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# Time to Diagnosis in Systemic Sclerosis: Is Gender a Factor?

Marie Hudson, MD MPH, Brett Thombs, PhD, Canadian Scleroderma Research Group (CSRG)*, Murray Baron, MD

***CSRG Investigators:** J. Markland, Saskatoon, Saskatchewan; J. Pope, London, Ontario; D. Robinson, Winnipeg, Manitoba; N. Jones, Edmonton, Alberta; P. Docherty, Moncton, New Brunswick; M. Abu-Hakima, Calgary, Alberta; N. A. Khalidi, Hamilton, Ontario; S. Le Clercq, Calgary, Alberta; E. Sutton, Halifax, Nova Scotia; C. D. Smith, Ottawa, Ontario; E. Kaminska, Hamilton, Ontario; J.-P. Mathieu, Montreal, Quebec; P. Rahman, St. John's, Newfoundland; S. Ligier, Montreal, Quebec

**Author institutional affiliations**: SMBD-Jewish General Hospital and McGill University, Montreal, Canada

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**Correspondence and request for reprints**: Dr Marie Hudson, SMBD-Jewish General Hospital, Room A-216, 3755 Cote Ste Catherine Road, Montreal, Quebec, H3T 1E2, tel. 514-340-8222 x. 8231, fax 514-340-7906, e-mail marie.hudson@mcgill.ca

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**Abstract**

**Objective** To determine whether gender plays a role in the time to diagnosis of systemic sclerosis (SSc).

**Methods** In the Canadian Scleroderma Research Group registry, dates of onset of Raynaud's phenomenon, the first non-Raynaud's disease symptom and diagnosis are recorded based on patient reports. Association between gender and time to diagnosis was assessed for the group as a whole and stratified based on extent of skin involvement, either limited or diffuse.

**Results** Of the 408 patients studied (347 women, 61 men, 44% with diffuse SSc), the time to diagnosis after the onset of Raynaud's was significantly longer for women than for men (log rank p = .001) but not significantly different after the onset of the first non-Raynaud's disease manifestation. In analysis stratified by limited or diffuse status, the time to diagnosis from onset of Raynaud's was also significantly longer for women than men with *diffuse* disease (log rank p = .008), a trend towards a longer period between onset of Raynaud's and SSc diagnosis was observed in women compared with men with *limited* disease (4.6 years in women versus 2.1 years in men, p = .085), and there was no gender difference in time to diagnosis after the onset of the first non-Raynaud's disease manifestation.

**Conclusion** In SSc, the time to diagnosis is longer for women than men after the onset of Raynaud's. This data suggests that there may be possible biological differences in the progression of disease or in the health care trajectories of men and women with early SSc.

Systemic Sclerosis (SSc) is a chronic, multi-system disorder characterized by thickening and fibrosis of the skin and internal organs. It affects mainly women in the prime of their life and is associated with significant morbidity, including pain, disability, depression and reduced quality of life, increased mortality and high costs. SSc is thought to affect over 16,000 Canadians and up to 100,000 Americans. There is currently no known cure.

Systemic sclerosis (SSc) can be difficult to identify in the general clinic due to its rarity and heterogeneity and this may give rise to delays in diagnosis. The onset of SSc is often heralded by Raynauds's phenomenon, but Raynaud's is not specific for SSc. In addition, primary Raynaud's is more common among women than men,[1] and thus may be less likely to raise suspicion of SSc in women. Finally, in the general patient population, medically unexplained symptoms are more prevalent among women than men and are sometimes mistakenly understood as psychosocial in nature, which can result in less vigorous efforts to seek a medical reason for complaints[2]. Skin tightening is often the telltale sign of SSc and gives rise to its two common clinical subsets recognized in terms of skin involvement, either **limited** (skin involvement distal to the elbows and knees) or **diffuse** (skin involvement proximal to the elbows and knees in addition to the trunk)[3]. However, although women are more commonly affected by SSc than men, little is known on gender differences in SSc, including differences in the onset of disease and the progression of early disease.

Given these considerations, we hypothesized that gender differences in the length of time to diagnosis could provide evidence of either differential health care trajectories or differential biological processes in women and men with SSc. Thus, we undertook this

study to determine whether there were gender differences in the length of time to diagnosis of SSc.

## Methods

*Design.* Cross-sectional study of a convenience sample of patients with SSc.

