The influence of immunosuppressants on non-melanoma skin cancer among patients with systemic lupus erythematosus and primary Sjögren's syndrome: a nationwide retrospective case-control study in Taiwan

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Abstract

Objective

To investigate the influence of corticosteroids and hydroxychloroquine on the association with non-melanoma skin cancer (NMSC) among patients with systemic lupus erythematosus (SLE) or primary Sjögren's syndrome (pSS).

Methods

This nationwide retrospective case-control study retrieved data from Taiwan National Health Insurance Research Database from 1995-2013. Cases with newly-diagnosed NMSC (n=19,603) and controls without NMSC were matched in a 1:1 ratio according to age, sex, and reference date. SLE, pSS, NMSC, and co-morbidities were determined by ICD-9-CM code. Cumulative drug exposures were defined by cumulative dosages or total defined daily dose (TDDD) of the Anatomical Therapeutic Chemical code of medicines. The analysis used conditional logistic regression and adjusted for age, sex, residential area, occupation, and co-morbidities. Case-control studies cannot infer the causality.

Results

Compared to patients without SLE or pSS, the patients with SLE had significantly higher associations with NMSC (cases/controls: n=23/10, adjusted odds ratio (AOR)=2.33, 95% confidence interval (CI) 1.08–5.01), particularly those using corticosteroids with a cumulative dosage >5g (cases/controls: n=17/5, AOR=2.96, 95%CI 1.06–8.23); and those using hydroxychloroquine with a cumulative dosage >100 TDDD (cases/controls: n=18/6, AOR=2.7, 95%CI 1.04–6.98). The patients with pSS had significantly higher associations with NMSC (cases/controls: n=28/11, AOR=2.56, 95%CI 1.25–5.23), particularly those using hydroxychloroquine with a cumulative dosage >100TDDD (cases/controls: n=20/4, AOR=5.41, 95%CI 1.82–16.11), and those using corticosteroids with a cumulative dosage >1g (cases/controls: n=13/3, AOR=4.92, 95%CI 1.37–17.61).

Conclusion

The patients with SLE or pSS had significantly increased associations with NMSC, especially those receiving higher cumulative doses of corticosteroids and hydroxychloroquine.

Key words

systemic lupus erythematosus, primary Sjögren's syndrome, non-melanoma skin cancer, corticosteroids, hydroxychloroquine, retrospective case-control study, Taiwan National Health Insurance Research Database

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Introduction

Recent epidemiologic evidences have proposed that certain cancers occur more frequently in patients with systemic lupus erythematosus (SLE), primary Sjögren's syndrome (pSS), dermatomyositis, and polymyositis, compared with the general population. The risk appears to be the highest for lymphoma (1-4). Several population-based cohort studies have reported an increased risk of squamous cell skin cancer in patients with SLE (1, 2, 5, 6). Patients with pSS who presented life-threatening systemic diseases usually received more glucocorticoids, immunosuppressants, intravenous immunoglobulines, and rituximab. Lymphoma was among the specially-concerned poor outcomes with high mortality rate in patients with pSS (7). A patient with pSS did not have histories of any systemic diseases within 10 years after diagnosis, and then he developed multiple squamous cell carcinoma on face and neck within 2 years (8).

Patients with connective tissue diseases (CTDs) require lifelong treatment to control disease activity. Non-melanoma skin cancer (NMSC) has been reported to be among the 10 leading types of cancer in Taiwan (9). Therefore, one particular concern is whether the risk of NMSC in patients with CTDs is increased by the long-term use of systemic corticosteroids, hydroxychloroquine, and other immunosuppressants.

Several epidemiological studies of CTDs have been conducted using the Taiwan National Health Insurance Research Database (NHIRD) (10-12). A previous cohort study investigated the incidence rate and risk of overall and specific malignancies in patients with inflammatory systemic autoimmune rheumatic diseases, and showed that the risk of skin cancer was not significantly higher in patients with any CTD than in the general population, except for those with polymyositis. The influence of treatment for CTDs was not considered (13). Another cohort study on patients with SLE showed that the risk of overall cancer was higher in those receiving cyclophosphamide and lower in those using hydroxychloroquine, however, the risk of NMSC was not reported (14). Previous reports seldom investigated the association between CTDs and skin cancer, especially SLE and pSS.

