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Title: Malignancy in systemic lupus erythematosus: a nationwide cohort study in Taiwan

Article Type: Clinical Research Study

Keywords: malignancy; systemic lupus erythematosus; nationwide cohort study; Taiwan

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Abstract: Background: An increased risk of malignancy in patients with systemic lupus erythematosus has been reported, but rarely in Asian populations. We aimed to investigate the relative risk of cancer and to identify high risk group for cancer in lupus patients.
Methods: We conducted a retrospective, nationwide cohort study which included 11,763 lupus patients without prior history of malignancies, utilizing the national health insurance database of Taiwan from 1996 to 2007. Standardized incidence ratios (SIR) of cancers were analyzed.
Results: A total of 259 cancers among lupus patients were observed. An elevated risk of cancer among systemic lupus erythematosus was noted (SIR 1.76, 95% confidence interval [CI], 1.74-1.79), especially for hematoloigc malignancies (SIR 4.96, 95% CI, 4.79-5.14). Younger patients carried a greater risk ratio of cancer than general population and the risk ratio reduced with age. The risk ratio of cancer reduced with time, yet remained elevated than general population. The risk of non-Hodgkin's lymphoma is greatest (SIR 7.27) among hematologic cancers. Among solid tumors, the risk for cancers of vagina/vulva (SIR 4.76), nasopharynx (SIR 4.18) and kidney (SIR 3.99) were of the greatest. An elevated risk for less common cancers including brain, oropharynx and thyroid glands were also observed.
Conclusions: Lupus patients are at increased risk of cancers and should receive age and gender appropriate malignancy evaluations, with additional assessment for vulva/vagina, kidney, nasopharynx and hematologic malignancy. Continued vigilance for development of cancers in follow-up is recommended.

*Cover Letter

Manuscript No.: 10-396R1

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Authors: Yi-Ju Chen, Yun-Ting Chang, Chang-Bi Wang, and Chun-Ying Wu

Dear editors and reviewers,

Thank you for offering us more time to do a better revision.

The main problem is about a question proposed by reviewer 2. He reminded us about the start date of observation in our included patients. We responded that all included patients got catastrophic illness certificate after 1997. We assumed the diagnosis date should be close to the issued date. However, when we again checked the count of included patients in each year, we found a triple number of patients at the year of 1997.We then searched for the application date of patients and we found many included subjects applied for the certificate in 1995 and 1996, especially in 1995. Since the NHIRD began in 1995, we though that many patients who were diagnosed earlier began to apply this certificate for medical fee exemption.

Therefore, we decided to exclude those applied for the certificate in 1995, since we did not accurately know how long he or she has been diagnosed with this disease. And we used the application date as the observation start date, and this would be more appropriate for our study design. Therefore, we are sure that each included patient is a newly diagnosed lupus.

The revised manuscript and table are attached and the revised part is highlighted. The major change is a decrease in number of included patients. Although this is a difficult decision, we though it is a more accurate and more appropriate revision for this study.

We are very sorry for this mistake that we should have noticed earlier.

Thanks again for your kindness to offer us this chance for further revision and we are looking forward to still having a positive response from you.

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Malignancy in systemic lupus erythematosus: a nationwide cohort study in Taiwan

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Running head: malignancy in systemic lupus erythematosus

Background: An increased risk of malignancy in patients with systemic lupus erythematosus has been reported, but rarely in Asian populations. We aimed to investigate the relative risk of cancer and to identify high risk group for cancer in lupus patients.

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Results: A total of 259 cancers among lupus patients were observed. An elevated risk of cancer among systemic lupus erythematosus was noted (SIR 1.76, 95% confidence interval [CI], 1.74-1.79), especially for hematoloigc malignancies (SIR 4.96, 95% CI, 4.79-5.14). Younger patients carried a greater risk ratio of cancer than general population and the risk ratio reduced with age. The risk ratio of cancer reduced with time, yet remained elevated than general population. The risk of non-Hodgkin's lymphoma is greatest (SIR 7.27) among hematologic cancers. Among solid tumors, the risk for cancers of vagina/vulva (SIR 4.76), nasopharynx (SIR 4.18) and kidney (SIR 3.99) were of the greatest. An elevated risk for less common cancers including brain, oropharynx and thyroid glands were also observed.

