

The Risk of Lymphoma Development in Autoimmune Diseases

A Meta-analysis

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Background: The risk of development of non-Hodgkin lymphoma (NHL) in autoimmune patients has been investigated in several cohort studies. These studies revealed inconclusive results. To shed some light on this controversy, we conducted a meta-analysis of all available cohort studies linking systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and primary Sjögren syndrome (pSS) to the risk of NHL development.

Methods: We searched the PubMed database (1974 to April 2005) for English-language cohort studies using the key words *systemic lupus erythematosus*, *SLE*, *rheumatoid arthritis*, *RA*, *Sjögren syndrome*, or *SS*; *non-Hodgkin lymphoma*; and *relative risk*, *RR*, *standardized incidence rate*, or *SIR*. All cohort studies that used established diagnostic criteria for SLE, RA, and pSS; had histologic confirmation of NHL; and provided standardized incidence rates (SIRs) were included in the meta-analysis.

Results: The 20 studies chosen for the analysis in-

cluded 6 for SLE, 9 for RA, and 5 for pSS. Overall, the meta-analysis suggested extreme heterogeneity among the studies ($P < .01$; $I^2 > 70\%$), high risk of NHL development for pSS (random effects SIR, 18.8; 95% confidence interval [CI], 9.5-37.3); moderate risk for SLE (random effects SIR, 7.4; 95% CI, 3.3-17.0); and lower risk for RA (random effects SIR, 3.9; 95% CI, 2.5-5.9). In RA, the random effects SIRs of NHL with conventional antirheumatic treatment, cytotoxic treatment, and treatment with a biological agent were 2.5 (95% CI, 0.7-9.0), 5.1 (95% CI, 0.9-28.6), and 11.5 (95% CI, 3.7-26.9), respectively.

Conclusions: Rheumatic disease may present a potential risk factor for development of NHL. In this regard, we focused on the underlying pathophysiologic mechanisms related to lymphomagenesis in pSS, SLE, and RA, to justify the varying potential for and background of NHL development.

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THE ASSOCIATION OF MALIGNANCY with autoimmune rheumatic diseases has been a subject of investigation for years. It has been shown that there is increased risk of malignancies, mainly non-Hodgkin lymphoma (NHL), in patients with rheumatoid arthritis (RA), primary Sjögren syndrome (pSS), and systemic lupus erythematosus (SLE). The findings were based mainly on case reports and a few cohort studies, but with disparate estimates. Therefore, there is inadequate conclusive evidence confirming the risk of NHL in these patients. The mechanism of lymphomagenesis is unclear in autoimmune disease. Observational studies have indicated that lymphoma can develop in individuals with immune dysregulation, those who are receiving immunosuppressive drugs, or those who

have been exposed to unknown environmental factors. A number of recent cohort studies indicate a high risk of lymphoma development in some autoimmune rheumatic diseases. Some studies suggested that the risk factor of lymphoma development is high,¹⁻³ others reported moderate risk,^{4,5} and one did not find any association.⁶ To provide an estimate of lymphoma development risk in autoimmune rheumatic disorders, we conducted a meta-analysis of all available cohort studies relating SLE, RA, and pSS to the risk of NHL development. In the meta-analysis, we calculated a pooled estimate of this risk that is expressed as a standardized incidence rate (SIR). In addition, the heterogeneity among studies and the existence of bias have been investigated. We also discuss the pathogenetic aspects of lymphomagenesis in these classic autoimmune disorders.

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METHODS

SEARCH STRATEGY

We searched PubMed (1974 through April 2005) for English-language articles using the following criteria: *systemic lupus erythematosus*, *SLE*, *rheumatoid arthritis*, *RA*, *Sjögren's syndrome*, or *SS*; *non-Hodgkin lymphoma*; and *relative risk*, *RR*, *standardized incidence rate*, or *SIR*. All data were then studied to assess their appropriateness for inclusion in the meta-analysis. All references cited in the retrieved articles were also reviewed to identify additional published work not indexed by PubMed, and the we reached consensus. Abstracts, case reports, editorials, and review articles were excluded.