The aim of this case-control study was to investigate the association between CTDs and NMSC, especially SLE and pSS, and evaluate the influence of their treatment on NMSC, focusing on systemic corticosteroids and hydroxychloroquine by using the Taiwan NHIRD.

Patients and methods

Data sources

The primary data source was the Taiwan NHIRD. The National Health Insurance programme in Taiwan has provided compulsory, single-payer and universal health insurance for all residents since 1995, and enrols around 99% of the whole population. The registration files and insurance claims data in the NHIRD include birth date, sex, area of residence, occupation categories, diagnostic codes, medications prescribed, surgery or procedures performed, hospitalisations, and expenditure.

The Longitudinal Health Insurance Database (LHID) 2010 contains the original claims data of one million beneficiaries who were enrolled and randomly sampled from all beneficiaries of the NHIRD in the year 2010, and were also followed from 1995 to 2013. The Taiwan catastrophic illness certificates database (TCICD) includes original claims data of all patients with a catastrophic illness certificate (CIC) extracted from the NHIRD from 1995 to 2013. Patients with CTDs or cancer are eligible for a CIC, and those with a CTD must fulfill the diagnostic criteria of the American College of Rheumatology classification. All patients with diagnosis of a CIC were confirmed by two specialists through a review of the patients' clinical presentation, laboratory data, pathological reports, and imaging studies because they are exempt from copayment. The TCICD covers approximately 99% of all eligible patients. To protect privacy, patient identification numbers are encrypted in the NHIRD, and therefore informed consent was waived for this study. This study was approved by the Institutional Review Board of Kaohsiung Veterans General Hospital (VGHKS15-EM10-02) com-

plying with the principles of Declaration of Helsinki.

Study design

This is a nationwide population-based retrospective case-control study with two study groups: a case group with NMSC and a control group without NMSC. The case group identified all patients with newly-diagnosed NMSC (number (n)=19,603) between January 1, 2000, and December 31, 2013 from the TCICD. The diagnoses were using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes. NMSC (ICD-9-CM code 173) includes basal cell carcinoma, squamous cell carcinoma, and malignant neoplasm of sebaceous and sweat glands. The first diagnosis date of NMSC in the TCICD was the reference date (calendar day/ month/ year) of each patient in the case group. After excluding patients with malignancies (ICD-9-CM codes 140-208, including skin cancer), the control group was matched to the case group in a 1:1 ratio by age, sex, and the reference date using propensity score matching (15) and as identified in the LHID2010 from 1995-2013. The patients with NMSC as the outcome were identified first to recruit a sufficient number, and then the patients with CTDs (ICD-9-CM code 710) [SLE (710.0), systemic sclerosis (SSc) (710.1), pSS (710.2), polymyositis (710.3), and dermatomyositis (710.4)] and co-morbidities were identified retrospectively as exposure before the reference date of the case and control group in the TCICD from 1995-2013. Primary Sjögren's syndrome (pSS) rather than secondary Sjögren's syndrome was identified in the TCICD. None of the control group had dermatomyositis or polymyositis were found in the control group, so dermatomyositis and polymyosities were not included in the analysis (n. in cases/controls: dermatomyositis: 3/0, polymyositis: 1/0). The information of patients with CTDs whose first diagnosed dates were in the first launched year of NHIRD (1995) was excluded in the analysis.

The patients with other co-morbidities were identified before the reference date of the case and control group from 1995-2013, including diabetes mellitus (DM; ICD-9-CM code 250), hypertension (HT; 401-405), coronary artery disease (CAD; 410-414, A270, and A279), chronic kidney disease (CKD; 585), chronic obstructive pulmonary disease (COPD; 490-496, a surrogate for smoking), obesity (278, 278.00, 278.01, and V778), and any organ transplant (OT; V42.0-V42.9). The diagnoses were based on at least two outpatient visits and a hospitalisation event with those diagnostic codes. Figure 1 shows the flowchart of patients' selection and exclusion criteria. The area of residence and occupation were used to represent the level of sun exposure in this study and they were adjusted as confounders.

