SCLERODERMA EPIDEMIOLOGY

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From the perspective of epidemiology, the following questions are relevant to scleroderma pathogenesis: What is the pattern of disease occurrence? Have the rates of incidence and prevalence been stable over time? What populations are most affected? What are the risk factors for disease development, expression, and survival? Does the overall population incidence rate obscure subpopulations at higher risk? If so, what are the characteristics of these subpopulations? By identifying risk factors and analyzing the relative contributions of these factors, a model can be formed and hypotheses tested regarding the cause(s) of this disease.

This article will deal only with systemic sclerosis, in both its limited and diffuse forms. Localized forms of scleroderma (including morphea and linear scleroderma) will not be considered. The 1980 systemic sclerosis classification criteria[50] greatly facilitated epidemiologic studies by providing a common definition for this disease. Earlier studies[11, 34, 35, 37] did not have this benefit, making direct comparisons between pre- and post-1980 studies somewhat problematical. Additionally, it has been estimated that the 1980 classification schema will miss some 10% of individuals with limited disease.[36] Noting these limitations, analyses of studies that describe disease patterns over time and in different areas are still valuable in contributing to our understanding of scleroderma.

INCIDENCE AND PREVALENCE

Table 1 lists selected US studies that have reported scleroderma incidence, prevalence, and gender distribution over a 44-year period. The Medsger study[34] was based on 86 hospitalized cases from 1947–1968 and derived, rather than measured, the prevalence rate from the incidence figure and the survival data. The Michet study[37] was based on 13 cases in Rochester, Minnesota, identified between 1950 and 1979. The Steen study[48] found 442 hospital-diagnosed cases in a single county over a 20-year period. More cases were identified in the

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Table 1. SELECTED US STUDIES REGARDING SCLERODERMA PREVALENCE AND INCIDENCE RATES AND GENDER DISTRIBUTION

Author	Period of Observation	Prevalence Rate (per million)	Incidence Rate (per million)	Female:Male Ratio
Medsger[34]*	1947–1952	4	0.6	
	1953–1958	7	1.5	
	1958–1962	21	4.1	
	1963–1968	28	4.5	
Michet[37]†	1950–1979	253	13	
Steen[48]‡	1963–1972	—	14.1	3:1
	1973–1982	—	19.1	
Maricq[27]§	1985	286	—	—
Mayes[29]‖	1989–1991	242	18.7	5:1

*Based on 86 hospitalized cases in Shelby County, Tennessee; prevalence rates are derived from incidence and survival data.

†Based on 13 cases for incidence and eight female cases for prevalence in Rochester, Minnesota.

‡Based on 442 hospitalized cases in the Pittsburgh/Allegheny County, Pennsylvania area.

§Based on two cases that met ACR classification criteria for scleroderma and using the most conservative estimate, from a random sample of the general population of South Carolina.

‖Based on 706 cases in the Detroit, Michigan metropolitan area.

1973–1982 period than in the previous decade, leading to higher incidence rates for that interval. The Maricq[27] prevalence rate was determined in a prospective study (the only prospective study in this group) that used the presence of Raynaud's phenomenon as the entry point for potential patient identification. Although this report described a larger number of patients who were labeled as having a scleroderma spectrum disorder, the prevalence rate noted here is based on the two individuals who met the 1980 scleroderma classification criteria.[50] The Mayes study[29] gathered cases from both inpatient hospital data and outpatient clinic information in a defined metropolitan area.

With the exception of the Michet study,[37] these studies seem to indicate that the incidence of scleroderma increased from 1947 to 1973, but has remained relatively stable from 1973 to the present. Considering the fact that the earlier studies were hospital based, however, and that classification criteria were not well established until 1980, these low figures may represent an undercount of cases. The two largest studies (Steen[48] and Mayes[29]) report remarkably similar incidence rates (19.1 and 18.7, respectively) even though together they span a 19-year period. This would suggest that the incidence rate of scleroderma may be stable over this period of time and in these populations.