*Study subjects* The study subjects consisted of those enrolled in the Canadian Scleroderma Research Group (CSRG) Registry. Patients in this Registry are recruited from 15 centers across Canada. They must have a diagnosis of SSc made by the referring rheumatologist, be $\geq$ 18 years of age and be fluent in English or French. The patients included in this study were those whose baseline visit was between August 2004 and August 2007. The CSRG registry patients are mostly female (85%), with median age of 55 years and median disease duration since diagnosis of 6 years. Except for race (> 90% Caucasian), the demographic profile of these patients is comparable to those of other large SSc cohorts described in the US and Europe[4, 5].

Patients recruited into the Registry undergo an extensive standardized evaluation including a history, physical evaluation, and laboratory investigations. Among other things, physicians document the dates of onset of Raynaud's phenomenon, onset of the first non-Raynaud's disease symptom, and diagnosis of SSc based on patient report. They also perform a complete skin examination and classify patients into limited and diffuse subsets, based on the definition of Leroy et al[3].

*Statistical Analysis* Descriptive statistics were used to summarize the baseline characteristics of the patients. The unadjusted association between gender and time to diagnosis was assessed using Kaplan-Meier curves and the logrank test. A multivariate Cox proportional hazards model was used to test the association between time to

diagnosis and gender, after adjusting for limited versus diffuse skin involvement, age, education, and marital status. Given that patients with limited disease may have a prolonged time between the onset of Raynaud's and other manifestations of SSc, we also undertook a stratified analysis. We repeated the above mentioned analyses, stratifying by extent of skin involvement, whether limited or diffuse, and adjusting for the demographic variables, namely age, education, and marital status.

All statistical analyses were performed with SPSS v. 15.

*Ethical considerations* Ethics committee approval for this study was obtained at each site and each patient provided informed written consent to participate in this study.

*Role of the funding sources* The funding sources had no role in the design of the study, analysis of the data, preparation of the manuscript and decision to submit for publication.

## Results

Of the 408 patients studied, the median age was 55 years, 85% were women, 71% were married, 45% had education beyond high school, 44% had diffuse SSc, and median time to diagnosis was 2.0 years (interquartile range (IQR) 0.5, 7.9) from the onset of Raynaud's and 0.8 (IQR 0.2, 3.0) years from the onset of the first non-Raynaud's disease manifestation (Table 1). In terms of means (standard deviations), mean disease duration since the onset of Raynaud's was 13.2 (10.0) years, since the onset of non-Raynaud's symptoms was 10.8 (8.9) years, and since diagnosis of SSc was 8.2 (7.6) years. Time to diagnosis from onset of Raynaud's was 5.0 (6.3) years and from non-Raynaud's symptoms was 2.6 (4.5) years.

In Kaplan-Meier analysis, the time to diagnosis was significantly longer for women than for men when disease onset was measured from the onset of Raynaud's (logrank p = .001, Figure 1A) but not significantly different from the onset of the first non-Raynaud's disease manifestation (logrank p = .093, Figure 1B). Similarly, in Cox proportional analyses adjusted for demographic variables and extent of skin involvement, time to diagnosis was also significantly different when measured from onset of Raynaud's but not from the onset of the first non-Raynaud's disease manifestation. Indeed, female sex was significantly related to longer time to diagnosis (HR 1.6 [95% confidence interval (CI) 1.2-2.1], p = .001) after the onset of Raynaud's. However, there was no significant difference in time to diagnosis between men and women after the onset of the first non-Raynaud's disease manifestation (HR 1.2 [95% CI 0.9-1.6], p = .139). Post-hoc testing of models with income as a covariate (N = 358) did not alter

results substantively, and income was not significantly related to time to diagnosis from onset of Raynaud's or non-Raynaud's symptoms.

Given differences in the natural course of limited and diffuse SSc, we repeated the abovementioned analyses, stratifying the patients into limited and diffuse groups (Table 2). In those with *limited* disease, the median time to diagnosis *after the onset of Raynaud's* was 4.6 years (95% CI 3.2-5.9) in women and 2.1 years (95% CI 0.3-3.8) in men. In those with *diffuse disease*, the median time to diagnosis *after the onset of Raynaud's* was 1.0 year (95% CI 0.8-1.2) in women and 0.7 year (95% CI 0.4-0.9) in men, thus suggesting a difference that could be as long as 0.8 years (9 ½ months). In Kaplan Meier analysis, although the time was more than twice as long for women than men with *limited* disease, this was not statistically significant (logrank p = .085). However, the difference between women and men with *diffuse* disease was statistically significant (logrank p = .008). There were no significant differences in the time to diagnosis between women and men, whether limited or diffuse, after the onset of the first non-Raynaud's disease manifestation. Similar results were obtained in analyses adjusting for demographic differences (data not shown).