The exclusion criteria were those with diagnoses of any cancer (ICD-9-CM code 140-208) before the reference date of the control group (n=54,645), an age <18 years (cases/controls: n=162/248,696), and incomplete NHIRD information (cases/controls: n=3/4). Patients with skin cancer identified before the first diagnosis of CTDs and co-morbidities in the cases and control groups were also excluded.

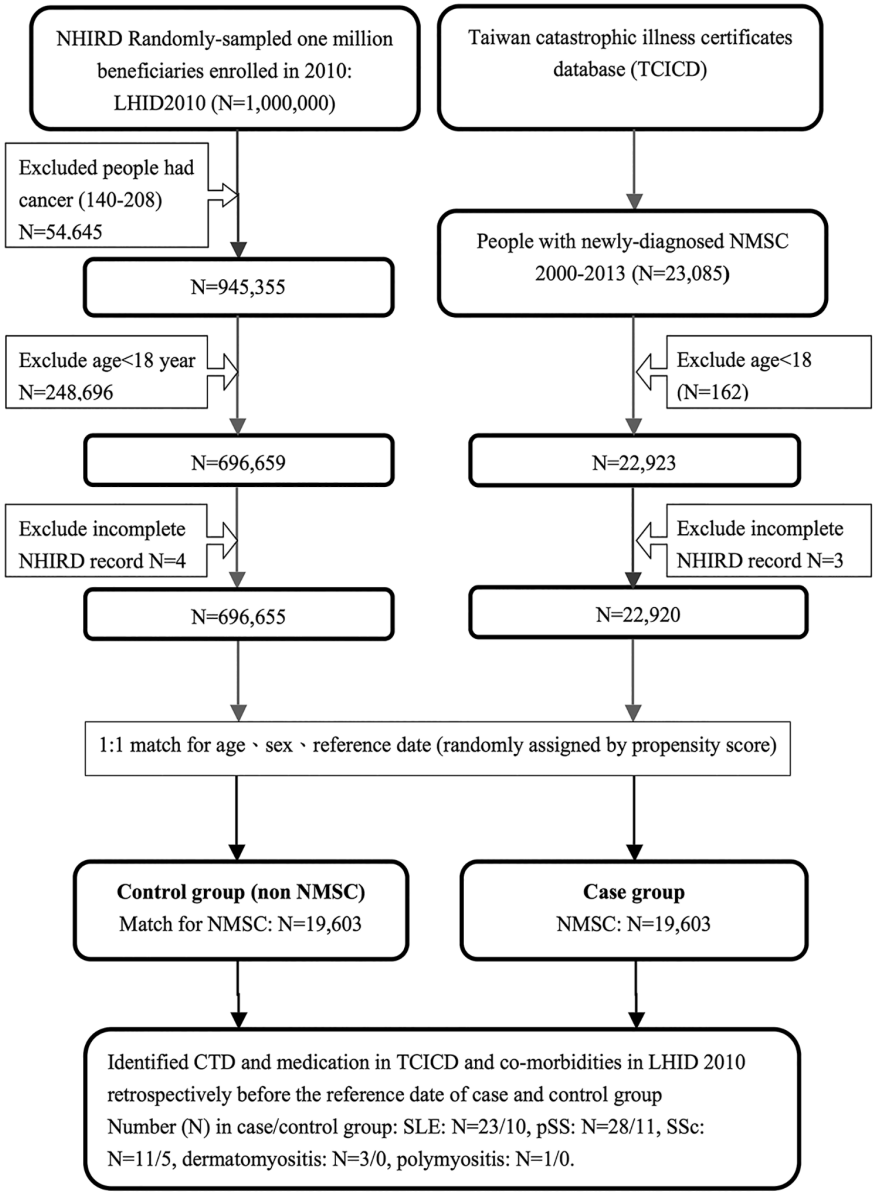

Fig. 1. Study design and flowchart of patient selection.
NHIRD: National Health Insurance Research Database; LHID: Longitudinal Health Insurance Database; TCICD: Taiwan catastrophic illness certificates database; NMSC: non-melanoma skin cancer; SLE: systemic lupus erythematosus; pSS: primary Sjögren's Syndrome; SSc: systemic sclerosis; N: number.

