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48-year trends in systemic sclerosis mortality, 1968–2015: A United States population-based study

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Abstract

Objective: To identify secular trends associated with systemic sclerosis (SSc) mortality over 48 years.

Methods: Using national mortality data compiled by the Center for Disease Control and Prevention's Wide-ranging Online Data for Epidemiologic Research, and population data from the United States Census Bureau, we calculated age-standardized mortality rate (ASMR) for SSc and non-SSc (all other causes), and the ratio of SSc-ASMR to non-SSc-ASMR for each year from 1968 through 2015. We then used a joinpoint regression model to evaluate mortality trends, overall, and by sex and race.

Results: From 1968 through 2015, there were 46,798 deaths with SSc recorded as the *underlying* cause of death and 106,058,839 non-SSc deaths. There were an additional 9,063 deaths with SSc recorded as a *contributing* cause of death from 1999 through 2015. Whereas the non-SSc-ASMR decreased throughout the 48 years, the SSc-ASMR increased from 1968–2000, followed by decreases each year from 2001 through 2015. The SSc-ASMR also decreased for deaths where SSc was a *contributing* cause from 1999 to 2015. Women and black persons had higher SSc-ASMRs and SSc-ASMR:non-SSc-ASMR ratios than men and white persons, respectively. Additionally, SSc-ASMRs and SSc-ASMR:non-SSc-ASMR ratios increased at higher rates in women and white persons than men and black persons, respectively, during the initial three decades.

Conclusion: Mortality attributable to SSc increased from 1968 through 2000, followed by a steady decline from 2001 through 2015. However, SSc mortality relative to non-SSc mortality remains high. SSc mortality has disproportionately changed by sex and race over the 48 years.

Keywords

Systemic sclerosis; Mortality; Epidemiology; Race; Sex

Introduction

Systemic sclerosis (SSc) is a systemic autoimmune disease that causes premature death due to complications from interstitial lung disease, pulmonary arterial hypertension, gastrointestinal dysmotility, renal crisis, and malnutrition (1, 2). Over the past two decades, advances in the treatment of SSc-associated complications may have affected outcomes (2). For example, with the availability of prostanoids for the treatment of pulmonary arterial hypertension, the two-year survival of patients with SSc-associated pulmonary arterial hypertension has improved from 47% to 71% (3). However, the influence of these advances on SSc mortality trends in the general population in the United States (US) is unknown.

The disease-specific mortality rate is an important measure of the burden of disease. The actual mortality burden of SSc is unknown. Previous studies of SSc mortality were based primarily on deaths in patient cohorts at referral centers (4–7), which does not capture changes in incidence over time and does not reflect the actual burden and trends of SSc mortality in the general population. A few studies have used population-based designs (8, 9) but were limited to specific regions, small samples, or relatively short durations. We, therefore, undertook a population-based observational study of all death counts in the US over five decades to examine temporal trends in SSc mortality, overall and by sex and race. To evaluate SSc mortality in the context of changes in overall mortality in the US population, we compared SSc mortality with non-SSc mortality from all other causes.

Methods

Data Sources

The Centers for Disease Control and Prevention (CDC)'s National Vital Statistics System maintains a mortality database that encompasses more than 99% of deaths of US residents in all 50 states and the District of Columbia. We used the CDC's WONDER (Wide-Ranging Online Data for Epidemiologic Research) web application (10) to gather data on SSc deaths from 1968 (the earliest year for which the CDC published county-level mortality data) through 2015.

The underlying cause of death, defined as "the disease or injury that initiated the events resulting in death" is provided on the death certificate as an International Classification of Diseases (ICD) code (11, 12). We identified specific ICD codes for SSc (ICD-8, 734.0; ICD-9, 710.1; and ICD-10, M34), and used standard methodology to ascertain race (13).

We obtained annual death counts in the entire US population and separately by sex (men, women) and race (white, black, and "other"). Information on Hispanic ethnicity and Asian

or Pacific Islander, or American Indian or Alaska Native racial categories is not available before 1999 in the CDC WONDER.

Since 1999, information on the *contributing* cause of death, defined as "other significant conditions contributing to death but not resulting in the underlying cause" (12), became available on CDC-WONDER. To address the possibility that SSc may have directly contributed to death but not listed as the *underlying* cause of death, such as patients who died of SSc complications, we reanalyzed our mortality data where SSc was listed as a *contributing* cause of death.

