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The risk of cancer in rheumatoid arthritis patients: a nationwide cohort study in Taiwan

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Abstract

Objective: The association of rheumatoid arthritis (RA) and malignancy has been rarely explored in Asian populations. We aimed to investigate the relative risk of cancer and to identify high-risk group for cancer in RA patients.

Methods: We conducted a nationwide cohort study regarding the risk of cancer among 23,644 RA 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 935 cancers among RA patients were observed. There was an elevated risk of cancer in RA patients (SIR 1.23, 95% confidence interval [CI] 1.22-1.23), especially for hematologic malignancies (SIR 2.74, 95% CI 2.68-2.81). The relative risk of cancer was higher among younger patients, compared to the general population. Most cancer cases were detected within the first year of diagnosis. The relative risk of cancer decreased with observation time. The risk of non-Hodgkin's lymphoma (NHL) was greatest (SIR 3.54, 95% CI 3.45-3.63) among hematologic cancers. Among solid tumors, the risk of cancers of kidney and vagina/vulva were of the most relevant. A decreased risk of cancers of cervix and non-melanoma skin cancer in RA were also observed.

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Conclusions: RA patients are at increased risk of cancer, especially hematologic and kidney cancers. The relative risk of cancer in RA patients decreased with long-term follow-up. Cancer screening with continued vigilance is recommended.

INTRODUCTION

Rheumatoid arthritis (RA) affects several organ systems including cardiovascular, musculoskeletal, respiratory and psychological systems, and leads to major co-morbidities and mortality. Chronic organ damage and late complications, such as malignancy and cardiovascular diseases, have become major adverse factors of both morbidity and mortality.(1) However, the association of malignancies with RA remains controversial. Some studies have reported a similar (2-6) incidence of malignant diseases in RA patients compared to the general population; yet other reports have indicated a lower (7;8) risk of malignant diseases in RA patients. Most studies have consistently indicated an increased incidence of lymphoma(3;5;9;10) and a decreased incidence of colorectal cancer in RA patients.(2;7;9) With relatively low prevalences of RA among Asian populations,(11-13) the relationship between malignancy and RA has rarely been reported in these counties.(14)

The pathogenetic mechanisms of interaction between these two diseases remain uncertain. Baecklund et al.(15) firstly demonstrated high disease activity, rather than its treatment, to be a major determinant in lymphoma risk of RA patients. However, other factors such as treatment modalities may also be involved. (16) Our aim was to investigate the relative risk of malignant diseases, including the specific cancer types,

after the diagnosis of RA in Taiwanese population based on a nationwide cohort database.

METHODS

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 more than 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, as detailed described in our previous studies.(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 RA

All study subjects 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. RA 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 patients with RA (ICD 9 code 714.0) were included between January 1, 1996 and December 31, 2005. Those younger than 16 years were excluded. All the included patients were followed-up until December 31, 2007 to make sure each included subject has a sufficient observation time for at least 2 years. Application of catastrophic illness certificate of RA requires a thorough clinical and laboratory survey which fulfills the ACR (American College of Rheumatism) criteria.(22) Patients with other autoimmune diseases such as SLE or Sjogren's syndrome were excluded. Subjects with prior history of malignancies were also excluded.

As the data set 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, CT scan or MRI 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 excluded 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 revision clinical modification format. We categorized these cancer cases into hematologic cancers and non-hematologic cancers. Hematologic cancers were subcategorized into leukemias (coded 204-208) and

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

Cancer risk and statistical analysis

All study subjects were followed up until a first time diagnosis of cancer, death, the end of follow-up in the medical records, or the end of 2007. We examined the association between RA and specific cancer types with standardized incidence ratios (SIR). SIR was calculated as follows: the number of cancer cases among RA 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 the Taiwan National Cancer Registry. We pooled the 10-year cancer registry reports of Taiwan from 1996 to 2006 as a standard.

To assess the age effect on the relative risk of malignancies, we analyzed the relative risk among those aged 0-39, 40-69, and more than 70 years at RA diagnosis. A further analysis was done to evaluate whether the association of malignancies varied according to the time after RA diagnosis. We divided follow-up time into six periods: 1 year or less, 1-2 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) was used to perform the statistical analysis of the data in this study.