Prevalence rates are strongly dependent on survival. The Mayes study[29] suggests that the average survival period from diagnosis is 13 years. Prevalence rates in retrospective studies, however, tend to be biased in the direction of longer survival, because individuals with rapidly fatal disease are less likely to be captured than those with a more prolonged course.

In terms of gender distribution, the data indicate that scleroderma occurs much more frequently in women than in men. Steen et al[48] found that the excess of female cases over male cases is somewhat more marked in the child-bearing years compared with older age groups (3.8:1 versus 2.4:1). This difference, however, is not as great as in SLE where the incidence rate for child-bearing-aged women is sixfold to tenfold greater than that of similarly aged men.[17, 37] The implication is that the female hormonal milieu or pregnancy-related events increase disease susceptibility.

The trend toward higher incidence rates in more recent studies (see Table 1) is a reflection of multiple factors. As noted earlier, the 1980 classification criteria for scleroderma facilitated uniform case definition and provided for the inclusion of individuals with limited skin disease who may have been overlooked in earlier studies, especially hospital-based studies. Additionally, the availability of computerized data bases in both outpatient and inpatient settings results in more complete case findings. The possibility remains that the overall incidence rate may, in fact, be increasing. The relatively close correlation between the Mayes[29] and Steen[48] studies, however, suggests that this is not the case, or at least not in the time span covered by these reports.

Trends in prevalence rates are markedly influenced by two factors: earlier diagnosis and improved survival. These factors have clearly changed in the past two decades. Increased awareness of scleroderma by both physicians and the lay public has had the most effect on timely diagnosis, and the 1981 introduction of angiotensin converting enzyme (ACE) inhibitors has had a strong positive effect on survival following renal crisis.[9] More recent estimates of the scleroderma prevalence rate in the United States, as noted in Table 2, are relatively uniform considering the different study methodologies. They indicate that the prevalence rate among adults is approximately 240/million.

To put these rates in perspective, comparative data for adult rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are as follows. The prevalence of RA is reported to be 0.8 cases/1,000 or approximately 1% of the adult US population and new cases of RA are estimated at 300/million adults/y.[25] Reported estimates of prevalence and incidence rates for SLE in the United States vary more widely than estimates for these rates in rheumatoid arthritis. Michet et al,[37] however, reported an overall prevalence rate of 400/million/y, and Hochberg[17] found an incidence rate of 46/million/y. In contrast, therefore, systemic sclerosis has an incidence rate approximately 40% that of SLE and 6% that of RA.

Table 2 summarizes data from several international studies on scleroderma prevalence and incidence rates. These studies suggest that scleroderma occurs more commonly in the United States than elsewhere. The prevalence rates for Britain[45] and Japan[52] are quite similar (31 and 38 per million, respectively). The nearly identical incidence rates between Britain and Iceland[14] (3.7 and 3.8 per

Table 2. SELECTED INTERNATIONAL STUDIES REGARDING SCLERODERMA PREVALENCE AND INCIDENCE RATES AND GENDER DISTRIBUTION

Country (period of observation)	Prevalence Rate (per million)	Incidence Rate (per million)	Female:Male Ratio
Britain[45]* (1985–1986)	30.8	3.7	6:1
Japan[52]† (1988)	38	—	14:1
Iceland[14]‡ (1975–1990)	71	3.8	8:1
United States			
Steen[48]	—	19.1	3:1
Maricq[27]	286	—	—
Mayes[29]	242	18.7	5:1

*Based on 156 cases in the West Midlands Region of England, from both outpatient and hospital records, including individuals over age 15.

†Based on 357 cases using the total population of Tokyo (both children and adults) and using the 1980 American Rheumatism Association criteria.

‡Based on 15 incident cases found and 18 prevalent cases using the entire population of Iceland (because they had one patient between 0 and 9 years of age) and using 1980 criteria.

million, respectively) suggest that the reported prevalence difference between these two countries is a reflection of longer survival in Iceland, perhaps due to less severe disease. Of the 18 cases identified in Iceland, five had diffuse disease and 13 were classified as limited. No patient had renal involvement.

