

Bidirectional Relationship Between Primary Sjögren Syndrome and Non-Hodgkin Lymphoma: A Nationwide Taiwanese Population-based Study

Li-Hui Wang¹, Wei-Ming Wang, Chun-Yu Lin, Sheng-Hsiang Lin, and Chi-Chang Shieh²

ABSTRACT. Objective. Bidirectional relationships between some autoimmune diseases and non-Hodgkin lymphoma (NHL) may exist. We conducted this nationwide population-based study in Taiwan to investigate whether there is a bidirectional relationship between primary Sjögren syndrome (pSS) and NHL.

Methods. Using the National Health Insurance Research Database of Taiwan, we identified 15,636 patients with new-onset pSS without previous cancer and 25,074 patients with new-onset NHL without previous pSS as 2 non-overlapping cohorts from 1998 to 2012, and followed them until 2013. Standardized incidence ratios (SIR) for NHL in the patients with pSS and SIR for pSS in the patients with NHL were compared with the general population.

Results. Among the 15,636 patients with pSS, 741 developed cancers, including 51 with NHL. The highest SIR of specific cancer risk in patients with pSS was that for NHL (SIR 4.6, 95% CI 3.4–6.0). Among the 25,074 patients with NHL, 49 developed pSS; the SIR was also increased (SIR 3.2, 95% CI 2.4–4.2). The risk was highest within 1 year after the diagnosis of each disease.

Conclusion. This nationwide population-based study is the first to report a bidirectional relationship between pSS and NHL. Our findings suggest being alert for patients with pSS or NHL who have early signs of the other disease in clinical care. The underlying mechanisms of the bidirectional relationship merit further investigation. (First Release August 1 2020; J Rheumatol 2020;47:1374–8; doi:10.3899/jrheum.191027)

Key Indexing Terms:

PRIMARY SJÖGREN SYNDROME

NON-HODGKIN LYMPHOMA

BIDIRECTIONAL RELATIONSHIP

Primary Sjögren syndrome (pSS) is a chronic systemic autoimmune disorder characterized by lymphocytic infiltration of the exocrine (mainly salivary and lacrimal) glands, leading to dry eyes and dry mouth¹. Cancer is a major health problem and a common cause of death worldwide. The relationship between autoimmune disease and cancer, however, is complex. Autoimmune diseases often result

from dysregulated and hyperactive immune responses, and active immune responses may be protective against cancer². On the other hand, autoimmune diseases often cause chronic inflammation, which may promote cancer development³. Therefore, autoimmune diseases may have an ambivalent role in suppressing and promoting cancers.

A higher risk of non-Hodgkin lymphoma (NHL) has been reported in many autoimmune diseases, including pSS^{4,5,6,7,8,9,10}. In previous studies, we found that patients had a higher risk of NHL not only after being diagnosed with an autoimmune disease, but also that NHL was frequently found before a diagnosis of an autoimmune disease^{4,5,6}. Moreover, a bidirectional relationship between systemic lupus erythematosus (SLE) and NHL has been reported⁴.

We conducted this study in Taiwan using the 1998–2013 nationwide database to first evaluate the overall and specific cancer risks in patients with pSS in comparison with the general population. We then further investigated whether there was a bidirectional relationship between pSS and NHL.

MATERIALS AND METHODS

Taiwan's National Health Insurance (NHI) program is a mandatory insurance system that covers more than 99% of the population. There are 30 categories of catastrophic illness defined by the NHI, including pSS and cancer¹¹. Once a patient is definitely diagnosed with a catastrophic illness,

From the Division of Immunology, Department of Pediatrics, Kuo General Hospital; Institute of Clinical Medicine, College of Medicine, National Cheng Kung University; Division of Allergy, Immunology and Rheumatology, and Department of Pediatrics, Department of Internal Medicine, and Department of Statistics, National Cheng Kung University Hospital, Tainan, Taiwan.