For calculation of mortality rates, we obtained the size of the population (total and each group) from the US Census Bureau for each year.

Annual Mortality Rates

We quantified age-specific crude mortality rates for SSc and non-SSc for each year from 1968 through 2015 as the number of deaths in each year divided by the number of persons in the US general population in that same year. This was done within age strata (Supplementary Table 1) for the total US population as well as separately for men and women, and each of the three racial groups.

To calculate the overall age-standardized mortality rate (ASMR) for the population for each year from 1968 through 2015, we combined the yearly age-specific crude mortality rates with the age distribution of the US population in 2000, as described in Supplementary Table 1 (14). We performed this analysis separately for the total US population, each sex, and race for both SSc and non-SSc deaths. We then computed the ratio of SSc-ASMR to non-SSc-ASMR for each year.

Statistical Analysis

We used a joinpoint regression model to assess trends in the annual SSc-ASMR, non-SSc-ASMR, and SSc to non-SSc ASMR ratio. Joinpoint regression identifies changes in trend data by fitting a set of joinpoints – the calendar years at which the change in the slope (of ASMR) is statistically significant – over the entire period. The model then computes the slope (year-to-year percentage change in annual ASMR) and the 95% CI over each linear trend segment between adjacent joinpoints, as described previously (14, 15). We calculated the annual percent change (APC) with 95% CI for each trend, and then figured the average APC (AAPC) with 95% CI for the entire study period (Supplementary Methods).

Results

There were 46,798 deaths with SSc listed as the underlying cause and 106,058,839 non-SSc deaths in the US from 1968 through 2015. The proportions of deaths among women and non-white persons were higher for SSc than for non-SSc (Table 1).

Mortality Trends for SSc

The ASMR for SSc was 2.7 (95% CI, 2.4 to 2.9) per million persons in 1968. SSc-ASMR increased at an APC of 1.0% from 1968 to 1987 and then increased at a higher APC (2.2%)

from 1987–2001, before decreasing starting in 2001 (APC, −2.6%, 2001–2015) (Figure 1). Despite the steady decrease for 15-years, the SSc-ASMR was 3.2 (95% CI, 3.0 to 3.4) per million persons in 2015, which is 18.5% higher in 2015 than in 1968 (Table 2). In contrast, the ASMR for non-SSc decreased continuously between 1968 and 2015 (Figure 1).

To highlight the changes in SSc mortality relative to non-SSc mortality, we calculated the ratio of the SSc-ASMR to the non-SSc ASMR (Figure 1). The ratio increased at higher rates between 1968 and 2001 followed by decreases each year starting in 2001, indicating decreases in the proportion of US deaths from SSc during 2001–2015. However, SSc-ASMR:non-SSc-ASMR was still 111.6% higher in 2015 than in 1968 (Table 2).

The reduction in SSc-ASMR after 2001 could be due to SSc not being recorded as the *underlying* cause on the death certificates for some patients. To address this possibility, we conducted a joinpoint analysis for deaths where a *contributing* cause was SSc (Figure 1, left panel). We identified 9,063 deaths with SSc listed as a contributing cause from 1999 to 2015. Like trends observed for deaths where the underlying cause was SSc, the ASMR for SSc as a contributing cause decreased from 1999 to 2015.

SSc Mortality Trends by Sex and Race

The SSc-ASMR was higher in women (3.5, 95% CI 3.1, 3.9) than in men (1.8, 95% CI 1.5, 2.1) in 1968 (Table 2). From 1968 to the early-2000s, SSc-ASMR increased at higher APCs in women (1.1% to 2.9%) than in men (0.3%), followed by similar decreases in both women and men (−2.3% and −3.0%, respectively) (Figure 2). This trend resulted in a cumulative change of +40.0% in women and −22.2% in men (Table 2) at an AAPC of +0.5% in women and −0.6% in men (Supplementary Table 2) over the 48 years.

