Risk of non-Hodgkin's lymphoma and thyroid cancer in primary Sjögren's syndrome measured using the Korean Health Insurance Claims Database

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ABSTRACT

Objective. *The aim of this study was to evaluate the incidence and risk of non-Hodgkin's lymphoma (NHL) and thyroid cancer in patients with primary Sjögren's syndrome (pSS) using the Korean National Health Insurance Service (NHIS) claims database.*

Methods. *pSS was identified using the Korean NHIS medical claims database between 2007 and 2017. The case definition required more than one visit based on the SS diagnostic code and the registration system for rare and incurable diseases. We included all admissions with a primary diagnosis of lymphoma and thyroid cancer.*

Results. *The pSS incidence was 1.88 cases/100,000 inhabitants. Female patients had a higher incidence than male patients, with a female-to-male ratio of 7.65:1. Of those, we identified 18 (0.34%), 1 (0.02%) and 29 (0.56%) patients with NHL, Hodgkin's disease and thyroid cancer, respectively. For pSS, the standardised incidence ratios for NHL and thyroid cancer were 6.32 (95% confidence interval [CI] 4.09–9.38) and 1.23 (95% CI 0.88–1.68), respectively. Compared with the general population, female patients with pSS had a 6.95-fold higher risk of developing NHL, while the male patients did not. Patients with pSS did not have a higher risk of developing thyroid cancer.*

Conclusion. *Although pSS is associated with a higher risk of developing NHL, the risk of NHL appears to have decreased compared with that in previous studies. Our study suggests that the risk of NHL or thyroid cancer with SS is not higher than that reported in previous studies.*

Introduction

Primary Sjögren's syndrome (pSS) is a chronic systemic autoimmune disease that mainly affects women, with a peak incidence at approximately 50 years of age (1, 2). The hallmark of SS is exocrinopathy, characterised by lymphocytic infiltration of the exocrine glands, leading to a significant loss of secretory function, resulting in oral and eye dryness. SS often affects organs other than the exocrine glands, leading to systemic manifestations in approximately 30% to 50% of these patients (2, 3). Although increased risk of lymphoma in pSS has been widely accepted, the lymphoma risk in SS patients seemed to be not so high in the outpatient clinic. There was also a controversy about the increased risk of thyroid cancer in the review article on SS (4). Therefore, we decided to focus on analysing the risk of these in primary SS.

The development of lymphomas is one of the most serious complications of SS and are most commonly extranodal non-Hodgkin B-cell lymphomas of the mucosa-associated lymphoid tissue (MALT), frequently appearing in salivary glands (3). This finding has been attributed to chronic B-cell activation, a characteristic of pSS (2, 3).

The estimated risk of lymphoma in patients with SS was 44-fold higher than in the general population (5). More recent studies have estimated that the risk of B-cell lymphoma is 6 to 20-fold higher among patients with pSS than in the general population (6-11). Although there is some degree of consensus regarding the higher risk of lymphoma in patients with SS, the risk of lymphoma has been reported to differ depending on each population's characteristics and ethnicity.

There was a controversy as to whether patients with pSS have an increased risk of non-haematologic malignancies (7, 12, 13). In the studies from Taiwan and Spain, the estimated risk of thyroid

cancer appears slightly increased in pSS compared with previous results (8, 10). Although pSS is a rare disease and many cases are required to determine the exact risk of malignancy in this condition, most epidemiological studies of pSS have been limited to a small number of cases such as case-control studies, leading to low-quality evidence. These results from a small number of case-control studies are unlikely to reflect the exact risk of cancer in pSS. A large sample size with a significant number of cases is therefore required to analyse the risk of lymphoma and thyroid cancer in pSS. In South Korea, the detection rate for thyroid cancer is high because of a routine health check program, which provides significant help in more accurately evaluating the risk of thyroid cancer in pSS.

Given the varying risk of lymphoma and thyroid cancer in pSS worldwide, we sought to estimate this risk by employing a large-scale assessment. Furthermore, we would like to use this result as a basis for making recommendations for the screening of lymphoma and thyroid cancer for patients with pSS in South Korea. We therefore aimed to investigate this risk by employing the National Health Insurance Service (NHIS) medical claims data, which covers all medical institutions in South Korea.