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L.H. Wang, MD, MS, Immunologist, Division of Immunology, Department of Pediatrics, Kuo General Hospital; W.M. Wang, MS, Biostatistician, National Cheng Kung University, Department of Statistics; C.Y. Lin, MD, Rheumatologist, National Cheng Kung University Hospital, Department of Internal Medicine; S.H. Lin, PhD, Associate Professor of Biostatistics, National Cheng Kung University College of Medicine, Institute of Clinical Medicine; C.C. Shieh, MD, PhD, Professor of Immunology, Rheumatology, and Pediatrics, National Cheng Kung University College of Medicine, Institute of Clinical Medicine.

Address correspondence to Dr. C.C. Shieh, Institute of Clinical Medicine, National Cheng-Kung University, 138 Sheng-Li Road, Tainan 70403, Taiwan. E-mail: cshieh@mail.ncku.edu.tw

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the attending physician will apply for a catastrophic illness certificate (CIC) immediately to provide exemption from copayment. We conducted this population-based retrospective cohort study by retrieving data on patients with pSS and NHL separately from the 23 million people included in the NHI Research Database (NHIRD) of Taiwan¹²; the study was approved by the Institutional Review Board of Kuo General Hospital (No. B-18-K018). The study process is shown in Figure 1.

The pSS cohort. We built a pSS cohort by identifying the people having CIC for pSS [International Classification of Diseases (ICD)-9 code 710.2] from Taiwan's NHIRD. We included only patients with new-onset pSS between January 1, 1998, and December 31, 2012. The index date was the application date of the CIC for pSS. Patients with previous cancer or other specific autoimmune disease (i.e., rheumatoid arthritis, SLE, systemic sclerosis, dermatomyositis, polymyositis) that might influence the risk of NHL were excluded. Due to the need for longterm treatment, all patients who met the American-European Consensus Group criteria for pSS¹³ were qualified to apply for a CIC to be exempt from copayment. Their attending physician would provide relevant information for a formal review. A committee consisting of expert rheumatologists reviewed the applications and issued CIC for pSS if the diagnoses were validated.

Followup for cancer development. The included patients with pSS were followed for cancer development until December 31, 2013. The followup time was calculated from the application date for the CIC for pSS to the application date for the CIC for cancer, death, or until December 31, 2013. To apply for a cancer CIC, pathology reports or imaging studies supporting the cancer diagnosis were required. Only patients fulfilling the criteria of a specific cancer diagnosis were issued with a cancer CIC.

The NHL cohort and followup for development of pSS. We built an NHL cohort by identifying people from Taiwan's NHIRD having CIC of new-onset NHL (ICD-9 code 200, 202) between January 1, 1998, and December 31, 2012. Patients with previous pSS were excluded. The included patients were followed for development of pSS until December 31, 2013.

Statistical analysis. To examine whether the patients with pSS had a higher risk of developing cancer than the general population, we calculated the standardized incidence ratios (SIR; a ratio of observed to expected cancers)¹⁴ of overall and specific cancers in the patients with pSS. The calculation process is shown in Supplementary Table 1 and Supplementary

Table 2, available with the online version of this article. The observed cancer number was the newly diagnosed cancer cases. The expected cancer number was calculated by a stratification method according to the cancer incidence rate of the general population multiplied by the person-years of the pSS cohort in each stratum and then accumulated. The cancer incidence was the average cancer incidence from 1998 to 2013 of the general population stratified by sex (male/female) and age (< 20, 20–39, 40–59, 60–79, and ≥ 80 yrs). Similarly, to examine whether the patients with NHL had a higher risk of developing pSS, we calculated the SIR of pSS in the patients with NHL. We used Fisher's exact test to estimate the p values, and $p < 0.05$ was considered statistically significant. Data analyses were conducted using SAS software version 9.4 (SAS Institute).

RESULTS

Cohort of patients with pSS. A total of 17,459 patients with pSS were newly diagnosed from 1998 to 2012. After excluding 636 patients with previous cancer and 1187 with specific autoimmune disease, a total of 15,636 patients were included in our pSS cohort study (Figure 1).

