Epidemiology, Environmental, and Infectious Risk Factors

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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 SSc 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 2013, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) updated classification criteria for SSc [3]. Prior to 2013, the ACR (previously the American Rheumatism Association) published classification criteria in 1980 to distinguish SSc from other connective tissue diseases and to standardize reporting [4]. 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) [5] to 580 cases/million (Alberta, Canada, 1994–2007) [6]. Accordingly, the annual incidence rates also vary widely between 1.96 cases/million from the time period 1950–1973 (New Zealand) [7] to 46 cases/million from the time period 2003–2008 (US managed care population) [8]. Table 2.1, modified and updated from Chifflot et al. [9], summarizes multiple reports of incidence rates and prevalence figures from different geographic locations and time periods reported as unadjusted [5–8, 10–34]. Only studies that included men and women are shown, and only figures for SSc 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. In addition, regions such as North American and Canada have specific subpopulations, Native Americans and First Nations, respectively, that reportedly have more SSc cases than expected, presumably on the basis of shared genetic risk factors.

Temporal Changes in Incidence Rates

Studies by Medsger et al. [10] and Steen et al. [12] reported changes in the incidence rate (number of new SSc cases per year) over time. Using a hospital record review approach in Tennessee [10], the incidence of SSc was reported to have increased from 0.6 cases/million/year for the years 1947–1952

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Table 2.1 Variations of incidence and prevalence of systemic sclerosis by region and time

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 [10]	Tennessee	Hospital record review	Study specific (n=60)	1947–1952	0.6	–	1.5:1
					4.5		
				1953–1968	2.7 (entire period)		
				1947–1968			
Michet [11]	Minnesota	Diagnostic retrieval system	ICDA (7th) (n=13)	1950–1979	10	138	12:1
Steen [12]	Pennsylvania	Hospital record review	ACR + study specific (n=44)	1963–1972	9.6	–	–
					18.7		
				1973–1982	13.9 (entire period)		
				1963–1982			
Maricq [13]	South Carolina	Multistage population survey	ACR + study specific (n=2)	1989	–	286	–
Mayes [14]	Michigan	Multiple sources (CR)	ACR and CREST (n=706)	1989–1991	21	276	4.6:1
Robinson [15]	2 medical/drug claim datasets	ICD diagnostic codes	–	2001–2002	–	300	–
Furst [8]	USA	Medical claims and ICD-9	Diagnosis codes	2003–2008	46	135–184	6.15:1
Bernatsky [16]	Quebec	Hospital and physician billing databases	ICD diagnostic codes	2003	–	443	–
Barnabe [6]	Alberta	Hospital and billing codes	1994–2007	–	508	–	5.8:1
Australia							
Wigley [5]	New Zealand	Hospital record review	Study specific	1950–1973	1.96	–	–
Eason [7]	New Zealand	Hospital record review and specialist practices	ACR (n=50)	1970–1979	6.3	30	3:1
Englert [17]	Sydney	Hospital record review	ACR + study specific	1974–1988	12	45.2 (1988)	–
Chandran [18]	South Australia	Hospital record review	ACR + study specific + overlap syndrome (n=215)	1987–1993	–	208	4:1
Roberts-Thomson [19]	South Australia	Multiple sources	ACR + study specific + overlap syndrome (n=548)	1993	15.1	200	4:1
				1999	22.8	232.4	–
Roberts-Thomson [20]	South Australia	Multiple sources	ACR + study specific (n=353)	1993–2002	20.4	232.2	–
Japan							
Tamaki [21]	Tokyo	Public health system	ACR (n=629)	1987	7.2	38	14:1
UK and Europe							
Silman [22]	England (West Midlands)	Multiple sources	Study specific (n=128)	1986	3.7	31	–
Allcock [23]	England (Newcastle)	Multiple sources	ACR + Leroy/Medsger (n=80)	2000	–	88	5.2:1
Geirsson [24]	Iceland	Multiple sources	ACR + CREST (n=18)	1975–1990	3.8	71	8:1
Kaipiainana [25]	Finland	Multiple sources	ACR + CREST (n=4)	1990	3.7	–	–
Le Guern [26]	France (Seine-St-Denis)	Multiple sources (CR)	ACR + Leroy/Medsger (n=15)	2001	–	158	11:1