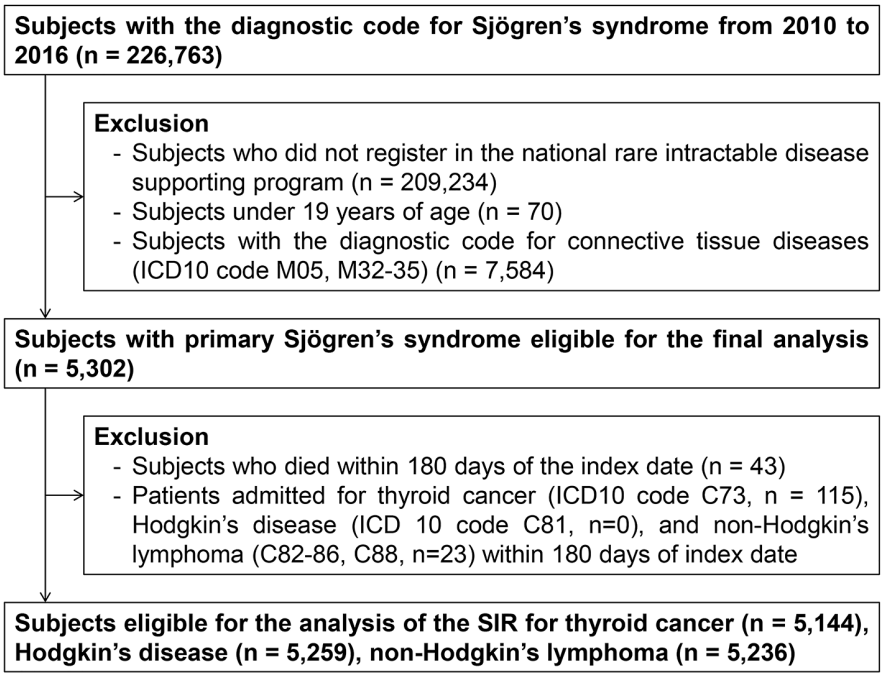

Fig. 1. Selection of study participants.
ICD: international classification of disease; SIR: standardised incidence ratio.

Materials and methods

Data source

We performed a cohort study on data from a nationwide registry; all data were linked with the NHIS database. We employed data from the NHIS database between January 2007 and December 2017. The NHIS is the only and compulsory public medical insurance system operated by the South Korean government. To claim payments for patient care, all clinics and hospitals in South Korea must submit data, including the patient's personal identification number, diagnosis, and prescription information to the NHIS (14). Almost the entire South Korean population is included in the NHIS database (15). The study was conducted within the framework of the Korean Health Insurance Review and Assessment Service (HIRA), which is responsible for claim reviews and quality assessment of the NHIS (16, 17).

Study population

We extracted pSS cases from HIRA database, as well as patient age, sex, main diagnosis codes (International Classification of Disease [ICD]-10), and sub-diagnosis codes (also in ICD-10). The case definition for pSS required more than one visit based on the SS ICD-10 diagnostic codes of M35.0, and the patient cohort with pSS was confined to those aged 19 years or older between 2007 and 2017. Sjögren's syndrome has been registered in the Individual Copayment Beneficiaries Program (ICBP) for rare and incurable diseases in South Korea since 2006, and cases recorded in this registry have been provided financial support from the government to reduce their medical expenses burden (14, 18). Application to this program for SS requires a thorough clinical and laboratory survey that fulfils the American-European Consensus Group (AECG) classification criteria for SS (19). The patient selection flowchart is shown in Figure 1.

A 3-year washout period was applied in our study to exclude patients who were diagnosed before their information was entered into the national rare and incurable disease database. Patients with any other autoimmune disease, such as systemic lupus erythematosus, rheumatoid arthritis, and other rheumatic diseases (*e.g.* systemic sclerosis, polymyositis, dermatomyositis and mixed connective tissue disease) are classified as having SS associated with other autoimmune diseases and were therefore excluded. The presence of a rheumatic disease before the SS diagnosis and within one year after the SS diagnosis was ruled out. We included all patient admissions with a primary diagnosis of lymphoma and thyroid cancer (classified as codes C81, C82 to C86, C88 and C73, per the ICD-10). Lymphoma and thyroid cancer were designated as one of four serious diseases (cancer, cerebrovascular disease, cardiovascular disease, and rare diseases) in South Korea in 2004. Serious diseases are hard to cure and require long treatments, and patients with these diseases pay only 5–10% of their medical costs as the deductible. Patients who had a lymphoma or thyroid cancer before the diagnosis of pSS were excluded, as were those who had these conditions within 6 months after the SS diagnosis. In these cases, we considered that SS would not have affected the development of lymphoma and thyroid cancer.