Characteristics of patients with pSS. Of the pSS cohort, 1727 were male and 13,909 were female. The mean age at diagnosis was 54.1 years. The mean followup time was 5.6 years (Table 1).

Overall cancer risk in patients with pSS. Among the 15,636 patients with pSS, 741 (4.7%) developed cancer. The SIR of overall cancer in the patients with pSS compared to the general population in Taiwan's NHIRD after standardization for sex, age, and period was 1.4 (95% CI 1.3–1.5; Table 2; and Supplementary Table 1, available with the online version of this article).

Specific cancer risk in patients with pSS. The numbers of specific cancers that occurred at least 5 times are listed in Table 2. The SIR for hematological malignancies (SIR 3.9, 95% CI 3.1–4.8) in patients with pSS was higher than

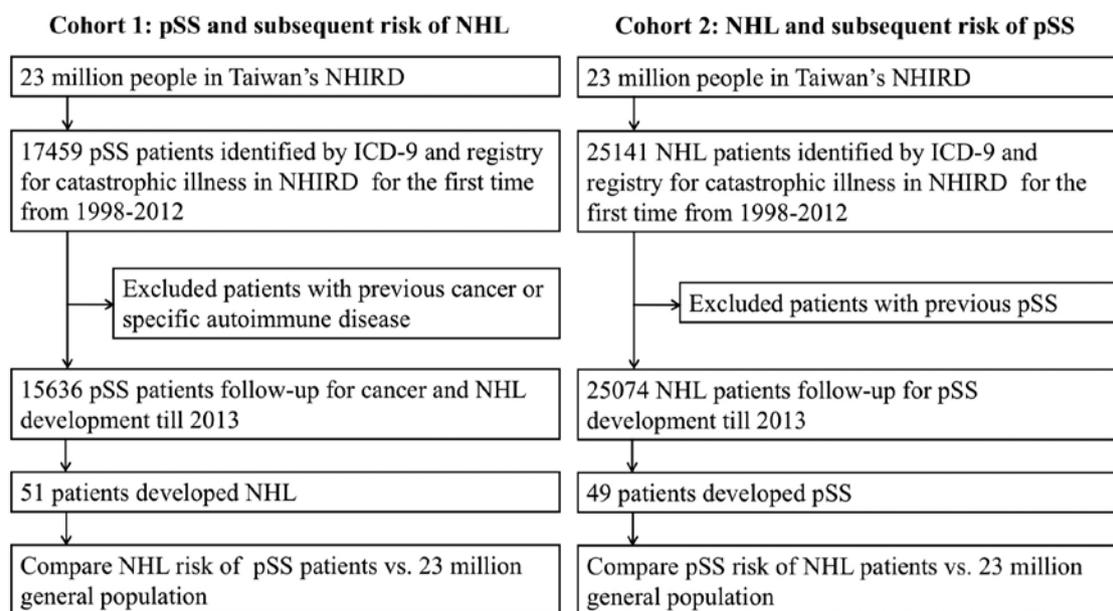


Figure 1. The study process. NHIRD: National Health Insurance Research Database; pSS: primary Sjögren syndrome; NHL: non-Hodgkin lymphoma; ICD: International Classification of Diseases.

Table 1. Characteristics of the 15,636 patients with primary Sjögren syndrome.

| Characteristics | |
|--|-----------------|
| Age at diagnosis, yrs, mean \pm SD | |
| Male | 59.6 \pm 15.5 |
| Female | 53.5 \pm 14.0 |
| All | 54.1 \pm 14.3 |
| Age groups, male, yrs, n (%) | |
| 0–9 | 2 (0.1) |
| 10–19 | 9 (0.5) |
| 20–29 | 62 (3.6) |
| 30–39 | 128 (7.4) |
| 40–49 | 278 (16.1) |
| 50–59 | 349 (20.2) |
| 60–69 | 372 (21.5) |
| 70–79 | 406 (23.5) |
| \geq 80 | 121 (7.0) |
| All | 1727 (100) |
| Age groups, female, yrs, n (%) | |
| 0–9 | 6 (0.04) |
| 10–19 | 109 (0.8) |
| 20–29 | 656 (4.7) |
| 30–39 | 1627 (11.7) |
| 40–49 | 3041 (21.9) |
| 50–59 | 4083 (29.4) |
| 60–69 | 2563 (18.4) |
| 70–79 | 1480 (10.6) |
| \geq 80 | 344 (2.5) |
| All | 13,909 (100) |
| Duration of followup, yrs, mean \pm SD | |
| Male | 5.6 \pm 3.8 |
| Female | 5.6 \pm 3.6 |
| All | 5.6 \pm 3.6 |