Table 2.1 (continued)

Reference	Region	Case ascertainment method	Inclusion criteria (n=number of cases)	Study period	Incidence (per million/year)	Prevalence per million	Female/male ratio
El Adssi [27]	Lorraine, France	Capture	ACR	2006	–	132.2	6.72:1
		Recapture					
Hoffman-Vold [28]	Norway	Survey	ACR	1999–2009	–	52–144	3.8:1
Alamanos [29]	Greece (northwest)	Multiple sources	ACR + Leroy/Medsger (n=109)	1981–2002	11	154	8.9:1
Arias-Nunez [30]	Spain (northwest)	Two-stage hospital-based survey	ACR + Leroy/Medsger (n=78)	1988–2006	23	277	–
	Italy	Retrospective hospital/clinic visit/ICD-9	ACR + Leroy/Medsger	1999–2007	32	254	9.7:1
Monaco [31]	Italy	Survey	ACR				
Sardu [32]	Italy	Survey	ACR	–	–	–	–
Andreasson	Sweden	Register	ACR 1980	–	14	235	3.6:1
South America							
Rosa [34]	Buenos Aires	Med Care Program	ACR + Leroy/Medsger 1999–2004	21.2	296	15:1	

Modified from Chifflot et al. [9]

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 [14] of 21 new cases/million/year for the study period of 1989–1991 suggesting that the increase in incidence did not continue. A recently published study by Furst et al., utilizing claims data from a large US managed care population, suggested a higher incidence and lower prevalence [8]. This study differed from the earlier Pennsylvania and Michigan-based studies, because it used data from across the USA. However, since this was based on claims rather than record review, there could be coding errors, and it is possible that the incidence rates are inflated because some could have had SSc prior to the study period.

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. Finally, incidence figures may change with the application of the 2013 ACR/EULAR criteria since those criteria were established to be more inclusive and to capture cases not previously identified by the 1980 criteria. With respects to that assumption, Andreasson et al. [33] reported incidence and prevalence figures in southern Sweden comparing the 1980 criteria and the 2013 criteria. The incidence rates for 1980 versus 2013 are 14 new cases/million/year for 1980 versus 19/million/year for 2013, and the prevalence estimates are 235 per million in 1980 and 305 per million in 2013. They concluded that application of the 2013 ACR/EULAR criteria results in a 30–40 % higher estimate of SSc incidence and prevalence compared to the previous criteria. It is likely that the new criterion successfully identifies more SSc cases. The above report found that a majority of recognized cases were anticentromere antibody positive and had limited cutaneous disease, some of whom would have been missed in the 1980 criteria. With further epidemiological studies using the new criteria, we should be able to better identify cases of SSc and have a more clear representation of incidence and prevalence. However, this will have to be taken into account in the consideration of temporal changes in disease occurrence.

Geographic Variations in SSc Occurrence

Higher prevalence figures have been consistently reported in North America and Australia as compared to Japan and Europe. Three US studies [13–15] 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 1989 South Carolina study [13] 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 SSc and an estimate of 3,790 cases/million of "scleroderma spectrum disease." 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 (RP) symptoms. The 2003 Michigan study [14] 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. A US population-based survey by Robinson et al. [15], 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. [16] 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, 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 [19, 20]. However, an earlier study from Sydney [17] 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. [21] in 1991 reported a survey based on a medical database and reported an incidence rate of 7.2 cases/million/year with a prevalence of 38–53 cases/million.

In the UK, two studies have reported prevalence estimates of 31 cases/million in 1986 [22] and 88 cases/million in 2000 [23].

Two Scandinavian studies have reported remarkably similar incidence rates of 3.8 cases/million/year in Iceland [24] and 3.7 for Finland [25]. Only the Icelandic study provided a prevalence figure of 71 cases/million.

