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# Cancer Risk in Patients With Inflammatory Systemic Autoimmune Rheumatic Diseases

## *A Nationwide Population-Based Dynamic Cohort Study in Taiwan*

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**Abstract:** The aim of this study was to determine whether inflammation is related to cancer development, and whether the incidence of cancer is increased and occurs in a site-specific manner in patients with systemic autoimmune rheumatic diseases (SARDs).

This study included a nationwide dynamic cohort of patients with various newly diagnosed SARDs from 1997 to 2010 with follow-up until 2012.

This study included 75,123 patients with SARDs. During 562,870 person-years of follow-up, 2844 patients developed cancer. Between 1997 and 2010, the highest number of newly diagnosed SARDs cases were rheumatoid arthritis (n = 35,182), followed by systemic lupus erythematosus (SLE, n = 15,623), Sjögren syndrome (n = 11,998), Kawasaki disease (n = 3469), inflammatory bowel disease (n = 2853), scleroderma (n = 1814), Behçet disease (n = 1620), dermatomyositis (n = 1119), polymyositis (n = 811), and vasculitis other than Kawasaki disease (n = 644). A significant standardized incidence ratio (SIR) of overall cancer was observed for patients with SLE (1.41; 95% confidence interval [CI], 1.28–1.56), Sjögren syndrome (1.19; 95% CI, 1.08–1.30), scleroderma (1.27; 95% CI, 1.02–1.59), dermatomyositis (4.79; 95% CI, 4.01–5.73), polymyositis (1.47; 95% CI, 1.05–2.06),

vasculitis excluding Kawasaki disease (1.75; 95% CI, 1.20–2.55), and Kawasaki disease (2.88; 95% CI, 1.60–5.20). Overall, patients with most SARDs had a significantly higher risk of inflammation-associated site-specific cancers and hematologic malignancies.

This study confirms that autoimmunity is associated with site-specific and hematological malignancies and provides clinical evidence of an association between inflammation and subsequent site-specific cancer development. These findings support the importance of inflammation in site-specific organ system carcinogenesis.

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**Abbreviations:** BD = Behçet disease, CD = Crohn disease, CIC = catastrophic illness certificates, DM = dermatomyositis, IBD = inflammatory bowel disease, ILD = interstitial lung disease, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, PM = polymyositis, RA = rheumatoid arthritis, SARDs = systemic autoimmune rheumatic diseases, SIR = standardized incidence ratio, SLE = systemic lupus erythematosus, SS = Sjögren syndrome, SSc = systemic sclerosis, UC = ulcerative colitis.

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## INTRODUCTION

Chronic inflammation and autoimmunity are associated with malignancy development.<sup>1–6</sup> Infection and chronic inflammation may contribute to carcinogenesis through inflammation-related mechanisms.<sup>3–7</sup> Inflammation is a beneficial response activated to restore tissue injuries. However, unregulated inflammation can become chronic, triggering cellular events that induce malignant cell transformation and carcinogenesis in surrounding tissues. The tumors generally arise in the inflammatory tissue, indicating that local inflammatory mediators play an important role in carcinogenesis. Inflammatory mediators include metabolites of arachidonic acid, cytokines, chemokines, and free radicals. Chronic exposure to these mediators leads to increased cell proliferation, mutagenesis, oncogene activation, and angiogenesis.<sup>2,4</sup> The ultimate result is the proliferation of cells that have lost normal growth control. Inflammatory systemic autoimmune rheumatic diseases (SARDs), such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren syndrome (SS), systemic sclerosis (SSc), Behçet disease (BD), polymyositis (PM), dermatomyositis (DM), inflammatory bowel disease (IBD), and vasculitis may increase the risk of malignancy development, especially for lymphoproliferative disorders.<sup>1</sup> Several clinical studies have reported associations between SARDs and malignancy; however, these reports are controversial.<sup>8–11</sup> SARDs involve activation of autoreactive T and B lymphocytes and release of proinflammatory cytokines, which may increase hematological cancer risk.<sup>4–6</sup> However, whether SARDs increase the risk of cancers

other than lymphoma is uncertain. Moreover, though several SARDs target-specific organs and tissues, little is known about autoimmunity (inflammation) and target site (site-specific) cancer risk. Therefore, we performed a large cohort study in a Taiwanese population.

This study used the Taiwan National Health Insurance Research Database (NHIRD), a billing database for healthcare service, to estimate the incidence rates (crude and age-specific) of malignancies (overall and site-specific) after diagnosis of SARDs including RA, SS, SLE, SSs, BD, DM, PM, IBD (including Crohn disease [CD] and ulcerative colitis [UC]), and vasculitis; and to determine whether malignancy risk was higher in SARD patients than the general population by computing standardized incidence ratios (SIRs). Patients with various newly diagnosed SARDs from 1997 to 2010 in Taiwan became part of a nationwide dynamic cohort and were followed-up until 2012. In a dynamic cohort study, patients can be recruited at different times. This has advantages over a fixed cohort study: the participant number does not decline over time, and patient aging is not a problem.<sup>12</sup>

## PATIENTS AND METHODS

### Data Sources

The National Health Insurance Research Database (NHIRD) in Taiwan was the primary data source for this study. Since 1995, the National Health Insurance (NHI) program has provided compulsory, single payer and universal health insurance for Taiwan residence. Under a single payer system operated by the Taiwanese government, national health insurance covered 98% of Taiwan's population. All insurance claim data was stored in NHIRD, including birthdate, gender, diagnostic codes, surgery or procedures performed, medications prescribed, admission date, hospitalization, discharge date, medical institution codes, and expenditure amounts. Patient identification numbers were already encrypted for privacy protection; therefore, informed consent was not necessary and was waived. The Institutional Review Board of Chang Gung Medical Foundation approved this study (101-2178B).