that for nonhematological malignancies (SIR 1.3, 95% CI 1.2–1.4). The highest SIR for specific cancer was that for NHL. Fifty-one patients with pSS developed NHL with an SIR of 4.6 (95% CI 3.4–6.0). Other significant SIR included a higher risk (only list SIR > 2) of multiple myeloma, leukemia, thyroid gland cancer, and mouth cancer, but a lower risk of colorectal cancer (Table 2; and Supplementary Table 2, available with the online version of this article).

NHL cohort. A total of 25,141 patients with NHL were newly diagnosed from 1998 to 2012. After excluding 67 patients with previous pSS, a total of 25,074 patients were included in our NHL cohort study (Figure 1).

Characteristics of patients with NHL. In the NHL cohort, 14,291 were male and 10,783 were female. The mean age at diagnosis was 58.2 years. The mean followup time was 6.6 years (Table 3).

Risk of pSS in patients with NHL. Among 25,074 patients with NHL, 49 developed pSS. The SIR of pSS in patients with NHL compared to the general population in Taiwan's NHIRD after standardization for sex, age, and period was 3.2 (95% CI 2.4–4.2; Table 4).

Risk according to followup year. The SIR of patients with pSS to develop NHL was 8.5 within the first year and then

declined. The SIR of patients with NHL to develop pSS was 7.4 within the first year and then declined. Both risks were highest within the first year (Table 5).

DISCUSSION

To our knowledge, this is the first study to report a bidirectional relationship between pSS and NHL. Our findings suggest that patients with pSS had a higher cancer risk of NHL, and that patients with NHL also had a higher risk of pSS. Moreover, the bidirectional relationship between pSS and NHL was strongest within 1 year after the diagnosis of each disease.

Regarding the cancer risk in patients with pSS, the results of a higher or lower risk of specific cancers were similar to previous large-scale studies^{7,8}. Our major results revealed that the patients with pSS had a slightly higher risk of overall cancer (SIR 1.4), a higher risk for hematological malignancies (SIR 3.9) than for nonhematological malignancies (SIR 1.3), and that the highest specific cancer risk was for NHL (SIR 4.6). Although the pathogenesis and clinical presentation vary in different autoimmune diseases, a higher risk of NHL in patients with certain autoimmune diseases, including pSS, has been widely reported^{4,5,6,7,8,9,10}. The possible mechanisms include^{15,16,17} (1) some pSS and NHL have similar genetic susceptibility or trigger factors (e.g., hepatitis C virus, Epstein-Barr virus); (2) B cell and T cell activation play crucial roles in the pathogenesis of both pSS and NHL; and (3) immunomodulators may increase the risk of NHL.

We further found that the patients with NHL also had a higher risk of pSS. Because this reverse relationship is first reported here and our investigative approach was based on the analysis of insurance claims data, the reason for this reverse relationship is not clear. The likely hypotheses include (1) some pSS may develop before NHL, but the symptoms and signs of pSS may be very mild and well tolerated, leading to a delayed diagnosis; (2) some pSS and NHL may have similar genetic or trigger factors^{15,16,17}; (3) radiotherapy or chemotherapy for NHL may cause dry mouth or dry eye^{18,19}; and (4) lymphoma cells may influence the immune system²⁰.

