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Cancer incidence in primary Sjögren's syndrome: Data from the French hospitalization database

Radjiv Goulabchand^{a,b,c}, Nicolas Malafaye^d, William Jacot^{b,e}, Philine Witkowski Durand Viel^{b,f}, Jacques Morel^{b,g,k}, Cédric Lukas^{b,g}, Pauline Rozier^{b,c}, Sylvain Lamure^{b,h}, Danièle Noel^c, Nicolas Molinari^{b,d,i}, Thibault Mura^{b,j,l}, Philippe Guilpain^{b,c,f,l,*}

^a Internal Medicine Department, CHU Nîmes, Univ Montpellier, Nîmes, France

^b University of Montpellier, Montpellier, France

^c IRMB, University of Montpellier, INSERM, Montpellier, France

^d Department of Medical Information, University Hospital of Montpellier, Montpellier, France

^e Montpellier Cancer Institute (ICM) Val d'Aurelle, 208 Avenue des Apothicaires, Parc Euromédecine, CEDEX 5, 34298 Montpellier, France

^f Department of Internal Medicine and Multi-Organic Diseases, Local Referral Center for Systemic and Autoimmune Diseases, St Eloi Hospital, 80 Avenue Augustin Fliche, 34295 Montpellier, France

^g Department of Rheumatology, Montpellier University Hospital, 371 avenue du Doyen Gaston Giraud, 34295, Montpellier, France

^h Department of Clinical Hematology, CHU Montpellier, UMR-CNRS 5535, Institut de Génétique Moléculaire de Montpellier, Montpellier, France

ⁱ IDESP, INSERM, Montpellier University, Montpellier University Hospital, Montpellier, France

^j Department of Biostatistics, Clinical Epidemiology, Public Health, and Innovation in Methodology, CHU Nîmes, University Montpellier, Nîmes, France

^k PhyMedExp, University of Montpellier, INSERM U1046, CNRS UMR 9214, Montpellier, France

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ABSTRACT

The relationship between cancer and primary Sjögren's syndrome (pSS) is uncertain. While the increased risk of hematological malignancies is well-known, data on the comparative incidence of solid neoplasms is conflicting. This study aimed to explore the associations between cancer and pSS. This nationwide population-based retrospective study from the French health insurance database (PMSI) evaluated patients hospitalized with new-onset pSS from 2011 to 2018 against age- and sex-matched hospitalized controls (1:10). The incidence of hematological malignancies and solid neoplasms was compared between the two groups. Mortality and multiple cancer incidence were also evaluated. Adjusted Hazard Ratios (aHR) calculations included confounding factors, such as low socioeconomic status. Among 25,661 hospitalized patients with pSS versus 252,543 matched patients (median follow-up of 3.96 years), we observed a higher incidence rate of lymphomas (aHR, 1.97 [95% CI, 1.59–2.43]), Waldenström macroglobulinemia (aHR, 10.8 [6.5–18.0]), and leukemia (aHR, 1.61 [1.1–2.4]). Thyroid cancer incidence was higher (aHR, 1.7 [1.1–2.8]), whereas bladder and breast cancer incidences were lower (aHR, 0.58 [0.37–0.89] and 0.60 [0.49–0.74], respectively). pSS patients with breast cancer exhibited a lower mortality rate. A limitation was that the database only encompasses hospitalized patients, and immunological and histological details are not listed. We confirmed the increased risk of hematological malignancies and thyroid cancers among patients with pSS. The lower risk of breast cancer suggests a role of hormonal factors and raises questions of the concept of immune surveillance within breast tissue. Epidemiological and translational studies are required to elucidate the relationships between pSS and cancer.

1. Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease

characterized by sicca syndrome, and is responsible for ocular and mouth dryness. It exhibits a wide spectrum of clinical manifestations, including joint, skin, lung, kidney, and (central and/or peripheral)

* Corresponding author at: Department of Internal Medicine and Clinical Immunology – St Eloi Hospital, Montpellier University, 80 Ave Augustin Fliche, Hopital St Eloi, CHU Montpellier, 34295 Montpellier, France.

E-mail address: p-guilpain@chu-montpellier.fr (P. Guilpain).

¹ Both authors contributed equally to this work.

nervous system. Pathophysiological mechanisms include B lymphocyte activation and inflammatory infiltrates in targeted organs. Interestingly, pSS can be considered as an autoimmune epithelitis, specifically involving exocrine glands with acinous structure (such as salivary and lacrimal glands [1], but also pancreatic, sebaceous, vulvovaginal glands, and mammary glands) [2]. It has a prevalence ranging from 0.22 to 1.6% [3], predominantly occurring in women around 50 years old [4], and shows an increased risk of mortality, associated with both a highly active systemic disease and cardiovascular complications, infections, and neoplasms, including hematological malignancies and solid neoplasms [5,6].

While the higher incidence and distribution of hematological malignancies (specifically non-Hodgkin's lymphoma (NHL)) are well established in pSS [5–7], the epidemiology of solid neoplasms is controversial. Some studies have reported an increased risk of solid neoplasms such as breast cancers [8,9], yet others, including meta-analyses, suggest no difference [10–13]. Thus, since previous methodological approaches were very heterogeneous (prevalence and incidence studies; several small series and some nationwide cohort studies; no large study on a European population), there is a need for clarification of the incidence of solid neoplasms in pSS, using a large cohort and integrating adjusting factors such as sociodemographic level. We aimed to evaluate the relative risk of incidence of solid neoplasms and hematological malignancies, using a nationwide approach on a population of French hospitalized pSS patients.