The female-to-male ratios also differ somewhat among these studies, with no clear-cut explanation. A female excess, however, is a consistent finding in these and in all previous studies.

It is difficult to attribute the difference in incidence rates between US and non-US locales to differences in study design alone. The degree of ascertainment of diagnosed cases for the British, Japanese, and Icelandic cases should be quite high due to the nature of their health care systems. A significant undercount of cases tends to occur because of failure to recognize scleroderma by a nonspecialist or delay in diagnosis of mild or limited cases. Nonetheless, this seems to be an implausible explanation for a fivefold difference in both incidence and prevalence rates.

Although the discrepancies among countries in the above rates may reflect methodologic differences in case ascertainment and case definition, they may also reflect true regional differences. These regional differences, in turn, may be due to differential susceptibility to scleroderma on a genetic basis, or to differential exposure to the putative environmental trigger(s). Evidence to suggest that genetic factors play a role in the development of scleroderma comes from studies that have compared racial and ethnic group differences in disease expression, and from studies that have examined the distribution of histocompatibility locus antigen (HLA) subtypes.

RACIAL AND ETHNIC FACTORS IN DISEASE DEVELOPMENT AND EXPRESSION

Several US studies have suggested that black patients have a higher age-specific incidence rate and more severe disease than white patients.[22] Figure 1 and Figure 2 show age-specific incidence rates of diffuse and limited scleroderma in 346 Michigan women by race for the period 1985 through 1991. (Diffuse skin disease is defined as the presence of skin thickness on the upper arms, thighs, or torso.[24])

Figure 1 shows a peak age-specific incidence (20/million/y) of diffuse disease in black women in the 35 to 44-year age group. This is higher and earlier than the peak incidence of similar disease in white women (8/million/y, see Fig. 2). These figures also illustrate that diffuse disease occurs more frequently (70% of black cases versus 31% of white cases, data not shown) and at an earlier age in black women compared with white women. Considering limited disease, peak incidence is quite similar for both white and black women, but age at diagnosis is still earlier in blacks.

In terms of male cases, the Steen study[48] found that black men also had an earlier age of onset of scleroderma than white men.

In the Laing study,[22] anticentromere (ACA) antibodies occurred more frequently among white women (101/264, 38%) than among black women (11/64, 17%). Anti–Scl-70 (also referred to as antitopoisomerase) antibodies were equally prevalent in both the diffuse and limited groups, and among blacks and whites (18.4% among blacks and 18.6% among whites). Racial differences in the frequency of scleroderma-related autoantibodies have been reported by Reveille et al[42] with white patients having anticentromere antibodies in 36% of cases compared with 4% for black patients. This study also found antitopoisomerase antibodies to be present in 37% of blacks compared with 17% of whites. Simi-