Black persons had higher SSc-ASMRs than white persons: 4.9 (95% CI, 3.8 to 6.1) and 2.4 (95% CI, 2.2 to 2.6), respectively, in 1968 (Table 2). After that, white persons had higher annual increases in SSc-ASMR than black persons from 1968 through the early 2000s, when it began to decrease at similar APCs in each race (Figure 2). Over the 48 years, the SSc-ASMR increased in white persons (cumulative, 33.3%), whereas it decreased in black persons (cumulative, −20.4%) (Table 2) at AAPCs of 0.4% and −0.4% in white and black persons, respectively (Supplementary Table 2).

In contrast to the increase-and-decrease trends in SSc-ASMRs, non-SSc-ASMRs decreased or stayed stable throughout the 48 years in all subpopulations (Supplementary Figure 1). Consequently, the SSc to non-SSc ASMR ratio initially increased at greater APCs in all demographic subgroups studied (Figure 2B). Starting in the 2000s, the ratio decreased in all subpopulations, although the differences were not statistically significant in black persons and other races. All subpopulations studied had a relative cumulative increase in the ratio from 1968 to 2015 (Table 2).

Discussion

Short of large-scale, population-based prospective studies covering almost all SSc deaths in the population, the national death certificates database remains a useful source for an

unbiased assessment of the mortality burden from a disease at the population level. This burden of disease data may be useful for healthcare policy planning, resource allocation, identification of high-risk population, and assessment of changes in disease management at the population level. This information cannot be obtained from limited cohort-based studies at referral centers, as the cause-specific mortality may vary due to changes in the incidence of disease, disease severity, or both over time.

Our joinpoint regression analysis of 55,861 SSc deaths in the US shows that mortality attributable to SSc has steadily decreased in the last 1½ decade after 33 years of sustained increase from 1968 through 2000. Despite these 15 years of steady improvement, mortality rates for SSc relative to non-SSc were still higher in 2015 than in 1968. The rise-and-decline trend in SSc mortality may reflect changes in disease incidence, SSc recognition, improved evaluation, and/or better management, as illustrated in Figure 3.

First, the incidence of SSc in the US increased between the 1960s and 1970s (16, 17) and doubled between the 1970s and 1980s (17). SSc incidence then stabilized over the next decade (9). Thus, changes in SSc incidence over time could partially explain the observed rising trends in SSc mortality from the 1960s to the 1990s.

Second, the establishment of SSc classification criteria in 1980 (18) and the introduction of SSc-associated autoantibodies in the 1980s could have contributed to the increase in the number of diagnosed cases and subsequently to the attribution of death to SSc. However, the increase in SSc recognition cannot explain the mortality trends in recent years. The description of skin scores and autoantibodies as predictors of disease course in the 1990s (19, 20) might have helped with early intervention and subsequently with declining SSc mortality in the 2000s. The development of classification criteria for early SSc in 2001 (21) might also have helped with early diagnosis and treatment, thus contributing to the improved SSc outcomes in recent years.

Third, medication toxicities in the 1960s-1980s and new treatments for SSc complications in the 1990s-2000s might have influenced mortality trends (Figure 3). D-penicillamine was used to treat SSc starting in the 1960s (22) until studies in the 1990s highlighted its inefficacy (23) and toxicity (23, 24). Additionally, corticosteroids used in the 1960s-1980s were implicated in precipitating SSc renal crisis (25), which was associated with high mortality, until the recognition in the 1990s of beneficial effects of angiotensin-converting enzyme inhibitors in preventing this complication (26). Furthermore, the benefits of early screening for alveolitis and selected use of cyclophosphamide in SSc-lung disease were reported in the early-2000s (27, 28). Finally, the introduction in the early-2000s of prostanoids, endothelin receptor-antagonists, and phosphodiesterase-5 inhibitors to treat SSc-associated pulmonary arterial hypertension has led to improved SSc outcomes (2, 3, 29). Together, multiple factors likely influenced the SSc mortality trends that we observed.