Three studies in Europe have reported occurrence figures, with similar prevalence estimates for France [26] and Greece [29] at 158 and 154 cases/million, respectively. A recent study in northwestern Spain [30] reported a prevalence of 277/million suggesting that there may be a geographic north-south gradient.

In addition, recent incidence and prevalence data from northeastern Italy were found to be higher than reported in various geographical areas (UK, US, Australia) but similar to other Italian studies [31].

The geographic variance may be related to the population in the region. For example Arnett et al. [35] reported a well-defined population of Choctaw Indians in Oklahoma with a high prevalence of SSc estimated at 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) haplotype was identified suggesting a genetic predisposition to disease. In addition, to the Native Americans, the First Nations population in Alberta, Canada, also had a high prevalence reported at 580 cases/million [6]. This high disease occurrence may be related to shared genetic ancestry with associated inherited risk alleles.

Clusters

The phenomenon of clustering in epidemiology refers to a higher than expected number of cases in a defined geographic, occupational, or ethnic population. There have been multiple reports of SSc clustering.

A higher SSc prevalence was reported in boroughs close to major airports near London [36], 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 SSc was reported in the town of Woodstock, Ontario, Canada, compared to two nearby communities also in southwestern Ontario [37]. Explanatory factors in terms of occupation and health habits were not identified.

Two other clusters have been reported – one in Western Victoria, Australia [38], and one in rural Italy [39] – but both involved a relatively small number of cases such that population estimates based on these figures may be unreliable.

Survival

Survival rates have recently been reported to have improved significantly compared to earlier published reports. According to Steen and Medsger [40], the 10-year cumulative survival rate improved in their Pittsburg cohort from 54 % in the 1970s to 66 % in the 1990s. Figure 2.1, adapted from Steen and Medsger, illustrates the changes in causes of SSc-related deaths between 1972 and 2001.

Another survival study from a large Italian cohort [41] 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 [40] reported changes in organ-specific causes of mortality and found that pulmonary fibrosis and pulmonary hypertension (PH) 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 [14].

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. [42] reported the following independent risk factors for mortality: proteinuria, pulmonary arterial hypertension (PAH), restrictive pulmonary disease, dyspnea greater than the New York Heart Association Class II, decreased pulmonary diffusion capacity, higher age at onset of Raynaud's phenomenon, and greater modified Rodnan skin score.

In a study from Pennsylvania, early mortality was seen in SSc patients that had significant muscle and cardiac disease, anticentromere antibody negative, and time to first non-Raynaud's phenomenon symptoms [43]. In a Norwegian cohort of SSc patients, factors that trended toward a worse outcome included PH, male sex, diffuse disease, and interstitial lung disease (ILD) [44]. There have been several studies that have found that ILD was a main prognostic factor associated with death [42, 44–49].

