

## EXTENDED REPORT

# Incidence of cancer in a nationwide population cohort of 7852 patients with primary Sjögren's syndrome in Taiwan

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## ABSTRACT

**Objective** Patients with primary Sjögren's syndrome (pSS) are at a higher risk of developing non-Hodgkin's lymphoma (NHL). However, little is known with regard to the risk of developing cancers other than NHL. The authors aimed in this study to compare the incidence of cancer in various sites among patients with pSS with the general population of Taiwan.

**Methods** The authors used National Health Insurance claims data to establish a nationwide population cohort of 7852 patients with pSS from 2000 to 2008 who did not have cancer prior to diagnosis of pSS. Incidence and standardised incidence ratios (SIRs) for cancer in various sites were calculated.

**Results** Among patients with pSS, 277 (2.9%) developed cancer. The SIR for cancer was 1.04 (95% CI 0.91 to 1.18) among patients of all ages with pSS and was 2.19 (95% CI 1.43 to 3.21) for patients aged 25–44 years. Female patients with pSS had a higher risk of NHL (SIR 7.1, 95% CI 4.3 to 10.3), multiple myeloma (SIR 6.1, 95% CI 2.0 to 14.2) and thyroid gland cancer (SIR 2.6, 95% CI 1.4 to 4.3) and a lower risk of colon cancer (SIR 0.22, 95% CI 0.05 to 0.65). In contrast, male patients with pSS were not at a higher risk of developing cancer in particular sites.

**Conclusion** Patients with pSS, overall, did not have higher risk of cancer, and only patients aged 25–44 years were at an increased risk of cancer compared with their counterparts in the general population. Cancer screening for patients with pSS, especially female patients, should focus on NHL and multiple myeloma and thyroid gland cancer.

## INTRODUCTION

Primary Sjögren's syndrome (pSS) is a chronic autoimmune disorder with polyclonal B-cell activation and lymphocytic infiltration of the exocrine glands, which is characterised by dry eyes and a dry mouth. The estimated annual incidence of pSS is 4–6 per 100 000 inhabitants, according to population-based studies.<sup>1–4</sup> Studies have shown that patients with pSS have a higher incidence of non-Hodgkin's lymphoma (NHL) compared with the general population, the standardised incidence ratio (SIR) ranging from 8.7 (95% CI 4.3 to 15.5) to 48.1 (95% CI 20.7 to 94.8).<sup>5–14</sup> However, due to the small number of patients observed in previous studies, little is known as to whether patients with pSS are also at a higher risk of developing cancers other than NHL.

The Taiwan National Health Insurance (NHI) programme is a mandatory single-payer health insurance system in which all citizens are obliged to participate. The NHI programme was implemented in 1995 and covered 99.5% of the population of Taiwan by the end of 2008.<sup>15</sup> The NHI Research Database has been released to researchers in an electronically encrypted form since 1999. The large sample sizes and high quality of cancer-related diagnosis of the claims data have ensured that this data set provides a valuable opportunity to estimate the incidence of cancer among patients with *Helicobacter pylori* infection,<sup>16 17</sup> diabetes mellitus<sup>18 19</sup> and autoimmune diseases.<sup>20–24</sup> We therefore aimed in this study to compare the incidence of cancer in various sites among patients with pSS with rates taken from the general population of Taiwan by using Taiwan NHI claims data.

## PATIENTS AND METHODS

### Data sources

The catastrophic illness file of the NHI claims data were used in this study. To avoid severe financial hardship for families coping with major injuries/illnesses, the NHI specifies 31 categories of catastrophic illness (eg, cancers, haemophilia, autoimmune diseases, chronic renal failure, etc) that are exempt from co-payment. The attending physician of a patient diagnosed as falling into one such category of catastrophic illness under the Department of Health guidelines can submit related information in application for a catastrophic illness certificate (CIC). Applications are formally reviewed by a committee, and if approved, patients are then exempted from co-payment.<sup>25</sup>