Information on medications was retrieved from the Pharmacy Prescription Database. Anatomical Therapeutic Chemical (ATC) code and defined daily dose (DDD) of a medication was defined according to the website of the Collaborating Centre for Drug Statistics Methodology of the World Health Organisation**.** Medications include corticosteroids (methylprednisolone (ATC code H02AB04, DDD 20mg) and prednisolone (H02AB06, DDD 10mg), hydroxychloroquine (ATC code P01BA02, DDD 516mg), azathioprine (L04AX01, DDD 150mg), mycophenolate mofetil (L04AA06, DDD 2g), cyclophosphamide (L01AA01), and methotrexate (L01BA01). Cumulative drug exposures were defined by cumulative total defined daily dose (TDDD) or cumulative dosages (gram) of a medication from the first prescription for specific CTD to the reference date of the case and control group. The retrieved information was independently verified by two statisticians. Hydroxychloroquine, azathioprine, methotrexate, and cyclophosphamide have been used since 1995, and mycophenolate mofetil have been used since 1997 according to the records of NHI Bureau.

Statistical analysis

Conditional logistic regression analysis was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between each CTD (exposure) and NMSC (outcome), and subgroup analysis of the influence of the use of corticosteroids, hydroxychloroquine, and other immunosuppressants (exposure) on NMSC among patients with SLE or pSS, with adjustments for age, sex, residential area, occupation, and co-morbidities.

NHIRD data were extracted using SAS v. 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical analyses were performed using IBM SPSS v. 20 (IBM Institute Inc., NY, USA). A 2-tailed *p*-value of <0.05 was considered to be statistically significant.

Results

The patients with NMSC (n=19,603) had a mean age (±standard deviation, range) of 68.11 (±15.87, 18-103) years, with a male to female ratio of 1.23. The demographics of SLE and pSS in cases and controls groups, and cumulative dosages of immunosuppressants are listed in Table I.

Table I. The demographics of patients with SLE and pSS and cumulative dosage of treatment.

	Case group	Control group
SLE[a] (n%)	23 (0.12)	10 (0.05)
Men/ women (n)	6 / 17	0 /10
Age at onset[a], year (mean±SD), (range)	60.2 ±16.2, (25.5-78.8)	63.23, (±16.9, 43.9-87.5)
Duration[b], year (mean±SD), (range)	9.6 ±4.2 (2-16.7)	9.3 ±5.3 (0.1-16.55)
Cumulative dosages of medication (mg or TDDD)	Minimum*, maximum	Minimum*, maximum
Corticosteroids (mg)	30, 36815.5	280, 73618.8
Hydroxychloroquine (TDDD)	10.9, 2432.6	10.9, 2608.5
Azathioprine (TDDD)	121.7, 526.3	3.7, 2019.7
Cyclophophamide (mg)	900, 44550	400, 700
Methotrexate (mg)	40, 1712.5	67.5, —
pSS[a] (n%)	28 (0.14)	11 (0.06)
Men/ women (n)	9 /19	4 / 8
Age at onset[a], year (mean±SD), (range)	64.5 ±11.3, (36.4-81.2)	71.4±6.4, (60.7-84.0)
Duration[b], year (mean±SD), (range)	3.8 ±2.8 (0.1-8.8)	2.7 ±3.2 (0.16-8.8)
Cumulative dosages of medication (mg or TDDD)	Minimum*, maximum	Minimum*, maximum
Corticosteroids (mg)	140, 15605	140, 8325
Hydroxychloroquine (TDDD)	10.85, 2159.7	21.7, 1399.6
Azathioprine (TDDD)	4.7, 74.7	—, —
Cyclophophamide (mg)	—, 18250	—, 3600
Methotrexate (mg)	267.5, 2520	—, —

n: number; SD: standard deviation; TDDD: total daily defined dose; mg: milligram; SLE: systemic lupus erythematosus; pSS: primary Sjögren syndrome.

a: excluded the information of patients whose first diagnosed date were in the first launched year of NHIRD (1995).

b: duration: diagnosis date of SLE and pSS to reference date of NMSC.