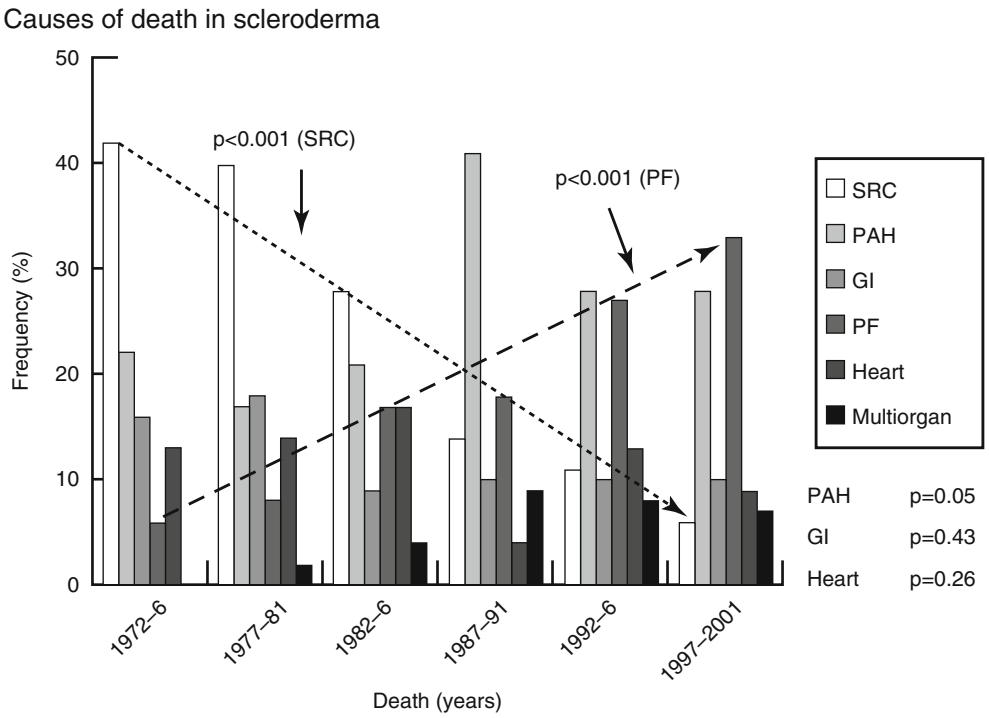

Fig. 2.1 Changes in causes of systemic sclerosis-related deaths between 1972 and 2001. *GI* gastrointestinal, *PAH* pulmonary arterial hypertension, *PF* pulmonary fibrosis, *SRC* scleroderma renal crisis (With permission from Steen and Medsger [40])

Similar results have been reported in studies from South Australia [45], in a meta-analysis from cases from the USA, Europe, and Japan [50], in French Canadians [51], and in cases from the UK [52].

The studies listed above have also found that diffuse skin involvement is associated with a poorer prognosis. A recent report by Domsic et al. [53] 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 [14, 54] believed due to more aggressive disease and perhaps due to health care disparities between these groups. In a recent study by Sharif et al. [55], African-American patients had a younger age of onset, higher frequency of digital ulcers and pericarditis and more severe lower gastrointestinal tract involvement. There was also a strong association with anti-fibrillarin antibodies (AFA) and African-American patients. Those patients with AFA compared to African-Americans patients without AFA had less severe lung involvement. However, the presence of AFA did not influence survival in this cohort.

Although SSc has a higher prevalence in females, the risk of death was higher in male patients as seen in several studies [45–47]. In addition to gender, older age was identified as a predictor of mortality [45, 46, 49]. However, in a study from Barcelona, after adjustment was made for population effects of age and sex, the standardized mortality ratio was found to be higher in younger patients [56].

In terms of prognostic factors for mortality, a Japanese study found that gastrointestinal involvement was associated with a worse mortality as was diffuse disease [57]. In addition other studies have found myositis to have an increase hazard ratio for mortality [43, 58].

With respects to PAH and mortality, Chung et al. [59] reported that severely reduced diffusion capacity of the lung for carbon monoxide (DLCO) and functional class IV at the time of PAH diagnosis was associated with a poorer prognosis. In patients with SSc and ILD, the extent of disease found on high-resolution computed tomography was an independent variable that predicted both mortality and ILD progression [60]. Although treatment for PAH is being initiated in SSc patients, to date there are no studies that have clearly demonstrated a survival benefit. What is known currently is that SSc patients being treated for PAH have higher mortality rates than non-SSc patients with PAH [61].

SSc-specific autoantibodies are associated with both risk and survival benefit. For instance, it has been reported that having an anticentromere antibody is associated with a better prognosis [43, 55]. However, having the anti-RNA polymerase III antibody was associated with scleroderma renal

crisis and increased mortality [46, 61]. In another study, the presence of anti-topoisomerase or anti-U1 RNP antibodies negatively impacted survival [45]. As noted above, the anti-fibrillarin antibody was associated with African-American patients but did not influence survival [55].

Risk Factors for Susceptibility of SSc

Risk factors for the development of SSc include gender, race, age, family history, birth order, and environmental factors including occupational exposures and possibly infections.