DATA EXTRACTION

We included cohort studies that used established diagnostic criteria for SLE, RA, and pSS; that included histologic confirmation of NHL; and that provided SIRs and 95% confidence intervals (CIs) or enough data to allow us to calculate these numbers. In the latter case, the SIR was defined as the ratio of the number of observed cases with NHL divided by the number of expected cases in the general population. The 95% CI was calculated using the standard error of the natural logarithm of the SIR, that is, $\ln(\text{SIR})$, which was estimated by the inverse of the square root of the observed number of cases.⁷⁻⁹ In addition to the SIR and 95% CI, we extracted information on data origin, diagnosis criteria used, cohort duration, cohort size, number of cases, and treatment with immunosuppressive agents. We excluded studies that provided SIRs for lymphomas or malignancies without specifying the NHL SIRs and studies that did not provide the expected number of NHL cases from registries or surveys. Lymphomas will hereafter be referred to as *NHL*.

DATA SYNTHESIS

In the meta-analysis, we calculated the pooled $\ln(\text{SIR})$ using as a weighted factor the inverse of the square root of the observed number of cases.¹⁰ We then calculated the 95% CI of the pooled SIR, by taking the exponential of the 95% limits of the $\ln(\text{SIR})$. The pooled $\ln(\text{SIR})$ was estimated using fixed-effects and random-effects (RE) models (DerSimonian-Laird). Random-effects modeling assumes a genuine diversity in the results of various studies, and it incorporates

into the calculations a between-study variance. Therefore, when there is heterogeneity between studies, the pooled $\ln(\text{SIR})$ is estimated using the RE model.¹⁰ The heterogeneity between studies was tested using the Q statistic, which is a weighted sum of squares of the deviations of individual-study $\ln(\text{SIR})$ estimates from the overall estimate.¹¹ If $P < .10$, then the heterogeneity was considered statistically significant. Heterogeneity was also quantified with the I^2 metric, which is independent of the number of studies in the meta-analysis.¹² We performed a cumulative meta-analysis to evaluate the trend of pooled $\ln(\text{SIR})$ over time.¹³ We also performed subgroup analyses for each sex and according to type of treatment, when the data were available. In addition, sensitivity analyses were carried out by excluding specific studies. The publication bias was tested using the Egger regression test for funnel plot asymmetry¹⁴ and the Begg-Mazumdar test, which is based on the Kendall tau.¹⁵ Analyses were performed using SAS routines (SAS Institute Inc, Cary, NC),¹⁰ StatsDirect (StatsDirect Ltd, Cheshire, England), and Compaq Visual Fortran (Hewlett Packard, Avondale, Pa) with the Institute of Museum and Library Sciences library, Washington, DC.¹⁶

RESULTS

The literature review identified 84 titles in PubMed that met the search criteria. We reviewed the abstracts of these articles and judged 26 articles to be potentially relevant. We read the full articles of the selected studies to assess their appropriateness for meta-analysis and assessed their references. We then selected 20 studies for the analysis, including 6 for SLE,^{1,4,6,17-19} 9 for RA,^{2,5,20-26} and 5 for pSS^{3,5,27-29} (**Tables 1, 2, and 3**). All studies were published between 1978 and 2005.

In 6 studies,^{2,3,20,23,26,27} the SIRs or the 95% CIs of SIRs were calculated from data provided in the articles. Two studies^{2,22} included only female patients. In 3 studies,^{3,5,20} the cohort consisted of cases with a mixture of rheumatic diseases. Only 3 RA studies^{2,20,21} reported SIR results by sex. Seven studies^{2,5,19-22,27} did not report the type of treatment before NHL diagnosis, and 4 studies^{4,6,17,28} reported no use of immunosuppressive therapy in documented NHL cases. Four RA studies reported the