Statistical analysis

We estimated the incidence per 100,000 individuals between 2010 and 2016 and calculated the annual incidence of pSS using the number of annual incident cases divided by the total population for that year. We calculated the incidence of lymphoma and thyroid cancer with pSS by sex and age group (19-49, 50-69, and ≥70 years of age). To determine whether the patients with pSS had a higher risk of developing lymphoma and thyroid cancer, we calculated their standardised incidence ratio (SIR) and 95% confidential intervals (CIs) for lymphoma and thyroid cancer. The categorical variables are presented as frequencies and percentages, and the continuous variables are presented as mean and standard deviation (SD) or median and interquartile ranges. We employed R software version 3.3.2 (The R Foundation; www.R-project.org) for the analyses. A *p*-value less than 0.05 was considered statistically significant.

Ethics statement

We reviewed the recorded data in the national health claims database of the HIRA service (2007-2017). The study was approved by the Institutional Review Board (IRB) committee of Kangbuk Samsung Hospital, Seoul, South Korea (IRB No. KBSMC 2019-03-013) and was exempt from an IRB review due to the use of existing, publicly available data and the fact that the participants could not be identified directly or through identifiers linked to the participants. The requirement for informed consent was waived because the patients could not be identified through the data. The study was conducted in accordance with the tenets of the Declaration of Helsinki.

Results

Demographics of patients with primary Sjögren's syndrome

We identified 5,302 patients aged 19 years or older (4,689 women and 613 men) with pSS from 2010 to 2016. The patients' mean age was 57.5±13.8 years (61.1±15.2 years for the men and 57.0 13.6 years for the women). Overall, SS tend to occur in all of the age groups as shown in Table I. The follow-up period in our study is 3.1 years. The mean duration from the diagnosis of pSS to the development of lymphoma and thyroid cancer was 3.1 years and 2.1 years, respectively.

Table I. Incidence and confidence interval for patients with primary Sjögren's syndrome by sex and age.

	Number	Incidence (per 100,000 person-year)	95% CI
Total	5,302	1.88	1.80-1.97
Men	613 (11.6)	0.44	0.40-0.48
Women	4,689 (88.4)	3.29	3.10-3.50
Age group, years			
19-49	1,447 (27.3)	0.86	0.80-0.92
50-69	2,223 (41.9)	2.62	2.42-2.84
≥70	1,632 (30.8)	5.75	5.06-6.54
Men per age group, n (%)			
19-49 years old	133 (21.7)	0.15	0.13-0.18
50-69 years old	193 (31.5)	0.46	0.39-0.55
≥70 years old	287 (46.8)	2.63	2.10-3.31
Women per age group, n (%)			
19-49 years old	1,314 (28.0)	1.60	1.47-1.75
50-69 years old	2,030 (43.3)	4.73	4.26-5.26
≥70 years old	1,345 (28.7)	7.73	6.60-9.10
Year			
2010	646 (12.2)	1.66	1.46-1.89
2011	677 (12.8)	1.73	1.53-1.97
2012	716 (13.5)	1.82	1.60-2.06
2013	703 (13.3)	1.78	1.57-2.01
2014	600 (11.3)	1.51	1.33-1.72
2015	930 (17.5)	2.32	2.06-2.61
2016	1,030 (19.4)	2.56	2.28-2.87

Data are expressed as numbers (percentages), unless otherwise indicated.
CI: confidence interval.

Table II. Incidence, SIR and 95% CI for Non-Hodgkin's lymphoma and thyroid cancer in patients with primary Sjögren's syndrome.

