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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-003569
Article Type:	Research
Date Submitted by the Author:	08-Jul-2013
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Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Epidemiology
Keywords:	Epidemiology < TROPICAL MEDICINE, RHEUMATOLOGY, RESPIRATORY MEDICINE (see Thoracic Medicine)

Interstitial Lung Disease in Primary Sjögren's Syndrome: Incidence-based Population Based Study

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Keywords: interstitial lung disease; Sjögren's syndrome; incidence; mortality

Word count: 2465

ABSTRACT

OBJECTIVE:

The reported frequency of pulmonary involvement in primary Sjögren's Syndrome (pSS) varies widely depending on the detection method employed and consists mainly of various forms of airways disease. We aimed to evaluate incidence and mortality impact of lung disease in pSS, focusing on interstitial lung disease (ILD).

METHODS: A population-based incidence cohort of patients diagnosed with pSS in 1976-2005 was assembled. Diagnosis was based on 2012 ACR consensus group criteria for pSS. ILD was defined using validated composite criteria. All subjects were followed longitudinally through their complete community medical records, until death, migration or December 31, 2011.

RESULTS: A total of 105 patients with pSS were identified (mean age 58.1 years; range 23-95; 91% female).

Among pSS patients without prior ILD, the cumulative incidence of ILD in patients with pSS was 10% (± 3%) at 1 year after diagnosis of pSS and increased to 20% (± 4%) by 5 years after pSS. The development of lung disease in pSS was associated with poor survival (hazard ratio 2.16; 95%CI: 0.99, 4.74) adjusted for age, sex, and calendar year. ILD was identified as the most frequent type of lung disease detected at or after pSS diagnosis (53%).

CONCLUSION: Patients with and ILD have increased premature mortality. Patients with pSS should be carefully assessed for lung disease including ILD in order to improve the detrimental survival experience.

Article summary:

Article focus:

1. To estimate the trends in incidence of pSS among Olmsted County residents, diagnosed with pSS between 1976 and 2005.

2. To estimate the cumulative incidence of interstitial lung disease among Olmsted County residents, diagnosed with pSS between 1976 and 2005.

3. To compare the survival of pSS patients with interstitial lung disease to pSS patients without respiratory system involvement.

Key messages

1. Patients with and ILD have increased premature mortality.

2. Patients with pSS should be carefully assessed for lung disease including ILD in order to improve the detrimental survival experience.

3. Development of a comprehensive population-based cohort of patients with pSS who have respiratory system involvement would be a valuable and unique resource for the study of this important disease complication. It will help define the epidemiology of this disease and, in doing so, may allow identification of secular trends in its occurrence and generate hypotheses regarding etiologies

Strengths and limitations

The current study will be the first to investigate the incidence, and mortality interstitial lung disase in a population based cohort of patients with primary Sjögren's syndrome.

Because of the retrospective nature of the study and the limited information available regarding direct assessment of treatment on pulmonary disease, it will not be possible to

draw firm conclusions about the effect of treatment on the disease course. Other limitations include the limited information on tests of lung disease, including radiographs, computed tomography, PFTs etc., available for each patient inherent to a retrospective study. This information is also affected by time trends (for example, computed tomography became available in the 1970's), so pertinent data are not available prior to this period. Despite these difficulties, the relevance of information coming to clinical attention will provide a strong resource to address the study aims.

INTRODUCTION

Sjögren's syndrome (SS) is a chronic autoimmune and systemic inflammatory disease that affects exocrine and extraglandular tissues,(1). It is known to occur alone (primary) or in association with other autoimmune disease states.

Very few studies describe the epidemiology of primary Sjögren's syndrome (pSS). The published studies of pSS in the general population report highly heterogeneous results. The wide-ranging prevalence estimates in adults varied from 0.098% to 3.59% while the incidence ranged from 3.9 to 5.3 per 100,000 population,(2, 3). This wide variation is due to the diverse populations using a restricted age range,(4), low sample size,(5), or low follow-up rate,(6). Studies of SS also have used a variety of classification criteria leading to difficulties when trying to compare results.

Extraglandular manifestations of pSS include a broad spectrum of lung disease. The reported frequency of pulmonary involvement in pSS varies widely ranging from 8 to 75% depending on the detection method employed and consists of various forms of airways disease (bronchiectasis, obstructive airways disease) and interstitial lung disease (ILD),(7). Lymphocytic interstitial pneumonia is well-defined in pSS patients,(8) but there is relatively little information regarding other ILD patterns occurring in pSS in terms of frequency and risk factors**.**

Extraarticular disease manifestations, including various forms of lung disease, are common in pSS and may be linked to an increased mortality,(9). Asymptomatic pulmonary changes are present in a majority of patients, but their impact on the disease course, mortality, and quality of life remain unclear.

Most studies have concentrated on ILD in consecutive samples of pSS patients in academic centers,(7,9-12). Consequently, little is known about the incidence of the full spectrum of respiratory system involvement in a representative sample of pSS patients from a population-based cohort. Previous studies that examined the incidence or prevalence of pSS-associated lung disease have differed widely in their estimates. This wide variance appears to be due to different diagnostic modalities used to detect the disease, to the changed criteria for the classification of SS, to previous failure to separate

out patients with primary or secondary SS, and referral bias in studies originating from large academic centers.

In non-population-based studies, pulmonary changes can be documented in a majority of patients with pSS,(10-12) and clinically overt ILD is present in 6 to 94% both in early and longstanding pSS,(7,10-12). There are no population-based estimates of the incidence of pSS and the incidence of pSS-associated ILD. Here, we report on the incidence, and impact on survival of ILD among Olmsted County, Minnesota residents with pSS.

PATIENTS AND METHODS

This was a retrospective medical record review to investigate the ILD in patients with pSS in Olmsted County, MN, diagnosed during the 45 years period from January 1, 1976 to December 31, 2005 and then followed until death, migration or December 31, 2011.

The population of Olmsted County, Minnesota is well-suited for investigation of long-term outcomes of patients with pSS. A medical records linkage system, the Rochester Epidemiology Project (REP), allows ready access to the complete (inpatient and outpatient) records from all health care providers for the local population, including the Mayo Clinic and its affiliated hospitals, the Olmsted Medical Center and its affiliated community hospital, local nursing homes, and the few private practitioners. The potential of this data system for population-based research has been previously described,(13-14). This system ensures virtually complete clinical and vital status information on all clinically recognized cases of pSS among Olmsted County residents. The study was approved by the institutional review boards at Mayo Clinic and Olmsted Medical Center.

Ascertainment of pSS cases

Using this data resource, a population-based incidence cohort of all cases of pSS, first diagnosed between January 1, 1976 and December 31, 2005, among Olmsted County, Minnesota residents ≥ 18 years of age was assembled. The cohort initially assembled between 1976 to 1992 was enriched adding new pSS patients diagnosed between 1993 and 2005,(3). All cases fulfilled the 2002 American-European Consensus Group diagnostic criteria for pSS,(15) and accordingly the 2012 published expert consensus

approach for pSS classification Criteria,(16). Incidence date is defined as the first date of fulfillment of four out of the six American-European Consensus Group diagnostic criteria.

All subjects were followed up longitudinally through their complete medical records beginning at age 18 (or date of migration to Olmsted County for those who became residents after age 18) and continuing until death, migration from Olmsted County, or December 31, 2011.

Data collection

The original and complete medical records of each pSS patient were reviewed by CN and AJ. Uncertainties regarding classification for pSS, presence and type of pulmonary disease, and underlying disease were adjudicated by JHR and/or ELM.

We abstracted demographic data (date of birth, gender), smoking status at pSS incidence date (never smoked/former smoker/current smoker) and smoking status at diagnosis of lung disease (never smoked/former smoker/current smoker). The date of last follow-up was recorded as well as the status at last follow-up (dead/alive).

SS features were abstracted and they included time variables (year of symptom onset, year of diagnosis according to American-European Consensus Group diagnostic criteria),(10), ocular and oral gland involvement (clinical judgment, Schirmer test, salivary glands biopsy and salivary scintigraphy) and laboratory features (rheumatoid factor [RF], ANA, anti SSA, anti SSB, immunoglobulin G level).

Definition and ascertainment of interstitial lung disease

The ascertainment of ILD was based on clinical data, pulmonary function test results [total lung capacity (TLC), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), diffusing capacity for carbon monoxide (DLCO), SaO2, at rest and with exercise], radiological studies (chest radiographs, computed tomography [CT]), bronchoalveolar lavage (BAL), and lung biopsy. The criteria used to classify ILD were validated in a previous study and are given in table 1,(17).

Statistical analysis

Descriptive statistics (means, medians, proportions, etc.) were used to summarize the data. Comparison of patient characteristics between time periods were performed using chi-square tests for categorical characteristics and Wilcoxon rank sum tests for continuous characteristics.

Overall incidence rates were age- and/or sex-adjusted to the 2000 white population of the United States. Age- and sex-specific incidence rates were calculated by using the number of incident cases as the numerator and population estimates based on decennial census counts as the denominator, with linear interpolation used to estimate population size for intercensal years,(18). In order to compute 95% confidence intervals (95% CI) for incidence rates, it was assumed that the number of incident cases followed a Poisson distribution. Trends in incidence rates were examined using Poisson regression methods using smoothing splines for age and calendar year,(19).

The percentage of pSS patients with respiratory system involvement at pSS incidence date was computed. Those with respiratory system involvement at pSS incidence date were excluded from the analysis of cumulative incidence. The cumulative incidence of respiratory system involvement (and subtypes) was estimated using product-limit life table methods, accounting for the competing risk of death,(20).

Product-limit life table methods were used to estimate the survival of patients with pSS. The expected number of deaths was determined from the National Center for Health Statistics life tables for the United States population, according to the age, sex and calendar year of the pSS cohort,(21). A standardized mortality ratio (SMR) was estimated by dividing the observed number of deaths by the expected number of deaths. Ninety-five percent confidence intervals (CI) for the SMR were calculated assuming that the expected rates were fixed and the observed rates followed a Poisson distribution. A Cox model was used to examine the impact of respiratory system involvement on mortality with a time-dependent covariate indicating development of respiratory system involvement and adjustment for age, sex and calendar year of diagnosis of pSS. Statistical analysis was performed using SAS software (version 9.3, SAS institute Inc., Cary, North Carolina, USA).

RESULTS

We identified 105 patients with incident pSS with a mean age at pSS diagnosis of 58.1 years (range 23-95); 91% were females. Demographic data and general characteristics of the study population are reported in table 2, 2a, 2b.

Considering the time periods patients differ significantly regarding the laboratory evaluation: rheumatoid factor, ANA, anti SSA and anti SSB were significantly more frequently detected in the 1993-2005 time period compared to the 1976-1992 cohort. Among clinical features, ocular signs tended toward statistical significance in 1993-2005 period with a p value of 0.06.

The annual incidence of pSS was 5.1 (95% CI: 4.1, 6.1) per 100,000 population, and increased with higher age at pSS diagnosis (18-44 years: 1.8/100,000 vs ≥75 years: 10.7/100,000) (Table 3). Female patients were more affected 8.7 per 100,000 population (95% CI: 6.9, 10.4), compared with males 1.1 per 100,000 (95% CI: 0.4, 1.9) (table 3).