2. Methods

2.1. National database characteristics

We performed a historical paired exposed-unexposed cohort study by analyzing data from the French national hospital discharge database (*programme de médicalisation des systèmes d'information (PMSI)*). Studies on anonymized national health insurance database data are authorized by the National Commission of Information Technology and Liberty (CNIL) and no specific consent is needed. This database covers over 99%

of the population (65 million people), collecting all hospital stays in private and public hospitals. The available data are: age, sex, entry and discharge dates, diagnoses codes associated to the hospitalization (according to international classification of diseases (ICD-10)), and insurance scheme (general, or associated to patients with low socioeconomic status (LSS)). These data are anonymous and linkable from one year to another for a given patient, over the 10-year study period. We also collected the deaths that occurred during hospitalizations. However, information concerning immunological status (SSa or SSb antibody positivity), disease activity (EULAR (European League Against Rheumatism) Sjögren's Syndrome Disease Activity Index (ESSDAI) scores), targeted organs, or treatment, are not available. We analyzed data from a 10-year period (the maximum available time period from the database), from January 1st 2009 to December 31st 2018.

2.2. Primary Sjögren's syndrome hospitalized patients (pSS)

We included all hospitalized pSS patients with at least one ICD-10 code of SS (M350) over the study period; the entry date, corresponding to the first hospitalization with this code, was considered the "index date" (Fig. 1). Patients with a potential secondary SS (sSS, hospitalization code of another autoimmune disease such as rheumatoid arthritis, lupus, vasculitis, sarcoidosis, etc.; cf. complete list and corresponding ICD-10 codes in **Supplementary Table 1**) were excluded. In order to restrict the selection of pSS to the incident patients, we excluded patients whose first code of SS was identified in 2009 or 2010 to provide a minimum of two years of medical history for each included patient. To avoid selecting patients with acute critical and severe illnesses at the index date in both groups, we excluded patients who died within 90 days after the index date and their corresponding matched controls. Excluding these patients meant that the control group presented a disease severity more comparable to the pSS patients.

2.3. Control group of non-pSS hospitalized patients

For each pSS patient, 10 hospitalized patients were randomly

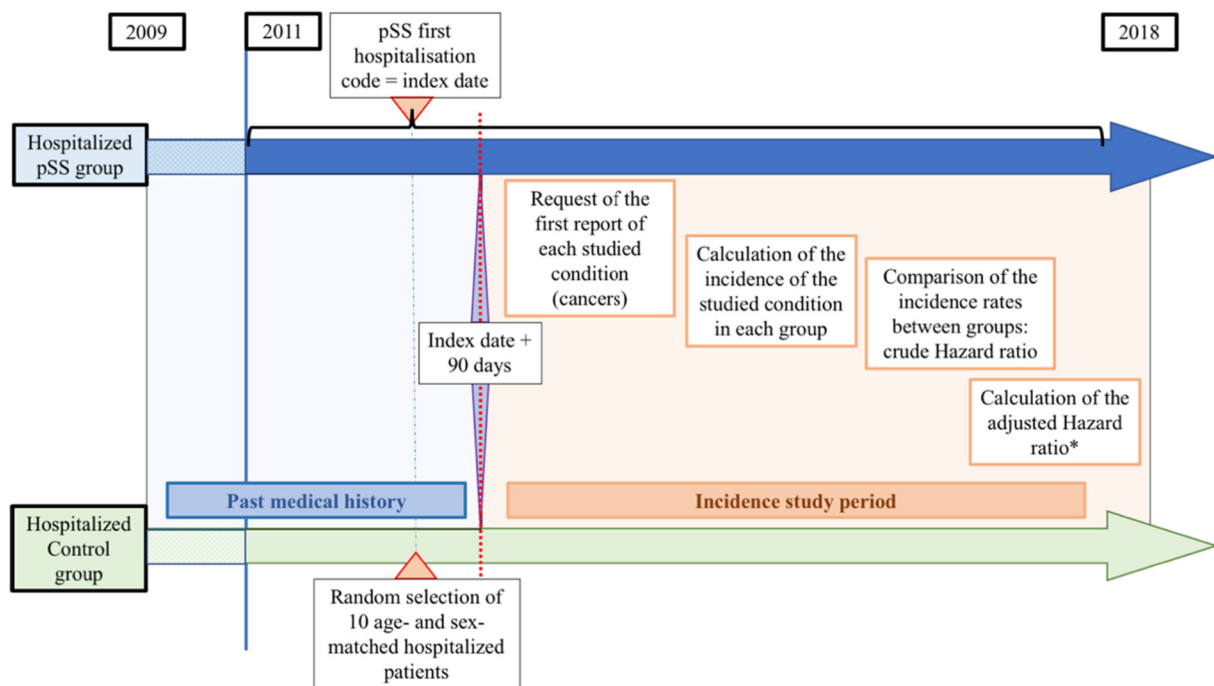


Fig. 1. Representation of the periods of study. The blue part represents the studied period of past medical history, and the orange part represents the incidence study period. (*) Adjusting factors combined previous reported occurrences of: low socioeconomic status, annual hospitalization rate, diabetes, hypertension, cardiovascular diseases, and neuropsychiatric disorders prior to index date +90 days.

selected from the database matched on age, sex, and entry date of hospitalization (+/− 31 days).