Conflicting results have been published about sex differences in SSc mortality. Standardized mortality ratios for SSc were similar between men and women in some reports (7, 30), but were higher in men than women in others (6). However, the standardized mortality ratios calculated in these studies may not have accounted for a higher incidence of SSc in women,

which appears to have increased between 1972 and 1982 (from 13 to 27.6 per million per year). In contrast, the incidence of SSc in men had remained relatively stable over this period (17). These observations may explain our finding that SSc mortality rates, which were higher in women than men in 1968, increased at an even higher rate in women than men until 2000. Since ASMR depends on both the prevalence and severity of the disease, we cannot exclude the possibility that SSc may be more severe in men than women. Accurate SSc prevalence rates across the US are needed to calculate the case-fatality rate that adjusts for differences in SSc prevalence between men and women. It is also plausible that SSc was recognized or recorded on death certificates more often in women than men from 1968 to 2000. Nevertheless, our data show that the ASMR that represents SSc mortality burden in the general population is higher in women than in men.

As reported previously (8, 31), SSc mortality rates were higher in black persons than in white persons. The potential causes for this disparity in SSc mortality may include higher SSc incidence, more severe disease, and younger age at diagnosis in black persons (32). However, SSc-ASMRs increased at a higher rate in white persons than black persons from 1968 until the early 2000s, when it began to decrease at similar rates in both races. Furthermore, SSc mortality in black persons had a cumulative decrease between 1968 and 2015 (−20%), whereas it increased in white persons during the same period (+33%). It is unclear, whether during 1968–2001, white persons experienced a more severe disease, a higher prevalence, increased recognition of SSc, or improved recording of SSc on the death certificates relative to black persons. Further analyses of mortality by race/ethnicity could not be reliably evaluated using the CDC-WONDER database, which does not have information on Hispanic, Asian, or Native American categories before 1999.

Strengths of this study include the use of an unbiased, systematic approach to assess SSc mortality in a large sample size comprising of all recorded deaths in the US over 48 years, the use of joinpoint regression analysis as a computational approach to identify trends, and computation of the ratio that compares SSc mortality relative to non-SSc mortality. Calculation of the standardized mortality ratio, reported in previous studies on SSc mortality (4–6), uses an indirect method of adjustment which depends on the age structure of the study population (SSc in this case) (33). However, the age structure may vary between different study cohorts, across populations of different regions and countries, and over time (34). Thus, the standardized mortality ratios computed for one population may not represent SSc mortality in another population. Therefore, we performed a direct method of adjustment using a standard population to calculate the ASMR for both SSc and non-SSc causes (33).

Our study has limitations. First, the validity of our findings depends on the accuracy of the physicians' coding of causes of death on death certificates, which is difficult to ascertain. Nevertheless, the strong associations that we detected cannot be explained by a low specificity on the cause of death on death certificates as random misclassification increases the similarity between the study population and the general population, creating an underestimation of the risk estimates. To the best of our knowledge, there are no reports on misclassification of SSc on the death certificates (i.e., SSc recorded on the death certificate for the decedent that did not have SSc). While misclassification on death certificates has been reported in other autoimmune diseases, it is still rare. For example,

for the 731 decedents for whom lupus was recorded on the death certificate, only 2 had lupus erroneously recorded as a cause of death (i.e., decedent did not have lupus) (35). Death certificates are unlike electronic health records and claims databases where a substantial proportion of subjects (about 25% in one study) coded as SSc did not fulfill criteria for SSc (36, 37), likely due to the entry of probable/possible/working diagnoses. In contrast, physicians who encounter patients at the time of death are likely to record the disease that was the most proximate or probable cause of death on death certificate. Thus, misclassification of SSc on the death certificates is less likely to have influenced SSc mortality rates substantially.

Second, SSc might be left off the death certificate in some portion of the 30%−50% of deaths among SSc patients that are caused by infection, cancer, and cardiovascular disease (7, 30). These proximate causes of death may be perceived to be unrelated to SSc, when in fact, the disease or the medications used for it predispose patients to them. Such underestimation of cause-specific mortality has been reported in other autoimmune diseases. For example, multiple sclerosis was not mentioned on death certificates in 6%−27% of patients who died of unrelated causes at an older age (38), and lupus was not recorded on the death certificates of some patients who died of complications such as infections, cardiovascular events, and respiratory diseases (39). Increasing awareness among primary care physicians and internists about the multi-organ complications of autoimmune diseases such as SSc and their varying presentations at the time of death would help assess the actual burden of SSc mortality in the future.

