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ORIGINAL ARTICLE

Malignancies associated with systemic lupus erythematosus in Taiwan: a nationwide population-based cohort study

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Abstract Patients with systemic lupus erythematosus (SLE) are suggestive to have a higher cancer risk. The aim of this study is to evaluate the possible association of malignancy and SLE in Taiwan. We used the data of the National Health Insurance system of Taiwan to assess this issue. The SLE cohort contained 2,150 patients, and each patient was randomly frequency matched to 8 people without SLE on age and sex. The Cox's proportion hazard regression analysis was conducted to estimate the effects of SLE on the cancer risk. In patients with SLE, the risk of developing overall cancer was marginally significantly higher [adjusted Hazard ratio (HR) = 1.26, 95% confidence interval (95% CI) = 0.99–1.59] and was significantly higher for developing prostate cancer (adjusted HR = 3.78, 95% CI = 1.30–11.0). Our study unexpectedly found that Taiwanese patients with SLE have a higher risk to develop prostate cancer.

Keywords Malignancy · Systemic lupus erythematosus · Prostate cancer

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that occurs predominantly in young women. It has numerous immunological and clinical manifestations and mainly involves the skin, kidneys, joints, mucous membranes, blood vessel walls, and nervous system. Because of the improvement of modern therapeutic and diagnostic resources, its prognosis is much better now. The life expectancy of such patients has improved from an approximate 4-year survival rate of 50% in the 1950s to a

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15-year survival rate of 80% today [1–3]. As a result of the increasing survival in patients with SLE, the incidence of chronic comorbidities, such as malignancy, had been rising [4]. This phenomenon also aroused investigators to evaluate the issue of the association between SLE and cancer [5–12]. Almost all studies reported that malignancy in patients with SLE may occur more commonly than in the general population. For most cohort studies, the parameter estimating cancer risk in SLE has been the standardized incidence ratio (SIR), which is the ratio of observed to expected cancer cases. The SIR estimates (for cancer overall) in these studies ranged from as low as 1.1 (95% confidence interval [CI] 0.7–1.6) [11] to as high as 2.6 (95% CI 1.5–4.4) [12]. Three largest cohort studies (sample size was more than 1,000) so far using tumor registry data as cancer ascertainment all found that the SIRs for all cancer overall were significantly higher [5–7]. For the specific cancer types, lymphoma, particularly non-Hodgkin lymphoma (NHL), is the most well-known to have the link with SLE. Again, the data from the three largest cohort studies demonstrated the SIR for NHL ranged from 2.9 (95% CI 2.0–4.0) [6] to 5.2 (95% CI 2.2–10.3) [7].

To the best of our knowledge, there are no large population-based studies discussing the relationship between malignancy and SLE in Taiwan. We would like to find if there is the same pattern of cancer risk for patients with SLE in Taiwan. These results presented in this paper were from a retrospective cohort study to assess if there is a higher risk of developing malignancy in patients with SLE. The original database was derived from the National Health Insurance (NHI) system in Taiwan.

Materials and methods

Study population

The present study used the reimbursement claims data of the universal NHI system of Taiwan. The health insurance program has covered more than 96% of population and contracted with 97% of hospitals and clinics since the end of 1996. [13].

This study obtained the claims data consisting of registries and claims reported from contracted health care facilities in the year of 1996–2008, from the National Health Research Institute (NHRI), Department of Health. We were able to use the encrypted identification number of each patient to link files, including the registry of medical facilities, details of inpatients orders, ambulatory cares, dental services, and prescriptions. The socio-demographic information for this study included gender, birth date, occupation, monthly income for premium estimation, and residential area were also available.

We used a sub-dataset composed of a one million insured population created by NHRI using a systematic random sampling method, with approximately 5% of the entire population included. Diagnoses were coded with The International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM).

Study subject

Our study identified newly diagnosed patients with SLE in the period of 1999–2002 from both ambulatory care and inpatient care as the exposure cohort (ICD-9-CM 710.0). For the comparison cohort, we randomly selected 8 insured people without SLE in the same period, frequency matched with the SLE cohort on age and sex. The age of each study subject was measured by the difference in time between the index date and the date of birth. Subjects with the history of malignant cancer (ICD-9-CM 140–230) diagnosed before index date were excluded. We finally included 19,357 subjects in this study.

Study end-point

We used the unique patient's identification number to link study subjects to the registry for Catastrophic Illness Patient Database to identify the newly diagnosed of cancer as the outcome of this study. The diagnosis of cancer in National Health Insurance Research Database (NHIRD) needs histological confirmation and report in the Catastrophic Illness Patient Database. Person-years of follow-up time were calculated for each person until cancer diagnosed or censored. The date of censoring was defined as: the date of study subjects died in follow-up period, the date of last withdrawal from NHI, or the date termination of the insured program.