2.4. Outcomes

We collected first occurrences of cancer and hematological malignancies within this cohort from the 90th day after the index date (subjects with previous cancer in the studied localization, prior to this date, and their matched patients (pSS or control), were excluded) (Fig. 1). For each disease, we searched for the first hospitalization with a disease code related to cancer. The list of the disease codes (ICD-10) and their combinations used for the search are available in **Supplementary table 2**.

We assessed skin cancers and solid neoplasms. Due to the sex ratio of pSS, we focused on women's cancers: invasive breast, in situ breast, uterus cervix, uterus body, uterus (combining uterus cervix, uterus body, and unspecified uterus cancer), and ovary. We combined all these women's cancer and unspecified cancer of external genital organs within the group "all women's cancers".

For hematological malignancies, we combined all kinds of lymphomas (including Hodgkin lymphoma) in "lymphomas". All types of leukemias were combined into "leukemias", including B-cell chronic lymphocytic leukemia (CLL).

Mortality: we compared the incidence of death among patients of each type of cancer between groups.

Multiple cancers: we searched the database for patients exhibiting at least one solid neoplasm and one hematological malignancy, and compared the number of these patients between groups.

2.5. Adjustment factors

We searched for covariates to be used as adjustment factors. We recorded the number of hospitalizations of each patient before the index date (prior annual rate of hospitalizations). Low socioeconomic status (LSS) was defined as the presence of at least one insurance scheme among "Couverture Médicale Universelle" (CMU), Complementary CMU, or Government Health insurance "Aide Médicale d'Etat" (AME) within the same period (before date index +90 days). Socioeconomic status is an adjustment factor associated with incidence of certain cancers (positively for lung cancer [14], or negatively for breast cancer [15]). We also searched for history of hospitalization before the index date for: (i) hypertension (combining primary and secondary hypertension); (ii) diabetes (combining type 1 and type 2 diabetes, malnutrition diabetes and unspecified diabetes); (iii) obesity; (iv) cardiovascular diseases (combining ischemic heart diseases, aortic and peripheral arterial disease, strokes, aortic dissection, and hypertensive chronic kidney disease); and (v) neuropsychiatric disorders (combining anxiety, depression and dementia).

2.6. Statistical analysis

The characteristics and past medical history of each patient at the beginning of the incidence study period were described according to pSS exposure. Categorical variables were presented with their frequency and proportions, and compared between groups using Chi square or Fisher exact test. Quantitative variables were presented with median and Inter Quartile Range (IQR), and compared between groups using Mann-Whitney rank-sum test.

The incidences of cancers were calculated in each exposure group, with their 95% confidence intervals (95% CI). A survival analysis by Cox proportional hazard models, with stratification on the matched subjects, was then performed to compare cancer incidence between exposure groups. Follow-up time was calculated as the interval between the index date and the date of the first hospitalization for cancer, or until December 2018, whichever occurred first. To take into account competitive risks, follow-up of patients who died before December

2018, without cancer, were censored at the date of death [16]. We first built a crude model, then an adjusted model taking into account potential confounding factors: LSS, medical history of hospitalization for hypertension, diabetes, obesity, cardiovascular diseases and neuropsychiatric disorders.

Mortality of patients with cancer was compared between pSS and controls using Cox proportional hazard models. Follow-up time was calculated as the interval between the first reported cancer, and hospital death or until December 2018, whichever occurred first. Analyses were first adjusted for sex, age at cancer diagnosis and year of cancer diagnosis. Then, a second model was used, adjusted as above.

Statistical analyses were performed at the conventional two-tailed α level of 0.05 using Statistical Analysis Systems Enterprise Guide 7.1 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Population

Our initial search identified 48,922 patients with a hospital stay coded for SS, of whom 22,795 were excluded for suspected sSS, and 8646 were excluded for SS first recorded in 2009 or 2010. After excluding patients from both groups dying within 90 days of the index date, 25,661 hospitalized patients with suspected pSS and 252,543 matched hospitalized control patients were finally retained. Of these, 87.7% were female with a mean age of 60.0 (± 16.3) years. The flow-chart of the selection of the population is shown in Fig. 2.

The main characteristics of both groups are shown in Table 1. The median follow-up time was 3.96 years. In the pSS group, 4.77% of patients were considered to have LSS versus 3.31% in the control group ($p < 0.001$). The annual rate of hospitalization before the incidence study period was higher in the pSS group ($p < 0.001$). The incidence of death was increased in pSS patients (Table 1). Considering the fact that pSS patients were more frequently hospitalized than their matched controls, we observed a higher rate of reported hypertension, diabetes, obesity and cardiovascular diseases in the pSS group during their hospital stays. Neuropsychiatric conditions were also more frequently reported among pSS patients. The data concerning the past medical reported history of cancers, prior to the incidence study period, are shown in **Supplementary Table 3**.

3.2. Cancer incidence study

3.2.1. Women's cancers

We observed 229 incident cases of breast cancers in the female pSS group versus 2769 in the control group, with a HR of 0.80 [0.69–0.91]. After adjustments on socioeconomic status, prior annual rate of hospitalizations, cardiovascular diseases and neuropsychiatric disorders, the adjusted HR (aHR) was 0.60 [0.48–0.73] ($p < 0.001$) (Table 2). We did not observe any difference in the incidence rate of in situ breast cancers and ovary cancers. However, there was a trend towards a lower incidence of uterus cancers in the pSS group (aHR, 0.66 [0.43–1.01], $p = 0.055$).

