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Epidemiology of primary Sjögren's syndrome in north-west Greece, 1982–2003

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Objectives. **To investigate the incidence and prevalence, as well as the mortality and survival rates, of primary Sjögren's syndrome (pSS) in a defined area of north-west Greece with a population of about 500 000 inhabitants.**
Methods. **Cases were recorded from the following sources: (i) in- and out-patients referred to the rheumatology clinics of the Ioannina University Hospital and the Ioannina General Hospital; and (ii) patients referred to private rheumatologists practising in the study area. All patients diagnosed between 1 January 1982 and 31 December 2003 who were resident in the study area were included as incident cases. Diagnosis was based on the American–European consensus criteria for SS. Incidence and prevalence rates were calculated as numbers of cases per 10^5 inhabitants. Population data were based on the National Censuses of 1981, 1991 and 2001.**
Results. **A total of 422 incident cases were identified for the study period 1982–2003. Age-adjusted mean annual incidence rate for this period was 5.3 (95% confidence interval [CI] 4.5–6.1) cases per 10^5 adult inhabitants. The female/male ratio of incident cases was about 20/1. The age-adjusted prevalence rate for the adult population was 92.8 (95% CI 83.7–101.9) cases per 10^5 inhabitants on 31 December 2003. The 5-yr survival rate in the incidence cohort was 96.6% and the 10-yr survival rate 92.8%. The standardized mortality ratio in comparison with the general population of the study area was 1.02 (95% CI 0.4–2.0). The main causes of death were cardiovascular diseases and cancer. The occurrence of the disease shows a slightly decreasing, but not statistically significant, trend with time.**
Conclusions. **The estimated incidence and prevalence of pSS in this study were slightly higher in comparison with data from other studies based on physician-diagnosed cases. The prevalence was significantly lower when compared with the findings of studies based on the examination of a sample of the general population. Mortality rates did not differ significantly between pSS patients and the general population.**

KEY WORDS: Sjögren's syndrome, Epidemiology, Incidence, Prevalence, Mortality.

Sjögren's syndrome (SS) is an autoimmune disease characterized by inflammation of exocrine glands, mainly the lachrymal and salivary glands. It can present in combination with other autoimmune diseases, such as rheumatoid arthritis or systemic lupus erythematosus. In this case it is classified as secondary SS, whereas in isolation the disease is classified as primary (pSS) [1–3]. Although symptoms of SS vary widely, patients with pSS may have major complaints, including several systemic features. The impact of these symptoms is considerable in terms of disability and quality of life of the subjects affected [4–7].

There are only a few descriptive epidemiological studies for pSS suggesting important variations in disease occurrence. The prevalence estimates vary widely. These variations reflect the different age groups studied, the different classification criteria used, and the different methods of case ascertainment. There are few data concerning disease incidence [4, 8–16].

Since the disease may have an insidious onset, a variable course and a wide spectrum of clinical manifestations, patients with pSS may be missed or misclassified or the diagnosis be delayed. Several sets of classification criteria for SS have been proposed [17–23]. As a consequence, the epidemiological studies published previously were based on several classification criteria. Recently the American–European Consensus criteria (AECC) were published, which are the most acceptable for the classification of patients with SS [24].

The aim of the present study was to investigate incidence, prevalence and mortality and survival rates for pSS in the general population of a defined area of north-west Greece, for a period of 22 yr, applying the AECC criteria. We used the systematic recording system for autoimmune rheumatic diseases implemented in the area.

Methods

The study area represents a population of 488 435 inhabitants according to the National Census of 2001, including four districts situated on the mainland (Districts of Ioannina, Arta, Preveza and Thesprotia) and two districts situated in islands (Districts of Corfu and Lefcada). Urban residents represented about one-third of the total population, living in the capitals of the districts.

Cases were recorded in the framework of a systematic recording system for autoimmune rheumatic diseases, using the multiple sources for retrieval that have been developed in this defined area of north-west Greece. The system records cases from the following

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sources: (i) in- and out-patients referred to the Rheumatology Clinic of the Ioannina University Hospital; as well as to the Rheumatology Clinic of the Ioannina General Hospital; (ii) patients referred to the private rheumatologists practising inside the study area (eight private rheumatologists). These sources represent all points where diagnosed SS patients could be referred to a specialist in the area studied. The patients contacted a rheumatologist directly or were referred by the five small general hospitals, which provide general health services in the region, or by the eye clinics in the university and general hospitals of Ioannina, or by the private ophthalmologists and dentists practising in the area.