use of therapy before NHL diagnosis,²³⁻²⁶ and 2 of those studies^{23,25} compared a group treated with a cytotoxic or a biological agent with a group of patients with RA who received conventional antirheumatic treatment. In more detail, 3 studies^{23,24,26} reported the use of cytotoxic therapy such as methotrexate,²⁴ azathioprine sodium,^{23,26} or cyclophosphamide,²⁶ and 1 study²⁵ used a biological agent (anti-tumor necrosis factor, ie, etanercept or infliximab). In the azathioprine study,²³ patients with RA not treated with azathioprine were used as control subjects. In the study assessing the efficacy of biological agents,²⁵ patients with RA exposed to etanercept or infliximab were compared with a cohort of patients with RA who were never exposed to any type of biological drug. In our meta-analysis, the controls of both studies underwent evaluation for the risk of NHL development as a separate group (conventionally treated patients). In 2 studies,^{5,27} it was not specified whether NHL appeared before or after diagnosis of the autoimmune disease. In 4 studies,^{2,17,20,22} the NHL development before the diagnosis of the autoimmune disease was not excluded. The duration of cohorts ranged from 11 to 24, 7 to 24, and 1 to 25 years for SLE, RA, and pSS, respectively. The median follow-up times for pSS, SLE, and RA were 22, 20.5, and 9.5 years, respectively. The median age at NHL diagnosis and the median time from autoimmune disease diagnosis to NHL development were reported in only 4 studies referring to SLE patients,^{4,6,17,18} and the interval between SLE diagnosis and NHL diagnosis was estimated to be 7.5 years.

In total, the studies included 8700 cases with SLE, 95 104 cases with RA, and 1300 cases with pSS. The SIR of NHL in patients with SLE in the 6 cohort studies ranged from 5.2 to 44.4; in patients with RA, from 1.9 to 24.0; and in patients with pSS, from 8.7 to 44.4. A significant heterogeneity ($P < .01$; $I^2 > 70\%$) was found for SLE, RA, and pSS studies. The RE pooled SIRs for NHL were 7.4 (95% CI, 3.3-17.0), 3.9 (95% CI, 2.5-5.9), and 18.8 (95% CI, 9.5-37.3) for SLE, RA, and pSS, respectively (**Figure**). Therefore, there

Table 1. Characteristics of the SLE Cohort Studies Considered in the Meta-analysis

Source (Country)	Data Origin and Diagnosis	SIR (95% CI)	No. of Lymphomas (Sex, No. F/M)	Immunosuppressive Treatment	No. of Patients in Cohort (Sex, No. F/M)	Duration of Follow-up, y
Pettersson et al, ¹ 1992 (Finland)	Data from Helsinki University Central Hospital Expected number from Finnish Cancer Registry Diagnosis of SLE according to 1971 criteria of ARA NHL developed after SLE diagnosis	44.4 (11.9-111.0)	4 (4/0)	1 Case with cyclophosphamide	205 (182/23)	21 (1967-1987)
Abu-Shakra et al, ¹⁷ 1996 (Canada)	Data from University of Toronto Lupus Clinic Database Expected number from Province of Ontario Registry Diagnosis using ACR criteria Does not exclude NHL cases before onset of SLE	5.4 (1.1-15.7)	3 (3/0)	No cases	724 (627/97)	24
Mellemkjaer et al, ¹⁸ 1997 (Denmark)	Data from Danish Hospital Discharge Register Expected number from Danish Cancer Registry Diagnosis according to 1982 ACR criteria Does not exclude cases before onset of SLE	Female, 4.1 (1.3-9.6) Male, 9.4 (1.9-27) Total, 5.2 (2.2-10.3)	8 (5/3)	7 Cases with corticosteroids and/or azathioprine	1585 (1316/269)	15 (1977-1991; 10 807 PY)
Bjornadal et al, ¹⁹ 2002 (Sweden)	Data from Hospital Discharge Register Expected number from National Swedish Cancer Registry Diagnosis based on ICD-7, ³⁰ ICD-8, ³¹ and ICD-9, ³² for 20 y at start Excludes cases before onset of SLE	2.9 (2.0-4.0)	32	Not reported	5715 (4201/1514)	50 246; 31 (1964-1994)
Sweeney et al, ⁶ 1995 (United States)	Data from University of Pittsburgh, Allegheny County, Pennsylvania Expected number from Pennsylvania Cancer Incidence Registry Diagnosis according to 1982 revised ACR criteria Excludes cases before onset of SLE	10.0 (0.25-55.7)	1 (1/0) also with sSS	No cases	219 (219/0)	11 (1981-1991; 560 637 PY)
Cibere et al, ⁴ 2001 (Canada)	Data from University of Saskatchewan Rheumatic Disease Unit Expected number from Province of Saskatchewan population statistics Diagnosis using ACR criteria, clinical diagnosis, for 16 y at start No patient had cancer after SLE diagnosis	7.0 (1.9-18.0)	4	No cases received azathioprine or methotrexate	297 (241/56)	20 (1975-1995; 3587 PY)

