DESCRIPTIVE EPIDEMIOLOGY OF MULTIPLE SCLEROSIS IN THE REPUBLIC OF SAN MARINO: a study of prevalence and incidence. Evidence for an increasing trend.

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Introduction Epidemiological studies of multiple sclerosis (MS) carried out in Europe over the last few decades, including those conducted in Italy, have shown significant increase of the disease prevalence and incidence [1]. The rather heterogeneous distribution of MS, especially in Southern Europe, has led to surmount the gradient-by-latitude theory of MS geographic distribution proposed by Kurtzke.
In the most recent studies the estimated incidence rate of MS in Italy varied from 4 to 6 per 100,000/year, with an incremental trend in several geographical areas, while the disease prevalence is on average higher than 100 per 100,000 population, with high prevalence outbreaks in Sicily and Sardinia. Previous epidemiological studies carried out in the Republic of San Marino between 1982 and 2007 [2, 3] showed that this is a high prevalence area for MS. In particular, Granieri et al. reported a prevalence rate of 166.7 per 100,000 (95% CI 123.7-220.0), and an incidence rate of 7.9 per 100,000/year (95% CI 5.3-11.1) in the period 1990 to 2005. This study aimed to update incidence and prevalence of MS in the Republic of San Marino.

Methods The Republic of San Marino is a little state in Southern Europe located within the northern Italian peninsula, completely surrounded by the Italian territory, i.e., Emilia-Romagna and Marche regions. San Marino is one of the smallest nations in the world, with a territorial extension of 61.2 km^2 and a population of 32,876 inhabitants, 16,176 men and 16,700 women as of 31 August 2015. The population is almost exclusively composed by natives in San Marino (85%) and Italians. The public health system allows a wide availability of data, from both paper and computerized administrative records. The main sources for case ascertainment were represented by medical records of the State Hospital Neurological Unit and administrative data based on hospitalization discharge codes (ICD9-CM 340). Only subjects with a definition of definite or probable MS according to Poser's criteria were included in the study. The present work is a community-based intensive prevalence and incidence survey, by adopting a complete enumeration approach.

INCIDENCE In the period 1 January 2005 to 31 December 2014, 24 patients were identified (5 men and 19 women) living in the Republic of San Marino, who had presented with symptoms later diagnosed as definite or probable MS. In the same period, the general population increased from 29,999 to 32,789 inhabitants, with a mean of 31,269 (15,343 men and 15,926 women). The annual crude incidence rate was 7.7 per 100,000 (95% CI 4.9-11.4), 3.3 (95% CI 1.1-7.6) for men and 11.9 (95% CI 7.2-18.6) for women, with a statistically significant difference between genders ($p<0.01$). The mean age (SD) of onset was 33.2 (10.8) years for the total population, 30.8 (11.0) years for men and 34.0 (10.7) for women. The mean (SD) age at onset was 30.5 (9.0) years in the relapsing-remitting form and 41.6 (12.0) years in the primary-progressive ($p<0.05$). The mean (SD) time period between the clinical onset and diagnosis for the patients with onset between 2005 and 2014 was 14.3 (23) months.
PREVALENCE On prevalence day 31 December 2014, 67 patients (19 men and 48 women) with definite or probable MS resided in San Marino, with a total population of 32,789 inhabitants (16,133 men and 16,656 women). The estimated total crude prevalence was 204.3 per 100,000 (95% CI 158.4-259.5), 117.8 (95% CI 70.9-183.7) for men and 288.2 (95% CI 212.4-383.3) for women, ($p=0.02$).

Conclusions As compared to those obtained from other areas in previous years, these higher estimates could be ascribed to the small size of the study population (wide 95% CI) and to more accurate case ascertainment. On the other hand, quite high prevalence and incidence were observed in studies carried out in neighbouring areas such as in the province of Ferrara [1] benefitting from multiple ascertainments of MS over a long time period.
Epidemiological descriptive studies of MS conducted in the Republic of San Marino over the past 35 years confirm this a high-risk area for the disease. Improvement of diagnostic facilities and awareness for the disease both among health operators and in the general population may account for such trends. However, the literature on incidence studies emphasizes the action of differently distributed exogenous, infectious, and/or lifestyle factors on the fluctuations of disease incidence over a relatively short time span.