Statistical analysis

The socio-demographic data, distributions of categorical age, gender, occupation, urbanization level, living region and income between patients with SLE and non-SLE patients were using Chi-square tests. We also calculated the incidence density with person-years by these variables in the SLE cohort and non-SLE cohort. The rate ratio of cancer was calculated by each variable.

The Cox's proportion hazard regression analysis was conducted to measure the effects of SLE on the risk of cancer. Hazard ratio (HR) and 95% confidence interval (CI) were calculated in the model.

All data measurements were performed by SAS statistical software (version 9.1 for Windows; SAS Institute, Inc., Cary, NC, USA), and the significance level was set to be 0.05.

Result

Characteristics of the study subjects

Table 1 compares distributions of demographic characteristics between the SLE cohort and the comparison cohort. There were more women subjects than men (77.4% vs. 22.6%). Most subjects were in 20–39 years of age (38.6% both in non-SLE cohort and non-SLE cohort). Patients with SLE were more likely to be white collar occupation (56.0% vs. 51.8%, $P < 0.0001$), living in highest urbanization level (35.5% vs. 31.1%, $P < 0.0001$) and central region (36.0% vs. 20.1%, $P < 0.0001$), and have higher income (14.7% vs. 11.7%, $P < 0.0001$).

Risk and crude rate ratio of cancer

Table 2 shows the incident densities and crude rate ratio (RR) of cancer by the baseline socio-demographic status. The SLE cohort had a higher incidence of cancer than the non-SLE cohort (51.2 vs. 41.9 per 10,000 person-years, RR = 1.22). In both SLE and non-SLE cohort, the incidence densities of cancer were higher in men (64.4 vs. 57.5 per 10,000 person-years, RR = 1.12) than in women (47.5 vs. 37.4 per 10,000 person-years, RR = 1.27). Compared with non-SLE cohort, the RR of cancer was higher in youngest group (<20 years; 14.7 vs. 2.3 per 10,000 person-years, RR = 6.5) and oldest group (≥80 years; 434.8 vs. 190.0 per 10,000 person-years, RR = 2.26).

Table 1 Comparisons in demographic characteristics between SLE patients' cohort and non-SLE cohort in 1999–2002

Variables	Total $N = 19{,}357$		SLE				P value*
			No $N = 17{,}207$		Yes $N = 2{,}150$		
	n	(%)	n	(%)	n	(%)	
Gender							0.99
Women	14,983	(77.4)	13,319	(77.4)	1,664	(77.4)	
Men	4,374	(22.6)	3,888	(22.6)	486	(22.6)	
Age, years							0.62
<20	2,340	(12.1)	2,080	(12.1)	260	(12.1)	
20–39	7,468	(38.6)	6,639	(38.6)	829	(38.6)	
40–59	6,099	(31.5)	5,428	(31.6)	671	(31.2)	
60–79	3,069	(15.9)	2,713	(15.8)	356	(16.6)	
≥80	381	(2.0)	347	(2.0)	34	(1.6)	
Occupation							<0.0001
White collar	10,120	(52.3)	8,917	(51.8)	1,203	(56.0)	
Blue collar	6,657	(34.4)	6,017	(35.0)	640	(29.8)	
Others	2,580	(13.3)	2,273	(13.2)	307	(14.3)	
Urbanization level							<0.0001
1	6,118	(31.6)	5,355	(31.1)	763	(35.5)	
2	5,556	(28.7)	4,942	(28.7)	614	(28.6)	
3	3,373	(17.4)	3,015	(17.5)	358	(16.7)	
4	4,300	(22.3)	3,895	(22.6)	415	(19.3)	
Region							<0.0001
North	8,852	(45.7)	7,973	(46.3)	879	(40.9)	
Central	4,227	(21.8)	3,454	(20.1)	773	(36.0)	
South	4,835	(25.0)	4,445	(25.8)	390	(18.1)	
East and island	1,443	(7.5)	1,335	(7.8)	108	(5.0)	
Income							<0.0001
<15,000	7,812	(40.4)	6,938	(40.3)	874	(40.7)	
15,000–29,999	9,215	(47.6)	8,255	(48.0)	960	(44.7)	
≥30,000	2,330	(12.0)	2,014	(11.7)	316	(14.7)	

Urbanization level: 1 indicates the highest level of urbanization and 4 the lowest

* Chi-square test

Table 2 Comparisons of incidence density of cancer between cohorts with and without SLE by socio-demographic factor