Conclusions: Lupus patients are at increased risk of cancers and should receive age and gender appropriate malignancy evaluations, with additional assessment for vulva/vagina, kidney, nasopharynx and hematologic malignancy. Continued vigilance for development of cancers in follow-up is recommended.

Introduction

A common association between malignancies and autoimmune rheumatic diseases has been observed, including systemic lupus erythematosus. [1-5] With a better management of this disease, the survival in lupus has improved in recent decades.[6] Yet the mortality and morbidity of patients with lupus remain higher than general population, not only for all-cause mortality but also for mortality from cancer. [6-9] Hematologic malignancies, especially non-Hodgkin's lymphoma were the most relevant ones in several population-based cohorts and multicenter clinical cohort studies. [10-16] The results for solid tumors, however, have not been as consistent. Increased risk of lung, liver, cervix, and vagina/vulva cancer among lupus has been reported in some studies.[12;14;16] To determine the potential high risk group of patients for cancer screening is ultimate important for long term prognosis in lupus. Our aim was to investigate the relative risk and specific types of malignant diseases after the diagnosis of lupus, and to identify the high risk group for cancer among lupus patients in Taiwanese population based on a nationwide cohort database.

Method

Data sources

This study was based on data from the National Health Insurance Research Database (NHIRD) released by the National Health Research Institute (NHRI). Taiwan began its National Health Insurance (NHI) program in 1995 to finance health care for all of its residents. There are currently >25 million enrollees in the program, representing approximately 99% of Taiwan's entire population. The database comprises comprehensive information on insured subjects, such as demographic data, dates of clinical visits, diagnostic codes, details of prescriptions, and expenditure amounts. This database has been the source of many epidemiological studies published in peer-reviewed journals.[17-21] International classifications of disease-9 (ICD-9) codes were used to define diseases during the study period. Personal information including family history, lifestyle and habits such as smoking and alcohol use was not available from the NHIRD.

Study subjects with SLE

All enrollees were obtained from the Registry of Catastrophic Illness Database, a subpart of the NHIRD. The insured who suffer from major diseases can apply for a catastrophic illness certificate which grants exemption from co-payment. The

applications of catastrophic illness certificates were validated by at least two specialists based on careful examinations of medical records, laboratory and images studies. Only those meet the diagnostic criteria of major diseases would be issued a catastrophic illness certificate. Systemic lupus erythematosus and cancer are statutorily included in the catastrophic illness category. Both outpatient and inpatient claims of beneficiaries with a catastrophic illness registry are collected in the catastrophic illness profile and distributed as a package. The prescription claims of beneficiaries are released in a different dataset and is not included in current catastrophic illness profile.

The enrollees with SLE (ICD 9 code 710.0) were followed up between January 1, 1996 and December 31, 2005. The observation period ranges from January 1, 1996 to December 31, 2007 to make sure each enrollee is followed up for at least 2 years. Application of catastrophic illness certificate of SLE requires a thorough clinical and laboratory survey which fulfills the diagnostic criteria proposed by American Rheumatism Association in 1982.[22] Patients with other autoimmune diseases such as RA or Sjogren's syndrome were excluded. All enrolled SLE patients with prior history of malignancies were excluded.

As the dataset used in this study consists of de-identified secondary data released to the public for research purposes, this study was exempt from full review by the Institutional Review Board.