*minimum: the smallest dose excluding the patient did not use this drug (cumulative dosage=0)

Corticosteroids: cumulative approximate equivalent dosages (mg) of methylprednisolone and prednisolone.

The associations between CTDs and NMSC using conditional logistic regression analysis and adjusting for covariates of age, sex, residential area, occupation, and co-morbidities are shown in Table II. The patients with SLE or pSS had statistically significantly higher associations with NMSC, respectively. (SLE: cases n(%)/controls n(%)=23(0.12)/10(0.05), adjusted odds ratio (AOR)=2.33, 95% confidence interval (CI) 1.08–5.01, *p*=0.03; pSS: cases n(%)/controls n(%)=28(0.14)/11(0.06), AOR=2.37, 95%CI 1.19–4.74, *p*=0.01). The patients with SSc had a borderline significantly higher association with NMSC (cases n(%)/controls n(%) =11(0.06)/5(0.03), AOR=2.57, 95% CI 0.87–7.61, *p*=0.09), and the number was very limited, so the analysis for medications in the patients with SSc was not included in this study.

The medical treatment of SLE and pSS were prescribed according to current recommendations, expert opinions, and disease severity. The influence of systemic medications on the associations with NMSC among the patients with SLE or pSS was compared using conditional logistic regression analysis.

Systemic corticosteroids and hydroxychloroquine in combination or in sequence are the first-line therapy for patients with SLE. Azathioprine and cyclophosophamide may be added for refractory SLE or lupus nephritis. In this study, the case group of patients with SLE did not seem to have higher maximum doses of medications than control group (Table I).

Compared to the patients without SLE, those with SLE using systemic corticosteroids had a borderline significantly higher association with NMSC (cases n(%)/controls n(%) =21(0.11)/99(0.046), AOR=2.24, 95%CI 1–5.03, *p*=0.05), and this was especially pronounced with a cumulative dosage >5g (cases n(%)/controls n(%) =17(0.09)/5(0.025), AOR=2.96, 95%CI 1.06–8.23, *p*=0.04). Those using hydroxychloroquine also had a significantly increased association

Table II. The crude and adjusted odds ratios of connect tissue diseases associated with non-melanoma skin cancer.

	Case n(%)	Control n(%)	COR (95% CI)	*p*-value	AOR[a] (95% CI)	*p*-value
SLE	23 (0.12)	10 (0.05)	**2.3 (1.1-4.83)**	**0.03**	**2.33 (1.08-5.01)**	**0.03**
pSS	28 (0.14)	11 (0.06)	**2.33 (1.19-4.59)**	**0.01**	**2.56 (1.25-5.23)**	**0.01**
SSc	11 (0.058)	5 (0.025)	2.2 (0.76-6.33)	0.14	2.57 (0.87-7.61)	0.09
RA[20]	127 (0.64)	53 (0.27)	**2.4 (1.74-3.3)**	**<0.001**	**2.23 (1.6-3.1)**	**<0.001**

Number of non-melanoma skin cancer =19,603. SLE: systemic lupus erythematosus; pSS: primary Sjögren's syndrome; SSc: systemic sclerosis; RA: rheumatoid arthritis; n: number; COR: crude odds ratio; AOR: adjusted odds ratio: a: adjusted covariate: residential regions, occupation, DM, CAD, HT, COPD, CKD, OT, obesity, age (continuous variable), and sex. Analysis by conditional logistic regression analyses. *p*-value <0.05: two-tailed statistical significance.