### Study Design

This was a nationwide dynamic cohort study. The NHIRD database is updated and released publically on an annual basis. Patients with newly diagnosed major SARDs between January 1, 1997, and December 31, 2010, in Taiwan were identified and followed until the initial cancer diagnosis, death, or December 31, 2012 (whichever came first).

### SARD Patient Identification

The following codes from the Ninth Revision of International Classification of Diseases, Clinical Modification (ICD-9-CM) identified patients in this study: 714.0 for RA, 710.2 for SS, 710.0 for SLE, 710.1 for SSs, 136.1 for BD, 710.4 for DM, 710.3 for PM, 555 for CD, 556 for UC, and 446.0–446.7 for vasculitis (including polyarteritis nodosa, Kawasaki disease, hypersensitivity angiitis, Wegener granulomatosis, giant cell arteritis, and Takayasu disease). In Taiwan, SARD patients are eligible for catastrophic illness certificates (CIC) after review by 2 specialists based on clinical presentation, laboratory studies, imaging studies, and fulfillment of diagnostic criteria according to American College of Rheumatology classification. An advantage of holding a CIC is an exemption from copayment for medical treatment for the catastrophic illnesses. To avoid

misclassification of SARDs, SARD patients in this study were those who have also obtained a catastrophic illness certificates (CIC). Because cancer incidence was the outcome variable, patients with primary or metastatic cancer (ICD-9-CM 196–199) before SARD diagnosis (118, 0.1%) were excluded.

### Ascertainment of Cancer

Patients with newly diagnosed cancer were identified using ICD-9-CM codes (140–208.91). Cancer diagnoses were verified using certificates of catastrophic illness in the catastrophic illness database. In Taiwan, cancer is designated as a catastrophic illness after evaluation of pathology and/or cytology and a comprehensive review for exemption from all copayments. We estimated that around 99% of the SARD and cancer cases were covered in this database because both SARD and cancer patients are waived from copayment so nearly all cases were included in the NHIR database.

### Statistical Analysis

Crude cancer incidence rates were calculated as the total number of patients with cancer during the follow-up period divided by the person-years at risk. The person-years at risk was the sum of time for all patients from SARD diagnosis to the initial cancer diagnosis, NHI program dropout, death, or December 31, 2012 (whichever came first). This study did not deal with a second or recurrent cancer. For age-specific rates, the age shifted over time to reflect the risk in different age groups. Individuals contributed his/her observation time to several 5-year age categories during the follow-up time. The total number of person-years was the sum of the amount of observation time contributed by all patients to given 5-year age categories. These person-years were the denominators of the rates for the 5-year age categories.<sup>13</sup> The numerators of the rates for the 5-year age categories were the number of patients with cancer based on age at cancer diagnosis, not SARD diagnosis. The SIR is the ratio of the number of patients with cancer in this study to the expected number of patients with cancer based on age- and time-specific incidence rates in 5-year age intervals in the general Taiwanese population recorded in the Taiwan National Cancer Registry (1996–2000, 2001–2005, and 2006–2010).<sup>14</sup> The data consist of cases and population data for specific age groups over a certain calendar time period, in the form of a matrix of 5-year age groups with 5-year intervals. This quinquennial method (5-year age group intervals × 5 calendar year cancer rates) could coincide with the national cancer incidence rate that is typically published by 5-year age intervals every 5 calendar years.<sup>13</sup> SIR confidence intervals (CIs) were computed based on the Poisson distribution of observed cancer cases.<sup>15</sup>

## RESULTS

### Overall Incidence of Cancer in Patients With SARDs

This study included 75,123 patients with SARDs. There were 2844 patients with malignancies during the study period. Between 1997 and 2010, the highest number of newly diagnosed SARDs patients had RA (n = 35,182), followed by SLE (n = 15,623), SS (n = 11,998), Kawasaki disease (n = 3469), IBD (n = 2853), SSs (n = 1814), BD (n = 1620), DM (n = 1119), PM (n = 811), and vasculitis other than Kawasaki disease (n = 644). There were more females than males, with the female to male ratio being highest in SS (7.98), followed by SLE (7.09), RA (3.31), SSs (2.93), PM (2.04), DM (2.03),

vasculitis excluding Kawasaki disease (1.48), and BD (1.31). Alternatively, more males had IBD (female/male = 0.60) and Kawasaki disease (female/male = 0.56). The mean age at diagnosis was youngest for Kawasaki disease (3.0 years), followed by SLE (35.3 years), BD (37.1 years), DM (43.6 years), vasculitis excluding Kawasaki disease (43.0 years), IBD (43.2 years), PM (49.0 years), SSc (50.1 years), RA (52.6 years), and SS (53.5 years) (Table 1).