There are several limitations to our study. First, we did not have personal information for patients such as smoking habit, family history of malignancy or pSS, and laboratory measures including specific virus infection, which may be associated with the development of NHL or pSS. Second, misclassification of diseases may occur when using an administrative database. To minimize this bias, we included only patients with a CIC for pSS or NHL. The diagnoses of patients with CIC are reliable, because issuing a CIC requires a formal review to confirm the diagnosis. Further, longterm treatment is needed for patients with pSS and NHL. Patients with a CIC are exempted from copayments. Because the longterm treatment of both diseases involves

Table 2. Cancer risk in 15,636 patients with primary Sjögren syndrome (list includes only cancer number ≥ 5).

| Specific Cancer | Observed | Expected | SIR (95% CI) | p |
|------------------|----------|----------|---------------|----------|
| All | 741 | 521.52 | 1.4 (1.3–1.5) | < 0.001* |
| Nonhematological | 657 | 500.03 | 1.3 (1.2–1.4) | < 0.001* |
| Mouth | 24 | 10.46 | 2.3 (1.5–3.4) | < 0.001* |
| Nasopharynx | 11 | 5.95 | 1.8 (0.9–3.3) | 0.08 |
| Esophagus | 8 | 4.59 | 1.7 (0.8–3.4) | 0.19 |
| Stomach | 23 | 24.91 | 0.9 (0.6–1.4) | 0.80 |
| Colorectal | 48 | 77.48 | 0.6 (0.5–0.8) | < 0.001* |
| Liver | 94 | 55.86 | 1.7 (1.4–2.1) | < 0.001* |
| Gall bladder | 7 | 7.44 | 0.9 (0.4–1.9) | 0.93 |
| Pancreas | 10 | 9.89 | 1.0 (0.5–1.9) | 1.00 |
| Lung | 90 | 58.19 | 1.5 (1.2–1.9) | < 0.001* |
| Skin | 18 | 10.77 | 1.7 (1.0–2.6) | 0.05 |
| Breast | 124 | 92.47 | 1.3 (1.1–1.6) | 0.002* |
| Uterus | 32 | 42.55 | 0.8 (0.5–1.1) | 0.11 |
| Ovary | 20 | 11.15 | 1.8 (1.1–2.8) | 0.02* |
| Prostate | 20 | 11.60 | 1.7 (1.1–2.7) | 0.03* |
| Bladder | 20 | 14.29 | 1.4 (0.9–2.2) | 0.18 |
| Kidney | 19 | 14.70 | 1.3 (0.8–2.0) | 0.32 |
| Brain | 7 | 4.73 | 1.5 (0.6–3.0) | 0.40 |
| Thyroid gland | 42 | 14.41 | 2.9 (2.1–3.9) | < 0.001* |
| Hematological | 84 | 21.49 | 3.9 (3.1–4.8) | < 0.001* |
| NHL | 51 | 11.11 | 4.6 (3.4–6.0) | < 0.001* |
| Multiple myeloma | 13 | 3.09 | 4.2 (2.2–7.2) | < 0.001* |
| Leukemia | 20 | 6.92 | 2.9 (1.8–4.5) | < 0.001* |

*p < 0.05. NHL: non-Hodgkin lymphoma; SIR: standardized incidence ratio.

Table 3. Characteristics of the 25,074 patients with non-Hodgkin lymphoma.

| Characteristics | |
|--------------------------------------|--------------|
| Age at diagnosis, yrs, mean ± SD | |
| Male | 58.5 ± 19.8 |
| Female | 57.8 ± 18.9 |
| All | 58.2 ± 19.4 |
| Age, male, yrs, n (%) | |
| 0–9 | 313 (2.2) |
| 10–19 | 497 (3.5) |
| 20–29 | 626 (4.4) |
| 30–39 | 1016 (7.1) |
| 40–49 | 1745 (12.2) |
| 50–59 | 2520 (17.6) |
| 60–69 | 2770 (19.4) |
| 70–79 | 3144 (22.0) |
| ≥ 80 | 1660 (11.6) |
| All | 14,291 (100) |
| Age, female, yrs, n (%) | |
| 0–9 | 198 (1.8) |
| 10–19 | 254 (2.4) |
| 20–29 | 549 (5.1) |
| 30–39 | 828 (7.7) |
| 40–49 | 1491 (13.8) |
| 50–59 | 2033 (18.9) |
| 60–69 | 2235 (20.7) |
| 70–79 | 2106 (19.5) |
| ≥ 80 | 1089 (10.1) |
| All | 10,783 (100) |
| Duration of followup, yrs, mean ± SD | |
| Male | 6.7 ± 4.8 |
| Female | 6.6 ± 4.7 |
| All | 6.6 ± 4.8 |