Abbreviations: ACR, American College of Rheumatology; ARA, American Rheumatism Association; CI, confidence interval; ICD-7, -8, and -9, *International Classification of Diseases, Seventh, Eighth, and Ninth Revisions*, respectively; NHL, non-Hodgkin lymphoma; PY, person-years; SIR, standardized incidence rate; SLE, systemic lupus erythematosus; sSS, secondary Sjögren syndrome.

was a high risk of NHL development in pSS, a lower risk in SLE, and an even lower risk in RA. However, the 95% CIs for SLE and RA overlapped, indicating lack of a real difference between the 2 diseases.

In RA, the subgroup analysis on sex produced large heterogeneity ($P < .01$; $I^2 > 70\%$) for both sexes, and the RE pooled SIRs were 3.8 (95% CI, 1.7-8.8) and 5.0 (95% CI, 1.3-19.1) for female and male patients, respectively, which did not deviate substantially from the overall estimate (Figure). The subgroup analysis for the studies not reporting the

type of treatment produced an RE pooled SIR of 3.3 (95% CI, 2.0-5.3). The subgroup analyses for the studies using cytotoxic drugs (methotrexate, azathioprine, and cyclophosphamide) and those using conventional antirheumatic treatment produced RE pooled SIRs of 5.1 (95% CI, 0.9-28.6) and 2.5 (95% CI, 0.7-9.0), respectively. The study²⁵ that used a biological agent produced an SIR of 11.5 (95% CI, 3.7-26.9). In a sensitivity analysis, when the study with the biological agent²⁵ was excluded, the RE pooled SIR was 3.48 (95% CI, 2.28-5.32), similar to

the overall SIR. Because the studies on SLE and pSS do not specify or report the treatment of each cohort (Tables 1 and 3), it is not possible to perform the subgroup analysis performed in RA. However, in a sensitivity analysis when the SLE studies with NHL cases that had not received any immunosuppressive treatment^{4,6,17} were excluded, the RE pooled SIR was 8.1 (95% CI, 2.1-32.0), a bit larger than the overall SIR. In addition, the subgroup analysis for these studies^{4,6,17} produced an SIR of 6.6 (95% CI, 3.3-13.3). In pSS, when the study with NHL cases that

Table 2. Characteristics of the RA Cohort Studies Considered in the Meta-analysis