The cancer incidence rate (per 100,000 person-years) was highest for DM (1653.8), followed by PM (669.0), vasculitis excluding Kawasaki disease (636.8), SSc (636.7), SS (633.0), RA (590.9), IBD (378.9), SLE (316.4), BD (284.7), and Kawasaki disease (34.7). Though more females had SARDs, the overall cancer incidence rate was higher in male patients, except for in BD and Kawasaki disease. Significant SIRs of overall cancer were observed for patients with SS (1.19), SLE (1.41), SSC (1.27), DM (4.79), PM (1.47), vasculitis excluding Kawasaki disease (1.75), and Kawasaki disease (2.88) (Table 1). When stratified by gender, females with SS, SLE, SSc, DM, and Kawasaki disease had significant SIRs of overall cancer. For males, only patients with SLE, DM, PM, and vasculitis had significant SIRs of overall cancer. Compared to the general population, the overall risk of cancer was strikingly high for younger patients (<20 years old) with SSc (SIR = 36.21), DM (SIR = 8.56), RA (SIR = 7.72), and Kawasaki disease (SIR = 3.13). For patients 20 to 39 years old, the SIRs were highest in patients with DM (8.46), PM (5.82), IBD (2.27), and SLE (1.37). For patients 40 to 64 years old, the SIRs were highest for patients with DM (5.18) and ranged from 0.80 to 1.87 for the other SARDs. For older patients (>65 years), only patients with DM (3.58) and SSc (1.15) had significant SIRs (Table 2). Stratifying patients by follow-up time after SARD diagnosis revealed that the overall risk of cancer was highest within the first year of follow-up and decreased thereafter. Cancer risk after SARD diagnosis was most striking in DM patients, where the SIR was 16.19 within the first year, declined to 5.19 between 1 and <2 years, was 1.91 to 2.04 from 2 to 6 years, and was 0.88 to 0.75 after 6 years (Table 3). The SIR for RA patients during the study period was 1.04 (95% CI, 0.99–1.09; Table 1). The SIR for the young age group was strikingly high (SIR = 7.72; 95% CI, 3.47–17.19). When stratified by follow-up time after RA diagnosis, the risk of cancer was highest within the first year (SIR = 1.21; 95% CI, 1.07–1.37) and decreased thereafter (Table 3).

### Risk of Hematological Cancers in SARD Patients

Patients with all major SARDs except PM had an elevated risk of non-Hodgkin lymphoma. Patients with vasculitis, excluding Kawasaki disease, had the highest SIR for non-Hodgkin lymphoma (18.76), followed by DM (11.70), Kawasaki disease (7.93), BD (6.18), IBD (6.04), SLE (5.65), SS (5.13), RA (3.40), and SSc (3.18). Only patients with RA and PM had significant SIRs for Hodgkin lymphoma (5.12 and 41.89, respectively). Only patients with PM, IBD, and Kawasaki disease had significant SIRs for leukemia (Table 4).

### Risk of Site-Specific Solid Cancer in SARD Patients

For site-specific solid cancers, nasopharyngeal cancer (NPC) risk was highest in patients with DM (SIR = 64.45), followed by PM (SIR = 8.06), SSc (SIR = 5.93), SLE (SIR = 2.30), and SS (SIR = 2.04). Scleroderma patients had a higher risk of nasal cavity, sinus, and ear cancers (SIR = 8.70).

Significantly increased risk of a specific cancer type was frequently associated with only 1 SARD: DM patients and esophageal cancer (SIR = 4.90); SLE patients and stomach cancer (SIR = 1.88) and hepatobiliary cancer (SIR = 1.50); PM patients and gallbladder and common bile duct cancer (SIR = 7.79); RA patients and retroperitoneal and peritoneal cancer (SIR = 3.25); and PM patients and melanoma (SIR = 17.01). A significant risk of lung cancer was observed in patients with SS (SIR = 1.29), SLE (SIR = 1.38), SSc (SIR = 2.40), and DM (SIR = 9.41). Only patients with PM and Kawasaki disease had a significantly higher risk of bone cancer and other soft tissue sarcomas (SIR = 13.81 and 7.04, respectively). A significantly higher risk of thyroid cancer was seen in patients with SS (SIR = 2.49) and SLE (SIR = 1.97). Female patients with DM had several significant risks (breast cancer, SIR = 3.53; cervical cancer, SIR = 3.63; and ovarian cancer, SIR = 13.42). Alternatively, a significantly lower risk of colorectal cancer was observed in patients with RA (SIR = 0.78; 95% CI, 0.68–0.91) and SS (SIR = 0.54; 95% CI, 0.38–0.77) (Table 4).

## DISCUSSION

SARDs are a heterogeneous group of diseases characterized by involvement of connective tissues, skin, subcutaneous tissues, muscles, joints, and various internal organs. Malignancy is an important SARD-associated comorbidity.<sup>1</sup> Chronic inflammation and autoimmunity are associated with malignancy development.<sup>1–6,8–11</sup> Typical examples of inflammation-related carcinogenesis include: papillomavirus infection and cervical cancer; *Helicobacter pylori* infection and stomach cancer; and chronic hepatitis B and C virus infection and liver cancer.<sup>4,16</sup> Whether inflammatory SARDs increase cancer risk is uncertain. This study estimated the relative risks of overall and site-specific malignancies in SARD patients in a large nationwide dynamic cohort. We confirmed that autoimmunity was associated with malignancy. Patients with most SARDs had a significantly higher risk of inflammation-associated site-specific cancers and hematologic malignancies. Systemic autoimmune rheumatic diseases (SARD) are a heterogeneous group of immunologically mediated inflammatory disorders that affect specific target organs or multiple organ systems. As expected in a multisystem disease, the entire organ systems are vulnerable to injury. However, certain organs or tissues are vulnerable to injuries. For example, in the present study, there is an increased prevalence of lung cancer in patients with systemic sclerosis (SSc), Sjögren syndrome, SLE, and dermatomyositis, particularly in those with pulmonary involvement. Interstitial lung disease (ILD) is recognized as a frequent and serious complication of SScs, SS, lupus, and inflammatory myositis. SARD-associated interstitial lung disease (ILD) is characterized by pulmonary infiltration of inflammatory cells and subsequent fibrosis of the lung parenchyma. Depending on the underlying autoimmune disease process, the pleura, pulmonary parenchyma, or airway may be predominantly affected. Theoretically, systemic autoimmune rheumatic diseases (SARDs) are initiated by the loss of immunological tolerance to self-antigens and are characterized by activation of B cells or T cells, or both, leading to pathology.<sup>17</sup> The continuous accumulation and the rapid proliferation of differentiated fibroblasts in the regions of repeated epithelial injury, in combination with an increased resistance in apoptosis, features of pulmonary fibrosis, represent pathogenic mechanisms similar to those followed by cancer cells, including unlimited cell