RESULTS

Risk of cancers in RA patients with no prior history of malignancy

We identified a total of 23,644 patients with RA who did not have previous malignancies. The mean age ± standard deviation (SD) among patients at diagnosis of RA was 53.08 ± 14.38 years. There were 18,527 (78.36%) female and 5,117 (21.64%) male patients among RA study group. The mean follow-up time for RA was 5.90 ± SD 2.87 years (Table 1). During the observation time of 139,555.47 person- years, a total of 935 cancers among RA were identified after diagnosis of disease. A slightly increased overall cancer risk in RA was observed (SIR 1.23, 95% confidence interval [CI] 1.22-1.23) (Table 2). Women and men were at similar risk of developing cancer.

The relative risk of cancer was greatest among younger patients with RA, and the risk ratio reduced with age (Table 2). The SIR was 2.35 (95% CI 2.28-2.42) among those younger than 40 years old. The SIRs reduced to 1.58 (95% CI 1.56-1.59) among those aged between 40-69 years, and 1.03 among those older than 70 years old. Malignant diseases in RA were mostly detected following the first year of diagnosis (SIR 58.96, 95% CI 58.13-59.96). The risk ratios gradually reduced with observation time. (Table 2) After 8 years of follow-up, the SIR of malignancies in RA fell to 0.31, less than that of general population.

Specific types of non-hematologic cancers associated with RA

Excluding hematologic cancers, a slightly increased risk of non-hematologic malignancies (SIR 1.12, 95% CI 1.11-1.13) was also observed. (Table 4) The highest risks were cancers originating from kidney and female genitalis, such as vulva and vagina. (Table 4) Other significantly associated cancers in RA included cancers originating from nasopharynx, melanoma, thyroid gland and lung. (Table 4)

On the contrary, a reduced risk of certain cancers was also observed, including cancers of colorectum, cervix and non-melanoma skin cancers. (Table 4)

Lymphohematopoietic cancers associated with RA

Among all comorbid malignant diseases, there were 75 cases (8.02%) of hematologic malignancies including 59 cases of non-Hodgkin's lymphoma (NHL), one case of Hodgkin's lymphoma (HL) and 15 cases of leukemia. A significantly elevated risk for lymphohematopoietic malignancies in RA was observed (SIR 2.74, 95% CI 2.68-2.81), especially in male patients. (Table 2) The risk of cancer varies by age. Middle-aged patients (aged 40-69 years) were at greatest relative risk for hematologic cancers, compared to general population with similar ages. (Table 2)

The risks for lymphohematopoietic cancers were extraordinarily high following the first 2 years of diagnosis. The relative risk of hematologic cancer reduced with

observation time. (Table 2) The SIR fell to 0.62 after 8 years of follow-up.

In regards to specific cancer types, the risk of NHL (including other lymphosarcoma, reticulosarcoma, multiple myeloma and other immunoproliferative neoplasms) was greatest (SIR 3.54, 95% CI 3.45-3.63), followed by HL (SIR 1.76, 95% CI 1.45-2.17) and leukemia (SIR 1.48, 95% CI 1.41-1.56). (Table 3)

DISCUSSION

This is the first large scale nationwide study to estimate the risk of cancer in RA patients with no prior history of malignancies based on a Taiwanese population. Consistent with prior cohort studies, the risks of lymphohematopoietic cancers including HL, NHL and leukemia are significantly higher in RA patients than in the general population. In addition to lymphohematopoetic cancers, RA patients are at higher risk of developing some less common cancers such as those of kidney, vulva, thyroid gland and nasopharynx than the general population.

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. However, when cancer cases observed in the first 2 years were excluded, there was a sustained elevated risk among RA patients until 8 years of follow-up, indicating a true link between these two diseases. Although the association between malignancy and RA remains controversial, the association of lymphoma with RA has been frequently observed. In addition to common genetic factors between autoimmune diseases and lymphomas, aberrant EBV expression, persistent inflammation, chronic activation of autoimmune B cells and immunosuppressive therapy have been proposed to contribute to lymphoma development.(23;24) The assessment of lymphoma risk in association with

immunomodulating therapy in patients with autoimmune disease is complex due to the inability to distinguish therapy-related effects from effects of the disease itself. The relationship among methotrexate, (15;25-28) nonsteroidal anti-inflammatory drugs (NSAID), aspirin(29;30) or corticosteroid(16;31;32) and lymphoma risk has been explored among RA patients, yet without consistent results. We were not able to examine this association since we did not have treatment information for the RA patients in our study.