Variables	SLE								Rate ratio
	No				Yes				
	N	Cases	Person-years	Rate*	N	Cases	Person-years	Rate*	
All	17,207	595	142,051	41.9	2,150	86	16,789	51.2	1.22
Gender									
Women	13,319	412	110,222	37.4	1,664	62	13,061	47.5	1.27
Men	3,888	183	31,829	57.5	486	24	3,729	64.4	1.12
Age, years									
<20	2,080	4	17,694	2.3	260	3	2,042	14.7	6.50
20–39	6,639	89	55,063	16.2	829	11	6,637	16.6	1.03
40–59	5,428	225	46,416	48.5	671	31	5,391	57.5	1.19
60–79	2,713	244	21,159	115.3	356	34	2,559	132.9	1.15
≥80	347	33	1,719	192.0	34	7	161	434.8	2.26
Occupation									
White collar	8,917	260	74,168	35.1	1,203	44	9,542	46.1	1.32
Blue collar	6,017	259	49,261	52.6	640	20	4,954	40.4	0.77
Others	2,273	76	18,622	40.8	307	22	2,293	95.9	2.35
Urbanization level									
1	5,355	168	44,352	37.9	763	30	5,953	50.4	1.33
2	4,942	173	40,953	42.2	614	23	4,853	47.4	1.12
3	3,015	97	24,877	39.0	358	11	2,826	38.9	1.00
4	3,895	157	31,869	49.3	415	22	3,158	69.7	1.41
Region									
North	7,973	250	65,732	38.0	879	29	6,683	43.4	1.14
Central	3,454	124	28,604	43.4	773	36	6,207	58.0	1.34
South	4,445	174	36,712	47.4	390	19	3,058	62.1	1.31
East and island	1,335	47	11,003	42.7	108	2	841	23.8	0.56
Income									
<15,000	6,938	239	56,816	42.1	874	46	6,671	69.0	1.64
15,000–29,999	8,255	296	67,938	43.6	960	33	7,552	43.7	1.00
≥30,000	2,014	60	17,297	34.7	316	7	2,566	27.3	0.79

* per 10,000 person-year

The further multivariate analysis for Cox's proportional regression model showed that the HR of cancer was significantly greater in the SLE cohort than that in the non-SLE cohort when we adjusted for age and gender (model 2, HR = 1.27, 95% CI = 1.01–1.59) (Table 3). However, after adjusting all the variables in Table 1, the risk of cancer became marginally significantly higher in patients with SLE (Model 3, HR = 1.26, 95% CI = 0.99–1.59).

Furthermore, the specific analyses on hematological malignance, colorectal cancer, liver cancer, lung cancer, breast cancer and gynecologic cancer for women, and prostate cancer for men are presented in Table 4. Compared to the men subjects without SLE in Cox's proportional regression analysis, the adjusted HR of developing prostate cancer was 3.78 folds higher for patients with SLE (95% CI = 1.30–11.0), and hematological malignancy had a marginally significantly higher rate for patients with SLE. We cannot observe any relationship between other types of cancer and SLE.

Discussion

In this large population-based study, we collected 2,150 patients with SLE from the NHRI of Taiwan. From the literature review regarding SLE and cancer, only 2 studies had more patients with SLE than the current study [14]. Our findings showed the overall cancer risk for patients with SLE is significantly higher when we did not adjust the variables or adjusted for age and gender. Because the demographic characteristics between SLE patients' cohort

Table 3 Hazard ratios and 95 percent confidence interval of cancer associated with SLE in Cox's regression analysis (all cancer)

Variables	Model 1		Model 2		Model 3	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
SLE						
No	1.00	(reference)	1.00	(reference)	1.00	(reference)
Yes	1.27	(1.01–1.59)*	1.27	(1.01–1.59)*	1.26	(0.99–1.59)

* Model 1 unadjusted

* Model 2 adjusted for age, gender

Model 3 adjusted for age, gender, area, occupation, urbanization, and income

* Significant difference

Table 4 Hazard ratios and 95 percent confidence interval of cancer associated with SLE in Cox's regression analysis in different cancer

Variable	Multivariate model*	
	HR	(95% CI)
Hematological malignancy**		
SLE		
No	1.00	(reference)
Yes	2.23	(0.95–5.24)
Colorectal cancer		
SLE		
No	1.00	(reference)
Yes	0.71	(0.30–1.65)
Liver cancer		
SLE		
No	1.00	(reference)
Yes	1.28	(0.66–2.47)
Lung cancer		
SLE		
No	1.00	(reference)
Yes	1.41	(0.70–2.84)
Breast cancer (women only)		
SLE		
No	1.00	(reference)
Yes	0.78	(0.41–1.45)
Uterus, cervical, ovary, and vagina cancer		
SLE		
No	1.00	(reference)
Yes	1.42	(0.66–3.03)
Prostate cancer (men only)		
No	1.00	(reference)
Yes	3.78	(1.30–11.0)*

