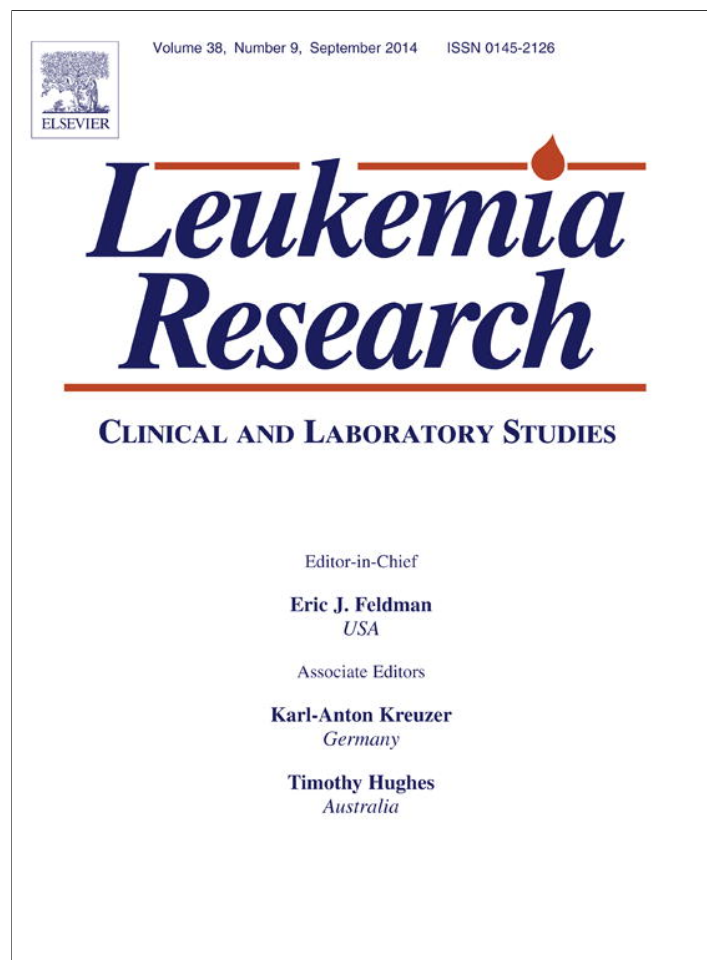




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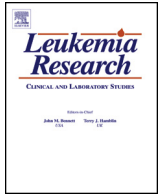
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Systemic lupus erythematosus is associated with increased incidence of hematologic malignancies: A meta-analysis of prospective cohort studies



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ABSTRACT

Our objective was to define the risk of lymphoma, leukemia and myeloma in adult patients with SLE with a meta-analysis of prospective cohort studies. A literature search from 1995 to 2013 revealed eight studies evaluating this association. The outcome of interest was the standardized incidence ratio (SIR). Our study included 401 cases in a cohort of approximately 68,000 SLE patients, and showed an increased incidence of all hematologic malignancies (SIR 2.9), non-Hodgkin lymphoma (SIR 5.7), Hodgkin lymphoma (SIR 3.1), leukemia (SIR 2.3) and myeloma (SIR 1.5) in SLE patients compared with the general population. The increased SIR was consistent regardless of age, sex or geographical region.

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1. Introduction

Hematologic malignancies are a heterogeneous group of diseases characterized by the abnormal (malignant) growth and/or accumulation of hematopoietic cells in the blood, bone marrow and/or lymph nodes. According to the Surveillance Epidemiology and End Results database, over 150,000 individuals were diagnosed with lymphoma, leukemia, and myeloma in the United States (US) in 2013 [1]. Although the development of hematologic malignancies have been linked to multiple processes, much of the underlying mechanisms that contribute to malignancy remain unclear.

Systemic lupus erythematosus (SLE) is an autoimmune inflammatory disease that can affect multiple systems and organs of the body including skin, kidneys, lungs, joints and nervous system, and affects about 1.5 million Americans, from which 90% are women between 15 and 44 years of age [2]. In a previous meta-analysis, there was a moderate risk of lymphoma incidence in patients with SLE with an estimated standardized incidence ratio (SIR) 7-times

higher compared with the general population [3]. This information was based on six studies that included 52 patients with lymphoma among approximately 8000 patients with SLE. Given the small sample, the estimate could have been an over- or an underestimation of the actual risk of developing lymphoma in SLE patients.