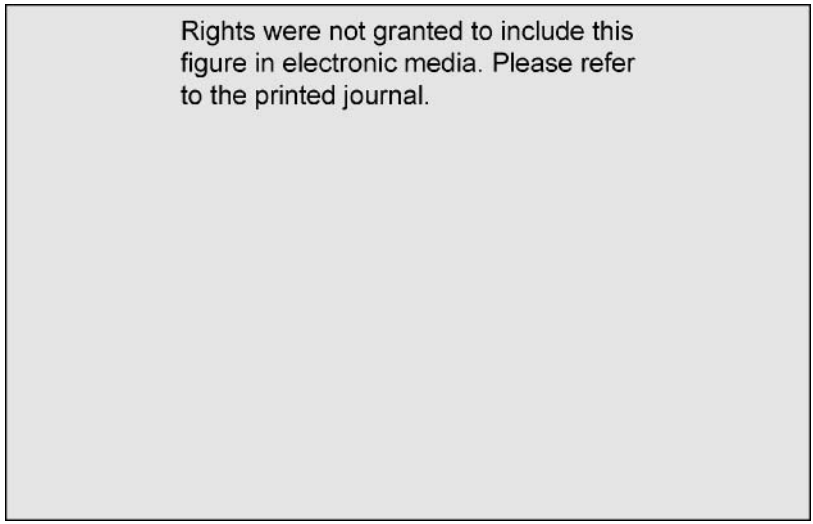

Figure 1. Age-specific incidence rates of diffuse and limited scleroderma for black women (n = 75) in Michigan for the period 1985–1991. (*Adapted from* Laing TJ, Gillespie BW, Toth MB, et al: Racial differences in scleroderma among Michigan women [abstract]. Arthritis Rheum 37:S259, 1994; with permission.)

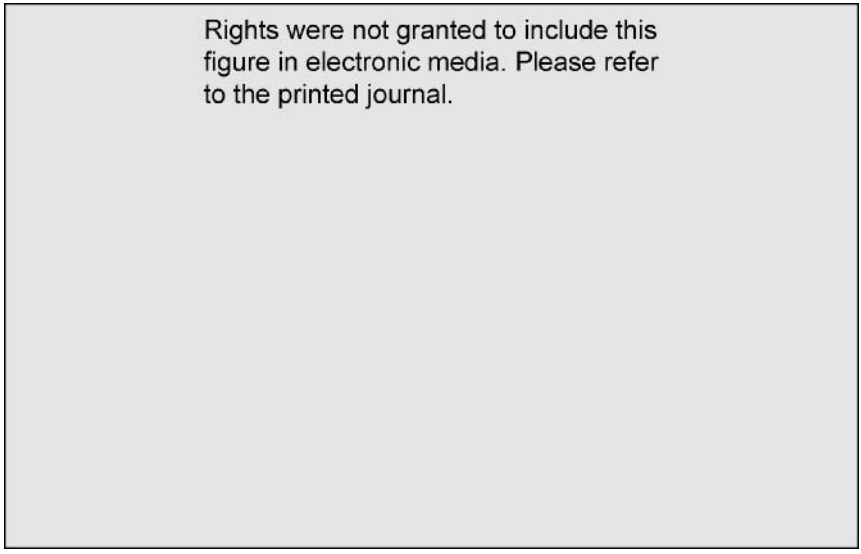

Figure 2. Age-specific incidence rates of diffuse and limited scleroderma for white women (n = 271) in Michigan for the period 1985–1991. (*Adapted from* Laing TJ, Gillespie BW, Toth MB, et al: Racial differences in scleroderma among Michigan women [abstract]. Arthritis Rheum 37:S259, 1994; with permission.)

larly, McNeilage et al[33] reported a high frequency of anti–Scl-70 antibodies (76%) and a low frequency of ACA (2%) detected in nonwhite Thais, in contrast to a low frequency of anti–Scl-70 (26%) and a high frequency of ACA (51%) in white Australians. All 49 of the Thai patients in this report had diffuse disease, compared with 15% of the Australians. In the Choctaw Indian cluster described below,[18, 53] 92% of the Choctaw patients had diffuse disease, compared with a 31% diffuse and 69% limited distribution in an American white (female) population.[22] Additionally, Giordano[16] reported that 89.6% of Italian scleroderma patients had the limited variant. In summary (Table 3) these data suggest that European, white American, and white Australian groups more frequently have limited disease while black American, some Native American, and Asian populations have more diffuse disease.

In the Laing study,[22] after adjusting for age, black women had worse survival than white women, due to their greater frequency of diffuse disease. After adjusting for both age and diffuse/limited status, no race effect was demonstrated.

It is clear from these studies that racial and ethnic background influence disease susceptibility, clinical expression, and serologic markers.

IMMUNOGENETIC LINKS

Multiple studies have tried to establish a link between HLA types and scleroderma.[3, 31, 39, 40, 43, 44, 51, 55] Evidence for such a link is not strong for systemic sclerosis in general. When scleroderma patients are divided into subpopulations, however, according to disease extent (diffuse versus limited) or according to serologic markers, distinct HLA patterns emerge (for review, see Arnett[2]).