Source (Country)	Data Origin and Diagnosis	SIR (95% CI)	No. of Lymphomas (Sex, No. F/M)	Immunosuppressive Treatment	No. of Patients in Cohort (Sex, No. F/M)	Duration of Follow-up, y
Hakulinen et al, ²⁰ 1985 (Finland)	Observed and expected cases from Social Insurance Institution's Population Register and Finnish Cancer Registry Diagnosis based on clinical, laboratory, and histologic evidence of keratoconjunctivitis sicca and xerostomia Does not exclude NHL cases before onset of RA; includes cases with ankylosing spondylitis	Female, 2.9 (1.7-4.5) Male, 2.8 (1.2-5.2) Total, 2.8 (2.0-3.9)	38 (25/13)	Not reported	46 101 (34 618/11 483)	7 (1967-1973; 213 911 PY)
Gridley et al, ²¹ 1993 (Sweden)	Data from Swedish Hospital Inpatient Register Expected number from Uppsala Health Care Region cancer incidence rates Hospital inpatient diagnosis using the ICD-7 ³⁰ and ICD-8 ³¹ Excludes cases before onset of RA.	Female, 1.9 (1.2-2.9) Male, 1.8 (1.0-3.0) Total, 1.9 (1.3-2.6)	36 (23/13)	Not reported	11 863 (7933/3750); (106 with sSS)	20 (1965-1984; 101 000 PY)
Prior, ² 1985 (United Kingdom)	Data from Queen Elizabeth Medical Centre, Birmingham, England Expected number from Birmingham Cancer Registry Diagnosis based on ARA criteria. Does not exclude NHL cases before onset of RA	Female, 18.8 (6.1-58.1) Male, 30.8 (11.6-82.0) Total, 24.1 (11.5-50.6)	7 (3/4)	Not reported	489	20 (1964-1983)
Kauppi et al, ⁵ 1997 (Finland)	Data from Finnish hospitals' National Discharge Registry Expected number from Finnish Cancer Registry	2.2 (1.5-3.1)	34	Not reported	9469 (7757/1712) (Includes cases with sSS)	24 (1970-1993; 65 391)
Mellemkjaer et al, ²² 1996 (Denmark)	Data from Danish Hospital Discharge Register Expected number from Danish Cancer Registry Hospital inpatient diagnosis using the ICD-8 ³¹	2.4 (1.9-2.9)	85	Not reported	20 699	11 (1977-1987)
Silman et al, ²³ 1988 (United Kingdom)	Azathioprine group, data from Newmarket Registry Conventional treatment group, data from London Hospital Registry Expected number from Office of Population Censuses and Surveys	10.0 (3.8-26.6) 4.8 (1.2-19.0)	4 (3/1) 2 (1/1)	Azathioprine Conventional treatment	202 (183/19) 202 (183/19)	12 (1964-1975) 14 (1970-1983)
Geborek et al, ²⁵ 2005 (Sweden)	Anti-TNF group: data from South Swedish Arthritis Treatment Group Conventional treatment group: data from Malmö University Hospital Expected number from South Swedish Cancer Registry and population census registers Diagnosis based on ACR classification criteria	11.5 (3.7-26.9) 1.3 (0.2-4.5)	5 2	Etanercept or infliximab Conventional treatment	757 (560/197) 800 (584/216)	4 (1999-2002; 1603) 4 (1999-2002; 3948)
Kinlen, ²⁶ 1985 (United Kingdom)	Data from CRC Cancer Epidemiology Unit, Edinburgh, Scotland Expected number from National Registry	12.9 (4.8-34.4)	4	Azathioprine or cyclophosphamide	643 (422/221)	1-12
Mariette et al, ²⁴ 2002 (France)	Data from 61 rheumatology departments Expected number from French National Cross-sectional Survey Diagnosis based on Revised European and American Lymphoma Classification	1.2 (0.7-1.9)	18	Methotrexate	27 000	3 (1996-1998)

Abbreviations: ACR, American College of Rheumatology; ARA, American Rheumatism Association; CI, confidence interval; CRC, Cancer Research Campaign; ICD-7 and -8, *International Classification of Diseases, Seventh and Eighth Revisions*, respectively; NHL, non-Hodgkin lymphoma; PY, person-years; RA, rheumatoid arthritis; SIR, standardized incidence rate; sSS, secondary Sjögren syndrome; TNF, tumor necrosis factor.

Table 3. Characteristics of the pSS Cohort Studies Considered in the Meta-analysis