The demographic and clinical characteristics of the patients were obtained retrospectively from clinical records. Patients were selected on the basis of previous clinical diagnosis. We reviewed all records of residents in the study area in whom pSS had been diagnosed clinically. Diagnosis of pSS was confirmed by our study group, based on the AECC criteria [24]. Table 1 shows the revised classification criteria of the AECC. All our patients answered the questionnaire for ocular and oral symptoms and all had ophthalmological examination, Schirmer's I test and rose bengal test, as well as salivary flow rate measurement. In addition, all patients underwent minor salivary gland biopsy and all had immunological tests after they had signed an informed consent form. For technical reasons, Ro(SSA) and La(SSB) antibodies were assessed in 402 and 400 patients, respectively. Only pSS cases were included in the study. Patients with a coexisting, well-defined autoimmune rheumatic disease were excluded. In addition, patients with a history or presence of viral hepatitis C infection, cryoglobulinaemia or acquired immunodeficiency disease were excluded from the study. All patients referred between 1 January 1982 and 31 December 2003, resident in the study area, were included in the study. An incidence case was defined as any pSS patient, diagnosed during the study period, resident in the study area for at least 1 yr before the diagnosis. A prevalence case was defined as any pSS patient who was a resident of the study area on 31 December 2003. Patients who died during the study period, emigrated outside the study area or were lost from follow-up are not included in the prevalence estimates. Patients diagnosed before 1 January 1982 who were still alive and resident in the study area on 31 December 2003 were included in the prevalence estimates.

All patients who were recorded (or their families) were searched out after 31 December 2003 in order to confirm if they were alive and still resident in the area. Causes and time of death were obtained from death certificates. Survival was calculated from the time of first diagnosis up to 31 December 2003, using the Kaplan–Meier method. Patients lost from follow-up were not included in the Kaplan–Meier analysis. The standardized mortality ratio (SMR) was calculated in comparison with the general population of the study area, adjusted for age and sex.

Incidence and prevalence rates were calculated as the numbers of cases per 10^5 inhabitants, and 95% confidence intervals (CIs) were estimated using the Poisson distribution. Age-adjusted rates were obtained by the direct method using the Greek population (2001 National Census). Population data were based on databases of the National Statistical Service (National Censuses 1981, 1991, and 2001).

The study was approved by the local institutional ethics committee.

Results

A total of 422 new cases was diagnosed among the population of the area studied between 1 January 1982 and 31 December 2003. Among them, 392 were recorded at the rheumatology clinics and 30 from private rheumatologists. Women represent a 20-fold higher number of patients than men, and the mean age at diagnosis was about 55 yr. The main characteristics of pSS patients are presented in Table 2. The majority of them experienced dry eyes and dry mouth complaints, which were confirmed by appropriate tests, while systemic manifestations were found less frequently. All patients fulfilled at least four out of six classification criteria, 369 (87%) satisfied five criteria, and 120 (28%) fulfilled all six criteria.

Figure 1 shows the incidence of the disease during the study period, by sex and age groups. The incidence rates were higher in the age group 46–55 for men and in the age group 56–65 for women. The age-adjusted mean annual incidence rate for the adult population was 5.3 (95% CI 4.6–6.3) cases per 10^5 inhabitants (0.5 for men and 10.1 for women).

The peak of age-specific prevalence was in the age group 66–75 for both sexes. The age-adjusted prevalence rate for the adult population was 92.8 (95% CI 83.8–102.5) cases per 10^5 inhabitants (8.4 for men and 177.4 for women).

The evolution of pSS incidence is presented in Table 3. There was a slight decrease in the mean annual incidence rates during

TABLE 1. Revised classification criteria for pSS [19]

Item	Signs and symptoms
I	Ocular symptoms: a positive response to at least one of the following questions: 1. Have you had daily, persistent, troublesome dry eyes for more than 3 months? 2. Do you have a recurrent sensation of sand or gravel in the eyes? 3. Do you use tear substitutes more than 3 times a day?
II	Oral symptoms: a positive response to at least one of the following questions: 1. Have you had a daily feeling of dry mouth for more than 3 months? 2. Have you had recurrently or persistently swollen salivary glands as an adult? 3. Do you frequently drink liquids to aid in swallowing dry food?
III	Ocular signs defined as a positive result for at least one of the following two tests: 1. Schirmer's I test, performed without anaesthesia ($\leq$5 mm in 5 min) 2. Rose Bengal score or other ocular dye score ($\geq$4 according to van Bijsterveld's scoring system)
IV	Histopathology: In minor salivary glands showing focal lymphocytic sialoadenitis, with a focus score $\geq$1 per 4 mm^2 of glandular tissue
V	Salivary gland involvement defined as a positive result for at least one of the following diagnostic tests: 1. Unstimulated whole salivary flow ($\leq$1.5 ml in 15 min) 2. Parotid sialography showing the presence of diffuse sialectasias without evidence of obstruction in the major ducts 3. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer
VI	Autoantibodies: presence in the serum of the following autoantibodies: 1. Antibodies to Ro(SSA) or La(SSB) antigens, or both