The overall incidence increased modestly during the study period (3.9 [95% CI: 2.2, 5.6] per 100,000 population in 1976-1985; 5.0 [95% CI: 3.3, 6.7] in 1986-1995; and 5.9 [95% CI: 4.2, 7.6] in 1996-2005; linear trend p=0.06) (table 4 and figure 1).

During a median follow-up of 9.2 years (1205 total person-years), 25 patients died. This was similar to the 29.5 expected deaths (SMR: 0.85, 95% CI; 0.55, 1.25), logrank p-value=0.41(figure 2).

ILD in primary Sjögren's syndrome:

Lung disease was present prior to diagnosis of pSS in 12 patients and developed after diagnosis of pSS in 35 patients with a median follow-up time of 9.2 years (1205 total person-years). Among pSS patients without prior ILD, the cumulative incidence of ILD in patients with pSS was 10% (± 3%) at 1 year after diagnosis of pSS and increased to 20% (± 4%) by 5 years, and 43% (± 7%) by 15 years after pSS onset. The development of lung disease in pSS was associated with poor survival with a hazard ratio of 2.16 (95% CI: 0.99, 4.74) adjusted for age, sex, and calendar year. ILD was identified as the most

frequent type of lung disease detected at or after pSS diagnosis (53%) followed by emphysema (13%).

DISCUSSION

We found that the annual incidence of pSS was 5.1 (95% CI: 4.1, 6.1) per 100,000 population and increases with higher age at pSS diagnosis (18-44 years: 1.8/100,000 vs ≥75 years: 10.7/100,000). Comparison to existing epidemiologic studies is complicated by differences in the definition and application of diagnostic. Until now only three studies have evaluated the incidence of pSS in general population, reporting values from 3.9 to 5.3 per 100,000 population,(3,22-23).

We found that the incidence of pSS may have increased modestly during the study period with a linear trend p value=0.06, although the overall trend is almost stable despite the differences among the diagnostic criteria occurring over the years. pSS has an incidence peak between 55 and 74 years of age with females more frequently affected than males.

The risk of death in patients with pSS in our study is similar to the general population (0.85; 95% CI: 0.55, 1.25). A prospective study of patients with pSS conducted in Greece reported a higher mortality risk than in general population (SMR 2.07; 95% CI: 1.03-3.71),(22). However when patients with adverse predictors (low levels of C4, presence of mixed monoclonal cryoglobulins and purpura) were excluded the mortality rate was identical to the general population (SMR 1.02),(24).

Similar to our study, most other studies reported a SMR that range between 1.2 and 1.42 without reaching statistical significance,(3,25,26-28). Therefore the survival of these patients is comparable with that of the general population,(29-30).

Lung involvement in primary Sjögren's syndrome represents one of the most intriguing aspects of the disease. In this study, pSS patients without prior ILD, have a cumulative incidence of ILD of 10% (± 3%) at 1 year after diagnosis of pSS which increases to 20% (± 4%) by 5 years after onset of pSS. Patients who developed ILD prior to their pSS diagnosis were calculated apart from our primary analysis in order to avoid incidence-prevalence bias. Therefore, the overall risk for individuals with pSS to be

affected by ILD either prior or after their diagnosis of pSS will be somewhat higher than our estimate. Additionally, patients with pSS have more frequent physician visits than the average patient in the population, and physicians may be more attuned to the possibility of lung disease in pSS patients than healthy people, leading to an overestimation of lung involvement in subjects with pSS compared to those without pSS (surveillance bias).

In contrast to these population based estimates, the existing literature on ILD and pSS is based upon studies of ILD prevalence in consecutive series of pSS patients in academic centers. In non-population-based studies, pulmonary changes can be documented in a majority of patients with pSS,(10-12) and clinically overt interstitial lung disease (ILD) is present in 6 to 94% of patients, both in early and longstanding pSS,(7,10-12). This wide variance appears to be due to different diagnostic modalities used to detect the disease, to the changed criteria for the classification of SS, to previous failure to separate out patients with primary or secondary SS and referral bias in studies originating from large academic centers.

Patients with pSS patients who have ILD have worse survival (hazard ratio 2.16; 95% CI: 0.99, 4.74). This is in contrast to a prospective cohort study which did not find increased all-cause mortality in patients with pSS compared with general population,(25). In a retrospective study conducted at Mayo Clinic among 18 patients who underwent lung biopsies, seven patients (39%) died including three deaths from acute exacerbation,(7).

Important limitations of our retrospective study approach should be acknowledged. Because of the inherent limitations of a chart review based diagnosis, it is likely that our estimates do not reflect the full extent of ILD in this population. The limited information on tests of lung disease (including radiographs, computed tomography, pulmonary function testing) available for each patient inherent to a retrospective study and the unavailability of some information due to time trend effects (for example, computed tomography became available in the 1970's), may lead to a misclassification bias. However, the use of rigorous criteria for ILD diagnosis established by the collaboration between an expert pulmonologist and rheumatologist should have reduced the possibility of this bias.

Our definition of ILD does represent a blend of many different types of parenchymal lung disease. Because of the changes in availability of diagnostic tools such as CT over time as well as the evolution of definitions used to characterize ILD, reliable assignment of ILD subtypes for every patient according to the most recent American Thoracic Society consensus classification,(31) was not possible.

In conclusion the incidence of pSS, evaluated using the new ACR classification criteria for pSS, was similar to that reported in a previous study from the same population based on physician diagnosis. The incidence of pSS appears to be increasing in recent years.. Our findings emphasize the high incidence of ILD among patients with pSS, and the adverse effect of this disease complication on survival. Patients with pSS should be carefully assessed for diagnosis and management of ILD in order to improve the detrimental survival experience.

Disclosure: We have no disclosures

Contributorships:

Nannini C MD, Matteson EL, Ryu JH contribute to:
Conception and design, acquisition of data, and interpretation of data.
Drafting the article or revising it critically for important intellectual content.
Final approval of the version published.

Crowson C contributed to:

Conception and design, acquisition of data, analysis and interpretation of data. Drafting the article or revising it critically for important intellectual content.
Final approval of the version published.

Adlene J. Jebakumar contributed to :

Acquisition of data, and interpretation of data.
Drafting the article or revising it critically for important intellectual content.
Final approval of the version published

There is no additional data available

Funding, Acknowledgements :
This work was made possible by the Rochester Epidemiology Project (R01 AG034676 from the National Institute on Aging).

Ethics:
All participants included in this retrospective chart review gave authorization for use of their medical records in research. This study was deemed a minimal risk protocol by the Mayo Clinic Institutional Review Board (IRB) and waiver of specific informed consent was approved by the IRB in accordance with 45 CFR 46.116(d) as justified by the investigator, and waiver of HIPAA authorization in accordance with applicable HIPAA

regulations. Performing a retrospective review of their charts would impose little to no risk to the patients.

References

1) Manthorpe R, Asmussen K, Oxholm P. Primary Sjögren's syndrome: diagnostic criteria, clinical features, and disease activity. VIth International Symposium on Sjögren's syndrome: Avon Connecticut, USA. J Rheumatol 1997;24(Suppl 50): 8–11.

2) Binard A, Devauchelle-Pensec V, Fautrel B, et al. Epidemiology of Sjögren's syndrome: where are we? Clin Exp Rheumatol 2007; 25: 1-4.

3) Pillemer SR, Matteson EL, Jacobsson LTH, et al. Incidence of physician-diagnosed primary Sjögren's syndrome in residents of Olmsted County, Minnesota. Mayo Clin Proceed 2001;76: 593-9.

4) Drosos AA, Andonopoulos AP, Costopoulos JS, et al Prevalence of primary Sjögren syndrome in an elderly population. Br J Rheumatol 1988; 27:123-7.

5) Hochberg MC, Schein OD, Munoz B et al. The prevalence of dry eye, dry mouth, autoimmunity and primary Sjögren's syndrome in the general population. Arthritis Rheum 1996;39: S66.

6) Dafni UG, Tzioufas AG, Staikos P, et al. The prevalence of primary Sjögren syndrome in a closed rural community. Ann Rheum Dis 1997; 56: 521-5.

7) Parambil JG, Myers JL, Lindell RM, Matteson EL, Ryu JH. Interstitial lung disease in primary Sjögren syndrome. Chest 2006; 130:1489–1495.

8) Parke AL. Pulmonary manifestations of primary Sjögren syndrome. Rheun Dis Clin N Am 2008; 34: 907-920.

9) Lin DF, Yan SM, Zhao Y et al. Clinical and prognostic characteristics of 573 cases of primary Sjögren's syndrome. Chin Med J (Engl). 2010;123(22):3252-7.

10) Gardiner P, Ward C, Allison A, et al. Pleuropulmonary abnormalities in primary Sjögren's sindrome J Rheumatol. 1993;20(5):831-7.

11) Deheinzelin D, Capelozzi VL, Kairalla RA et al. Interstitial lung disease in primary Sjögren's syndrome. Clinical-pathological evaluation and response to treatment. Am J Respir Crit Care Med. 1996;154(3 Pt 1):794-9.

12) Ju-Hong Shi, Hong-Rui Liu, Weng-Bin Xu et al. Pulmonary manifestations in Sjögren's Syndrome. Respiration 2009;78:377–386.

13) St Sauver JL, Grossardt BR, Yawn BP, Melton LJ, 3rd, Rocca WA. Use of a medical records linkage system to enumerate a dynamic population over time: the Rochester epidemiology project. Am J Epidemiol. 2011;173(9):1059-68.

14) Melton LJ, III. History of the Rochester Epidemiology Project. Mayo Clin Proc 1996; 71(3):266-274.

15) Vitali C, Bombardieri S, Jonsson R et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002 61: 554-558

16) Shiboski SC, Shiboski CH, Criswell LA et al. American College of Rheumatology Classification Criteria for Sjögren Syndrome: a data driven, expert consensus approach in the Sjögren international collaborative clinical alliance cohort. Arthritis Care Res2012; 64(4):475-87.

17) Bongartz T, Nannini C, Medina-Velasquez YF, Achenbach SJ, et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. Arthritis Rheum. 2010;62(6):1583-91.

18) Bergstralh EJ, Offord KP, Chu CP, Beard CM, O'Fallon WM, Melton LJ III. Technical Report Series No. 49. Calculating incidence, prevalence and mortality rates for Olmsted County, Minnesota: an update. Section of Biostatistics, Mayo Clinic,Rochester (MN); 1992.

19) McCullagh P, Nelder JA. Generalized linear models. New York: Chapman & Hall; 1983

20) Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med. 1999;18(6):695-706.

21) Therneau TM, Offord J. Expected survival based on hazard rates (updated). Technical Report Series No. 63. Rochester (MN): Mayo Clinic Department of Health Sciences Research; 1999

22) Alamanos Y, Tsifetaki N, Vulgari PV, et al Epidemiology of primary Sjögren's syndrome in north-west Greece 1982-2003. Rheumatology 2006;45:187-91

23) Novljan MP, Rozman B, Hocevar A, et al. Incidence of primary Sjögren's syndrome in Slovenia. Ann Aheum Dis 2004; 63:874-6.