Female Gender

As summarized in Table 2.1, all epidemiology studies that have reported gender have noted that women consistently 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. There are relatively few published reports that have investigated the relationship of pregnancy with development of SSc. A Swedish population-based study [62] found that nulliparity was associated with an increased risk of SSc (odds ratio [OR] = 1.37, 95 % confidence interval [CI] = 1.22–1.55), whereas increasing parity was associated with a decreased risk. However, the increased risk with lower parity could also be explained, at least in part, by infertility due to subclinical or early disease. A more recent study by Cockrill et al. [63] 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 SSc or other autoimmune diseases [64], and it has been suggested as an explanation for the increased female to male ratio in these diseases. However, these data remain controversial, and to date the mechanism responsible for this association has not been identified.

Race

In the Michigan study previously noted above, Mayes et al. [14] 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 [65].

Similar findings were described by Le Guern et al. [26] 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 ILD (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 greater detail in another section of this book.

Age at Onset

SSc is rare in childhood. In the Michigan study [14], African-American patients were significantly younger at the time of diagnosis compared with European-American patients ($p < 0.001$). Figure 2.2, adapted from Mayes et al. [14], 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 reported in SSc. Feghali-Bostwick et al. [66] 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. Most recently, Frech et al. [67] studied 1,037 unique SSc cases and, linking the Utah Population Database and billing codes from the

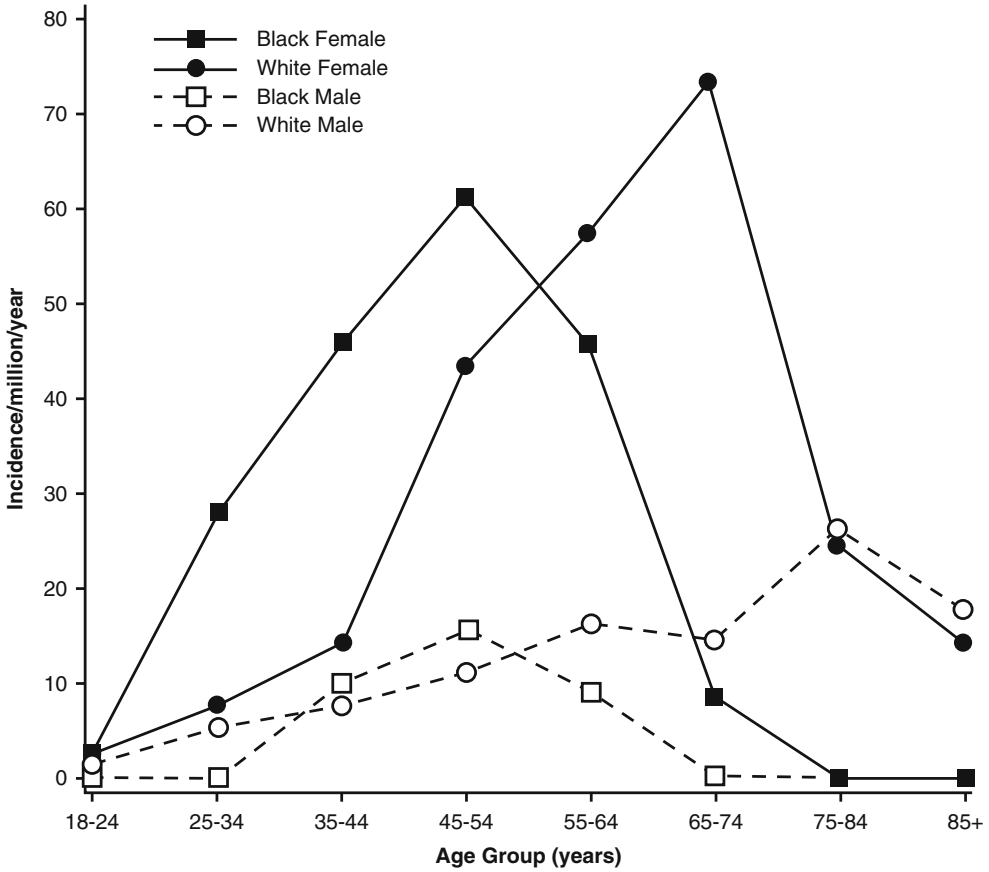

Fig. 2.2 Age-specific incidence of systemic sclerosis by race and sex (Adapted with permission from Mayes et al. [14])

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 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. [68] 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 [69] found increased frequency of multiple autoimmune disease in family members but did not find an increased relative risk for SSc.