Identification of cancer cases

We identified the diagnoses of cancers with the records from the Registry of Catastrophic Illness Patient Database. To apply for a cancer catastrophic illness certificate, cytological or pathological reports or evidence such as additional laboratory and image studies supporting the diagnosis of cancer, including tumor marker surveys, X ray, bone scan, computed tomography scan or magnetic resonance imaging scan, should be provided. At least two other oncologists will examine the medical records and laboratory information carefully including images studies. Only those meet the criteria of diagnoses would be issued the certificates. We did not include those with in-situ malignancies because in-situ malignant diseases do not qualify for a catastrophic illness certificate. The diagnostic codes of malignancies were defined as those from 140 to 208.91 in the ICD-9 CM format. We categorized these cancer cases as hematologic cancers and non-hematologic cancers. Hematologic cancers were subcategorized as leukemia (coded 204-208) and lymphomas (including non-Hodgkin's lymphoma [coded

200, 202-203] and Hodgkin's lymphoma [coded 201]), according to the method of Cancer Registry in Taiwan.

Cancer risk analysis

All enrolled study subjects were followed up until a first time diagnosis of cancer (except malignancy in–situ, metastasis or secondary cancers), death, the end of follow-up in the medical records, or the end of 2007. Standardized incidence ratios (SIR) of cancers were analyzed. Stratified analyses according to age at diagnosis, gender, and years of follow-up were conducted.

Statistical analysis

The demographic data of the study population were first analyzed. Follow-up for each patient with systemic lupus erythematosus began at the date of diagnosis and ended at the date of censorship, i.e. the date of diagnosis of cancer, death or the end of follow-up period, and was measured in numbers of years. We examined the association among lupus and specific cancer types with SIR. SIR was calculated as follows: the number of cancer cases that arose among lupus patients divided by the expected number of cancer cases according to national age-specific, gender-specific, and period-specific

cancer rates. Yearly reports of cancer rates were obtained from Taiwan National Cancer Registry. We pooled the 10-year cancer registry reports of Taiwan from 1997 to 2006 as a standard.

To assess the age effect on the relative risk for malignancies, we analyzed the relative risk among those aged between 0-19, 20-39, 40-59, 60-79 years, and more than 80 years at SLE diagnosis. A further analysis was done to evaluate whether the association of malignancies varied according to the time after lupus diagnoses. We divided follow-up time into six periods, 1 year or less, between 1 to 2 years, 2-4 years, 4-6 years, 6-8 years and more than 8 years.

The SAS statistical package (SAS System for Windows, version 9.1; SAS Institute, Cary, North Carolina) and SPSS statistics (SPSS statistics for window, version 15.0; SPSS Incorporation, Chicago, Illinois) were used to perform the statistical analysis of the data in this study.

Results

We identified a total of 11,763 patients with systemic lupus erythematosus who did not have previous malignancies. The demographic data of study subjects are presented in Table 1. A total of 259 cancers (2.2%) were identified after diagnosis of lupus. An elevated overall cancer risk in lupus patients was observed (Table 2). Women had a slightly higher risk than men. The risk ratio of cancer is greater in lupus patients younger than 40 years when compared with subjects of similar ages in general population, and the risk ratio reduced with age. (Table 2)

Comorbid malignant diseases in systemic lupus erythematosus were mostly detected following the first year of diagnosis. The risk ratios gradually reduced with time. After 8 years of observation, the SIR of malignancies was even lower than general population. (Table 2) An elevated risk for hematologic malignancies in lupus patients was observed, especially in male patients. (Table 2) Middle-aged patients (aged 40-69 years) carried the greatest risk ratio for hematologic cancers. (Table 2)

Of all comorbid malignant diseases, 31 cases (11.97%) were hematologic malignancies, including 24 cases of non-Hodgkin's lymphomas and 7 cases of leukemias. No Hodgkin's lymphoma was observed in our cohort. The risks for hematologic cancers were extraordinarily high following the first 2 years of diagnosis. (Table 2)

Among hematologic cancers, the risk for non-Hodgkin's lymphoma (including other lymphosarcoma, reticulosarcoma, multiple myeloma and other immunoproliferative neoplasms) is greatest. The risk of leukemias, to a lesser extent, is also elevated. (Table 3)

Lupus patients also carried an increased risk for non-hematologic malignancies. (Table 4) The most relevant cancers were originating from female genitalis, such as vulva and vagina and cervix. A decreased risk of prostate and ovary cancer was observed compared to general population. (Table 4)

Other associated cancers were presented in Table 4, including cancers of kidney, nasopharynx, sinus and ears; oropharynx, brain, and thyroid gland.