More recently, multiple studies evaluating a relation between SLE and hematologic malignancies have been published. Therefore, a larger sample size could provide additional and more reliable information on the role that SLE plays in the incidence of hematological malignancies. Hence, the primary objective of this meta-analysis of prospective cohort studies was to evaluate the possible association between SLE and hematologic malignancies in adults. Prospective cohort studies provide the basis of a causal role between exposure (SLE) and outcome (hematologic malignancy). A secondary objective was to evaluate the potential differences in incidence according to geographical distribution.

2. Methods

Two of the investigators performed a Pubmed search from January 1, 1995 through December 31, 2013 looking for prospective cohort studies reporting on the association between SLE and the incidence of hematologic malignancies. The search keyword was "lupus AND (leukemia OR lymphoma OR myeloma)". Additional searches in EMBASE, Google Scholar and the Cochrane Database of Systematic Reviews did not render additional studies. If there were multiple publications from

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the same study, the most relevant was selected, while using the other publications to clarify methodology, if necessary. Studies focusing on drug-induced lupus and on localized lupus were excluded. Reviews, letters to the editor without original data, editorials, case reports, case-control and cross-sectional studies were excluded. Study selection was performed independently by two of the authors.

The data extraction was performed independently by two of the authors. Data gathered included author, year of publication, country of origin, source of the cohort, source of the expected incidence, years of follow-up, sample size, inclusion and exclusion criteria, methods of ascertainment of SLE and hematologic malignancy, outcome measured, and variables used for adjustment. Any discrepancies were addressed by joint reevaluation of the original article and consensus. For missing information, attempts were made to contact the authors of the original studies. The Newcastle Ottawa Scale (NOS) [4] was used to assess the quality of each study. The NOS assigns a maximum of four points for selection, two points for comparability, and three points for outcome. Arbitrarily, NOS scores of 0–3, 4–6 and 7–9 were considered poor, intermediate and high quality, respectively.

The outcome of interest was the standardized incidence ratio (SIR) and 95% confidence interval (CI) of hematological malignancies in adult patients with SLE in comparison with the general population. The SIR of hematologic malignancies in each study was estimated based on the number of cases observed within the SLE cohort in comparison with the number of cases expected according to the incidence rates of the geographical region of each cohort. The outcome was estimated using the random-effects model (REM), which adjusts for inter-study heterogeneity [5]. The presence of heterogeneity was assessed using the I^2 index [6]; values of 25%, 50% and 75% indicate low, moderate and high heterogeneity, respectively. The presence of publication bias was investigated by funnel plot observation [7], and assessed by the trim-and-fill analysis [8]. The trim-and-fill method assumes that the effect sizes of the studies distribute normally around the center of a funnel plot; if asymmetry is found, it adjusts for the potential effect that imputed non-published studies might have had on the measured outcome. Meta-analyses were performed for all hematologic malignancies and for lymphoma, leukemia, and myeloma, separately. Lymphoma was further divided in Hodgkin and non-Hodgkin lymphoma (HL and NHL, respectively). Subset analyses were performed according to age, sex, race, geographical region, histological subtype and SLE latency, if possible. In subsets with only two studies, meta-analyses were performed but heterogeneity or publication bias analyses were not done. In subsets with only one study, formal meta-analyses were not performed and the results are shown descriptively. Sensitivity analyses were performed by excluding one study at a time, by excluding studies included in a previous meta-analysis [3], and by excluding studies that did not use ACR criteria for SLE diagnosis. All calculations and graphics obtained using Comprehensive Meta-Analysis version 2.2.050 (Biostat, New Jersey, USA).

3. Results

3.1. Characteristics of the studies

Our initial search rendered 1012 potentially relevant articles, from which eight prospective cohort studies were included [9–16]. Our search flow is shown in Fig. 1. Four studies (50%) were from Europe, two (25%) from Asia, one (12.5%) from the US, and one (12.5%) was a multi-national study. In this meta-analysis, we are including 401 cases of hematologic malignancies identified in a total cohort of 67,929 individuals, 59,671 women (88%) and 8258 men (12%), with a diagnosis of SLE selected characteristics of the included studies are shown in Table 1.