	Observed	Expected	Incidence	95% CI	SIR	95% CI
NHL						
Total	18	2.58	0.26	0.15-0.44	6.32	4.09-9.38
Sex						
Male	2	0.54	0.29	0.03-1.50	3.68	0.65-11.58
Female	16	2.30	0.26	0.14-0.45	6.95	4.36-10.55
Age group, years						
19-49	3	0.31	0.14	0.03-0.48	9.53	2.60-24.64
50-69	6	1.08	0.20	0.07-0.49	5.57	2.42-10.99
≥70	9	1.45	0.53	0.21-1.26	6.19	3.23-10.80
Thyroid cancer						
Total	29	23.49	0.43	0.27-0.68	1.23	0.88-1.68
Sex						
Male	0	0.59	0.00	0.00-0.69	0.00	0.00-5.05
Female	29	22.9	0.48	0.29-0.75	1.27	0.91-1.73
Age group, years						
19-49	7	7.68	0.33	0.12-0.81	0.91	0.43-1.71
50-69	16	12.72	0.55	0.28-1.05	1.26	0.79-1.91
≥70	6	3.09	0.35	0.11-0.94	1.94	0.85-3.83

Data are expressed as numbers (percentages), unless otherwise indicated.
CI: confidence interval; NHL: Non-Hodgkin's lymphoma; SIR: standardised incidence ratio.

Incidence of primary Sjögren's syndrome

We estimated the annual incidence rate of pSS at 1.88 cases per 100,000 inhabitants. Table I shows the overall

Table III. Type of non-Hodgkin's lymphoma among patients with primary Sjögren's syndrome in Korea, 2010-2017.

ICD-10	Disease	Total	%
C83.0	Small cell B-cell lymphoma	2	11.1
C83.1	Mantle cell lymphoma	2	11.1
C83.3	Diffuse large B-cell lymphoma	4	22.2
C84.4	Peripheral T-cell lymphoma	1	11.1
C85.9	Non-Hodgkin lymphoma, unspecified	3	16.7
C88.0	Waldenstrom macroglobulinaemia	1	11.1
C88.4	MALT lymphoma	5	27.8
Total		18	100.0

MALT lymphoma: mucosa-associated lymphoid tissue.

incidence and the age-specific and sex-specific annual incidence of pSS. The incidence rates were 0.44 and 3.29 per 100,000 inhabitants for the men and women, respectively, with a female-to-male ratio of 7.65:1. The incidence rate and absolute number of patients with pSS during this period was generally stable, with a slight increase over a 7-year period (Table I).

The risk of lymphoma and thyroid cancer in primary Sjögren's syndrome

Of the patients with pSS, we identified 18 (0.34%), 1 (0.02%) and 29 (0.56%) patients with non-Hodgkin's lymphoma (NHL), Hodgkin's disease (HD) and thyroid cancer, respectively, after the pSS diagnosis and during the observation period (Table II). The most frequent type of NHL was B-cell lymphoma (including 5 MALT and 6 non-MALT B-cell lymphomas) (Table III).

For patients with pSS, the SIRs for NHL and thyroid cancer were 6.32 (95% CI 4.09-9.38) and 1.23 (95% CI 0.88-1.68), respectively. The SIRs for NHL and thyroid cancer categorised by sex for the various age groups are listed in Table II. The SIR for NHL was 9.53 for patients aged 19-49 years, 5.57 for patients aged 50-69 years and 6.19 for patients aged ≥70 years. The SIR for thyroid cancer was 0.91 for patients aged 19–49 years, 1.26 for patients aged 50–69 years and 1.94 for patients aged ≥70 years. For patients with pSS, the SIRs for NHL were 3.68 (95% CI 0.10–9.33) and 6.95 (95% CI 2.98–8.81) for the men and women, respectively. Since HD occurred only in one case, no analysis of SIR was performed. The risk of thyroid cancer was not significantly higher for the patients with pSS than for the general population.

Discussion

In this nationwide population-based database that included almost the entire South Korean population, the mean annual incidence of pSS was estimated at 1.88 cases per 100,000 inhabitants, and women had a higher incidence than men. The risk of NHL is 6.32-fold higher among patients with pSS than in the general population. The women with pSS had a 6.95-fold higher risk of developing NHL than the general population, while the men did not. Patients with pSS did not have a higher risk of developing thyroid cancer.

The annual incidence of pSS ranges from 2.34 to 16.0 cases per 100,000 inhabitants, with higher rates observed in Asia (1, 18, 20-24). The mean annual incidence rate for pSS in our study population was 1.88 cases per 100,000 inhabitants (95% CI 1.80–1.97). In this study, the estimated incidence of pSS was lower than in other studies (1, 18,

Table IV. Summary of studies assessing lymphoma risk in primary Sjögren's syndrome.