3.2.2. Other solid neoplasms

The number of incident cases of thyroid cancers was higher in the pSS group (HR, 1.73 [1.07–2.79], $p < 0.05$). Bladder cancer incidence was lower (HR, 0.58 [0.37–0.89], $p < 0.05$) (Table 3). We observed a trend towards a lower incidence of colon cancers in the pSS group (HR, 0.80, [0.65–0.97]), that was not confirmed after adjustment. Of note, there were 4 cases of thymus cancer in the pSS group, and 8 in the control group. We did not observe any difference in skin cancer incidence.

3.2.3. Hematological malignancies

After adjustments, we observed a higher incidence of the following

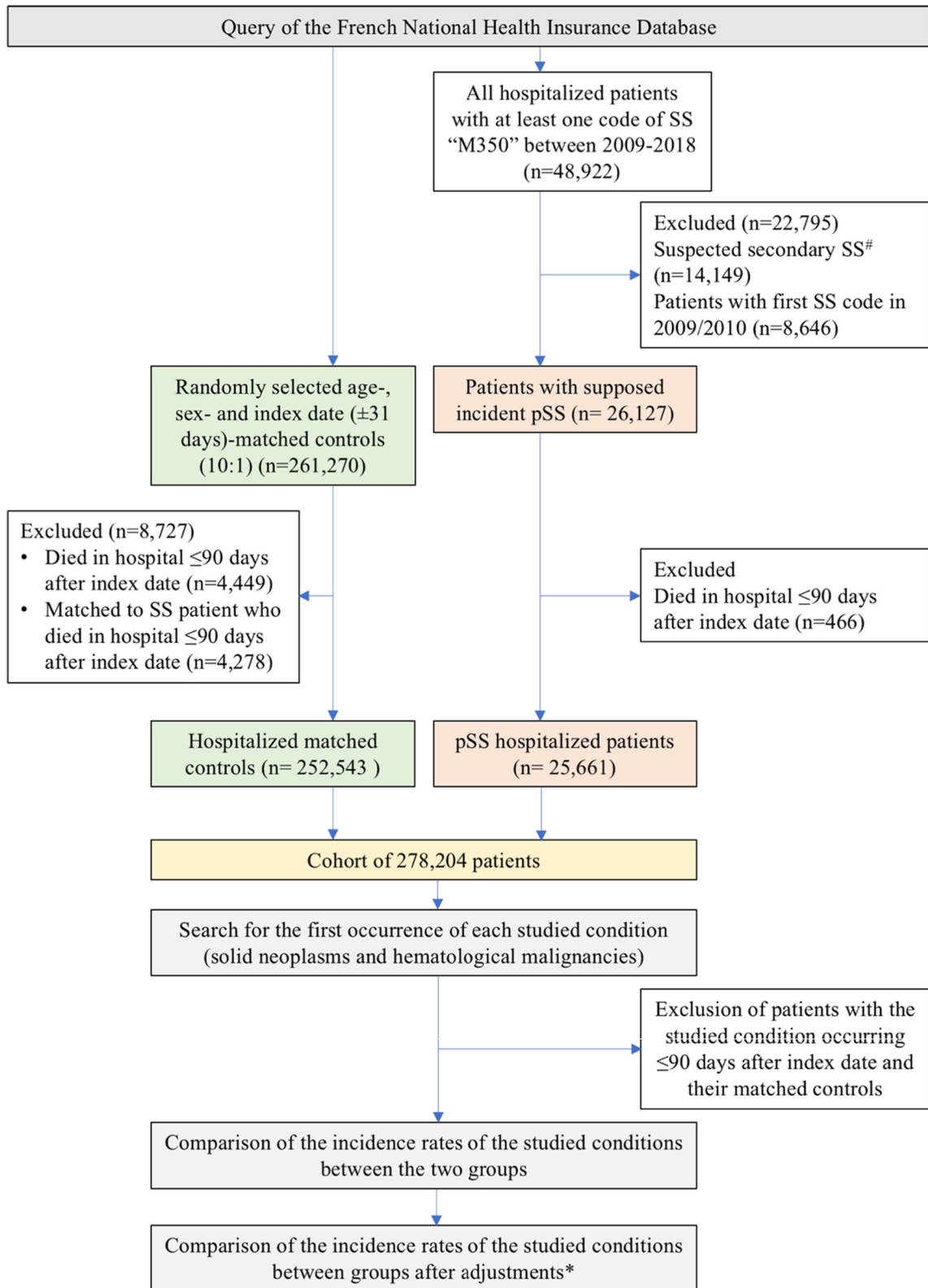


Fig. 2. Flow chart of the selection of hospitalized primary Sjögren's syndrome patients and their matched-patients from the French national hospitalization health database. Explanation on the algorithm of research of incidence of cancers and malignant blood diseases is detailed. #Presence of another code of autoimmune disease during the same study period; autoimmune diseases classifying SS as secondary are reported in Supplementary table 1. *Adjustments factors included: low socioeconomic status, annual hospitalization rate, diabetes, hypertension, cardiovascular diseases, and neuropsychiatric disorders.

Table 1
Demographical and social characteristics of hospitalized primary Sjögren's syndrome patients and their matched controls, and adjustments factors.