### Cohort of patients with pSS

In this study, the cohort of patients with pSS is confined to those aged  $\geq 25$  years between 2000 and 2008 who were approved for the CIC as a result of their pSS. To get a CIC for pSS, the patient's attending physician is required to provide relevant clinical and laboratory information as part of the application for review, and the review committee will assess applications according to the criteria of the American-European Consensus Group for pSS.<sup>26</sup>

We excluded patients with a CIC for pSS and a CIC for any other autoimmune disease, such

as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and other connective tissue diseases, who should instead be classified as having secondary SS. Patients who had a CIC for cancer before obtaining a CIC for pSS were also excluded.

### Identification of cancer

Cancer is one of 31 categories of catastrophic illness defined by NHI. To approve a CIC for cancer, the attending physician should provide pathology evidence and imaging studies supporting the diagnosis of cancer, which include radiographs, bone scans and CT or MRI scans. The records are reviewed by a committee, and only patients who meet the criteria for the diagnoses are issued with a CIC. The *International Classification of Diseases, Ninth Revision, Clinical Modification* codes were used to define cancer in various sites.

### Statistical analysis

We first calculated incidence of cancer (cases per 1000 person-years) in patients with pSS by sex and age (25–44, 45–64 and  $\geq 65$  years). To examine whether patients with pSS had a higher risk of developing cancer, we computed the SIRs and 95% CIs for cancer in patients with pSS. The expected number of cancer cases was estimated according to incidence of cancer among the general population matched for sex, age and periods (2000–2002, 2003–2005 and 2006–2008). We also calculated SIRs by the periods that were data-tracked (<1, 1–2, 3–4 and  $\geq 5$  years) to determine if the probability of a cancer diagnosis appearing in the claims data was affected by the length of period observed.

**Table 1** Characteristics of 7852 patients with pSS in Taiwan

|  |               |
|--|---------------|
| Age at diagnosis $\pm$ SD (years)              |               |
| Men  | 62 $\pm$ 14   |
| Women  | 53 $\pm$ 13   |
| Age, men (years, n (%))                        |               |
| 25–44  | 125 (13)      |
| 45–64  | 356 (38)      |
| $\geq 65$                                      | 460 (49)      |
| All ( $\geq 25$ )                              | 941 (100)     |
| Age, women (years, n (%))                      |               |
| 25–44  | 1881 (27)     |
| 45–64  | 3636 (53)     |
| $\geq 65$                                      | 1394 (20)     |
| All ( $\geq 25$ )                              | 6911 (100)    |
| Duration of follow-up (years, (mean $\pm$ SD)) |               |
| Men  | 3.4 $\pm$ 2.4 |
| Women  | 3.6 $\pm$ 2.4 |

**Table 2** Incidence and 95% CI for cancer in patients with pSS in Taiwan by sex and age

| Sex and age       | No  | Person-year | Incidence | 95% CI       |
|-------------------|-----|-------------|-----------|--------------|
| Women (years)     |     |             |           |              |
| 25–44             | 23  | 6926        | 3.3       | 2.1 to 5.0   |
| 45–64             | 85  | 12528       | 6.8       | 5.4 to 8.4   |
| $\geq 65$         | 73  | 4365        | 16.7      | 13.1 to 21.0 |
| All ( $\geq 25$ ) | 181 | 23819       | 7.6       | 6.5 to 8.8   |
| Men (years)       |     |             |           |              |
| 25–44             | 3   | 405         | 7.4       | 1.5 to 21.7  |
| 45–64             | 11  | 1304        | 8.4       | 4.2 to 15.1  |
| $\geq 65$         | 32  | 1718        | 18.6      | 12.7 to 26.3 |
| All ( $\geq 25$ ) | 46  | 3427        | 13.4      | 9.8 to 17.9  |

### RESULTS

A total of 7852 patients (6911 women and 941 men) aged  $\geq 25$  years were identified with pSS between 2000 and 2008. The average data-tracking period was 3.5 years. The mean age (SD) at the time of diagnosis of pSS was 54 (14) years, and most patients were 45–64 years of age (table 1).