3.2. Outcome assessment for all hematologic malignancies

There was an increased SIR for all hematologic malignancies (SIR 2.9, 95% CI 2.0–4.4; $p < 0.001$; Fig. 2) with high heterogeneity ($I^2 = 96\%$) based on data from five studies [9–11,13,14]. Publication bias analysis identified one imputed study, which would have not altered our results (SIR 3.1, 95% CI 2.2–4.4). There was an increased SIR in European (SIR 2.5, 95% CI 2.2–3.0; $p < 0.001$), US/Canada (SIR 2.2, 95% CI 1.7–3.0; $p < 0.001$) and Asian studies (SIR 5.0, 95% CI 4.8–5.1; $p < 0.001$). Two studies evaluated the effect of age [9,11], with SIR for individuals <40 and ≥ 40 years of 4.4 (95% CI 4.2–4.7; $p < 0.01$) and 3.8 (95% CI 2.9–5.1; $p < 0.001$). Three studies evaluated the SIR of hematologic malignancies according to sex [9,11,13]. The SIR in women was 3.9 (95% CI 2.5–6.0; $p < 0.001$) with high heterogeneity ($I^2 = 91\%$) but without publication bias. In men, the SIR was 5.0 (95% CI 3.5–7.1; $p < 0.001$) with moderate heterogeneity ($I^2 = 56\%$). Publication bias analysis identified one imputed study,

Table 1
Selected characteristics of the prospective cohort studies evaluating the association between systemic lupus erythematosus and hematologic malignancies.

Study	Year	Country	Source of cohort	Hematologic malignancy assessment	SLE assessment	Follow-up period (median)	Total cohort	No. of patients	NOS
Bernatsky	2013	Multi-national	30-Center International Cohort (US/Canada, Europe, Asia)	Regional tumor registries	ACR criteria, except Scotland cohort	1958–2009 (7.4 years)	16,409	111	7
Bjornadal	2002	Sweden	Hospital Discharge Register	National Swedish Cancer Register	ICD-7, ICD-8 and ICD-9 codes	1964–1995 (8.8 years)	5715	64	9
Chen	2010	Taiwan	Registry of Catastrophic Illness Database	Registry of Catastrophic Illness Database	ACR criteria	1996–2007 (Minimum 2 years)	11,763	31	8
Kang	2010	Korea	Outpatient Clinic in Kangnam St. Mary's Hospital	Medical records and histological confirmation	ACR criteria	1997–2007 (6.2 years)	914	3	6
Mellemkjaer	1997	Denmark	Hospital Discharge Register and Central Population Register	Danish Cancer Registry	ICD-8 codes	1977–1991 (6.8 years)	1585	13	5
Parikh-Patel	2008	United States	California Office of Statewide Health Planning and Development	California Cancer Registry	ICD-9 codes	1991–2002 (5.1 years)	30,478	167	7
Pettersson	1992	Finland	Fourth Department of Medicine, Helsinki University Central Hospital	Finnish Cancer Registry	ACR criteria	1967–1987 (11.4 years)	205	7	7
Tarr	2007	Hungary	Third Department of Internal Medicine, University of Debrecen	Imaging, laboratory and histopathologic examination	ACR criteria	1970–2004 (NR)	860	5	8

ACR: American College of Rheumatology; ICD: International Classification of Diseases; NOS: Newcastle-Ottawa Scale; SLE: systemic lupus erythematosus; NR: not reported.

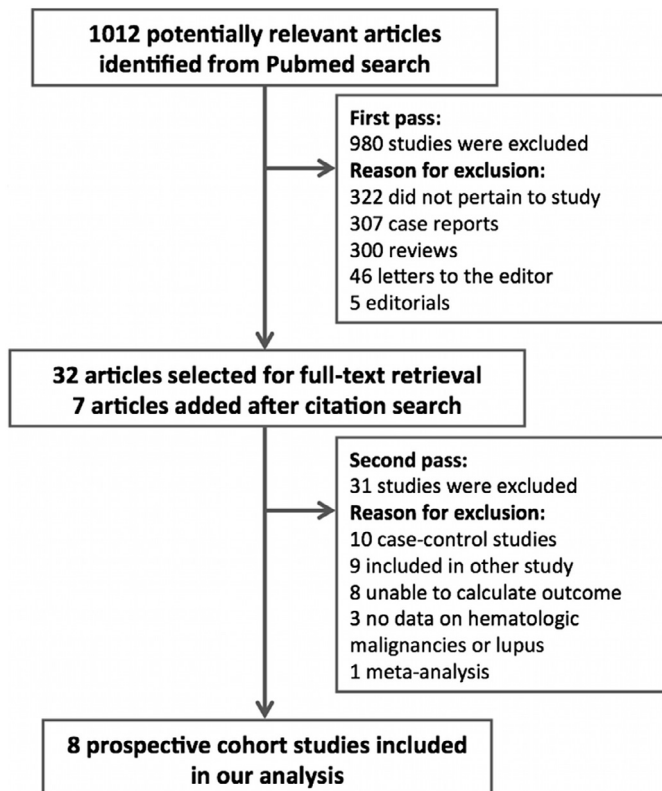


Fig. 1. Search results.