* adjusted for age, gender, area, occupation, urbanization, and income

** ICD-9-CM: hematological malignancy, 200.xx-203.xx and 205.xx-208.xx; colorectal cancer, 153.xx and 154.xx; liver cancer, 155.xx; lung cancer, 162.xx; breast cancer, 174.xx and 175.xx; uterus, cervical, ovary and vagina cancer, 179.xx-184.xx; prostate cancer, 185.xx

and non-SLE cohort showed significant difference in the occupation, urbanization level, region, and income (Table 1), and the rate ratio of cancer in patients with SLE also showed the difference by the 4 characteristics mentioned earlier (Table 2), the model 3 which adjusted these variables is more appropriate to evaluate the relationship between the SLE and cancer. By this model, our patients with SLE showed a marginally significantly higher rate for cancer with the HR of 1.26 and 95% CI is 0.99–1.59. The results are compatible with previous researches in both the magnitude and direction, indicating an overall increased risk of cancer among patients with SLE [5, 6, 10, 12, 15].

Gayed et al. did a literature review to assess the existing evidence for the relationship and found patients with SLE have an increased susceptibility to cancer, and the trend of statistical significance seemed to be compatible with the sample size [14]. The most powerful study to date is performed by Bernatsky et al. [5]. They collected 9,547 patients with SLE from 23 centers for a total 76,948 patient-years and found 431 malignancies in an average 8-year follow-up. The SIR estimate was 1.15 (95% CI = 1.05–1.27) for all cancer combined.

We used the retrospective cohort study design for optimal flexibility and efficiency. The subjects for our comparison cohort were randomly selected 8 insured people without SLE in the same period, frequency matched with each patient in the SLE cohort on age and sex. It is different from the studies using the general population as the comparison group. The strength of this design is to clearly separate the study groups into with exposure (with SLE) and without exposure (without SLE), and use the group without SLE as the reference to compare. We used RR instead of SIR to estimate the risk. SIR was calculated as the ratio of observed to expected cancer cases. The general population used for comparison could include the patients with SLE as well; even the percentage is expected too small to affect the result.

The hematologic malignancy was the most well-know cancer type to be related to the SLE. Most data from the earlier studies strongly suggested an increase incidence of hematologic cancers in patients with SLE, especially in non-Hodgkin's lymphoma [5, 7, 10–12]. This study found a marginally significantly higher risk for developing all the hematologic malignancies. The 95% CI became wider when we focused on non-Hodgkin's lymphoma or Hodgkin's disease, and both were not statistically significant (data not shown). Some studies found the increased occurrence for lung cancer and liver cancer in patients with SLE [5–7, 15, 16]. Lung cancer and liver cancer are two common malignancies and led the first two cancer mortality in Taiwan [17]; therefore, we were interested in knowing if they are related to the SLE. Our data showed a 1.41 and 1.28 fold increased

risk for lung cancer and liver cancer, respectively, but both are not statistically significant.

The current study showed a significantly higher risk for developing prostate cancer in patients with SLE. Most prior studies did not find the increased risk of prostate cancer in patients with SLE [5–7, 18], or even a lower risk [19]. To the best of our knowledge, there was only one earlier paper presented a significantly higher risk. Nived et al. did a study from an inception cohort in southern Sweden and found the estimated SIR for prostate cancer was 6.41 with 95% CI = 1.3–18.7 [20]. The finding is contradicted to expectation because male patients with autoimmune disorders have increased levels of antibodies against the estrogen receptors, which may decrease the protective effect of estrogen for prostate cancer [21]. Some possible undetermined complex mechanisms between the relationship of SLE and prostate cancer are still needed to be explored and larger studies are mandatory before any further conclusions can be made.

In conclusion, this population-based retrospective cohort study found marginally significant increase in overall cancer and hematologic malignancies in Taiwanese patients with SLE, and unexpectedly identified significant increase in developing prostate cancer. The age-adjusted incidence rate of prostate cancer in Taiwan increased dramatically from 2002–2006, and it is currently the 5th commonest malignancy among Taiwanese male [17]. The findings may arouse the attention of NHI of Taiwan to reconsider the policy regarding follow-up and cancer screening in patients with SLE.