**TABLE 1. Incidence of Cancer in Patients With Systemic Autoimmune Rheumatic Diseases From 1997 to 2012 in Taiwan**

	RA	SS	SLE	SSc	BD	DM	PM	IBD	Vasculitis**	Kawasaki
N (75123)	35182	11988	15623	1814	1620	1119	811	2853	644	3469
Age of SARD onset	52.56 ± 15.53	53.54 ± 14.42	35.34 ± 16.19	50.08 ± 16.1	37.04 ± 12.85	43.55 ± 19.23	49.03 ± 16.17	43.17 ± 16.46	43.00 ± 18.69	3.02 ± 3.81
Female/male	27018/8164	10653/1335	13693/1930	1353/461	920/700	750/369	544/267	1066/1787	384/260	1252/2217
F/M ratio	3.31	7.98	7.09	2.93	1.31	2.03	2.04	0.60	1.48	0.56
Cancer (O) (2844)	1604	461	395	79	37	120	34	76	27	11
Person-years	1115/489	376/85	330/65	56/23	23/14	72/48	19/15	23/53	14/13	5/6
Incidence	271443.40	72828.89	124832.45	12407.58	12994.62	7255.97	5081.92	20056.12	4239.99	31729.64
Female	590.92	632.99	316.42	636.71	284.73	1653.81	669.04	378.94	636.79	34.67
Male	523.14	579.03	297.93	581.47	312.20	1410.35	536.02	311.16	517.87	43.60
Expected (E)	838.65	1076.96	462.05	828.30	248.77	2231.66	975.76	418.50	846.01	29.61
Female	1548.98	387.82	279.17	62.05	31.06	25.03	23.08	79.30	15.45	3.82
Male	1080.15	301.24	231.12	41.44	17.40	16.12	14.18	27.27	8.36	1.31
SIR (95% CI)	1.04 (0.99, 1.09)	1.19* (1.08, 1.30)	1.41* (1.28, 1.56)	1.27* (1.02, 1.59)	1.19 (0.86, 1.64)	4.79* (4.01, 5.73)	1.47* (1.05, 2.06)	0.96 (0.77, 1.20)	1.75* (1.20, 2.55)	2.88* (1.60, 5.20)
Female	1.03 (0.97, 1.09)	1.25* (1.13, 1.38)	1.43* (1.28, 1.59)	1.35* (1.04, 1.76)	1.32 (0.88, 1.99)	4.47* (3.54, 5.63)	1.34 (0.85, 2.09)	0.84 (0.56, 1.27)	1.68 (0.99, 2.83)	3.81* (1.59, 9.16)
Male	1.04 (0.95, 1.14)	0.98 (0.79, 1.21)	1.35* (1.06, 1.72)	1.12 (0.74, 1.68)	1.02 (0.61, 1.73)	5.39* (4.06, 7.15)	1.69* (1.02, 2.80)	1.02 (0.78, 1.33)	1.83* (1.06, 3.16)	2.39* (1.08, 5.33)

BD = Behçet disease, CI = confidence interval, DM = dermatomyositis, IBD = inflammatory bowel disease, O = observed, PM = polymyositis, RA = rheumatoid arthritis, SARD = systemic autoimmune rheumatic disease, SIR = standardized incidence rate, SLE = systemic lupus erythematosus, SS = Sjögren syndrome, SSc = systemic sclerosis.

\* $P < 0.05$ .

\*\*Vasculitis: vasculitis excluding Kawasaki disease.