which would not have affected our results (SIR 4.6, 95% CI 3.1–6.7). One US study evaluated SIR according to race [14]. The SIR in whites was 2.3 (95% CI 1.8–3.0), in blacks 2.3 (95% CI 0.9–4.8), in Hispanics 6.1 (95% CI 3.8–9.2) and in Asians/Pacific Islanders 7.3 (95% CI 3.1–14.1). Three studies evaluated the effect of the latency of SLE diagnosis on the SIR of HM [9–11]. The SIR for patients diagnosed with SLE 1–5, 5–10 and >10 years before diagnosis of HM were 4.4 (95% CI 2.6–7.4; $p < 0.001$), 2.5 (95% CI 1.9–3.4; $p < 0.001$), and 1.5 (95% CI 0.5–4.1; $p = 0.48$), respectively. For 5–10 years SLE latency, there was no heterogeneity ($I^2 = 0\%$) and the publication bias analysis showed 2 imputed studies, which would have not altered our results (SIR 2.9, 95% CI 2.1–4.0). For >10 years SLE latency, there was high heterogeneity ($I^2 = 97\%$) and one imputed study that would have not changed our results (SIR 1.2, 95% CI 0.5–2.7).

3.3. Outcome assessment for NHL

There was an increased SIR of NHL (SIR 5.7, 95% CI 3.6–9.1; $p < 0.001$; Fig. 3, top) with high heterogeneity ($I^2 = 95\%$). Publication bias analysis detected one imputed study, which would have

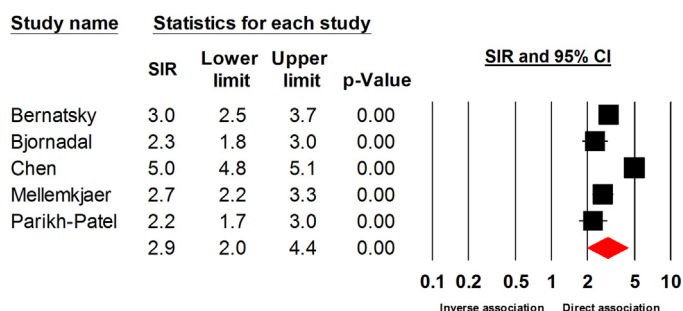


Fig. 2. Standardized incidence ratio estimates of all hematologic malignancies in patients with systemic lupus erythematosus.

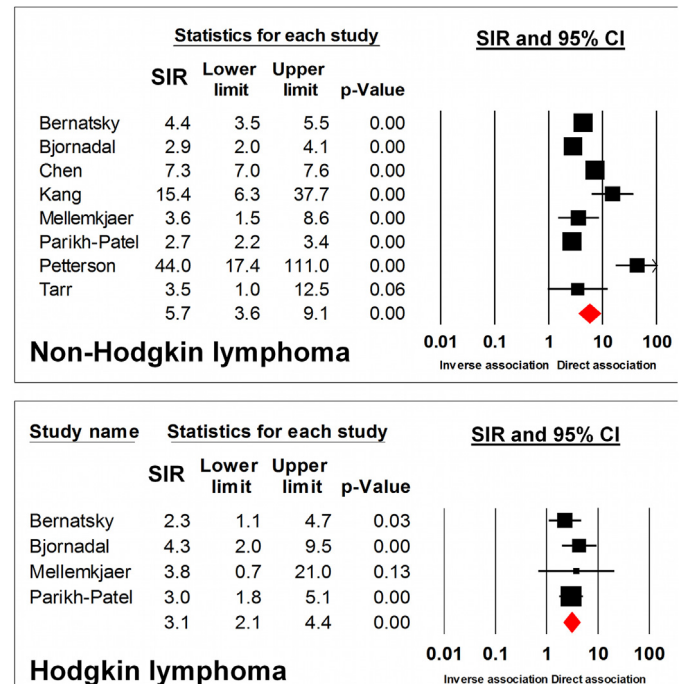


Fig. 3. Standardized incidence ratio estimates of non-Hodgkin lymphoma (top) and Hodgkin lymphoma (bottom) in patients with systemic lupus erythematosus.