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References

1. Petri M (2006) Systemic lupus erythematosus and related diseases: clinical features. In: Rose NR, Mackay IR (eds) The autoimmune diseases (forth Edition). Elsevier Academic Press, London, pp 351–356
2. Abu-Shakra M, Urowitz MB, Gladman DD, Gough J (1995) Mortality studies in systemic lupus erythematosus. Results from a single center. II. Predictor variables for mortality. J Rheumatol 22:1265–1270
3. Ruiz-Irastorza G, Khamashta MA, Castellino G, Hughes GR (2001) Systemic lupus erythematosus. Lancet 357:1027–1032
4. Nossent J, Cikes N, Kiss E, Marchesoni A, Nassonova V, Mosca M, Olesinska M, Pokorny G, Rozman B, Schneider M, Vlachoyiannopoulos PG, Swaak A (2007) Current causes of death in systemic lupus erythematosus in Europe, 2000–2004: relation to disease activity and damage accrual. Lupus 16:309–317
5. Bernatsky S, Boivin JF, Joseph L, Rajan R, Zoma A, Manzi S, Ginzler E, Urowitz M, Gladman D, Fortin PR, Petri M, Edworthy S, Barr S, Gordon C, Bae SC, Sibley J, Isenberg D, Rahman A, Aranow C, Dooley MA, Steinsson K, Nived O, Sturfelt G, Alarcón G, Senécal JL, Zummer M, Hanly J, Ensworth S, Pope J, El-Gabalawy H, McCarthy T, St Pierre Y, Ramsey-Goldman R, Clarke A (2005) An international cohort study of cancer in systemic lupus erythematosus. Arthritis Rheum 52:1481–1490
6. Bjornadal L, Lofstrom B, Yin L, Lundberg I, Ekbom A (2002) Increased cancer incidence in a Swedish cohort of patients with systemic lupus erythematosus. Scand J Rheumatol 31:66–71
7. Mellemkjaer L, Andersen V, Linet MS, Gridley G, Hoover R, Olsen JH (1997) Non-Hodgkin's lymphoma and other cancers among a cohort of patients with systemic lupus erythematosus. Arthritis Rheum 40:761–768
8. Kiss E, Kovacs L, Szodoray P (2010) Malignancies in systemic lupus erythematosus. Autoimmun Rev 9:195–199
9. Ragnarsson O, Grondal G, Steinsson K (2003) Risk of malignancy in an unselected cohort of Icelandic patients with systemic lupus erythematosus. Lupus 12:687–691
10. Cibere J, Sibley J, Haga M (2001) Systemic lupus erythematosus and the risk of malignancy. Lupus 10:394–400
11. Abu-Shakra M, Gladman DD, Urowitz MB (1996) Malignancy in systemic lupus erythematosus. Arthritis Rheum 39:1050–1054
12. Pettersson T, Pukkala E, Teppo L, Friman C (1992) Increased risk of cancer in patients with systemic lupus erythematosus. Ann Rheum Dis 51:437–439
13. Lu JF, Hsiao WC (2003) Does universal health insurance make health care unaffordable? Lessons from Taiwan. Health Aff (Millwood) 22:77–88
14. Gayed M, Bernatsky S, Ramsey-Goldman R, Clarke AE, Gordon C (2009) Lupus and cancer. Lupus 18:479–485
15. Thomas E, Brewster DH, Black RJ, Macfarlane GJ (2000) Risk of malignancy among patients with rheumatic conditions. Int J Cancer 88:497–502
16. Ruiz-Irastorza G, Ugarte A, Egurbide MV, Garmendia M, Pijoan JI, Martinez-Berriotxoa A, Aguirre C (2007) Antimalarials may influence the risk of malignancy in systemic lupus erythematosus. Ann Rheum Dis 66:815–817
17. Cancer incidence and mortality in Taiwan in (2007) Taiwan cancer registry, Department of health, executive Yuan, Taiwan, ROC
18. Sultan SM, Ioannou Y, Isenberg DA (2000) Is there an association of malignancy with systemic lupus erythematosus? An analysis of 276 patients under long-term review. Rheumatology 39:1147–1152
19. Parikh-Patel A, White RH, Allen M, Cress R (2008) Cancer risk in a cohort of patients with systemic lupus erythematosus (SLE) in California. Cancer Causes Control 19:887–894
20. Nived O, Bengtsson A, Jönsen A, Sturfelt G, Olsson H (2001) Malignancies during follow-up in an epidemiologically defined systemic lupus erythematosus inception cohort in southern Sweden. Lupus 10:500–504
21. Feldman M (1987) Steroid receptor antibodies in autoimmune disorders. Biochem Biophys Res Commun 145:1342–1348