Table III. The adjusted odds ratios of systemic lupus erythematosus associated with non-melanoma skin cancer in immunosuppressants by conditional logistic regression analyses.

	case n(%)	control n(%)	AOR (95%CI)	*p*-value
Non-SLE	Reference group			
Corticosteroids				
Ever use	21 (0.11)	9 (0.046)	2.24 (1.0-5.03)	**0.05**
≤5g	4 (0.02)	4 (0.02)	1.24 (0.3-5.19)	0.77
>5g	17 (0.09)	5 (0.025)	**2.96 (1.06-8.23)**	**0.04**
Hydroxychloroquine				
Ever use	20 (0.1)	7 (0.036)	**2.57 (1.06-6.22)**	**0.04**
1-100 TDDD	5 (0.025)	4 (0.02)	1.7 (0.44-6.54)	0.44
>100 TDDD	18 (0.09)	6 (0.03)	**2.7 (1.04-6.98)**	**0.04**
Azathioprine				
No use	17 (0.09)	7 (0.036)	2.60 (1.05-6.47)	0.04
Ever use	6 (0.03)	3 (0.015)	1.74 (0.42-7.19)	0.44
1-100 TDDD	0 (0)	2 (0.01)	NC	NC
>100 TDDD	6 (0.03)	1 (0.005)	4.37 (0.52-36.75)	0.18
Cyclophosphamide				
No use	14 (0.07)	7 (0.036)	2.27 (0.89-5.79)	0.09
Ever use	9 (0.046)	3 (0.015)	2.45 (0.64-9.37)	0.19
1-700 mg	0 (0)	3 (0.015)	NC	NC
>700 mg	9 (0.045)	0 (0)	NC	NC
Methotrexate				
No use	19 (0.097)	9 (0.046)	2.23 (0.98-5.08)	0.06
Ever use	4 (0.02)	1 (0.005)	3.07 (0.34-27.58)	0.32
1-70 mg	1 (0.005)	1 (0.005)	0.73 (0.05-11.75)	0.83
>70 mg	3 (0.015)	0 (0.015)	NC	NC

SLE: systemic lupus erythematosus; n: number; g: gram; mg: milligram; CI: confidence interval; TDDD: total defined daily dose; NC: non-calculable.
Cumulative drug exposures were defined by cumulative total defined daily dose (TDDD) or cumulative dosages (gram) of a medication from the first prescription for specific CTD to the reference date of the case and control group
Corticosteroids: cumulative approximate equivalent dosage of prednisolone and methylprednisolone.
AOR: adjusted odds ratio: adjusted covariate: residential regions, occupation, DM, CAD, HT, COPD, CKD, OT, obesity, sex, and age (continuous variable). *p*-value <0.05: two-tailed statistical significance.

with NMSC (cases n(%)/controls n(%)=20(0.1)/7(0.036), AOR=2.57, 95%CI 1.06–6.22, *p*=0.04), and this was especially prominently with a cumulative dosage >100TDDD (cases n(%)/controls n(%)=18(0.09)/6(0.03), AOR=2.7, 95%CI 1.04–6.98, *p*=0.04) (Table III).

Hydroxychloroquine was the first-line therapy for patients with pSS. Low dose corticosteroids would be added-on for constitutional symptoms or mild extra-glandular manifestations, and large dose corticosteroids were used only when major organ involvement. In this study, the maximum dose and total cumulative dose of corticosteroids were much less than those in patients with SLE. The case group of patients with pSS had much higher maximum cumulative doses of medications than the control group (Table I).

Compared to the patients without pSS, those with pSS using hydroxychloroquine had a significantly increased association with NMSC (cases n(%)/controls n(%)=27(0.14)/8(0.04), AOR=3.48, 95%CI 1.56–7.78, *p*=0.002) and this was especially prominently with a cumulative dosage >100 TDDD (cases n(%)/controls n(%)=20(0.1)/4(0.02), AOR= 5.41, 95%CI 1.82–16.11, *p*=0.002). Those using corticosteroid had a significantly higher association with NMSC (cases n(%)/controls n(%)=18(0.09)/6(0.03), AOR=3.12, 95%CI 1.22-8.0, *p*=0.02), and this was especially pronounced with a cumulative dosage >1g (cases n(%)/controls n(%)=13(0.066)/3(0.015), AOR=4.92, 95%CI 1.37–17.61, *p*=0.01). The patients with pSS using both corticosteroids and hydroxychloroquine had a significantly stronger association with NMSC (cases n(%)/controls n(%)=18(0.09)/6(0.03), AOR=3.17, 95%CI 1.24–8.13, *p*=0.02) (Table IV).