24) Skopouli FN, Dafni U, Ioannidis JP, et al. Clinical evaluation morbidity and mortality of primary Sjögren's syndrome. Semin Arthritis Rheum 2000 29(5) 296-304.

25) Theander E, Manthorpe R, Jacobsson LT. Mortality and cause of death in primary Sjögren's syndrome: a prospective cohort study, Arthritis Rheum 2004; 50; 1262-1269.

26) Ionnidis JP, Vassiliou VA, Moutsopoulos HM. Long term risk of mortality and lymphoproliferative disease and predictive classification of primary Sjögren's syndrome. Arthritis Rheum 2002;46(3):741-747.

27) Ramos Casals M, Brito-Zeron P, Yague J, et al. Hypocomplementaemia as an immunological marker of morbidity and mortality in patients with primary Sjögren's syndrome. Rheumatology 2005;44(1):89-94.

28) Brito-Zeron P, Ramos-Casals M, Bova A, et al. Predicting adverse outcomes in primary Sjögren's syndrome: identification of prognostic factors. Rheumatology 2007; 46(8):1359-1362

29) Martens PB, Pillmer SR, Jacobsson LTH, et al. Survivorship in a population based cohort of patients with Sjögren's syndrome 1976-1992. J Rheumatol 1999;26:1296-300.

30) Kruize AA, Hene RJ, Van Der Heide A, et al. Long term follow up of patients with Sjögren's syndrome. Arthritis Rheum 1996; 39: 297-303

31) American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Resp Crit Care Medicine 2002;165(2):277-304.

Table 1. Classification criteria for interstitial lung disease (ILD) in primary Sjögren's syndrome

Probable ILD:	chest radiograph or computed tomography described as "fibrosis" or "consistent with ILD or parenchymal lung disease" or physician's diagnosis of "interstitial lung disease", "pulmonary fibrosis", "interstitial pneumonia", etc.
Definite ILD:	Diagnosis of ILD by a pulmonologist, based on chest radiograph/high resolution chest CT and pulmonary function testing (restrictive ventilatory pattern or reduced DLCO) or lung biopsy (bronchoscopic or surgical)

Table 2: Characteristics of 105 patients with primary Sjögren's syndrome

	1976-1992 (n=50)		1993-2005 (n=55)		Total (n=105)		p-value
	N	Value*	N	Value*	N	Value*	
Sex, female (%)	50	48 (96)	55	48 (87)	105	96 (91)	0.11
Age at incidence, years	50	57.5 (23 – 95)	55	59.2 (26 – 86)	105	59.2 (23 – 95)	0.96
Length of follow-up, years	50	17.2 (0.4 - 34.2)	55	7.7 (0.1 - 17.3)	105	9.2 (0.1 - 34.2)	--

*Value is n (%) or median (minimum, maximum). Percentages are calculated based on available N.

N: number of patients with parameter reported in the medical records

Table 2a: Laboratory assessment of 105 patients with primary Sjögren's syndrome

	1976-1992 (n=50)		1993-2005 (n=55)		Total (n=105)		p-value
	N	Value*	N	Value*	N	Value*	
Rheumatoid factor, positive (%)	37	14 (38)	45	32 (71)	82	46 (56)	0.002
Anti-nuclear antibodies, positive (%)	37	20 (54)	52	42 (81)	89	62 (70)	0.007
Anti-SSA, positive (%)	17	7 (41)	48	38 (79)	65	45 (69)	0.004
Anti-SSB, positive (%)	18	6 (33)	48	30 (63)	66	36 (55)	0.034
Hypergammaglobulinemia, present (%)	38	16 (42)	44	26 (59)	82	42 (51)	0.12
Histopathology, available (%)	0	-	6	3 (50)	6	3 (50)	-

*Value is n (%) or median (minimum, maximum). Percentages are calculated based on available N.

N: number of patients with parameter reported in the medical records

Table 2b: Clinical characteristics of 105 patients with primary Sjögren's syndrome

	1976-1992 (n=50)		1993-2005 (n=55)		Total (n=105)		p-value
	N	Value*	N	Value*	N	Value*	
Ocular symptoms, present (%)	48	45 (94)	54	52 (96)	102	97 (95)	0.55
Oral symptoms, present (%)	45	42 (93)	50	48 (96)	95	90 (95)	0.56
Ocular signs, present (%)	30	30 (100)	9	8 (89)	39	38 (90)	0.06
Oral signs, present (%)	46	3 (7)	1	0 (0)	47	3 (6)	-
Ocular signs/symptoms, present (%)	48	45 (94)	54	52 (96)	102	97 (95)	0.55
Oral signs/symptoms, present (%)	49	42 (86)	50	48 (96)	99	90 (91)	0.08

*Value is n (%) or median (minimum, maximum). Percentages are calculated based on available N.

N: number of patients with parameter reported in the medical records

Table 3: Annual incidence of primary Sjögren's Syndrome diagnosed between 1976 and 2005 in Olmsted County, Minnesota Residents ≥18 years of age, by sex and age group*

Age group	Male (n=9)		Female (n=96)		Total (N=105)	
	No. of patients	Rate per 100,000	No. of patients	Rate per 100,000	No. of patients	Rate per 100,000
18-44 years	3	0.5	22	3.1	25	1.8
45-54 years	1	0.5	20	10.6	21	5.6
55-64 years	0	0.0	20	15.3	20	7.9
65-74 years	1	1.3	21	21.8	22	12.7
≥75 years	4	7.5	13	12.3	17	10.7
Total (95% CI)	9	1.1 (0.4, 1.9)†	96	8.7 (6.9, 10.4)†	105	5.1 (4.1, 6.1)‡

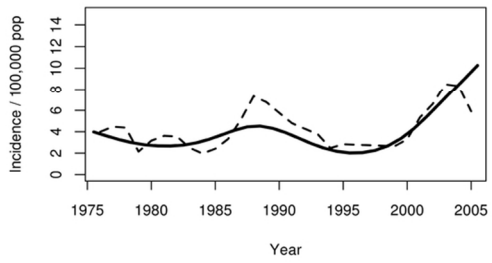
* Values are the annual incidence rate (95% confidence interval [95% CI]) per 100,000 population.
† Age-adjusted to the 2000 US white population.
‡ Age- and sex-adjusted to the 2000 US white population.

Table 4. Annual Incidence of pSS diagnosed between 1976 and 2005 by decade in Olmsted County, Minnesota residents ≥18 years of age, by sex and age group*

Age group	Male (n=9)		Female (n=96)		Total (N=105)	
	No. of patients	Rate per 100,000	No. of patients	Rate per 100,000	No. of patients	Rate per 100,000
1976-1985	1	0.7 (0.0, 2.2)†	20	6.8 (3.8, 9.9)†	21	3.9 (2.2, 5.6)‡
1986-1995	1	0.6 (0.0, 1.6)†	34	9.1 (6.0, 12.2)†	35	5.0 (3.3, 6.7)‡
1996-2005	7	1.9 (0.4, 3.3)†	42	9.5 (6.6, 12.4)†	49	5.9 (4.2, 7.6)‡

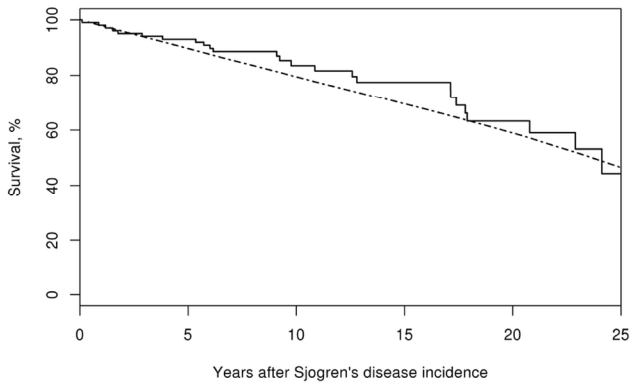
* Values are the annual incidence rate (95% confidence interval [95% CI]) per 100,000 population.
† Age-adjusted to the 2000 US white population.
‡ Age- and sex-adjusted to the 2000 US white population.

Figure 1. Annual incidence of pSS per 100,000 population in residents of Olmsted County, Minnesota, 1976–2005. The broken line was calculated as a 3-year–centered moving average, and the solid line depicts trends in the incidence rates after adjustment for age and sex **(linear trend p-value =0.06).**



91x33mm (300 x 300 DPI)

Figure 2. Survival in patients with primary Sjögren's syndrome (solid line) compared to the general population (dotted line) (logrank p=0.41).



121x59mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ open

Primary Sjögren's Syndrome 1976-2005 and Associated Interstitial Lung Disease: A Population Based- Study of Incidence and Mortality

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-003569.R1
Article Type:	Research
Date Submitted by the Author:	08-Oct-2013
Complete List of Authors:	Nannini, Carlotta; Ospedale Misericordia e Dolce, Rheumatology Jebakumar, Adlene; Mayo Clinic, Rheumatology Crowson, Cindy; Mayo, Health Sciences Research Ryu, Jay; Mayo Clinic, Pulmonary and Critical Care Medicine MATTESON, Eric; Mayo Clinic, Rheumatology
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Epidemiology
Keywords:	Epidemiology < TROPICAL MEDICINE, RHEUMATOLOGY, RESPIRATORY MEDICINE (see Thoracic Medicine)

Primary Sjögren's Syndrome 1976-2005 and Associated Interstitial Lung Disease: A Population Based- Study of Incidence and Mortality

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Keywords: interstitial lung disease; Sjögren's syndrome; incidence; mortality

ABSTRACT

OBJECTIVE:

Very few studies describe the epidemiology of primary Sjogren's syndrome (pSS). The reported frequency of pulmonary involvement in primary Sjögren's Syndrome (pSS) varies widely depending on the detection method employed and consists mainly of various forms of airways disease. We aimed to evaluate the incidence and mortality of pSS and of lung disease in pSS, focusing on interstitial lung disease (ILD).

METHODS: A population-based incidence cohort of patients diagnosed with pSS in 1976-2005 was assembled. Diagnosis was based on 2002 American-European consensus group criteria for pSS. Cumulative incidence adjusted for the competing risk of death was estimated. A Cox model with a time-dependent covariate was used to determine the incidence and the standardized mortality hazard ratio (HR) of pSS.

RESULTS: 85 patients with pSS were identified (mean age 59.9 years; 91% female). The annual incidence of pSS was 4.2 95% CI (3.3, 5.1) per 100,000 population and it increased with higher age at pSS diagnosis (18-44 years: 2.1/100,000 vs ≥75 years: 12.3/100,000). Standardized mortality ratio in pSS compared to the general population was: 0.92, 95%CI (0.57, 1.41).

A total of 105 patients with pSS and ILD were identified (mean age 58.1 years; 91% female). Among pSS patients without prior ILD, the cumulative incidence of ILD in patients with pSS was 10% (± 3%) at 1 year after diagnosis of pSS and increased to 20% (± 4%) by 5 years after pSS. The development of lung disease in pSS was associated with poor survival (hazard ratio 2.16; 95% CI: 0.99, 4.74).

CONCLUSION: pSS incidence seems to be almost the same as was reported in a previous study conducted among Olmsted County Minnesota population. Survival among pSS patients and general population does not differ substantially. However, patients with pSS who have ILD likely have increased premature mortality.