Results

Incidence

Temporal trend of mean annual MS incidence (per 100,000) and 95%CI, in the Republic of San Marino, 1990-2014 [2,3]

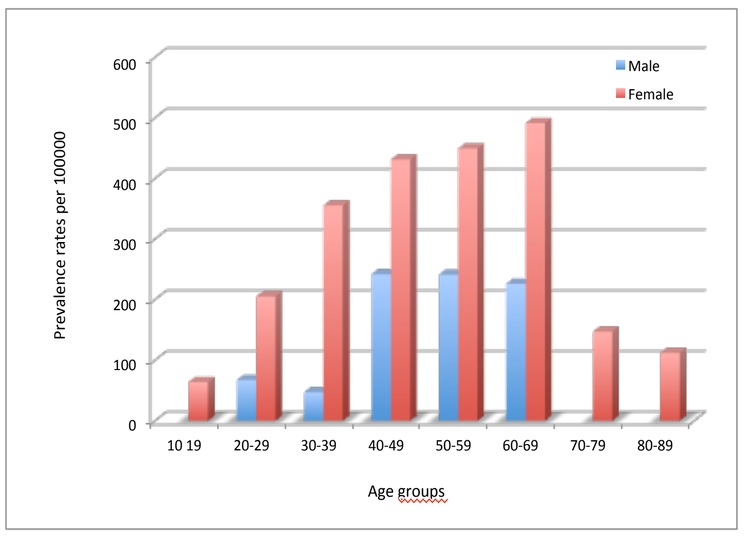
Time	Rate	95% CI
1990-1994	11	5.9-18.9
1995-1999	6.4	2.8-12.6
2000-2004	6.4	3.2-11.4
2005-2009	**9.2**	**5.0-15.5**
2010-2014	**6.2**	**2.3-11.4**

Clinical onset of MS incidence in the period 2005-14 in the Republic of San Marino

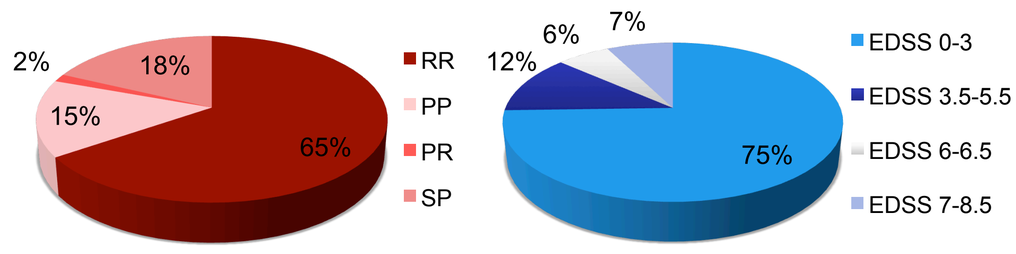
Clinical Onset	% of total
Plurisymptomatic	**20.8**
Brainstem	12.5
Sensory	20.8
Visual	**29.2**
Cerebral or Mental	4.2
Other (epileptic seizures, headache)	12.5

Prevalence

Crude age- and sex-specific MS prevalence (per 100,000) in the Republic of San Marino, on prevalence day 31 December 2014



MS distribution of prevalence cases by disease course and EDSS in the Republic of San Marino, on prevalence day 31 December 2014



Acknowledgements *This work has been supported by Research Program Regione Emilia Romagna-University (Innovative Research), entitled "Regional Network for Implementing a Biological Bank to Identify Biological Markers of Disease Activity Related to Clinical Variables in Multiple Sclerosis".*

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