To determine if familial scleroderma differed from spontaneously occurring disease, Assassi et al. [70] 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 [71] 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. [63] who studied 974 sibships and found that the opposite situation held in scleroderma, that is, 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. However, a study by Russo et al. [72] involving 387 SSc cases did not find a statistically significant relationship between SSc and birth order or SSc and parity. The incongruity between these two reports can be resolved only by further studies in multiple cohorts.

Environmental Triggers

Table 2.2 summarizes the well-documented environmental associations with SSc and SSc-like illnesses. Although there have been several case reports of SSc occurring after

Table 2.2 Environmental exposures associated with SSc or SSc-like illnesses

Exposure	Disease	Evidence (reference)
Crystalline silica/silica dust	SSc	Meta-analysis [73, 74]
Solvents	SSc	Meta-analysis [77]
Vinyl chloride monomer	Vinyl chloride disease	Investigation of outbreak [78]
Adulterated cooking oil	Toxic oil syndrome	Investigation of outbreak [79]
Tryptophan	Eosinophilic myalgia syndrome	Investigation of outbreak [80]
Gadolinium	Nephrogenic systemic fibrosis	Multiple case series (review [82, 83])
Drugs		
Bleomycin	Pulmonary fibrosis	Multiple observations (review [85, 86])
Pentazocine	Localized dermal fibrosis at injection site	Multiple observations (review [87])

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 [73] in addition to SSc. In a meta-analysis published by McCormic et al. [74], 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 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.

A prospective study to evaluate the association between SSc and occupational exposure by Marie et al. [75] revealed that silica, white spirit, aromatic solvents, trichloroethylene, ketones, and welding fumes had increased odds ratio for development of SSc. In male patients, a strong association was seen with exposure to the above agents. In female patients, the association was found with white spirit, aromatic solvents, any solvents, and ketones. However, these exposures were reported by a relatively small number of cases, usually men, and thus do not explain the vast majority of SSc cases predominantly 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. [75, 76] concluded that there was in fact no association between SSc and breast implants.

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 meta-analysis of 11 case-control studies by Kettaneh et al. [77] 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 alternative molecules to generate self-antigens that could 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 [78]. 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. [79] 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 (EMS) [80, 81], 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. The recent study by Marie et al. [75] mentioned above did not find an association between L-tryptophan and defined SSc.

Again, once the causal agent for EMS was identified and removed from the market in 1989, the syndrome essentially disappeared, although sporadic cases are still reported in the absence of apparent ingestion of this supplement.

Gadolinium and Nephrogenic Systemic Fibrosis (See Chap. 9)

Nephrogenic systemic fibrosis (NSF, previously called nephrogenic fibrosing dermopathy) was first reported by Cowper in 2000 ([82], for review see [83]) and characterized by rapidly progressive skin thickening with the early development of flexion contractures affecting the lower extremities more than the upper extremities and typically sparing the face. There can also be internal organ fibrosis involving skeletal muscle, myocardium, and lung. NSF 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 pathogenic mechanism remains unclear, it is thought that fibrosis results from activation of the transforming growth factor beta (TGF-beta) pathway [84].

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 [85]. The central event is endothelial damage to the pulmonary vasculature, and those who survive this complication usually recover completely with normalization of pulmonary function.

There have been 12 case reports of SSc (fulfilling 1980 classification criteria) occurring in the setting of bleomycin therapy for malignancy [86]. 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 [87]. This was first reported in 1975 [88] 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.