ARTICLE SUMMARY

STRENGHTS: This is a population based study therefore we tried to do a real estimation of incidence and mortality among patients with pSS and to report the incidence of ILD among patients with pSS and what is its impact on pSS morality.
Attention to the occurrence of, and improved management of ILD in patients with pSS, may contribute to reduction of the disease burden of the disease.

LIMITATIONS: The major concern is related to the chart review based diagnosis, our estimates could not reflect the full extent of ILD in this population. The limited information on tests of lung disease available for each patient inherent to a retrospective study and the unavailability of some information due to time trend effects may lead to a misclassification bias.
Moreover an overestimation of lung involvement in subjects with pSS compared to those without pSS (surveillance bias) could be present.

- pSS incidence seems to be almost the same as was reported in a previous study conducted among Olmsted County Minnesota population
- Survival among pSS patients and general population does not differ substantially
- Patients with pSS who have ILD likely have increased premature mortality
- the occurrence of, and improved management of ILD in patients with pSS, may contribute to reduction of the disease burden of the disease.

INTRODUCTION

Sjögren's syndrome (SS) is a chronic autoimmune and systemic inflammatory disease that affects exocrine and extraglandular tissues,(1). It is known to occur alone (primary) or in association with other autoimmune disease states.

Very few studies describe the epidemiology of primary Sjögren's syndrome (pSS). The published studies of pSS in the general population report highly heterogeneous results. The wide-ranging prevalence estimates in adults varied from 0.098% to 3.59% while the incidence ranged from 3.9 to 5.3 per 100,000 population,(2, 3). This wide variation is due to the diverse populations using a restricted age range,(4), low sample size,(5), or low follow-up rate,(6). Studies of SS also have used a variety of classification criteria leading to difficulties when trying to compare results.

Extraglandular manifestations of pSS include a broad spectrum of lung disease. The reported frequency of pulmonary involvement in pSS varies widely ranging from 8 to 75% depending on the detection method employed and consists of various forms of airways disease (bronchiectasis, obstructive airways disease) and interstitial lung disease (ILD),(7). Lymphocytic interstitial pneumonia is well-defined in pSS patients,(8) but there is relatively little information regarding other ILD patterns occurring in pSS in terms of frequency and risk factors**.**

Extraarticular disease manifestations, including various forms of lung disease, are common in pSS and may be linked to an increased mortality,(9). Asymptomatic pulmonary changes are present in a majority of patients, but their impact on the disease course, mortality, and quality of life remain unclear.

Most studies have concentrated on ILD in consecutive samples of pSS patients in academic centers,(7,9-12). Consequently, little is known about the incidence of the full spectrum of respiratory system involvement in a representative sample of pSS patients from a population-based cohort. Previous studies that examined the incidence or prevalence of pSS-associated lung disease have differed widely in their estimates. This wide variance appears to be due to different diagnostic modalities used to detect the disease, to the changed criteria for the classification of SS, to previous failure to separate

out patients with primary or secondary SS, and referral bias in studies originating from large academic centers.

In non-population-based studies, pulmonary changes can be documented in a majority of patients with pSS,(10-12) and clinically overt ILD is present in 6 to 94% both in early and longstanding pSS,(7,10-12). There are no population-based estimates of the incidence of pSS and the incidence of pSS-associated ILD. Here, we report on the incidence, and impact on survival of ILD among Olmsted County, Minnesota residents with pSS.

PATIENTS AND METHODS

This was a retrospective medical record review to investigate the ILD in patients with pSS in Olmsted County, MN, diagnosed during the 45 years period from January 1, 1976 to December 31, 2005 and then followed until death, migration or December 31, 2011.

The population of Olmsted County, Minnesota is well-suited for investigation of long-term outcomes of patients with pSS. A medical records linkage system, the Rochester Epidemiology Project (REP), allows ready access to the complete (inpatient and outpatient) records from all health care providers for the local population, including the Mayo Clinic and its affiliated hospitals, the Olmsted Medical Center and its affiliated community hospital, local nursing homes, and the few private practitioners. The potential of this data system for population-based research has been previously described,(13-14). This system ensures virtually complete clinical and vital status information on all clinically recognized cases of pSS among Olmsted County residents. The study was approved by the institutional review boards at Mayo Clinic and Olmsted Medical Center.

Ascertainment of pSS cases

Using this data resource, a population-based incidence cohort of all cases of pSS, first diagnosed between January 1, 1976 and December 31, 2005, among Olmsted County, Minnesota residents ≥ 18 years of age was assembled. The cohort initially assembled between 1976 to 1992 was enriched adding new pSS patients diagnosed between 1993 and 2005,(3). All cases fulfilled the 2002 American-European Consensus Group diagnostic criteria for pSS,(15). Incidence date is defined as the first date of fulfillment of

four out of the six American-European Consensus Group diagnostic criteria.

All subjects were followed up longitudinally through their complete medical records

Statistical analysis

Descriptive statistics (means, medians, proportions, etc.) were used to summarize the data. Comparison of patient characteristics between time periods were performed using chi-square tests for categorical characteristics and Wilcoxon rank sum tests for continuous characteristics.

Overall incidence rates were age- and/or sex-adjusted to the 2000 white population of the United States. Age- and sex-specific incidence rates were calculated by using the number of incident cases as the numerator and population estimates based on decennial census counts as the denominator, with linear interpolation used to estimate population size for intercensal years,(17). In order to compute 95% confidence intervals (95% CI) for incidence rates, it was assumed that the number of incident cases followed a Poisson distribution. Trends in incidence rates were examined using Poisson regression methods using smoothing splines for age and calendar year,(18).

The percentage of pSS patients with respiratory system involvement at pSS incidence date was computed. Those with respiratory system involvement at pSS incidence date were excluded from the analysis of cumulative incidence. The cumulative incidence of respiratory system involvement (and subtypes) was estimated using product-limit life table methods, accounting for the competing risk of death,(19).

Product-limit life table methods were used to estimate the survival of patients with pSS. The expected number of deaths was determined from the National Center for Health Statistics life tables for the United States population, according to the age, sex and calendar year of the pSS cohort,(20). A standardized mortality ratio (SMR) was estimated by dividing the observed number of deaths by the expected number of deaths. Ninety-five percent confidence intervals (CI) for the SMR were calculated assuming that the expected rates were fixed and the observed rates followed a Poisson distribution. A Cox model was used to examine the impact of respiratory system involvement on mortality with a time-dependent covariate indicating development of respiratory system involvement (whereby patients were modeled as unexposed during the followup time prior to development of respiratory system involvement and were then modeled as exposed following the development of respiratory system involvement) and adjustment for age, sex and calendar

year of diagnosis of pSS. Statistical analysis was performed using SAS software (version 9.3, SAS institute Inc., Cary, North Carolina, USA).

RESULTS

We identified 105 patients with incident pSS with a mean age at pSS diagnosis of 58.1 years (range 23-95); 91% were females. Demographic data and general characteristics of the study population are reported in table 2, 2a, 2b.

Considering the time periods patients differ significantly regarding the laboratory evaluation: rheumatoid factor, ANA, anti SSA and anti SSB were significantly more frequently detected in the 1993-2005 time period compared to the 1976-1992 cohort. Among clinical features, ocular signs tended toward statistical significance in 1993-2005 period with a p value of 0.06.

The annual incidence of pSS was 5.1 (95% CI: 4.1, 6.1) per 100,000 population, and increased with higher age at pSS diagnosis (18-44 years: 1.8/100,000 vs ≥75 years: 10.7/100,000) (Table 3). Female patients were more affected 8.7 per 100,000 population (95% CI: 6.9, 10.4), compared with males 1.1 per 100,000 (95% CI: 0.4, 1.9) (table 3).

The overall incidence increased modestly during the study period (3.9 [95% CI: 2.2, 5.6] per 100,000 population in 1976-1985; 5.0 [95% CI: 3.3, 6.7] in 1986-1995; and 5.9 [95% CI: 4.2, 7.6] in 1996-2005; linear trend p=0.06) (table 4 and figure 1).

During a median follow-up of 9.2 years (1205 total person-years), 25 patients died. This was similar to the 29.5 expected deaths (SMR: 0.85, 95% CI; 0.55, 1.25), logrank p-value=0.41(figure 2).

ILD in primary Sjögren's syndrome:

Lung disease was present prior to diagnosis of pSS in 12 patients and developed after diagnosis of pSS in 35 patients with a median follow-up time of 9.2 years (1205 total person-years). Among pSS patients without prior ILD, the cumulative incidence of ILD in patients with pSS was 10% (± 3%) at 1 year after diagnosis of pSS and increased to

20% (± 4%) by 5 years, and 43% (± 7%) by 15 years after pSS onset. The development of lung disease in pSS was associated with poor survival with a hazard ratio of 2.16 (95% CI: 0.99, 4.74) adjusted for age, sex, and calendar year although this did not reach statistical significance. ILD was identified as the most frequent type of lung disease detected at or after pSS diagnosis (53%) followed by emphysema (13%).

DISCUSSION

We found that the annual incidence of pSS was 5.1 (95% CI: 4.1, 6.1) per 100,000 population and increases with higher age at pSS diagnosis (18-44 years: 1.8/100,000 vs ≥75 years: 10.7/100,000). Comparison to existing epidemiologic studies is complicated by differences in disease definition and classification criteria. Until now only three studies have evaluated the incidence of pSS in general population, reporting values from 3.9 to 5.3 per 100,000 population,(3,21-22).

We found that the incidence of pSS may have increased modestly during the study period with a linear trend p value=0.06, although the overall trend is almost stable despite the differences among the diagnostic criteria occurring over the years. pSS has an incidence peak between 55 and 74 years of age with females more frequently affected than males.

The risk of death in patients with pSS in our study is similar to the general population (0.85; 95% CI: 0.55, 1.25). A prospective study of patients with pSS conducted in Greece reported a higher mortality risk than in general population (SMR 2.07; 95% CI: 1.03-3.71),(21). However when patients with adverse predictors (low levels of C4, presence of mixed monoclonal cryoglobulins and purpura) were excluded the mortality rate was identical to the general population (SMR 1.02),(23).

Similar to our study, most other studies reported a SMR that range between 1.2 and 1.42 without reaching statistical significance,(3,24,25-27). Therefore the survival of these patients is comparable with that of the general population,(28-29).

Case findings was based on 2002 AECG criteria, used for this study since the cohort was assembled in two time periods, 1976-1992 and 1993-2005. Because the new 2012 published expert consensus approach for pSS classification Criteria,(30) feature increased

reliance on serologic evaluation compared to the older criteria, we were concerned that our study would be affected by the time trend effects affecting classification and therefore used the AECG criteria. Nonetheless, clinical features important in classification have remained unchanged in the two time periods reported on (Table 2b).

Lung involvement in primary Sjögren's syndrome represents one of the most intriguing aspects of the disease. In this study, pSS patients without prior ILD, have a cumulative incidence of ILD of 10% (± 3%) at 1 year after diagnosis of pSS which increases to 20% (± 4%) by 5 years after onset of pSS. Patients who developed ILD prior to their pSS diagnosis were calculated apart from our primary analysis in order to avoid incidence-prevalence bias. Therefore, the overall risk for individuals with pSS to be affected by ILD either prior or after their diagnosis of pSS will be somewhat higher than our estimate. Additionally, patients with pSS have more frequent physician visits than the average patient in the population, and physicians may be more attuned to the possibility of lung disease in pSS patients than healthy people, leading to an overestimation of lung involvement in subjects with pSS compared to those without pSS (surveillance bias).