Discussion

It has been accepted nowadays that systemic lupus erythematosus is at increased risk of certain cancers. Different cohort studies produced various estimates of the cancer risk of lupus patients; however, the risk of specific cancer types was inconclusive. [16;23-27] Most cancer cases in our cohort were detected within the first 2 years after diagnosis. Aggressive surveillance for cancer during that period may have resulted in a detection bias. When cancer cases observed in the first 2 years were excluded, a sustained elevated risk existed among lupus patients until 8 years of follow-ups, indicating a true link between these two diseases.

The underlying mechanisms linking malignancies and lupus remained unclear. There is no clear explanation regarding the inflammatory nature of lupus or the immunosuppressive treatment in association with malignancies. Bernatsky et al., has firstly explored the relationship between cancer and exposures of medication and other risk factors in lupus patients.[28] Their study indicated older age, disease activity and tobacco exposure were associated with an increased cancer risk in systemic lupus erythematosus. The relationship between immunosuppressive drugs and cancers may vary considerably with different type of cancers. For example, increased cancer rates among lupus patients, especially with respect to lymphomas and leukemias, have been

linked to treatment with drugs including cyclophosphamide, azathioprine, and methotrexate in some reports. [29-32] An increased risk of hematologic malignancies was observed after at least 5 years of immunosuppressice drug exposure.[28] However, a recent nested case control study focusing on the association between non-Hodgkin's lymphoma and lupus indicated that it is the hematologic aberrations (leuco-/thrombocytopenia, or hematoloigc anemia), sicca symptoms, or recurrent pneumonias predict the prognosis among lupus patients. It also indicated that use of azathioprine and cyclophosphamide did not increase the risk of non-Hodgkin's lymphoma. [33] Several case series have indicated an increased risk of bladder cancer among lupus patients because of the treatment with cyclophosphamide. [29-32] We were not able to examine this association since we did not have treatment information on these patients. Nevertheless, the finding of a gradual reduction of cancer risk ratios during observation in our lupus patients implied that cancer risk is not completely explained by cumulative toxicity of immunosuppressive drugs.

The finding of younger lupus patients bearing greater risk ratio of cancer has not been reported until recently. [34] Our study is the first regarding the age effect and cancer risk of lupus patients in Asian populations. Since malignant diseases generally increase with age among the general population, it is reasonable that the higher prevalence of

cancer cases among aged patients makes the difference in incidence non-significant between elderly lupus patients and elderly subjects from the general population. The relationship between severity of lupus and malignant diseases may be another plausible explanation. Previous reports have indicated that the majority of severe cases of systemic lupus erythematosus occur in younger women, particularly women other than non-Hispanic whites. [35] In addition, younger patients with severe disease may be treated with more aggressively with immunosuppressive agents, which may also lead to an increased risk of cancer.

Increased mortality risk due to cancer in lupus, especially non-Hodgkin's lymphoma and lung cancer, has been demonstrated.[7] A poorer prognosis in lupus patients complicated with non-Hodgkin's lymphoma has been reported.[36] However, it is unknown if this is related to more aggressive histological subtypes on diagnosis,[13;14] delayed cancer diagnosis, or others.

Most of the data from previous cohort studies suggested a three to fourfold risk of hematologic malignancies, especially non-Hodgkin's lymphoma in lupus than general population. [8;12] Comparable to previous studies, our results demonstrated an even higher risk of non-Hodgkin's lymphoma (SIR 7.27) and to a lesser extent, leukemia (SIR 2.64) among lupus patients. Studies specifically investigating subtypes of lymphoma and lupus

have indicated an increased proportion of the aggressive diffuse large B cell lymphomas.[12;37;38] The risk of large B cell lymphoma among lupus was also significantly elevated than general population.[34] We did not subcategorize our non-Hodgkin's lymphoma patients by subtypes because standardized cancer estimates by specific lymphoma subtypes in Taiwan were not available.