Antitopoisomerase (also known as anti–Scl-70) antibody expression has been associated with several HLA-DQB1 alleles sharing a common tyrosine residue in position 30 of the binding domain.[39, 43, 56] In contrast, anticentromere antibodies are strongly associated with DQB1 alleles with a glycine or tyrosine residue in position 26.[40] It is postulated that these particular residues play a key role in determining the configuration properties of the antigen that can be

Table 3. WORLDWIDE DIFFERENCES IN ANTIBODY EXPRESSION AND DISEASE SUBTYPE

Author: Ethnic Group	Disease Subtype (%)		Antibody Expression (%)	
	Limited	Diffuse	Anti-Centromere	Anti-Scl 70
McNeilage[33]:				
White Australians	85	15	51	26
Nonwhite Thais	0	100	2	76
Reveille[42]:				
American Black	—	—	4	37
American White	—	—	36	17
Laing[22]:				
American Black	30	70	14	18.4
American White	69	31	35	18.6
Tan[53]:				
Choctaw	8	92	—	83
Giordano[16]:				
Italian	90	10	—	—

bound. Thus, one of several DQB1 alleles may confer susceptibility to disease development or at least to a particular autoantibody response when the appropriate antigen is presented.

Although less well studied, T-cell receptor genes may be differentially distributed in the scleroderma population, compared with normal controls.[3, 21] Additionally, C4A and C4B null alleles have been reported to occur in both limited and diffuse scleroderma[6, 38, 41] at a higher rate than in the general population. C4A null alleles are considered to be a genetic risk factor for the development of SLE (for review see Arnett and Reveille[4]).

In summary, multiple immunogenetic factors have been associated with scleroderma. It is unclear what level of risk they confer on disease susceptibility or disease expression.

SURVIVAL

Improved survival rates have been reported in some recent studies[7, 21] compared with earlier ones.[11, 35] This improvement is both apparent and real. Earlier diagnosis (for reasons discussed above) is a factor that artifactually prolongs observed survival. Additionally, survivor bias, in which the rapidly progressive and fatal diffuse cases tend not to be captured at the same frequency as the more mild limited cases with protracted courses, would prejudice studies in the direction of increased survival. Nonetheless, advances in treatment, most notably the use of ACE inhibitors in renal crisis, have led to a real decrease in the mortality from hypertensive renal disease. The factors that most influence survival are the presence and severity of internal organ involvement, which are positively correlated with the presence of diffuse rather than limited skin disease.

Figure 3 shows the probability of survival for 276 women diagnosed between 1985 and 1991 in Michigan[22] and followed for 8 years, according to the extent of skin involvement and compared with expected survival. For limited disease, survival is calculated both from date of scleroderma diagnosis and from date of diagnosis of Raynaud's phenomenon. The probability of surviving for 7 years is 87% for limited disease from Raynaud's diagnosis, 81% for limited disease from scleroderma diagnosis, and 72% for diffuse disease. This study indicated that overall 7-year survival was 76.5%. This is in good agreement with Bulpitt et al,[7] who found an estimated 5-year survival rate of 68% based on 48 patients followed from 1982 to 1987, most of whom (73%) had diffuse disease.

Figure 4 shows the relationship between organ involvement and survival. Renal disease accounted for significant early mortality. Additionally, pulmonary involvement (including both pulmonary fibrosis and pulmonary hypertension) was a significant risk factor for mortality. After adjusting for age and for other organ system involvement, gastrointestinal disease did not constitute a significant risk factor for death. From this study, as well as earlier studies, it is clear that pulmonary disease accounts for much of the mortality in both limited and diffuse forms. Renal involvement remains as a significant component of mortality risk. Gastrointestinal involvement clearly contributes to the morbidity of the disease, but is less clearly responsible for fatal events.