A total of 227 (2.9%) patients with pSS were identified to have cancer after the diagnosis of pSS during the observation period of 27 246 person-years. The incidence of cancer among patients with pSS increased with age, and male patients had higher incidence than female patients (table 2).

The SIR for cancer was 1.04 (95% CI 0.91 to 1.18) for patients of all ages with pSS ( $\geq 25$  years), 2.19 (95% CI 1.43 to 3.21) for patients aged 25–44 years, 1.02 (95% CI 0.82 to 1.24) for patients aged 45–64 years and 0.94 (95% CI 0.76 to 1.12) for patients aged  $\geq 65$  years. The SIRs for cancer categorized by sex for various age groups are illustrated in table 3.

Most of the cancers were diagnosed during the first 2 years following the diagnosis of pSS. Where data representing longer periods of time were tracked, there was a lower probability of a cancer diagnosis being indicated—the greater the number of years, the lesser the chance of a cancer diagnosis appearing in the data (table 4).

Table 5 presents SIRs and 95% CI for cancers in various sites, showing the number of incident cancer types to be at least three. Female patients with pSS had a higher risk of NHL (SIR 7.08, 95% CI 4.25 to 10.3), multiple myeloma (MM) (SIR 6.09, 95% CI 1.98 to 14.2) and thyroid gland cancer (SIR 2.56, 95% CI 1.40 to 4.30) but had a lower risk of colon cancer (SIR 0.22, 95% CI 0.05 to 0.65). Male patients with pSS were not at a higher risk of developing cancer in some particular sites.

### DISCUSSION

The findings of this study suggest that the incidence of cancer among patients with pSS increased with age, and male patients had

**Table 3** SIR and 95% CI for cancer in patients with pSS in Taiwan by sex and age

| Sex and age       | Observed | Expected | SIR  | 95% CI       |
|-------------------|----------|----------|------|--------------|
| Women (years)     |          |          |      |              |
| 25–44             | 23       | 12.6     | 1.83 | 1.16 to 2.74 |
| 45–64             | 85       | 80.5     | 1.06 | 0.84 to 1.31 |
| $\geq 65$         | 73       | 62.7     | 1.16 | 0.91 to 1.46 |
| All ( $\geq 25$ ) | 181      | 155.8    | 1.16 | 0.99 to 1.33 |
| Men (years)       |          |          |      |              |
| 25–44             | 3        | 0.6      | 5.00 | 1.03 to 14.6 |
| 45–64             | 11       | 9.1      | 1.21 | 0.61 to 2.17 |
| $\geq 65$         | 32       | 35.9     | 0.89 | 0.61 to 1.26 |
| All ( $\geq 25$ ) | 46       | 45.6     | 1.01 | 0.74 to 1.35 |

**Table 4** SIR and 95% CI for cancer in patients with pSS in Taiwan by years of follow-up

| Years of follow-up | Observed | Expected | SIR  | 95% CI       |
|--------------------|----------|----------|------|--------------|
| Women (years)      |          |          |      |              |
| <1                 | 55       | 19.1     | 2.89 | 2.17 to 3.76 |
| 1–2                | 66       | 31.6     | 2.09 | 1.61 to 2.66 |
| 3–4                | 41       | 45.5     | 0.90 | 0.65 to 1.22 |
| $\geq 5$           | 19       | 59.6     | 0.32 | 0.19 to 0.50 |
| Men (years)        |          |          |      |              |
| <1                 | 17       | 4.8      | 3.56 | 2.07 to 5.70 |
| 1–2                | 14       | 6.0      | 2.32 | 1.27 to 3.89 |
| 3–4                | 11       | 10.3     | 1.07 | 0.54 to 1.92 |
| $\geq 5$           | 4        | 24.5     | 0.16 | 0.04 to 0.42 |