The presence of any four of the six items is indicative of pSS, as long as either item IV or VI is positive, or the presence of any three of the four objective criteria items (III, IV, V, VI).

the later years of the study period. The trend was decreasing at a statistically significant level (χ^2 test) only for men.

Sixteen of 422 incident patients (3.8%) were lost from follow-up. Forty-seven deaths were recorded in this incidence cohort during the study period. The total number of patient-years at risk was 4423 and the median observation time was 11 yr. SMR in comparison with the general population of the study area was 1.02 (95% CI 0.4–2.0). The 5-yr survival rate for the total cohort of pSS patients was 96.6% (94.4–98.8) and the 10-yr survival rate 92.8% (91.1–94.5). The main causes of death were cardiovascular diseases and cancer. Three deaths were related to malignant lymphoma.

TABLE 2. Characteristics of pSS patients diagnosed during the period 1982–2003 in north-west Greece

Total number of patients	422
Women/men	402/20
Age at diagnosis (yr): mean (S.D.) [range]	55.4 (12.5) [18–81]
Positive response of ocular symptoms: *n* (%)	422 (100)
Schirmer's I test	402 (95.2)
Rose bengal test	420 (99.5)
Both tests	400 (94.8)
Positive response of oral symptoms: *n* (%)	397 (94.0)
Salivary flow rate	369 (87.4)
Presence of parotid gland enlargement: *n* (%)	110 (26.0)
Systemic manifestations	
Arthralgias/arthritis: *n* (%)	165 (39.0)
Raynaud's phenomenon: *n* (%)	146 (34.6)
Lymphadenopathy: *n* (%)	28 (6.6)
Purpura: *n* (%)	20 (4.7)
Interstitial lung disease: *n* (%)	11 (2.6)
Immunological profile	
IgM rheumatoid factor: *n* (%)	136 (32.2)
Antinuclear antibodies: *n* (%)	397 (94.0)
Ro(SSA):[a] *n* (%)	203 (50.5)
La(SSB):[a] *n* (%)	160 (40.0)
Cryoglobulins:[b] *n* (%)	107 (28.0)
Histopathology of minor salivary gland: *n* (%)	417 (98.8)

[a]Ro(SSA) antibodies were tested in 402 patients and La(SSB) antibodies were tested in 400 patients.
[b]Cryoglobulins were tested in 381 patients.

Discussion

Only a few epidemiological studies of pSS have been published suggesting wide variation in disease prevalence, although this is considered to be one of the most common autoimmune diseases. The prevalence estimates for pSS have varied between about 0.02% and 6% [4, 8–11, 14–16]. It is difficult to interpret the differences observed because of important methodological differences among studies. Some of these studies focus on specific age groups with high prevalence of the disease. The classification criteria used differs among studies [17–23]. Another important methodological difference concerns the methods of case ascertainment. Studies based on the examination of a sample of the general population give a several-fold higher prevalence of the disease than studies based on physician-diagnosed cases. Table 4 summarizes the prevalence and incidence rates estimated and the criteria applied in studies carried out in the general population.

Our study estimates the prevalence and incidence of the disease in the general adult population of a defined area. The estimated prevalence rate was about 0.09%. Studies carried out in different populations, based on the examination of a sample, give prevalence estimates between 0.3 and 0.6% [4, 8–10]. However, a study based on physician-diagnosed and -treated cases in the general population of Japan gave an estimated prevalence rate of about 0.02% [11]. Only two studies of the incidence of the disease have been published, one in a defined area of the USA and another in a defined area of Slovenia. Both of them were based on physician-diagnosed cases [12, 13]. The estimated annual incidence rate was about 0.004% in both of these studies, and about 0.005% in our study. As a consequence, our study suggests an occurrence of the disease slightly higher than other studies based on physician-diagnosed cases, and significantly lower prevalence rates than studies based on the examination of a sample of the general population. On the other hand, the present study is the first using the AECC criteria, and it is difficult to estimate to what extent the use of these criteria might have contributed to a lower estimated frequency of pSS. It is interesting to note that studies of the epidemiology of other autoimmune rheumatic diseases carried out by our group in the same area of north-west Greece suggest a relatively low frequency of these diseases in our