significant financial burden, nearly all eligible patients apply for a CIC, in the authors' experience.

To our knowledge, this is the first study to report a bidirectional relationship between pSS and NHL. This is another autoimmune disease that has a bidirectional relationship with NHL (in addition to SLE)⁴. Our results may suggest being alert for patients with pSS or NHL who have early signs of the other disease. The underlying mechanisms of the bidirectional relationship merit further investigation.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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Table 4. Risk of primary Sjögren syndrome in the 25,074 patients with non-Hodgkin lymphoma by sex and age.

| Age | Incidence (1/1000) | Person-yr | Expected | Observed | SIR (95% CI) |
|-------------|--------------------|-----------|----------|----------|-----------------|
| Male, yrs | | | | | |
| < 20 | 0.0002 | 4503.7 | 0 | 0 | 0 |
| 20–39 | 0.0039 | 10,521.0 | 0.04 | 0 | 0 |
| 40–59 | 0.0155 | 25,318.8 | 0.39 | 3 | 7.7 (1.6–22.5) |
| 60–79 | 0.0465 | 36,371.4 | 1.69 | 4 | 2.4 (0.6–6.1) |
| ≥ 80 | 0.0449 | 18,328.2 | 0.82 | 1 | 1.2 (0.03–6.8) |
| All | | 95,043.2 | 2.94 | 8 | 2.7 (1.2–5.4) |
| Female, yrs | | | | | |
| < 20 | 0.0031 | 2591.5 | 0.01 | 0 | 0 |
| 20–39 | 0.0485 | 8260.9 | 0.40 | 7 | 17.5 (7.0–36.1) |
| 40–59 | 0.1792 | 21,408.1 | 3.84 | 22 | 5.7 (3.6–8.7) |
| 60–79 | 0.2425 | 27,931.1 | 6.77 | 12 | 1.8 (0.9–3.1) |
| ≥ 80 | 0.1245 | 11,422.5 | 1.42 | 0 | 0 |
| All | | 71,614.2 | 12.44 | 41 | 3.3 (2.4–4.5) |
| Total | | | | | |
| All | | 166,657.4 | 15.38 | 49 | 3.2 (2.4–4.2) |

SIR: standardized incidence ratio.

Table 5. Risk of developing the other disease according to years of followup.

| Years of Followup | Patients with pSS to Develop NHL | | | Patients with NHL to Develop pSS | | |
|-------------------|----------------------------------|-------|----------------|----------------------------------|-------|----------------|
| | O | E | SIR (95% CI) | O | E | SIR (95% CI) |
| < 1 | 15 | 1.76 | 8.5 (4.8–14.1) | 17 | 2.31 | 7.4 (4.3–11.8) |
| 1–3 | 16 | 3.53 | 4.5 (2.6–7.4) | 14 | 3.96 | 3.5 (1.9–5.9) |
| 3–5 | 7 | 2.68 | 2.6 (1.1–5.4) | 4 | 3.17 | 1.3 (0.3–3.2) |
| ≥ 5 | 13 | 3.14 | 4.1 (2.2–7.1) | 14 | 5.94 | 2.4 (1.3–4.0) |
| Total | 51 | 11.11 | 4.6 (3.4–6.0) | 49 | 15.38 | 3.2 (2.4–4.2) |

Observed (O): observed number. Expected (E): expected number. pSS: primary Sjögren syndrome; NHL: non-Hodgkin lymphoma; SIR: standardized incidence ratio.

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