not affected our results (SIR 6.5, 95% CI 4.2–10.0). An increased SIR of NHL was seen in European (SIR 6.4, 95% CI 2.9–13.8; $p < 0.001$), US/Canada (SIR 4.6, 95% CI 2.6–8.3; $p < 0.001$), and Asian studies (SIR 9.2, 95% CI 4.7–18.2; $p < 0.001$). Two studies evaluated the effect of age [13,14]. The pooled SIR for patients <40 and ≥40 years or older were 8.6 (95% CI 4.8–15.4; $p < 0.001$) and 3.5 (95% CI 1.8–6.7; $p < 0.001$), respectively. One study evaluated NHL incidence according to sex [13]. Women had SIR 4.1 (95% CI 1.3–9.6) and men had SIR 9.4 (1.9–27.0). Two studies evaluated the effect of latency of SLE duration on NHL incidence [10,13]. Patients with 1–5, 5–10 and >10 years after SLE diagnosis had SIR for NHL of 3.7 (95% CI 2.1–6.4; $p < 0.001$), 4.2 (95% CI 2.6–6.9) and 2.7 (95% CI 0.8–9.1), respectively. One study evaluated the SIR for NHL subtypes in SLE patients [14]. The SIR for diffuse large B-cell lymphoma (SIR 3.3, 95% CI 2.3–4.4) and follicular lymphoma (SIR 2.9, 95% CI 1.9–4.2) were increased in SLE patients.

3.4. Outcome assessment for HL

SLE was associated with a high SIR of HL (SIR 3.1, 95% CI 2.1–4.4; $p < 0.001$; Fig. 3, bottom) without heterogeneity ($I^2 = 0\%$). Publication bias analysis detected two imputed studies, which would have not affected our results (SIR 2.7, 95% CI 2.0–3.8). The SIR of HL was increased in European (SIR 4.2, 95% CI 2.1–8.6; $p < 0.001$) and US/Canada studies (SIR 2.7, 95% CI 1.8–4.2; $p < 0.001$). One study evaluated the effect of latency of SLE diagnosis in HL incidence [10]. Patients with a latency of 1–5 and 5–10 years had SIR of 5.8 (95% CI 1.2–16.9) and 8.1 (95% CI 1.7–23.8), respectively.

3.5. Outcome assessment for leukemia

SLE was associated with increased SIR of leukemia (SIR 2.3, 95% CI 1.9–2.7, $p < 0.001$; Fig. 4, top) with moderate heterogeneity ($I^2 = 39\%$). Publication bias analysis identified three imputed studies, which would have not changed our results (SIR 2.5, 95% CI 2.2–2.8). The SIR of leukemia was increased in European (SIR 2.0, 1.3–3.0; $p = 0.001$) and US/Canada studies (SIR 2.0, 1.6–2.5;

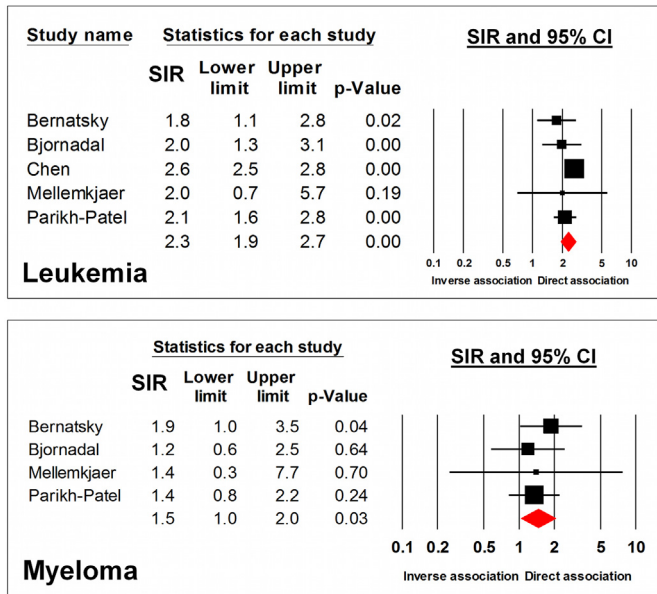


Fig. 4. Standardized incidence ratio estimates of leukemia (top) and myeloma (bottom) in patients with systemic lupus erythematosus.