	Sjögren's syndrome patients (n = 25,661)	Matched controls (n = 252,543)	p value
Sex (female) (n, %)	22,489 (87.66%)	224,887 (87.65%)	0.995
Low socioeconomic status (n, %)	1224 (4.77%)	8482 (3.31%)	<0.001
Age, years (mean, SD)	60.2 (± 16.3)	60.0 (± 16.3)	0.075*
		Age ranks, years (n, %)	
00–17	106 (0.41%)	1070 (0.42%)	1
18–29	881 (3.43%)	8812 (3.43%)	.
30–39	2123 (8.27%)	21,219 (8.27%)	.
40–49	3374 (13.15%)	33,737 (13.15%)	.
50–59	5287 (20.61%)	52,874 (20.61%)	.
60–69	5933 (23.13%)	59,338 (23.13%)	.
70–79	4697 (18.31%)	46,965 (18.31%)	.
80–89	2878 (11.22%)	28,774 (11.22%)	.
> 90	377 (1.47%)	3771 (1.47%)	.
Number of hospitalizations before index date (mean, SD)	3.7 (± 9.0)	0.21 (± 1.1)	<0.001*
	Annual rate of hospitalizations before index date (n, %)		
≤ 0.25 per year	10,245 (39.93%)	244,107 (95.15%)	<0.001
Between 0.25 and 0.5 per year	5959 (23.23%)	8679 (3.38%)	.
Between 0.5 and 1 per year	5430 (21.16%)	2807 (1.09%)	.
Between 1 and 5 per year	3704 (14.44%)	908 (0.35%)	.
> 5 per year	318 (1.24%)	59 (0.02%)	.
Deaths (incidence [#] , CI)	14.4 [13.7–15.2]	10.5 [10.3–10.7]	<0.001
Follow-up time after index date (median, [IQR], years)	3.96 [1.96–5.96]	3.96 [1.96–6.04]	0.003*
Past medical history mentioned in previous hospitalizations (used as adjustment covariates)			
Hypertension	274 (1.07%)	884 (0.34%)	<0.001
Diabetes	657 (2.56%)	2852 (1.11%)	<0.001
Obesity	294 (1.15%)	1395 (0.54%)	<0.001
Cardiovascular diseases	1360 (5.30%)	8828 (3.44%)	<0.001
Neuropsychiatric disorders	667 (2.60%)	2529 (0.99%)	<0.001

pSS, primary Sjögren's syndrome; n, number; SD, standard deviation; CI, confidence interval; [#] Number of incident deaths per 1000 person-years; all comparisons were performed with Chi2 test except those marked with an *, performed with Wilcoxon-Mann-Whitney rank-sum test.

blood diseases in the pSS group compared to the control group: (i) lymphomas (aHR, 1.97, 95% CI [1.59–2.43], $p < 0.001$), including NHL (aHR, 1.93, 95% CI [1.56–2.40], $p < 0.001$); (ii) Waldenström macroglobulinaemia (aHR, 10.84, 95% CI [6.53–17.99], $p < 0.001$), including marginal zone lymphomas (aHR, 5.86, 95% CI [3.23–10.61], $p < 0.001$); (iii) and leukemias (aHR, 1.61, 95% CI [1.07–2.41], $p = 0.022$). B-cell CLL did not exhibit a higher incidence among pSS patients after adjustments (Table 4).

3.3. Mortality

Among patients with breast cancers, pSS patients had a lower risk of death than matched controls, but this did not reach significance (HR = 0.77, 95% CI [0.48–1.22], $p = 0.27$). After adjustment, aHR was 0.47 (95% CI [0.22–0.97], $p = 0.04$).

Considering lung, colon, bladder cancers, or lymphoma, the incidence of deaths among pSS patients was not statistically different from the controls, regardless of the adjustment factors included.

Table 2
Women's cancers incidence in hospitalized female primary Sjögren's syndrome patients compared to hospitalized matched controls.

	pSS patients				Matched controls				p value				
	Incident cases	Py	Incidence [#]	95%CI	Incident cases	Py	Incidence [#]	95%CI					
Breast	229	89,016	2.57	[2.24–2.9]	2769	865,259	3.20	[3.08–3.32]	0.80	[0.69–0.91]	0.001	[0.49–0.74]	<0.001
Breast (in situ)	31	90,732	0.34	[0.22–0.46]	248	900,973	0.28	[0.25–0.31]	1.23	[0.84–1.78]	0.277	[0.71–1.94]	0.530
Uterus cervix	17	90,876	0.19	[0.1–0.28]	183	902,956	0.20	[0.17–0.23]	0.92	[0.56–1.51]	0.754	[0.3–1.33]	0.226
Uterus body	35	90,696	0.39	[0.26–0.52]	447	895,797	0.50	[0.45–0.55]	0.79	[0.55–1.11]	0.181	[0.44–1.16]	0.174
Uterus	46	90,631	0.51	[0.36–0.66]	578	898,276	0.64	[0.59–0.69]	0.80	[0.59–1.08]	0.149	[0.43–1.01]	0.055
Ovary	32	90,804	0.35	[0.23–0.47]	350	901,505	0.39	[0.35–0.43]	0.90	[0.62–1.3]	0.589	[0.57–1.58]	0.833
All women's cancers	310	88,441	3.51	[3.12–3.9]	3612	854,364	4.23	[4.09–4.37]	0.82	[0.73–0.92]	0.001	[0.57–0.81]	<0.001

pSS, primary Sjögren's syndrome; Py, person-years; 95%CI, 95% confidence interval; [#] Number of incident cases per 1000 person-years; HR, hazard ratio; aHR, adjusted hazard ratio; adjusting factors combined reported past occurrences of: low socioeconomic status, annual hospitalization rate, diabetes, hypertension, cardiovascular diseases, and neuropsychiatric disorders prior to index date +90 days.

