381–90. [Epub ahead of print] PMID: 20546058.
35. Ioannidis JP, Vlachoyiannopoulos PG, Haidich AB, Medsger Jr TA, Lucas M, Michet CJ, Kuwana M, Yasuoka H, van den Hoogen F, Te Boome L, van Laar JM, Verbeet NL, Matucci-Cerinic M, Georgountzos A, Moutsopoulos HM. Mortality in systemic sclerosis: an international meta-analysis of individual patient data. Am J Med. 2005;118(1):2–10.
36. Scussel-Lonzetti L, Joyal F, Raynauld JP, Roussin A, Rich E, Goulet JR, et al. Predicting mortality in systemic sclerosis: analysis of a cohort of 309 French Canadian patients with emphasis on features at diagnosis as predictive factors for survival. Medicine. Baltimore. 2002;81:154–67.
37. Bryan C, Knight C, Black CM, Silman AJ. Prediction of five-year survival following presentation with scleroderma: development of a simple model using three disease factors at first visit. Arthritis Rheum. 1999;42:2660–5.
38. Domsic RT, Rodriguez-Reyna T, Lucas M, Fertig N, Medsger Jr TA. Skin thickness progression rate: a predictor of mortality and early internal organ involvement in diffuse scleroderma. Ann Rheum Dis. 2011;70(1):104–9. PMIT 20679474.
39. Mendoza F, Derk CT. Systemic sclerosis mortality in the United States: 1999–2002 implications for patient care. J Clin Rheumatol. 2007;13(4):187–92.
40. Lambe M, Bjornadal L, Neregard P, Nyren O, Cooper GS. Childbearing and the risk of scleroderma: a population-based study in Sweden. Am J Epidemiol. 2004;159:162–6.
41. Cockrill T, del Junco D, Arnett FC, et al. Separate influences of birth order and gravity/parity on the development of systemic sclerosis. Arthritis Care Res. 2010;62:418–24.
42. Adams Waldorf KM, Nelson JL. Autoimmune disease during pregnancy and the microchimerism legacy of pregnancy. Immunol Invest. 2008;37(5):631–44 PMID: 18716941.
43. McNearney TA, Reveille JD, Fischbach M, Friedman AW, Lisse JR, Goel N, Tan FK, Zhou X, Ahn C, Feghali-Bostwick CA, Fritzler M, Arnett FC, Mayes MD. Pulmonary involvement in systemic sclerosis: associations with genetic, serologic, sociodemographic, and behavioral factors. Arthritis Rheum. 2007;57(2):318–26.
44. Feghali-Bostwick C, Medsger Jr TA, Wright TM. Analysis of systemic sclerosis in twins reveals low concordance for disease and high concordance for the presence of antinuclear antibodies. Arthritis Rheum. 2003;48:1956–63.
45. Frech T, Khanna D, Markewitz B, Mineau G, Pimentel R, Sawitzke A. Heritability of vasculopathy, autoimmune disease, and fibrosis in systemic sclerosis: a population-based study. Arthritis Rheum. 2010;62(7):2109–16.
46. Arnett FC, Cho M, Chatterjee S, Aquilar MB, Reveille JD, Mayes MD. Familial occurrence frequencies and relative risk for systemic sclerosis (scleroderma) in three United States cohorts. Arthritis Rheum. 2001;44:1359–62.
47. Hudson M, Rojas-Villarraga A, Coral-Alvarado P, López-Guzmán S, Mantilla RD, Chalem P, Baron M, Anaya JM, Canadian Scleroderma Research Group; Colombian Scleroderma Research Group. Polyautoimmunity and familial autoimmunity in systemic sclerosis. J Autoimmun. 2008;31(2):156–9.
48. Assassi S, Arnett FC, Reveille JD, Gourh P, Mayes MD. Clinical, immunologic, and genetic features of familial systemic sclerosis. Assassi S, Arnett FC, Reveille JD, Gourh P, Mayes MD. Arthritis Rheum. 2007;56(6):2031–7. PMID: 17530643.
49. McKeever TM, Lewis SA, Smith C, Collins J, Heatlie H, Frischer M, Hubbard R. Siblings, multiple births, and the incidence of allergic disease: a birth cohort study using the West Midlands general practice research database. Thorax. 2001;56(10):758–62.
50. Makol A, Reilly MJ, Rosenman KD. Prevalence of connective tissue disease in silicosis (1985–2006)-a report from the state of Michigan surveillance system for silicosis. Am J Ind Med. 2010;54(4):255–62. [Epub ahead of print] PMID: 20957678.
51. McCormic ZD, Khuder SS, Aryal BK, Ames AL, Khuder SA. Occupational silica exposure as a risk factor for scleroderma: a meta-analysis. Int Arch Occup Environ Health. 2010;83(7):763–9.
52. Janowsky EC, Kupper LL, Hulka BS. Meta-analyses of the relation between silicone breast implants and the risk of connective-tissue diseases. N Engl J Med. 2000;342:781–90.
53. Kettaneh A, Al Moufti O, Tiev KP, Chayet C, Toledano C, Fabre B, et al. Occupational exposure to solvents and gender-related risk of systemic sclerosis: a metaanalysis of case-control studies. J Rheumatol. 2007;34:97–103.
54. Nicholson WJ, Henneberger PK, Seidman H. Occupational hazards in the VC-PVC industry. Prog Clin Biol Res. 1984;141:155–75.
55. de la PM Posada, Philen RM, Borda AI. Toxic oil syndrome: the perspective after 20 years. Epidemiol Rev. 2001;23(2):231–247.
56. Kilbourne EM, Philen RM, Kamb ML, Falk H. Tryptophan produced by Showa Denko and epidemic eosinophilia-myalgia syndrome. J Rheumatol Suppl. 1996;46:81–8. discussion 89–91. Review. PMID: 8895184.
57. Kaufman LD, Seidman RJ. L-tryptophan-associated eosinophilia-myalgia syndrome: perspective of a new illness. Rheum Dis Clin North Am. 1991;17(2):427–41. Review. PMID: 1862249.
58. Cowper SE, Su LD, Bhawan J, Robin HS, LeBoit PE. Nephrogenic fibrosing dermopathy. Am J Dermatopathol. 2001;23(5):383–93.
59. Chen AY, Zirwas MJ, Heffernan MP. Nephrogenic systemic fibrosis: a review. J Drugs Dermatol. 2010;9(7):829–34 Review. PMID: 20677539.
60. Schieren G, Gambichler T, Skrygan M, Burkert B, Altmeyer P, Rump LC, Kreuter A. Balance of profibrotic and antifibrotic [corrected] signaling in nephrogenic systemic fibrosis skin lesions. Am J Kidney Dis. 2010;55(6):1040–9.
61. Sleijfer S. Bleomycin-induced pneumonitis. Chest. 2001;120(2):617–24 Review. PMID: 11502668.
62. Palestine RF, Millns JL, Spigel GT, Schroeter AL. Skin manifestations of pentazocine abuse. J Am Acad Dermatol. 1980;2(1):47–55.
63. Levin BE, Engel WK. Iatrogenic muscle fibrosis. Arm levitation as an initial sign. JAMA. 1975;234(6):621–4.