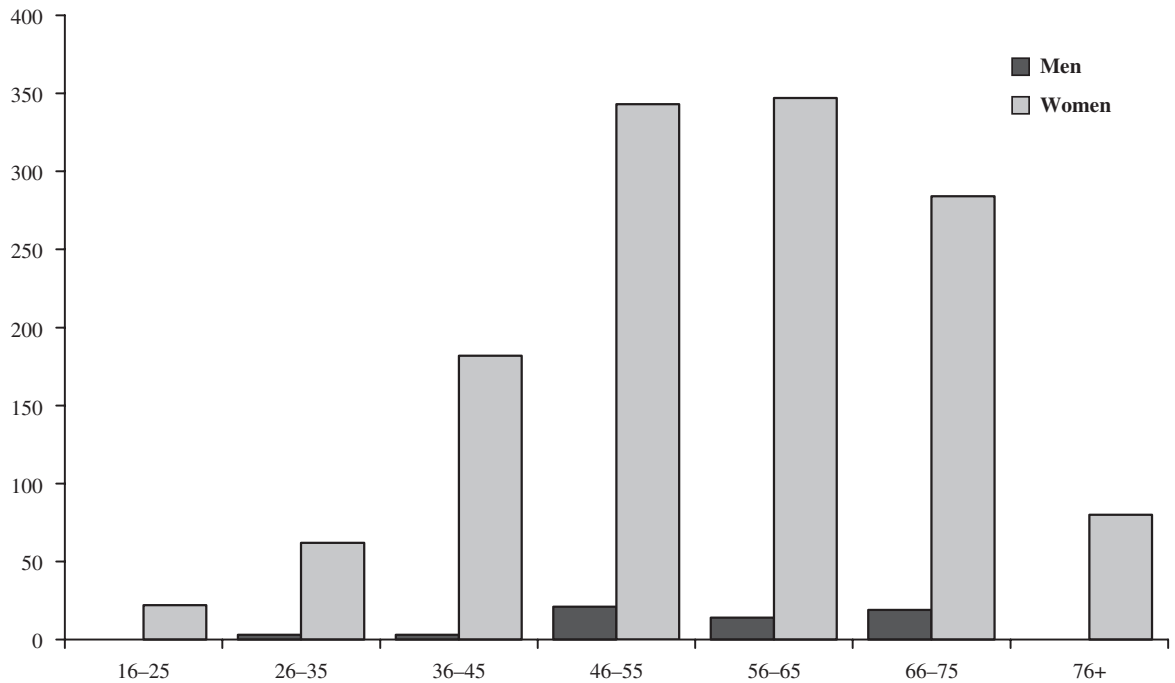

FIG. 1. Age- and sex-specific incidence rates of pSS in north-west Greece (cases per 10^5 inhabitants for the period 1982–2003).

Table 3. New cases of pSS during the period 1982–2003

	1982–1987	1988–1993	1994–1998	1999–2003	*P*
Males	0.8 (0.2–1.4)	0.6 (0.1–1.1)	0.3 (0.1–0.5)	0.2 (0.1–0.4)	0.02
Females	12.1 (9.9–14.3)	11.1 (9.0–11.2)	8.1 (6.1–10.1)	10.3 (8.2–12.4)	0.37
Total	6.6 (5.7–7.5)	6.4 (5.5–7.3)	4.2 (3.5–4.9)	5.3 (4.5–6.1)	0.29

Data are mean annual incidence rates per 10^5 inhabitants and 95% CIs.