Reference	Country	Year	Number	Criteria	Observation time	Follow-up duration	Lymphoma, n	SIR (95% CI)	Study design
Kassan *et al*. (5)	USA	1978	142	N/A	N/A	1.8 years	4	44.4 (16.7-118.4)	Cohort study
Theander *et al*. (12)	Sweden	2006	507	1993 European or AECG	1984-2002	8 years	11 (NHL)	15.57 (7.8- 27.9)	Prospective cohort study
Zhang *et al*. (7)	China	2010	1,320	AECG	1990 - 2005	4.4 years	8	48.1 (20.7-94.8)	Cohort study
Weng *et al*. (8)	Taiwan	2012	7,852	AECG	2000-2008	3.5 years	23 (NHL)	7.08 (4.25-10.3)	Population-based cohort study
Johnsen *et al*. (11)	Norway	2013	443	AECG	1980-2009	3,813 PY	7 (NHL)	9.0 (7.1-26.3)	Population-based cohort study
Brito-Zeron *et al*. (10)	Spain	2017	1,300	AECG	2005-2016	7.6 years	12 (NHL)	6.04 (3.4-10.6)	Cohort study
Chiu *et al*. (34)	Taiwan	2017	16,396	N/A	2000-2010	69,086 PY	30 (NHL)	4.31 (2.78 - 6.69)	Population-based cohort study
This study	South Korea	2019	5,302	AECG	2010-2016	3.1 years	18 (NHL)	6.32 (4.09-9.38)	Population-based cohort study

AECG: the American-European Consensus Group; NHL: non-Hodgkin's lymphoma; PY: person-years; SIR: standardised incidence ratio; N/A; not available.

21-24). A lower prevalence has been reported in recent study with strict criteria (25). We employed AECG classification criteria to diagnose patients with SS. As shown in Figure 1, approximately 30% of the enrolled patients with SS were excluded during the process for excluding SS associated with other autoimmune diseases. Epidemiologic studies that employ health claims data might be confounded by variations in study populations, study design and differences in the classification criteria and operational definitions employed to identify cases. Studies in which cases are defined using administrative codes can overestimate the incidence, while studies in which cases are defined using classification criteria can underestimate the incidence (14). In other words, patients with mild symptoms who do not meet the classification criteria might not be included because patients with mild symptoms or early signs of SS might not be referred to specialists, which could explain the lower annual incidence measured in our study compared with other studies. In South Korea, the advanced medical delivery system enables patients with mild symptoms to consult a rheumatologist at any time for an accurate diagnosis and treatment. NHIS has covered almost 100% of the total population of South Korea (approximately 50 million as of 2014) (15), and therefore patient enrolment was close to optimum, based on the organisation of the health system and the coverage of NHIS in South Korea. The mean age in this study seemed to be much higher in comparison with hospital-based studies. The mean age of a nationwide, population-based Korean study and a longitudinal analysis of the Korean Initiative of pSS cohort was not significantly different from that of our study (18, 26). pSS disproportionately affects women, with the female/male ratio in incidence data ranging from 6 to 20 (1, 8, 18, 20-24, 27). The female preponderance with a female to male ratio of about 8:1 in our study was similar to that of other studies (1, 8, 18, 21-24, 27). The incidence rate and absolute number of patients with pSS was generally stable, with a slight increase in the 2 last years (nearly 1000 cases) in comparison with figures reported in the preceding 5 years (around 600-700 cases), which was likely due to improved reporting of SS by government policies such as ICBP registration to reduce their medical expenses burden.

Chronic activation of autoimmune B cells is a key feature in pSS and most likely the main factor contributing to SS-associated lymphomagenesis in patients with pSS compared with the general population or with patients with other systemic autoimmune diseases (3). There is reliable information in the literature regarding the connection between SS and lymphoma, as well as the risk factors for developing lymphoma in these patients (3, 4).