$p < 0.001$). One study reported on SLE latency [10]. Patients with SLE diagnosis for 1–5, 5–10, 10–15 and >15 years had SIR of 3.5 (95% CI 1.7–6.5), 1.6 (95% CI 0.4–4.1), 1.3 (95% CI 0.2–4.5) and 1.6 (95% CI 0.2–5.7), respectively. Two studies reported SIR of myeloid leukemia in SLE patients [10,14] with a SIR of 3.4 (95% CI 2.2–5.1). One study reported on lymphoid leukemia (SIR 1.0, 95% CI 0.5–2.0) [14]. The effect of SLE latency in acute myeloid leukemia was reported by one study [10]. The SIR in patients with SLE diagnosis for 1–5 years, 5–10 years and 10–15 years were 6.1 (95% CI 2.0–14.1), 1.3 (95% CI 0.0–7.4) and 4.1 (95% CI 0.5–14.6).

3.6. Outcome assessment for myeloma

A weak association was found between SLE and myeloma (SIR 1.5, 95% CI 1.0–2.0, $p = 0.03$; Fig. 4, bottom) without heterogeneity ($I^2 = 0\%$). Publication bias analysis detected one imputed study, which would have not affected our results (SIR 1.5, 95% CI 1.1–2.1). The SIR of myeloma was increased in USA/Canada (SIR 1.5, 95% CI 1.1–2.3; $p = 0.03$) but not in European studies (SIR 1.2, 95% CI 0.6–2.4; $p = 0.56$).

3.7. Sensitivity analyses

The results of this meta-analysis were not affected by sensitivity analyses, which were performed by excluding one study at a time, by removing studies included in the previous meta-analysis by Tzintzaras and colleagues, and by removing studies in which the diagnosis of SLE was not made by ACR criteria (data not shown). Specifically in the NHL analysis, we removed the two studies that showed extremely high SIRs [12,15], which did not alter our results (data not shown).

4. Discussion

Based on the results of our meta-analysis, the incidence of NHL, HL and leukemia is increased 6-fold, 3-fold and 2-fold in patients with adult patients with a diagnosis of SLE when compared with the general population. We were also able to show that the increased risk of hematologic malignancies in patients with SLE appears consistent among different populations.

Our results are consistent with the findings of a pooled analysis from the InterLymph consortium, which included approximately 13,000 NHL cases and 16,000 cancer-free controls [17]. In this study, 57 and 26 patients had SLE in the case and control groups, respectively, for an odds ratio (OR) of NHL of 2.7 (95% CI 1.7–4.3) for SLE cases. Given the small number of SLE patients among cases and controls (i.e. rare disease assumption), the OR and RR are virtually equivalent. Based on the design of case-control studies, the association found between exposure and outcome might not be necessarily causal. In some cases, reverse causality might be the reason for any detected association (i.e. NHL patients might have a higher risk of developing SLE). To investigate a causal relation between exposure and outcome, prospective cohort studies are better suited; hence, our attempt on performing a meta-analysis exclusively of prospective cohort studies.

Whether causality can be demonstrated in meta-analyses of epidemiological studies is a matter of debate. However, meta-analyses can help to our understanding of causal criteria [18]. Commonly used criteria to support causality include consistency, strength of association, dose-response and plausibility [19]. In our analysis, we observe consistency, as an increased incidence of hematologic malignancies, including leukemia and lymphoma, can be seen regardless of age, sex and geographical region. Our subset analyses give way to areas of heterogeneity, which are expected given the nature of our study but should not be used to discount the potential association between SLE and hematologic malignancies [18]. In the subject of strength of association, we have shown that SLE can increase the SIR for hematologic malignancies 3-fold. Intuitively, the SIR for some malignancies is higher than others; we have found an increased risk of NHL (6-fold) and to a lesser degree for HL (3-fold) and leukemia (2-fold). Our study, however, provides higher precision of the risk of hematologic malignancies in SLE patients by virtue of the sample size analyzed. Our meta-analysis also supports a dose-response relation between SLE and hematologic malignancies. However, the patterns of association differ between NHL, HL and leukemia. The risk for NHL does not change with longer SLE latency, while the risk of HL increases and the risk of leukemia decreases. These results support a biological difference between these malignancies, which is expected given their distinct clinicopathological features.