Table 4. Prevalence and incidence rates (and 95% CIs) of pSS in studies carried out in adult general populations

Study	Population or sample size	Study design	Criteria applied	Country	Prevalence (per 100)	Incidence (per 100)
Thomas *et al.*, 1998 [4]	1000 (sample)	Sample survey	European [17]	UK	3.3 (2.2–4.4)	
Tomsic *et al.*, 1999 [8]	889 (sample)	Sample survey	European [19]	Slovenia	0.6 (0.1–2.2)	
Dafni *et al.*, 1997 [9] (female population)	837 women (total community population)	Sample survey	European [17]	Greece	0.6 (0.2–1.4)	
Zhang *et al.*, 1995 [10]	2066 (total community population)	Sample survey	San Diego [20]	China	0.3	
			Copenhagen [22]		0.8	
Miyasaka *et al.*, 1995 [11]	~120 000 000 (total Japanese population)	Population-based	Japanese [21]	Japan	0.02 (0.01–0.03)	
Pillemer *et al.*, 2001 [12]	(total population of Olmsted County, Minnesota)	Population-based		USA		0.004 (0.003–0.005)
Plesivcnik *et al.*, 2004 [13]	~600 000 (total population of Ljubljana region)	Referral centre	European [17–19]	Slovenia		0.004 (0.001–0.01)
Alamanos *et al.* (present study)	~500 000 (total population of north-west Greece)	Population-based	American–European [24]	Greece	0.09 (0.08–0.10)	0.005 (0.004–0.006)

area [25–29]. It is possible that environmental factors, such as dietary or climatological factors, could be related to the lower frequency observed.

In the present study we used several sources for case ascertainment, in the framework of a systematic recording system, in order to reduce a potential underestimation of pSS cases and avoid bias. The same recording system was used for the study of other autoimmune rheumatic diseases [25–29]. The establishment of population-based registries could be considered as one of the most appropriate ways to study the descriptive epidemiology of many autoimmune rheumatic diseases. However, it is possible that a number of pSS patients could escape the recording system. This could be true mainly for milder cases of the disease. A number of pSS cases might be diagnosed and treated by other physicians, such as dentists and ophthalmologists. Other patients could remain undiagnosed, mainly in rural areas, where health services are less developed than in urban areas. Misclassification of some cases could also be a source of underestimation.

It is important to note that access to the rheumatology clinics of the area is relatively easy for all inhabitants of the area studied, and private rheumatologists are practising in four of the six districts of the area. Patients initially diagnosed by other physicians are usually also referred to a rheumatologist. As a consequence, we can say that only a few mild pSS cases firstly diagnosed by other physicians escape our recording system. The differences observed between studies based on physician-diagnosed cases and studies based on the examination of a population sample suggest the existence of a large number of milder undiagnosed cases in the general population. On the other hand, studies based on the examination of a population sample may overestimate the prevalence of the disease because of their low response rates, possibly related to selection bias [4].

The sex ratio of incidence and prevalence cases was about 20:1. This female predominance is found in all studies, and in some studies all pSS patients were women. The peak of incidence was found in the age group 45–54 for men and 55–64 for women, while the peak of prevalence was in the elderly. This is consistent with findings of other studies [4, 8–14].

In this study we did not find a significantly increased mortality rate among pSS patients in comparison with the general population. It is possible that patients lost from follow-up represent an increased percentage of death. However, these cases represent a small percentage of all incident cases (3.7%) and cannot be the source of significant bias for the estimated mortality. Our data are consistent with the findings of other studies suggesting increased mortality only among pSS patients with adverse predictors, or in patients with secondary SS. Malignant lymphoma was the cause of death for three patients, representing one-third of cancer mortality in our cohort. It is possible that a number of deaths recorded as 'deaths for unknown reasons' represent additional cases of lymphomas. This finding is also consistent with other studies suggesting that the increased number of deaths in patients with pSS is attributable to lymphoma [30–35].

A slight decrease in pSS occurrence was observed during the study period. There are no data on time trends of pSS in the literature. In this study we do not expect that the slightly decreasing incidence of pSS with time could be related to incomplete ascertainment during the later years. It is important to state that epidemiological studies based on the same recording system indicate an increase or stability in the incidence of other autoimmune rheumatic diseases with time in the same study area [25–29].

In conclusion, the estimated incidence and prevalence of pSS in this study was slightly higher in comparison with data presented by other studies based on physician-diagnosed cases. The prevalence was significantly lower when compared with the findings of studies based on the examination of a sample of the general population. The incidence of the disease is particularly low among men. Mortality rates do not differ significantly between pSS patients and the general population. The occurrence of the disease presents a slightly decreasing, but not statistically significant, trend with time.

Rheumatology	Key messages
	• The incidence and prevalence rates of pSS were slightly higher in comparison with data presented by other studies based on physician-diagnosed cases. • Mortality rates did not differ significantly between pSS patients and the general population.

No conflict of interest has been declared by the authors.

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