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COHORT STUDIES

Incidence of cancer in a cohort of patients with primary Sjögren syndrome in Argentina

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Abstract

Primary Sjögren syndrome (pSS) is usually a mild disease, but serious complications such as non-Hodgkin lymphoma—and hypothetically other malignancies—may develop. The aim of this study was to evaluate both overall and specific incidence of cancer in a cohort of patients with pSS compared to the expected incidence in general population of Argentina. Retrospective analytic study of pSS patients fulfilling American-European Consensus Group (AECG) criteria, followed from the time of their diagnosis until the end of the study, death, loss of follow- up, or being given a diagnosis of cancer. Cancer incidence for the general population was obtained from *GLOBOCAN 2018,* and demographic information was obtained from the national institute for statistics and census. Age- and sex-specific Standardized Incidence Ratio (SIR) were then calculated. One hundred fifty-seven patients, with a mean age of 57.8 years (SD 18.3), were included. Mean patient follow-up duration was 7.37 years (SD 4.2), contributing to a total of 1158 patient/years. Fifteen patients developed a malignancy during follow-up. Cancer incidence for pSS patients was compared with the general population's incidence through SIRs. Female patient's SIRs for overall cancer was 4.17 (95% CI 2.30–6.87), non-Hodgkin lymphoma 41.40 (95% CI 10.12–102.1), multiple myeloma 41.49 (95% CI 1.14–167.28), tongue cancer 44.4 (95% CI 1.23–177.31), uterus cancer 8.39 (95% CI 0.19–40.73), lung cancer 4.51 (95% CI 0.1–22.16), and breast cancer 3.76 (95% CI 1.04–9.45). An increased overall cancer risk, and particularly for non-Hodgkin lymphoma, multiple myeloma, breast cancer and tongue cancer was observed in female pSS patients compared to control group.

Keywords Sjogren's syndrome [D012859] · Hematologic neoplasms [D019337] · Lymphoma · Non-Hodgkin [D008228] · Neoplasms [D009369]

Introduction

Sjögren syndrome is a chronic systemic autoimmune disease characterized by epithelitis and lymphocytic infiltration of glands, accompanied by polyclonal or oligoclonal B cell activation and autoantibodies' production [1]. It can present as an entity by itself, called primary Sjögren syndrome (pSS), or in addition to another autoimmune disease, known as secondary Sjögren syndrome.

Primary Sjögren syndrome is a relatively common disease. Its prevalence and incidence vary throughout the literature depending on the diagnostic criteria used. The disease's incidence ranges between 3.9 and 5.3 cases per 100.000 patients/year, and prevalence is estimated between 0.2 and 2.7% [2]. It has a female to male ratio of 9:1 and a bimodal age distribution, with a first peak in the 20s and a second peak in the mid-50s [3].

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Symptoms are generally mild, eye and mouth dryness being the primary complaints. Exocrine glands are the primary affected tissue in Sjögren syndrome, but almost any organ can be involved. Consequently, Sjögren syndrome can show a broad clinical spectrum and a variety of serious complications such as tubulointerstitial nephritis, interstitial lung disease, neuropathy, and non-Hodgkin lymphoma (NHL) [4]. The latter is the most severe associated affection, and MALT lymphoma the most prevalent subtype. It is believed to be caused by the persistent B lymphocyte activation due to a high level of circulating BLyS [5], and persistent mucosal inflammation [6] secondary to the loss of the protective effect of secretions such as saliva. Moreover, recent publications suggest that there is an augmented risk for all types of cancer, and there is debate as to the existence of increased risk for non-hematological and hematological malignancies different from NHL [7]. Finally, geographical differences affect the disease's phenotype [6, 8, 9], and Latin-American population has never before been studied regarding this aspect.

The objective of this study was to evaluate the incidence of all types of cancer in a cohort of pSS patients in Argentina and compare it with the expected incidence for the general population.

Patients and methods

Patients

A retrospective analytical study was performed in a large teaching hospital that functions as a Health Management Organization (HMO) and receives 2,800,000 consultations/year. The electronic medical records of all patients who complained of sicca symptoms or presented positive results for Anti-Ro (Ss-A) or Anti-La (Ss-B) on ELISA between 01/01/2000 and 12/31/2015 were analyzed. All patients fulfilling 2012 American-European Consensus Group (AECG) criteria [10] for pSS were included, and those who presented alternative causes for sicca symptoms or secondary Sjögren syndrome, defined as the occurrence of Sjögren syndrome in presence of another underlying rheumatic disease, were excluded. Patients were followed from the time of their diagnosis until the end of study (05/31/2017), death, loss of follow-up, or when a diagnosis of cancer was given.