In contrast to these population based estimates, the existing literature on ILD and pSS is based upon studies of ILD prevalence in consecutive series of pSS patients in academic centers. In non-population-based studies, pulmonary changes can be documented in a majority of patients with pSS,(10-12) and clinically overt interstitial lung disease (ILD) is present in 6 to 94% of patients, both in early and longstanding pSS,(7,10-12). This wide variance appears to be due to different diagnostic modalities used to detect the disease, to the changed criteria for the classification of SS, to previous failure to separate out patients with primary or secondary SS and referral bias in studies originating from large academic centers.

Patients with pSS patients who have ILD have worse survival (hazard ratio 2.16; 95% CI: 0.99, 4.74). This is in contrast to a prospective cohort study which did not find increased all-cause mortality in patients with pSS compared with general population,(24). In a retrospective study conducted at Mayo Clinic among 18 patients who underwent lung biopsies, seven patients (39%) died including three deaths from acute exacerbation,(7).

Important limitations of our retrospective study approach should be acknowledged. Because of the inherent limitations of a chart review based diagnosis, it is likely that our estimates do not reflect the full extent of ILD in this population. The limited information on tests of lung disease (including radiographs, computed tomography, pulmonary function testing) available for each patient inherent to a retrospective study and the unavailability of some information due to time trend effects (for example, computed tomography became available in the 1970's), may lead to a misclassification bias. However, the use of rigorous criteria for ILD diagnosis established by the collaboration between an expert pulmonologist and rheumatologist should have reduced the possibility of this bias.

Our definition of ILD does represent a blend of many different types of parenchymal lung disease. Because of the changes in availability of diagnostic tools such as CT over time as well as the evolution of definitions used to characterize ILD, reliable assignment of ILD subtypes for every patient according to the most recent American Thoracic Society consensus classification,(31) was not possible.

In conclusion the incidence of pSS, evaluated using the new ACR classification criteria for pSS, was similar to that reported in a previous study from the same population based on physician diagnosis. The incidence of pSS appears to be increasing in recent years. Our findings emphasize the high incidence of ILD among patients with pSS, and the adverse effect of this disease complication on survival. Patients with pSS should be carefully assessed for diagnosis and management of ILD in order to improve the detrimental survival experience.

Disclosure: We have no disclosures

Acknowledgements and **Funding**: This work was made possible by the Rochester Epidemiology Project (R01 AG034676 from the National Institute on Aging).

Contributorship: All the authors took part in the following steps:
Conception and design, acquisition of data, analysis and interpretation of data
Drafting the article or revising it critically for important intellectual content.
Final approval of the version published

Data sharing
No additional data available

Figure legends
Figure 1 – Annual incidence of pSS per 100,000 populations in residents of Olmsted County, Minnesota, 1976-2005. The broken line was calculated as a 3-year-centered moving average, and the solid line depicts trends in the incidence rates after adjustment for age and sex (linear trend p-value= .06)
Figure 2 – Survival in patients with primary Sjogren's (solid line) compared to the general population (dotted line) (logrank p=0.41).

References

1) Manthorpe R, Asmussen K, Oxholm P. Primary Sjögren's syndrome: diagnostic criteria, clinical features, and disease activity. VIth International Symposium on Sjögren's syndrome: Avon Connecticut, USA. J Rheumatol 1997;24(Suppl 50): 8–11.

2) Binard A, Devauchelle-Pensec V, Fautrel B, et al. Epidemiology of Sjögren's syndrome: where are we? Clin Exp Rheumatol 2007; 25: 1-4.

3) Pillemer SR, Matteson EL, Jacobsson LTH, et al. Incidence of physician-diagnosed primary Sjögren's syndrome in residents of Olmsted County, Minnesota. Mayo Clin Proceed 2001;76: 593-9.

4) Drosos AA, Andonopoulos AP, Costopoulos JS, et al Prevalence of primary Sjögren syndrome in an elderly population. Br J Rheumatol 1988; 27:123-7.

5) Hochberg MC, Schein OD, Munoz B et al. The prevalence of dry eye, dry mouth, autoimmunity and primary Sjögren's syndrome in the general population. Arthritis Rheum 1996;39: S66.

6) Dafni UG, Tzioufas AG, Staikos P, et al. The prevalence of primary Sjögren syndrome in a closed rural community. Ann Rheum Dis 1997; 56: 521-5.

7) Parambil JG, Myers JL, Lindell RM, Matteson EL, Ryu JH. Interstitial lung disease in primary Sjögren syndrome. Chest 2006; 130:1489–1495.

8) Parke AL. Pulmonary manifestations of primary Sjögren syndrome. Rheun Dis Clin N Am 2008; 34: 907-920.

9) Lin DF, Yan SM, Zhao Y et al. Clinical and prognostic characteristics of 573 cases of primary Sjögren's syndrome. Chin Med J (Engl). 2010;123(22):3252-7.

10) Gardiner P, Ward C, Allison A, et al. Pleuropulmonary abnormalities in primary Sjögren's sindrome J Rheumatol. 1993;20(5):831-7.

11) Deheinzelin D, Capelozzi VL, Kairalla RA et al. Interstitial lung disease in primary Sjögren's syndrome. Clinical-pathological evaluation and response to treatment. Am J Respir Crit Care Med. 1996;154(3 Pt 1):794-9.

12) Ju-Hong Shi, Hong-Rui Liu, Weng-Bin Xu et al. Pulmonary manifestations in Sjögren's Syndrome. Respiration 2009;78:377–386.

13) St Sauver JL, Grossardt BR, Yawn BP, et al. Use of a medical records linkage system to enumerate a dynamic population over time: the Rochester epidemiology project. Am J Epidemiol. 2011;173(9):1059-68.

14) Melton LJ, III. History of the Rochester Epidemiology Project. Mayo Clin Proc 1996; 71(3):266-274.

15) Vitali C, Bombardieri S, Jonsson R et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002 61: 554-558

16) Bongartz T, Nannini C, Medina-Velasquez YF, et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. Arthritis Rheum. 2010;62(6):1583-91.

17) Bergstralh EJ, Offord KP, Chu CP, et al. Technical Report Series No. 49. Calculating incidence, prevalence and mortality rates for Olmsted County, Minnesota: an update. Section of Biostatistics, Mayo Clinic,Rochester (MN); 1992.

18) McCullagh P, Nelder JA. Generalized linear models. New York: Chapman & Hall; 1983

19) Gooley TA, Leisenring W, Crowley J, et al. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med. 1999;18(6):695-706.

20) Therneau TM, Offord J. Expected survival based on hazard rates (updated). Technical Report Series No. 63. Rochester (MN): Mayo Clinic Department of Health Sciences Research; 1999

21) Alamanos Y, Tsifetaki N, Vulgari PV, et al Epidemiology of primary Sjögren's syndrome in north-west Greece 1982-2003. Rheumatology 2006;45:187-91

22) Novljan MP, Rozman B, Hocevar A, et al. Incidence of primary Sjögren's syndrome in Slovenia. Ann Aheum Dis 2004; 63:874-6.

23) Skopouli FN, Dafni U, Ioannidis JP, et al. Clinical evaluation morbidity and mortality of primary Sjögren's syndrome. Semin Arthritis Rheum 2000 29(5) 296-304.

24) Theander E, Manthorpe R, Jacobsson LT. Mortality and cause of death in primary Sjögren's syndrome: a prospective cohort study, Arthritis Rheum 2004; 50; 1262-1269.

25) Ionnidis JP, Vassiliou VA, Moutsopoulos HM. Long term risk of mortality and lymphoproliferative disease and predictive classification of primary Sjögren's syndrome. Arthritis Rheum 2002;46(3):741-747.

26) Ramos Casals M, Brito-Zeron P, Yague J, et al. Hypocomplementaemia as an immunological marker of morbidity and mortality in patients with primary Sjögren's syndrome. Rheumatology 2005;44(1):89-94.

27) Brito-Zeron P, Ramos-Casals M, Bova A, et al. Predicting adverse outcomes in primary Sjögren's syndrome: identification of prognostic factors. Rheumatology 2007; 46(8):1359-1362

28) Martens PB, Pillmer SR, Jacobsson LTH, et al. Survivorship in a population based cohort of patients with Sjögren's syndrome 1976-1992. J Rheumatol 1999;26:1296-300.

29) Kruize AA, Hene RJ, Van Der Heide A, et al. Long term follow up of patients with Sjögren's syndrome. Arthritis Rheum 1996; 39: 297-303

30) Shiboski SC, Shiboski CH, Criswell LA et al. American College of Rheumatology Classification Criteria for Sjögren Syndrome: a data driven, expert consensus approach in the Sjögren international collaborative clinical alliance cohort. Arthritis Care Res2012; 64(4):475-87.

31) American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Resp Crit Care Medicine 2002;165(2):277-304.

Table 1. Classification criteria for interstitial lung disease (ILD) in primary Sjögren's syndrome

Probable ILD:	chest radiograph or computed tomography described as "fibrosis" or "consistent with ILD or parenchymal lung disease" or physician's diagnosis of "interstitial lung disease", "pulmonary fibrosis", "interstitial pneumonia", etc.
Definite ILD:	Diagnosis of ILD by a pulmonologist, based on chest radiograph/high resolution chest CT and pulmonary function testing (restrictive ventilatory pattern or reduced DLCO) or lung biopsy (bronchoscopic or surgical)

Table 2: Characteristics of 105 patients with primary Sjögren's syndrome

	1976-1992 (n=50)		1993-2005 (n=55)		Total (n=105)		p-value
	N	Value*	N	Value*	N	Value*	
Sex, female (%)	50	48 (96)	55	48 (87)	105	96 (91)	0.11
Age at incidence, years	50	57.5 (23 – 95)	55	59.2 (26 – 86)	105	59.2 (23 – 95)	0.96
Length of follow-up, years	50	17.2 (0.4 - 34.2)	55	7.7 (0.1 - 17.3)	105	9.2 (0.1 - 34.2)	--
Smoking Never Current Former	44	 29 (66) 8 (18) 7 (16)	52	 27 (52) 4 (8) 21 (40)	96	 56 (58) 4 (8) 21 (40)	0.020

*Value is n (%) or median (minimum, maximum). Percentages are calculated based on available N.

N: number of patients with parameter reported in the medical records

Table 2a: Laboratory assessment of 105 patients with primary Sjögren's syndrome

	1976-1992 (n=50)		1993-2005 (n=55)		Total (n=105)		p-value
	N	Value*	N	Value*	N	Value*	
Rheumatoid factor, positive (%)	37	14 (38)	45	32 (71)	82	46 (56)	0.002
Anti-nuclear antibodies, positive (%)	37	20 (54)	52	42 (81)	89	62 (70)	0.007
Anti-SSA, positive (%)	17	7 (41)	48	38 (79)	65	45 (69)	0.004
Anti-SSB, positive (%)	18	6 (33)	48	30 (63)	66	36 (55)	0.034
Hypergammaglobulinemia, present (%)	38	16 (42)	44	26 (59)	82	42 (51)	0.12
Histopathology, available (%)	0	-	6	3 (50)	6	3 (50)	-

*Value is n (%) or median (minimum, maximum). Percentages are calculated based on available N.