Bulpitt et al[7] in a prospective study of 48 patients, Lee et al[23] in a prospective study of 237 patients, and Altman et al[1] in a prospective study of 264 patients found that the early presence (especially within the first year of presentation) of cardiac, pulmonary, gastrointestinal, or renal disease was predictive of reduced

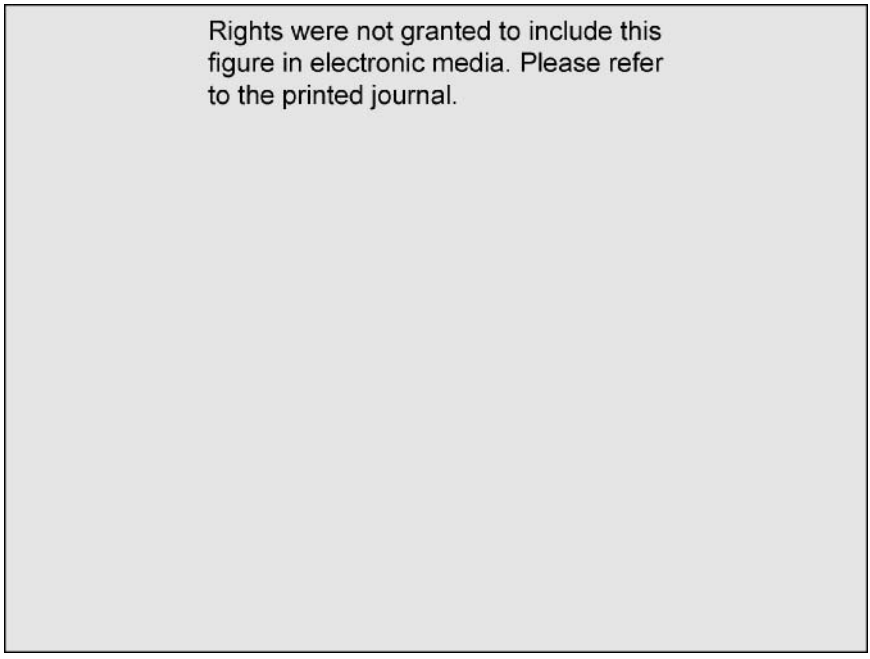

Figure 3. Probability of survival from time from diagnosis to death compared to expected survival for diffuse and limited scleroderma in Michigan women (n=276) for the period 1985–1992. (*Adapted from* Laing TJ, Gillespie BW, Toth MB, et al: Racial differences in scleroderma among Michigan women [abstract]. Arthritis Rheum 37:S259, 1994; with permission.)

survival. In a Japanese study,[19] patients with the anticentromere antibody had a significantly better survival than those who were centromere negative.

Although many patients survive for an extended period of time, the survival curves do not appear to level off over time with respect to normal survival. Earlier studies with 15-year survival data[5, 15] indicate that there continues to be excess long-term mortality due to scleroderma.

GEOGRAPHIC CLUSTERS

There have been several reports of clustering of scleroderma in particular areas. A cluster can be defined as a greater than expected occurrence of disease cases, in a geographically defined region, that is unlikely to have resulted by chance alone.[20] Two elements are necessary in determining a cluster: (1) the underlying disease prevalence and incidence rates should be known with some reliability; and (2) the boundaries of the geographic area have to reasonably conform to natural population patterns, in the sense that the area was not artificially constructed to include the maximum number of cases. Ascertainment bias can be a considerable problem, because close scrutiny of a population by

specialists may result in recognition of previously undiagnosed cases. Limiting cases to those previously diagnosed can partially address this issue.

In 1990, Silman et al[46] reported a cluster of scleroderma in London in the three boroughs adjacent to Heathrow and Gatwick airports, a heavily industrialized area. They found a prevalence rate of 150/million, based on 52 cases alive as of January 1987, in these boroughs; this rate was significantly elevated from the reference population in the West Midlands area of England. One of the authors, however, C. M. Black, has a known interest in scleroderma and conducts her teaching and practice unit in the area. Thus, the level of disease recognition and rate of diagnosis may be higher than in the reference locale.