Demographic, clinical, laboratory, and histopathologic information available on patients' electronic medical records was registered and analyzed. Malignant tumors were diagnosed according to histopathologic results and classified under the International Classification of Diseases (ICD 10) criteria.

All procedures were in accordance with the 1964 Helsinki Declaration, and with the ethical standards of the institutional research board (Approval IRB00010193, protocol number #5141, 07/27/2019, *Comité de Ética de Protocolos de Investigación del Hospital Italiano de Buenos Aires*). This being a retrospective study, patients could not sign an ad hoc informed consent. Instead, in accordance with IRB's guidelines, patients had signed a generic informed consent authorizing the use of clinical data in an anonymized way for such studies on the first visit to the hospital.

Variables

Registered clinical variables were sex, age, age at diagnosis, and follow-up time. In addition, presence of dry eyes or dry mouth, salivary glandular enlargement, Raynaud phenomenon, neuropathy, vasculitis, arthralgia, and arthritis were registered as dichotomous variables. Included laboratory variables were hemoglobin level (g/dL, spectrophotometry, Beckman Coulter®, USA), white cell count (cells/mL, volumetric impedance, Beckman Coulter®, USA), platelets count (cells/mL, volumetric impedance, Beckman Coulter®, USA), Erythrocyte Sedimentation Rate (ESR) (mm/h, capillary photometry, Test1®, Alifax®, Italy), Anti-Nuclear Antibodies (ANA) titer (Indirect Immunofluorescence on HEP-2 cells, Kallestad HEP-2®, Bio-Rad®, USA), anti-Ro (SS-A) and/or anti-La (SS-B) (IU/mL, ELISA, ORG 660 and ORG 509, Orgentec®, Germany), rheumatoid factor titer (IU/mL, quantitative immunoturbidimetry, Optilite® rheumatoid factor kit, The Binding Site®, USA), Anti-Citrullinated Peptide Antibodies (ACPA) (IU/mL, quimioluminiscence, Quanta Flash CCP3®, Inova Diagnostics®, USA), complement fractions C3 and C4 level (mg/dL, immunonephelometry, Immage 800®, Beckman Coulter®, USA), cryoglobulinaemia (%, immunofixation, Hydrasys®, Sebia®, France), gammaglobulinemia and monoclonal immunoglobulinaemia (mg/dL, immunonephelometry, Immage 800®, Beckman Coulter®, USA).

Normal laboratory values were defined according to our laboratory reference values, which is certified by the *Collage of American Pathologists*, and in conformance with international consensus. Anemia was defined by a hemoglobin value under 11.5 g/dL, leukopenia with a white cell count under 4000 cells/mL, and thrombocytopenia under 150,000 platelets/mL. ANA was considered positive with a titer over 1/80, positive rheumatoid factor when value was over 14 IU/mL, ACPA when value was over 20, anti-Ro and anti-La when value over 25 IU/mL, elevated Erythrocyte sedimentation rate when value over 20 mm/h, low complement when C3 fraction was under 83 mg/dL or C4 under 10 mg/dL, and hypergammaglobulinemia when gammaglobulinaemia was over 1.47 g/dL.

Statistical analysis

Cancer incidence and 95% confidence interval (95% CI), were calculated and stratified by sex and age in groups of 20–39, 40–59, and over 60 years, both for the general population and patients with pSS. Cancer incidence, both for expected cancer rate in general population and for our cohort, was calculated using the number of new cases of cancer in the numerator and the total number of patient-years in the denominator, and were expressed as per 100,000 person years.

Data of cancer in the general population were obtained from *GLOBOCAN 2018´*s [11] estimations of new cases in 2018 in Argentina, while demographical information was obtained from the projections for 2018 made by the National Institute for Statistics and Census (INDEC) [12]. Regarding this cohort, all patients diagnosed with pSS contributed to the total time at risk (measured in patient-years) until cancer diagnosis, loss of follow up, or end of the study.

Standardized Incidence Ratios (SIR), also stratified by sex and age, were calculated as the ratio of the observed number of cases of cancer in pSS patients to the expected number of cases in the general population. CI95 was then calculated for each SIR. Tongue cancer is not a category by itself in GLOBOCAN, so the SIR of tongue cancer in the cohort studied was compared with the SIR for "lip, oral cavity" that encompassed the categories C01–C02 that describe tongue cancer.