N: number of patients with parameter reported in the medical records

Table 2b: Clinical characteristics of 105 patients with primary Sjögren's syndrome

	1976-1992 (n=50)		1993-2005 (n=55)		Total (n=105)		p-value
	N	Value*	N	Value*	N	Value*	
Ocular symptoms, present (%)	48	45 (94)	54	52 (96)	102	97 (95)	0.55
Oral symptoms, present (%)	45	42 (93)	50	48 (96)	95	90 (95)	0.56
Ocular signs, present (%)	30	30 (100)	9	8 (89)	39	38 (90)	0.06
Oral signs, present (%)	46	3 (7)	1	0 (0)	47	3 (6)	-
Ocular signs/symptoms, present (%)	48	45 (94)	54	52 (96)	102	97 (95)	0.55
Oral signs/symptoms, present (%)	49	42 (86)	50	48 (96)	99	90 (91)	0.08

*Value is n (%) or median (minimum, maximum). Percentages are calculated based on available N.

N: number of patients with parameter reported in the medical records

Table 3: Annual incidence of primary Sjögren's Syndrome diagnosed between 1976 and 2005 in Olmsted County, Minnesota Residents ≥18 years of age, by sex and age group*

Age group	Male (n=9)		Female (n=96)		Total (N=105)	
	No. of patients	Rate per 100,000	No. of patients	Rate per 100,000	No. of patients	Rate per 100,000
18-44 years	3	0.5	22	3.1	25	1.8
45-54 years	1	0.5	20	10.6	21	5.6
55-64 years	0	0.0	20	15.3	20	7.9
65-74 years	1	1.3	21	21.8	22	12.7
≥75 years	4	7.5	13	12.3	17	10.7
Total (95% CI)	9	1.1 (0.4, 1.9)†	96	8.7 (6.9, 10.4)†	105	5.1 (4.1, 6.1)‡

* Values are the annual incidence rate (95% confidence interval [95% CI]) per 100,000 population.
† Age-adjusted to the 2000 US white population.
‡ Age- and sex-adjusted to the 2000 US white population.

Table 4. Annual Incidence of pSS diagnosed between 1976 and 2005 by decade in Olmsted County, Minnesota residents ≥18 years of age, by sex and age group*

Age group	Male (n=9)		Female (n=96)		Total (N=105)	
	No. of patients	Rate per 100,000	No. of patients	Rate per 100,000	No. of patients	Rate per 100,000
1976-1985	1	0.7 (0.0, 2.2)†	20	6.8 (3.8, 9.9)†	21	3.9 (2.2, 5.6)‡
1986-1995	1	0.6 (0.0, 1.6)†	34	9.1 (6.0, 12.2)†	35	5.0 (3.3, 6.7)‡
1996-2005	7	1.9 (0.4, 3.3)†	42	9.5 (6.6, 12.4)†	49	5.9 (4.2, 7.6)‡

* Values are the annual incidence rate (95% confidence interval [95% CI]) per 100,000 population.
† Age-adjusted to the 2000 US white population.
‡ Age- and sex-adjusted to the 2000 US white population.

Primary Sjögren's Syndrome 1976-2005 and Associated Interstitial Lung Disease: A Population Based- Study of Incidence and Mortality

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Keywords: interstitial lung disease; Sjögren's syndrome; incidence; mortality

ABSTRACT

OBJECTIVE:

Very few studies describe the epidemiology of primary Sjogren's syndrome (pSS). The reported frequency of pulmonary involvement in primary Sjögren's Syndrome (pSS) varies widely depending on the detection method employed and consists mainly of various forms of airways disease. We aimed to evaluate the incidence and mortality of pSS and of lung disease in pSS, focusing on interstitial lung disease (ILD).

METHODS: A population-based incidence cohort of patients diagnosed with pSS in 1976-2005 was assembled. Diagnosis was based on 2002 American-European consensus group criteria for pSS. Cumulative incidence adjusted for the competing risk of death was estimated. A Cox model with a time-dependent covariate was used to determine the incidence and the standardized mortality hazard ratio (HR) of pSS.

RESULTS: 85 patients with pSS were identified (mean age 59.9 years; 91% female). The annual incidence of pSS was 4.2 95% CI (3.3, 5.1) per 100,000 population and it increased with higher age at pSS diagnosis (18-44 years: 2.1/100,000 vs ≥75 years: 12.3/100,000). Standardized mortality ratio in pSS compared to the general population was: 0.92, 95%CI (0.57, 1.41).

A total of 105 patients with pSS and ILD were identified (mean age 58.1 years; 91% female). Among pSS patients without prior ILD, the cumulative incidence of ILD in patients with pSS was 10% (± 3%) at 1 year after diagnosis of pSS and increased to 20% (± 4%) by 5 years after pSS. The development of lung disease in pSS was associated with poor survival (hazard ratio 2.16; 95% CI: 0.99, 4.74).

CONCLUSION: pSS incidence seems to be almost the same as was reported in a previous study conducted among Olmsted County Minnesota population. Survival among pSS patients and general population does not differ substantially. However, patients with pSS who have ILD likely have increased premature mortality.

ARTICLE SUMMARY

STRENGHTS: This is a population based study therefore we tried to do a real estimation of incidence and mortality among patients with pSS and to report the incidence of ILD among patients with pSS and what is its impact on pSS morality.
Attention to the occurrence of, and improved management of ILD in patients with pSS, may contribute to reduction of the disease burden of the disease.

LIMITATIONS: The major concern is related to the chart review based diagnosis, our estimates could not reflect the full extent of ILD in this population. The limited information on tests of lung disease available for each patient inherent to a retrospective study and the unavailability of some information due to time trend effects may lead to a misclassification bias.
Moreover an overestimation of lung involvement in subjects with pSS compared to those without pSS (surveillance bias) could be present.

- pSS incidence seems to be almost the same as was reported in a previous study conducted among Olmsted County Minnesota population
- Survival among pSS patients and general population does not differ substantially
- Patients with pSS who have ILD likely have increased premature mortality
- the occurrence of, and improved management of ILD in patients with pSS, may contribute to reduction of the disease burden of the disease.

INTRODUCTION

Sjögren's syndrome (SS) is a chronic autoimmune and systemic inflammatory disease that affects exocrine and extraglandular tissues,(1). It is known to occur alone (primary) or in association with other autoimmune disease states.

Very few studies describe the epidemiology of primary Sjögren's syndrome (pSS). The published studies of pSS in the general population report highly heterogeneous results. The wide-ranging prevalence estimates in adults varied from 0.098% to 3.59% while the incidence ranged from 3.9 to 5.3 per 100,000 population,(2, 3). This wide variation is due to the diverse populations using a restricted age range,(4), low sample size,(5), or low follow-up rate,(6). Studies of SS also have used a variety of classification criteria leading to difficulties when trying to compare results.

Extraglandular manifestations of pSS include a broad spectrum of lung disease. The reported frequency of pulmonary involvement in pSS varies widely ranging from 8 to 75% depending on the detection method employed and consists of various forms of airways disease (bronchiectasis, obstructive airways disease) and interstitial lung disease (ILD),(7). Lymphocytic interstitial pneumonia is well-defined in pSS patients,(8) but there is relatively little information regarding other ILD patterns occurring in pSS in terms of frequency and risk factors.

Extraarticular disease manifestations, including various forms of lung disease, are common in pSS and may be linked to an increased mortality,(9). Asymptomatic pulmonary changes are present in a majority of patients, but their impact on the disease course, mortality, and quality of life remain unclear.

Most studies have concentrated on ILD in consecutive samples of pSS patients in academic centers,(7,9-12). Consequently, little is known about the incidence of the full spectrum of respiratory system involvement in a representative sample of pSS patients from a population-based cohort. Previous studies that examined the incidence or prevalence of pSS-associated lung disease have differed widely in their estimates. This wide variance appears to be due to different diagnostic modalities used to detect the disease, to the changed criteria for the classification of SS, to previous failure to separate

out patients with primary or secondary SS, and referral bias in studies originating from large academic centers.

In non-population-based studies, pulmonary changes can be documented in a majority of patients with pSS,(10-12) and clinically overt ILD is present in 6 to 94% both in early and longstanding pSS,(7,10-12). There are no population-based estimates of the incidence of pSS and the incidence of pSS-associated ILD. Here, we report on the incidence, and impact on survival of ILD among Olmsted County, Minnesota residents with pSS.

PATIENTS AND METHODS

This was a retrospective medical record review to investigate the ILD in patients with pSS in Olmsted County, MN, diagnosed during the 45 years period from January 1, 1976 to December 31, 2005 and then followed until death, migration or December 31, 2011.

The population of Olmsted County, Minnesota is well-suited for investigation of long-term outcomes of patients with pSS. A medical records linkage system, the Rochester Epidemiology Project (REP), allows ready access to the complete (inpatient and outpatient) records from all health care providers for the local population, including the Mayo Clinic and its affiliated hospitals, the Olmsted Medical Center and its affiliated community hospital, local nursing homes, and the few private practitioners. The potential of this data system for population-based research has been previously described,(13-14). This system ensures virtually complete clinical and vital status information on all clinically recognized cases of pSS among Olmsted County residents. The study was approved by the institutional review boards at Mayo Clinic and Olmsted Medical Center.

Ascertainment of pSS cases

Using this data resource, a population-based incidence cohort of all cases of pSS, first diagnosed between January 1, 1976 and December 31, 2005, among Olmsted County, Minnesota residents ≥ 18 years of age was assembled. The cohort initially assembled between 1976 to 1992 was enriched adding new pSS patients diagnosed between 1993 and 2005,(3). All cases fulfilled the 2002 American-European Consensus Group diagnostic criteria for pSS,(15). Incidence date is defined as the first date of fulfillment of

four out of the six American-European Consensus Group diagnostic criteria.

All subjects were followed up longitudinally through their complete medical records beginning at age 18 (or date of migration to Olmsted County for those who became residents after age 18) and continuing until death, migration from Olmsted County, or December 31, 2011.

Data collection

The original and complete medical records of each pSS patient were reviewed by CN and AJ. Uncertainties regarding classification for pSS, presence and type of pulmonary disease, and underlying disease were adjudicated by JHR and/or ELM.

We abstracted demographic data (date of birth, gender), smoking status at pSS incidence date (never smoked/former smoker/current smoker) and smoking status at diagnosis of lung disease (never smoked/former smoker/current smoker). The date of last follow-up was recorded as well as the status at last follow-up (dead/alive).

SS features were abstracted and they included time variables (year of symptom onset, year of diagnosis according to American-European Consensus Group diagnostic criteria),(15), ocular and oral gland involvement (clinical judgment, Schirmer test, salivary glands biopsy and salivary scintigraphy) and laboratory features (rheumatoid factor [RF], ANA, anti SSA, anti SSB, immunoglobulin G level).