## Clinical and epidemiological research

**Table 5** SIR and 95% CI in patients with pSS in Taiwan by cancer sites

| Cancer sites (ICD-9 code)      | Observed | Expected | SIR  | 95% CI       |
|--------------------------------|----------|----------|------|--------------|
| <b>Women</b>                   |          |          |      |              |
| Mouth (140–145)                | 3        | 2.1      | 1.42 | 0.29 to 4.16 |
| Nasopharynx (147)              | 3        | 1.8      | 1.63 | 0.34 to 4.77 |
| Stomach (151)                  | 10       | 6.4      | 1.56 | 0.75 to 2.86 |
| Colon (153)                    | 3        | 13.5     | 0.22 | 0.05 to 0.65 |
| Rectum (154)                   | 5        | 8.2      | 0.61 | 0.20 to 1.42 |
| Liver (155)                    | 18       | 14.0     | 1.28 | 0.76 to 2.03 |
| Pancreas (157)                 | 3        | 2.6      | 1.13 | 0.23 to 3.31 |
| Lung (162)                     | 20       | 14.3     | 1.40 | 0.85 to 2.16 |
| Skin, excluding melanoma (173) | 4        | 2.6      | 1.56 | 0.42 to 3.99 |
| Breast, women (174)            | 37       | 37.4     | 0.99 | 0.70 to 1.36 |
| Cervix uteri (180)             | 7        | 10.8     | 0.65 | 0.26 to 1.34 |
| Ovary (183.0)                  | 6        | 4.1      | 1.46 | 0.54 to 3.19 |
| Bladder (188)                  | 6        | 3.4      | 1.77 | 0.65 to 3.84 |
| Kidney (189)                   | 5        | 4.2      | 1.18 | 0.38 to 2.76 |
| Thyroid gland (193)            | 14       | 5.5      | 2.56 | 1.40 to 4.30 |
| NHL (200, 202)                 | 23       | 3.2      | 7.08 | 4.25 to 10.3 |
| Multiple myeloma (203)         | 5        | 0.8      | 6.09 | 1.98 to 14.2 |
| <b>Men</b>                     |          |          |      |              |
| Liver (155)                    | 5        | 7.3      | 0.69 | 0.22 to 1.61 |
| Lung (162)                     | 9        | 7.3      | 1.23 | 0.56 to 2.33 |
| Prostate (185)                 | 7        | 5.0      | 1.41 | 0.57 to 2.91 |
| NHL (200, 202)                 | 3        | 1.0      | 3.10 | 0.64 to 9.05 |

ICD-9, *International Classification of Diseases, Ninth Revision*; NHL, non-Hodgkin's lymphoma.

a higher incidence than female patients. However, compared with the same sex–age group, patients with pSS, overall, did not have a higher risk of developing cancer, and only patients with pSS aged 25–44 years were at a significantly higher risk of cancer. Consistent with previous studies, patients with pSS in this study also had a higher risk of developing NHL. With regard to cancers other than NHL, this study found that female patients with pSS also had a higher risk of MM and thyroid gland cancer and a lower risk of colon cancer.

One of the strengths of this study has been that it was the first of its kind to use a nationwide population cohort, having the largest sample size compared with previous studies, this allowed us to calculate incidence of cancer among patients with pSS by sex–age group and to estimate the risk of cancers other than NHL.

With regard to the sex differences relating to rates of cancer among patients with pSS, we found a higher incidence of cancer developing in men than in women. A previous study in Taiwan also indicated higher mortalities among male patients with pSS than female patients with pSS, despite the fact that the incidence of pSS itself was higher in women than in men.<sup>4</sup> In other words, men are less likely to have pSS than women; however, once diagnosed with pSS, the male patient will have a poorer prognosis than a woman with pSS.