To address potential biological differences in progression of disease, we repeated the analyses comparing the time between onset of Raynaud's and onset of first non-Raynaud's symptom between women and men. Again, we found significant gender differences in patients with diffuse disease, with female sex significantly related to longer time between onset of Raynaud's and first non-Raynaud's disease symptom in both unadjusted (logrank p.046) and adjusted (HR 1.8, 95% CI 1.1-2.8) analyses.

## Conclusion

In SSc, the time to diagnosis is long, and it is longer for women than men. In stratified analysis, this remains significantly true for women with diffuse disease after the onset of Raynaud's disease, where the difference in time to diagnosis could be as long as 0.8 years (9 ½ months). Although not statistically significant, the time to diagnosis after the onset of Raynaud's was still more than twice as long in women (4.6 years) compared to men (2.1 years) with limited disease. Although this study remains hypothesis-generating, the findings are both concerning and thought-provoking. They provide impetus for further research to identify possible biological differences of and differences in the delivery of health care to women and men with this devastating disease.

This study was designed to determine whether or not there were gender differences in time to diagnosis, not to explain why those differences exist. This is well beyond the scope of our current data. However, possible reasons for the differences found could include the following: perceptual bias of physicians toward understanding complaints of women more than men as psychosomatic, gender differences in the communication of symptoms, gender differences in health care trajectories, and potential biological differences in the onset and progression of early disease, including the impact of gender-based lifestyle (nutrition, stress, exposure to infection, etc) differences. Our finding that the time between onset of Raynaud's and the first non-Raynaud's disease symptom is longer in women compared to men with diffuse disease certainly supports the possibility that progression of early disease may, in fact, be different between men and women. Understanding the mechanisms underlying such possible biological differences

will require further investigation of genetic, hormonal, vascular, immunologic and other environmental differences between women and men with this disease.

The time of onset of SSc remains a matter of uncertainty. Many have specifically used the time of onset of the first non-Raynaud's disease manifestation[6, 7]. However, others have not clearly specified whether Raynaud's is included as a symptom signaling the onset of SSc. This may explain why a wide range of times to diagnosis have been reported. For example, in one study of 813 Canadian patients, mean time between the "onset of symptoms" (not otherwise defined) and diagnosis was 2.4 years[8]. This is in contrast to another study of 127 French and 247 American patients in which mean time between onset of symptoms "attributable to disease" and diagnosis was reported to be 5.1 years[9]. Our study is the first detailed description of the time to diagnosis both from the onset of Raynaud's and from the onset of the first non-Raynaud's disease manifestation. In either case, the time to diagnosis was considerable (median of 2.0 years from the onset of Raynaud's and 0.8 years from the onset of the first non-Raynaud's disease manifestation). In addition, our data is unique in that, to date, no study had examined differences in time to diagnosis between men and women with SSc.

One limitation of our study was that due to the relatively small number of men in the cohort, it was not possible to reasonably evaluate whether the type of first non-Raynaud's symptoms differed across gender. Another limitation is that this is a retrospective study and the main outcome variables are based on recall. There are two main possible origins of recall bias in this study. One may originate from the clinician enquiring about the onset of symptoms, and the other may originate from the patient recalling their history. Both may result in biased reporting of symptoms and these may

differ by gender. However, the extent and direction of such bias is difficult to ascertain in our study. Finally, Raynaud's phenomenon is not a necessary pre-condition to the diagnosis of SSc. However, it is well established that the vast majority of patients with SSc have Raynaud's and it usually presents before or at the time of disease onset[10]. Thus, for the purpose of this analysis, we selected only patients who had Raynaud's and our data is generalizable only to SSc patients who have Raynaud's.

The significance of our findings lies in the facts that, based on current prevalence estimates, SSc likely affects close to 100,000 North Americans, the majority of which are women[4], and, in diffuse SSc, skin thickening and severe internal organ involvement generally occur in the first 3 years of disease[11]. Thus, earlier diagnosis for women could potentially reduce the hardship associated with the uncertainty present before SSc is diagnosed[12] and allow them to access potentially beneficial treatments in a timely manner. However, to reduce any delays in diagnosis and to understand why there is a greater delay in diagnosis of women compared to men with diffuse disease, further research will be required to investigate possible biological differences in the natural progression of the disease and/or behavioural differences in the health care trajectories of men and women with SSc.