Third, the under-reporting of SSc on death certificates might selectively occur in specific subpopulations. For example, SLE was not recorded on the death certificate in older patients, those without health insurance, and those with low education levels in other autoimmune rheumatic diseases (40, 41). Nevertheless, the significant differences in SSc mortality by sex and race are less likely to be artifacts from the misclassification of cause of death in any meaningful way, because greater underreporting of SSc as the cause of mortality in underprivileged groups would lead to a larger underestimation of SSc mortality in the groups that we found the death to be higher in, e.g., females and black persons. Our data show that mortality attributable to SSc increased at higher rates in women and white persons relative to men and black persons, respectively, from the 1970s to the 1990s. This finding raises the possibility of whether factors related to disease evaluation, healthcare delivery, or socio-economic issues led to a differential recognition and reporting of SSc by sex and race during this period.

Fourth, ICD revisions between ICD-8 and ICD-9 and between ICD-9 and ICD-10 might have influenced the estimation of mortality trends. However, studies that measured the effects of ICD revisions have reported good comparability ratios for disease classification between revisions (42, 43).

Finally, changes in the physicians' reporting of SSc as the *underlying* versus *contributing* cause of death over time could have influenced SSc mortality trends. However, analysis of deaths for which SSc was recorded as a *contributing* cause during 1999–2015 showed a

similar pattern, suggesting that errors in the coding of cause of death did not substantially bias the findings at least over the last 15 years.

In conclusion, SSc mortality has begun to improve after the year 2000. Still, the improvement in SSc mortality has not kept up with an improvement in mortality from other causes in the general population. Comprehensive examination using prospective, population-based data could help clarify the mechanisms of the changing disparities in SSc mortality and identify modifiable risk factors that could be altered to improve outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Significance and Innovations

Our joinpoint regression analysis of 55,861 systemic sclerosis deaths in the United States shows that mortality attributable to systemic sclerosis has steadily decreased in the last 1½ decade after continuously increasing for the previous 33-years.

Systemic sclerosis mortality has disproportionately changed by sex and race over the 48-year period: it increased in women and white persons but decreased in men and black persons.

The recent, steady improvement in systemic sclerosis could have resulted from advances in the management of its complications, such as pulmonary hypertension and renal crisis.
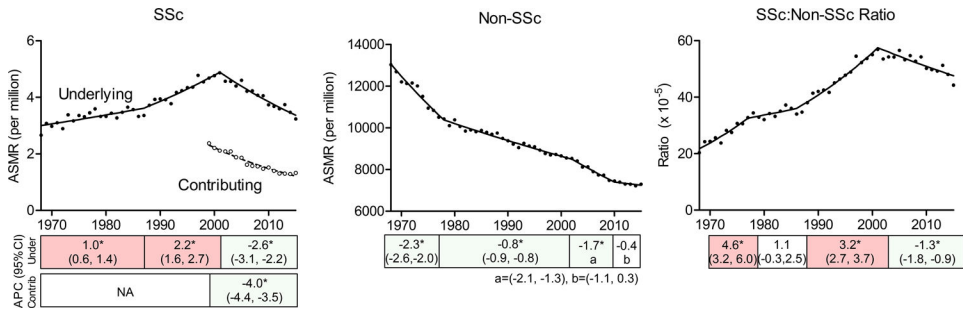
Figure 1. Trends in ASMR for SSc and Non-SSc causes, and Ratio of SSc to Non-SSc Mortality Rates, 1968–2015.

ASMR per million persons for SSc and non-SSc causes are shown in the left and middle panels, respectively. ASMR for SSc as a *contributing* cause of death, which became available on CDC WONDER since 1999, is also shown in the left panel. Data are displayed per calendar year of death with lines fitted based on joinpoint analysis.

SSc represented as the underlying cause in 46,798 deaths from January 1, 1968, through December 31, 2015, and as a contributing cause in 9,063 deaths from January 1, 1999, to December 31, 2015. The annual numbers of deaths ranged from 466 to 1,401 for SSc and 1,898,350 to 2,700,382 for non-SSc causes.

The right panel shows the ratio of SSc to non-SSc ASMRs (x 10^{-5}). A positive slope indicates an increased risk for death from SSc vs. non-SSc causes, whereas a negative slope indicates a decreased risk of death from SSc.