The finding of younger RA patients with higher risks of cancer has not been reported until recently.(33) Since malignant diseases increase with age among the general population (data not presented), it is reasonable that the higher prevalence of cancer cases among aged patients makes the difference in incidence non-significant between elderly RA patients and elderly subjects from the general population.

Most of the data from previous cohort studies have shown an average twofold risk of lymphoma in RA when compared with the general population.(3;34-36) Our results demonstrated similar risks to those of previous studies for NHL (SIR 3.54), HL (SIR 1.76) and, to a lesser extent, leukemia (SIR 1.48) among RA patients. We did not subcategorize our NHL patients by subtype because standardized cancer estimates by specific lymphoma subtypes were not available.

Increased risks of various solid tumors were observed in our RA patients. In addition to lung cancer (SIR 1.23), significantly elevated risks for certain less common cancers were observed, such as those of the kidney (SIR 2.12), melanoma (SIR 1.47), thyroid gland (SIR 1.41), and nasopharynx (SIR 1.39). The findings of increased risks of these cancers highlight the power of our present study to detect differences in rare cancers. Cigarette smoking, possibly contributing to RA via the production of antibodies recognizing citrullinated proteins,(37) is also a strong risk factor for cancers of lungs, kidney(38) and urinary bladders.(39) Other factors linking lung cancer and RA have been proposed including chronic inflammation(40) and the presence of interstitial lung disease(41;42). It was not until recently that an association between RA and kidney cancers was demonstrated. A cohort study in a South European population indicated that RA patients with lung or kidney cancer have a higher mortality rate than expected.(2) An elevated risk of vagina/vulva (SIR1.69) was observed in our RA patients, which may be explained by an increased prevalence of high risk human papillomavirus (HPV) infection in RA patients.(43) Cytotoxic drugs and biologics such as tumor necrosis factor (TNF)-α blockade may also increase susceptibility to HPV infection in RA patients.(44)

Increased incidence of melanoma has been reported in RA patients treated with methotrexate (45) and biologics.(6) Our study demonstrated an increased risk of

melanoma. Yet, with only three cases of melanoma observed in our RA cohort, a longer observation time or additional pharmacologic information may benefit in exploring the link between these two diseases.

There are several limitations to our present study. First, we did not have personal information of patients, such as lifestyle, body mass index (BMI), smoking habit and alcohol use, family history of malignancy or other autoimmune diseases, or information regarding systemic treatment which may contribute to cancer risk. Second, misclassification of diseases may happen based on an administrative database. To minimize this bias, we only enrolled patients from the catastrophic illness profile who met the criteria of RA. The number of RA patients may therefore be underestimated. Finally, most RA patients undergo regular physical and laboratory check-ups during observation. 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 RA conducted in an Asian population. RA patients are at risk to develop certain cancers when compared with that in general population, especially in younger patients. In addition to a high prevalence of lymphohematopoietic cancers, especially NHL, an increased risk of several less common cancers, such as

vagina/vulva, kidney, nasopharynx, prostate and melanoma were also observed. Finally, a gradual reduction of relative cancer risk in RA patients following observation time was observed. A decrease of disease activity, long term exposure to immunomodulatory drugs or early mortality among patients with severe diseases or complicated with other comorbidities may all contribute to a decreased trend in the relative risk of cancer. Current treatments for RA in Taiwan are a combination of several immunomodulative drugs, mainly prednisolone, various NSAID, methotrexate, and biologics (adalimumab or etarnecept). Other DMARDs such as azathioprine, hydroxylcholoroquinine, cyclophosphamide, mycophenolate mofetil, etc., are occasionally used. Since some of these medications may result in end organ damage or cancer risks, the direct effect of immunosuppressive treatment on cancer risk in RA patients need further studies.