**TABLE 2. Cancer Risk Stratified by Age in Patients With Systemic Autoimmune Rheumatic Diseases**

	RA	SS	SLE	SSc	BD	DM	PM	IBD	Vasculitis**	Kawasaki
n	35182	11988	15623	1814	1620	1119	811	2853	644	3469
Observed/ expected	1604	461	395	79	37	120	34	76	27	11
<20 years	6/0.78	0/0.04	1/1.33	2/0.06	0/0.07	1/0.12	0/0.02	0/0.10	0/0.04	11/3.51
20–39 years	32/28.07	10/8.12	57/41.71	2/1.65	7/3.87	11/1.30	5/0.86	10/4.41	2/0.99	0/0.15
40–64 years	694/669.32	209/169.16	249/155.12	47/30.45	26/22.93	76/14.67	21/11.94	32/40.05	14/7.48	0/0.11
65+ years	872/850.82	242/210.50	88/81.02	28/29.90	4/4.19	32/8.94	8/10.26	34/34.74	11/6.94	0/0.05
SIR (95% CI)	1.04 (0.99, 1.09)	1.19* (1.08, 1.30)	1.41* (1.28, 1.56)	1.27* (1.02, 1.59)	1.19 (0.86, 1.64)	4.79* (4.01, 5.73)	1.47* (1.05, 2.06)	0.96 (0.77, 1.20)	1.75* (1.20, 2.55)	2.88* (1.60, 5.20)
<20 years	7.72* (3.47, 17.19)	0	0.75 (0.11, 5.55)	36.21* (9.06, 144.78)	0	8.56* (1.21, 60.73)	0	0	0	3.13* (1.73, 5.65)
20–39 years	1.14 (0.81, 1.61)	1.23 (0.66, 2.29)	1.37* (1.05, 1.77)	1.21 (0.30, 4.86)	1.81 (0.86, 3.80)	8.46* (4.69, 15.28)	5.82* (2.42, 13.98)	2.27* (1.22, 4.21)	2.02 (0.50, 8.07)	0
40–64 years	1.04 (0.96, 1.12)	1.24* (1.08, 1.42)	1.61* (1.42, 1.82)	1.54* (1.16, 2.06)	1.13 (0.77, 1.67)	5.18* (4.14, 6.49)	1.76* (1.15, 2.70)	0.80 (0.56, 1.13)	1.87* (1.11, 3.16)	0
65+ years	1.02 (0.96, 1.10)	1.15* (1.01, 1.30)	1.09 (0.88, 1.34)	0.94 (0.65, 1.36)	0.95 (0.36, 2.54)	3.58* (2.53, 5.06)	0.78 (0.39, 1.56)	0.98 (0.70, 1.37)	1.59 (0.88, 2.86)	0

BD = Behçet disease, CI = confidence interval, DM = dermatomyositis, IBD = inflammatory bowel disease, O = observed, PM = polymyositis, RA = rheumatoid arthritis, SIR = standardized incidence rate, SLE = systemic lupus erythematosus, SS = Sjögren's syndrome, SSc = systemic sclerosis.

\* $P < 0.05$ .

\*\*Vasculitis: vasculitis excluding Kawasaki disease.

**TABLE 3. Risk of Cancer Stratified by Follow-Up Time After Systemic Autoimmune Rheumatic Disease Diagnosis**

	RA	SS	SLE	SSc	BD	DM	PM	IBD	Vasculitis**	Kawasaki
n	35182	11988	15623	1814	1620	1119	811	2853	644	3469
Observed/ expected	1604	461	395	79	37	120	34	76	27	11
<1 year	254/209.27	103/73.00	66/37.05	24/9.95	10/3.59	79/4.88	17/4.34	18/11.56	8/2.80	2/0.63
1–<2 years	214/196.31	81/62.30	39/32.05	12/8.31	2/3.45	16/3.08	4/3.26	10/10.22	3/2.19	1/0.56
2–<4 years	365/349.72	101/100.64	78/57.27	11/14.35	8/6.63	10/5.24	6/5.26	16/18.23	6/3.60	2/0.89
4–<6 years	272/290.18	73/73.30	72/50.04	13/10.90	6/6.24	9/4.41	4/4.05	14/15.12	6/2.82	0/0.55
6–<8 years	224/225.99	60/48.13	55/42.08	10/8.44	4/4.93	3/3.43	3/3.08	6/11.65	0/1.97	2/0.44
8+ years	275/277.51	43/30.45	85/60.68	9/10.09	7/6.21	3/3.99	0/3.08	12/12.54	4/2.07	4/0.75
SIR (95% CI)	1.21* (1.07, 1.37)	1.41* (1.16, 1.71)	1.78* (1.40, 2.27)	2.41* (1.62, 3.60)	2.78* (1.50, 5.17)	16.19* (12.98, 20.18)	3.92* (2.43, 6.30)	1.56 (0.98, 2.47)	2.86* (1.43, 5.71)	3.17 (0.79, 12.69)
<1 year	1.09 (0.95, 1.25)	1.30* (1.05, 1.62)	1.22 (0.89, 1.67)	1.44 (0.82, 2.54)	0.58 (0.14, 2.32)	5.19* (3.18, 8.47)	1.23 (0.46, 3.27)	0.98 (0.53, 1.82)	1.37 (0.44, 4.26)	1.77 (0.25, 12.57)
1–<2 years	1.04 (0.94, 1.16)	1.00 (0.83, 1.22)	1.36* (1.09, 1.70)	0.77 (0.42, 1.38)	1.21 (0.60, 2.41)	1.91* (1.03, 3.55)	1.14 (0.51, 2.54)	0.88 (0.54, 1.43)	1.66 (0.75, 3.70)	2.25 (0.56, 8.99)
2–<4 years	0.94 (0.83, 1.06)	1.00 (0.79, 1.25)	1.44* (1.14, 1.81)	1.19 (0.69, 2.05)	0.96 (0.43, 2.14)	2.04* (1.06, 3.92)	0.99 (0.37, 2.62)	0.93 (0.55, 1.56)	2.13 (0.96, 4.73)	0
4–<6 years	0.99 (0.87, 1.13)	1.25 (0.97, 1.61)	1.31* (1.00, 1.70)	1.18 (0.64, 2.20)	0.81 (0.28, 2.16)	0.88 (0.28, 2.72)	0.97 (0.31, 3.02)	0.52 (0.23, 1.15)	0	4.57* (1.14, 18.27)
6–<8 years	0.99 (0.88, 1.12)	1.41* (1.05, 1.90)	1.40* (1.13, 1.73)	0.89 (0.46, 1.71)	1.13 (0.54, 2.36)	0.75 (0.24, 2.33)	0	0.96 (0.54, 1.69)	1.93 (0.72, 5.14)	5.34* (2.01, 14.24)

BD = Behçet disease, CI = confidence interval, DM = dermatomyositis, IBD = inflammatory bowel disease, O = observed, PM = polymyositis, RA = rheumatoid arthritis, SIR = standardized incidence rate, SLE = systemic lupus erythematosus, SS = Sjögren's syndrome, SSc = systemic sclerosis.