Data were analyzed using STATA v.12 (StataCorp, 4905 Lakeway Drive, College Station, Texas 77845 USA).

Results

One hundred fifty-seven patients with Primary SS were included, with a female-to-male ratio of 9:1 and a mean age of 57.8 (SD 18.3). Mean follow-up time was 7.37 years (SD 4.2), contributing to a cumulative follow-up of 1158 patient-years. Table 1 shows patients' characteristics and laboratory data.

Fifteen patients developed a malignancy during their follow-up: three non- Hodgkin lymphomas (two MALT lymphomas of the parotid and one disseminated lymphoma), one multiple myeloma, four skin (non-melanoma) cancer, and seven solid organ cancer (four breast, one lung, one uterus,

Table 1 pSS patient characteristics

	pSS patients ($n=157$)
Females, *n* (%)	150 (95.5)
Mean age, years (SD)	57.8 (18.3)
Mean age at diagnosis, years (SD)	49.4 (19)
Dry eyes complaint, *n* (%)	152 (96.8)
Dry mouth complaint, *n* (%)	139 (89.1)
Salivary gland enlargement, *n* (%)	26 (16.6)
Arthralgia, *n* (%)	106 (67.5)
Arthritis, *n* (%)	14 (9)
Positive ANA, *n* (%)	153 (96.8)
Positive Anti Ro, *n* (%)	149 (94.9)
Positive Anti La, *n* (%)	94 (60.3)
Positive rheumatoid factor, *n* (%)	66 (44.9)
Positive Anti CCP, *n*/*n* performed (%)	3/45 (6.7)
Low C3/C4, *n*/*n* performed (%)	30/111 (27)
Elevated Erythrocyte sedimentation rate, *n* (%)	130 (83.3)
Hypergammaglobulinemia, *n* (%)	95 (63)
Presence of Cryoglobulines, *n*/*n* performed (%)	5/50 (10)
Anemia, *n* (%)	47 (30.1)
Leukopenia, *n* (%)	51 (32.7)
Thrombocytopenia, *n* (%)	23 (14.7)
Compatible minor salivary glands biopsy, *n*/*n* performed (%)	24/32 (75)
Schirmer I test under 5 mm in 5 min, *n*/*n* performed (%)	49/68 (72)
Disease duration/follow up, years, median (IQR)	7.7 (8)
Deaths during follow up, *n* (%)	2 (1.2)

n number of patients, *SD* standard deviation, *IQR* inter quartile range, *ANA* antinuclear antibodies, *Anti CCP* antibodies anti-cyclic citrullinated peptide

one tongue). All of them were females except for a male with a non-melanoma skin cancer.

Table 2 shows the cancer incidence rates for this cohort and for the general population, both with their corresponding 95% CI and expressed over 100,000 patient-years, and the comparison of those with the SIR and its 95% CI. Male patients were excluded from the table since there were only seven patients, and presented just 1 non-melanoma skin cancer. Females between 20 and 39 were also excluded from the table because they presented no cancer, although they were taken in account for the analysis under the category *female combined*.

Compared with the general population, female patients with pSS presented a fourfold increase of overall cancer risk (SIR 4.17, 95% CI 2.30–6.87), a 41-fold increased risk for non-Hodgkin lymphoma (SIR 41.40, 95% CI 10.12–102.1), a 41-fold increased risk for multiple myeloma (SIR 41.49, 95% CI 1.14–167.28), a 44-fold increased risk for tongue cancer (SIR 44.4, 95% CI 1.23–177.31), and a threefold increased risk for breast cancer (SIR 3.76, 95% CI 1.04–9.45).

Two patients died during follow-up: the patient with multiple myeloma and the patient with tongue cancer. All the patients with NHL completed chemotherapy treatment and are in remission of the disease.

Discussion

The association between pSS and increased risk for NHL was first described by Talal et al. in 1963 [13], and since then, multiple publications confirmed it. NHL is

Table 2 Neoplasia incidence rate in this pSS cohort compared with the general population