The SIR for developing NHL in pSS was 6.32 in this study. When analysed by age-group, the risk of NHL has increased across all ages. When performing a subgroup analysis by sex, the men with pSS did not have a higher risk of developing NHL, and only the women were at a significantly higher risk of NHL. Consistent with previous studies, patients with pSS in our study had a higher risk of developing NHL compared with the general population (5, 7, 8, 12, 13, 28-32). Table IV summarises the most important studies reporting the risk of lymphoma development in SS (5, 7, 8, 12, 13, 24, 28-33). Using the Taiwan National Health Insurance database between 2000 and 2008 and between 2000 and 2010, studies have reported an SIR of 7.08 and a hazard ratio of 4.3, respectively, for the risk of developing lymphoma in patients with SS (8, 34). The inconsistencies regarding lymphoma risk in pSS patients have several possible explanations. Considering how long it takes for SS to affect the onset of lymphoma, we excluded lymphoma cases that occurred within 6 months after the diagnosis of SS and any patients with a history of lymphoma prior to the follow-up. The risk is generally higher for SS associated with other autoimmune diseases than for pSS (33). A number of studies have calculated the risk of developing lymphoma regardless of pSS or SS associated with other autoimmune diseases. Given that the risk of developing lymphoma increases with the time since the SS diagnosis (35), the relatively low SIR for NHL might be due to this study's relatively short observation periods.

Advances in diagnostic techniques have significantly facilitated the diagnosis of lymphoma. The ICBP system's registration of rare and incurable diseases and malignancies might have increased physician awareness regarding SS and lymphoma in South Korea. Nevertheless, recent studies (including ours) have reported that the risk of developing lymphoma in pSS appears to have decreased in recent years (7-10).

We assessed the association between pSS and the risks of thyroid cancer. Among the non-hematologic malignancy, the reason why thyroid cancer was selected for analysis in patients with SS is as follows. First, previous studies found the association of pSS and autoimmune thyroid diseases, particularly with Hashimoto's thyroiditis (36, 37). There seems to be an association between Hashimoto's thyroiditis and papillary thyroid cancer (38). Second, South Korea has the highest incidence of thyroid cancer in the world (39). Third, these diseases have a common feature of female predominance. Considering these, a significant association might exist between pSS and the risk of thyroid cancer. It is reported that South Korea has the highest incidence rate of thyroid cancer in the world, most likely as a result of widespread use of routine health check program (39). This situation has likely been instrumental in assessing the exact risk of thyroid cancer in pSS. Unlike previous studies (8, 10), this study's findings seem to indicate that there is no association between pSS and the risk of thyroid cancer (SIR, 1.23; 95% CI 0.88–1.68). Considering the current "epidemic" in thyroid cancer in South Korea (40), it is unlikely that the risk of thyroid cancer development in pSS is underestimated in this study. In previous studies, while screening tests for thyroid cancer may have not been carried out in the general population, many patients with SS may have been well screened for thyroid cancer because patients with SS are known to have a higher incidence

of autoimmune thyroid disease such as Hashimoto's thyroiditis (36-39). On the other hand, in South Korea, screening for thyroid cancer has been well performed in both the general population and patients with SS, which may lead to increased detection rates of thyroid cancer in both groups. For these reasons, it is inferred that the increase of SIR was not shown in our study while two previous studies found an increased risk of thyroid cancer in patients with pSS. However, this would need to be confirmed by further studies.

Studies on the association between SS and malignancies, including the present study, may be used as a basis for identifying specific subsets in pSS cohorts at greater risk for malignancies. Furthermore, phenotype-based clustering of pSS using immunologic biomarkers and artificial neural networks may help physicians to offer a more personalised, cost-effective medical care in patients with pSS (41-43).

Our study's strengths are that it was a large, population-based study that employed an NHIS database covering almost the entire population. There are, however, several limitations stemming from the inherent nature of health claims data. First, the data did not include cumulative records from laboratories (specifically on the severity of the conditions) because the data were collected for administrative purposes and not for research. The lack of highly-specific information about the disease (percentage of Ro/La antibodies, focal lymphocytic sialadenitis) limits understanding of the specific characteristics of this cohort of SS patients. Second, there might be discrepancies between the patient's actual diseases and the diagnosis entered into the data. Third, South Korea has a system for registering rare and incurable diseases that meet the classification criteria, and patients registered in this system have been provided financial support, thereby affecting patient recruitment.

According to this study's findings, South Korean patients with pSS have a higher risk of developing NHL than the general population, even if the risk of NHL is lower than that reported in previous studies. Women had a significantly higher risk of NHL than men; however, the patients with pSS did not have a higher risk of thyroid cancer. This encouraging data suggest that the risks of NHL and thyroid cancer in patients with SS are not higher than those reported in previous studies and could help reduce the unnecessary fear and screening expenses of malignancies in SS.

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