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Table 1. Demographic data of RA patients

	RA
	N=23,644 (%)
Mean age at diagnosis (SD)	53.08 (14.38)
Age	
15-39	4,295(18.17)
40-69	16,338(69.10)
□70	3,011(12.73)
Gender	
Male	5,117(21.64)
Female	18,527(78.36)
Mean follow-up year (SD)	5.90 (2.87)

N, number; SD, standard deviation.

Table 2. SIRs and 95% CIs of cancers, according to age, gender, duration of follow-up of RA patients in Taiwan

Characteristics	All cancers*				Hematologic cancers			
	Observed	Expected	SIR	95% CI	Observed	Expected	SIR	95% CI
All	**935**	**762.19**	**1.23**	**1.22-1.23**	75	27.35	2.74	2.68-2.81
Gender								
Female	634	535.40	1.18	1.17-1.19	39	18.90	2.06	2.00-2.13
Male	301	228.13	1.32	1.30-1.33	36	8.23	4.38	4.23-4.52
Age, years								
15-40	43	18.33	2.35	2.28-2.42	2	1.30	1.54	1.33-1.77
40-69	698	442.85	1.58	1.56-1.59	52	14.90	3.49	3.40-3.59
□70	194	188.66	1.03	1.01-1.04	21	7.22	2.91	2.79-3.04
Follow-up, yrs								
< 1	160	2.71	58.96	58.13-59.96	14	0.10	139.08	132.76-147.53
1-2	150	8.25	18.19	17.89-18.48	13	0.30	42.67	41.01-45.75
2-4	246	102.85	2.39	2.36-2.42	17	3.71	4.59	4.37-4.81
4-6	165	156.57	1.05	1.04-1.07	18	5.62	3.21	3.06-3.35
6-8	128	165.15	0.78	0.76-0.79	7	5.88	1.19	1.10-1.28
≧8	86	273.97	0.31	0.31-0.32	6	9.72	0.62	0.57-0.67

*All cancers including hematologic cancers; SIR, standardized incidence ratio, 95% CI, 95% confidence interval;

Table 3. SIR of hematopoietic malignancies in RA in Taiwan

Cancer types	Observed	Expected	SIR	95% CI
All	75	27.35	2.74	2.68-2.81
Leukemia	15	10.12	1.48	1.41-1.56
Hodgkin's lymphoma	1	0.56	1.76	1.45-2.17
Non-Hodgkin's lymphoma and others*	59	16.66	3.54	3.45-3.63

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 of RA patients in Taiwan

Specific cancer types	Observed	Expected	SIR	95% CI
All cancers	**860**	**769.30**	**1.12**	**1.11-1.13**
Kidney	30	14.17	2.12	2.04-2.19
Others‡	26	14.42	1.80	1.73-1.87
Vulva/vagina†	5	2.96	1.69	1.54-1.84
Nasopharynx, sinus, ears	22	15.79	1.39	1.34-1.45
Lung and mediastinum	123	90.47	1.36	1.34-1.38
Thyroid gland	23	16.28	1.41	1.36-1.47
Prostate	22	16.82	1.31	1.25-1.36
Stomach	54	42.93	1.26	1.22-1.29
Skin cancer				
Melanoma	3	2.04	1.47	1.31-1.65
NMSC¶	20	22.93	0.87	0.83-0.91
Uterus	20	15.68	1.28	1.22-1.33
Breast	123	101.44	1.21	1.19-1.23
Liver and gallbladder	126	108.59	1.16	1.14-1.18
Urinary bladder	26	22.51	1.15	1.11-1.20
Esophagus	11	10.01	1.10	1.03-1.17

Pancreas	15	13.86	1.08	1.03-1.14
Oropharynx and larynx	31	29.26	1.06	1.02-1.10
Cancer of ill-defined sites	14	13.79	1.02	0.96-1.07
Ovary	14	14.27	0.98	0.93-1.03
Colon and rectum	102	107.99	0.94	0.93-0.96
Brain	5	5.34	0.94	0.86-1.02
Cervix	45	52.14	0.86	0.84-0.89

†Vulva/ vagina tumors including other unspecified female genital organs

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

¶ NMSC, non-melanoma skin cancer