Neoplasia	Incidence in pSS cohort per 100,000 person/years (95% CI)	Incidence in general population per 100,000 person/years (95% CI)*	SIR (95% CI)
Female 40–59 year ($n=52$)			
Non Hodgkin lymphomas	244.94 (61.24–1356.98)	7.34 (6.61–8.13)	**33.35 (9.26–166.91)**
Multiple myeloma	0	1.90 (1.54–2.32)	–
Skin (non melanoma)	0	No data	No data
Breast	244.94 (61.24–1356.98)	158.02 (154.55–161.54)	1.55 (0.40–8.40)
Lung	244.94 (61.24–1356.98)	20.87 (19.62–22.18)	**11.74 (3.12–61.18)**
Uterus	0	14.67 (13.62–15.77)	–
Tongue	0	2.36 (1.95–2.83)	–
Overall	734.83 (151.86–2130.99)	398.55 (393.05–404.11)	1.84 (0.39–5.27)
Female over 60 year ($n=80$)			
Non Hodgkin lymphomas	320.22 (38.43–1151.17)	24.13 (22.62–25.73)	**13.27 (1.70–44.74)**
Multiple myeloma	160.11 (3.20–888.60)	9.67 (8.72–10.70)	16.55 (0.37–83.09)
Skin (non melanoma)	480.32 (99.27–1397.74)	No data	No data
Breast	480.32 (99.27–1397.74)	307.96 (302.49–313.51)	1.56 (0.33–4.46)
Lung	0	87.45 (84.55–90.43)	–
Uterus	160.11 (3.20–888.60)	42.08 (40.07–44.16)	3.81 (0.08–20.12)
Tongue	160.11 (3.20–888.60)	8.04 (7.17–8.98)	19.92 (0.45–98.95)
Overall	1761.18 (882.19–3128.50)	1068.42 (1058.25–1078.66)	1.65 (0.83–2.90)
Female combined ($n=150$)			
Non Hodgkin lymphomas	267.91 (55.37–781.40)	6.47 (5.47–7.65)	**41.40 (10.12–102.1)**
Multiple myeloma	89.30 (1.79–495.63)	2.15 (1.56–2.96)	**41.49 (1.14–167.28)**
Skin (non melanoma)	267.91 (55.37–781.40)	No data	no data
Breast	357.21 (97.34–911.78)	95.09 (93.73–96.48)	**3.76 (1.04–9.45)**
Lung	89.30 (1.79–495.63)	19.78 (17.49–22.36)	4.51 (0.10–22.16)
Uterus	89.30 (1.79–495.63)	10.64 (9.30–12.17)	8.39 (0.19–40.73)
Tongue	89.30 (1.79–495.63)	2.01 (1.45–2.80)	**44.40 (1.23–177.31)**
Overall	299.49 (295.32–303.73)	1250.23 (680.48–2087.0)	**4.17 (2.30–6.87)**

Data highlighted in bold corresponds to the items whose confidence interval does not include the "1"

SIR standardized incidence ratio, *CI* confidence interval

*Calculated using data from *GLOBOCAN 2018* (Global Cancer Observatory, International Agency for Research on Cancer, World Health Organization Cancer Today. http://gco.iarc.fr/today/home. Accessed 27 Jul 2019) and Argentinean demographic information from *INDEC* (Instituto Nacional de Estadísticas y Censos Republica Argentina Proyecciones Nacionales. https://www.indec.gob.ar/indec/web/Nivel4-Tema-2-24-84. Accessed 27 July 2019)

considered to be the most severe complication of pSS, and it is associated with an excess mortality of 2.53 deaths/1000 person/year [14].

A significantly increased incidence of NHL was observed in this cohort compared to the general population, with an incidence rate of 267.91 cases every 100,000 patient-years (95% CI 55.37–781.40). These results are in conformance with a recent multi-centric and nationwide study of patients with pSS in Argentina which described an incidence of lymphoma of 540 cases per 100,000 patient-years [15]. Additionally, and in concordance with the work of Voulgarelis et al. [16], salivary glands were the most common initial site of degeneration into NHL in our cohort.

Several publications had suggested that NHL is not the only malignancy associated with pSS. Zhang et al. described a significant increase for all type of cancer, and both non-hematological and hematological (NHL, Multiple Myeloma) malignancies [7]. Tomi et al. found an increased risk for multiple myeloma among SS patients, especially those who presented a higher disease activity and presence of monoclonal gammapathy [17]. Additionally, Yu et al. described an increased risk for nasopharynx, lung, and thyroid cancer [6], and Brito-Zerón et al. highlighted an association between SS and hematological malignancies (NHL, Hodgkin lymphoma and multiple myeloma) and solid organ malignancies such as thyroid, oral cavity, and stomach cancer [18]. Liang et al. published a meta-analysis published on 2014 that confirmed an overall increased risk for all types of cancer (SIR 1.53) and specifically for Non-Hodgkin Lymphoma (SIR 13.76) and Thyroid cancer (SIR 2.58) [8]. It is hypothesized that systemic inflammation, loss of protective secretions, and persistent tissue damage and repair are the underlying cause of the increased cancer risk [6, 7, 18].