In terms of age differences relating to the occurrence of cancer among patients with pSS, it is expected that the incidence increases with age. However, if we compared the incidence of cancer among patients with pSS with their sex–age group counterparts in the general population, we found that only patients aged 25–44 years had a higher risk of developing cancer. This finding is consistent in patients with other autoimmune diseases such as SLE and RA, in which younger patients are also at a higher risk of developing cancer.<sup>20 24 27</sup>

Similar to previous studies on SLE and RA,<sup>20 24</sup> we also found that the risk of developing cancer decreased as the data-tracking period increased in years. Most of the cancers were identified within the first 2 years after diagnosis of pSS in this cohort. One possible explanation was that once pSS was diagnosed, the

attending physicians would vigilantly screen for cancers, which resulted in an earlier detection of cancer.

Consistent with previous studies,<sup>5–14</sup> patients with pSS in our study had a higher risk of developing NHL compared with the general population. However, the SIR for NHL in this study was 7.1, which was lower than previous studies that ranged from 8.7 to 48.1. Due to the different references used in calculating SIR, we could not compare the SIRs of different studies directly. However, we were still able to propose that the relatively low SIR for NHL in this cohort might be due to relatively short observation periods in this study.

In terms of the risk of cancers other than NHL, previous studies were inconclusive because of the small sample sizes for observation. In this study, we found that women with pSS also had a significantly higher risk of MM and thyroid gland cancer while having a lower risk of colon cancer.

The association between pSS and MM has been suggested in case reports.<sup>28–30</sup> The hypothesis was based on the observation that many patients with pSS had benign monoclonal gammopathy, and the association between benign monoclonal gammopathy and MM was well established.

Previous studies already found a high prevalence of thyroid disease, especially Hashimoto's thyroiditis, in patients with pSS.<sup>31–33</sup> It has been reported that Hashimoto's thyroiditis might be associated with an increased risk of developing papillary thyroid cancer among women.<sup>34</sup> This is a possible mechanism explaining the elevated risk of thyroid cancer in patients with pSS.

One accidental finding of this study was that patients with pSS had a lower risk of having colon cancer. There have been similar findings among patients with RA in Taiwan.<sup>20</sup> One possible explanation was that many patients with pSS also have fibromyalgia,<sup>31 35</sup> with an associated higher use of non-steroid anti-inflammatory drugs (NSAIDs) to relieve the pain. Since it has been suggested that NSAIDs decrease the risk of colon cancer,<sup>36 37</sup> it appears plausible that such a reduced risk of that condition in patients with pSS may be due to higher use of NSAIDs. Further studies are needed to examine the above-mentioned hypotheses.

Several limitations should be noted in this study. First, there were no laboratory data available in the claims data to which our study referred; we thus could not analyse in detail the predicting factors for cancer. Second, we included only patients with a CIC for pSS; some patients with pSS who did not apply for a CIC for this condition were not included in the cohort. Third, by the same token, some patients with cancer might not apply for a CIC for cancer, a situation which would not be identified in this study. Fourth, the average period that was data-tracked (3.5 years) in this study was relatively insufficient and should ideally be increased. Fifth, unlike the study of Lazarus *et al*<sup>12</sup> which included cancer either before or after diagnosis of pSS, we excluded those who had cancer before obtaining a CIC for pSS. In other words, some patients who had pSS and, then, had carcinogenesis changes long before applying for a CIC for pSS were excluded from this study. In consideration of the above-mentioned limitations, the risk of cancer was underestimated in this study.

In conclusion, according to the findings of this study, patients with pSS, overall, did not have a higher risk of cancer. Patients with pSS aged 25–44 years were at an increased risk of cancer compared with their counterparts in the general population. Female patients with pSS are associated with a higher risk of certain cancers such as NHL, MM and thyroid gland cancer. Physicians caring for patients with pSS should screen NHL, a

well-known cancer with elevated risk among patients with pSS, MM and thyroid gland cancer. Further studies are needed to investigate possible mechanisms associated with pSS and these cancers.

**Contributors** M-YW and T-HL initiated the study design and wrote the manuscript. Y-TH performed the analysis. All authors critically revised the manuscript.

**Competing interests** None.

**Ethics approval** The study was approved by the institutional review board of National Cheng Kung University Hospital.

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