\* $P < 0.05$ .

\*\*Vasculitis: vasculitis excluding Kawasaki disease.

TABLE 4. Risk of Site-Specific Cancer in Patients With Systemic Autoimmune Rheumatic Diseases

	RA	SS	SLE	SSc	BD	DM	PM	IBD	Vasculitis**	Kawasaki
n	35182	11988	15623	1814	1620	1119	811	2853	644	3469
Observed	1604	461	395	79	37	120	34	76	27	11
Expected	1625.53	392.74	299.62	69.85	31.38	29.71	26.56	22.72	17.36	3.89
SIR (95% CI)	1.04 (0.99, 1.09)	1.19 (1.09, 1.30)	1.41 (1.28, 1.56)	1.27* (1.02, 1.59)	1.19 (0.86, 1.64)	4.79* (4.01, 5.73)	1.47* (1.05, 2.06)	0.96 (0.77, 1.20)	1.75* (1.20, 2.56)	2.88* (1.60, 5.20)
Oral cavity	0.85 (0.62, 1.16)	1.58 (0.92, 2.72)	1.47 (0.81, 2.65)	2.04 (0.76, 5.43)	0.88 (0.22, 3.52)	1.94 (0.48, 7.74)	0	0.36 (0.09, 1.45)	1.46 (0.21, 10.35)	0
Oropharynx, hypopharynx, and larynx	0.68 (0.40, 1.18)	1.22 (0.46, 3.25)	1.23 (0.40, 3.81)	2.38 (0.59, 9.51)	0	2.42 (0.34, 17.19)	2.47 (0.35, 17.54)	0.43 (0.06, 3.09)	0	0
Nasopharynx	1.34 (0.91, 1.99)	2.04* (1.02, 4.07)	2.30* (1.27, 4.16)	5.93* (2.47, 14.25)	1.12 (0.16, 7.96)	64.45* (44.50, 93.34)	8.06* (2.60, 25.01)	0	0	0
Nasal cavity, sinus, and ear	1.81 (0.75, 4.36)	1.60 (0.23, 11.34)	0	8.70* (1.23, 61.79)	0	0	0	0	0	0
Esophagus	0.64 (0.37, 1.11)	1.37 (0.57, 3.28)	0.83 (0.21, 3.30)	1.16 (0.16, 8.21)	0	4.90* (1.22, 19.58)	0	0.45 (0.06, 3.18)	0	0
Stomach	0.92 (0.72, 1.16)	1.00 (0.63, 1.58)	1.88* (1.21, 2.91)	0.70 (0.17, 2.79)	0	1.88 (0.47, 7.52)	0	0.53 (0.13, 2.11)	0	0
Small intestine	0.98 (0.44, 2.19)	0	1.08 (0.15, 7.63)	0	0	0	0	0	0	0
Colorectum	0.78 (0.68, 0.91)	0.54* (0.38, 0.77)	1.05 (0.75, 1.45)	0	1.38 (0.57, 3.31)	1.47 (0.61, 3.53)	1.2 (0.45, 3.20)	0.89 (0.48, 1.66)	0.46 (0.07, 3.29)	0
Hepatobiliary	0.97 (0.84, 1.11)	1.26 (0.97, 1.63)	1.50* (1.09, 2.06)	0.38 (0.12, 1.19)	1.06 (0.40, 2.82)	1.62 (0.67, 3.89)	0.97 (0.31, 3.00)	0.66 (0.33, 1.32)	1.48 (0.48, 4.60)	0
Gallbladder and CBD	1.03 (0.66, 1.59)	0.82 (0.31, 2.18)	1.61 (0.60, 4.29)	0	0	3.94 (0.56, 27.98)	7.79* (1.95, 31.15)	1.23 (0.17, 8.73)	0	0
Pancreas	0.81 (0.55, 1.20)	0.52 (0.20, 1.39)	1.50 (0.68, 3.35)	0	0	2.40 (0.34, 17.01)	2.38 (0.34, 16.89)	1.39 (0.35, 5.56)	0	0
Retropitoneum and peritoneum	3.25* (1.63, 6.50)	0	3.73 (0.93, 14.90)	0	0	0	0	0	0	0
Lung	1.13 (0.99, 1.29)	1.29* (1.00, 1.65)	1.38* (1.00, 1.92)	2.40* (1.51, 3.80)	0.74 (0.19, 2.96)	9.41* (6.41, 13.83)	2.20 (0.99, 4.91)	0.71 (0.34, 1.49)	1.63 (0.52, 5.04)	0