The stack bars under each panel represent the APC for each trend in SSc-ASMR, non-SSc-ASMR, and the ratio of SSc to non-SSc ASMR. Each stack is segmented at the year in which the change in slope is statistically significant and is aligned with the trend line. Numbers in each stack denote the APC (95% CI). The red-shaded stacks indicate an increasing trend, unshaded stacks represent a non-significant trend, and the light green-shaded stacks represent a decreasing trend. *P < 0.05 for slope change.

Abbreviations: APC, annual percent change; ASMR, age-standardized mortality rate; CI confidence interval; Contrib, contributing cause of death; NA, not available; SSc, systemic sclerosis; Under, underlying cause of death.
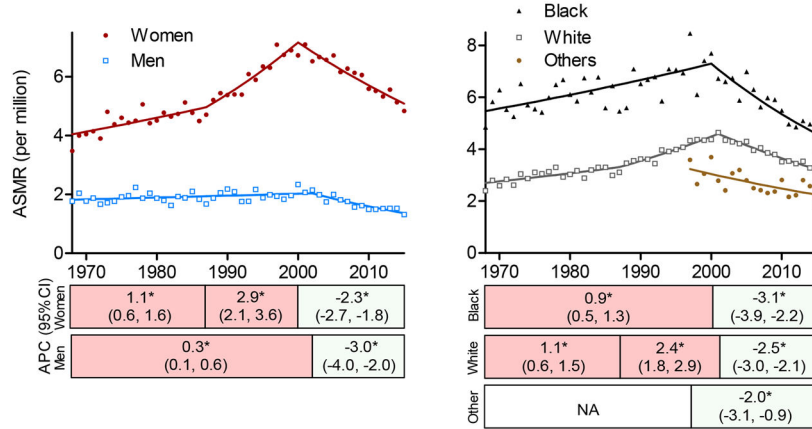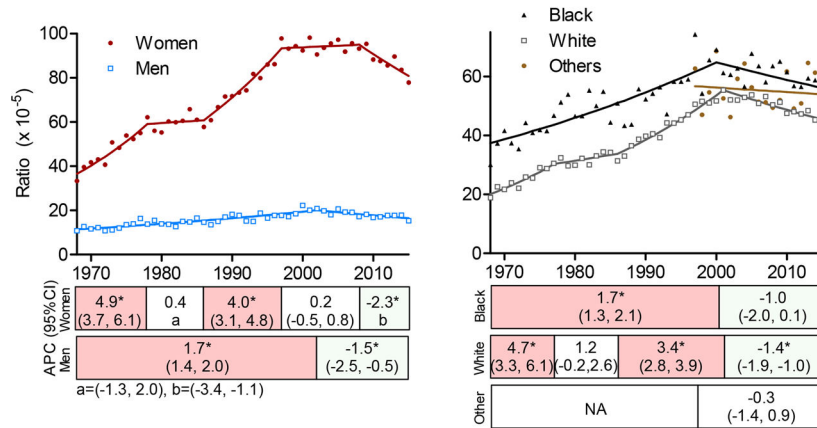
Figure 2. Trends in SSc ASMR and in Ratio of SSc to Non-SSc Mortality Rates by Sex and Race, 1968–2015.

Results are shown as ASMR for systemic sclerosis (SSc) per million persons (**A**), and the ratio of SSc to non-SSc mortality rates (**B**). Data are displayed per calendar year of death with lines fitted based on joinpoint trend analysis.

The annual number of SSc deaths ranged from 321 to 1,116 among women, 144 to 293 among men, 378 to 1,138 among white persons, and 80 to 234 among black persons. Data for other races are shown only for the 1997–2015 period (n = 26–58), because data before 1997 are unreliable due to small numbers of SSc deaths (less than 20) per year in this subpopulation. Because information on Hispanic ethnicity was not available before 1999, ethnicity was not included in the joinpoint analysis.

The stack bars below each panel represent the APC for each trend for each subpopulation. Each stack is segmented at the year in which the change in slope is statistically significant and is aligned with the trend line. Numbers in each stack denote the APC (95% CI). The red-shaded stacks indicated an increasing trend, unshaded stacks represent a non-significant trend, and the light green-shaded stacks represent a decreasing trend. *P < 0.05 for slope change.