An additional geographic cluster was reported by Valesini et al[54] in a rural area in the province of Rome. They found two previously diagnosed cases (both labeled as calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia [CREST]) and, during the study, three additional cases (one CREST and two labeled scleroderma) from a total adult population in the electoral ward of 572 individuals. Although the authors did not calculate a prevalence rate, this would amount to a prevalence of 3497/million considering only the original three cases, and 8741/million for all five cases. These authors found an additional 11 people with scleroderma-like features and eight individuals with antinuclear antibodies without any connective tissue disease features. HLA analysis did not reveal any significant associations among the

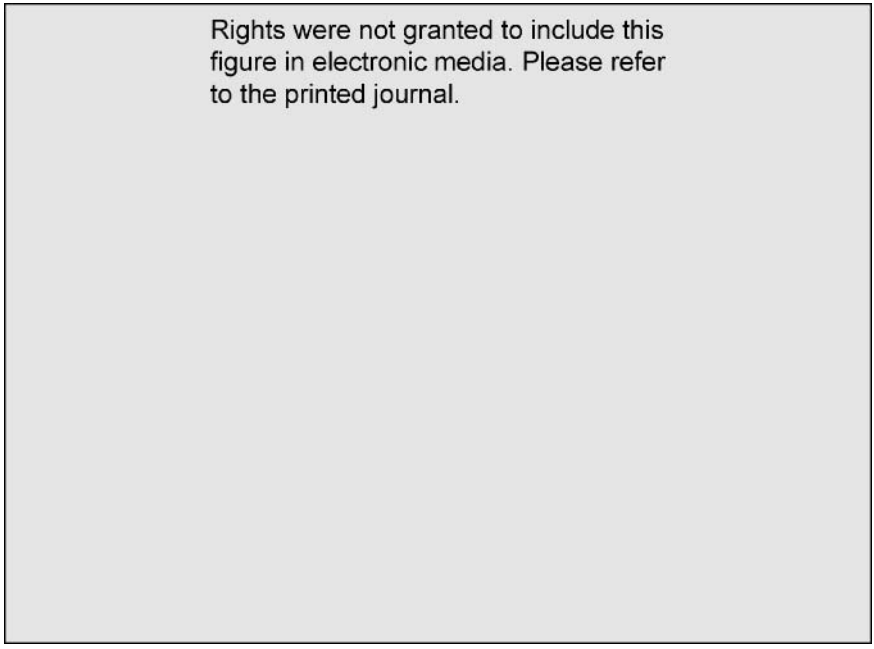

Figure 4. Probability of survival from time from diagnosis to death according to organ system involvement in Michigan women (n = 346) for the period 1985–1992. (*Adapted from* Laing TJ, Gillespie BW, Toth MB, et al: Racial differences in scleroderma among Michigan women [abstract]. Arthritis Rheum 37:S259, 1994; with permission.)

patients compared with healthy controls from the same village or other healthy Italian subjects. No apparent environmental factor was identified to link the patients.

Finally, in 1993 Howard et al[18] reported a clustering of scleroderma among Choctaw Native Americans, and in 1994, Tan et al[53] expanded these observations. They found 19 cases of systemic sclerosis in a population of 21,145 Choctaw in a defined geographic area in southeastern Oklahoma for a prevalence rate of 610/million. The prevalence rate increased as the quantum of Choctaw blood increased, but the numbers of actual cases were small. As noted earlier, 92% of patients had diffuse skin disease and 83% had antitopoisomerase antibodies. A case-control study revealed no significant environmental risk factors. The haplotype HLA-DR2(DRB1*1602), QB1*0301, however, was identified as a significant genetic risk factor.

Taken together, these three studies suggest that scleroderma may occur in a nonrandom fashion, with the Choctaw study providing the most convincing evidence to date. Although genetic factors may confer increased risk, the nature of the environmental trigger remains obscure.