Bone and other soft tissue sarcoma	1.02 (0.53, 1.95)	0.92 (0.23, 3.67)	0.84 (0.21, 3.36)	2.68 (0.38, 19.06)	3.85 (0.54, 27.30)	5.63 (0.79, 39.97)	13.81* (3.45, 55.22)	0	0	7.04* (1.76, 28.16)
Melanoma	1.20 (0.50, 2.89)	2.87 (0.93, 8.90)	0	0	0	0	17.01* (2.40, 120.74)	0	0	0
Non-melanoma skin cancer	0.82 (0.60, 1.12)	0.97 (0.55, 1.70)	0.87 (0.39, 1.93)	1.14 (0.28, 4.55)	3.18 (0.79, 12.70)	3.17 (0.79, 12.67)	0	0.47 (0.07, 3.31)	0	0
Female breast	0.98 (0.86, 1.12)	1.18 (0.94, 1.48)	1.20 (0.96, 1.51)	0.99 (0.51, 1.90)	1.31 (0.62, 2.75)	3.53* (2.09, 5.95)	0.64 (0.16, 2.57)	0.67 (0.25, 1.77)	0.50 (0.07, 3.54)	0
Uterus	0.88 (0.62, 1.25)	0.45 (0.19, 1.09)	0.31 (0.10, 0.95)	2.55 (0.96, 6.79)	1.17 (0.16, 8.28)	0	1.88 (0.26, 13.35)	0.99 (0.14, 7.03)	3.01 (0.42, 21.35)	0
Cervix	0.92 (0.72, 1.19)	0.84 (0.49, 1.41)	1.75* (1.22, 2.52)	1.49 (0.36, 3.97)	0	3.6* (1.36, 9.67)	1.13 (0.16, 8.01)	0	1.83 (0.26, 12.99)	0
Ovarian	1.03 (0.72, 1.49)	1.60 (0.93, 2.75)	0.93 (0.46, 1.86)	1.67 (0.42, 6.67)	1.67 (0.42, 6.67)	13.42 (6.4, 28.14)	0	1.25 (0.18, 8.90)	0	0
Prostate	1.04 (0.78, 1.40)	1.44 (0.86, 2.44)	0.54 (0.14, 2.16)	1.09 (0.27, 4.37)	2.33 (0.33, 16.51)	0	0	0.57 (0.14, 2.27)	1.73 (0.24, 12.27)	0
Bladder	1.21 (0.91, 1.62)	1.21 (0.87, 2.18)	1.08 (0.45, 2.59)	2.69* (1.01, 7.18)	3.87 (0.97, 15.46)	1.86 (0.26, 13.23)	1.85 (0.26, 13.12)	2.38 (0.99, 5.72)	16.27* (7.31, 36.22)	0
Kidney (except pelvis)	0.46 (0.22, 0.97)	0.27 (0.04, 1.94)	0.82 (0.21, 3.29)	1.66 (0.23, 11.77)	0	0	0	2.27 (0.57, 9.06)	0	0
Brain	1.23 (0.68, 2.22)	1.85 (0.70, 4.94)	1.74 (0.65, 4.64)	0	3.81 (0.54, 27.05)	0	6.87 (0.97, 48.76)	3.67 (0.92, 14.67)	0	0
Thyroid	1.24 (0.92, 1.67)	2.49* (1.68, 3.69)	1.97* (1.35, 2.87)	1.27* (0.32, 5.09)	0	2.66 (0.67, 10.64)	1.71 (0.24, 12.17)	0.65 (0.09, 4.63)	2.37 (0.33, 16.85)	0
Non-Hodgkin lymphoma	3.40 (2.81, 4.10)	5.13 (3.79, 6.95)	5.65 (4.02, 7.95)	3.18 (1.19, 8.48)	6.18 (2.32, 16.46)	11.70 (5.26, 26.05)	0	6.04 (3.25, 11.23)	18.76* (8.43, 41.75)	7.93* (1.98, 31.71)
Hodgkin lymphoma	5.12 (2.30, 11.40)	0	0	0	0	0	41.89* (5.90, 297.42)	0	0	0
Leukemia	1.21 (0.85, 1.73)	1.58 (0.85, 2.94)	1.35 (0.65, 2.84)	1.01 (0.14, 7.17)	3.66 (0.92, 14.65)	0	5.37 (1.34, 21.45)	5.82 (2.91, 11.65)	3.71 (0.52, 26.32)	4.15* (1.73, 9.98)