Definition and ascertainment of interstitial lung disease

The ascertainment of ILD was based on clinical data, pulmonary function test results [total lung capacity (TLC), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), diffusing capacity for carbon monoxide (DLCO), SaO2, at rest and with exercise], radiological studies (chest radiographs, computed tomography [CT]), bronchoalveolar lavage (BAL), and lung biopsy. The criteria used to classify ILD were validated in a previous study and are given in table 1,(16).

Statistical analysis

Descriptive statistics (means, medians, proportions, etc.) were used to summarize the data. Comparison of patient characteristics between time periods were performed using chi-square tests for categorical characteristics and Wilcoxon rank sum tests for continuous characteristics.

Overall incidence rates were age- and/or sex-adjusted to the 2000 white population of the United States. Age- and sex-specific incidence rates were calculated by using the number of incident cases as the numerator and population estimates based on decennial census counts as the denominator, with linear interpolation used to estimate population size for intercensal years,(17). In order to compute 95% confidence intervals (95% CI) for incidence rates, it was assumed that the number of incident cases followed a Poisson distribution. Trends in incidence rates were examined using Poisson regression methods using smoothing splines for age and calendar year,(18).

The percentage of pSS patients with respiratory system involvement at pSS incidence date was computed. Those with respiratory system involvement at pSS incidence date were excluded from the analysis of cumulative incidence. The cumulative incidence of respiratory system involvement (and subtypes) was estimated using product-limit life table methods, accounting for the competing risk of death,(19).

Product-limit life table methods were used to estimate the survival of patients with pSS. The expected number of deaths was determined from the National Center for Health Statistics life tables for the United States population, according to the age, sex and calendar year of the pSS cohort,(20). A standardized mortality ratio (SMR) was estimated by dividing the observed number of deaths by the expected number of deaths. Ninety-five percent confidence intervals (CI) for the SMR were calculated assuming that the expected rates were fixed and the observed rates followed a Poisson distribution. A Cox model was used to examine the impact of respiratory system involvement on mortality with a time-dependent covariate indicating development of respiratory system involvement (whereby patients were modeled as unexposed during the followup time prior to development of respiratory system involvement and were then modeled as exposed following the development of respiratory system involvement) and adjustment for age, sex and calendar

year of diagnosis of pSS. Statistical analysis was performed using SAS software (version 9.3, SAS institute Inc., Cary, North Carolina, USA).

RESULTS

We identified 105 patients with incident pSS with a mean age at pSS diagnosis of 58.1 years (range 23-95); 91% were females. Demographic data and general characteristics of the study population are reported in table 2, 2a, 2b.

Considering the time periods patients differ significantly regarding the laboratory evaluation: rheumatoid factor, ANA, anti SSA and anti SSB were significantly more frequently detected in the 1993-2005 time period compared to the 1976-1992 cohort. Among clinical features, ocular signs tended toward statistical significance in 1993-2005 period with a p value of 0.06.

The annual incidence of pSS was 5.1 (95% CI: 4.1, 6.1) per 100,000 population, and increased with higher age at pSS diagnosis (18-44 years: 1.8/100,000 vs ≥75 years: 10.7/100,000) (Table 3). Female patients were more affected 8.7 per 100,000 population (95% CI: 6.9, 10.4), compared with males 1.1 per 100,000 (95% CI: 0.4, 1.9) (table 3).

The overall incidence increased modestly during the study period (3.9 [95% CI: 2.2, 5.6] per 100,000 population in 1976-1985; 5.0 [95% CI: 3.3, 6.7] in 1986-1995; and 5.9 [95% CI: 4.2, 7.6] in 1996-2005; linear trend p=0.06) (table 4 and figure 1).

During a median follow-up of 9.2 years (1205 total person-years), 25 patients died. This was similar to the 29.5 expected deaths (SMR: 0.85, 95% CI; 0.55, 1.25), logrank p-value=0.41(figure 2).

ILD in primary Sjögren's syndrome:

Lung disease was present prior to diagnosis of pSS in 12 patients and developed after diagnosis of pSS in 35 patients with a median follow-up time of 9.2 years (1205 total person-years). Among pSS patients without prior ILD, the cumulative incidence of ILD in patients with pSS was 10% (± 3%) at 1 year after diagnosis of pSS and increased to

20% (± 4%) by 5 years, and 43% (± 7%) by 15 years after pSS onset. The development of lung disease in pSS was associated with poor survival with a hazard ratio of 2.16 (95% CI: 0.99, 4.74) adjusted for age, sex, and calendar year although this did not reach statistical significance. ILD was identified as the most frequent type of lung disease detected at or after pSS diagnosis (53%) followed by emphysema (13%).

DISCUSSION

We found that the annual incidence of pSS was 5.1 (95% CI: 4.1, 6.1) per 100,000 population and increases with higher age at pSS diagnosis (18-44 years: 1.8/100,000 vs ≥75 years: 10.7/100,000). Comparison to existing epidemiologic studies is complicated by differences in disease definition and classification criteria. Until now only three studies have evaluated the incidence of pSS in general population, reporting values from 3.9 to 5.3 per 100,000 population,(3,21-22).

We found that the incidence of pSS may have increased modestly during the study period with a linear trend p value=0.06, although the overall trend is almost stable despite the differences among the diagnostic criteria occurring over the years. pSS has an incidence peak between 55 and 74 years of age with females more frequently affected than males.

The risk of death in patients with pSS in our study is similar to the general population (0.85; 95% CI: 0.55, 1.25). A prospective study of patients with pSS conducted in Greece reported a higher mortality risk than in general population (SMR 2.07; 95% CI: 1.03-3.71),(21). However when patients with adverse predictors (low levels of C4, presence of mixed monoclonal cryoglobulins and purpura) were excluded the mortality rate was identical to the general population (SMR 1.02),(23).

Similar to our study, most other studies reported a SMR that range between 1.2 and 1.42 without reaching statistical significance,(3,24,25-27). Therefore the survival of these patients is comparable with that of the general population,(28-29).

Case findings was based on 2002 AECG criteria, used for this study since the cohort was assembled in two time periods, 1976-1992 and 1993-2005. Because the new 2012 published expert consensus approach for pSS classification Criteria,(30) feature increased

reliance on serologic evaluation compared to the older criteria, we were concerned that our study would be affected by the time trend effects affecting classification and therefore used the AECG criteria. Nonetheless, clinical features important in classification have remained unchanged in the two time periods reported on (Table 2b).

Lung involvement in primary Sjögren's syndrome represents one of the most intriguing aspects of the disease. In this study, pSS patients without prior ILD, have a cumulative incidence of ILD of 10% (± 3%) at 1 year after diagnosis of pSS which increases to 20% (± 4%) by 5 years after onset of pSS. Patients who developed ILD prior to their pSS diagnosis were calculated apart from our primary analysis in order to avoid incidence-prevalence bias. Therefore, the overall risk for individuals with pSS to be affected by ILD either prior or after their diagnosis of pSS will be somewhat higher than our estimate. Additionally, patients with pSS have more frequent physician visits than the average patient in the population, and physicians may be more attuned to the possibility of lung disease in pSS patients than healthy people, leading to an overestimation of lung involvement in subjects with pSS compared to those without pSS (surveillance bias).

In contrast to these population based estimates, the existing literature on ILD and pSS is based upon studies of ILD prevalence in consecutive series of pSS patients in academic centers. In non-population-based studies, pulmonary changes can be documented in a majority of patients with pSS,(10-12) and clinically overt interstitial lung disease (ILD) is present in 6 to 94% of patients, both in early and longstanding pSS,(7,10-12). This wide variance appears to be due to different diagnostic modalities used to detect the disease, to the changed criteria for the classification of SS, to previous failure to separate out patients with primary or secondary SS and referral bias in studies originating from large academic centers.

Patients with pSS patients who have ILD have worse survival (hazard ratio 2.16; 95% CI: 0.99, 4.74). This is in contrast to a prospective cohort study which did not find increased all-cause mortality in patients with pSS compared with general population,(24). In a retrospective study conducted at Mayo Clinic among 18 patients who underwent lung biopsies, seven patients (39%) died including three deaths from acute exacerbation,(7).

Important limitations of our retrospective study approach should be acknowledged. Because of the inherent limitations of a chart review based diagnosis, it is likely that our estimates do not reflect the full extent of ILD in this population. The limited information on tests of lung disease (including radiographs, computed tomography, pulmonary function testing) available for each patient inherent to a retrospective study and the unavailability of some information due to time trend effects (for example, computed tomography became available in the 1970's), may lead to a misclassification bias. However, the use of rigorous criteria for ILD diagnosis established by the collaboration between an expert pulmonologist and rheumatologist should have reduced the possibility of this bias.

Our definition of ILD does represent a blend of many different types of parenchymal lung disease. Because of the changes in availability of diagnostic tools such as CT over time as well as the evolution of definitions used to characterize ILD, reliable assignment of ILD subtypes for every patient according to the most recent American Thoracic Society consensus classification,(31) was not possible.

In conclusion the incidence of pSS, evaluated using the new ACR classification criteria for pSS, was similar to that reported in a previous study from the same population based on physician diagnosis. The incidence of pSS appears to be increasing in recent years. Our findings emphasize the high incidence of ILD among patients with pSS, and the adverse effect of this disease complication on survival. Patients with pSS should be carefully assessed for diagnosis and management of ILD in order to improve the detrimental survival experience.

Disclosure: We have no disclosures

Acknowledgements and Funding: This work was made possible by the Rochester Epidemiology Project (R01 AG034676 from the National Institute on Aging).

Contributorship: all the authors took part in abstracting data, interpretation and drafting the paper. Mrs Crowson analysed the data

References

1) Manthorpe R, Asmussen K, Oxholm P. Primary Sjögren's syndrome: diagnostic criteria, clinical features, and disease activity. VIth International Symposium on Sjögren's syndrome: Avon Connecticut, USA. J Rheumatol 1997;24(Suppl 50): 8–11.

2) Binard A, Devauchelle-Pensec V, Fautrel B, et al. Epidemiology of Sjögren's syndrome: where are we? Clin Exp Rheumatol 2007; 25: 1-4.

3) Pillemer SR, Matteson EL, Jacobsson LTH, et al. Incidence of physician-diagnosed primary Sjögren's syndrome in residents of Olmsted County, Minnesota. Mayo Clin Proceed 2001;76: 593-9.

4) Drosos AA, Andonopoulos AP, Costopoulos JS, et al Prevalence of primary Sjögren syndrome in an elderly population. Br J Rheumatol 1988; 27:123-7.

5) Hochberg MC, Schein OD, Munoz B et al. The prevalence of dry eye, dry mouth, autoimmunity and primary Sjögren's syndrome in the general population. Arthritis Rheum 1996;39: S66.

6) Dafni UG, Tzioufas AG, Staikos P, et al. The prevalence of primary Sjögren syndrome in a closed rural community. Ann Rheum Dis 1997; 56: 521-5.

7) Parambil JG, Myers JL, Lindell RM, Matteson EL, Ryu JH. Interstitial lung disease in primary Sjögren syndrome. Chest 2006; 130:1489–1495.

8) Parke AL. Pulmonary manifestations of primary Sjögren syndrome. Rheun Dis Clin N Am 2008; 34: 907-920.

9) Lin DF, Yan SM, Zhao Y et al. Clinical and prognostic characteristics of 573 cases of primary Sjögren's syndrome. Chin Med J (Engl). 2010;123(22):3252-7.