Source (Country)	Data Origin and Diagnosis	SIR (95% CI)	No. of Lymphomas	Immunosuppressive Treatment	No. of Patients in Cohort (Sex, No. F/M)	Duration of Follow-up, y
Kassan et al, ³ 1978 (United States)	Data from NIH Clinical Center Expected number from Connecticut Cancer Register Diagnosis based on clinical, laboratory, and histologic evidence of keratoconjunctivitis sicca and xerostomia Excludes cases before onset of pSS	44.4 (16.7-118.4)	4	2 Cases	142 (136/6) (58 with RA)	22 (1954-1975; 1099 PY)
Kauppi et al, ⁵ 1997 (Finland)	Data from Finnish hospitals' National Discharge Registry Expected number from Finnish Cancer Registry	8.7 (4.3-15.5)	11	Not reported	676 (572/104)	22 (1970-1991; 5336 PY)
Davidson et al, ²⁷ 1999 (United Kingdom)	Data from UK hospitals' registry Expected number from cancer registry statistic Diagnosis based on Fox's and European criteria	14.4 (4.7-44.7)	3	Not reported	100 (100/0) (41 Definite pSS; 59 possible SS)	8 (1981-1988)
Valesini et al, ²⁸ 1997 (Italy)	Data from Italian Immunorheumatology Study Group (8 centers) Expected number from 7 cancer registries Diagnosis according to preliminary European criteria Excludes cases before onset of pSS	33.3 (17.3-64.0)	9	No cases	295 (295/0)	25 (1756 PY)
Pertovaara et al, ²⁹ 2001 (Finland)	Data from Tampere University Hospital Expected number from regional population Diagnosis according to modified Californian criteria Excludes cases before onset of pSS	13 (2.7-3.8.0)	3	None of cases reported	110 (107/3)	15 (1977-1992)

Abbreviations: CI, confidence interval; NIH, National Institutes of Health; pSS, primary Sjögren syndrome; PY, person-years; RA, rheumatoid arthritis; UK, United Kingdom.

did not receive immunosuppressive therapy was excluded, the SIR was 15.7 (95% CI, 7.4-33.2).

In cumulative meta-analysis, the RE pooled SIR in SLE declined from 44.4 in 1992 to 27.10 in 1995 and to 7.42 in 2001. In RA, the SIR declined from 9.3 in 1985 to 5.3 in 1993 and to 3.2 in 2005. In pSS, the SIR declined from 44.4 in 1978 to 22.5 in 1997 and to 20.3 in 1999. In all diseases, there has been a monotonic decrease since the first study. However, the values of SIRs were not correlated with the duration of follow-up; the Spearman rank correlation coefficients for SLE, RA, and pSS were -0.43 ($P=.31$), 0.20 ($P=.56$), and 0.31 ($P=.61$), respectively. In addition, there was no clear pattern that the magnitude of SIR was related to patient selection (clinic or hospital) in all autoimmune diseases.

There was no evidence of publication bias in SLE and pSS ($P>.10$ for the Egger and Begg-Mazumdar tests). In RA, there was marginal significance ($P=.08$ and $P=.09$ for the Egger and Begg-Mazumdar tests, respectively), indicating the existence of a differential magnitude of effect in large vs small studies.³³ However, this result might not be reliable, because the number of studies is relatively small.³⁴ Some studies had a selection bias because patients were hospitalized (data were obtained from hospital discharge registries), and therefore the more severe cases were considered.

COMMENT

The meta-analysis results showed that NHL is more common in pa-

tients with autoimmune diseases than in the general population, especially in patients with pSS and SLE. Because the follow-up time in the RA group was shorter than those for pSS and SLE, the possibility of overlooking RA-associated NHL cases that developed later in the disease process cannot be excluded. The fact that certain studies in RA did not show an increase in SIR is probably owing to the short duration of the follow-up.²⁴ In several studies, particularly RA studies, the use of cytotoxic agents (eg, methotrexate, azathioprine, and cyclophosphamide) before NHL development is not reported. In the RA studies in which the treatment is reported, the risk of NHL with cytotoxic or biological agents is greater than the risk with conventional antirheumatic treatment. In the assess-