Infection Risk

The hypothesis that infectious agents play a role in the pathogenesis of autoimmune disease has been extensively studied with mixed results. It has been suggested that the production of SSc-specific autoantibodies results from an antigen-driven response called molecular mimicry [89]. The following will review the suggested role of some infections in the development of SSc, including parvovirus B19, cytomegalovirus (CMV), and *Helicobacter pylori* (*H. pylori*).

Parvovirus B 19 DNA has been detected in the bone marrow of SSc patients ($n=17$ cases positive for viral DNA out of 29 total cases studied or 17/29) and but not in the bone marrow of healthy individuals ($n=0/10$) [90]. The SSc patients with bone marrow persistence of parvovirus B 19 DNA had a shorter mean duration of disease and showed more severe perivascular and active endothelial injury than SSc cases without demonstrable viral DNA [91]. Although

intriguing, it is difficult to establish a causal link between this common infection and the subsequent development of a rare autoimmune disease.

CMV infection has also been postulated to contribute to SSc pathogenesis because of the virus' ability to infect both endothelial cells and monocytes and persist in a latent form. Interestingly, Lunardi et al. [92] reported that antibodies directed against the CMV-derived protein UL94 cross-reacted with a cell surface membrane protein of endothelial cells inducing apoptosis and activating fibroblasts suggesting a possible role of CMV in the triggering and maintenance of SSc. In fact, human CMV infection has been implicated in the initiation and/or persistence of multiple autoimmune diseases including SSc, systemic lupus erythematosus, rheumatoid arthritis, and others (for review see [93]). Again, there is difficulty in establishing a causal relationship between CMV infection and SSc, since CMV infection is common (found in 60–90 % of healthy adults) whereas SSc is a rare disease.

There has been an increasing amount of interest and research regarding a link between *H. pylori* and SSc. In a 1998 study [94] of patients with primary Raynaud's phenomenon (RP) and coincidental *H. pylori* infection, those patients who were treated and cured of *H. pylori*, reported either complete disappearance of RP or reduction of symptoms. In patients that were not cured of their *H. pylori* infection, RP did not improve. A recent study about the effect of *H. pylori* and disease severity revealed that SSc patients with *H. pylori* infection had a higher severity score compared to those without the disease [95]. However, there is conflicting data about *H. pylori* because other studies have not found a difference in SSc patients with and without the infection or an impact of treatment on Raynaud's phenomenon [96]. Therefore, this remains controversial.

In a similar fashion to CMV, Epstein-Barr virus (EBV) has been associated with SSc [97, 98]. It has been reported that EBV is able to persistently infect human SSc fibroblast in vitro and produce an aberrant innate immune response [98]. However, EBV is also found in a large proportion of the population suggesting that it may play a role but certainly is not the sole contributing factor to the development of SSc.

With respect to chlamydia infection, it has been postulated that such an infection may play a role in SSc as well as other immune-related diseases. However, in one study [99], skin biopsies from patients with SSc and controls were negative for chlamydia species.

Considering all the evidence to date, although several studies have linked various infectious diseases to SSc, there are conflicting data and a clear, direct association is missing. It is possible, although not yet proven, that infectious agents serve as "cofactors" in disease causation or persistence contributing to both tissue damage (via direct or indirect cellular toxicity) and immune dysregulation (via molecular mimicry or superantigen stimulation). Such considerations remain speculative at present.

Conclusion

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. The implementation of the 2013 ACR/EULAR classification criteria will lead to identification of more cases than the previous criteria allowed, thus causing an apparent (but not real) increase in incidence and prevalence. This will have to be taken into account in future studies.

Survival in SSc has clearly 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. ILD and pulmonary vascular disease have replaced renal failure as the most common cause of death. New treatments for both these complications may improve survival, but evidence for this is not yet available.

In terms of fender differences, 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 the Choctaw Native American/First Nations 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 infectious 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, an 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 SSc is unclear.

Finally, several infectious diseases have been implicated in the development of autoimmune disease; however, to date this remains controversial and no clear association has been demonstrated.

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