A common association of hematologic malignancies, especially non-Hodgkin's lymphoma, in patients with autoimmune diseases has been observed for decades. Shared eiopathogeneic factors and genetic predisposition commonly in both autoimmune diseases and lymphomas included uncontrolled B cell proliferation,[39] defected apoptosis,[40] oncogene translocation[36] and aberrant Epstein-Barr virus expression[41]. Chronic lymphocyte activation related to autoimmune diseases has been proposed to be a possible underlying mechanism.[6;37;42-44]

An increased risk of various solid tumors was observed in our lupus patients. In addition to commonly reported lung and hepatobiliary cancers, an elevated risk for certain rare cancers was observed, such as kidney (SIR 3.99), nasopharynx, sinus or ears (SIR 4.28), brain (SIR 3.30) and thyroid (SIR 2.24) in lupus patients. The findings of increased risks of these rarer cancers highlighted the power of our present study to detect differences in rare cancers.

An elevated risk of vagina/vulva (SIR 4.76) and cervix cancers (SIR 1.39) was observed in our lupus patients. Only few studies have mentioned about the high prevalence of vagina/vulva cancer in lupus patients.[14;34] An increased prevalence of human papillomavirus in women with lupus may be a possible explanation for the elevated risk of these two cancer types. [45;46] A decreased risk of some hormone-sensitive malignancies such as breast and endometrial cancers was described in some cohort study;[12;34] on the contrary, except for the cancers of prostate and ovary, we demonstrated an elevated risk of breast and uterus cancers.

There are several limitations in our present study. First, we did not have personal information of patients, such as life style, body mass index, smoking and alcohol use, family history of malignancy, or the information of systemic treatment which may contribute to cancer risk. Second, misclassification of diseases may happen based on administrative database of NHIRD in Taiwan. To minimize the possible bias, we enrolled the patients from the catastrophic illness profile in which only those with definite diagnoses would be included. Finally, most lupus patients undergo regular physical and laboratory check-ups for many years. A surveillance bias may contribute to some of the increased frequency of cancer in these patients.

However, our study provides important information. This is the first large scale

nationwide cohort study of cancer and lupus conducted in Asian population. Younger lupus patients are at greatest risk to develop certain cancers when compared with that in general population. In addition to a high prevalence of hematologic cancers especially non-Hodgkin's lymphoma, an increased risk of several less common cancers, such as vagina/vulva, kidney, nasopharynx, urinary bladder, brain and thyroid gland were also observed. We therefore suggest a thorough history taking, physical and laboratory examinations for these rare cancers in all lupus patients. Although most cancers were detected within the early course of observation, we suggest a continuous cancer screening in lupus patients for at least 8 years, especially for those of hematologic origins.

Acknowledgement

This study is based in part on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health and managed by the National Health Research Institute. The interpretation and conclusions contained herein do not represent those of the Bureau of National Health Insurance, Department of Health or the National Health Research Institute.

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Table(s)

Table 1. Demographic data of SLE patients

	SLE (N=11,763)
Mean age at diagnosis (SD)	34.73 (15.61)
Age	
< 40	7,886 (67.04%)
40-69	3,531 (30.02%)
≧70	346(2.94%)
Gender	
Male	1,369 (11.64%)
Female	10,394(88.36%)
Mean follow-up year (SD)	6.10 (3.06)

Table 2. Standardized incidence ratios (SIRs) and 95% confidence intervals (95% CIs) of cancers, according to age, gender, duration of follow-ups in SLE.