BD = Behçet disease, CBD = common bile duct, CI = confidence interval, DM = dermatomyositis, IBD = inflammatory bowel disease, PM = polymyositis, RA = rheumatoid arthritis, SIR = standardized incidence rate, SLE = systemic lupus erythematosus, SS = Sjögren syndrome, SSc = systemic sclerosis.

\*P < 0.05.

\*\*Vasculitis: vasculitis excluding Kawasaki disease.

multiplication, cellular immortality, and rapid immigration, which characterize cancer metastasis.<sup>17</sup> Similarly to previous reports, we found that SARDs, particularly idiopathic inflammatory myopathies, vasculitis, SLE, SS, and scleroderma, increased risk of site-specific malignancies.<sup>1,2,4,8–11,18–22</sup> Malignancy was of greatest concern for patients with DM and, to a lesser degree, PM; these SARDs have well-documented associations with a wide range of cancers. The malignancy spectrum associated with DM and PM parallels the distribution in the general population.<sup>23,24</sup> For example, NPC is the malignancy most commonly associated with inflammatory myositis in Taiwan,<sup>22</sup> but is rare in other countries.<sup>24</sup> Furthermore, Hodgkin and non-Hodgkin lymphoma were increased in RA patients, and non-Hodgkin lymphoma was increased in SLE patients. Notably, the decreased risk of colorectal cancer in RA and SS patients may be due to long-term nonsteroidal anti-inflammatory drug (NSAID) use.<sup>25,26</sup> The only exception was BD, where the risk of cancer, other than non-Hodgkin lymphoma, was not increased. Moreover, alimentary tract cancer was not increased in IBD patients, either because of insufficient observation time or lack of increased risk. In previous studies of IBD, overall cancer risk was elevated in patients with CD, but not in patients with UC.<sup>27</sup> However, we found that overall cancer incidence and mortality risk were similar between IBD patients and the general population. Separating data for CD and UC did not change the results significantly (data not shown).

Inflammation-related cancer incidence varies geographically. Ethnicity may also influence cancer risk. For example, NPC is rare in most of the world, but is common in Southern China and Southeast Asia.<sup>28</sup> NPC risk was increased in patients with SS, SLE, SSC, DM, and PM. The role of Epstein-Barr virus infection in certain SARDs patients with malignancies should be studied further. Recent epidemiological studies show that inflammation-related cancers occur in a complex background influenced by patient age, gender, geographical region, era, and county development.<sup>1,4</sup> Inflammatory environments also accelerate epigenetic alterations, which could cause inflammation-related carcinogenesis.<sup>1–11,29</sup> Cancer risk has been extensively studied in RA patients, with most studies finding associations between RA and a higher risk of hematopoietic malignancies and a lower risk of colorectal cancer.<sup>1,8–11</sup> Inflammatory SARDs involve activation of autoreactive T and B lymphocytes and release of proinflammatory cytokines that can increase hematological cancer risk.<sup>30,31</sup> Overall cancer risk was not increased in RA patients in our study; however, their risk of lymphoma and retroperitoneal and peritoneal malignancies was significantly increased. These increased risks were offset by the significantly decreased colorectal cancer risk. The role of RA drug treatment in lymphoma development is very controversial and requires further evaluation.<sup>1,10</sup> A novel finding in this study was that BD and vasculitis were associated with a higher risk of non-Hodgkin lymphoma than SLE, SS, RA, and SSC.

In this study, the SIRs for most SARDs were significantly elevated for the first year, but became insignificant after 2 years of follow-up. When stratified by follow-up time after SARD diagnosis, overall cancer risk for most SARDs patients was highest for the first year of follow-up and decreased thereafter. It is unclear why cancer risk was highest during the first year after SARD diagnosis. Once possibility is increased surveillance and health checkups for younger patients with SARDs, but this requires further investigation. Malignancy risk was increased both early and later for SLE and SS patients, but was most significantly elevated during the first year. This

suggests that undiagnosed malignancies may have been pre-existing in a proportion of SARDs patients, rather than SARDs predisposing the patients to malignancy. Moreover, the possibility that occult chronic inflammation present with SARDs onset uncovered the oncogenesis process concomitant with the occult chronic inflammatory process cannot be excluded and should be studied further. The pathogenesis of cancer in SARDs patients remains unclear. Further studies are needed to clarify the mechanisms linking SARDs and cancer.

Our study had several limitations. First, we lacked information concerning cancer-associated covariates including smoking habits, alcohol consumption, body mass index, disease activity, physical activity, high-fat diet, and family history of malignancy. Also, the sample size might be small for examining associations with cancer at certain sites. Additionally, patients with mild disease may not have obtained catastrophic illness certificates (CIC). However, these patients composed of <1% of cases. Another limitation stems from coding and keying errors, which should be minimal as the quality of these data sets is monitored routinely. Another limitation is that it is unclear whether the drugs used to treat SARDs, including alkylating agents, azathioprine, methotrexate, and anti-TNF- $\alpha$  therapy, contribute to malignancy risk.<sup>1,10</sup> Finally, extrapolating our results to a Caucasian population requires caution. A strength of this study was its large and representative sample that included nearly all newly diagnosed patients with SARDs in Taiwan from 1997 to 2010. The dynamic cohort format prevented inclusion of a number of participants who were declining and aging.<sup>12</sup> Another strength is that misclassification of SARDs and cancer is unlikely as these diseases are designated as catastrophic illnesses, which requires clinical presentation, laboratory and imaging examinations for SARDs, pathology, imaging, and/or cytology evidence for cancer. Moreover, cancer patients with paraneoplastic syndrome will not apply for SARD catastrophic cards and vice versa, so misclassification and confounding by paraneoplastic syndromes should be minimal or nonexistent. Another strength was our age-specific cancer rates that were calculated by shifting patients between age groups over time, and our calculation of SIRs using the quinquennium method, which should minimize statistical errors.

In summary, this study assessed cancer risk in a large SARDs cohort ( $n = 75,123$ ). We investigated overall cancer risk, the risk of specific cancers, and the risk of site- and gender-specific malignancies in patients with SARDs in order to provide clinical evidence of associations between local inflammation and site-specific cancer development. This study supports the role of inflammation in cancer and the risk of cancer in patients with immune-mediated inflammatory SARDs. Future studies are necessary to determine how cancer risk is impacted by different drug classes used in SARD treatment, including biologicals such as TNF- $\alpha$  inhibitors, corticosteroids, nonsteroid anti-inflammatory drugs, and disease-modifying antirheumatic drugs.

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