Abbreviations: APC, annual percent change; ASMR age-standardized mortality rate; CI confidence interval; NA, not available.
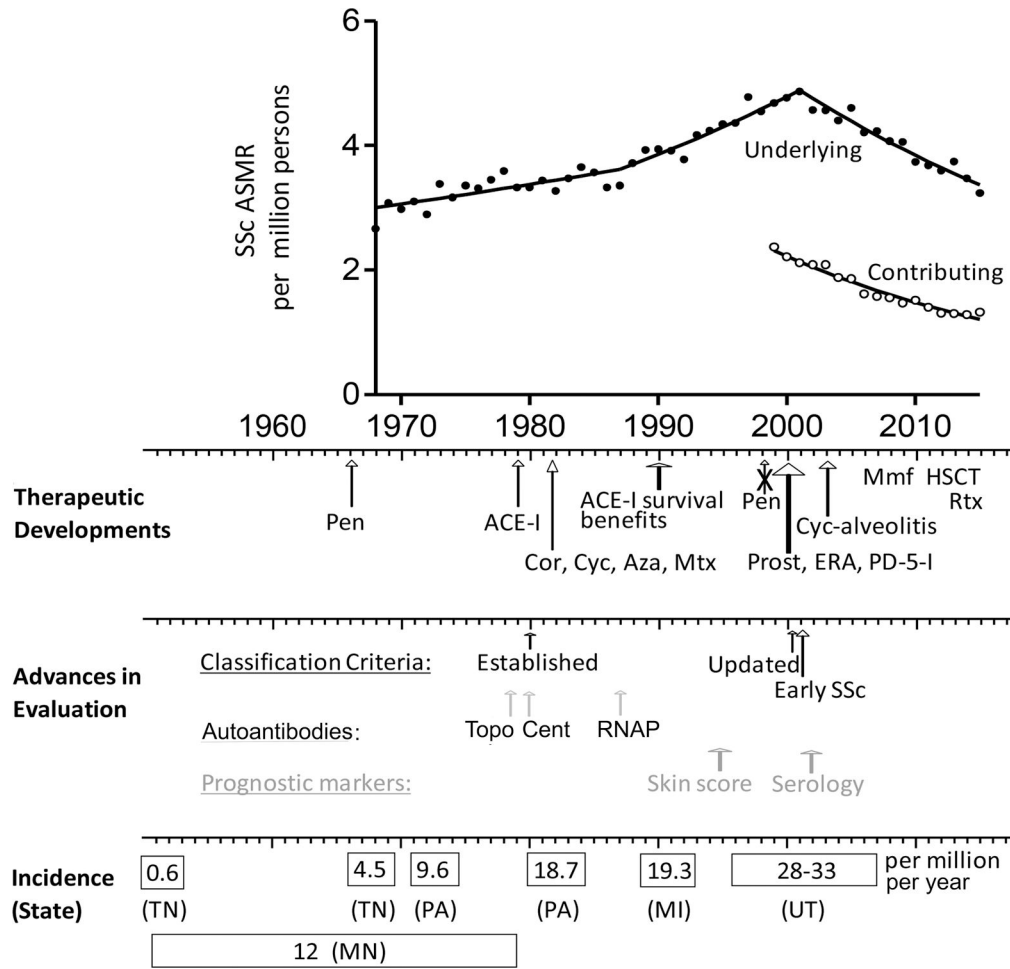
Figure 3. SSc Evaluation and Management Milestones and Changes in Incidence over Time in Relation to SSc Mortality Trends, 1968–2015.

ASMR per million persons for systemic sclerosis (SSc) as the underlying or contributing causes of death (Figure 1, *left*) is shown in relation to major therapeutic developments for SSc (top, underneath the trendline), advances in SSc evaluation (middle), and changes in SSc incidence over time (bottom).

(Bottom), SSc incidence rates in the US appear to have increased from 0.6 new cases per million persons annually in the 1940s (in Tennessee) (16) to 12 per million per year (Minnesota) (44), 19 per million per year in the 1990s (Michigan) (9) and 28–33 per million per year during the 1990s to 2007 (Utah) (45). Analysis of US administrative healthcare datasets also suggests a higher prevalence of SSc (0.03–0.05%) from 2001 to 2002 (46) than previously reported in 1991 (0.02%) (9).