Characteristics	N	Exp	SIR	95% CI
Total cancer	259	147.42	1.76	1.74-1.79
Gender				
Female	221	122.04	1.81	1.79-1.83
Male	38	25.67	1.48	1.43-1.53
Age, years				
< 40	75	24.65	3.04	2.97-3.11
40-69	166	88.88	1.87	1.84-1.90
≧70	18	17.60	1.02	0.98-1.07
Follow-up, years				
< 1	58	0.80	72.26	70.65-74.39
1-2	34	1.72	19.72	19.12-20.44
2-4	64	16.72	3.83	3.73-3.92
4-6	57	26.68	2.14	2.93-3.05
6-8	26	30.49	0.85	0.82-0.89
≧8	20	52.66	0.38	0.36-0.40
Hematologic cancers				
Gender				
Female	25	5.10	4.90	4.71-5.10
Male	6	1.12	5.36	4.94-5.80
Age, years				
< 40	10	2.27	4.41	4.14-4.69
40-69	19	2.97	6.41	6.11-6.69
≧70	2	0.68	2.96	2.55-3.38
Follow-up, years				
< 1	6	0.03	193.31	184.32-216.66
1-2	4	0.07	60.56	51.68-63.03
2-4	12	0.70	17.21	16.19-18.14
4-6	5	1.11	4.50	4.12-4.92
6-8	3	1.31	2.28	2.04-2.56
≧8	1	2.41	0.42	0.33-0.50

N, observed cancer number; Exp, expected cancer number.

Table 3. SIR of hematopoietic malignancies in SLE in Taiwan

Cancer types	N	Exp	SIR	95% CI
All	31	6.25	4.96	4.79-5.14
Leukemia	7	2.65	2.64	2.45-2.84
Hodgkin's lymphoma	0	-	-	-
Non-Hodgkin's lymphoma and others*	24	3.30	7.27	6.98-7.57

N, observed number; Exp, expected number; SIR, standardized incidence ratio; CI, confidence interval.

*Others include lymphosarcoma, reticulosarcoma, multiple myeloma and other immunoproliferative neoplasms.

Table 4. SIRs of non-hematologic malignancies and specific cancer types in systemic lupus erythematosus (SLE) in Taiwan

Specific cancer types	N	Exp	SIR	95% CI
All	228	148.37	1.54	1.52-1.56
Reproductive cancers				
Breast	45	29.03	1.55	1.51-1.60
Uterus	5	3.90	1.28	1.17-1.40
Cervix	22	15.83	1.39	1.33-1.45
Ovary	3	4.18	0.72	0.64-0.80
Prostate	2	2.55	0.79	0.68-0.90
Vagina/vulva	3	0.63	4.76	4.24-5.33
Others				
Skin cancer	7	4.19	1.67	1.55-1.80
Oropharynx and larynx	9	4.43	2.03	1.90-2.17
Liver and gallbladder	28	15.32	1.83	1.76-1.90
Colon and rectum	14	17.10	0.82	0.78-0.86
Stomach	14	6.74	2.08	1.97-2.19
Esophagus	2	1.23	1.63	1.41-1.87
Pancreas	4	2.00	2.00	1.81-2.21
Lung and mediastinum	16	13.03	1.23	1.17-1.29
Urinary bladder	2	3.05	0.66	0.57-0.75
Nasopharynx, sinus, ears	10	2.39	4.18	3.93-4.45
Cancer of ill-defined sites	4	2.18	1.84	1.66-2.02
Kidney	9	2.25	3.99	3.74-4.27
Brain	5	1.52	3.30	3.00-3.59
Thyroid gland	14	6.26	2.24	2.12-2.36
Others†	10	2.81	3.56	3.34-3.79

N, observed number; Exp, expected number; SIR, standardized incidence ratio; CI, confidence interval.

†Other tumors include malignancies of salivary glands, intestine, retroperitoneum, bone, cartilage, and connective tissue.

Clinical significance

1. Systemic lupus erythematosus carries an elevated risk of various cancers, especially non-Hodgkin's lymphoma, cancers of vagina/vulva, nasopharynx and kidney.
2. The risk ratio of cancer in systemic lupus erythematosus was greatest among those younger than 40 years old; and the risk ratio decreased with age.
3. The risk ratio of cancer in systemic lupus erythematosus was greatest within the first year after diagnosis, and remained elevated than general population until 8 years of observation.

*Conflict of Interest Statement

Statement of Conflicts of Interest

The authors declare that they do not have financial or non-financial conflicts of interests in relation to this manuscript.

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