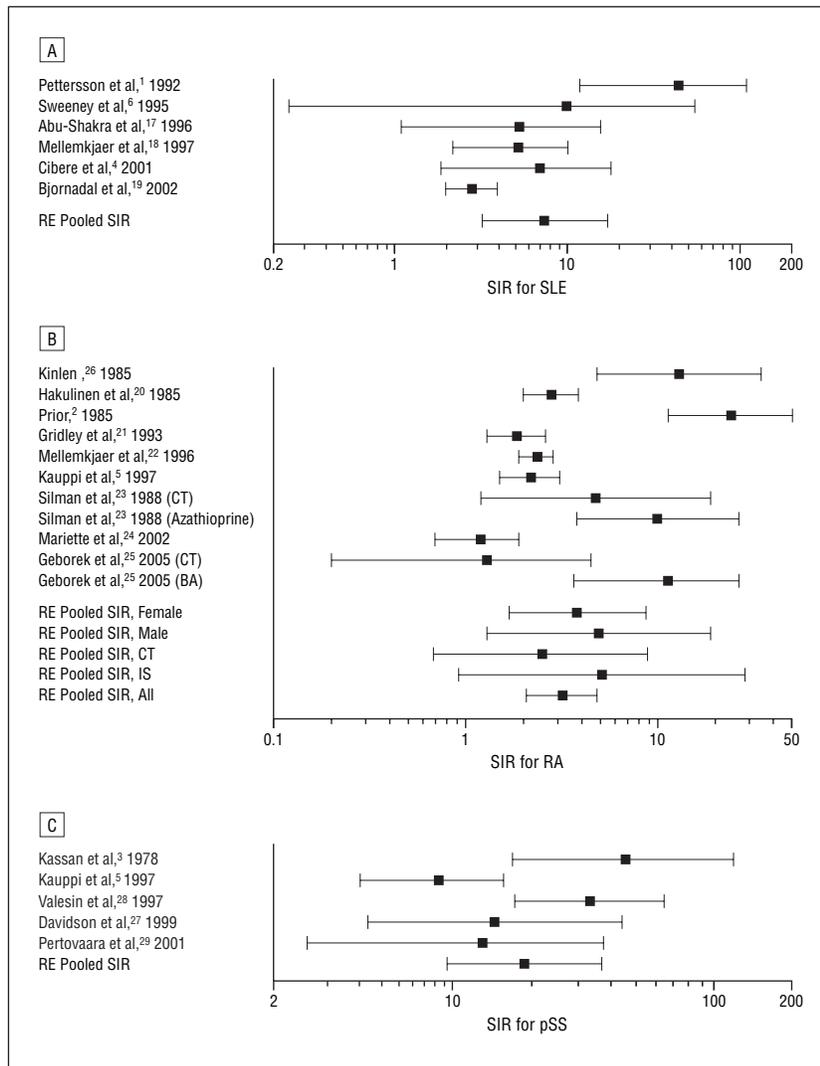


Figure. Standardized incidence rate (SIR) estimates of development of non-Hodgkin lymphoma with the corresponding 95% confidence intervals of studies included in the meta-analysis for systemic lupus erythematosus (SLE) (A), rheumatoid arthritis (RA) (B), and primary Sjögren syndrome (pSS) (C). The random-effects (RE) pooled SIRs are shown. The horizontal axis is plotted on a logarithmic scale. BA indicates biological agent; CT, conventional antirheumatic treatment; and IS, cytotoxic treatment.

ment of the impact of treatment on lymphomagenesis in RA, only 1 study used biological agents. Although the comparison of etanercept and infliximab with other treatment modalities in this group of patients does not seem fair, these drugs have a high likelihood of being associated with NHL development. However, the information on the role of these cytotoxic or immunomodulatory agents in lymphomagenesis in RA is rather limited, and any inferences cannot be taken for granted. In addition, these phenomena need to be considered against the background that the occurrence of NHL in patients with RA might be associated with disease activity or severity. In this regard, cytotoxic or bio-

logical therapy may be indicative of a specific group of patients with RA who have more severe disease and a high predisposition for NHL development. For several decades, it has been known that patients with RA have an increased risk of NHL development.^{20-22,35,36} The reason is still not fully understood, and controversy remains as to whether the risk is a consequence of immunosuppressive therapy.^{23,24,37-41} Recent data suggest that high and longstanding inflammatory activity in RA may itself contribute to the development of lymphomas, which are preferentially of the aggressive, diffuse, extranodal, large B-cell type.⁴² Because indolent extranodal marginal-zone B-cell lymphoma of the

mucosa-associated lymphoid tissue is the most common type of lymphoma in pSS,⁴³ this dissimilarity indicates different mechanisms underlying lymphoma development in these 2 diseases. The specific diffuse, extranodal, large B-cell lymphoma subtype in RA implies an underlying immunodeficiency status.⁴⁴ Peripheral mononuclear cells from patients with RA who were not receiving cytotoxic or long-acting antirheumatic drugs were found to be hypoproliferative in vitro to a battery of soluble recall antigens.⁴⁵⁻⁴⁷ Therefore, an impaired T-cell function could be relevant to an impairment of immune responses toward emerging malignant B cells.