Regarding plausibility, the relation between SLE and lymphoma appears intuitive. When B-cells leave the bone marrow, they are “naïve”, in the sense that they have not been exposed to antigen. Naïve B-cells carry, among other antigens, membrane IgM, CD20, an incipient B-cell receptor and an unmutated immunoglobulin heavy chain gene. Once in the follicle of a lymph node, B-cells get exposed to antigen and undergo two separate and likely concurrent processes, somatic hypermutation (SHM) and class-switching recombination (CSR), the so-called germinal center reaction [20–22]. The purpose of the germinal center reaction is to produce the most specific antibody against a given antigen. The clones producing anergic or hypersensitive (autoimmune) antibodies should undergo apoptosis. As expected, several clones of B-cells are tested and only a few are selected. Such clones will become plasma cells or memory cells and leave the germinal center. The processes of SHM and CSR induce genomic instability and allow for the introduction of point mutations or translocation that could induce a malignant behavior [23]. As an example, lymphoma-specific translocations commonly involve the genes responsible of the transcription of the light and heavy immunoglobulin chains [24].

Based on this, SLE can increase the risk of lymphoma in diverse ways [25]. On one hand, autoimmune conditions such as SLE and rheumatoid arthritis, among others, induce a systemic inflammatory state characterized by chronic antigen stimulation, which would favor genomic translocation by means of increasing B-cell proliferation. This is a similar process by which chronic infections

such as *Helicobacter pylori* induce lymphomagenesis. On the other hand, autoimmune as well as malignant B-cell clones should be removed from our system by immunosurveillance and other mechanisms. However, such processes appear to be defective in these cases, providing a common state of autoimmunity–malignancy. These hypotheses, however, provide only a limited explanation for the relation between SLE and lymphoma and further research is needed.

The relation between SLE and leukemia is rather unclear. One could hypothesize that some of the drugs used to treat SLE, such as the alkylator cyclophosphamide among others, can increase the risk of developing myeloid neoplasms such as myelodysplastic syndrome (a pre-leukemic state) and acute myeloid leukemia [26]. Whether SLE increases the risk of lymphoid leukemia is an unanswered question. Chronic and acute lymphoid leukemias have not been associated with chronic antigen stimulation or exposures to drugs. The current data did not allow assessment of the risk of specific leukemia subtypes in patients with SLE. Finally, the association with myeloma appears weak and no definitive conclusion can be drawn from this analysis.

Strengths of our study include the potential causal inference between SLE and hematologic malignancies provided by the evaluation of prospective cohorts, and the inclusion of studies from diverse areas of the world allowing for generalization of our results. Additionally, most of the studies had long follow-up, which permits for the occurrence of the outcome of interest, and excluded cases identified within one year of SLE diagnosis. Finally, the sample size permits more precise and reliable estimates of risk. Our study, however, carries several weaknesses. First, most of the studies included in our analysis obtained the diagnosis of hematologic malignancy based on registry data, which might have introduced selection bias. This issue could be especially important for NHL, since SLE can alter the architecture of the lymph node and if an excisional biopsy is not performed, it can confound the diagnosis. Second, the diagnosis of SLE was assessed in some studies by ICD codes rather than the more widely accepted ACR criteria, which could have also affected selection of the participants allowing for inclusion of patients with localized forms or SLE or SLE-like conditions. Our sensitivity analysis, however, did not show differences when removing studies that did not make the diagnosis of SLE based on ACR criteria. Third, we were not able to investigate gender differences, as most of the studies did not separate the outcomes of male and female patients with SLE. One large study has suggested an increased incidence of hematologic malignancies in men with SLE [9]. Finally, the evaluation of the association between therapy for SLE and development of hematologic malignancies was not possible based on the available data. The association between SLE therapy and hematologic malignancies has been suggested in a large multi-center case-cohort study [27].

Despite our limitations, we show that SLE patients have a higher risk not only of developing NHL but also HL, leukemia and possibly myeloma. Such risk seems to be consistent regardless of the geographical region. Further research is needed to investigate the biological association between SLE and hematologic malignancies as well as the role that SLE therapy might play on carcinogenesis.

Conflict of interest

The authors have no conflict of interest to disclose.

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Portions of this study have been presented as a poster at the 2013 American Society of Hematology Annual Meeting in New Orleans, Louisiana.

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