For those using azathioprine, cyclophosphamide, or methotrexate, the number of users and the cumulative dosages in the case group were mostly higher than those in the control group for patients with SLE or pSS (SLE: case n/control n: azathioprine: >100TDDD: n=6/1, 1-100TDDD: n=0/2, cyclophosphamide: >700mg: n=9/0, ≤700mg: n=0/3; methotrexate: >70mg n=3/0, ≤70mg: n=1/1; mycophenolate mofetil: n=1/1; pSS: azathioprine: n=2/0, cyclophosphamide n=1/1, methotrexate n=2/0).

Discussion

The patients with SLE or pSS had significantly higher associations with NMSC. Those using systemic corticosteroids had significantly higher associations with NMSC, especially pronounced with a cumulative dosage >5g for SLE and >1g for pSS. Those using hydroxychloroquine had significantly increased associations with NMSC, especially prominently with a cumulative dosage >100TDDD for SLE or pSS.

The mean age of patients with NMSC in this study was similar to the mean age reported in the Taiwan cancer registry annual reports at around 70 years (16). In this study, the mean age of the patients with SLE and pSS was higher than that reported in the nationwide studies in Taiwan, but still in the same

Table IV. The adjusted odds ratio of primary Sjögren syndrome associated with non-melanoma skin cancer in corticosteroids and hydroxychloroquine by conditional logistic regression analyses.

	case n (%)	control n (%)	AOR (95%CI)	*p*-value
Non-pSS	Reference group			
Corticosteroids				
Ever use	18 (0.09)	6 (0.03)	**3.12 (1.22-8.0)**	**0.02**
≤1g	5 (0.026)	3 (0.015)	1.48 (0.35-6.28)	0.6
>1g	13 (0.066)	3 (0.015)	**4.92 (1.37-17.61)**	**0.01**
Hydroxychloroquine				
Ever use	27 (0.14)	8 (0.04)	**3.48 (1.56-7.78)**	**0.002**
1-100 TDDD	7 (0.004)	4 (0.02)	1.65 (0.47-5.74)	0.43
>100 TDDD	20 (0.1)	4 (0.02)	**5.41 (1.82-16.11)**	**0.002**
Both corticosteroids and hydroxychloroquine				
Ever use	18 (0.09)	6 (0.03)	**3.17 (1.24-8.13)**	**0.016**

pSS: primary Sjögren syndrome; n: number; CI: confidence interval; TDDD: total defined daily dose; g: gram. Cumulative drug exposures were defined by cumulative total defined daily dose (TDDD) or cumulative dosages (gram) of a medication from the first prescription for specific CTD to the reference date of the case and control group. Corticosteroids: cumulative approximate equivalent dosage of prednisolone and methylprednisolone. AOR: adjusted odds ratio: adjusted covariate: residential regions, occupation, DM, CAD, HT, COPD, CKD, OT, obesity, sex, and age (continuous variable). *p*-value <0.05: two-tailed statistical significance.

range of higher incidence (10, 11). In this study, the patients diagnosed with SLE and pSS at an older age tended to have a higher risk of NMSC than those diagnosed at a younger age. The mean duration from a diagnosis of pSS to NMSC was shorter than that for SLE to NMSC, because a diagnosis of pSS was often delayed for several years. However, it was similar to that reported in the study by Weng e*t al*. (17).

The patients with NMSC were predominantly male, and the patients with SLE and pSS are predominantly female. In this study, the male-to-female ratio was higher in the case group with SLE compared to the control group. This indicates that the male patients with SLE tended to get NMSC, but this was not found in patients with pSS.

Patients with SLE and dermatomyositis experienced photosensitivity, and strict sun-protection is recommended. Patients with SSc, dermatomyositis and polymyositis tend to have a limited range of movement. Therefore, those reasons may explain the limited number of NMSC occurred.