Table 3
Solid neoplasm incidence in hospitalized primary Sjögren's syndrome patients compared to hospitalized matched-controls.

	pSS patients				Matched controls				Crude HR	Crude 95% CI	Crude p value	Adjusted HR	Adjusted 95% CI	Adjusted p value
	Incident cases	Py	Incidence [#]	95%CI	Incident cases	Py	Incidence [#]	95%CI						
Solid neoplasms														
Brain	17	102,841	0.17	[0.09–0.25]	167	1,023,148	0.16	[0.14–0.18]	1.03	[0.62–1.7]	0.910	1.35	[0.72–2.53]	0.349
Lung	109	102,412	1.06	[0.86–1.26]	1053	1,016,101	1.04	[0.98–1.1]	1.03	[0.84–1.25]	0.798	0.81	[0.63–1.03]	0.090
Thyroid	38	102,563	0.37	[0.25–0.49]	236	1,020,068	0.23	[0.2–0.26]	1.61	[1.14–2.27]	0.007	1.73	[1.07–2.79]	0.025
UADT	15	102,832	0.15	[0.08–0.22]	156	1,022,918	0.15	[0.13–0.17]	0.955	[0.56–1.62]	0.864	0.71	[0.36–1.37]	0.303
Thymus	4	102,862	0.04	[0–0.08]	8	1,024,053	0.01	[0–0.02]	5.00	[1.51–16.6]	0.009	3.55	[0.59–21.3]	0.167
Skin cancers														
Melanoma	14	102,767	0.14	[0.07–0.21]	215	1,021,598	0.21	[0.18–0.24]	0.65	[0.38–1.11]	0.113	0.73	[0.37–1.44]	0.361
Squamous cell	149	101,821	1.46	[1.23–1.69]	1705	1,004,847	1.7	[1.62–1.78]	0.85	[0.72–1.01]	0.063	0.86	[0.7–1.07]	0.171
Basal cell	23	102,644	0.22	[0.13–0.31]	139	1,021,519	0.14	[0.12–0.16]	1.68	[1.08–2.62]	0.021	1.31	[0.69–2.5]	0.411
Gastro-intestinal tract neoplasms														
Pancreas	45	102,747	0.44	[0.31–0.57]	421	1,021,748	0.41	[0.37–0.45]	1.07	[0.79–1.46]	0.654	0.84	[0.55–1.28]	0.409
Liver	31	102,808	0.3	[0.19–0.41]	250	1,023,190	0.24	[0.21–0.27]	1.23	[0.85–1.79]	0.274	1.01	[0.62–1.65]	0.967
Esophagus	9	102,850	0.09	[0.03–0.15]	114	1,023,264	0.11	[0.09–0.13]	0.79	[0.4–1.56]	0.494	0.42	[0.16–1.14]	0.090
Stomach	28	102,792	0.27	[0.17–0.37]	225	1,022,444	0.22	[0.19–0.25]	1.25	[0.84–1.85]	0.268	1.26	[0.78–2.05]	0.342
Small bowel	7	102,868	0.07	[0.02–0.12]	72	1,023,881	0.07	[0.05–0.09]	0.94	[0.43–2.04]	0.872	1.25	[0.44–3.56]	0.682
Colon	104	102,172	1.02	[0.82–1.22]	1270	1,009,602	1.26	[1.19–1.33]	0.80	[0.65–0.97]	0.027	0.84	[0.65–1.07]	0.151
All digestive tract cancers	147	101,925	1.44	[1.21–1.67]	1677	1,005,484	1.67	[1.59–1.75]	0.85	[0.72–1.01]	0.057	0.89	[0.72–1.1]	0.275
Kidney	38	102,685	0.37	[0.25–0.49]	346	1,021,033	0.34	[0.3–0.38]	1.09	[0.78–1.52]	0.629	0.79	[0.51–1.23]	0.301
Bladder	28	102,625	0.27	[0.17–0.37]	451	1,019,018	0.44	[0.4–0.48]	0.62	[0.42–0.91]	0.015	0.58	[0.37–0.89]	0.014
All urothelial cancers	63	102,422	0.62	[0.47–0.77]	747	1,015,880	0.74	[0.69–0.79]	0.84	[0.65–1.08]	0.172	0.72	[0.52–0.98]	0.035
All first solid neoplasms	767	97,713	7.85	[7.29–8.41]	7456	934,552	7.98	[7.8–8.16]	0.97	[0.9–1.04]	0.400	0.92	[0.84–1.01]	0.095

pSS, primary Sjögren's syndrome; CI; confidence interval; py. person-years; # Number of incident cases per 1000 person-years; HR, hazard ratio; aHR, adjusted hazard ratio; adjusting factors combined reported occurrences of: low socioeconomic status, annual hospitalization rate, diabetes, hypertension, cardiovascular diseases, and neuropsychiatric disorder (dementia. Depression, anxiety) prior to index date +90 days. UADT, Upper aerodigestive tract.