FAMILIAL SCLERODERMA

Several multicase families have been reported in the literature.[26, 30, 31, 32, 47, 49] These reports include index scleroderma cases who have family members with either scleroderma or scleroderma spectrum diseases, as well as index cases having family members with other autoimmune diseases. Although it is clear that there is occasional familial clustering, these reports tend to exaggerate the familial tendency. In the author's personal series of 349 consecutive patients with scleroderma from whom detailed family histories were obtained, only three patients (by self report) claimed to have a first degree relative with scleroderma (unpublished data, 1996). Three other patients reported more distant relatives as having scleroderma. Of note is that an additional two individuals had affected family members who were related only by marriage. This means that over 99% of scleroderma patients report no first-degree relatives who have been diagnosed with scleroderma, and 98% report no other affected family member of any degree of blood relation.

Familial aggregation of primary Raynaud's phenomenon has also been reported,[13] with 24% (38/157) of probands' family members having idiopathic Raynaud's disease as compared with 2.2% (2/93) of controls. No cases of secondary Raynaud's or positive antinuclear antibodies (ANAs) were found.

Twin studies are of particular relevance for this issue. In a study by Feghali and Wright,[12] 34 twin pairs were evaluated in which one or both twins had systemic sclerosis. They found the overall concordance rate was 5.9%, with the rate among identical and fraternal twins not being significantly different. Interestingly, they found the concordance rate for ANA positivity to be 100% in the identical twins and 63.6% in the fraternal twins, although none of the healthy twins displayed scleroderma-specific autoantibodies.

Similar findings of ANA positivity in relatives as well as spouses of scleroderma patients have been reported in multiple studies.[10, 31, 41] There remains only one case in the literature, reported in 1984, of scleroderma occurring in both husband and wife,[8] an event which now appears to have occurred by chance.

This body of data suggests that inherited genetic factors play a role in the tendency/ability to produce autoantibodies, but that the major factor in disease

development involves an acquired environmental exposure, the nature of which remains obscure.

CONCLUSION

In summary, the overall incidence rate of systemic sclerosis in the adult population of the United States is approximately 17 per million with no compelling evidence that this rate has increased in the last two decades. Recent population studies suggest that the incidence rate in the United States is greater than in Europe or the Pacific but has also been fairly stable over the past 2 decades. This implies that exposure to the putative causal agent or agents is also stable in the population. Women are affected more frequently than men. Age-specific incidence rates are higher in black women than in white women, with the greatest difference occurring in the young to middle adult age group (less than 54 years of age).

Diffuse disease also appears to occur more commonly in the black population than in the white. Age of onset of diffuse disease is younger, on average, than age of onset of limited disease. Age-adjusted survival is worse in black women than in white women due to their predilection for diffuse disease.[22]

The prevalence rate for scleroderma in the United States also appears to be stable, with a prevalence rate for adults of 240 per million.[29] Renal disease accounts for most of the early mortality, but pulmonary disease has emerged as a major cause of death. Cardiac disease is also correlated with a poorer prognosis. Gastrointestinal involvement contributes to morbidity and, indirectly, to mortality, but the magnitude of this contribution is difficult to assess. Overall survival from diagnosis at 7 years was 76.5%.[22]

Risk factors for disease development include female gender and may include HLA-DQ type; risk factors for development of diffuse disease include black race or Choctaw heritage coupled with residence in southwest Oklahoma. Risk factors for the development of limited disease, other than female gender, remain to be elucidated.

Risk factors for reduced survival include the presence of diffuse disease, older age at onset (reflecting the not very profound nor very original observation that advancing age is positively correlated with greater risk of dying), and the presence of renal, cardiac, pulmonary, or gastrointestinal involvement.

Geographic clustering is intriguing; the reported clusters in London and Italy have not yet resulted in the identification of potential causal factors. The Choctaw cluster suggests that an HLA-DQ allele is an important risk factor, but by itself is not sufficient for the development of diffuse scleroderma.

The relative paucity of familial cases and the results of a single twin study suggest that genetic factors may play a permissive role while environmental factors play a more direct or causal role in disease occurrence.

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