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**Table 1 Baseline characteristics of the study cohort, by gender (N 408)**

| | All | Women | Men |
|---|---|---|---|
| N (%) | 408 (100) | 347 (85) | 61 (15) |
| Median age, years (IQR) | 55 (47, 63) | 55 (47, 63) | 53 (47, 63) |
| More than high school education, N (%) | 185 (45%) | 160 (46) | 25 (41) |
| Married, N (%) | 288 (71%) | 242 (70) | 46 (75) |
| Diffuse skin involvement, N (%) | 180 (44%) | 148 (43) | 32 (53) |
| Median disease duration, years (IQR) | | | |
| Since the onset of Raynaud's | 11.5 (4.9, 19.5) | 11.8 (4.9, 19.6) | 7.8 (4.5, 17.0) |
| Since the onset of the first non-Raynaud's disease manifestation | 8.9 (3.7, 15.1) | 9.4 (3.7, 15.2) | 6.3 (3.4, 13.6) |
| Since diagnosis | 6.1 (2.2, 12.5) | 6.3 (2.2, 12.4) | 5.3 (2.0, 12.7) |
| Median time to diagnosis, years (IQR) | | | |
| After the onset of Raynaud's | 2.0 (0.5, 7.9) | 2.3 (0.5, 8.9) | 1.0 (0.3, 3.2) |
| After the onset of the first non-Raynaud's disease manifestation | 0.8 (0.2, 3.0) | 0.7 (0.2, 3.0) | 0.8 (0, 1.3) |

IQR – interquartile range

**Table 2 Time to diagnosis from either the onset of Raynaud's or the first non-Raynaud's disease manifestation, stratified by gender and limited or diffuse subsets**

| | N | Median time to diagnosis from the onset of Raynaud's, years (95% confidence interval) | Log rank p | Median time to diagnosis from the onset of the first non-Raynaud's disease manifestation, years (95% confidence interval) | Log rank p |
|---|---|---|---|---|---|
| Limited | | | | | |
| Women | 199 | 4.6 (3.2-5.9) | .085 | 1.0 (0.6-1.4) | .271 |
| Men | 29 | 2.1 (0.3-3.8) | | 0.9 (0.2-1.7) | |
| Diffuse | | | | | |
| Women | 148 | 1.0 (0.8-1.2) | .008 | 0.6 (0.5-0.7) | .344 |
| Men | 32 | 0.7 (0.4-0.9) | | 0.6 (0.3-0.8) | |

**Figure 1A Kaplan Meier curve showing the time to diagnosis after the onset of Raynaud's phenomenon, by gender**

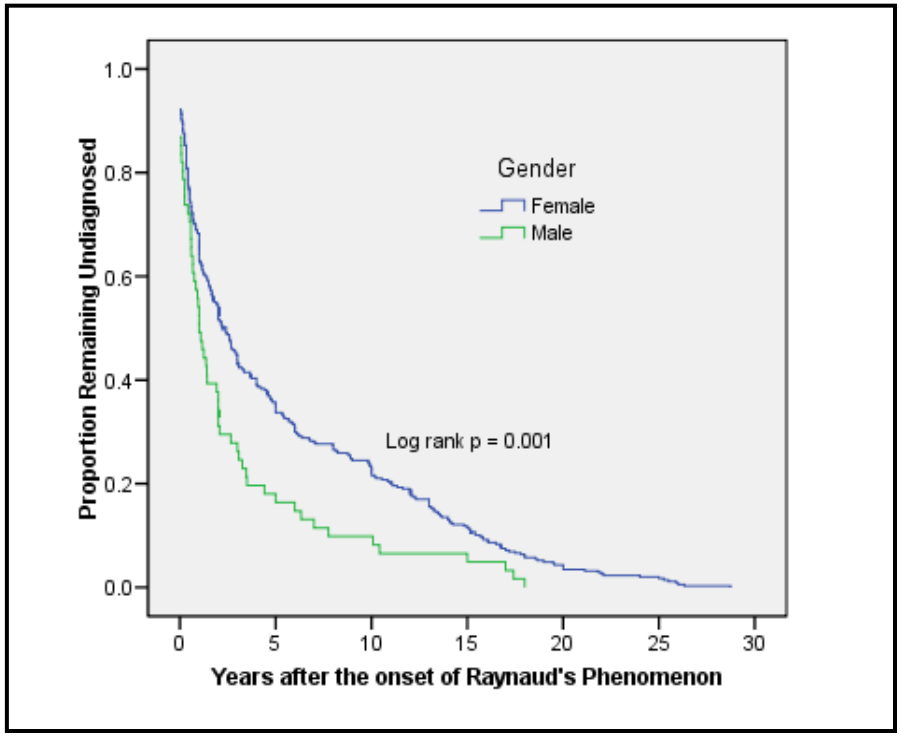


**Figure 1B Kaplan Meier curve showing the time to diagnosis after the onset of the first non-Raynaud's disease manifestation, by gender**