Table 4 Malignant blood disease incidence in hospitalized primary Sjögren's syndrome patients compared to hospitalized matched controls.

	pSS patients				Matched controls				Crude HR	Crude 95% CI	Crude p value	Adjusted HR	Adjusted 95% CI	Adjusted p value
	Incident cases	Py	Incidence#	95% CI	Incident cases	Py	Incidence#	95% CI						
Lymphomas	179	101,100	1.77	[1.51-2.03]	834	1,005,557	0.83	[0.77-0.89]	2.10	[1.79-2.47]	<0.001	1.97	[1.59-2.43]	<0.001
Non-Hodgkin lymphoma	172	101,188	1.7	[1.45-1.95]	811	1,006,401	0.81	[0.75-0.87]	2.08	[1.76-2.45]	<0.001	1.93	[1.56-2.4]	<0.001
Waldenström macroglobulinaemia	68	102,403	0.66	[0.5-0.82]	73	1,020,850	0.07	[0.05-0.09]	9.34	[6.69-13.07]	<0.001	10.84	[6.53-17.99]	<0.001
Marginal zone lymphoma	42	102,498	0.41	[0.29-0.53]	66	1,021,263	0.06	[0.04-0.08]	6.35	[4.29-9.41]	<0.001	5.86	[3.23-10.61]	<0.001
Multiple myeloma and malignant plasma cell neoplasms	23	102,681	0.22	[0.13-0.31]	182	1,021,335	0.18	[0.15-0.21]	1.24	[0.81-1.92]	0.327	0.98	[0.55-1.75]	0.937
Myelodysplastic syndromes	34	102,619	0.33	[0.22-0.44]	206	1,020,787	0.2	[0.17-0.23]	1.66	[1.15-2.39]	0.007	0.93	[0.54-1.6]	0.784
Leukemias	53	102,586	0.52	[0.38-0.66]	261	1,019,885	0.26	[0.23-0.29]	2.06	[1.53-2.77]	<0.001	1.61	[1.07-2.41]	0.022
B cell Chronic lymphocytic Leukemia	17	102,766	0.17	[0.09-0.25]	79	1,022,763	0.08	[0.06-0.1]	2.23	[1.31-3.79]	<0.001	1.81	[0.86-3.8]	0.115

pSS, primary Sjögren's syndrome; CI, confidence interval; py, person-years; # Number of incident cases per 1000 person-years; HR, hazard ratio; aHR, adjusted hazard ratio; adjusting factors combined reported occurrences of: low socioeconomic status, annual hospitalization rate, diabetes, hypertension, cardiovascular diseases, and neuropsychiatric disorders prior to index date +90 days.

3.4. Patients with multiple cancers

The proportion of patients with at least one solid neoplasm and one hematological malignancy during the incidence study was higher in the pSS group (0.70% versus 0.31%, $p < 0.000001$).

4. Discussion

We report an analysis of the largest study of cancer incidence within a European population of pSS patients, integrating adjustment factors such as LSS or annual rate of hospitalization. Our study population exhibits the classical demographical features of pSS (age and sex) [17], and a higher annual hospitalization rate than controls.

As expected, a higher incidence of hematological malignancies was observed among pSS patients. We confirmed within our large population the well-known increased risk of NHL in pSS [8,9,12,13,18], linked to a higher incidence of marginal zone lymphoma and Waldenström macroglobulinemia [19]. This association is supported by the many mechanisms involving monoclonal-IgM secreting B-cell, narrowing pSS pathogenesis and lymphomagenesis [7,20-24], as illustrated by implication of the CXCR5/CXCL13 axis [20,25,26]. Interestingly, a bidirectional relationship between NHL and pSS was previously suggested by Wang et al. who observed a higher incidence rate of NHL among 15,636 pSS Taiwanese patients, and a higher incident rate of pSS among NHL patients [9]. We also found an increased risk of incident thymic tumors in the pSS population, although this was not confirmed after adjustments due to the extremely low frequency of those events in the population. This association is rarely reported, except for one case of epithelial thymic tumor [27], and a few cases of thymic primary MALT (mucosa-associated lymphoid tissue) lymphoma [28-30], in line with the above-mentioned risk for this lymphoma. Unfortunately, the lack of information on thymic histology prevents further speculation. We did not confirm either the findings by Wang et al. of a higher incidence of multiple myeloma [9], whose incidence is heterogeneously reported in literature [8,12,13,31], nor the findings by Brito-Zerón et al. [13] of a higher incidence of Hodgkin's disease. As already reported by Wang et al. [9], we found a slightly increased risk (RR = 1.61) of leukemia incidence among pSS patients, which was not related to a higher risk of B-cell CLL. Our results remain to be verified in further studies, since the ICD-10 codes for leukemias used (C91-C95) encompass multiple types of leukemias. Additional studies with a longer study period and a larger population are required to confirm this surprising result. Finally, the association of at least one solid neoplasm and any hematological malignancy was higher in the pSS group, as suggested previously [32,33].

Our results were heterogeneous for solid neoplasms. We did not confirm the reported increased incidence of lip or oral cavity, stomach, and liver cancers among pSS patients [8,9,13]. Concerning lung cancers, we found similar results to other studies involving European people [8,10,13], demonstrating no difference in incidence rate comparing pSS and matched patients, whereas two other studies involving patients from South-East Asia [9,34] reported a higher Standardized Incidence Ratio (SIR) of about 1.5 in pSS. We observed a lower incidence of colon cancer among pSS patients, as previously reported [9,11], although this did not remain significant after adjustments, which is in line with the meta-analysis by Liang et al. [12].