10) Gardiner P, Ward C, Allison A, et al. Pleuropulmonary abnormalities in primary Sjögren's sindrome J Rheumatol. 1993;20(5):831-7.

11) Deheinzelin D, Capelozzi VL, Kairalla RA et al. Interstitial lung disease in primary Sjögren's syndrome. Clinical-pathological evaluation and response to treatment. Am J Respir Crit Care Med. 1996;154(3 Pt 1):794-9.

12) Ju-Hong Shi, Hong-Rui Liu, Weng-Bin Xu et al. Pulmonary manifestations in Sjögren's Syndrome. Respiration 2009;78:377–386.

13) St Sauver JL, Grossardt BR, Yawn BP, Melton LJ, 3rd, Rocca WA. Use of a medical records linkage system to enumerate a dynamic population over time: the Rochester epidemiology project. Am J Epidemiol. 2011;173(9):1059-68.

14) Melton LJ, III. History of the Rochester Epidemiology Project. Mayo Clin Proc 1996; 71(3):266-274.

15) Vitali C, Bombardieri S, Jonsson R et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002 61: 554-558

16) Bongartz T, Nannini C, Medina-Velasquez YF, Achenbach SJ, et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. Arthritis Rheum. 2010;62(6):1583-91.

17) Bergstralh EJ, Offord KP, Chu CP, Beard CM, O'Fallon WM, Melton LJ III. Technical Report Series No. 49. Calculating incidence, prevalence and mortality rates for Olmsted County, Minnesota: an update. Section of Biostatistics, Mayo Clinic,Rochester (MN); 1992.

18) McCullagh P, Nelder JA. Generalized linear models. New York: Chapman & Hall; 1983

19) Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med. 1999;18(6):695-706.

20) Therneau TM, Offord J. Expected survival based on hazard rates (updated). Technical Report Series No. 63. Rochester (MN): Mayo Clinic Department of Health Sciences Research; 1999

21) Alamanos Y, Tsifetaki N, Vulgari PV, et al Epidemiology of primary Sjögren's syndrome in north-west Greece 1982-2003. Rheumatology 2006;45:187-91

22) Novljan MP, Rozman B, Hocevar A, et al. Incidence of primary Sjögren's syndrome in Slovenia. Ann Aheum Dis 2004; 63:874-6.

23) Skopouli FN, Dafni U, Ioannidis JP, et al. Clinical evaluation morbidity and mortality of primary Sjögren's syndrome. Semin Arthritis Rheum 2000 29(5) 296-304.

24) Theander E, Manthorpe R, Jacobsson LT. Mortality and cause of death in primary Sjögren's syndrome: a prospective cohort study, Arthritis Rheum 2004; 50; 1262-1269.

25) Ionnidis JP, Vassiliou VA, Moutsopoulos HM. Long term risk of mortality and lymphoproliferative disease and predictive classification of primary Sjögren's syndrome. Arthritis Rheum 2002;46(3):741-747.

26) Ramos Casals M, Brito-Zeron P, Yague J, et al. Hypocomplementaemia as an immunological marker of morbidity and mortality in patients with primary Sjögren's syndrome. Rheumatology 2005;44(1):89-94.

27) Brito-Zeron P, Ramos-Casals M, Bova A, et al. Predicting adverse outcomes in primary Sjögren's syndrome: identification of prognostic factors. Rheumatology 2007; 46(8):1359-1362

28) Martens PB, Pillmer SR, Jacobsson LTH, et al. Survivorship in a population based cohort of patients with Sjögren's syndrome 1976-1992. J Rheumatol 1999;26:1296-300.

29) Kruize AA, Hene RJ, Van Der Heide A, et al. Long term follow up of patients with Sjögren's syndrome. Arthritis Rheum 1996; 39: 297-303

30) Shiboski SC, Shiboski CH, Criswell LA et al. American College of Rheumatology Classification Criteria for Sjögren Syndrome: a data driven, expert consensus approach in the Sjögren international collaborative clinical alliance cohort. Arthritis Care Res2012; 64(4):475-87.

31) American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Resp Crit Care Medicine 2002;165(2):277-304.

Table 1. Classification criteria for interstitial lung disease (ILD) in primary Sjögren's syndrome

Probable ILD:	chest radiograph or computed tomography described as "fibrosis" or "consistent with ILD or parenchymal lung disease" or physician's diagnosis of "interstitial lung disease", "pulmonary fibrosis", "interstitial pneumonia", etc.
Definite ILD:	Diagnosis of ILD by a pulmonologist, based on chest radiograph/high resolution chest CT and pulmonary function testing (restrictive ventilatory pattern or reduced DLCO) or lung biopsy (bronchoscopic or surgical)

Table 2: Characteristics of 105 patients with primary Sjögren's syndrome

	1976-1992 (n=50)		1993-2005 (n=55)		Total (n=105)		p-value
	N	Value*	N	Value*	N	Value*	
Sex, female (%)	50	48 (96)	55	48 (87)	105	96 (91)	0.11
Age at incidence, years	50	57.5 (23 – 95)	55	59.2 (26 – 86)	105	59.2 (23 – 95)	0.96
Length of follow-up, years	50	17.2 (0.4 - 34.2)	55	7.7 (0.1 - 17.3)	105	9.2 (0.1 - 34.2)	--
Smoking Never Current Former	44	 29 (66) 8 (18) 7 (16)	52	 27 (52) 4 (8) 21 (40)	96	 56 (58) 4 (8) 21 (40)	0.020

*Value is n (%) or median (minimum, maximum). Percentages are calculated based on available N.

N: number of patients with parameter reported in the medical records

Table 2a: Laboratory assessment of 105 patients with primary Sjögren's syndrome

	1976-1992 (n=50)		1993-2005 (n=55)		Total (n=105)		p-value
	N	Value*	N	Value*	N	Value*	
Rheumatoid factor, positive (%)	37	14 (38)	45	32 (71)	82	46 (56)	0.002
Anti-nuclear antibodies, positive (%)	37	20 (54)	52	42 (81)	89	62 (70)	0.007
Anti-SSA, positive (%)	17	7 (41)	48	38 (79)	65	45 (69)	0.004
Anti-SSB, positive (%)	18	6 (33)	48	30 (63)	66	36 (55)	0.034
Hypergammaglobulinemia, present (%)	38	16 (42)	44	26 (59)	82	42 (51)	0.12
Histopathology, available (%)	0	-	6	3 (50)	6	3 (50)	-

*Value is n (%) or median (minimum, maximum). Percentages are calculated based on available N.

N: number of patients with parameter reported in the medical records

Table 2b: Clinical characteristics of 105 patients with primary Sjögren's syndrome

	1976-1992 (n=50)		1993-2005 (n=55)		Total (n=105)		p-value
	N	Value*	N	Value*	N	Value*	
Ocular symptoms, present (%)	48	45 (94)	54	52 (96)	102	97 (95)	0.55
Oral symptoms, present (%)	45	42 (93)	50	48 (96)	95	90 (95)	0.56
Ocular signs, present (%)	30	30 (100)	9	8 (89)	39	38 (90)	0.06
Oral signs, present (%)	46	3 (7)	1	0 (0)	47	3 (6)	-
Ocular signs/symptoms, present (%)	48	45 (94)	54	52 (96)	102	97 (95)	0.55
Oral signs/symptoms, present (%)	49	42 (86)	50	48 (96)	99	90 (91)	0.08

*Value is n (%) or median (minimum, maximum). Percentages are calculated based on available N.

N: number of patients with parameter reported in the medical records

Table 3: Annual incidence of primary Sjögren's Syndrome diagnosed between 1976 and 2005 in Olmsted County, Minnesota Residents ≥18 years of age, by sex and age group*

Age group	Male (n=9)		Female (n=96)		Total (N=105)	
	No. of patients	Rate per 100,000	No. of patients	Rate per 100,000	No. of patients	Rate per 100,000
18-44 years	3	0.5	22	3.1	25	1.8
45-54 years	1	0.5	20	10.6	21	5.6
55-64 years	0	0.0	20	15.3	20	7.9
65-74 years	1	1.3	21	21.8	22	12.7
≥75 years	4	7.5	13	12.3	17	10.7
Total (95% CI)	9	1.1 (0.4, 1.9)†	96	8.7 (6.9, 10.4)†	105	5.1 (4.1, 6.1)‡

* Values are the annual incidence rate (95% confidence interval [95% CI]) per 100,000 population.
† Age-adjusted to the 2000 US white population.
‡ Age- and sex-adjusted to the 2000 US white population.

Table 4. Annual Incidence of pSS diagnosed between 1976 and 2005 by decade in Olmsted County, Minnesota residents ≥18 years of age, by sex and age group*

Age group	Male (n=9)		Female (n=96)		Total (N=105)	
	No. of patients	Rate per 100,000	No. of patients	Rate per 100,000	No. of patients	Rate per 100,000
1976-1985	1	0.7 (0.0, 2.2)†	20	6.8 (3.8, 9.9)†	21	3.9 (2.2, 5.6)‡
1986-1995	1	0.6 (0.0, 1.6)†	34	9.1 (6.0, 12.2)†	35	5.0 (3.3, 6.7)‡
1996-2005	7	1.9 (0.4, 3.3)†	42	9.5 (6.6, 12.4)†	49	5.9 (4.2, 7.6)‡

* Values are the annual incidence rate (95% confidence interval [95% CI]) per 100,000 population.
† Age-adjusted to the 2000 US white population.
‡ Age- and sex-adjusted to the 2000 US white population.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Figure 1. Annual incidence of pSS per 100,000 population in residents of Olmsted County, Minnesota, 1976–2005. The broken line was calculated as a 3-year–centered moving average, and the solid line depicts trends in the incidence rates after adjustment for age and sex **(linear trend p-value =0.06).**

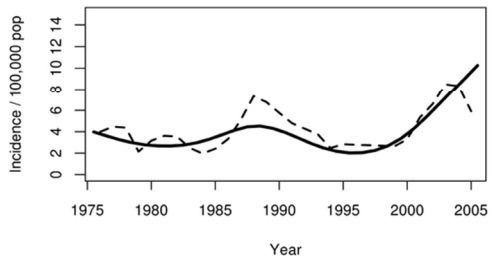

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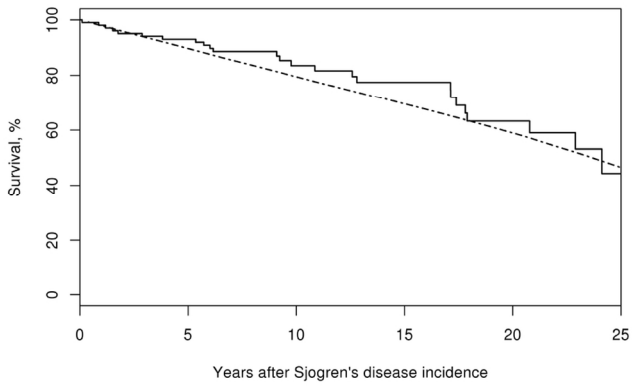
Figure 2. Survival in patients with primary Sjögren's syndrome (solid line) compared to the general population (dotted line) (logrank p=0.41).



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