(Middle), Timeline for major advances in SSc evaluation: The development of new criteria for the classification of early SSc in 2001 (21) and identification of relation between autoantibodies and prognosis (19, 20) appears to have coincided with the improvement in SSc mortality.

(Top), Timeline for major changes in the management of SSc: Early recognition and treatment of SSc renal crisis with angiotensin-converting enzyme (ACE) inhibitors (26) and early screening for alveolitis and selected use of cyclophosphamide in patients with

SSc lung disease (27, 28) may have helped with improving SSc mortality. Prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors were introduced in the late 1990s to the early 2000s to treat pulmonary arterial hypertension (29, 47–49) and were shown to improve the short-term survival in patients with SSc-associated PAH (3).

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ASMR, age-standardized mortality rate; Aza, azathioprine; Cent, anti-centromere antibody; Cor, corticosteroids; Cyc, cyclophosphamide; ERA, endothelin receptor antagonist; HSCT, hematopoietic stem cell transplant; MI, Michigan; Mmf, mycophenolate mofetil; Mtx, methotrexate; PD-5-I, phosphodiesterase-5 inhibitor; PA, Pennsylvania; Pen, D-penicillamine; Prost, prostanoids; RNAP, anti-RNA polymerase antibodies; Rtx, rituximab; TN, Tennessee; Topo, anti-topoisomerase (Scl-70) antibody; UT, Utah.

Table 1.

Demographic Characteristics of SSc and Non-SSc Deaths, 1968–2015

Characteristic	SSc Deaths[*]		Non-SSc Deaths[*]		Average Population Size[†]	
	Number	%	Number	%	Number	%
Total Deaths	46,798		106,058,839		258,208,302	
Sex						
Men	10,150	21.7	54,915,106	51.8	126,273,136	48.9
Women	36,648	78.3	51,143,733	48.2	131,935,166	51.1
Race						
White	38,060	81.3	91,729,629	86.5	214,348,874	83.0
Black	7,630	16.3	12,555,274	11.8	32,518,150	12.6
Other Race[‡]	1,108	2.4	1,773,936	1.7	11,341,278	4.4

[*] Absolute number of deaths from all 50 states and the District of Columbia.

[†] Average annual population derived from US Census Bureau files.

[‡] Information on Asian or Pacific Islander, or American Indian or Alaska Native racial categories and on Hispanic ethnicity is not available before 1999 and is therefore not shown.

Abbreviations: SSc, systemic sclerosis.

Table 2.

Cumulative Percentage Change in SSc ASMR, Non-SSc ASMR, and Ratio of SSc to Non-SSc ASMR between 1968 and 2015

Variable	SSc							Non-SSc [*]			SSc:Non-SSc ASMR Ratio		
	ASMR per million (95% CI), No. of Deaths						% Change	ASMR per million		% Change	Ratio x 10^{-5}		% Change
	1968			2015			1968–2015	1968	2015	1968–2015	1968	2015	1968–2015
All	2.7	(2.4–2.9)	466	3.2	(3.0–3.4)	1195	18.5	13032.9	7298.1	−44.0	20.7	43.8	111.6
Sex													
Men	1.8	(1.5–2.1)	145	1.4	(1.2–1.5)	227	−22.2	16334.6	8591.6	−47.4	11.0	16.3	47.9
Women	3.5	(3.1–3.9)	321	4.9	(4.6–5.2)	968	40.0	10422.2	6215.7	−40.4	33.6	78.8	134.7
Race													
White	2.4	(2.2–2.6)	378	3.2	(3.0–3.4)	987	33.3	12706.2	7319.7	−42.4	18.9	43.7	131.5
Black	4.9	(3.8–6.1)	80	3.9	(3.3–4.5)	166	−20.4	16118.3	8463.8	−47.5	30.4	46.1	51.6
Other Race	NA[†]			1.8	(1.3–2.5)	42	NA[†]	9295.4	4253.1	−54.2	NA[†]	42.3	NA[†]

[*] Total non-SSc deaths in 1968 and 2015 were 1,928,931 and 2,700,382, respectively.

[†] Data are not shown because of small sample size (<20 SSc deaths) in 1968 in this subpopulation.

Abbreviations: ASMR, age-standardized mortality rate; CI, confidence interval; NA, not available; SSc, systemic sclerosis.