With regards to the association between SLE and NMSC, a population-based cohort study of 5,715 hospitalised SLE patients in Sweden followed 1964-1995 showed a 1.53-fold increased risk of squamous cell skin cancer with borderline significance, and this was most pronounced after more than 15 years of follow-up (1). A study in Iceland found that squamous cell skin cancer was the only type of cancer that was statistically increased in patients with SLE (5). A hospital-based cohort study of 576 SLE patients in the Danish Cancer Registry reported a 2-fold higher incidence rate of NMSC (6). A meta-analysis also showed that patients with SLE had a 1.5-fold higher associated with NMSC (18). Singh *et al*. reported no increased risk of skin cancer in patients with cutaneous lupus erythematosus compared to the general population (19). An established increased association between pSS and lymphoma has been reported, but the association between pSS and NMSC has not been reported yet (3, 17).

Disease severity fluctuates among patients with CTDs, and they must receive several kinds of medications in combinations or in sequence for their lifelong diseases. Instead of the average daily dose, the higher cumulative dosage of each drug may reflect higher daily doses or longer duration of treatment and can be used to summarise the patients' disease severity and immunocompromised status during follow-up. However, only a few studies have reported on the influence of systemic corticosteroids and hydroxychloroquine therapy on the association between each CTD and skin cancer. Tseng et al reported that patients with rheumatoid arthritis had significantly increased associations with NMSC, especially those receiving higher cumulative doses of corticosteroids and methotrexate (20).

Long-duration of systemic corticosteroid treatment can induce an immunosuppressive status in the patients with inflammatory and autoimmune diseases (21). Hydroxychloroquine has both anti-inflammatory and immunomodulatory effect that have been proposed to upregulate apoptosis and to downregulate autoimmunity by eliminating autoreactive lymphocytes. It has also been shown to inhibit the autophagy of lysosomes (22). The highest concentration of hydroxychloroquine has been found in the melanin-containing cells. The skin is a long-term reservoir of hydroxychloroquine that can exert effect or toxicity during and after treatment (23).

Autophagy plays a context-dependent role in cancer. Autophagy pathways first suppress the initiation of tumour growth during the early stages of cancer, and it may lead to better survival of tumour cells during the later stages of established cancer because it acts as a source of nutrient replenishment against metabolic and therapeutic stresses (24, 25). Hydroxychloroquine is the only clinically-approved autophagy inhibitor (26). Therefore, the high accumulation of hydroxychloroquine in the skin may initiate the growth of early-stage NMSC in those who need to take this drug for many years.

The influence of systemic corticosteroids and hydroxychloroquine on the risk for NMSC cannot be totally discriminated, because most of the patients with SLE or pSS received the two drugs in combination or in sequence. Among the patients with pSS, the number and AOR of those using hydroxychloroquine were higher than those using corticosteroids. Therefore, hydroxychloroquine therapy may play a more important role for NMSC than corticosteroids. The control group rarely used azathioprine, cyclophosphamide, or methotrexate, and had lower cumulative dosages of them. Those immunosuppressants may contribute to some effect for NMSC in case group. Nonetheless, the higher as-

sociation between those who did not use azathioprine, cyclophosphamide, or methotrexate and NMSC might be attributed to the effect of using corticosteroids and hydroxychloroquine.

The strengths of this study were the population-based study design, large sample size of patients with skin cancer, and minimal misclassification and diagnosis bias because NMSC and CTDs were recorded in the TCICD.

There were several limitations to this study, especially with regards to the NHIRD. Personal histories, laboratory data, and actual disease severity were unavailable in NHIRD. Nevertheless, the cumulative dosages of immunosuppresants were already considered to represent disease severity and duration. In addition, the incidence rates of each CTD and skin cancer were relatively low and this may have affected the statistical power. Moreover, the characteristics of the case group were not similar to those of the general population. Finally, the results should be carefully applied to other ethnic groups because of differences in people's skin type, genetic factors, exogenous exposure, geographic factors, and social culture.

With regards to the advantages and disadvantages of a case-control study design, the advantages are that it is suitable for rare diseases, for those with long durations between exposure and outcome, and for the population with follow-up difficultly. The disadvantages are uncalculated incidence, selection or observation bias in exposure information, and inefficiency for rare exposure. Causality also cannot be inferred (27, 28).

In conclusion, the patients with SLE or pSS had significantly higher associations with NMSC. Those who used systemic corticosteroids or hydroxychloroquine had significantly increased associations with NMSC, especially pronounced in those with higher cumulative dosages.

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