Interestingly, we observed significant relationships between pSS and thyroid, bladder, and breast cancers. As already reported, we observed an increased incidence of thyroid cancer in pSS (SIR varying from 1.2 to 5.2) [11-13,18,35]. This finding may be linked to the higher prevalence of Hashimoto's autoimmune thyroiditis among pSS patients [36] (including in our population, *data not shown*), which is classically associated with the development of papillary thyroid cancer [37,38]. Since histological characteristics were not available, we cannot conclude on the histological types, and an increased incidence of thyroid MALT lymphoma cannot be excluded [39,40].

In addition, we found a significantly lower risk of bladder cancer,

maintained after adjustments (0.58 [0.37–0.89]), which differs from three previous studies on smaller populations ($n = 507$ [10], $n = 7852$ [11] and $n = 1300$ [13] pSS patients). Nevertheless, we cannot conclude that this is entirely due to pSS since we lack data on vital confounding factors, such as exposure to environmental agents (e.g. tobacco). Moreover, the potential interplay with interstitial cystitis has to be further investigated, since this condition is more frequently observed in pSS patients [41–44], as well as in our study (*data not shown*).

One of the most interesting findings is the reduced risk of incidental breast cancer among pSS patients for all stages, except in situ cancers. This is in line with the lower SIR of 0.46 (0.26–0.75) for breast cancer incidence observed by Hemminki et al., when comparing a Swedish population of 1516 SS patients to the general population [45]. This is also consistent with Chen et al. who compared 54,311 women with breast cancer to 217,244 matched females. They reported a lower incidence of SS, even after adjustments (HR 0.21 (0.09–0.48)) [46]. However, the literature data is heterogeneous: some studies have not shown any difference for breast cancer incidence in pSS patients [10–13]; one recent study involving 15,636 pSS Taiwanese patients [9] showed a higher incidence of breast cancer (SIR 1.3). However, the Taiwan study cannot be directly compared to ours, as the population included outpatients and considered a population with a different genetic and environmental background which could potentially influence both SS and cancer onset, and because the methodology did not involve adjusting factors. In our study, the incidence rate of in situ breast cancer was not different between the two groups (Table 3), suggesting that the lower rate of progressive breast cancers is not influenced by an earlier detection of cancers in the pSS group. Thus, any pSS protective effect would only apply to more aggressive/extended breast cancers. This result is consistent with our finding of a lower death rate among pSS patients with breast cancers.

This lower risk of developing breast cancer raises several pathophysiological points. Firstly, these findings might be linked to a lower estrogen exposure in pSS patients, as proposed by McCoy et al. [47]. Indeed, parity, breastfeeding, and contraceptive pill use are associated with breast cancer risk [48], as well as obesity [49,50], which was included as an adjustment factor in our analysis. The relationship between hormonal profile and immune system activation may also be involved. Secondly, we could hypothesize about a protective effect of pSS against breast cancer through immune control. Indeed, breast tissue exhibits similarities with salivary glands, and we have previously documented that pSS can target breast tissue, with histological features similar to salivary gland typical patterns (lymphocytic infiltrates, sometimes resembling classical “foci”, and duct ectasia) [51]. The immunological patterns of breast-associated mucosal tissue are also different in pSS patients (higher proportion of CD4+ T cells), suggesting a different behavior towards local antigens such as neoplastic cells [51]. This cannot be confirmed here, since our study did not consider immunological or histological features. Thus, this hypothesis of “immune surveillance” against breast cancer remains to be documented in pSS, as well as the relationship between local immunity and cancer in more general conditions [52,53]. This tight interaction between immune system and cancer is in line with the high proportion of autoimmune diseases and symptoms observed among patients with cancer and checkpoint inhibitors therapies [54], including sicca syndrome [55,56].

The limitations of this study include the possibility of missing some cases of hospitalized pSS patients or patients with associated autoimmune diseases (and thus sSS) because of potential under-reporting of such diseases in the database. However, the long inclusion period makes it unlikely that we missed a significant proportion of them. In addition, all cancer diagnoses and treatment in France are recorded in the hospitalization database, thus we can be confident that we did not miss any incident cancer in pSS patients. Our approach may have underestimated the occurrence of death (especially sudden deaths from trauma or cardiovascular causes occurring outside of hospital), but such a bias would equally affect both groups. Notably, potential confounding factors, such

as tobacco or alcohol consumption, were not available for analysis. However, we were able to incorporate cardiovascular diseases in our models to moderate this bias.

Despite these limitations, one major strength of this study is its large sample size. Indeed, we can assume that the power of our study was good enough to detect a moderate effect for most of the cancers we studied: 80% power to detect HR = 0.75 with a bilateral alpha risk of 5% for lung or colon cancer, minimum power of 80% to detect HR = 2 for all other cancers, except for rare cancers such as esophagus or thymus for which we may have lacked power.

5. Conclusion

Our large database study confirms literature data concerning the increased risk of hematological malignancies and thyroid cancers among hospitalized pSS patients. Interestingly, we observed a reduced risk of breast cancer incidence. Further epidemiological studies are required to also include pSS outpatients, and should integrate additional risk factors for adjustments. Moreover, the pathophysiological relationships between pSS and cancer and especially the hypothesis of “immune surveillance” against breast cancer should be strengthened by other approaches, including animal models and translational immunological studies.

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Declaration of Competing Interest

None

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