In contrast, various authors [8, 19, 20], including the very recent review by Pego-Reigosa et al. [21], state that the increase in the overall risk of cancer is only due to the high incidence of lymphomas. Nevertheless, Giat et al. highlighted the difficulty of comparing studies of cancer in pSS due to the heterogeneity of analyzed populations resulting in the use of different diagnostic criteria and follow-up periods, and the underrepresentation of non-European population [22]. In the same line, Liang et al. highlighted the need for studies from regions other than Europe [8], since they found different cancer risk for European and Asian population.

Some limitations for this study should be mentioned: first, the small size of our sample diminishes the odds of finding an infrequent association and widens the range of the confidence intervals, and consequently, the standard error. Second, since the study was carried on a reference hospital, a bias towards more severe patients cannot be discarded. Third, due to the retrospective nature of the study, comorbidities known to be associated with cancer development such as smoking and drinking habits, physical activity, and disease activity could not be collected in all patients, and thereafter, analyzed. Fourth, male patients could not be analyzed due to the small number of male patients that presented pSS in this cohort. Finally, due to the absence of official governmental information on cancer incidence in Argentina, cancer incidence in the general population was obtained from *GLOBOCAN 2018.* Argentina's data on cancer incidence are listed by *GLOBOCAN´*s authors as *High Quality* but with an estimated population coverage of 10–50%. Nevertheless, since this study is based on Argentina´s capital city, collected data are believed to be representative of our population.

On the other hand, this study shows several strengths: it was performed in a teaching hospital that functions as a health management organization with a large pool of associates. Previous studies performed at this hospital demonstrated that the HMO's population is representative of the general population [23]. Second, since patients affiliated with the hospital's HMO can only be treated in the hospital, and cancer is a hard outcome, collected data are very reliable and under-registration is very unlikely. Third, since *GLOBOCAN 2018* did not list tongue cancer as an entity, but did it as part of the "lip, oral cavity" item, the existence of an increased risk despite this shows a stronger association. Finally, all included patients strictly fulfilled AECG criteria.

In conclusion, female patients with pSS presented an increased risk for all cancer, and particularly, for non-Hodgkin lymphoma, multiple myeloma, breast, and tongue cancer compared to the general population. Larger studies are needed to further validate these findings. Strict cancer screening and periodical monitoring for monoclonal gammapathy and risk factors for NHL [7, 24] are advised for pSS patients.

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Compliance with ethical standards

Conflict of interest Martin Brom declares that he has no conflict of interest. Sebastian Moyano declares that he has no conflict of interest. Ignacio Javier Gandino declares that he has no conflict of interest. Marina Scolnik declares that she has no conflict of interest. Enrique Roberto Soriano reports grants and personal fees from Roche, grants and personal fees from Novartis, grants and personal fees from Abbvie, grants and personal fees from Glaxo, personal fees from Pfizer, personal fees from Lilly, personal fees from Sanofi, personal fees from AMGEN, personal fees from Bristol Myers Squibb, personal fees from Genzyme, outside the submitted work. All listed authors meet the ICMJE 4 criteria for authorship and have approved the final manuscript. All co-authors take full responsibility for the integrity of the study and the final manuscript. This study has been presented in the 2018 PAN-

LAR meeting, abstract #38 (Brom M, Moyano S, Scolnik M, Gandino JI, Soriano ER (2018) Incidence of Cancer in a cohort of patients with primary Sjögren syndrome. Abstracts, 20th PANLAR Meeting. JCR J Clin Rheumatol 24:S1–S174. https://doi.org/10.1097/RHU.0000000000000802), and in the 2017 ACR meeting, abstract #1483 (Brom M, Moyano S, Scolnik M, Soriano ER (2017) Incidence of Cancer in a Cohort of Patients with Primary Sjögren Syndrome [abstract]. 2017 ACR/ARHP Annual Meeting Abstract Supplement. Arthritis Rheumatol 69:1–4481. https://doi.org/10.1002/art.40321).

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

IRB approval IRB00010193, protocol number #5141, *Comité de Ética de Protocolos de Investigación del Hospital Italiano de Buenos Aires*).

Informed consent Patients sign a general informed consent on their first visit to our institution, authorizing the use of their medical data in an anonymized way for retrospective studies.

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