Although this meta-analysis provided a more precise estimate of the relative risk of NHL in relation to autoimmune diseases than did the individual studies, because it has used a vast amount of patients, its major limitation is the large heterogeneity between studies. The heterogeneity might be owing to different baseline risk populations, study designs, and data sources. Therefore, the results should be interpreted with caution. The meta-analysis was restricted to NHL because adequate studies established strong associations between B-cell lymphoproliferation and autoimmunity. Studies that investigated the incidence rate of lymphomas (NHL or Hodgkin disease) without specifying the rates separately were not included.^{37,48} In addition, studies that did not provide information about the expected number of NHL cases in the general population were omitted from the analysis.^{42,49-52} However, exclusion of such studies may have biased the results. Moreover, 4 studies included cases with NHL that developed before the diagnosis of the autoimmune diseases. The inclusion of these cases in the cohort studies may obscure the interpretation of the autoimmunity-NHL association. Regardless of these limitations, the meta-analysis showed that autoimmune diseases are associated with an increased risk of NHL. Assuming that the expected cases (E) of NHL can be estimated by the weighted mean of the expected cases provided by the included studies in

the meta-analysis, and using the number of patients as weights, then $E=1.7$. Thus, the RE pooled SIR for RA of 3.9 means that there is a 3.9-times increase in the incidence, or $(SIR \times E)/100\,000 = 66$ cases per 100 000 patient-years, and the RE pooled SIR for SLE of 7.4 means that there is a 7.4-times increase in the incidence or 126 cases per 100 000 patient-years, and the RE pooled SIR for pSS of 18.8 means that there is an 18.8-times increase in the incidence or 320 cases per 100 000 patient-years. In this setting, the association of NHL with autoimmune diseases generates increasing interest because it may concern the mechanisms of lymphomagenesis in general.

The B-cell disorder seen in patients with pSS is particularly severe compared with the B-cell dysfunction seen in other autoimmune diseases such as SLE. It has been shown that patients with pSS have higher incidence and higher serum levels of B-cell activating factor compared with patients with SLE.^{53,54} Furthermore, patients with active SLE have decreased numbers of CD19⁺/CD27⁻ naive B cells and increased numbers of CD19⁺/CD27⁺ memory B cells,⁵⁵ in contrast to patients with pSS who are characterized by a significant reduction in the number of the peripheral CD27⁺ memory B cells.^{56,57} Given the vigor with which immunoglobulin genes are modified during immune responses, it is plausible to hypothesize that some of the critical transforming events are the product of an intense ectopic germinal center reaction in pSS. In this regard, patients with pSS with an increased risk of NHL are characterized by splenomegaly, lymphadenopathy, mixed monoclonal cryoglobulinemia, and parotid swelling, all indicators of an extensive lymphoproliferation.^{3,58,59} This could possibly explain why lymphoid malignancies are more common in pSS than in SLE. In the diseases studied, the risk of NHL development since the first study was reduced and may be attributed to revised and/or more accurate classification of NHL during this period or to more effective treatment of the underlying B-cell dysregulation of autoimmune diseases.⁶⁰

Despite the limitations of this meta-analysis, it provides new and sustained evidence establishing differences of NHL development risk in various autoimmune disorders. We focused on the underlying pathophysiologic mechanisms related to lymphomagenesis in pSS, SLE, and RA to justify the varying potential for and background of NHL development. Further studies are warranted to correlate our epidemiologic data with the underlying disease mechanisms. In addition, the risk of NHL in patients receiving immunosuppressive drugs must be investigated.

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